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Expedient Enantioselective Synthesis of the Δ^4-Oxocene Cores of (+)-Laurencin and (+)-Prelaureatin‡

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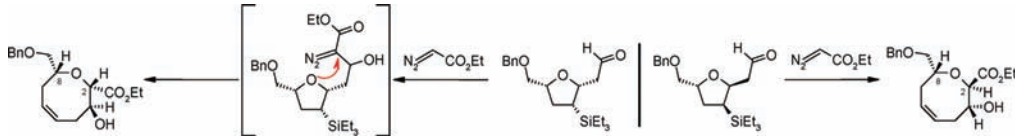
ABSTRACT



An expedient enantioselective synthesis of the Δ^4-oxocene cores present in (+)-laurencin and (+)-prelaureatin was accomplished in eight steps via a novel one-pot regio- and stereoselective ring cyclization−fragmentation−expansion cascade from the tetrahydrofuran precursors which were prepared by stereocontrolled cyclization from vinylsilanes. This process is highlighted by an intramolecular oxo-carbenoid insertion and a *β*-silyl fragmentation sequence.

It is well documented that the species of red algae genus *Laurencia* produce diverse, unique, halogenated secondary metabolites, including a distinctive class of marine natural products with halogenated C_{15} cyclic ethers in various ring sizes.[1] Laurencin **1**[2] and laurenyne **2**[3] are two well-known prototypical examples containing *cis* α,α′-disubstituted eight-membered cyclic ethers (Figure 1).[4] The second structural subgroup is represented by prelaureatin **3**[5] which is constituted with a *trans* α,α′-disubstituted oxocene core.[6]

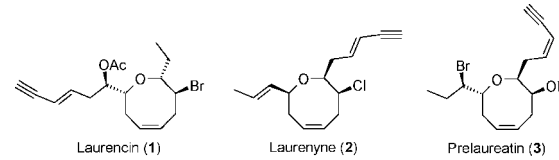


Figure 1. Laurencin (**1**), laurenyne (**2**), and prelaureatin (**3**).

These structurally unique *Laurencia* marine natural products have been attractive targets to the synthetic community which had led to both development of new strategies for the construction of medium-size cyclic ethers[7,8] and the total syntheses of laurencin **1**, laurenyne **2**, prelaureatin **3**, and other structurally related natural products.[9,10]

Our own investigations of these natural products focused on the construction of the Δ^4-oxocene core via a novel one-

‡ Dedicated to Professor K. C. Nicolaou.

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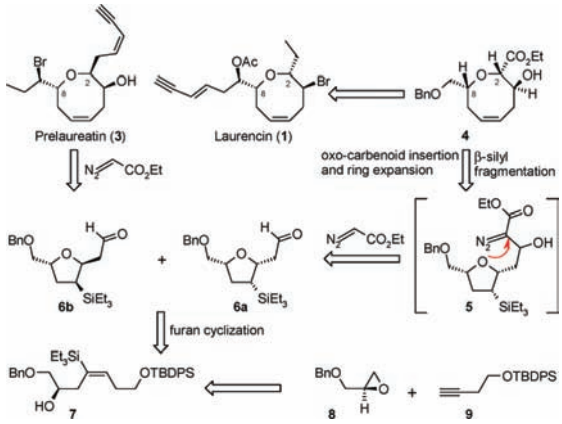
pot regio- and stereoselective ring cyclization−fragmentation−expansion cascade in a stereocontrolled manner. Herein, we report an expeditious stereoselective synthesis of Δ^4-oxocene demonstrating this new approach for the first time.

Our retrosynthetic approach to (+)-laurencin **1** and (+)-prelaureatin **3** is illustrated in Scheme 1. Simplification of the

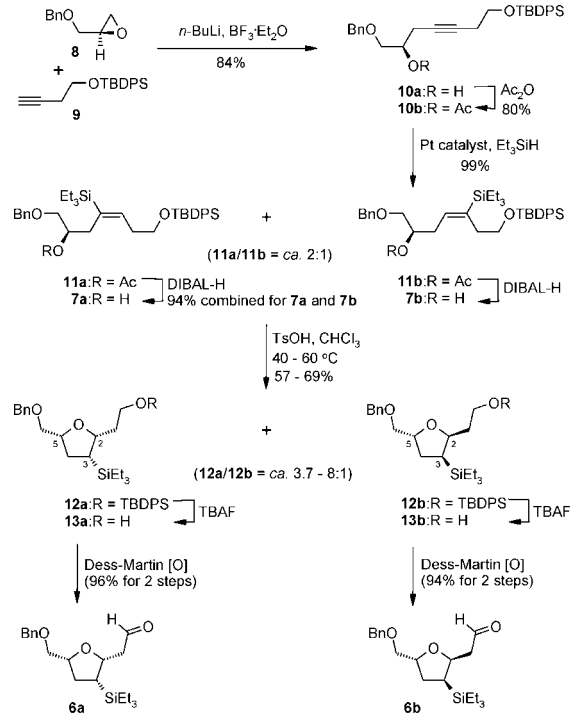
Scheme 1. Retrosynthetic Analysis of Laurencin (**1**) and Prelaureatin (**3**)



alkyl side chains and the bromine in laurencin **1** would render Δ^4-oxocene **4**. We envision that oxocene **4** could be derived from the key α-diazo-*β*-hydroxy ester **5** intermediate via an intramolecular oxo-carbenoid insertion and followed by a *β*-silyl fragmentation cascade. α-Diazo-*β*-hydroxy ester **5** would then be readily originated from aldehyde intermediate **6a** via an Aldol reaction with ethyl diazoacetate. An acid-mediated intramolecular tetrahydrofuran cyclization of vinylsilane **7** would subsequently lead to aldehyde precursor **6a** upon functional group manipulation. Finally, enantiomerically pure chiral vinylsilane **7** would be readily assembled from commercially available (*R*)-glycidyl benzyl ether **8** and alkyne **9** precursor. The *trans* α,α′-disubstituted oxocene core in (+)-prelaureatin **3** can be derived in a similar manner from the (2*S*,3*S*,5*R*)-diastereomer tetrahydrofuran intermediate **6b**.

The synthesis of the requisite tetrahydrofuran intermediates **6a** and **6b** is outlined in Scheme 2. Enantiomerically pure

Scheme 2. Synthesis of Tetrahydrofuran Intermediates **6a** and **6b**



homopropargyl alcohol **10a** was readily obtained in 84% yield by treating terminal alkyne **9** with 1.0 equiv of *n*-BuLi at −78 °C, followed by a regioselective epoxide ring opening of commercially available (*R*)-glycidyl benzyl ether **8** in the presence of 1 equiv of $BF_3{\cdot}Et_2O$. Establishing the absolute stereoconfiguration of the hydroxyl group in **10a** at this stage proved to be pivotal for the success of the later key transformation. Although the newly generated alcohol **10a** could be directly converted into the desired regioisomers of **7a** and **7b**, we found that protecting the hydroxyl group as acetate in **10b** would provide a better yield for the subsequent hydrosilyation step.[11] Stereoselective catalytic *cis*-hydrosilylation (1.2 equiv of Et_3SiH, 0.006 equiv of $H_2PtCl_6{\cdot}H_2O$) of alkyne **10b** smoothly led to a mixture of *trans*-vinylsilyl regioisomers **11a** and **11b** (ca. 2:1 ratio) in nearly quantitative yield.[12] Deacetylation of the resulting mixture of **11a** and **11b** to the separable regioisomers **7a** and **7b** (ca. 2:1 ratio, 94% yield) was readily accomplished with DIBAL-H at −78 °C. Although each pure vinylsilane

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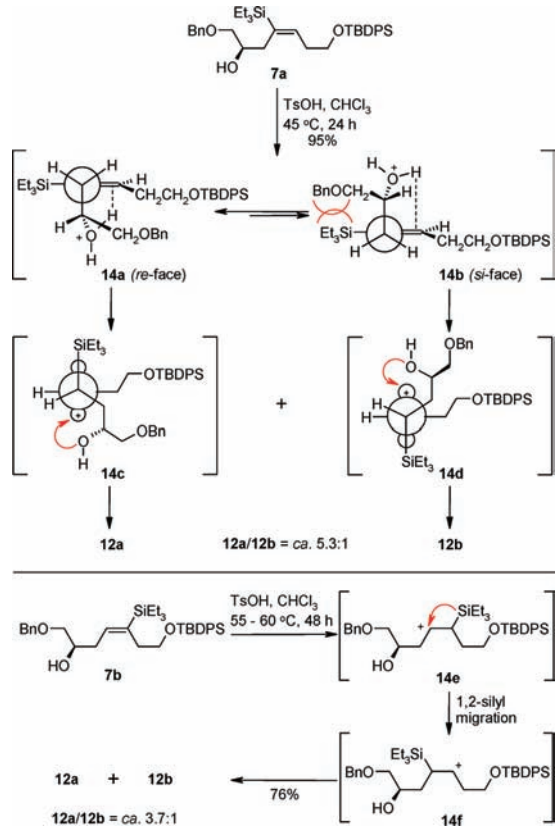
could separately lead to the desired tetrahydrofurans **12a** and **12b**, it was more practical to take this mixture of regioisomers **7a** and **7b** to the cyclization step directly. Under the influence of a catalytic amount of TsOH (0.05−0.2 equiv) at 40−60 °C, this mixture of *trans*-vinylsilanes **7a** and **7b** was effectively cyclized to two readily separable tetrahydrofuran diastereomers **12a** and **12b** (ca. 3.7−8:1 ratio) in 57−69% isolated yield, while some starting materials were recovered.[13] The stereochemical assignments of **12a** and **12b** were confirmed by the NOE experiments. Key tetrahydrofuran intermediate **6a** was finally derived from the corresponding **12a** via a two-step sequence. The TBDPS group in **12a** was initially cleaved by the treatment with TBAF, and the resulting primary alcohol **13** was subsequently oxidized to aldehyde **6a** with Dess-Martin periodinane in 96% yield over two steps. Similarly, intermediate **12b** was converted into aldehyde **6b** in 94% overall yield.

We observed that the product yield and ratio of the two tetrahydrofurans from this cyclization were governed by the catalyst loading, reaction temperature, and time.[14] Decomposition of both starting materials (**7a** and **7b**) and products (**12a** and **12b**) was observed under either prolonged reaction time or at elevated reaction temperature. However, it was noteworthy that acid-catalyzed cyclization of vinylsilane **7a** was more facile than **7b** under the given reaction conditions (Scheme 3). Formation of tetrahydrofurans **12a** and **12b** (ca. 5.3:1 ratio) in 95% yield from the pure vinylsilane **7a** was achieved smoothly under the optimized milder reaction conditions (0.05 equiv of TsOH at 45 °C for 24 h). In contrast to **7a**, the conversion of vinylsilane **7b** to tetrahydrofurans **12a** and **12b** (ca. 3.7:1 ratio) required higher temperature (55−60 °C) and catalyst loading (0.10 equiv of TsOH) over 48 h. The resulting lower yield (76% yield) from **7b** was likely caused by the undesired protodesilylation under the more forceful reaction conditions. The diastereoselectivity outcomes of the acid-promoted tetrahydrofuran cyclization could be rationalized by the proposed mechanism from Hosomi and co-workers.[15] The stereochemical configurations of both the silyl groups and the side chains at the C(2) positions in tetrahydrofurans **12a** and **12b** were influenced by the chirality of the homoallylic hydroxyl group we previously installed in **7a**, during the stereoselective protonation step (Scheme 3). Two possible stabilized diastereomeric β-silylcarbenium intermediates **14c** and **14d** were formed upon TsOH-mediated protonation of vinylsilane **7a**. Preferential protonation from the *re*-face of the vinylsilane in transition state **14a** over the *si*-face in **14b** was due to the absence of steric

Scheme 3. Formation of Tetrahydrofurans **12a** and **12b**



clash between the large Et_3Si group and the methylene in the CH_2OBn residue displayed in **14b**. Subsequently, the more accessible transition state **14a** led to β-silycarbenium transition state **14c**, and the further intramolecular cyclization provided tetrahydrofuran **12a** as the major product while the less favorable transition state **14b** afforded **12b** as the observed minor product. For the transformation of vinylsilane **7b** to **12a** and **12b**, an additional 1,2-silyl group migration was required from β-silylcarbenium **14e** to **14f** prior the tetrahydrofuran cyclization. The stereochemical assignments of **12a** and **12b** were confirmed by the NOE studies.[16]

With aldehydes **6a** and **6b** in hand, we set the stage for introducing the α-diazo-β-hydroxy ester side chain in intermediate **5** via the procedure reported by Holmquist and Roskamp[17] (Scheme 4). Gratifyingly, treating aldehyde **6a** with a slight excess of ethyl diazoacetate (1.2 equiv) in the presence of a catalytic amount of anhydrous $SnCl_2$ (0.1 equiv) in CH_2Cl_2 at ambient temperature cleanly afforded the anticipated β-keto ester **15** (62−70% yield), accompanied with Δ^4-oxocene **4** as a single diastereomer (20−25% yield).[18] We were delighted to confirm the structure of **4** which resembled the desired eight-

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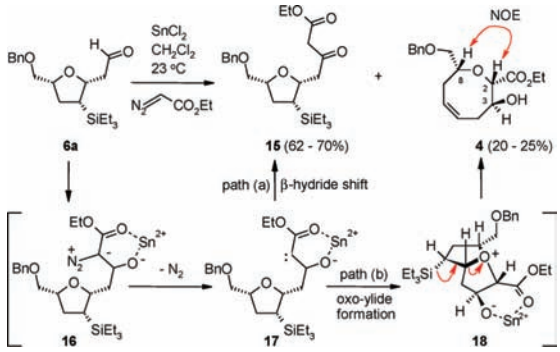
(14) We did not fully optimize the stereoselectivity of this cyclization with the mixture of **7a** and **7b** since we would prefer to utilize both diastereomers **12a** and **12b** for the syntheses of *cis*- and *trans*-oxocenes, respectively.

(15) (a) Miura, K.; Hondo, T.; Takahashi, T.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 2129–2132. (b) Miura, k.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *J. Org. Chem.* **1997**, *62*, 8292–8293.

(16) The result of the 2,3-*cis* relationship described here is also similar to the cyclization of 2-silyl-3-alkenols reported by Landais and co-workers in ref 13e.

(17) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260.

Scheme 4. Synthesis of Oxocene **4** via a Ring Formation−Fragmentation−Expansion Cascade

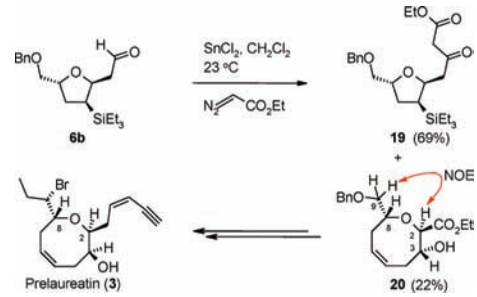


membered cyclic ether core in (+)-laurencin **1**. It not only regioselectively introduced the *cis*-Δ^4-olefin, the hydroxyl group, and two alkyl side chains in the correct positions but also stereoselectively established the desired *cis*-orientation of the C(2) and C(8) side chains adjacent to the oxygen atom in the core. The stereochemical assignments of this eight-membered cyclic ether core of **4** were confirmed by NOE studies.[19]

We postulated this Δ^4-oxocene **4** was constructed through a novel stereocontrolled ring cyclization−fragmentation−expansion process as illustrated in Scheme 4. From the initial Sn^{2+}-mediated Aldol reaction, the diastereomeric adduct **16** subsequently loses N_2 to form the carbene intermediate **17**. The resulting carbene **17** undergoes a known β-hydride shift to give the expected β-keto ester product **15** (pathway a).[17,20] In the second plausible pathway, a tricyclic oxo-ylide transition state **18** is stereoselectively formed via an oxo-carbenoid insertion by the oxygen atom from the tetrahydrofuran ring in **17**.[21,22] In this highly organized hydrindane-type transition state **18**, the enforcing proximity of three reacting partners accounts for the observed stereoselectivity in **4**. It is noteworthy that H(2) adapts a preferable (*S*)-orientation in **18** that would avoid the potential steric clash with the Et_3Si group sitting below the furan ring in a highly congested environment. From transition state **18**, a ring expansion from the [3,3,0]bicyclooctane-like core can occur, followed by a simultaneous β-Et_3Si group *syn* elimination, to give Δ^4-oxocene **4** in a highly regio- and stereoselective manner.

Similarly, aldehyde **6b** was also smoothly converted into β-keto ester **19** (69% yield) and *trans* α,α'-disubstituted oxocene **20** (22% yield) (Scheme 5). The *trans* configuration

Scheme 5. Synthesis of Oxocene **20**



in **20** resembles the laurenan core structure in (+)-prelaureatin **3**, another member in the *Laurencia* family. NOE experiments clearly indicated the *trans* relationship based on the interaction between H(2) and H(9), yet lacked of any interaction between H(2) and H(8) as displayed in oxocene **4**. The installed chirality at C(8) from the early stage was able to direct the subsequent stereochemical outcomes of the C(2) and C(3) positions in both oxocene transformations. Further manipulation of both α and α′ side chains in oxocenes **4** and **20** should lead to (+)-laurencin **1** and (+)-prelaureatin **3**.

In summary, an expedient enantioselective synthesis of eight-membered cyclic ethers was achieved in eight steps (ca. 11% overall yield for **4**) from commercially available materials. This work highlights the unique one-pot ring cyclization−fragmentation−expansion cascade via a rapid stereocontrolled oxo-carbenoid insertion and subsequent β-silyl fragmentation process from the tetrahydrofuran precursor. Application of this methodology has led to the construction of both enantiomerically pure *cis* α,α'- and *trans* α,α'-disubstituted Δ^4-oxocenes as precursors with all the requisite elements toward the total syntheses of marine natural products, (+)-laurencin **1**, (+)-prelaureatin **3**, and other members in the *Laurencia* family. This work will be reported in due course.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra of new compounds, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) We have found that $SnCl_2$ was the most effective catalyst for this transformation based on our preliminary studies with the Lewis acid catalysts reported in ref 17.

(19) The stereochemical assignment of C(3) is based on our studies of an oxocene **4** analogue, via the ester group reduction (LAH) in **4** and converting the resulting diol to the diacetate. NMR spectroscopic analysis of this diacetate compound indicated a 2,3-*trans* relationship, and its data also were different from the 2,3-*cis* diacetate oxocene analogue reported by Crimmins et al. in ref 9d. The ^1H NMR coupling constant ($J = 9.4$ Hz) between H(2) and H(3) in **4**, as suggested by one reviewer, is also in agreement with an *anti*-configuration reported in the studies on related oxocenes by Holmes et al. in ref 9e.

(20) In our preliminary studies, **15** was also demonstrated to serve as a precursor to the oxocene. The side chain in compound **15** was first converted into an α-diazo-β-keto ester, and the resulting tetrahydrofuran then underwent the $SnCl_2$-mediated oxo-carbenoid insertion−ring−fragment−expansion cascade to the β-keto ester oxocene via a two-step process similar to the one-pot process described in Schemes 1 and 4.

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(22) In contrast to our observation here, a carbenoid C−H insertion and ylide formation of a similar tetrahydrofuran intermediate were reported in the synthetic studies of neoliacinic acid: (a) Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040–1055.