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The first total synthesis of (+)-rogioloxepane A

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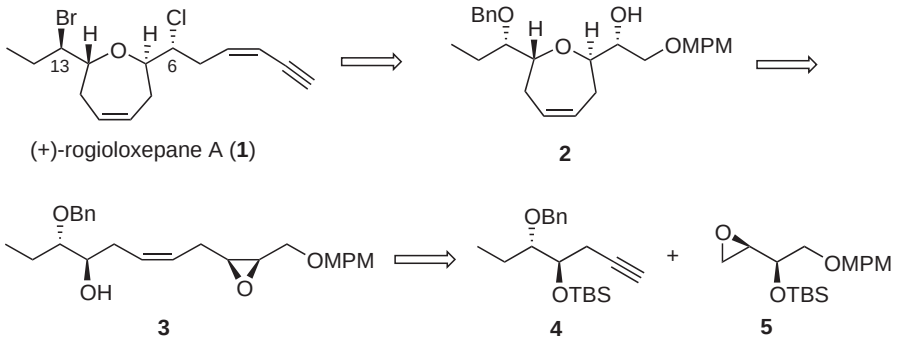
Abstract—The first total synthesis of (+)-rogioloxepane A is described. The α,ω-*trans*-disubstituted oxepene skeleton was stereoselectively constructed via cyclization of the hydroxy epoxide promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system. The proposed configurations of 6*R* and 13*R* were confirmed through this synthetic study. © 2001 Elsevier Science Ltd. All rights reserved.

Red algae of the genus *Laurencia* produce a variety of oxacyclic C_{15} acetogenins.[1] In particular, medium-sized oxacyclics are unique and characteristic compounds. Owing to synthetic challenge, these metabolites have been popular targets for synthetic investigation and a number of new methodologies have been developed so far.[2] Among this group, (+)-rogioloxepane A (**1**), isolated from *L. microcladia* in 1992 by Pietra's group,[3] has the particular feature of an oxepene core possessing alkyl substituents at the α- and ω-positions with *trans* orientation. In addition, the configurations of the halogenated carbons at the side chains have remained uncertain, although they were deduced to be 6*R* and 13*R* by comparing coupling constants obtained by molecular-mechanics calculation.[3]

It is obvious that the most crucial part in the synthesis of (+)-**1** is an efficient construction of the oxepene ring as well as the stereocontrolled introduction of *trans*-oriented alkyl side chains. While some efficient methods towards stereoselective synthesis of α,ω-*cis*-oxepanes were developed,[4] few methods are available for the α,ω-*trans*-oxepane system found in (+)-**1**.[4e,5] Recently, we reported a new methodology towards the stereoselective construction of α,ω-*cis*- and α,ω-*trans*-oxepanes.[6] Our approach is a direct construction via hydroxy–epoxide cyclization promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system. Subsequently, a formal synthesis of (+)-isolaurepinnacin, which is a representative α,ω-*cis*-disubstituted oxepene, was accomplished by utilizing the above-mentioned protocol as a key step.[7] In this communication, we examined the further applicability of the methodology to the synthetic study of (+)-**1** as a part of our research program.

We designed a synthetic strategy involving hydroxy epoxide **3** as a key precursor (Scheme 1). Application of the foregoing protocol to **3** would result in the direct



Scheme 1.

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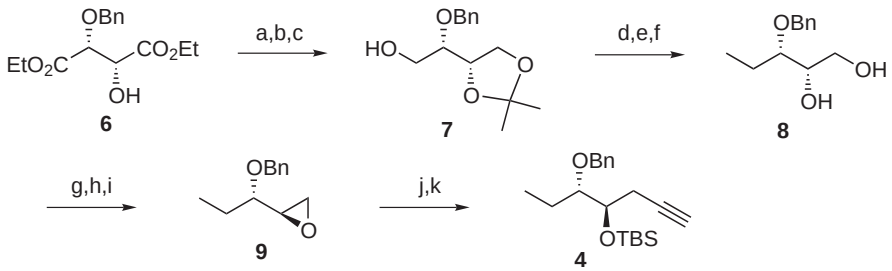
formation of α,ω-*trans*-oxepene **2** possessing all of the requisite chiral centers for manipulation of the side chains. Stereoselective introduction of a terminal *cis*-enyne moiety and two halogen substituents into **2** would complete our synthesis. In turn, the precursor **3** could be accessible from acetylene **4** and epoxide **5**.

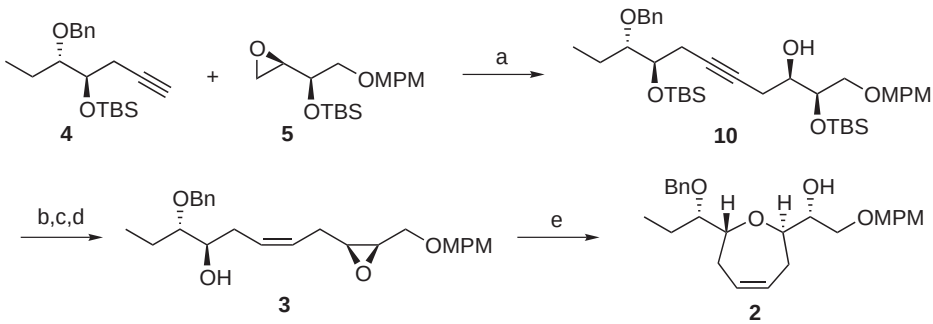
According to the retro-synthetic scheme, the synthesis of the acetylene **4** was investigated at the outset of this research (Scheme 2). Benzyl ether **6**, prepared from (+)-diethyltartrate according to the Ohno procedure,[8] was protected with a 1-methyl-1-methoxyethyl group, and subsequently treated with $LiAlH_4$ to give the corresponding diol, which was exposed to PPTS to convert into 1,2-acetonide **7** with a trace amount of the 1,3-isomer. Homologation of **7** via the corresponding tosylate followed by deprotection of the acetonide group afforded diol **8**. The diol moiety of **8** was stereoselectively converted to epoxide **9** through a three-step sequence: (i) selective protection of the primary hydroxy group with a TBS ether, (ii) mesylation of the remaining secondary hydroxy group, (iii) deprotection of the TBS group with TBAF and spontaneous formation of an epoxide. Regioselective addition of lithium acetylide in DMSO, and subsequent protection with a TBS group provided the acetylene **4**. All steps proceeded in excellent yields.

Coupling of **4** with **5**[6b] was easily achieved by the Yamaguchi method[9] in 78% yield (Scheme 3). The resulting acetylene **10** was hydrogenated in the presence of Lindlar catalyst to afford the *cis*-olefinic product. Mesylation under the usual conditions followed by deprotection of the TBS groups and concomitant epoxide-formation provided hydroxy epoxide **3** in high yield. With the key precursor **3** for the cyclization in hand, the crucial step in this synthesis was next examined. The hydroxy epoxide **3** was treated with $(Bu_3Sn)_2O$ in refluxing toluene followed by $Zn(OTf)_2$ at 90°C. The reaction proceeded smoothly and stereoselectively as described in our previous work[6] to afford the desired oxepene **2** in 75% yield as the sole product.

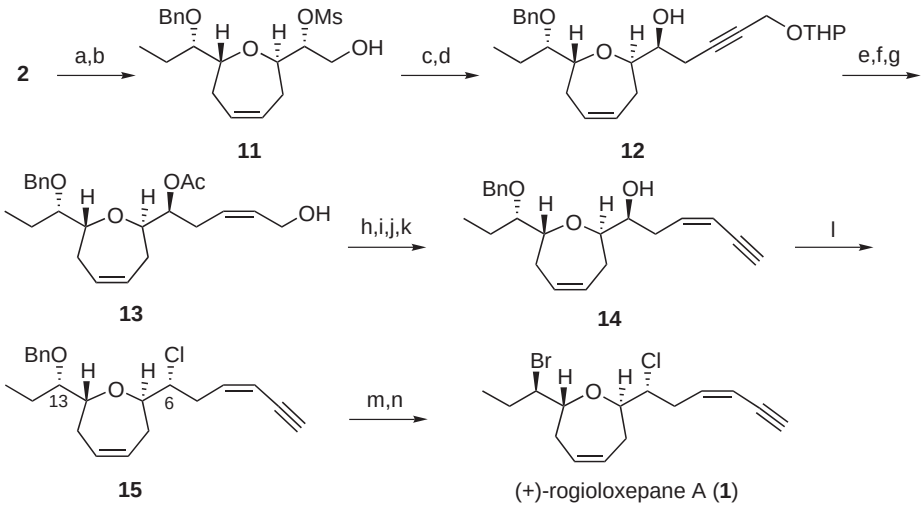
Next, we examined installation of the *cis*-enyne terminus. Mesylation of the oxepene **2** followed by the cleavage of the MPM ether with PhSH and $ZnCl_2$ in CH_2Cl_2 afforded **11** (93%) (Scheme 4). Use of DDQ[10] in the latter reaction was unsuccessful because of competitive deprotection of the benzyl group. After conversion of the alcohol **11** into epoxide (98%), the regioselective addition of THP propynyl ether afforded acetylene **12** in quantitative yield. Hydrogenation of **12** with Lindlar catalyst followed by protection–deprotection sequence provided *cis*-olefin **13** in high yield. Conversion of **13** into *cis*-enyne **14** was achieved by the following sequence involving the modified Corey method.[11] Chemoselective oxidation of the allyl alcohol moiety with MnO_2 afforded *cis*-α,β-unsaturated aldehyde, which due to easy isomerization (vide infra) was immediately treated with CBr_4 and HMPT in THF to provide the corresponding 1,1-dibromo-*cis*-diene. Use of HMPT instead of commonly used PPh_3 was a key to the success of this conversion. Under the conditions,



Scheme 2. *Reagents and conditions*: (a) 2-methoxypropene, $POCl_3$, CH_2Cl_2, 100%; (b) $LiAlH_4$, THF, 0°C, 91%; (c) 2-methoxypropene, PPTS, CH_2ClCH_2Cl, 60°C, 86%; (d) TsCl, TEA, DMAP, CH_2Cl_2, 100%; (e) Me_2CuLi, Et_2O, −65 to 0°C, 93%; (f) PPTS, EtOH, 80°C, 97%; (g) TBSCl, TEA, DMAP, CH_2Cl_2, 60°C, 100%; (h) MsCl, TEA, DMAP, CH_2Cl_2, 98%; (i) TBAF, THF, 96%; (j) ≡Li·EDA, DMSO, 0°C, 93%; (k) TBSCl, $AgNO_3$, Py, CH_3CN, 98%.



Scheme 3. *Reagents and conditions*: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, 78%; (b) H_2, Lindlar cat., quinoline, MeOH, 99%; (c) MsCl, TEA, DMAP, CH_2Cl_2, 98%; (d) TBAF, THF, 50°C, 91%; (e) $(Bu_3Sn)_2O$, toluene, reflux, then $Zn(OTf)_2$, 90°C, 75%.



Scheme 4. *Reagents and conditions*: (a) MsCl, TEA, DMAP, CH_2Cl_2, 100%; (b) PhSH, $ZnCl_2$, CH_2Cl_2, 0°C, 93%; (c) K_2CO_3, MeOH–CH_2Cl_2 (1:1), 98%; (d) HC≡CCH_2OTHP, *n*-BuLi, $BF_3{\cdot}OEt_2$, −78°C, 99%; (e) H_2, Lindlar cat., quinoline, AcOEt, 100%; (f) Ac_2O, TEA, DMAP, CH_2Cl_2, 97%; (g) PPTS, EtOH, 50°C, 98%; (h) MnO_2, $CHCl_3$–benzene (1:2); (i) CBr_4, HMPT, THF, 0°C; (j) K_2CO_3, MeOH; (k) *n*-BuLi, THF, −90 to −40°C, 56% (four steps), *cis*:*trans*=20:1; (l) CCl_4, $(Oct)_3P$, 1-methyl-1-cyclohexene, toluene, 80°C, 49%; (m) DDQ, CH_2ClCH_2Cl–H_2O (9:1), 50°C, 100%; (n) CBr_4, $(Oct)_3P$, 1-methyl-1-cyclohexene, toluene, 70°C, 70%.

the reaction was completed in 1 minute without isomerization of the double bond in conjugation to the aldehyde group. Deprotection of the acetyl group followed by treatment with *n*-BuLi furnished the *cis*-enyne **14** in 56% yield over four steps as a 20:1 mixture of *Z*:*E* stereoisomers. The *cis*-enyne **14** was purified by MPLC at this stage and subjected to further manipulations.

Several attempts to introduce the chlorine functionality at C_6 with inversion of configuration were unsuccessful due to the competitive elimination. The best method finally founded for this transformation was CCl_4 and $(Oct)_3P$ in toluene in the presence of 1-methyl-1-cyclohexene to afford chloride **15** in 49% yield along with the elimination product (24%). In the absence of 1-methyl-1-cyclohexene, a trace amount of by-products halogenated on the double bond(s) were formed, separation of which from the desired product was troublesome. DDQ was employed for cleavage of the benzyl ether of **15** according to our earlier observation (vide supra). Finally, the resulting hydroxy group at C_{13} was brominated by the procedure of Murai[12] with addition of 1-methyl-1-cyclohexene to furnish (+)-**1** in 70% yield with complete inversion of configuration. The synthetic material was identical in all respects (^1H NMR, ^{13}C NMR, $[\alpha]_D$, and MS)[3] to those reported for natural (+)-**1**.

In conclusion, the first total synthesis of (+)-rogioloxepane A (**1**) was accomplished with high stereoselectivity. This synthesis has established that the cyclization of hydroxy epoxides promoted by the $(Bu_3Sn)_2O/Zn(OTf)_2$ system is an efficient methodology for the synthesis of highly functionalized seven-membered oxacyclics. In addition, the proposed 6*R* and 13*R* configurations[3] were synthetically confirmed.

Acknowledgements

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