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Synthesis of (+)-laurencin via ring expansion of a *C*-glycoside derivative

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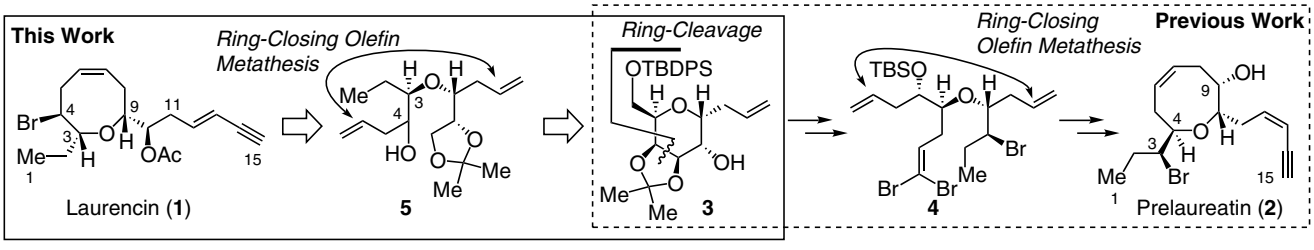
Abstract—Laurencin was efficiently synthesized from a *C*-glycoside derivative based on ring expansion of the oxane part of the starting compound into an eight-membered cyclic ether via a ring-cleavage/ring-closing olefin metathesis process, stereoselective introduction of a bromo group at C4, and convergent construction of the side-chain part using a lithiated enyne unit.

The lauthisan[1] and *trans*-laurenan[2] families of bromoether compounds, represented by (+)-laurencin (**1**)[3] and (+)-prelaureatin (**2**),[4] respectively, were isolated from some local species of the red algae *Laurencia*[5] in the sea around the Japanese islands and were hypothesized to be biosynthesized from a common precursor, laurediol.[6] The hypothesis has inspired us to design a divergent chemical synthesis of **1** and **2** from common *C*-glycoside substrate **3** by ring expansion of the oxane part of **3** into eight-membered ring systems corresponding to **1** and **2** through a common ring-cleavage/ring-closing olefin metathesis (RCM)[7] process (Scheme 1).[8] Although quite many synthetic approaches to lauthisan and *trans*-laurenan natural compounds and several total syntheses were reported so far,[9,10] there were only a few synthetic methods appropriate for both of them.[9i–l,10a,c,11] Recently, we have synthesized **2** through a route involving site-selective RCM reaction of triene **4** according to our scheme.[10b] Here, the successful synthesis of **1** from **3**, the other goal of our divergent plan, based on the RCM reaction of **5** and convergent construction of the C10–C15 side-chain part using a lithiated enyne unit is described.

First, the ethyl side-chain part of **1** was constructed at the initial stage (Scheme 2). The substrate **3**, prepared from β-D-galactose pentaacetate (**6**) according to our previously reported procedure,[10b] was transformed into **8** (overall 81%) by a two-step process [(i) protection with PMBBr and (ii) removal of the TBDPS group]. Alcohol **8** was converted to **10** via triflate **9** by the Kotsuki procedure (overall 95%),[12] thereby providing the ethyl side-chain part.

Then, an eight-membered ring ether **14** was synthesized by ring expansion of **10** via a ring-cleavage/RCM



Scheme 1.

Keywords: Marine natural product; Total synthesis; Medium-ring ether; Ring-closing olefin metathesis; (+)-Laurencin.
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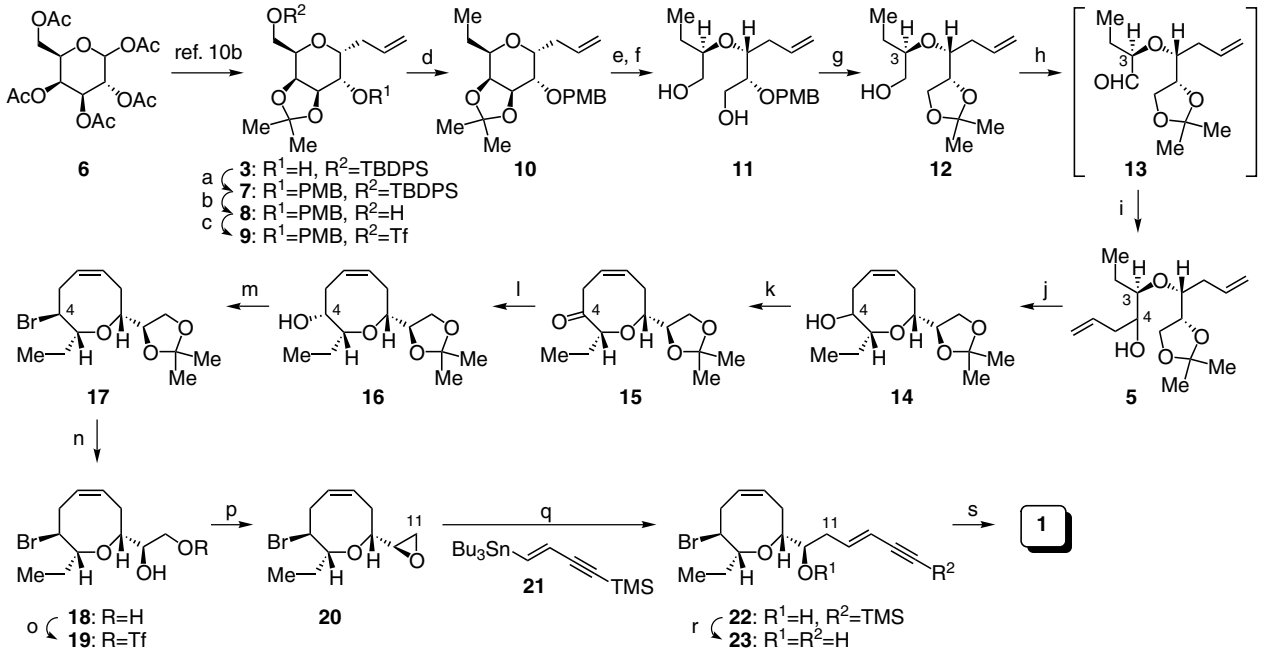

Scheme 2. Reagents and conditions: (a) NaH, PMBBr, Bu_4NI, THF, 23 °C, 1.5 h, 88%; (b) Bu_4NF, THF, 25 °C, 3.5 h, 92%; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min; (d) MeMgBr, CuI (cat.), THF–Et_2O, 4 °C, 38 h, 95% from **8**; (e) 2 M HCl aq–THF (1:1), 22 °C, 9 h, 100%; (f) $NaIO_4$, *t*-BuOH–pH 7 buffer (3:1), 0 °C, 3 h, then $NaBH_4$, MeOH, 0 °C, 15 min, 100%; (g) DDQ, CH_2Cl_2, 26 °C, 15 min, then TsOH–H_2O, acetone, 26 °C, 1 h; 79%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 to 0 °C, 15 min; (i) $CH_2{=}CHCH_2MgCl$, THF, −78 °C, 15 min, 100% from **12**; (j) $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (0.1 equiv), CH_2Cl_2, reflux, 45 min, 81%; (k) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 to 0 °C, 10 min, 90%; (l) LS-Selectride®, THF, −78 °C, 10 min, **16**: 91%, 4-*epi*-**16**: 5%; (m) Ph_3P, CBr_4, toluene, 70 °C, 1.5 h, 90%; (n) $HS(CH_2)_2SH$, $Zn(OTf)_2$, $NaHCO_3$, CH_2Cl_2, 0 °C, 1 h, 86%; (o) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, 10 min; (p) K_2CO_3, MeOH, 23 °C, 30 min, 94% from **18**; (q) **21**, BuLi, THF, −30 °C, 1 h, then **20**, then $Et_2O{\cdot}BF_3$, −30 °C, 30 min, 73%; (r) Bu_4NF, THF, 23 °C, 5 min, 87%; (s) AcCl, pyridine, CH_2Cl_2, 0 °C, 1 h, 87%.

process. After acidic hydrolysis of **10** (100%), the resulting diol was cleaved with $NaIO_4$ into a dialdehyde, which was immediately reduced by one-pot treatment with $NaBH_4$ to give **11** (100%). Although the reaction of **11** with DDQ under anhydrous conditions afforded a *p*-methoxybenzylidene acetal, it was so unstable as to decompose gradually during purification and could not be used for further synthesis. Therefore, **11** was converted to **12** by the reaction with DDQ and the subsequent one-pot acetal exchange reaction (79%). While alcohol **12** could be facilely oxidized to aldehyde **13**, rapid epimerization at C3 of **13** was observed during the work-up and purification. After several attempts, we found that one-pot treatment of the reaction solution obtained just after Swern oxidation[13] of **12** with large excess of allyl magnesium chloride provided **5** in excellent yield (overall 100%) without epimerization at C3 though it was given as a 1:1 mixture of diastereomers at C4.[14] The diene **5** was cyclized with second-generation Grubbs' catalyst[15] into **14** in good yield (81%). Thus, the eight-membered ring ether part of **1** was successfully constructed.

Next, stereoselective bromination at C4 was performed. Oxidation of **14** followed by reduction with LS-Selectride® selectively gave **16** (91%),[16] which was treated with Ph_3P and CBr_4 in toluene at 70 °C to produce **17** (90%) with complete inversion of configuration at C4.[17]

At the last stage of the synthesis, a convergent method using a lithiated enyne unit was efficiently employed for the side-chain construction. Deprotection[18] of **17** (86%) followed by regioselective formation of triflate **19** and the subsequent basic treatment afforded epoxide **20** (94% for two steps). After treatment of **21**[19] with BuLi, the resulting *E*-1-lithio-4-(trimethylsilyl)but-1-en-3-yne was treated first with **20** and then with $Et_2O{\cdot}BF_3$ at −30 °C to provide **22** (73%),[20,21] which was transformed into **1** through a two-step desilylation/acetylation process (76% for two steps). The spectral data (^1H and ^{13}C NMR as well as IR) and optical rotation {$[\alpha]_D^{23}$ +69.6 (*c* 0.093, $CHCl_3$); Lit.[3b]: $[\alpha]_D^{27}$ +70.2 (*c* 1.0, $CHCl_3$)} of the resulting **1** agreed well with those of the literature.[3] Thus, the synthesis of **1** was achieved in 16% overall yield for total 21 steps including three one-pot, two-step processes from **3**.

In conclusion, laurencin (**1**) was efficiently synthesized from *C*-galactoside derivative **3**, the common substrate of our previous synthesis of prelaureatin (**2**), based on ring expansion of **3** into eight-membered ring ether **14** via a ring-cleavage/RCM process, stereoselective introduction of a bromo group at C4, and coupling reaction of epoxide **20** with a lithiated enyne unit, thereby achieving the divergent synthesis of **1** and **2** from **3**.

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Agriculture, Hokkaido University) for the measurements of mass spectra. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government.

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