Stereocontrolled Synthesis of the Hemibrevetoxin Ring System *via* an Allylic Tin Method

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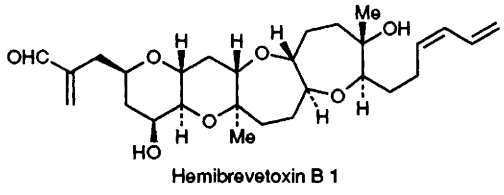
Stereocontrolled synthesis of the 7,7,6,6-tetracyclic ether skeleton of the hemibrevetoxin skeleton has been accomplished *via* the intramolecular allylic tin–aldehyde (and ketone) condensation.

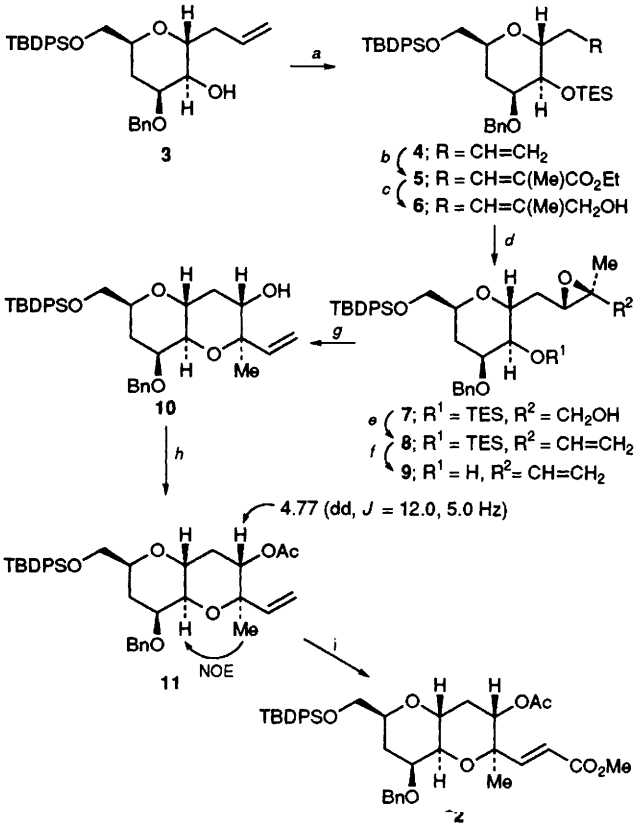
Hemibrevetoxin B **1**, isolated from cultured cells of the red tide organism *Gymnodinium breve* by Y. Shimizu in 1989,[1] has a 7,7,6,6-tetracyclic ether skeleton and contains 10 stereocentres. Much attention has been paid to the synthesis of polycyclic ethers including hemibrevetoxin B owing to their unusual structural framework, novel functionalities, and biological activities.[2] Recently, Nicolaou and coworkers have reported the first total synthesis of hemibrevetoxin B.[3] However, the formation of the seven-membered rings *via* the hydroboration method was not stereoselective; the first

seven-membered ether was obtained as a 4 : 1 mixture and the second as a 3 : 2 mixture.[3]

We report the stereocontrolled synthesis of the hemibrevetoxin framework by using intramolecular allylic tin–aldehyde condensation. We have already reported the stereocontrolled synthesis of a 6,7,7,6 tetracyclic ether skeleton *via* the allylic tin method.[4] It was expected that extension of techniques discovered in the synthesis of the 6,7,7,6 system would lead to a stereoselective preparation of the 7,7,6,6 system if the cyclization of an ω-tributylstannyl ether ketone proceeded smoothly with high diastereoselectivity as observed in the case of the corresponding aldehyde; hemibrevetoxin B has a tertiary trimethylmethanol centre and this requires the stereoselective intramolecular cyclization of an allylic stannane with a methyl ketone derivative.



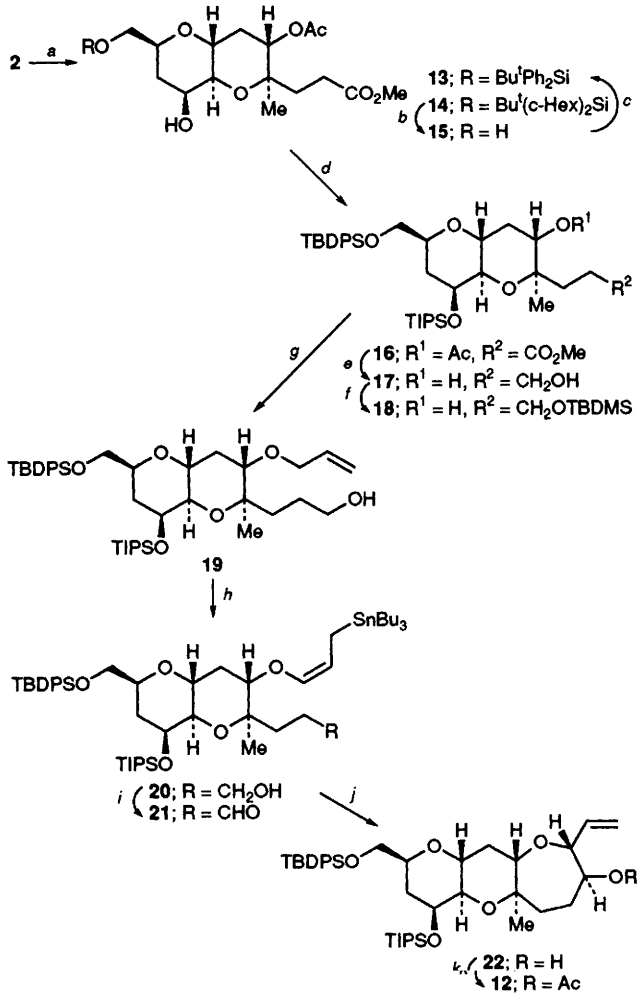
Hemibrevetoxin B 1



Scheme 1 *Reagents and conditions*: † (*a*) TESCl, imidazole, DMF, 25 °C, 100%; (*b*) (i) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 25 °C; (ii) Ph_3P=C(Me)CO_2Et, benzene, 80 °C, 75%; (*c*) DIBAL, CH_2Cl_2, −78 °C, 95%; (*d*) (+)-DET, $Ti(OPr^i)_4$, Bu^tOOH, molecular sieve, CH_2Cl_2, −20 °C, 93%; (*e*) (i) SO_3·pyridine, Et_3N, CH_2Cl_2–DMSO, 25 °C; (ii) Ph_3PMeBr, NaHMDS, THF, 0 °C, 92%; (*f*) TBAF, THF, 0 °C, 97%; (*g*) CSA, CH_2Cl_2, 0 °C, 53%; (*h*) Ac_2O, pyridine, CH_2Cl_2, 25 °C, 97%; (*i*) (i) O_3, MeOH, −78 °C, then Me_2S, 25 °C; (ii) Ph_3P=$CHCO_2Me$, benzene, 80 °C, 81%

† Bn = $PhCH_2$; TES = Et_3Si; DMF = dimethylformamide; DIBAL = Bu^i_2AlH; DET = diethyl tartrate; DMSO = dimethyl sulfoxide; NaHMDS = sodium hexamethyldisilazide; THF = tetrahydrofuran; TBAF = tetrabutylammonium fluoride; CSA = camphorsulfonic acid; TBDPS = Bu^tPh_2Si; TBDMS = Bu^tMe_2Si; TMEDA = tetramethylethylenediamine; TIPS = Pr^i_3Si.

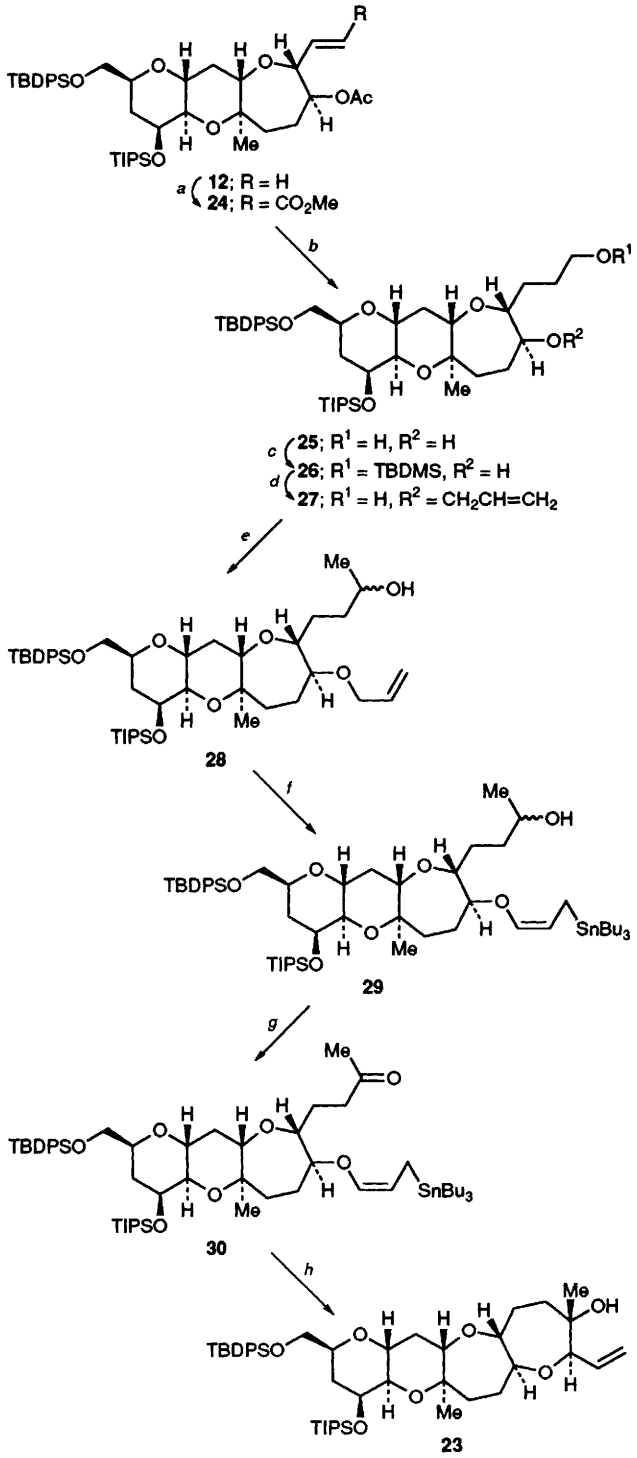
The preparation of the 6,6-ring system **2** was carried out primarily based on the modified Nicolaou method (Scheme 1). D-Mannose was converted to the deoxygenated *C*-glycoside **3** by the literature procedures.[2a] Protection with the triethylsilyl group gave **4** in quantitative yield. Ozonolysis of the double bond followed by treatment of the resulting aldehyde with a Wittig reagent afforded **5** in 75% yield. Reduction with diisobutylaluminium hydride gave **6** in 95% yield, which was converted to the epoxide **7** in 93% yield upon treatment with the Sharpless epoxidation reagent. Oxidation of the primary alcohol of **7** with SO_3·pyridine–DMSO–Et_3N[5] followed by olefination with a Wittig reagent afforded **8** in 92% yield. Selective removal of the TES protecting group by using tetrabutylammonium fluoride afforded **9** in 97% yield. Ring opening and cyclization with camphorsulfonic acid gave **10** in 53% yield. NOEs were observed between the methyl and α-hydrogen of **11**, which was obtained in 97% yield through acetylation of **10**. The β-hydrogen to the methyl group appeared at δ 4.77 ($CDCl_3$, dd) with coupling constants J = 12.0 and 5.0 Hz, indicating the *trans* configuration as shown in **11**. Ozonolysis of the double bond of **11** followed by chain elongation of the resulting aldehyde with a Wittig reagent gave **2** in 81% yield.



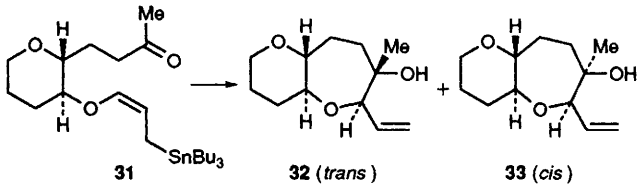
Scheme 2 *Reagents and conditions*: † (*a*) H_2, $Pd(OH)_2$–C, MeOH, 25 °C, **13**: 49%; **14**: 10%; (*b*) TBAF, THF, 25 °C, 82%; (*c*) TBDPSCl, imidazole, DMF, 25 °C, 91%; (*d*) $Pr^i_3SiOSO_2CF_3$, 2,6-lutidine, DMF, 70 °C, 97%; (*e*) $LiAlH_4$, diethyl ether, 0 °C, 94%; (*f*) TBDMSCl, imidazole, DMF, 0 °C, 98%; (*g*) (i) allyl bromide, KH, THF, 25 °C; (ii) AcOH–THF–H_2O, 60 °C, 86%; (*h*) Bu^sLi, TMEDA, THF, −78 °C then Bu^n_3SnCl, 25 °C, 81%; (*i*) SO_3·pyridine, Et_3N, CH_2Cl_2–DMSO, 25 °C, 96%; (*j*) BF_3·OEt_2, CH_2Cl_2, −78 °C, 95%; (*k*) Ac_2O, pyridine, CH_2Cl_2, 25 °C, 99%

The stereocontrolled synthesis of the 7,6,6-ring system **12** is shown in Scheme 2. Hydrogenation of **2** with H_2–cat. $Pd(OH)_2$–C produced a mixture of **13** (49%) and **14** (10%). Interestingly, the catalytic hydrogenation reduced the phenyl ring of the TBDPS group to some extent in addition to the double bond reduction and reactive removal of the benzyl protection. The unexpected and unwanted product **14** was converted to **13** *via* **15**. The free OH of **13** was protected using triisopropylsilyl trifluoromethanesulfonate–2,6-lutidine to give **16** in 97% yield. Reduction of **16** with $LiAlH_4$ afforded **17** in 94% yield. We then used the method for seven-membered ring formation based on allylic tin–aldehyde condensation.[4] Selective protection of the primary alcohol using *tert*-butyldimethylsilyl chloride gave **18** in 98% yield, which was converted to **19** in 86% yield. Formation of the corresponding allylic anion followed by trapping with Bu_3SnCl afforded **20** in 81% yield, oxidation with SO_3·pyridine–DMSO–Et_3N produced **21** in 96% yield. This oxidant gives better results than the Bu^tOMgBr–RCON=NCOR system we used previously with similar primary alcohols.[4] Cyclization of **21** with BF_3·OEt_2 proceeded smoothly and stereoselectively to give **22** in 95% yield, which was converted to **12** by acetylation. No diastereoisomers were detected in the cyclization step.

The stereoselective synthesis of the 7,7,6,6-ring system **23** *via* allylic tin–ketone condensation is shown in Scheme 3. Ozonolysis of **12** followed by chain elongation gave **24** in 96% yield. Reduction with H_2–Pd–C and $LiAlH_4$ afforded **25** in 90% yield; the catalyst (Pd–C) did not reduce the phenyl ring of the TBDPS group. Selective protection of the primary OH with TBDMSCl gave **26** in quantitative yield, which was converted to **27** in 95% yield by the usual method for the synthesis of allyl ethers. Oxidation of the primary OH to the aldehyde and subsequent treatment with methylmagnesium bromide gave **28** (as a 1 : 1 diastereoisomer mixture) in 87% yield. Usual allylic anionic formation followed by trapping with Bu_3SnCl afforded **29** in 37% yield along with recovered starting material. The tin-trapping step used for **19** and in the previous paper[4] proceeded without trouble, but here the chemical yield of **29** was low, although significant amounts of **28** were recovered. Neither prolonged nor shorter reaction times gave a better result. Deprotonation of the sterically bulky allylic ether **28** would possibly be quite slow and the decomposition of the resulting allylic anion would compete if a prolonged reaction time was employed. Oxidation of **29** gave **30** in 79% yield. Before trying the cyclization of **30**, we examined a model system for intramolecular allylic tin–ketone condensation (Scheme 4). The reaction of **31** with certain Lewis acids afforded the cyclization products **32** and **33**. Surprisingly, BF_3·OEt_2 which was commonly used for aldehydes did not give the cyclized product at all with the ketone here. Titanium and aluminium Lewis acids gave **32** exclusively or with very high diastereoselectivity. Among the reagents examined, $AlCl_3$·OEt_2 afforded the best result in respect of both chemical yield and diastereoselectivity. Accordingly, we applied this Lewis acid to **30**, and obtained **23** in 55% yield. No diastereoisomers were obtained. The stereochemistry of **23** was unambiguously determined by NOE experiments and proton chemical shifts.



Scheme 3 *Reagents and conditions*: † (*a*) (i) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 25 °C; (ii) Ph_3P=$CHCO_2Me$, benzene, 80 °C, 96%; (*b*) (i) H_2, 10% Pd–C, AcOEt, 25 °C, 98%; (ii) $LiAlH_4$, diethyl ether, 0 °C, 92%; (*c*) TBDMSCl, imidazole, DMF, 0 °C, 100%; (*d*) (i) allyl bromide, KH, THF, 25 °C; (ii) AcOH–THF–H_2O, 60 °C, 95%; (*e*) (i) SO_3·pyridine, Et_3N, CH_2Cl_2–DMSO, 25 °C; (ii) MeMgBr, THF, 0 °C, 87%; (*f*) Bu^sLi, TMEDA, THF, −78 °C, then Bu^n_3SnCl, 25 °C, 37%; (*g*) SO_3·pyridine, Et_3N, CH_2Cl_2–DMSO, 25 °C 79%; (*h*) $AlCl_3$·OEt_2, CH_2Cl_2, −78 °C, 55%



Lewis acid	Ratio (**32** : **33**)	Yield (%)
BF_3·OEt_2	—	0
$TiCl_4$	98 : 2	57
$TiCl_4$–PPh_3	98 : 2	52
$AlCl_3$·OEt_2	100 : 0	71
$EtAlCl_2$	100 : 0	66

Scheme 4

We have thus prepared the 7,7,6,6 skeleton of hemibrevetoxin B in a totally stereocontrolled manner. Connection of two side chains to **23** is in progress.

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