

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

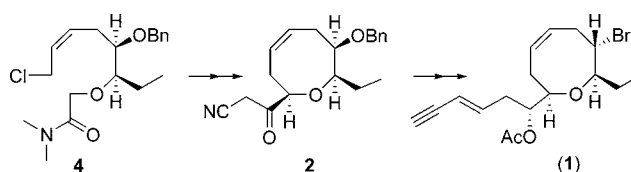
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ABSTRACT



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 octahydrodeacetyl laurencin derivative⁴ 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 (\pm)-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

(1) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091–1099.

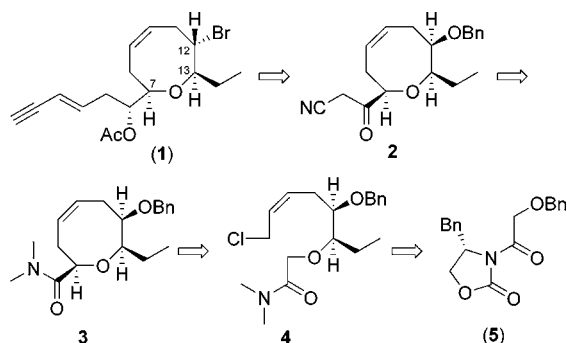
(2) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, 24, 4193–4205.

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(4) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc. B* **1969**, 559–564.

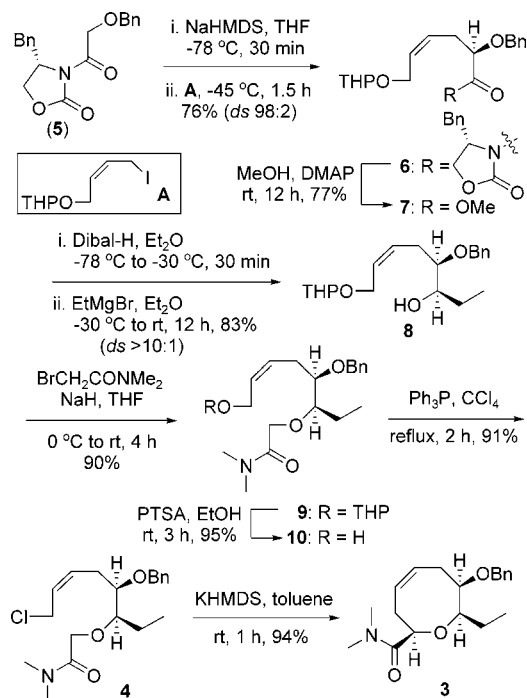
(5) For a racemic total synthesis, see: (a) Murai, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, 2507–2510. For asymmetric total syntheses, see: (b) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, 33, 4345–4348. (c) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, 117, 5958–5966. (d) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, 119, 7483–7498. (e) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, 1, 2029–2032. For asymmetric formal syntheses, see: (f) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983–984. (g) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, 119, 7499–7504. (h) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, 121, 5653–5660.

(6) (a) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, 125, 10238–10240 and references cited therein. For recent examples of C–C bond-forming approaches to oxocene construction, see: (b) Suh, Y.-G.; Koo, B.-A.; Kim, E.-N.; Choi, N.-S. *Tetrahedron Lett.* **1995**, 36, 2089–2092. (c) Alvarez, E.; Delgado, M.; Diaz, M. T.; Hanxing, L.; Perez, R.; Martin, J. D.; *Tetrahedron Lett.* **1996**, 37, 2865–2868. (d) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, 119, 6919–6920. (e) Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, 40, 4267–4270. (f) Coster, M. J.; De Voss, J. J. *Org. Lett.* **2002**, 4, 3047–3050. (g) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, 43, 7263–7266. (h) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, 60, 7361–7365. (i) Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, 45, 8639–8642.

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.

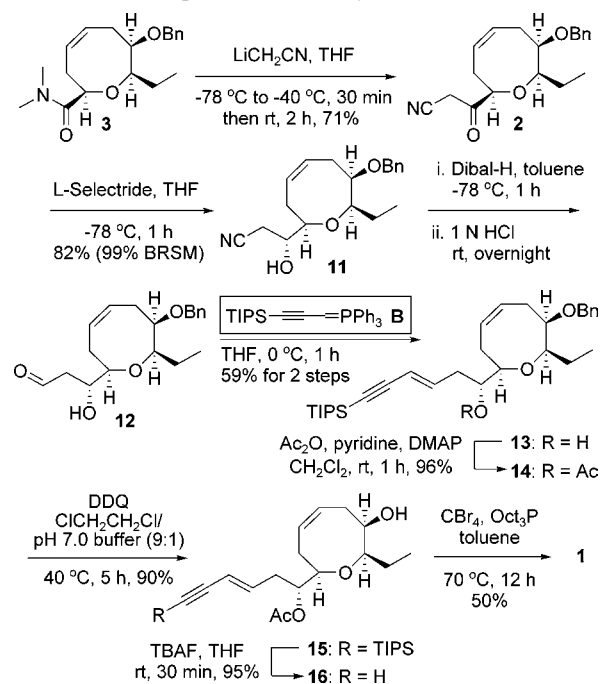
To commence the synthesis, alkylation of readily available glycolate oxazolidinone **5** with the known⁸ allylic iodide **A** yielded the corresponding allylated product **6** (76%, *ds* = 98:2, ¹H NMR analysis) (Scheme 2). Methyl ester **7**, obtained

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" protocol¹⁰ to furnish the desired *syn*-alcohol **8** in 83% yield with high diastereoselectivity (10:1, ¹H 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 anion¹² 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

(7) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739. (b) Evans, D. A.; Cage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961–1963. (c) Crimmins, M. T.; Emmitt, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165–2167.

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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, $E/Z > 9:1$, ^1H 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 solution¹⁴ 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,

(11) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86–87.

(12) For recent examples of the two-carbon homologation of carboxylic acid derivatives to β -keto nitrile by use of acetonitrile anion, see: (a) Stuk, T. L.; Haight, A. R.; Scarpetti, D.; Allen, M. S.; Menzia, J. A.; Robbins, T. A.; Parekh, S. I.; Langridge, D. C.; Tien, J.-H. J.; Pariza, R. J.; Kerdesky, F. A. *J. Org. Chem.* **1994**, *59*, 4040–4041. (b) Wittenberger, S. J. *J. Org. Chem.* **1996**, *61*, 356–358. (c) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1997**, *62*, 3036–3037. (d) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1999**, *64*, 2830–2834. (e) Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443–9448. (f) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 4932–4934. (g) Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003**, *5*, 1617–1620.

(13) Starting material (17%) was recovered, probably due to enolization.

(14) Schreiber, S. L.; Ikemoto, N. *J. Am. Chem. Soc.* **1992**, *114*, 2524–2536.

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 ^1H 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 ^1H and ^{13}C NMR spectra, see Supporting Information.