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The first total synthesis of (+)-(*Z*)-laureatin

Masashi Sugimoto,[a] Toshio Suzuki,[b,*] Hisahiro Hagiwara[a] and Takashi Hoshi[b]

[a]*Graduate School of Science and Technology, Niigata University, 2-Nocho, Ikarashi, Niigata 950-2181, Japan*
[b]*Faculty of Engineering, Niigata University, 2-Nocho, Ikarashi, Niigata 950-2181, Japan*

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Abstract—The stereoselective total synthesis of (+)-(*Z*)-laureatin is described. The 3,8-dioxabicyclo[5.1.1]nonane skeleton possessing trans-orientated alkyl substituents at the α,α′-positions to the ether linkage was stereoselectively constructed via formation of the oxetane arising from 4-*exo* cyclization of hydroxy epoxide existing on the oxocene core.

Red algae of the genus *Laurencia* produce a wide variety of medium-sized cyclic ethers as distinctive members of marine natural products.[1] Among them, eight-membered cyclic ethers are abundant constituents, and are divided into two subclasses, the lauthisan type and the laurenan type, in view of the structural features arising from the biogenetic pathway.[2] Much synthetic effort has been directed toward these compounds. As a result, several successful total syntheses of the lauthisan structural class exemplified by (+)-laurencin have been reported so far.[3] In contrast, there have been few reports[4,5] on synthetic studies of the laurenan compounds, such as (+)-prelaureatin (**1**),[6] (+)-laurallene (**2**),[7] (+)-(*Z*)-laureatin (**3**),[8] (+)-(*Z*)-isolaureatin (**4**),[8] and geometric isomers regarding the enyne moieties of (+)-**3** and (+)-**4** (Fig. 1).[9] This is due to certain problems incurred in assembling eight-membered cyclic ether systems as well as the stereoselective introduction of alkyl substituents into the α- and α′-positions of a cyclic ether with trans-orientation. Particularly in the synthesis of bicyclic compounds such as (+)-**2**, (+)-(*Z*)-**3**, and (+)-(*Z*)-**4**, a crucial problem, regio- and stereocontrolled construction of bicyclic skeletons is included.

Intensive biogenetic studies by the Ishihara and Murai group led to a proposal of the biogenetic pathway of laurenan compounds; the bromo-cationic cyclization of an acyclic precursor, (6*S*,7*S*)-laurediol, affords (+)-prelaureatin (**1**) and its geometric isomer which were converted to bicyclic compounds, (+)-laurallene (**2**), (+)-(*Z*)-laureatin (**3**), (+)-(*Z*)-isolaureatin (**4**) and their geometric isomers, via the subsequent bromo-cationic cyclization.[2] According to the biogenetic pathway, we accomplished the total synthesis of (+)-**2** via a two-step cyclization sequence (Scheme 1).[4a] The α,α′-*trans*-oxocene core **6**, structural equivalent of (+)-**1**, was stereoselectively constructed via 8-*exo* cyclization of hydroxy epoxide **5** promoted by $Eu(fod)_3$,[5a] and the subsequent 5-*exo* cyclization between the C7 hydroxy group and the epoxide installed on the alkyl substituent provided the dioxabicyclic skeleton of (+)-**2**. In this Letter, we examined the availability of the synthetic strategy toward other bicyclic laurenan compounds, (+)-(*Z*)-**3** and (+)-(*Z*)-**4** via the α,α′-*trans*-oxocene core **6** along the biogenetic pathway. For the successful synthesis of

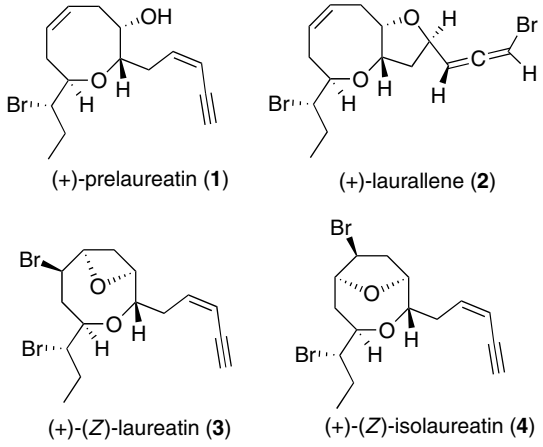

Figure 1.

Keywords: (+)-Laureatin; Oxocenes; Medium-ring heterocycles; Cyclization; Hydroxy epoxides.
* Corresponding author. Tel./fax: +81 25 262 6780; e-mail: suzuki@eng.niigata-u.ac.jp

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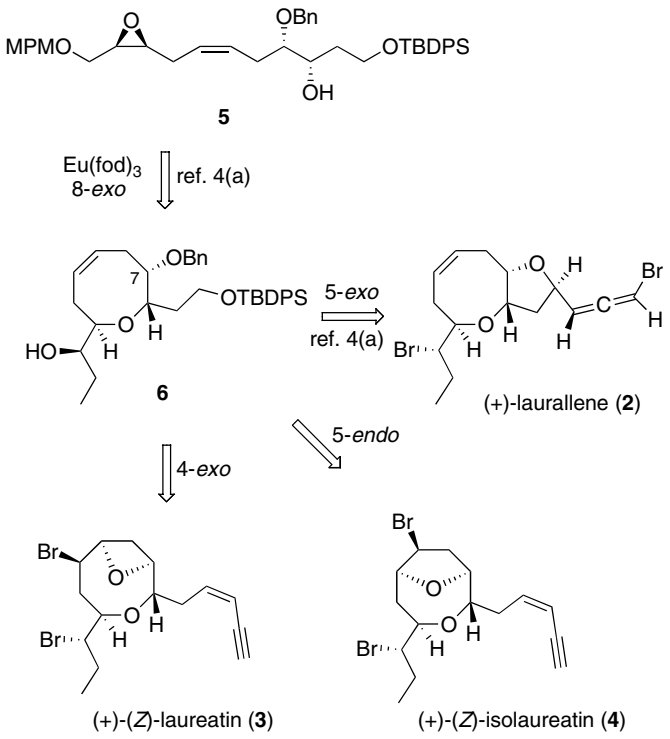
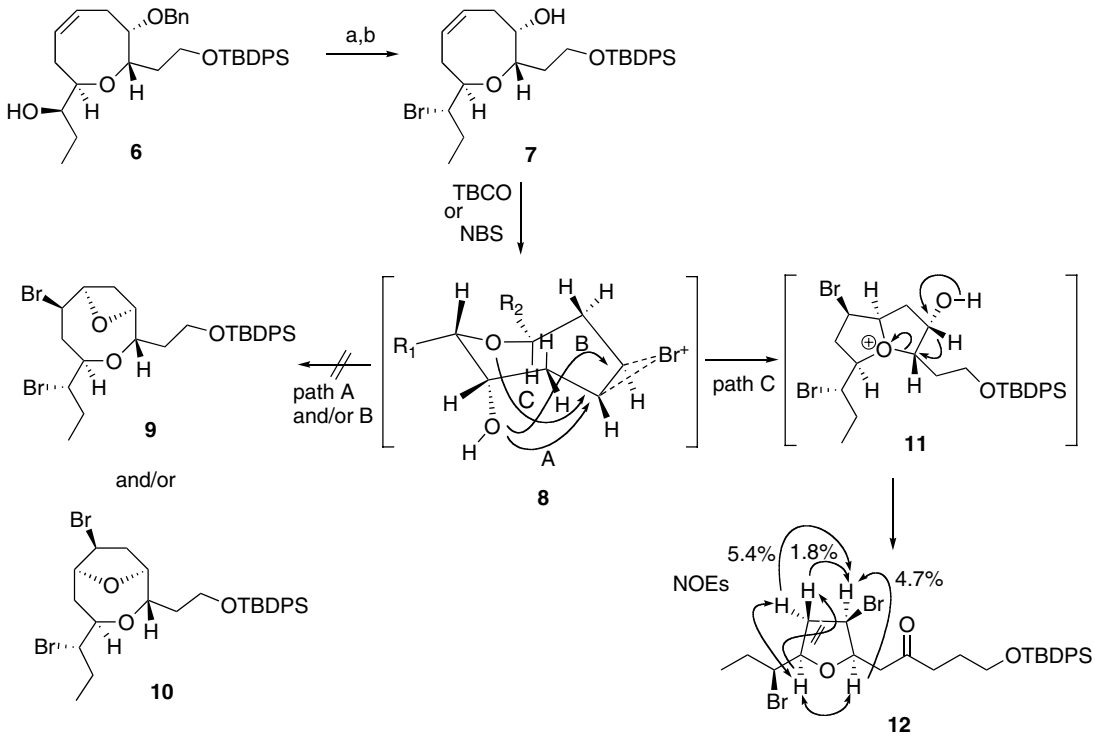


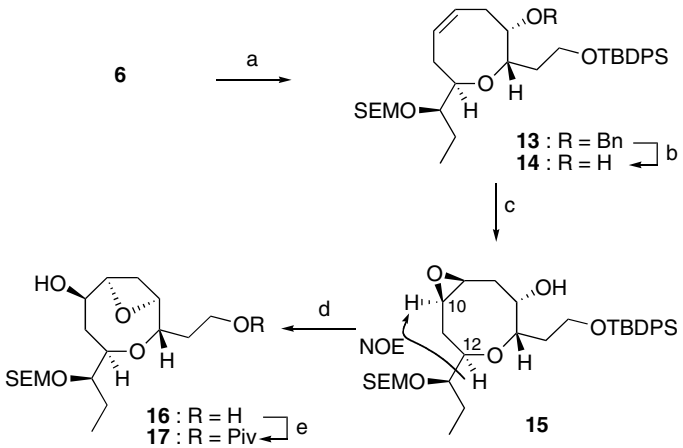
Scheme 1.

them, a crucial problem, regio- and stereocontrolled conversion of **6** to bicyclic skeletons, must be resolved.

In an initial attempt, we examined the conversion of oxocene **6** to bicyclic skeleton(s) **9** and/or **10** via the bromo-cationic cyclization analogously to the biogenetic pathway (Scheme 2). The requisite intermediate **7** was derived from **6** through bromination of a hydroxy group followed by deprotection of a benzyl group. Treatment of **7** with 2,4,6,6-tetrabromo-2,5-cyclohexadienone



Scheme 2. Reagents and conditions: (a) $P(oct)_3$, CBr_4, 1-methyl-1-cyclohexene, Py, toluene, 70 °C, 90%; (b) DDQ, pH = 7.5 buffer, CH_2ClCH_2Cl, 35 °C, 62%.

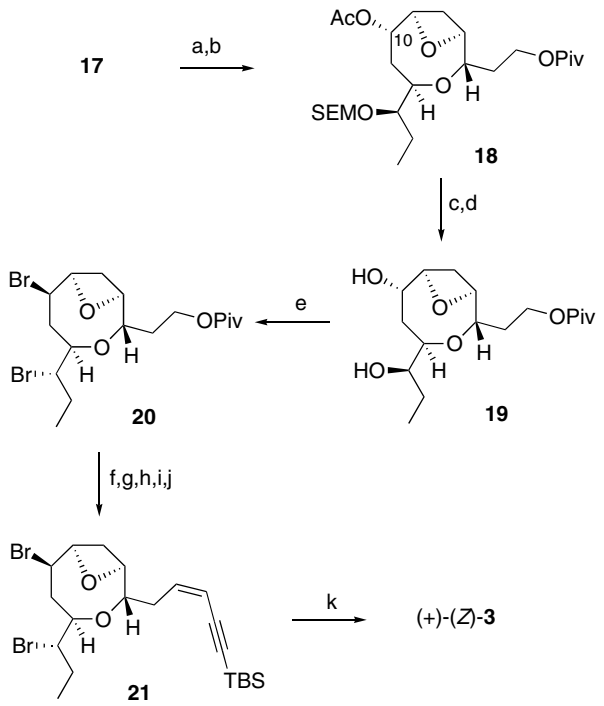


Scheme 3. Reagents and conditions: (a) SEMCl, *i*-Pr_2NEt, *n*-Bu_4NI, CH_2ClCH_2Cl, 94%; (b) DDQ, pH = 7.46 buffer, CH_2ClCH_2Cl, 45 °C, 85%; (c) MCPBA, CH_2Cl_2, 0 °C to rt, 96%; (d) aq KOH, DMSO, 80 °C, 97%; (e) PivCl, TEA, CH_2Cl_2, 80%.

(TBCO) or NBS provided no trace of 4-*exo* and/or 5-*endo* cyclized product(s) **9** and/or **10**. In these reactions, the tetrahydrofuran derivative **12** was mainly obtained. The stereochemistries on the tetrahydrofuran ring were determined by NOE correlations. Conformation analysis of **7** by MM2 calculation predicted to generate β-bromonium ion **8** in the conformation as shown in Scheme 1. Transannular attack of the etherial oxygen via path C prior to attack of the hydroxy group via path A and/or B followed by pinacol-type rearrangement of the resultant oxonium ion **11** would result in the formation of **12**.

The entirely unexpected result led our turning attention to the approach including cyclization of hydroxy epoxide (Scheme 3). Epoxidation of SEM ether **13**, derived from **6**, was expected to proceed mainly from β-phase in the conformation analogous to that of **8** described above. Actually, treatment of **13** with MCPBA provided β-epoxide along with its α-isomer with a ratio of 80:20 in a combined yield of 97%. When **14**, obtained by deprotection of the benzyl group in **13**, was used for the epoxidation substrate, the β-selectivity was interestingly improved up to 96% and the desired epoxide **15** was obtained in an isolated yield of 96%. It was presumably due not to a directive effect of the hydroxy group but a slight change of the conformation. The stereochemistry of epoxide **15** was confirmed by an NOE correlation between C10–H and C12–H. With the key intermediate **15** in hand, we examined cyclization reaction toward the laureatin and/or isolaureatin bicyclic skeleton(s). Treatment of **15** with several Lewis acids (e.g., $Zn(OTf)_2$; Eu(fod)$_3$) gave a complex mixture, whereas exposure to aqueous KOH in DMSO[10] resulted in regioselective 4-*exo* cyclization to provide the laureatin bicyclic system **16** in 97% yield along with simultaneous deprotection of the TBDPS group. In the reaction, formation of the isolaureatin bicyclic system arising from the alternative 5-*endo* cyclization was not detected. Protection of the resulting hydroxy group as its pivaloyl ester afforded **17** in 80% yield.

With **17** successfully in hand, our attention was focused on the synthesis of (+)-(*Z*)-laureatin (**3**) (Scheme 4). The



Scheme 4. Reagents and conditions: (a) MsCl, TEA, DMAP, CH_2Cl_2, 100%; (b) CsOAc, 18-crown-6, xylene, 110 °C, 88%; (c) guanidine, EtOH–CH_2Cl_2 (5:1), 92%; (d) MeSTMS, ZnI_2, *n*-Bu_4NI, CH_2ClCH_2Cl, 0 °C, 99%; (e) P(oct)$_3$, CBr_4, TEA, toluene, 80 °C, 82%; (f) DIBAL, toluene, −78 °C to −30 °C, 96%; (g) Dess–Martin periodinane, CH_2Cl_2, 93%; (h) HMPT, CBr_4, THF, 0 °C, 93%; (i) Bu_3SnH, $Pd(PPh_3)_4$, benzene, 82%; (j) (*t*-butyldimethylsilyl)acetylene, $Pd(PPh_3)_4$, CuI, *i*-Pr_2NH, benzene, 90%; (k) TBAF, THF, 93%.

next task was the stereoselective introduction of the bromine moiety at the C10 position. Although the direct bromination of **17** using SO_2Br_2 in CH_2Cl_2[11] with retention of configuration was unsuccessful, the targeted reaction was realized via the following stepwise process. Namely, mesylation of **17** (100%) followed by treatment with CsOAc and 18-crown-6 in toluene[12] provided acetate **18** in 88% yield with complete inversion. After deprotection of the acetyl and SEM groups, the

resulting two hydroxy groups were simultaneously brominated via the S_N2 process under Murai's conditions[13] to afford dibromide **20** in high yield.

With **20** in hand, the stage was set for the installation of the *Z*-enyne moiety. The pivaloyl group in **20** was reductively deprotected (96%), and the resulting alcohol was converted by the following sequence similar to that reported by the Murai group:[14] (i) oxidation with Dess–Martin periodinane (93%), (ii) treatment with CBr_4 and HMPT in THF (93%),[15] (iii) stereoselective hydrogenolysis of 1,1-dibromoalkene by Uenishi's method (82%),[16] (iv) Sonogashira coupling of the resulting *Z*-1-bromoalkene with (*t*-butyldimethylsilyl)acetylene (90%).[17] Finally, deprotection of the TBS group in **21** led to the completion of (+)-(*Z*)-laureatin (**3**). The optical rotation of synthetic (+)-(*Z*)-**3** [$[\alpha]_D^{20}$ +103 (*c* 0.35, CCl_4)] coincided with that of the natural product [$[\alpha]_D$ +96 (*c* 2.00, CCl_4)].[8] The comparison of the spectral data of synthetic (+)-(*Z*)-**3** (^1H, ^{13}C NMR,[18] and IR) with those of the natural product revealed that they were identical.

In conclusion, the first total synthesis of (+)-(*Z*)-laureatin (**3**) was accomplished with high stereoselectivity. Although the bromo-cationic cyclization of the oxocene derivative **7** according to the biogenetic pathway for the stereoselective construction of the bicyclic skeleton gave unsuccessful result, the purpose was indigenously achieved via a sequence of stereoselective epoxidation of **14** followed by regioselective 4-*exo* cyclization.

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