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Highly Stereoselective and Efficient Total Synthesis of (+)-Laurencin

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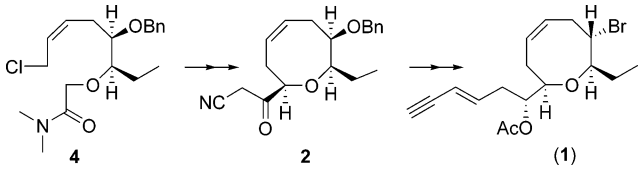
ABSTRACT



A highly stereoselective and efficient asymmetric total synthesis of (+)-laurencin (1) has been accomplished from the known oxazolidinone 5 in 15 steps. The route features an efficient internal alkylation to form oxocene 3 from 4 and a novel use of acetonitrile anion as a two-carbon acetaldehyde equivalent for direct synthesis of ketone 2 from α-alkoxy amide 3.

(+)-Laurencin (**1**), a halogenated C_{15} acetogenin, was first isolated from the red alga *Laurencia glandulifera* by Irie and co-workers in 1965.[1] Its structure was elucidated by a combination of chemical degradation, spectroscopic methods, and X-ray crystallography.[1−3] The absolute stereochemistry of this oxacyclic marine natural product was assigned by the application of Prelog atrolactic acid method to its octahydrodeacetyllaurencin derivative[4] and confirmed later by the first asymmetric total synthesis by Murai and co-workers.[5b] The interesting molecular structure of this oxocene natural product has served as an attractive target for synthetic organic chemists to test new synthetic strategies for stereoselective construction of eight-membered ring ethers.[5,6] Since the report of the first total synthesis of (±)-laurencin by the Masamune group in 1977,[5a] four asymmetric total syntheses and three formal syntheses of the natural product have been reported to date.[5] Described here is a new, efficient, and highly stereoselective total synthesis of (+)-laurencin (**1**) based upon our olefin geometry-dependent internal alkylation methodology[6a] for the construction of eight-membered ether rings and a novel strategy for the manipulation of the side chain appendage at C(7) (laurencin numbering).

As shown in Scheme 1, we envisaged that (+)-laurencin (**1**) might be secured via a new synthetic sequence from cyano ketone **2**, which in turn could be obtained by addition

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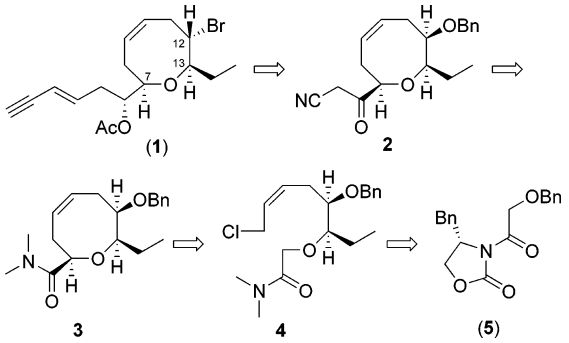
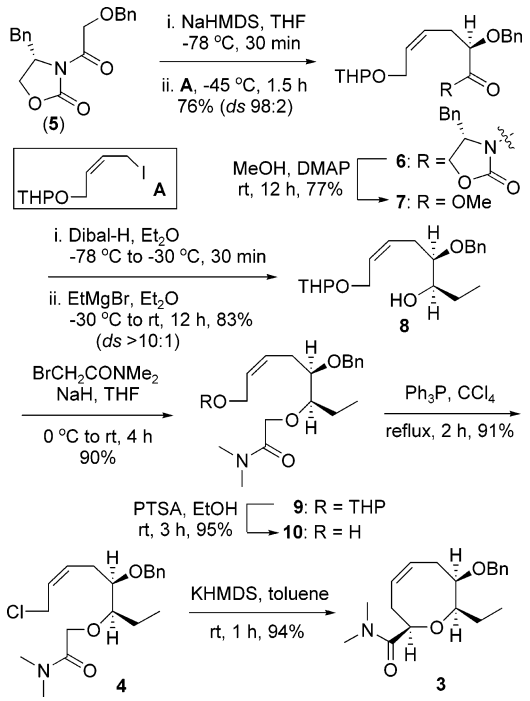
Scheme 1. Retrosynthetic Plan for (+)-Laurencin (**1**)



of acetonitrile anion to oxocene α-alkoxy amide **3**. We further envisioned that our olefin geometry-dependent internal alkylation of chloro amide **4**, prepared from glycolate oxazolidinone **5** by Crimmin's protocol,[7] would lead to key oxocene **3** in a highly stereo- and regioselective manner.

To commence the synthesis, alkylation of readily available glycolate oxazolidinone **5** with the known[8] allylic iodide **A** yielded the corresponding allylated product **6** (76%, ds = 98:2, ^{1}H NMR analysis) (Scheme 2). Methyl ester **7**, obtained

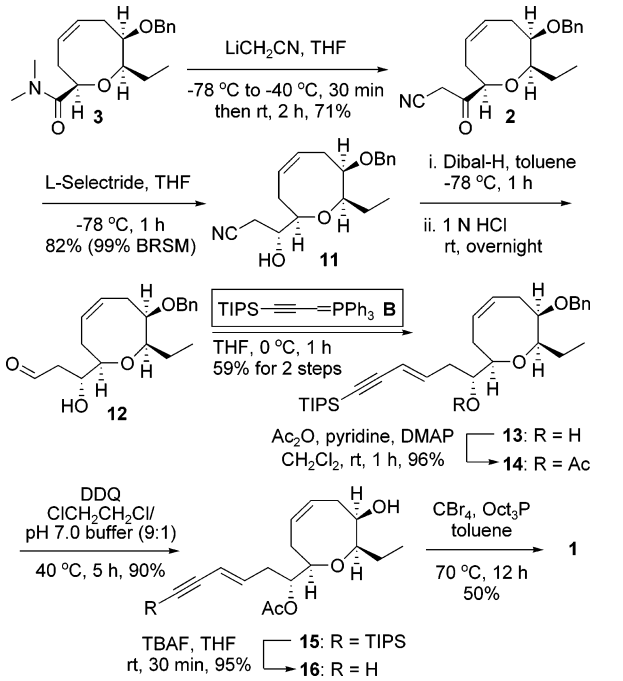
Scheme 2. Synthesis of Oxocene **3**



by methanolysis of amide **6** in the presence of DMAP,[9] was subjected to a one-pot Dibal-H "reduction and chelation-controlled nucleophilic addition" protocol[10] to furnish the desired *syn*-alcohol **8** in 83% yield with high diastereoselectivity (10:1, ^{1}H NMR analysis). A straightforward three-step sequence then led to the key internal alkylation substrate **4** in 78% overall yield: O-alkylation with *N*,*N*-dimethyl bromoacetamide, removal of the THP protecting group under acidic conditions, and chlorination by the Hooz protocol.[11] In a pivotal step, treatment of chloro amide **4** with KHMDS in toluene at room temperature for 1 h led to the formation of the desired oxocene **3** with excellent diastereoselectivity (>25:1) and in high yield (94%). The relative stereochemistry of the newly generated C(7) stereocenter of oxocene **3** was assigned as cis relative to C(13) by NOESY studies.

With key intermediate **3** in hand, we next turned our attention to the elaboration of the (*E*)-enyne side chain, which turned out to be quite problematic in our hands, despite ample precedents in other laurencin syntheses.[5,6] Among the many approaches tried, the following route, featuring use of acetonitrile anion[12] as an acetaldehyde equivalent, proved to be the most satisfactory. Thus, addition of the lithium anion of acetonitrile to α-alkoxy amide **3** resulted in ketone **2** (71%), which was subjected to stereo- and chemoselective reduction with L-Selectride to yield *β*-hydroxy nitrile **11** (82%) (Scheme 3).[13] To the best of our knowledge, this

Scheme 3. Completion of Total Synthesis of (+)-Laurencin



constitutes the first example of an addition of acetonitrile anion to an α-alkoxy amide to give a ketone. Dibal-H reduction of *β*-hydroxy nitrile **11**, followed by Wittig

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olefination of the resulting β-hydroxy aldehyde **12** with known phosphorane **B**, produced the requisite enyne **13** (59% for the two steps, $E/Z > 9:1$, ^{1}H NMR analysis).[5] Acetylation of secondary alcohol **13** and removal of the benzyl protecting group in intermediate **14** with wet DDQ using pH 7 buffer solution[14] yielded alcohol **15** in 81% overall yield for two steps. It is worthwhile mentioning at this point that use of a TIPS protecting group in **14** turned out to be quite important experimentally. Use of this group allowed us not only to separate the (*E*)/(*Z*)-mixture of enynes **14** by simple chromatography but also to remove the benzyl protecting group in **14** using DDQ with minimal isomerization (less than 3%) of the enyne system, which was reported as a serious problem in a similar but differently protected system.[5e] Finally, deprotection of TIPS-enyne **15** with TBAF (90%) and subsequent bromination of the resulting alcohol **16** by a known procedure[5e] gave rise to (+)-laurencin (**1**), whose spectral characteristics and optical rotation were in agreement with those of the natural product.[15]

In summary, we have accomplished a highly stereoselective and efficient total synthesis of (+)-laurencin (**1**) from known oxazolidinone (**5**) in 15 steps and 5.4% overall yield. The key features of the present synthesis include an efficient internal alkylation to form oxocene (**3**) and a novel use of acetonitrile anion as an acetaldehyde equivalent for the direct synthesis of a ketone from an α-alkoxy *N*,*N*-dimethylamide.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data for compounds **1**−**4**, **6**−**11**, and **13**−**16** along with copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For copies of ^{1}H and ^{13}C NMR spectra, see Supporting Information.