Biomimetic-Type Synthesis of Halogenated Tetrahydrofurans from *Laurencia*. Total Synthesis of *trans*-(+)-Deacetylkumausyne

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An important group of marine natural products are a series of nonterpenoid C15-metabolites generically named *lauroxanes* that are derived from fatty acid metabolism (acetogenins).[1] The structural diversity of this kind of molecule is very wide, but all have in common the presence of polysubstituted cyclic ethers with a defined stereochemistry in the substituents and ring size changing from five to nine members (Figure 1). Such cyclic ethers are considered to be biogenetically originated from laurediols through electrophilic cyclizations usually induced by bromonium ion.[1]

Many compounds of this class contain a tetrahydrofuran ring usually with a *syn*-stereochemistry in the alkyl substituents close to the oxygen atom of the cycle.[1] Substances of this class are *trans*-(−)-kumauseine (**1**) and *trans*-(+)-deacetylkumausine (**2**) isolated from *Laurencia nipponica* Yamada.[2] To the best of our knowledge, until now only two syntheses of kumauseine (**1**) have been reported: in one case in racemic form, reported by Overman et al.,[3] and the other in enantiomeric form, reported by Osumi et al.[4] In our group, synthetic studies directed to the enantiomeric synthesis of this compound have also been carried out, mainly directed toward the stereocontrolled synthesis of the substituted tetrahydrofuran by intramolecular cyclization of hydroxyalkenes induced by a bromonium ion.[5] Unfortunately, we were unable to extend our methodology to the final natural products mainly because the difficulties encountered to construct the carbon framework.[6]

As pointed out above, we have considered an approach to the synthesis of *exo*-bromotetrahydrofurans by a procedure that is formally similar to that considered as the responsible of the biogenetic origin of this kind of structural unit.[5] On the other hand, we have also performed the total enantiomeric synthesis of laurediols, which are assumed to be the biogenetic precursors of the whole series of compounds.[7] Our synthesis of such precursors was performed in a lineal manner and was not considered as optimal to scale the final products to perform electrophilic cyclization studies. In this paper, we report a different approach to (+)-deacetylkumausine,

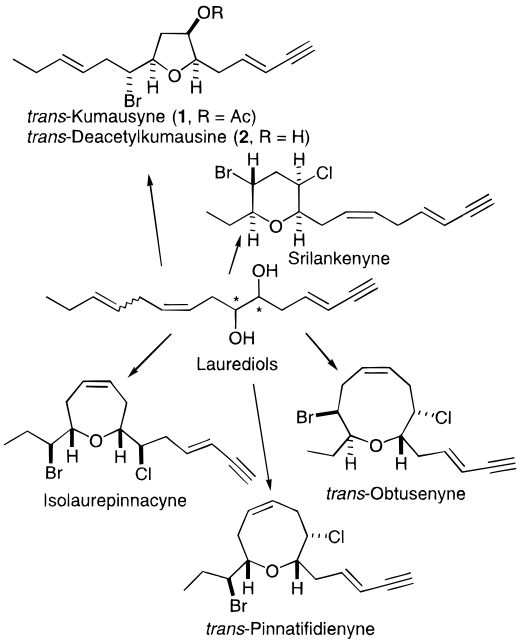
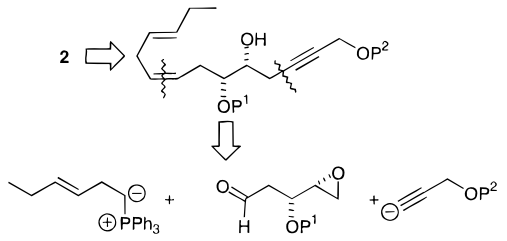
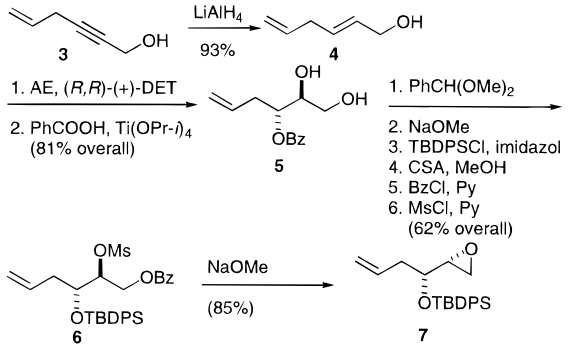


Figure 1.

Scheme 1



Scheme 2



as an example of a compound of this class, based on the retrosynthetic analysis, outlined in Scheme 1, in which we tried to solve both problems discussed above: convergence in the synthesis of the hydroxyalkene precursors with the possibility of scaling up the amount of final product obtained and stereochemical control in the synthesis of the cyclic ether with facilities to build the whole molecule.

Our synthesis of **2** started from the silyl-protected *threo*-1,2-epoxy-3-alcohol **7** easily available from the known enyne **3**[8] (Scheme 2). In this procedure, especially remarkable is the new method to obtain the *threo*-epoxy alcohol from the diolbenzoate **5** by intramolecular displacement of the secondary mesylate group with the

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(3) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378.

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(6) Añorbe, B.; Martín, V. S. Unpublished results.

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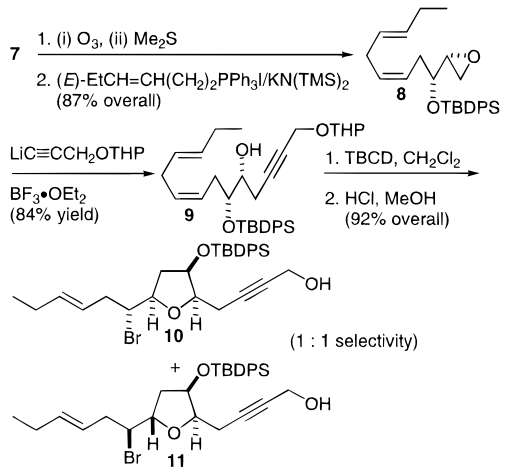
Scheme 3



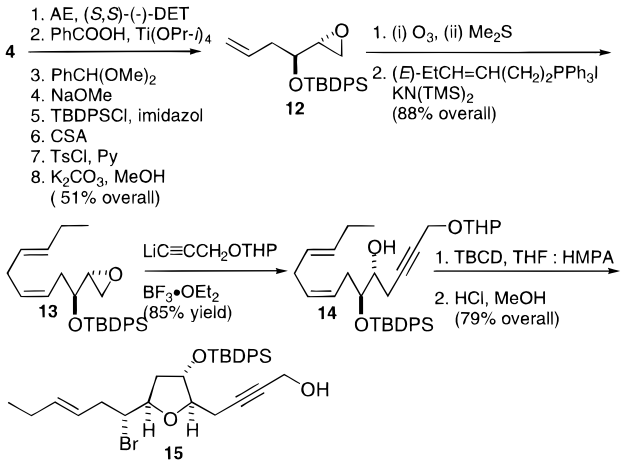
primary alkoxide. This method is actually an alternative to that previously reported from our laboratory.[9]

The silyl epoxy ether **7** was used as the central fragment to homologate the chain in both directions. Thus, the double bond was cleaved with ozone under reductive conditions and the resulting aldehyde submitted to the corresponding Wittig reaction yielding the diene **8** with excellent stereocontrol (Scheme 3). On the other hand, the terminal epoxide was opened with the lithium salt of protected propargylic alcohol yielding the lineal chain **9** in which all hydroxy groups are chemically differentiated, being suitable to perform the cyclization reaction.[10] Thus, **9** was treated in CH_2Cl_2 with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) as source of Br^+,[11] yielding, after the cleavage of the THP group, the 1:1 mixture of the tetrahydrofurans **10** and **11**.[12]

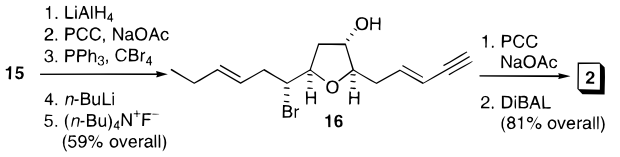
Although the stereochemistry of **10** is concordant with that present in the natural products, we considered the possibility of improving the stereoselection in the cyclization reaction, basically performing this step with a precursor in which the stereochemistry in the silyl-protected carbinol was changed. Thus, **13** was obtained by a similar sequence of reactions through the *erythro*-epoxy ether **12** (Scheme 4). In this case, gratifyingly, the desired *syn*-2,5-disubstituted tetrahydrofuran **15** was obtained in a ratio of 5:1.

The one-carbon homologation to the *trans*-enyne **16** was performed in accordance with our previously reported procedure[7] using Corey's methodology (Scheme 5).[13] Finally, the inversion of configuration of the secondary carbinol by a consecutive sequence of oxidation and reduction reactions afforded (+)-deacetylkumausine (**2**) $[\alpha]^{25}_D = +6.5$ (*c* 0.8, $CHCl_3$) [lit.[4] $[\alpha]^{20}_D = +6.5$ (*c* 1.08, $CHCl_3$)].

Scheme 4



Scheme 5



In summary, we have described a convergent and stereocontrolled synthesis of a halogenated tetrahydrofuran natural product in which the key step is a bromonium ion-induced cyclization of a suitable hydroxy alkene; this type of reaction is considered as the biogenetic origin of *Laurencia* halogenated cyclic lipids. Application of this methodology to other halogenated tetrahydrofurans is in progress and will be published elsewhere.

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Supporting Information Available: Copies of NMR spectra of compounds **2**, **10**, **11**, and **13**−**16** and experimental details for the synthesis of **13**−**15** (15 pages).

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(12) The use of highly polar solvents such us THF:HMPTA yielded a poorer stereoselection of **10** relative to **11** (1:2). See ref 5.

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