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Total synthesis of (+)-laurallene

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Abstract—The stereoselective total synthesis of (+)-laurallene is described. The required key oxocene skeleton possessing *trans*-orientated alkyl substituents at the α,α′-positions was stereoselectively constructed via the cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$.

Red algae of the genus *Laurencia*, particularly *Laurencia* nipponica, 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 towards the lauthisan structural class exemplified by (+)-laurencin.[3,5a] 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] and (+)-(*Z*)-isolaureatin (**4**) (Fig. 1).[8] This might be due to certain problems incurred in assembling eight-membered cyclic ether systems and, moreover, the stereoselective introduction of alkyl substituents into the α- and α′-positions of a cyclic ether with *trans*-orientation.

Recently, we reported an efficient method towards the stereoselective construction of α,α′-*cis*- and α,α′-*trans*-oxocenes by cyclization of hydroxy *cis*-epoxides promoted by $Eu(fod)_3$.[9] The method has a potential advantage in that stereochemistry at the α- and α′-positions could be controlled stereospecifically since the reaction proceeds via an S_N2 process and *exo* mode selectivity regardless of the configuration of the hydroxyl and epoxide groups. In this communication, we examined applicability of the methodology to the synthesis of (+)-laurallene (**2**) as a part of our research program. Recently, the first total synthesis of (+)-**2** has been reported by the Crimmins group.[4b]

Our synthetic plan is envisaged in Scheme 1. Hydroxy epoxide **8**, which could be obtained by coupling of epoxide **9** with acetylene **10**, was postulated as a key precursor. Application of the foregoing protocol to **8** would result in the formation of α,α′-*trans*-oxocene **7** possessing the additional chiral centers at the C7 and C13 positions required for further manipulations. Dioxabicyclic skeleton **5** would be accessible from epoxide **6**, derived from **7** including the Sharpless epoxidation

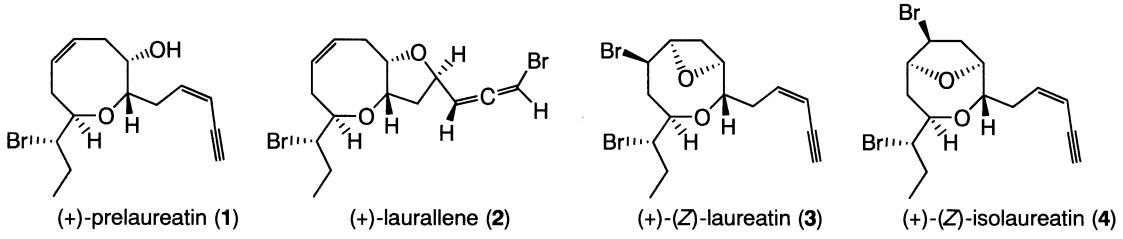

Figure 1.

Keywords: (+)-laurallene; oxocenes; medium-ring heterocycles; cyclization; hydroxy epoxides.
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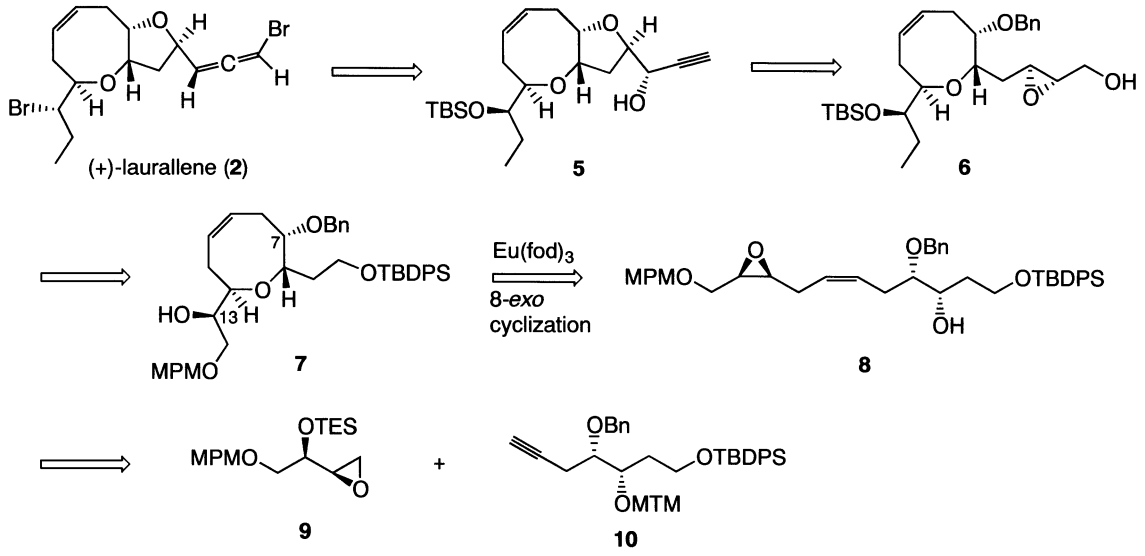
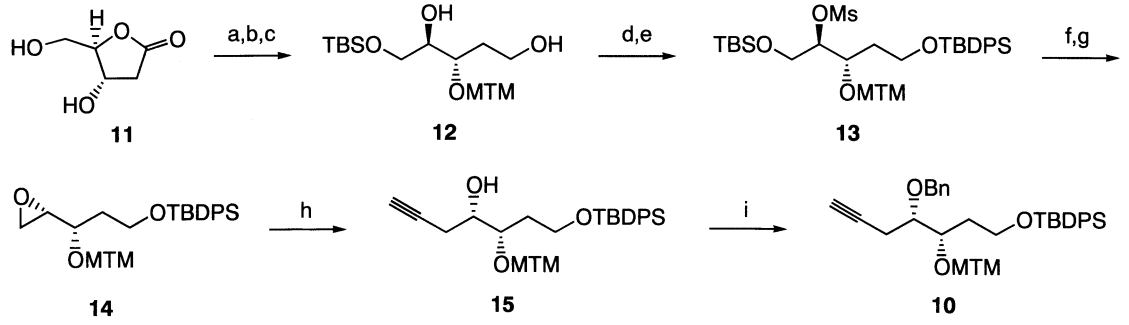


Scheme 1.

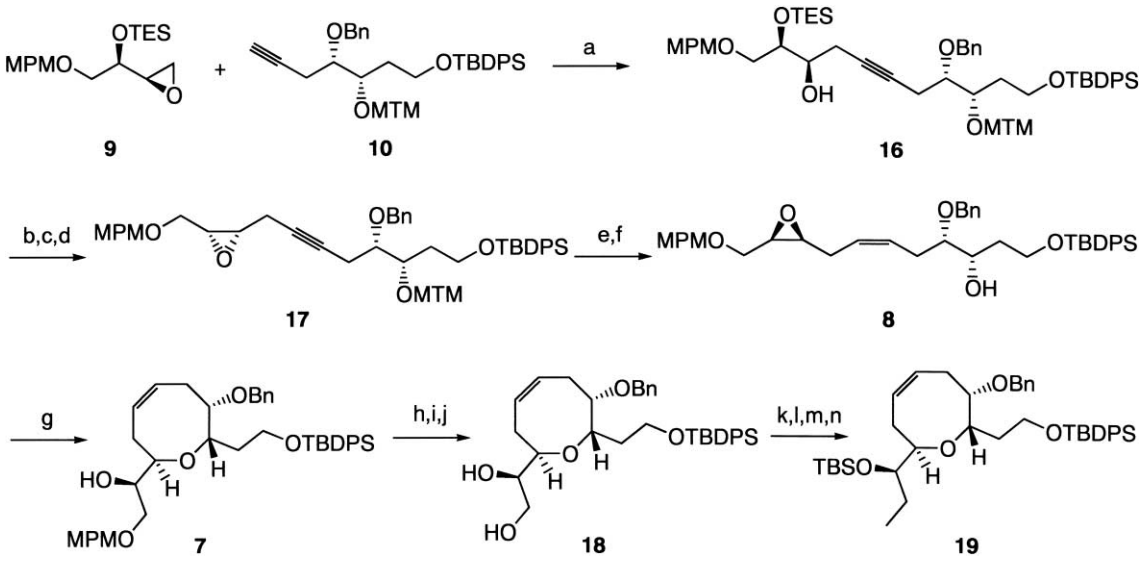
step.[10] Stereoselective introduction of a bromoallene moiety and a bromine functionality into **5** would complete our synthesis.

According to the retro-synthetic scheme, the synthesis of the acetylene **10** was investigated at the outset of this research (Scheme 2). Diol **11**, prepared from D-(+)-ribonic γ-lactone according to the Chen procedure,[11] was successively protected with TBS (70%) and MTM groups (81%), and subsequently treated with $LiBH_4$ to afford diol **12** (87%). Selective protection of the primary hydroxyl group as a TBDPS ether followed by mesylation of the remaining secondary hydroxy group provided compound **13** in 90% overall yield. Selective cleavage of the TBS ether was conducted by exposure to 1N HCl–MeOH–THF (78%). For this purpose, TBAF or TBAF–AcOH conditions were not available because of competitive deprotection of the TBDPS group. The resulting hydroxy mesylate was treated with K_2CO_3 in MeOH–CH_2Cl_2 to give epoxide **14** in 86% yield. Next, the epoxide **14** was reacted with lithium acetylide in DMSO. In the reaction, partial migration of the TBDPS group of **14** and **15** into the acetylene terminus of **15** was observed. Acetylene **15** was obtained effectively by quenching after consumption of nearly half of **14** and recycling the recovered **14**. The resulting hydroxy group was protected as a benzyl ether to afford acetylene **10** in 97% yield.

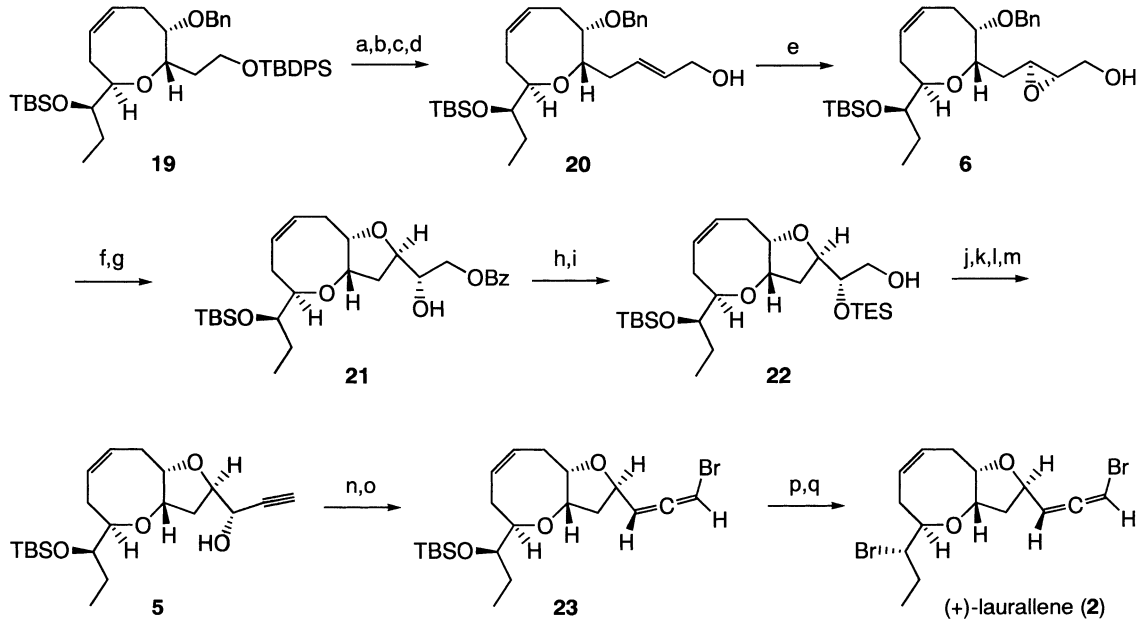
Coupling of epoxide **9**, derived from (–)-DET by our reported procedure,[12] with acetylene **10** was easily achieved by the Yamaguchi method[13] in 80% yield (Scheme 3). Mesylation of the resulting hydroxy group followed by cleavage of the TES ether gave the corresponding alcohol, which was treated with a base to afford epoxide **17** in high yield. Deprotection of the MTM group of **17** (100%) followed by hydrogenation in the presence of Lindlar catalyst provided hydroxy epoxide **8** (98%). With the key precursor **8** for the cyclization reaction in hand, the crucial step in this synthesis was examined. The hydroxy epoxide **8** was treated with $Eu(fod)_3$ in refluxing toluene. The reaction proceeded smoothly to afford the desired α,α′-*trans*-oxeocene **7** in 70% yield as the sole cyclized product. Next, we examined homologation of the side chain. The exocene **7** was converted into diol **18** by a protection–deprotection sequence. Selective tosylation of the pri-



Scheme 2. *Reagents and conditions*: (a) TBSCl, $AgNO_3$, Py, CH_3CN, 70%; (b) Ac_2O, AcOH, DMSO, 70°C, 81%; (c) $LiBH_4$, Et_2O, 87%; (d) TBDPSCl, imidazole, DMF; (e) MsCl, Py, DMAP, CH_2Cl_2, 90% (two steps); (f) 1N HCl–MeOH–THF (1:10:4), 78%; (g) K_2CO_3, MeOH–CH_2Cl_2 (1:1), 86%; (h) HC≡CLi·EDA, DMSO–THF (6:1), 51% (recovered **14**, 39%); (i) BnBr, NaH, Bu_4NI, THF, 97%.



Scheme 3. *Reagents and conditions*: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, 80%; (b) MsCl, TEA, DMAP, CH_2Cl_2, 98%; (c) 80% aq. AcOH–THF (5:2), 98%; (d) K_2CO_3, MeOH–CH_2Cl_2 (1:1), 99%; (e) MeI, $NaHCO_3$, acetone–H_2O (9:1), 40°C, 100%; (f) H_2, Lindlar cat., quinoline, AcOEt, 98%; (g) $Eu(fod)_3$, toluene, 110°C, 70% (recovered **8**, 21%); (h) Ac_2O, TEA, DMAP, CH_2Cl_2, 99%; (i) DDQ, CH_2Cl_2–phosphate buffer (pH 7.5) (9:1); (j) K_2CO_3, MeOH–CH_2Cl_2 (1:1), 77% (two steps); (k) $(Bu_3Sn)_2O$, toluene, reflux, then TsCl, CH_2Cl_2, 97%; (l) K_2CO_3, MeOH–CH_2Cl_2 (1:1), 100%; (m) Me_2CuLi, Et_2O, −78°C, 100%; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 96%.



Scheme 4. *Reagents and conditions*: (a) NaH, propargyl alcohol, HMPA–THF (1:1), 0°C, 88%; (b) Dess–Martin periodinane, CH_2Cl_2, 88%; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C, 95%; (d) DIBAL, toluene, −78 to −30°C, 97%; (e) *t*-BuO_2H, (+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, 4 Å MS, CH_2Cl_2, −20°C, 62%, 91% de; (f) BzCl, TEA, DMAP, CH_2Cl_2, 97%; (g) DDQ, CH_2ClCH_2Cl, phosphate buffer (pH 6.7) (9:1), 35°C, 61%; (h) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0°C, 97%; (i) DIBAL, toluene, −78°C, 88%; (j) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 85%; (k) CBr_4, HMPT, THF, 94%; (l) TBAF, THF, 0°C, 88%; (m) *n*-BuLi, THF, −78 to −30°C, 97%; (n) 2,4,6-$[(CH_3)_2CH]_3C_6H_2SO_2Cl$, DMAP, CH_2ClCH_2Cl, 60°C, 93%; (o) $LiCuBr_2$, THF, 80°C, 67%; (p) CSA, MeOH, 50°C, 88%, (q) CBr_4, $(Oct)_3P$, 1-methyl-1-cyclohexene, toluene, 70°C, 87%.

mary hydroxy group of **18** via stannylene acetal[14] followed by treatment with K_2CO_3 in MeOH–CH_2Cl_2 led to epoxide in high yield with retention of configuration. Regioselective addition of Me_2CuLi (100%), and subsequent protection of the resulting hydroxy group as a TBS ether provided **19** (96%).

With **19** in hand, the stage was set for the construction of the dioxabicyclic skeleton of (+)-**2**. Selective deprotection of the TBDPS group of **19** co-existing with the TBS ether was carried out by the Shekhani method[15] with the following modifications: addition of propargyl alcohol (10 equiv.) and use of THF–HMPA (1:1) as a solvent system (Scheme 4). Under the conditions, high discrimination between the TBDPS and TBS groups was attained. Dess–Martin oxidation of the resulting alcohol followed by Horner–Emmons reaction gave the corresponding α,β-unsaturated ester, which was treated with DIBAL to afford *trans*-allyl alcohol **20** in high yield. Diastereoselective epoxidation of **20** by the Sharpless protocol[10] provided the desired α-epoxide **6** (62%, 91% de). Protection of **6** with a benzoyl group (97%) followed by cleavage of the benzyl ether with DDQ resulted in the spontaneous formation of a tetrahydrofuran ring to provide dioxabicyclic skeleton **21** (61%). Next, we examined installation of the bromoallene moiety. Conversion of **22**, derived from **21** via a protection–deprotection sequence, into **5** having a propargyl alcohol moiety was achieved through the following sequence involving the Corey method:[16] (i) oxidation of the primary hydroxy group with Dess–Martin periodinane; (ii) treatment with CBr_4 and HMPT in THF; (iii) deprotection of the TES group; (iv) treatment with *n*-BuLi in THF. All steps proceeded in excellent yields. According to the reported method,[17] **5** was trisylated and subsequently treated with $LiCuBr_2$ to provide the desired **23** (67%), its bromoallene diastereomer (5%), and the corresponding S_N2 product (12%). Bromoallene **23** separated by HPLC was desilylated under the acidic conditions. Finally, the resulting hydroxy group was brominated with inversion of configuration by the procedure of Murai[3e] with addition of 1-methyl-1-cyclohexene[18] to furnish (+)-**2** in 87% yield. The synthetic material was identical in all respects (^1H, ^{13}C NMR, $[\alpha]_D$) to those reported for natural (+)-**2**.[7]

In conclusion, the total synthesis of (+)-laurallene (**2**) was accomplished with high stereoselectivity. This synthetic study demonstrated that the cyclization of hydroxy epoxides promoted by $Eu(fod)_3$ is an efficient approach to the stereoselective synthesis of highly functionalized oxocenes. Further applications of this methodology on the synthesis of related medium-sized cyclic ethers are in progress in our laboratory.

References

1. For reviews, see: (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, pp. 43–121; (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. 5, pp. 131–257; (c) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49. See also his previous reviews in *Nat. Prod. Rep.*
2. Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371–8382.
3. (a) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660; (b) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499–7504; (c) 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; (d) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958–5966; (e) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345–4348.
4. (a) Fujiwara, K.; Souma, S.; Mishima, H.; Murai, A. *Synlett* **2002**, 1493–1495; (b) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476; (c) Edward, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267–4270.
5. For the selective synthesis of α,α′-*trans*-eight-membered cyclic ethers, see: (a) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728–9738; (b) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153–5161.
6. Fukuzawa, A.; Takasugi, Y.; Murai, A. *Tetrahedron Lett.* **1991**, *32*, 5597–5598.
7. Fukuzawa, A.; Kurosawa, E. *Tetrahedron Lett.* **1979**, 2797–2800.
8. Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron* **1970**, *26*, 851–870.
9. Saito, T.; Suzuki, T.; Onodera, N.; Sekiguchi, H.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 2709–2712.
10. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
11. Chen, S.-Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2168–2174.
12. Matsumura, R.; Suzuki, T.; Sato, K.; Oku, K.; Hagiwara, H.; Hoshi, T.; Ando, M.; Kamat, V. P. *Tetrahedron Lett.* **2000**, *41*, 7701–7704.
13. Yamaguchi, M.; Hirano, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
14. Tsuda, Y.; Haque, M. E.; Yoshimoto, K. *Chem. Pharm. Bull.* **1983**, *31*, 1612–1624.
15. Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669–1670.
16. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
17. (a) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534; (b) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468–2477.
18. Matsumura, R.; Suzuki, T.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 1543–1546.