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

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*Received February 28, 2000*

**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 bromoallenes. 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 laurenan 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 3*E*,6*R*,7*R*-laurediol into deacetyllaurencin[2] and 3*Z*,6*S*,7*S*-laurediol into prelaureatin **1** through a bromo cationic cyclization (Figure 2).[3] Deacetyllaurencin is further transformed to laurefucin[4] and laurexanyne[5] by a second bromo cation cyclization or to laurencin[6] by acetylation. Prelaureatin **1**[7] has been shown to be the biogenetic precursor[8] of several members of the laurenan structural subclass such as laureatin **2**, isolaureatin **3**,[9] and laurallene **4** (Figure 3).[10] Laureatin **2** and isolaureatin **3** display significant larvacidal activity (IC$_{50}$ = 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 laurencin.[12–15] A wealth of new strategies
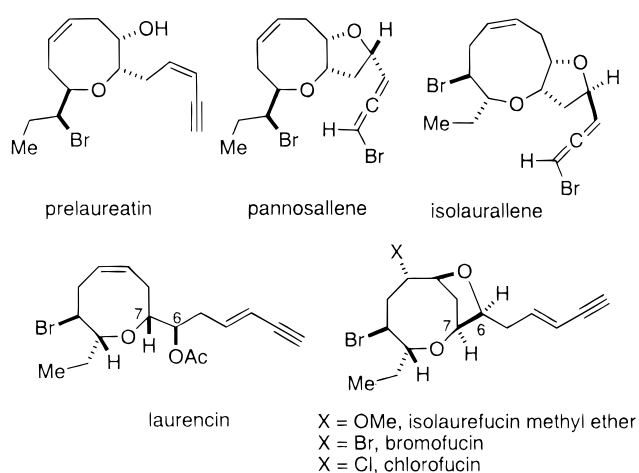


**Figure 1.** Medium ring ether natural products.

for the construction of medium ring ethers has resulted from the synthetic efforts toward laurencin.[16] The laurenan structural 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 strategy[12] for the construction of the oxocene core of laurencin and a second-generation synthesis of laurencin based on an asymmetric alkylation–ring-closing

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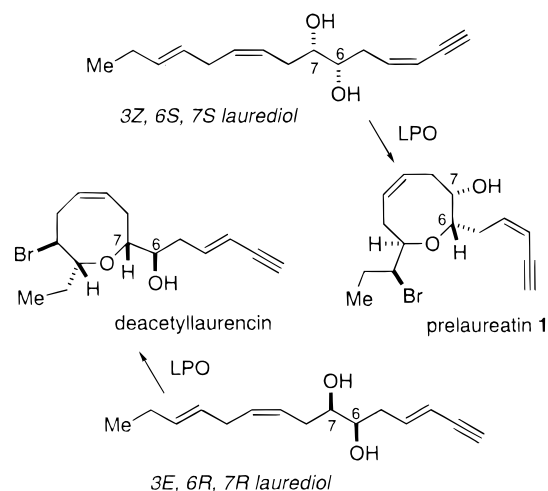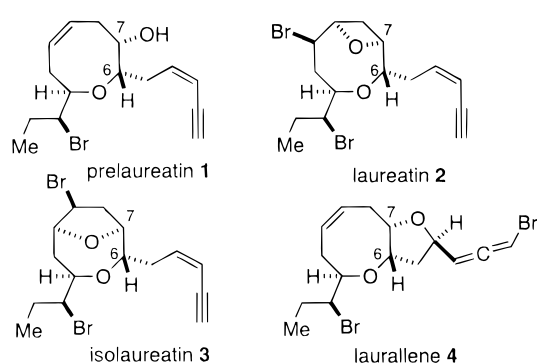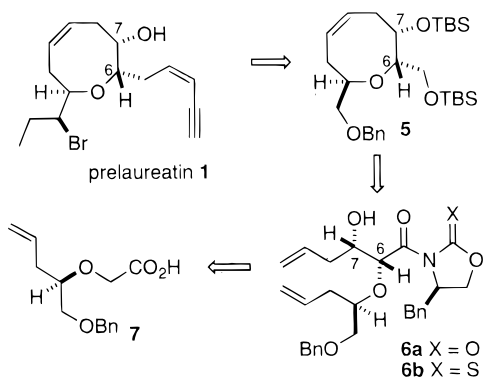
**Figure 2.**



**Figure 3.**



**Figure 4.** Retrosynthetic plan for prelaureatin.

metathesis approach.[13] Here we disclose the total synthesis of (+)-prelaureatin and (+)-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.[7] 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,[18,19] exploiting the gauche *effect*[20] of the C6 and C7 oxygen substituents to accelerate the ring closure. An asym-

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**Scheme 1**
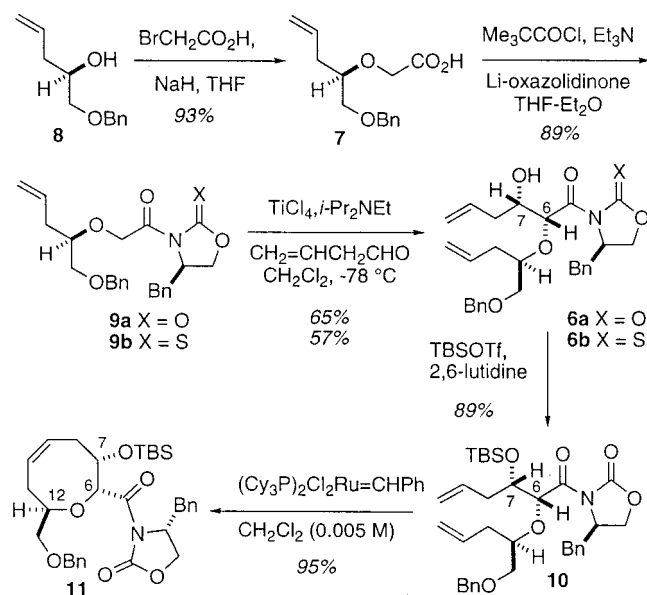


metric aldol reaction between 3-butenal[21] and the chlorotitanium enolate of the acyl oxazolidinethione[22,23] (or oxazolidinone) derived from acid **7** would serve to establish the C6 and C7 stereocenters of the oxocene core. Since the critical C6 and C7 stereogenic centers are set in the asymmetric 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.[24] 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 Δ-4-oxocene **11** in 95% yield with no detectable dimerization. While

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(19) For other applications of ring-closing metathesis in the synthesis of medium ring ethers see: Clark, J. S.; Hamelin, O. *Angew. Chem. In. Ed.* **2000**, *39*, 372−374 and references therein.

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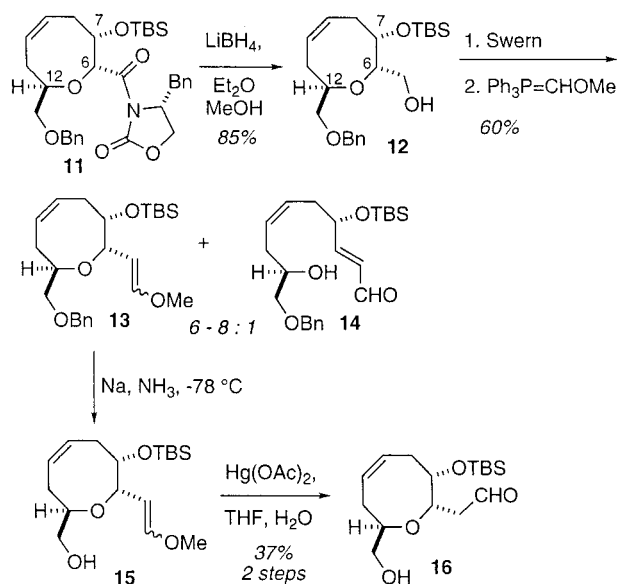
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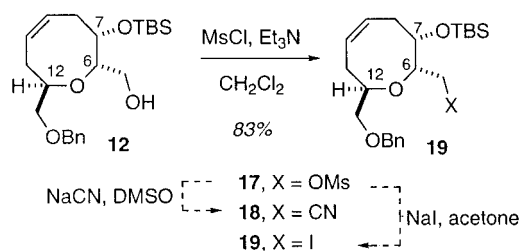
**Scheme 2**



**Scheme 3**



**Scheme 4**



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,[26] 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 α,α'-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[27] 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 °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 β-elimination
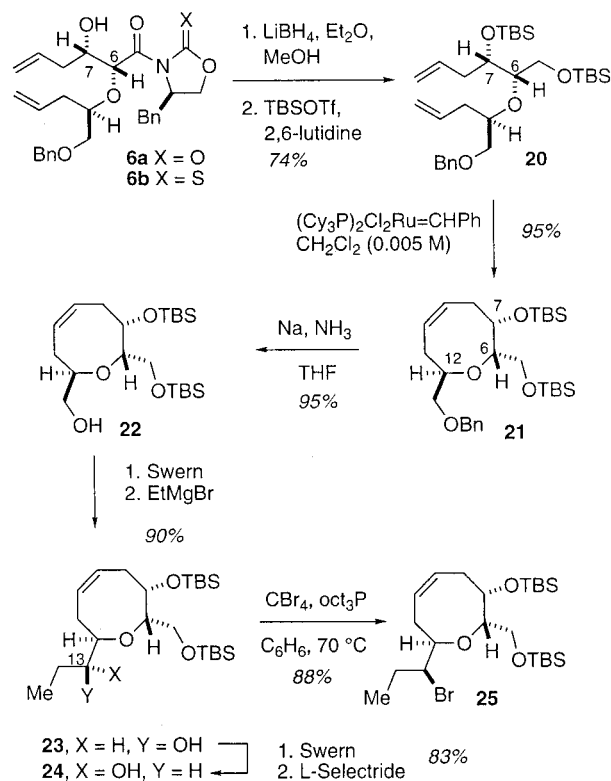
in the production of aldehyde **16**, it was decided to pursue the extension of the C12 side chain prior to the attachment of the C5 enyne.

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** (see Scheme 4). The diene **20** was treated with the Grubbs ruthenium catalyst[25] resulting in smooth conversion to the Δ-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[27] 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[13] examples indicate that chelation control is apparently limited in α-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.[28] 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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**Scheme 5**



**Scheme 6**
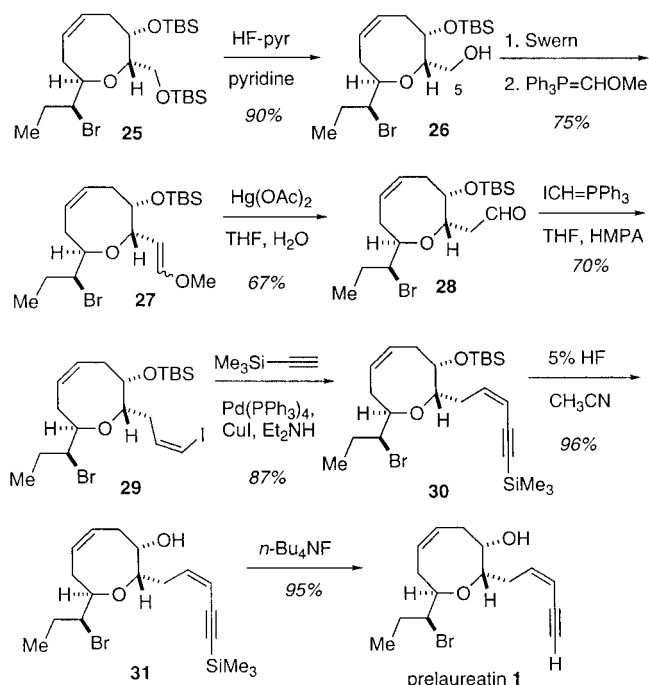


with L-selectride[15] gave excellent stereocontrol for the desired diastereomer **24** (>95:5 diastereoselectivity). Exposure of alcohol **24** to trioctylphosphine and CBr$_4$[29] cleanly effected incorporation of the C13 bromide providing bromide **25** in 88% yield.

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[27] oxidation of **26** followed by methoxymethylenation proceeded in good yield to give a mixture of the vinyl ethers **27** that were immediately hydrolyzed to the aldehyde **28**. Exposure of aldehyde **28** to the ylide developed by Stork[30] provided Z vinyl iodide **29** in 70% yield. Due to the lability of the vinyl ethers **27** and the aldehyde **28**, it was important to process the alcohol **26** to the vinyl halide **29** as quickly as possible. Rapid processing led to reproducible, workable yields from **26** to **29**. The vinyl iodide **29** was converted to the enyne **30** in 87% yield through a Sonogashira[31] coupling with trimethylsilylacetylene. Removal of the trimethylsilyl and *tert*-butyldimethylsilyl protecting groups could be accomplished concomitantly with *n*-Bu$_4$NF (THF, 0 °C) to give prelaureatin **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 (+)-prelaureatin was spectroscopically identical ($^1$H NMR, $^{13}$C NMR, IR, [α]$_d$) with that reported for the natural material.[7]
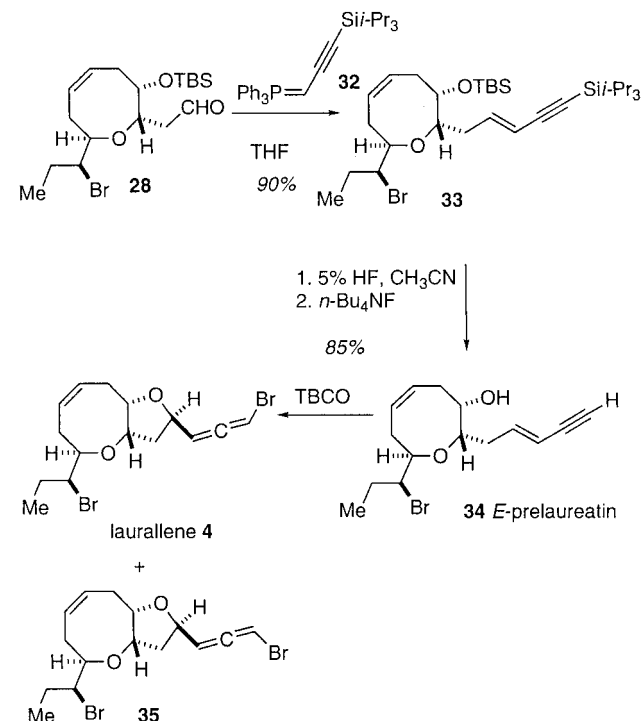
Aldehyde **28** was also converted directly to a 3:1 mixture of *E* and *Z* enynes **33** upon exposure to Wittig reagent **32** as illustrated in Scheme 6. Removal of the alcohol and the acetylene protecting groups as before afforded a 3:1 mixture of *E*-prelaureatin **34** and prelaureatin **1**. The *E*-enyne was treated with tetrabromocyclohexadienone according to the procedure described by Murai[8] to produce laurallene **4** and its bromoallene diastereomer **35** in 53% yield. The isomeric bromoallenes were separated by HPLC to give pure (+)-laurallene **4** and the bromoallene isomer **35**. Synthetic (+)-laurallene illustrated identical physical properties ($^1$H NMR, $^{13}$C NMR, IR, [α]$_d$) to those reported for the natural product.[10]

The first total syntheses of (+)-prelaureatin, (+)-*E*-prelaureatin, and (+)-laurallene 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.

**Supporting Information Available:** Spectral data and experimental procedures for compounds **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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