TOTAL SYNTHESIS OF HEMIBREVETOXIN B VIA THE ALLYLIC TIN METHODOLOGY

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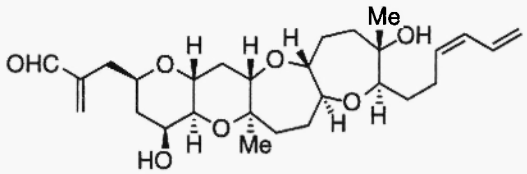
Abstract: The total synthesis of Hemibrevetoxin B is described. A new cyclization approach, based on the Lewis acid mediated intramolecular cyclization of the γ-oxo-substituted allylic tin having an aldehyde group, produced the 6-6-7-7 polycyclic ether skeleton of the natural product with high stereoselectivity. The ^{1}H and ^{13}C-NMR spectra of synthetic hemibrevetoxin B was identical with those of natural product.

Introduction

Hemibrevetoxin B **1**, isolated from cultured cells of the red tide organism *Gymnodinium breve* by Y. Shimizu in 1989,[1] has a 6,6,7,7-tetracyclic ether skeleton and contains 10 stereocenters (Scheme I). Much attention has been paid to the synthesis of polycyclic ethers including hemibrevetoxin B owing to their unusual structural framework, novel functionalities, and biological activities.[2] Recently, Nicolaou and coworkers have reported the first total synthesis of hemibrevetoxin B.[3] We have reported the stereocontrolled synthesis of the 6,6,7,7-tetracyclic ether skeleton of **1** via the intramolecular allylic tin-aldehyde (and ketone) condensation.[4] Chain elongation to the left-hand side aldehyde from this intermediate was difficult, and therefore we utilized **2** having a hydroxypropyl side chain as a starting material. We now report the total synthesis of **1** via the allylic tin methodology.[5]

Scheme I. Structure of Hemibrevetoxin B (**1**)



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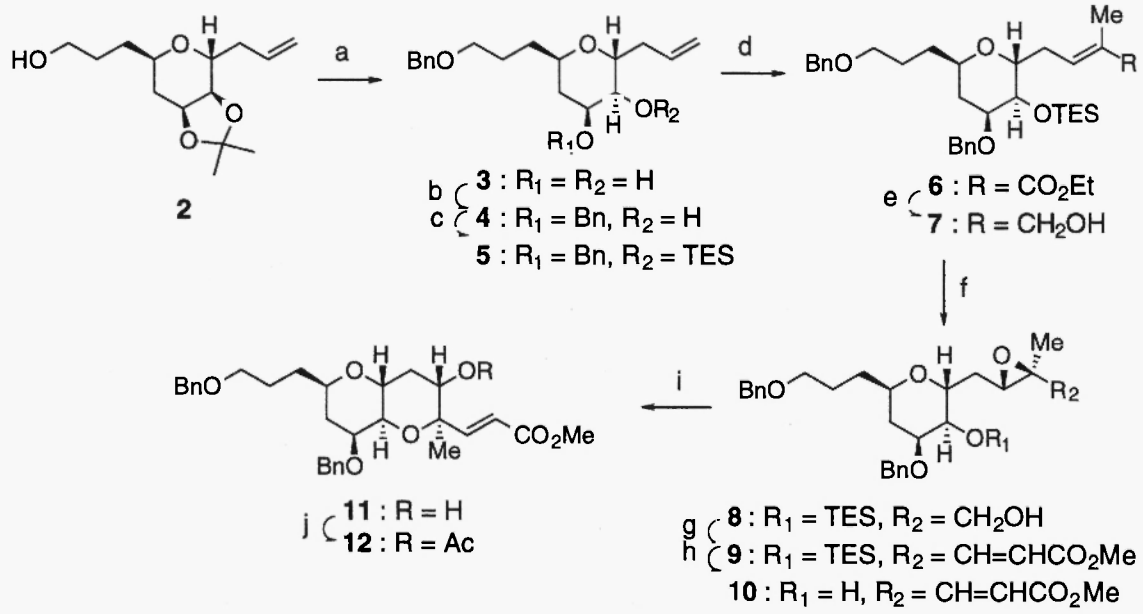
Results and Discussion

The preparation of 6,6-ring system was carried out primarily based on the modified Nicolaou's method (Scheme II). The mannose-derived stating material **2**[2b] was converted into **5** by benzylation followed by removal of the acetonide protection and selective elaboration of the liberated diol using Bu_2SnO/BnBr and TESCl/imidazole. Ozonolysis of the double bond followed by treatment of the resulting aldehyde by a Wittig reagent afforded **6** in 91% yield. Reduction with diisobutyl-aluminium hydride gave allylic alcohol **7** in 87% yield, which was converted into the epoxide **8** upon treatment with the Sharpless epoxidation reagent. Oxidation of the primary alcohol of **8** with SO_3•py-DMSO-Et_3N followed by Wittig reaction afforded **9** in 82% overall yield. Removal of the TES protecting group by using tetrabutylammonium fluoride afforded **10** in quantitative yield. Ring opening and cyclization with camphorsulphonic acid gave **11** in 79% yield, which was converted the acetate **12** in 95% yield.

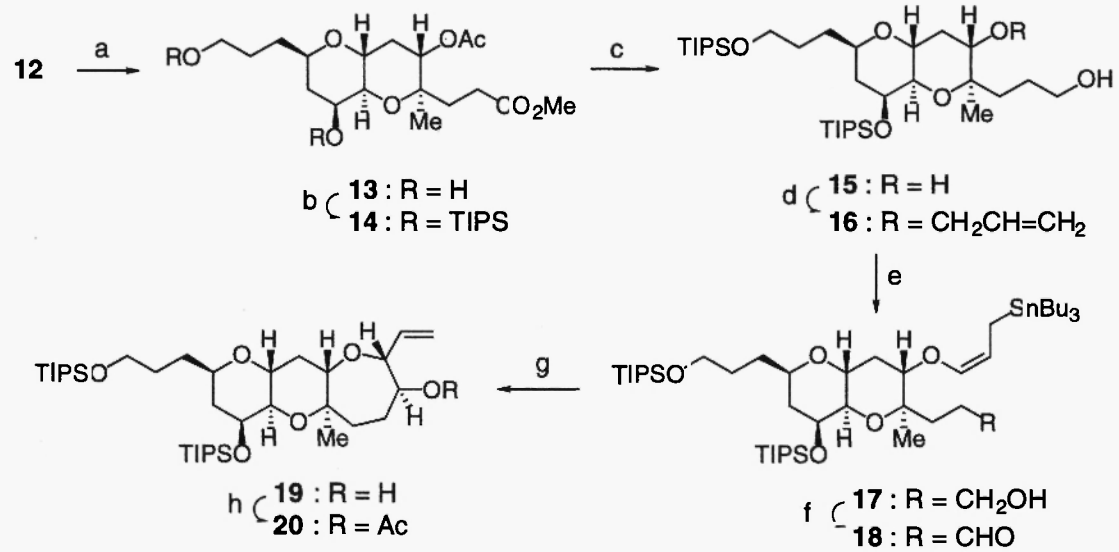
Scheme II[a]



[a](a) (i) BnBr, KH, THF, rt, 91%; (ii) HCl, MeOH, rt, 100%; (b) (i) Bu_2SnO, MeOH, reflux; (ii) BnBr, CsF, DMF, rt, 80%; (c) TESCl, imidazole, DMF, rt, 91%; (d) (i) O_3, CH_2Cl_2, -78 °C, then Ph_3P, rt; (ii) Ph_3P=C(Me)CO_2Et, benzene, reflux, 91%; (e) DIBAL-H, CH_2Cl_2, -78 °C, 87%; (f) (+)-DET, Ti(O^{i}Pr)$_4$, *t*-BuOOH, MS4A, CH_2Cl_2, -20 °C; (g) (i) SO_3•py, DMSO, Et_3N, CH_2Cl_2, rt; (ii) Ph_3P=CHCO_2Me, benzene, reflux (82% from three steps); (h) TBAF, THF, rt, 100%; (i) CSA, CH_2Cl_2, rt, 79%; (j) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 95%.

The stereocontrolled synthesis of the 6,6,7-ring system is shown in Scheme III. Debenzylation and hydrogenation of the double bond of **12** was achieved by using H_2/$Pd(OH)_2$-C to give **13** in 82% yield. The free OH groups were protected with TIPSOTf/2,6-lutidine to give **14** in 97% yield. Reduction of **14** with $LiAlH_4$ afforded **15** in quantitative yield. The method for seven-membered ring formation based on allylic tin-aldehyde condensation was then used. Selective protection of the primary alcohol with TESCl/Et_3N followed by allylation of the secondary alcohol and selective cleavage of the TES ether gave **16** in 83% yield. Formation of the corresponding allylic anion followed by trapping with Bu_3SnCl afforded **17** in 69% yield. Oxidation with SO_3•py/DMSO/Et_3N produced **18** in 90% yield. Cyclization of **18** with BF_3•OEt_2 proceeded smoothly and stereoselectively to give **19** in 94% yield, which was converted to **20** by acetylation. Only one diastereoisomer was detected in the cyclization step.

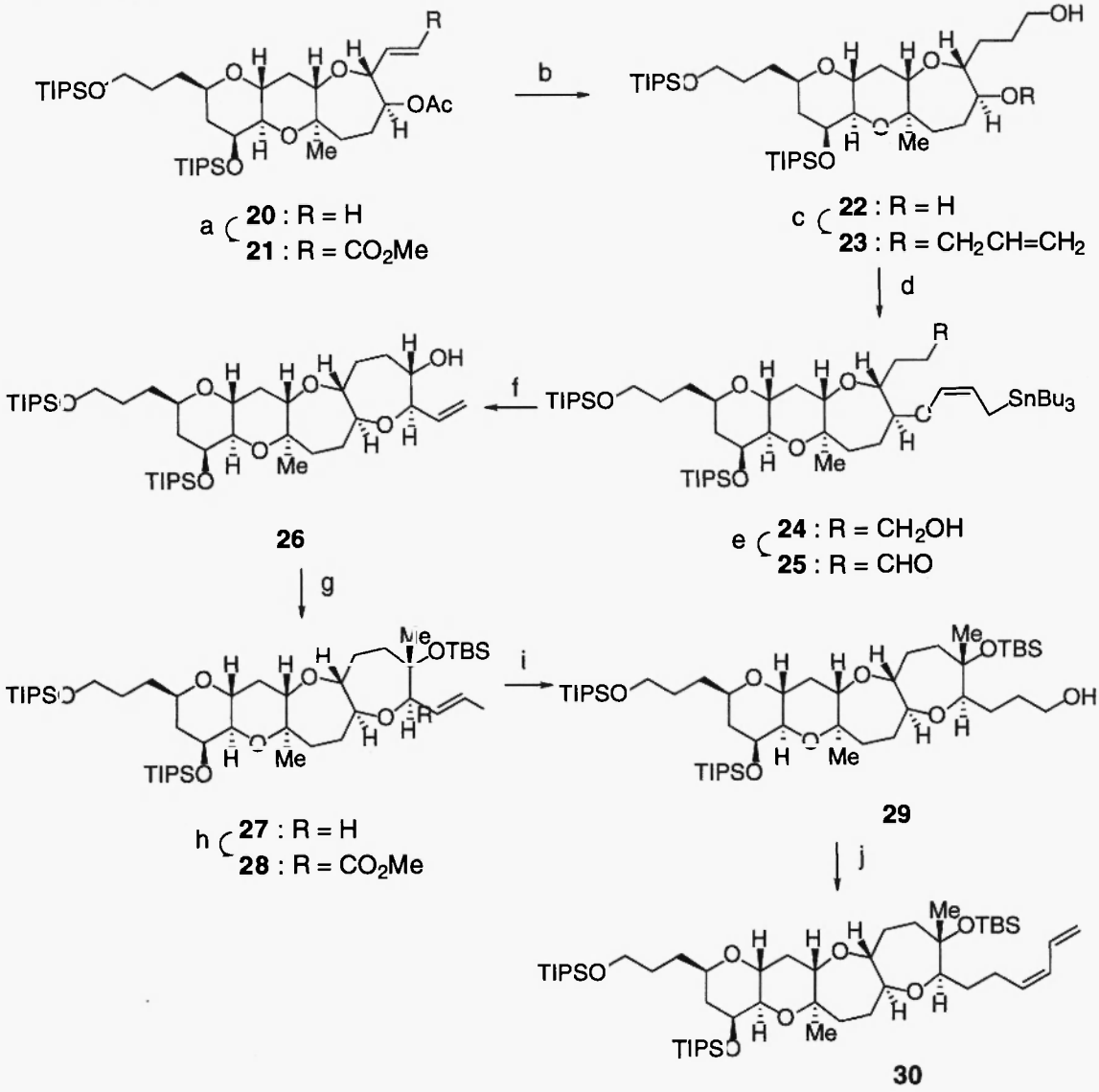
Sheme III[a]



[a](a) H_2, $Pd(OH)_2$-C, MeOH, rt, 82%; (b) TIPSOTf, 2,6-lutidine, DMF, rt to 70 °C, 97%; (c) $LiAlH_4$, ether, 0 °C, 100%; (d) (i) TESCl, Et_3N, CH_2Cl_2, -15 °C; (ii) allyl bromide, KH, THF, rt; (iii) Amberlyst-15, EtOH, rt, 83%; (e) *sec*-BuLi, TMEDA, THF, -78 °C, then Bu_3SnCl, -78 °C to rt, 69%; (f) SO_3•py, DMSO, Et_3N, CH_2Cl_2, rt, 90%; (g) BF_3•OEt_2, CH_2Cl_2, -78 °C, 94%; (h) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 100%.

The stereoselective construction of the 6,6,7,7-ring system is shown in Scheme IV. Ozonolysis of **20** followed by chain elongation gave **21** in 99% yield. Reduction with H_2/Pd-C and $LiAlH_4$ afforded **22** in 98% yield.

Scheme IV[a]

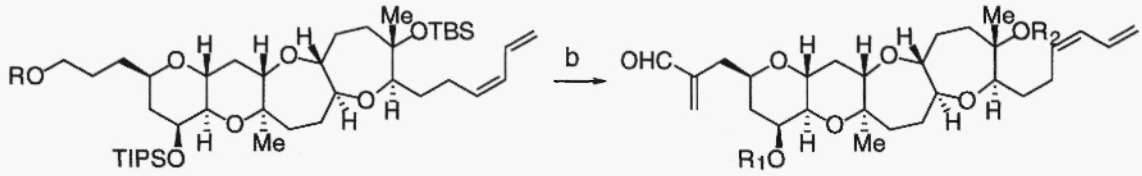


[a](a) (i) O_3, CH_2Cl_2, -78 °C, then Ph_3P, -78 °C to rt; (ii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 0 °C to rt, 99%; (b) (i) H_2, 10% Pd-C, AcOEt, rt; (ii) $LiAlH_4$, ether, 0 °C, 98%; (c) (i) TESCl, Et_3N, CH_2Cl_2, -15 °C; (ii) allyl bromide, KH, THF, rt; (iii) Amberlyst-15, EtOH, rt, 94%; (d) *sec*-BuLi, TMEDA, THF, -78 °C, then Bu_3SnCl, -78 °C to rt, 18%; (e) SO_3•py, DMSO, Et_3N, CH_2Cl_2, rt, 79%; (f) BF_3•OEt_2, CH_2Cl_2, -78 °C, 98%; (g) (i) Swern oxidation; (ii) MeMgBr, ether, -78 °C to rt; (iii) TBSOTf, 2,6-iutidine, CH_2Cl_2, rt, 89% (*ca.* 1:1 mixture of isomers); (h) (i) O_3, CH_2Cl_2, -78 °C, then Ph_3P, -78 °C to rt; (ii) $Ph_3P{=}CHCO_2Me$, benzen, reflux, 78%; (i) (i) H_2, 10% Pd-C, AcOEt, rt; (ii) $LiAlH_4$, ether, 0 °C, 92%; (j) (i) Dess-Martin periodinane, CH_2Cl_2, rt; (ii) $PhSe(CH_2)_3Ph_3P^+I^-$, *n*-BuLi, HMPA, -78 °C to rt; (iii) H_2O_2, $NaHCO_3$, THF, rt, 52%.

Selective allylation of the secondary alcohol gave **23** in 94% yield by the usual method as shown in Sheme III. Usual allylic anion formation followed by trapping with Bu_3SnCl afforded **24** in 18% yield along with the recovered

starting material. The tin-trapping step used for **16** proceeded smoothly but here the chemical yield of **24** was low, although significant amounts of **23** were recovered. Neither prolonged nor shorter reaction times gave a better result. Deprotonation of the sterically bulky allylic ether **23** would possibly be quite slow and the decomposition of the resulting allylic anion would compete if a prolonged reaction time was employed. Oxidation of **24** gave **25** in 79% yield. The BF_3•OEt_2 mediated cyclization of **25** afforded **26** as a sole product in 98% yield. Oxidation of **26**, Grignard reaction with MeMgBr, and TBS protection gave a 1:1 mixture of epimeric isomers in 89% yield, from which the desired isomer **27** was isolated by chromatography.[6] Ozonolysis of **27** followed by Wittig reaction gave **28** in 78% yield. Reduction with H_2/Pd-C and $LiAlH_4$ afforded **29** in 92% yield. Dess-Martin oxidation of **29** followed by treatment with the ylid derived from $PhSe(CH_2)_3Ph_3P^+I^-$ and *n*-BuLi, and oxidation-*syn*-elimination using H_2O_2 and $NaHCO_3$ afforded diene **30** in 52% yield.[3]

Scheme V[a]



a (**30** : R = TIPS; **31** : R = OH)

c (**32** : R_1 = TIPS, R_2 = TBS; **1** : R_1 = R_2 = H)

[a](a) TBAF, THF, rt, 73%; (b) (i) Dess-Martin periodinane, CH_2Cl_2, rt; (ii) $Me_2(CH_2)N^+I^-$, Et_3N, CH_2Cl_2, rt, 55%; (c) SiF_4, CH_2Cl_2-CH_3CN (1:1), rt, 68%.

The final stage of our synthetic study is shown in Scheme V. Selective desilylation of **30** using tetrabutylammonium fluoride gave **31** in 73% yield. Dess-Martin oxidation followed by treatment with Eschenmoser's salt afforded **32** in 55% yield.[7] Finally, the silyl protecting groups were removed by using SiF_4 to give hemibrevetoxin B (**1**) in 68% yield. The ^1H and ^{13}C-NMR spectra of synthetic hemibrevetoxin B (**1**) were identical with those of the natural product. The epimer of hemibrevetoxin B (**1**) was also synthesized from the epimer of **27** *via* the similar procedures as shown above.

Acknowledgments

This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, by the Shorai Foundation for Science and Technology, by the Terumo Life Science Foundation, and by the Foundation for Chemical Materials.

References and Notes

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(6) We examinded the cyclization of the allylic tin-methyl ketone (derived from **23**), since previously this type of cyclization proceeded smoothly.[4] However, such attempts resulted in a failure in this case.

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Received: December 22, 1995 - Accepted: January 22, 1996 - Accepted in revised camera-ready form: March 11, 1996