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Formal synthesis of (+)-isolaurepinnacin

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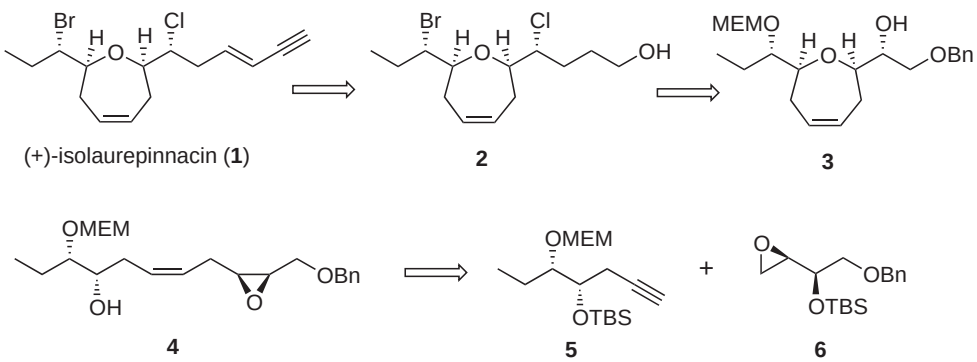
Abstract—The stereoselective formal synthesis of (+)-isolaurepinnacin is described. The required key oxepene skeleton possessing *cis*-oriented alkyl substituents at the α,ω-positions was stereoselectively constructed via the cyclization of the corresponding hydroxy epoxide promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system. © 2000 Elsevier Science Ltd. All rights reserved.

Red algae of the genus *Laurencia* are unique in terms of producing C_{15} acetogenins.[1] Medium-sized oxacyclics bearing an enyne or allenic side chain moiety and halogen group(s) are the main structural characteristics of this group. In addition, most of the compounds possess alkyl substituents with *cis*- or *trans*-orientation at the α- and ω-position on the cyclic ethereal skeleton. Owing to the synthetic challenges associated with the unique structural features, a number of new methods for the construction of such a system have been investigated.[2] Among this group, (+)-isolaurepinnacin (**1**), isolated from *Laurencia pinnata* Yamada,[3] is a representative seven-membered oxacyclic having α,ω-*cis*-oriented alkyl substituents. Intensive synthetic investigations towards (+)-**1** have resulted in several reports for the stereoselective construction of the oxepane core of (+)-**1**.[4] Consequently, in 1993, the first total synthesis of (+)-**1** was reported by the Overman group.[5]

Recently, we reported the development and the synthetic utility of hydroxy-epoxide cyclizations promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system for the stereoselective construction of the α,ω-*cis*- and α,ω-*trans*-disubstituted oxepane skeletons.[6] The reaction proceeded via an *exo* mode coupled with an S_N2 process and was independent of the stereochemistry of the hydroxy and epoxy groups to afford the corresponding cyclic product. In this communication, we describe a stereoselective formal synthesis of (+)-**1** featuring the above protocol as a key step.

Our synthetic plan is envisaged in Scheme 1. Hydroxy epoxide **4**, which could be obtained by coupling of



Scheme 1.

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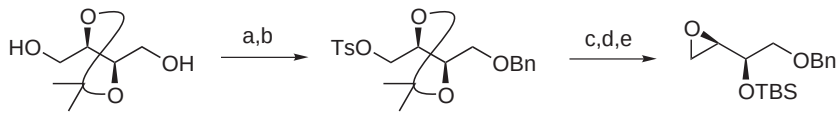
acetylene **5** with epoxide **6**, was postulated as a key intermediate. Application of the earlier cited protocol to **4** would afford the corresponding oxepene skeleton **3** possessing the desired stereochemical outcome and the appropriate functionalities for further transformations. Introduction of two halogens and homologation of the side chain would give **2**, which is the intermediate reported by Overman.[5] Accordingly, **2** was set as the target molecule for our synthetic study.

According to the synthetic plan, we started with efficient preparation of the epoxide **6** and the acetylene **5** from (−)- and (+)-2,3-*O*-isopropylidenthreitol, respectively. Successive introduction of benzyl (76%) and tosyl groups (88%) to the hydroxy groups of (−)-**7** led to **8** (Scheme 2). Hydrolytic deprotection of **8** (67%), followed by treatment with K_2CO_3 in MeOH–CH_2Cl_2 furnished the corresponding epoxide in 87% yield. Reprotection of the hydroxy group with a TBS group was effected with TBSCl, $AgNO_3$ and pyridine in acetonitrile[7] to afford the epoxide **6** in 96% yield. On the other hand, the acetylene **5** was synthesized as follows. Benzyl ether **9**, which is an antipode of **8** derived from (+)-**7**, was methylated with Me_2CuLi (89%) and then converted into **10** in high yield via an analogous sequence to the synthesis of the epoxide **6** (Scheme 3). After protection with an MEM group (89%), the epoxide was reacted with lithium acetylide in DMSO (91%); subsequently, the resulting hydroxy group was protected as a TBS ether to provide the acetylene **5** in 79% yield.

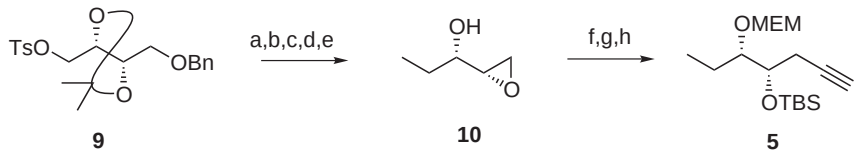
Coupling of **5** with **6** was easily achieved by the Yamaguchi method[8] to afford **11** in 76% yield (Scheme 4). Mesylation of the resulting hydroxy group (99%), followed by treatment with TBAF in THF provided the corresponding epoxide in 85% yield. Hydrogenation in the presence of the Lindlar catalyst gave the intermediate **4** (99%), which was then subjected to the key cyclization reaction. For this purpose, the tin ether prepared by reacting **4** with $(Bu_3Sn)_2O$ (0.6 equiv.) was treated with $Zn(OTf)_2$ (0.4 equiv.) in toluene. The reaction proceeded smoothly to afford the α,ω-*cis*-oxepene **3** as the sole cyclized product in 97% yield.

With the desired oxepene **3** in hand, we turned our investigation to modification of the side chains. Since several attempts to introduce the required halogens into C_6 and C_{13} with retention of configuration were unsuccessful, the reaction sequence was manipulated in the following order to achieve the desired goal. Acetylation of **3** (99%), followed by removal of the MEM group generated the corresponding alcohol in 81% yield. Exposure to Mitsunobu conditions[9] gave **12** (82%) possessing inverted configuration at C_{13}. The benzyl group of **12** was deprotected by the Nicolaou method,[10] and subsequently treated with TBAF to remove the partially existing TMS ether. Under the reaction conditions, migration of the acetyl group occurred to give a mixture of **13** and **14**. Fortunately, the equilibrium could be shifted almost exclusively towards **14** by exposure of the mixture to silica gel in CH_2Cl_2. The resulting hydroxy group was immediately mesylated to give **15**, which was subsequently treated with a base to provide the respective epoxide in 80% yield from **12**. The generated hydroxy group was protected as a TBS ether to give **16** in 76% yield. Regioselective opening of the epoxy moiety with lithiated acetonitrile (74%), followed by introduction of the chlorine functionality with $(Oct)_3P$ and CCl_4[11] in the presence of pyridine resulted in formation of **17** (51%) with inversion of configuration at C_6. Removal of the TBS group with HF·Py, followed by exposure to the bromination conditions reported by Murai[12] provided **18** (84% from **17**) with complete inversion. Finally, reduction of the cyano group of **18** to the primary alcohol via a two-step sequence provided **2** in 85% yield. The synthetic sample was identical in all aspects (^1H, ^{13}C NMR, IR and $[\alpha]_D$) to those reported by Overman.[5a]

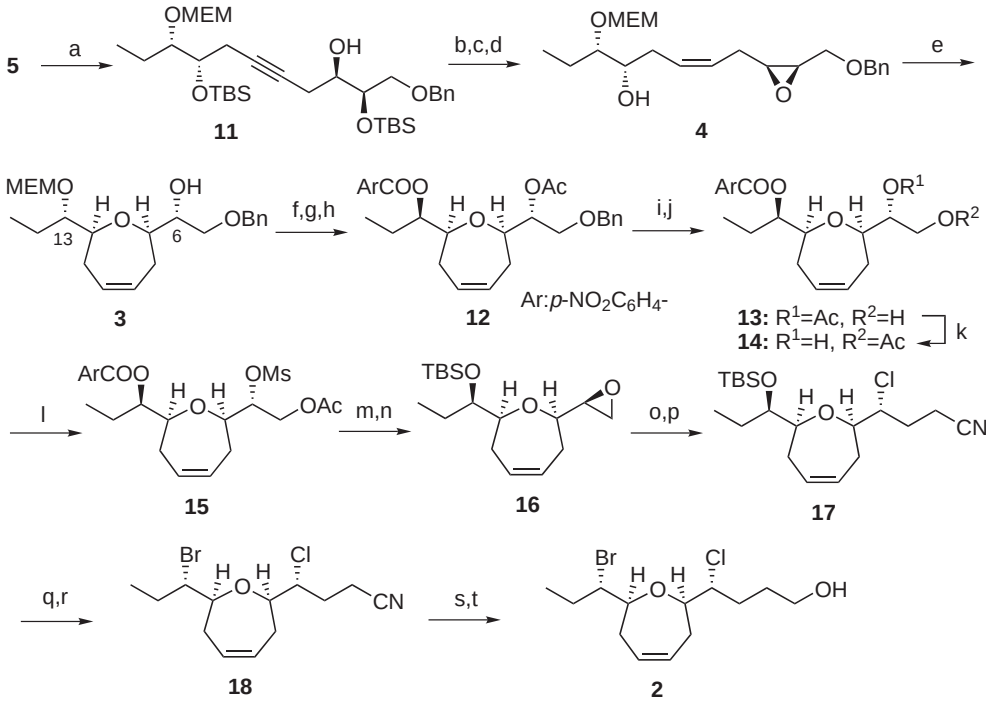
In conclusion, a formal synthesis of (+)-isolaurepinnacin (**1**) was accomplished with high stereoselectivity. The stereoselective construction of the oxepene core was performed by employing cyclization of the hydroxy epoxide promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system. This synthetic study demonstrated that this protocol is an efficient approach to the stereoselective synthesis of highly functionalized seven-membered oxacyclics.



Scheme 2. Reagents and conditions: (a) BnBr, NaH, DMF, 76%; (b) TsCl, TEA, DMAP, CH_2Cl_2, 88%; (c) Amberlyst 15, MeOH, 67%; (d) K_2CO_3, MeOH, CH_2Cl_2, 87%; (e) TBSCl, $AgNO_3$, Py, CH_3CN, 96%.



Scheme 3. Reagents and conditions: (a) Me_2CuLi, Et_2O, −78°C–rt, 89%; (b) H_2, $Pd(OH)_2$, AcOEt, 92%; (c) TsCl, TEA, DMAP, CH_2Cl_2; (d) Amberlyst 15, MeOH, 85% (two steps); (e) K_2CO_3, MeOH, CH_2Cl_2, 94%; (f) MEMCl, *i*-Pr_2NEt, DMAP, CH_2ClCH_2Cl, 50°C, 89%; (g) ≡Li·EDA, DMSO, 0°C, 91%; (h) TBSCl, NaH, THF, 79%.



Scheme 4. Reagents and conditions: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, then **6**, 76%; (b) MsCl, Py, DMAP, CH_2Cl_2, 99%; (c) TBAF, THF, 85%; (d) H_2, Lindlar cat., MeOH, 99%; (e) $(Bu_3Sn)_2O$, toluene, reflux, then $Zn(OTf)_2$, 90°C, 97%; (f) Ac_2O, TEA, DMAP, CH_2Cl_2, 99%; (g) $ZnBr_2$, CH_2ClCH_2Cl, 81%; (h) *p*-$NO_2C_6H_4CO_2H$, DEAD, Ph_3P, THF, 82%; (i) PhSTMS, ZnI_2, Bu_4I, CH_2Cl_2; (j) TBAF, THF; (k) silica gel, CH_2Cl_2; (l) MsCl, TEA, DMAP, CH_2Cl_2; (m) K_2CO_3, MeOH, CH_2Cl_2, 80% (five steps); (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, −70°C, 76%; (o) $LiCH_2CN$, THF, 0°C, 74%; (p) $(Oct)_3P$, Py, CCl_4, 50°C, 51%; (q) HF·Py, CH_2Cl_2–THF (7:1), 100%; (r) $(Oct)_3P$, CBr_4, toluene, 50°C, 84%; (s) DIBAL, toluene, −78°C, 100%; (t) $NaBH_4$, EtOH, 0°C, 85%.

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