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Total Synthesis of (+)-Laurencin: An Asymmetric Alkylation–Ring-Closing Metathesis Approach to Medium Ring Ethers

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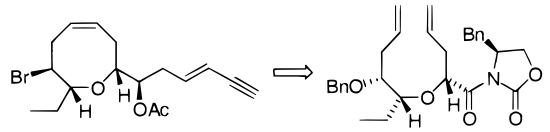
ABSTRACT



1 2

The enantioselective total synthesis of (+)-laurencin 1 is achieved in 18 steps from (*S*)-(+)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone. The key steps in this synthesis are an asymmetric glycolate alkylation leading to acyl oxazolidinone 2 and a subsequent ring-closing olefin metathesis to construct the oxocene core of 1. The approach to medium ring ethers utilized in this synthesis provides a general and efficient route to the cyclic core of other marine natural products.

Red algae and marine organisms that feed on *Laurencia* species have produced a diverse collection of natural products containing medium ring ethers (Figure 1).[1] A representative

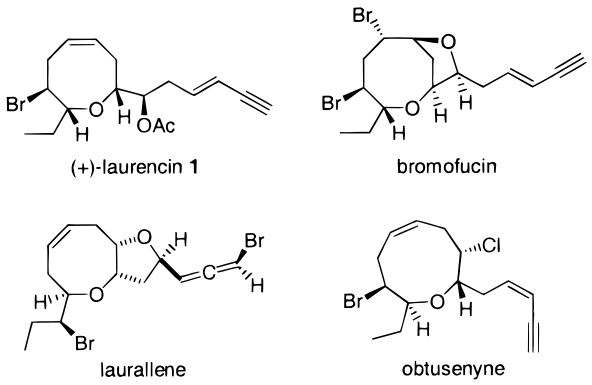


Figure 1. Medium ring natural products.

member of this group of marine metabolites, (+)-laurencin **1**, was isolated from the extracts of *Laurencia glandulifera* by Irie and Masamune in 1965.[2] The notable challenge in assembling medium ring ethers has led to significant work directed toward the development of strategies for the assembly of the oxocene core of (+)-laurencin. These efforts have resulted in several formal and total syntheses of the natural product.[3,4]

We recently reported the development of an asymmetric aldol-ring-closing metathesis strategy for the rapid construc-

(1) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155−198. Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113−158. Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259−302. Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75−125 and earlier reviews in the same series.

(2) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091−1099. Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193−4205.

(3) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660.

(4) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127−134. Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135−141. Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966. Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983−984. Krüger, J.; Hoffman, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499−7504. Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728−9738. 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. Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345−4348.

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tion of substituted seven-, eight-, and nine-membered rings.[3,5] The medium ring closure was effected without the use of cyclic conformational constraints by exploiting the known *gauche effect* of 1,2-dioxygen substitution. The preferred conformations of the α,*ω*-diene chain is dictated by the preference for a gauche disposition of the two oxygen substituents, resulting in the stabilization of one of the conformations with the two olefinic chains gauche. The *gauche effect* results in substantial rate increases in the ring-closing metathesis reaction, based on comparison to examples without vicinal oxygen substitution, thus allowing for the formation of medium rings without significant dimerization. The ability to construct medium ring ethers without the use of cyclic constraints allows rapid access to the cyclic ether core and renders the strategy easily adaptable to a number of targets. With the success encountered in this recent study in mind, we reasoned that an asymmetric alkylation−ring closing metathesis strategy might, in certain cases, provide a more direct route to medium ring natural products. The implementation of this plan resulting in a second-generation total synthesis of (+)-laurencin is the subject of this Letter.

A brief retrosynthetic analysis of our approach to (+)-laurencin demonstrates the efficiency of this strategy (Figure 2). Introduction of the (*E*)-pentenyl side chain of **1** would

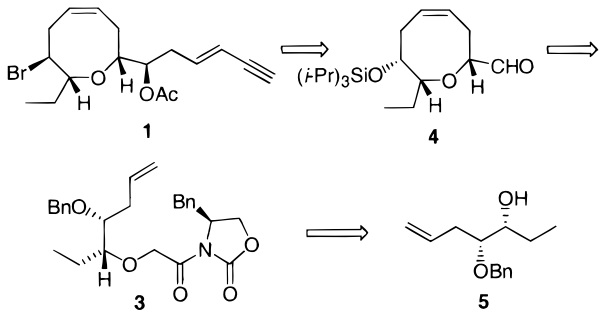
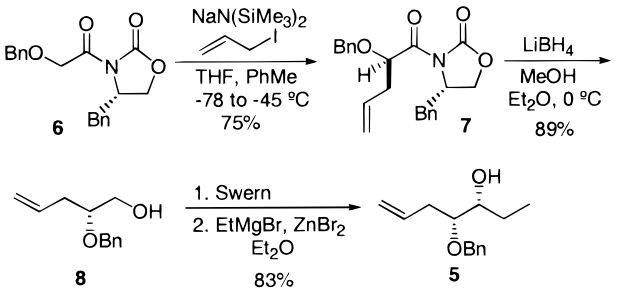


Figure 2. Retrosynthetic analysis.

be accomplished through elaboration of the acetate aldol adduct of aldehyde **4**. Aldehyde **4** would be accessible by applying the key asymmetric alkylation−ring-closing metathesis strategy to acyl oxazolidinone **3**. The synthesis of **3** required only the development of an efficient, scaleable route to chiral alcohol **5**. It was this endeavor that we deemed the first goal of the project.

The preparation of chiral alcohol **5** began with (*S*)-(+)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone **6** (Scheme 1).[6] Alkylation of the sodium enolate of **6** with allyl iodide provided a 75% yield of acyl oxazolidinone **7** (>98:2 ds).[7]

Scheme 1. Synthesis of Chiral Alcohol **5**



Reductive removal of the chiral auxiliary with lithium borohydride gave chiral alcohol **8** in 89% yield. Swern oxidation[8] followed by a chelation-controlled addition of ethylmagnesium bromide, according to the method of Asami,[9] provided the desired secondary alcohol **5** in 83% yield over two steps (>95:5 ds). To the best of our knowledge, this is the first example using a simple asymmetric glycolate alkylation of an acyl oxazolidinone to construct these types of protected homoallylic alcohols.[10] It is clear that a similar approach could be used to assemble a variety of these functionalized glycolate structures.

With an efficient route to **5**, we were ready to test the key glycolate alkylation−metathesis sequence to complete the construction of the oxocene core of (+)-laurencin (Scheme 2). The sodium alkoxide of **5** was alkylated with the sodium salt of bromoacetic acid to give an 88% yield of acid **9** and 5% of recovered starting alcohol. The mixed pivalic anhydride of acid **9** was treated with lithiated (*S*)-(+)-4-benzyl-2-oxazolidinone to provide acyl oxazolidinone **3** in 76% yield. Treatment of the sodium enolate of **3** with allyl iodide at −45 °C resulted in rapid, stereoselective alkylation to furnish diene **2** in 71% yield (>95:5 ds). Exposure of diene **3** to ring-closing metathesis conditions (5 mol % of $[(C_6H_{11})_3P]_2Cl_2Ru{=}CHPh$, 0.005 M, CH_2Cl_2, 40 °C, 3 h) gave oxocene **10** in 94% yield. Although we had hoped to carry the benzyl ether through until the (*E*)-pentenyl side chain was introduced, all attempts to remove the benzyl ether after incorporation of the enyne led to partial isomerization of the *trans* olefin. In addition, preliminary experiments indicated that a nonchelating silicon protecting group led to enhanced selectivity in the acetate aldol addition of **14** to aldehyde **4**. Consequently, the benzyl ether was cleaved with DDQ to provide alcohol **11**[11] and the resultant alcohol treated with (*i*-Pr)$_3$SiOTf to provide the triisopropylsilyl ether **12** in 83% yield over two steps. Reductive removal of the chiral auxiliary with lithium borohydride yielded 90% of the primary alcohol, which was subsequently oxidized under Swern conditions[8] to provide aldehyde **4** in 97% yield. With aldehyde **4** in hand, all that remained to complete the total

(5) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548−7549.

(6) Compound **6** was prepared in one step from commercially available benzyloxyacetic acid and (*S*)-(+)-4-benzyl-2-oxazolidinone. See also: Evans, D. A.; Cage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961−1963.

(7) All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, and optical rotation. Yields are for isolated, chromatographically purified products.

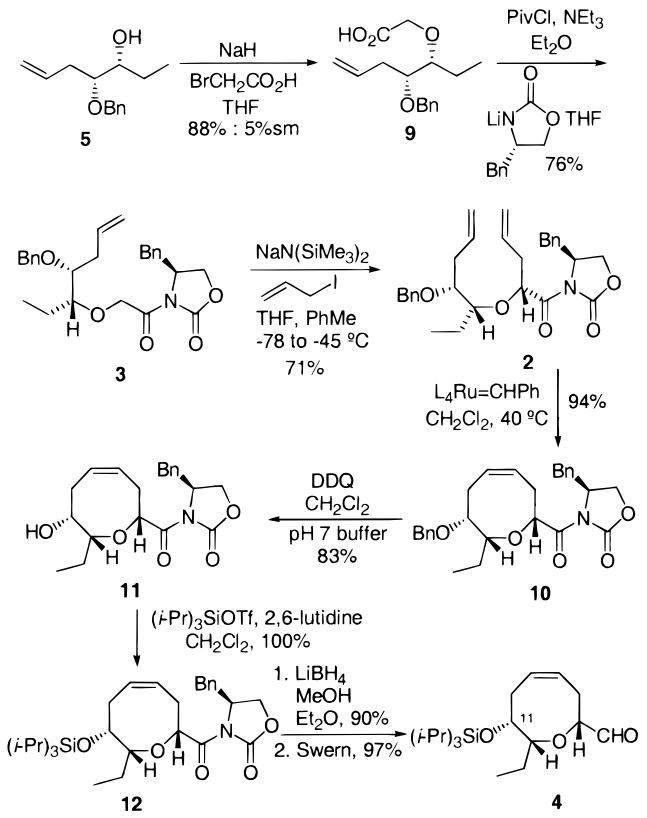
(8) Swern, D.; Mancuso, A. J.; Huang, S. *J. Org. Chem.* **1978**, *43*, 2480−2482.

(9) Asami, M.; Kimura, R. *Chem. Lett.* **1985**, 1221−1222.

(10) For a more complex example, see: Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627.

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

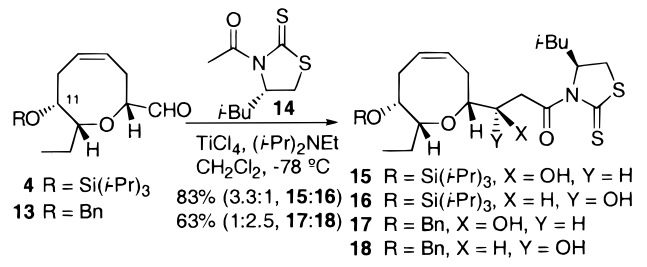
Scheme 2. Construction of the Oxocene Core



synthesis of (+)-laurencin was introduction of the (*E*)-pentenyl side chain and conversion of the protected alcohol at C11 to the alkyl bromide.

The strategy for installation of the unsaturated side chain centered on an asymmetric acetate aldol addition to aldehyde **4** (Scheme 3). The aldol reaction was accomplished by

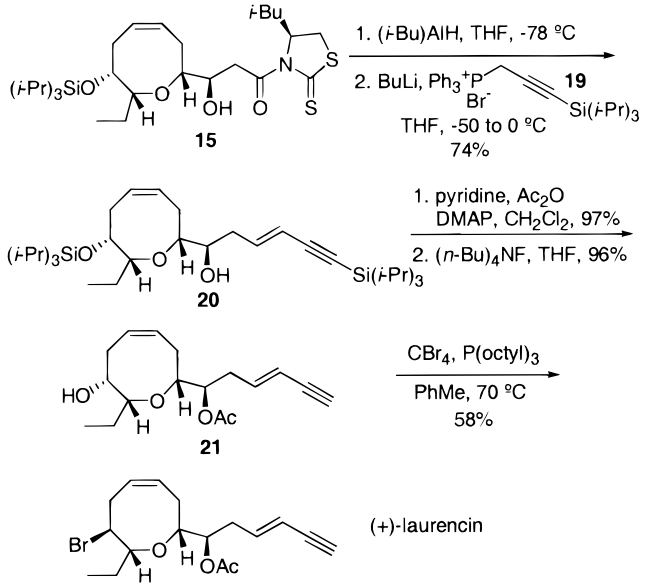
Scheme 3. Asymmetric Acetate Aldol



adding a dichloromethane solution of the aldehyde **4** to the chlorotitanium enolate of (*S*)-(+)-3-acetyl-4-isobutyl-2-thiazolidinethione **14** at −78 °C.[12] The reaction provided an 83% yield of a 3.3:1 (**15**:**16**) mixture of alcohols, which were easily separable by simple flash chromatography. Initially we had hoped to take advantage of a chelation-controlled addition to aldehyde **4** to control the diastereoselectivity in this aldol addition. Unfortunately, aldehyde **4** shows an unanticipated preference for the Felkin addition of nucleophiles. In fact, addition of the chlorotitanium enolate of the achiral 3-acetyl-2-thiazolidinethione provided a 2:1 mixture of diastereomers in favor of the Felkin product. In addition, complexation of aldehyde **4** with titanium tetrachloride prior to the addition of the chlorotitanium enolate of **14** failed to enhance the diastereoselectivity. It is also interesting to note that the same conditions when applied to aldehyde **13** resulted in a reversal in selectivity. In this case, the C11 benzyl ether and the aldehyde carbonyl may be chelated to the metal center, thus altering the facial selectivity.

Direct reduction of the chiral auxiliary of alcohol **15** with (*i*-Bu)$_2$AlH provided the corresponding aldehyde, which was immediately exposed to the ylide generated from phosphonium salt **19** to give enyne **20** in 74% yield over two steps (Scheme 4). The enyne **20** was isolated as a 5.5:1 mixture

Scheme 4. Completion of (+)-Laurencin



in favor of the desired *trans* enyne. Treatment of the alcohol with acetic anhydride gave the acetate ester in excellent yield. Removal of both triisopropylsilyl protecting groups was accomplished in 96% yield upon treatment with (*n*-Bu)$_4$NF. Secondary alcohol **21** was treated with carbon tetrabromide and trioctylphosphine at 70 °C in toluene to provide (+)-laurencin in 58% yield. The synthetic sample was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, and $[\alpha]^{24}_D$)[13] to those reported for natural (+)-laurencin.[2,4]

In conclusion, this synthesis has established that the asymmetric alkylation−ring-closing metathesis strategy for

(12) For an example of a similar acetate aldol with simple aldehydes, see: González, Á; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949−8952.

(13) $[\alpha]^{24}_D = +51.7°$ (lit.[2] $[\alpha]^{27}_D = +70.2°$). The low value of the specific rotation is presumably due to contamination of the sample with a minor amount of the *cis* enyne diastereomer of (+)-laurencin.

the synthesis of medium ring ethers is an efficient and practical approach to marine natural products. The total synthesis of (+)-laurencin was accomplished in 18 steps from (*S*)-(+)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone **6**. The success of the second, more complex glycolate alkylation portends well for the use of this general strategy for the preparation of α,α′-*trans*-disubstituted medium ring ethers such as bromofucin, laurallene, and obtusenyne. The α,α′-*trans*-disubstituted systems have proven more difficult to access using other methods for medium ring ether synthesis. Current efforts are focused on the expansion of this strategy to these and other medium ring ether containing natural products.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available via the Internet at http://pubs.acs.org.

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