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Stereoselective synthesis of the cyclic ether core of (+)-laurenyne

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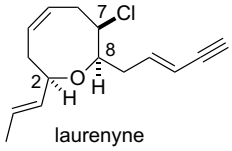
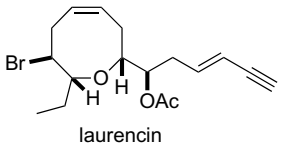
Abstract—A concise enantioselective synthesis of the cyclic ether core of the marine natural product (+)-laurenyne has been accomplished using ring-closing metathesis for medium-ring construction.

Laurenyne was first isolated from a sample of the alga *Laurencia obtusa* collected in the Aegean Sea off the coast of Turkey by Thomson and co-workers in 1980.[1] It is one of a large number of C_{15} medium-ring ether metabolites to have been isolated from *Laurencia* algae and organisms that feed on them.[2] The prototypical member of the family, laurencin, was isolated from *Laurencia glandulifera* in 1965 and has been the subject of several successful total syntheses.[3,4]



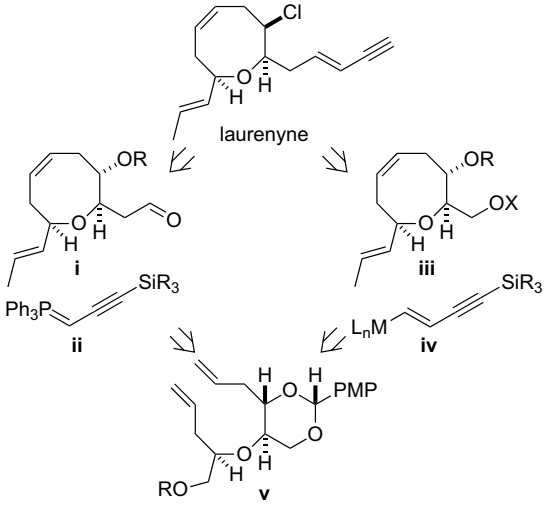
laurenyne



laurencin

The structure of laurenyne was established by Thomson and co-workers using X-ray crystallography, and the absolute configuration was incorrectly assigned to be 2*S*,7*S*,8*S* on the basis of their X-ray data.[1] The absolute configuration was corrected to 2*R*,7*R*,8*R* following the landmark synthesis of (−)-laurenyne by Overman and Thompson in 1988,[5a] in which an intramolecular Prins-type reaction was used to construct the key cyclic ether intermediate. A second total synthesis of laurenyne has been reported recently by Boeckman and co-workers; in this case, a retro-Claisen rearrangement was employed to assemble the medium-ring ether core of the natural product.[5b]

In our retrosynthetic analysis of laurenyne, we envisaged initial disconnection by cleavage of the enyne side chain and replacement of the chlorine substituent with a masked hydroxyl group (Scheme 1). Disconnection of the enyne side chain across the alkene revealed the aldehyde **i** and the acetylenic Wittig reagent **ii** as



Scheme 1.

Keywords: Marine natural product; Cyclic ether; Ring-closing metathesis.
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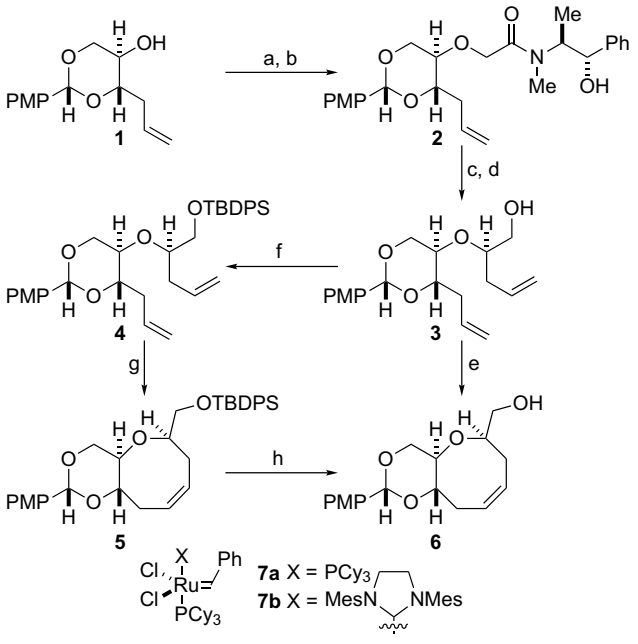
synthetic intermediates, whereas disconnection of the entire enyne unit suggested the activated alcohol derivative **iii** and the vinylic organometallic reagent **iv** as late stage intermediates. The first disconnection implies a Wittig reaction of an aldehyde and the phosphonium ylide **ii** late in the synthesis, and is attractive because both previous syntheses of laurenyne have used this coupling reaction to construct the enyne side chain at a late stage.[5] Disconnection of laurenyne into the intermediates **iii** and **iv** suggests a more adventurous and convergent alternative strategy involving displacement of a suitable leaving group (e.g., X is a triflate or tosylate) to install the enyne side chain in a single operation. Both the eight-membered cyclic ethers **i** and **iii** can be disconnected to reveal the acyclic diene precursor **v** by a retrosynthetic operation that implies ring-closing metathesis be used for construction of the eight-membered cyclic ether core of laurenyne. It should be noted that Crimmins has used an analogous ring-closing metathesis reaction for the total synthesis of laurencin and other *Laurencia* metabolites.[4h,6,7]

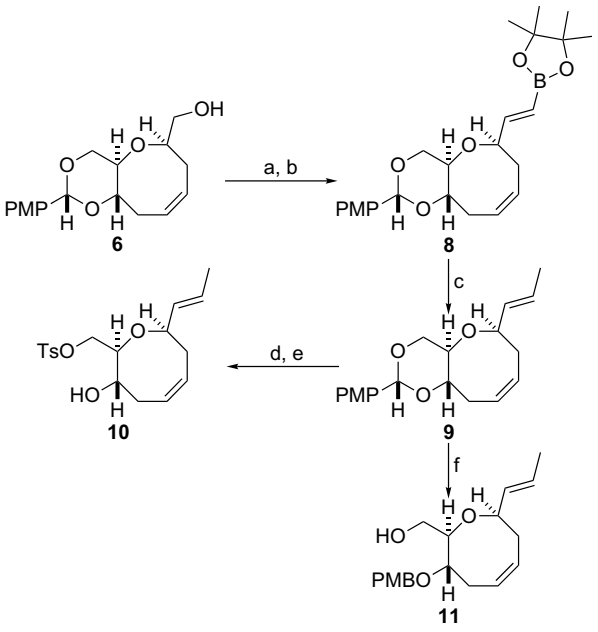
Our synthesis of the eight-membered cyclic ether core of laurenyne commenced with the alcohol **1** (Scheme 2). We have previously employed the alcohol **1** and homologous compounds as the key starting materials for the construction of medium-ring ethers by ring-closing metathesis during our work concerning the synthesis of marine polyether toxins.[7,8] The alcohol **1** is a versatile intermediate and can be prepared in three steps and on large scale from (*R*)isopropylideneglyceraldehyde.[9] The diene precursors **3** and **4** (analogous to the diene **v** in Scheme 1) required to explore the key ring-closing metathesis reaction were prepared from the alcohol **1** in just four or five steps using Myers auxiliary methodology to control the configuration of the remote stereogenic centre (Scheme 2).[10] The alcohol **1** was deprotonated and the resulting alkoxide was alkylated using methyl bromoacetate in the presence of tetra-*n*-butylammonium iodide.[10] The chiral auxiliary was then introduced in high yield by treatment of the methyl ester with (+)-pseudoephedrine and sodium methoxide. The resulting amide **2** was deprotonated with LDA in the presence of lithium chloride and then alkylated with allyl iodide at 0 °C, following the Myers protocol for related substrates.[10] Subsequent reductive removal of the chiral auxiliary using lithium amidotrihydroborate delivered the alcohol **3** in excellent yield and NMR analysis confirmed that a single diastereoisomer was present at this stage.[11]



Scheme 2. Reagents and conditions: (a) NaH, *n*-Bu_4NI, $BrCH_2CO_2Me$, THF, 0 °C → rt (81%); (b) (+)-pseudoephedrine, NaOMe, THF, rt (84%); (c) (i) LDA, LiCl, THF, −78 °C, (ii) CH_2CHCH_2I, 0 °C (75%); (d) LDA, NH_3–BH_3, THF, 0 °C (88%); (e) **7a** (5 mol%), CH_2Cl_2, rt (48%)/**7a** (5 × 2 mol%), CH_2Cl_2, rt (63%)/**7b** (5 mol%), PhMe, 80 °C (75%); (f) *t*-$BuPh_2SiCl$, imidazole, DMF, rt (98%); (g) **7b** (2 mol%), PhMe, 80 °C (99%); (h) TBAF, THF, rt (91%).

The key ring-closing metathesis reaction to give the eight-membered cyclic ether was then explored. Ring-closing metathesis of the diene **3** using the Grubbs first generation ruthenium catalyst **7a** (5 mol%) delivered the cyclic ether **6** in 48% yield. Increasing the amount of catalyst used and adding it to the diene in a portion-wise manner (5 × 2 mol%) resulted in an improvement in yield (63%), but prolonged reaction times (several days) were necessary.[12] When the reaction was performed using the ruthenium catalyst **7b**, the yield of the cyclic ether **6** increased to 75% and the reaction time was reduced to 1 h. To improve the yield of the RCM reaction further, we protected the free primary hydroxyl group as its *t*-butyldiphenylsilyl ether giving the diene **4** in excellent yield. The ring-closing metathesis reaction of the diene **4** mediated by the Grubbs second generation ruthenium catalyst **7b** proceeded to give the cyclic ether **5** in essentially quantitative yield, and high-yielding removal of the *t*-butyldiphenylsilyl group then delivered the alcohol **6**. Thus, the overall yield for the three-step route to the alcohol **6** from the diene **3** was significantly higher than the yield obtained by direct RCM of the diene **3**.

Rapid access to the cyclic ether **6** on multi-gram scale allowed us to explore side chain functionalisation (Scheme 3). Introduction of the propenyl side chain was investigated first and proved to be more problematic than anticipated. Oxidation of the free hydroxyl group to give the required aldehyde was performed using the Parikh–Doering oxidation protocol.[13] At this stage, we expected to be able to introduce the propenyl side chain using a Wittig or Julia olefination reaction. However, standard Wittig or Julia coupling conditions (including the Kocienski variant)[14] either failed to give acceptable product yields or delivered inseparable mixtures of isomeric alkene products with poor selectivity. Ultimately, we installed the propenyl side chain by first converting the aldehyde derived from the alcohol **6** into the boronic ester **8** using the chromium-mediated reaction developed by Takai et al.[15] The crystalline boronic ester **8** was obtained in excellent yield and with high stereoselectivity (>10:1) for the *E*-alkene isomer. Crystals of the boronic ester **8** suitable for X-ray analysis were obtained upon



Scheme 3. Reagents and conditions: (a) SO_3, pyridine, Et_3N, DMSO, rt (81%); (b) $Cl_2CHB(OCMe_2CMe_2O)$, $CrCl_2$, LiI, THF, rt (75%, *E*:*Z* > 10:1); (c) $Pd(PPh_3)_4$, K_3PO_4, MeI, dioxane, 60 °C (51%); (d) PPTS, MeOH, rt (84%); (e) *p*-$MeC_6H_4SO_2Cl$, DMAP, Et_3N, CH_2Cl_2, rt (71%); (f) *i*-Bu_2AlH, CH_2Cl_2, −78 °C (68%).

recrystallisation and this confirmed its structure and stereochemistry.[16] (Fig. 1) Assembly of the propenyl side chain was then completed by Suzuki coupling of the boronic ester **8** and methyl iodide. Although the yield of the coupled product **9** was modest (~50%), the Suzuki reaction delivered a single alkene isomer.[17]

Further functionalisation of the medium-ring ether core in preparation for installation of the enyne side chain was explored (Scheme 3). Acid mediated removal of the *p*-methoxybenzylidene acetal and selective conversion of the resulting 1,3-diol into the primary tosylate delivered the alcohol **10**, which would serve as the intermediate **iii** shown in Scheme 1. Regioselective ring opening of the *p*-methoxybenzylidene acetal using diisobutylaluminium hydride at −78 °C delivered the alcohol **11** in reasonable yield.[18] The alcohol **11** was then subjected to side chain homologation by sequential oxidation to give aldehyde **12**, Wittig reaction with (methoxymethylene)triphenylphosphorane to give the

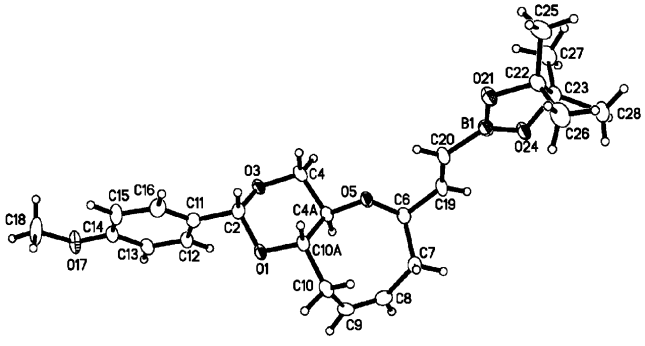
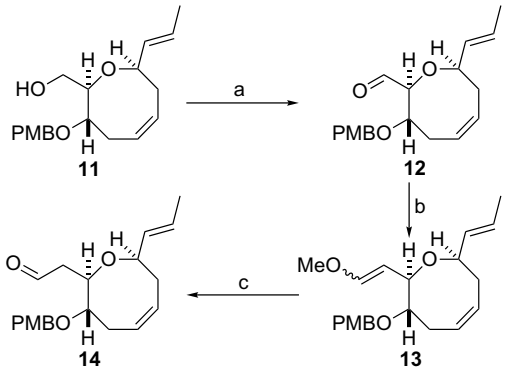


Figure 1. X-Ray crystal structure of the boronic ester **8**.



Scheme 4. Reagents and conditions: (a) PCC, NaOAc, 4 Å sieves, CH_2Cl_2, rt (66%); (b) $Ph_3P^+CH_2OMeCl^-$, KHMDS, THF, −78 °C (67%); (c) $Hg(OAc)_2$, THF–H_2O, rt (78%).

enol ether **13** as a mixture of *E* and *Z* isomers and finally mercuric acetate mediated hydrolysis to give the aldehyde **14** (Scheme 4). The aldehyde **14** can be regarded as the synthetic equivalent of the intermediate **i** shown in the retrosynthetic analysis (Scheme 1).

In summary, we have prepared advanced intermediates (**10** and **14**) for the synthesis of (+)-laurenyne using a route in which ring-closing metathesis is employed to construct the eight-membered cyclic ether core in excellent yield. The tosylate **10** and the aldehyde **14** have been synthesised in a highly stereoselective and concise manner (10 and 12 steps, respectively) from the readily available alcohol **1**. Both late stage intermediates possess the functionality required for completion of the synthesis of (+)-laurenyne by installation of the enyne side chain and chlorination.

Acknowledgements

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16. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 247622. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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