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Formal total synthesis of hemibrevetoxin B by a convergent strategy

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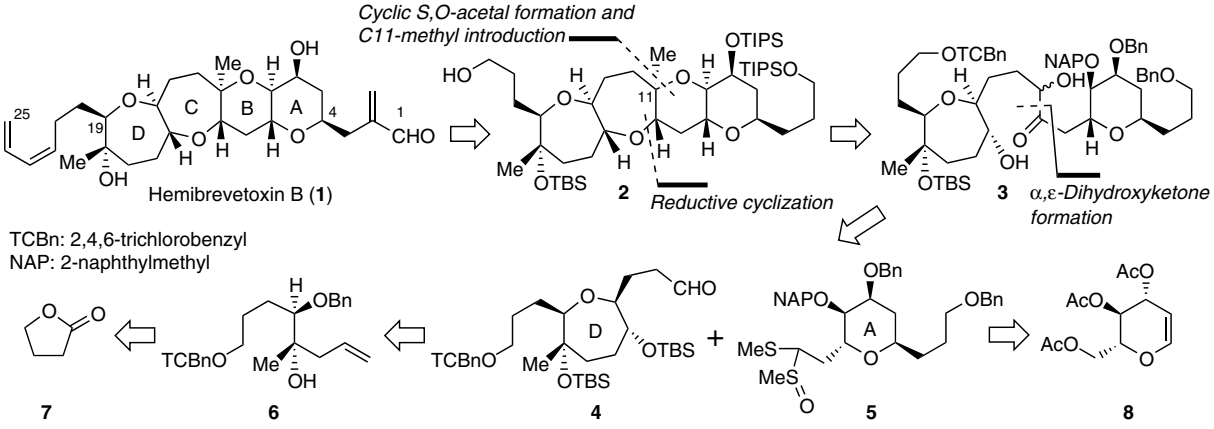
Abstract—Concise construction of the *trans*-fused 7/7/6/6 tetracyclic ether part of hemibrevetoxin B (**1**) was achieved by a convergent strategy based on coupling reaction of an acyl anion equivalent, reductive cyclization of an α,ε-dihydroxyketone, and introduction of a methyl group at the central ring junction by the Nicolaou method. The resultant tetracyclic ether was transformed into the known intermediate, which was already converted to **1** by the Yamamoto group, thereby completing the formal total synthesis of **1**.

Hemibrevetoxin B (**1**), isolated as a congener of brevetoxins from dinoflagellate *Gymnodinium breve* by Prasad and Shimizu in 1989,[1] has a *trans*-fused 7/7/6/6 tetracyclic ether structure. So far, many research groups have finished the total synthesis of **1**.[2] Notably, all of them, except the Holton group,[2k] adopted a linear synthetic strategy, though a convergent strategy would have comparable efficiency even in the synthesis of such small polyether. In this context, synthesis of **1** through a convergent strategy, which would allow the large-scale preparation of **1**, was planned. Here, a concise formal total synthesis of **1** from the A- and D-ring segments (**5** and **4**, respectively) is described.

Our synthetic plan, illustrated in Scheme 1, focuses on a short-step construction of the central BC-ring part of **1**. We envisioned the synthesis of tetracyclic ether **2**, which was already converted to **1** by the Yamamoto group,[2d]



Scheme 1.

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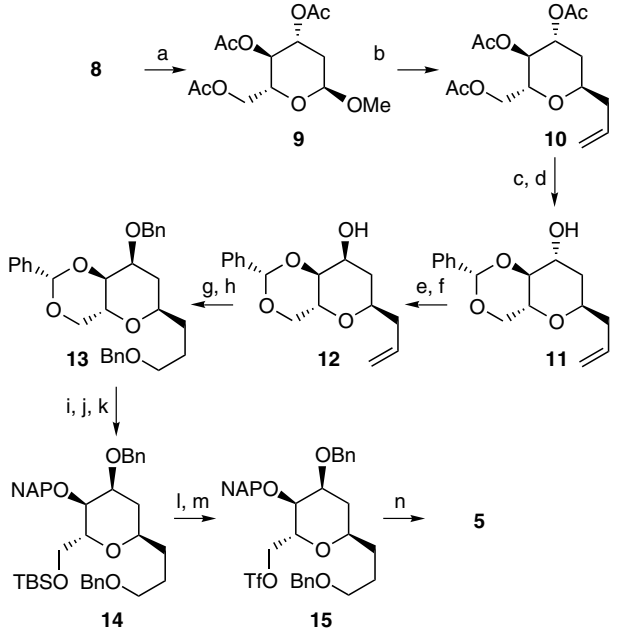
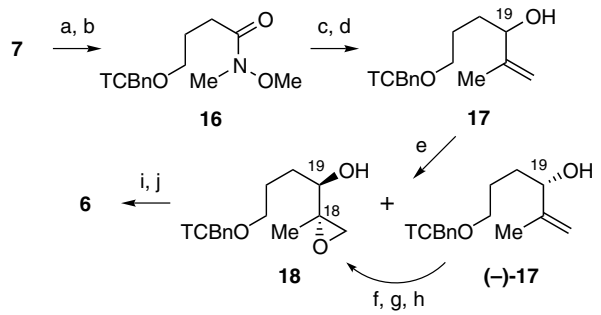
through reductive cyclization of α,ε-dihydroxy ketone **3**[3,4b,c] followed by *S*,*O*-acetal formation and introduction of a methyl group at C11 according to the Nicolaou procedure.[5] The intermediate **3** would be constructed by a coupling reaction of the A-ring **5** having a dimethyldithioacetal mono-*S*-oxide group as an acyl anion equivalent with the D-ring **4**, and the subsequent deprotection.[4,6] The D-ring **4** could be synthesized from γ-butyrolactone **7** via **6** and the A-ring **5** could be prepared from tri-*O*-acetyl D-glucal **8**.

Synthesis of **5** is shown in Scheme 2. Transformation of **8** into methyl acetal **9** under the Yadav conditions[7] followed by allylation gave **10** as a single stereoisomer in 63% yield for two steps. The triacetate **10** was subjected to methanolysis and the subsequent selective protection of the 1,3-diol part to produce **11** in 70% overall yield, in which the free α-hydroxy group was inverted through Swern oxidation[8] followed by reduction with K-Selectride to afford **12** in 95% yield for two steps. Conversion of **12** to a diol by hydroboration/oxidation and protection of the resulting diol part provided **13** in 55% overall yield. The benzylidene acetal part of **13** was removed to give a diol, which was selectively protected with a TBS group at a primary hydroxy group and with a 2-naphthylmethyl (NAP) group[9] at a secondary hydroxy group to



Scheme 2. Reagents and conditions: (a) MeOH, NaI, $CeCl_3 \cdot 7H_2O$, MeCN, reflux, 3.5 h, 66%; (b) allyltrimethylsilane, TMSOTf, MeCN, 0 → 23 °C, 1.5 h, 96%; (c) NaOMe, MeOH, 0 → 23 °C, 3 h, 88%; (d) PhCHO, $TsOH \cdot H_2O$ (cat.), PhH–DMF (3:1), reflux, 7 h, 79%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 → 0 °C, 30 min, 100%; (f) K-Selectride, THF, −78 °C, 1 h, 95%; (g) 9-BBN, THF, 23 °C, 1 h, then TBHP, 3 M NaOH, 0 → 23 °C, 40 min; (h) BnBr, ^{t}BuOK, Bu_4NI, THF, 23 °C, 4 h, 55% from **12**; (i) 6 M HCl–THF (1:1), 23 °C, 10 h, 94%; (j) TBSCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 160 min, 99%; (k) NAPBr, NaH, Bu_4NI, THF, 0 → 25 °C, 14 h, 100%; (l) TBAF, THF, 25 °C, 2 h, 99%; (m) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, 30 min, 100%; (n) $MeSCH_2S(O)Me$, BuLi, THF, −78 °C, 20 min, then **15**, −78 → −20 °C, 30 min, 96%.

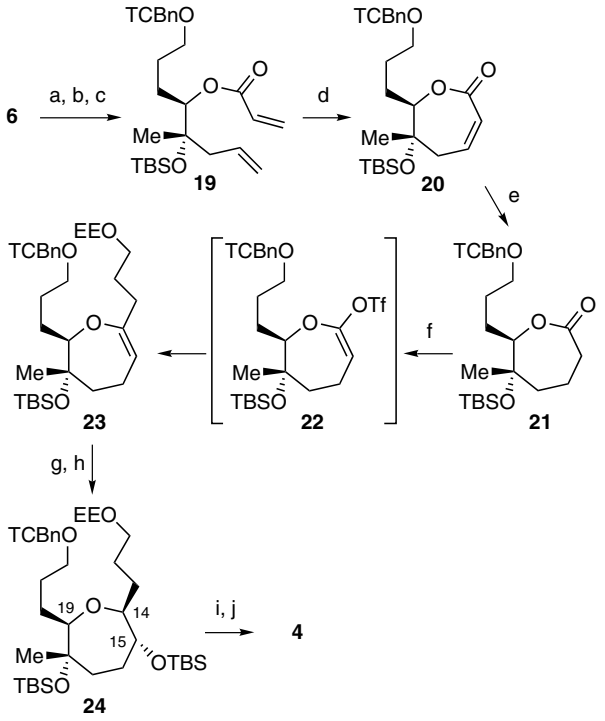


Scheme 3. Reagents and conditions: (a) HNMe(OMe)·HCl, $AlMe_3$, CH_2Cl_2, 0 °C, 3 h; (b) NaH, DMF, 2,4,6-trichlorobenzyl bromide, 0 → 23 °C, 4 h, 84%; (c) isopropenyl magnesium bromide, THF, −78 → −20 °C, 4 h, 98%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 22 °C, 1 h, 98%; (e) (−)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −25 °C, 12 h, (−)-**17**: 47% (97% ee), **18**: 44% (88% ee); (f) $PhCO_2H$, DEAD, Ph_3P, THF, 23 °C, 6.5 h, 77% (92% ee); (g) DIBAH, CH_2Cl_2, −78 °C, 30 min, 98%; (h) $VO(acac)_2$, TBHP, PhH, 23 °C, 6.5 h, 80%; (i) NaH, BnBr, Bu_4NI, THF, 0 → 23 °C, 17 h, 100%; (j) $Sn(CH{=}CH_2)_4$, BuLi, THF, −78 °C, 1 h, then CuCN, −78 °C, 10 min, then $BF_3 \cdot OEt_2$, −78 °C, 10 min, then benzyl ether of **18**, −78 → 0 °C, 80 min, 99%.

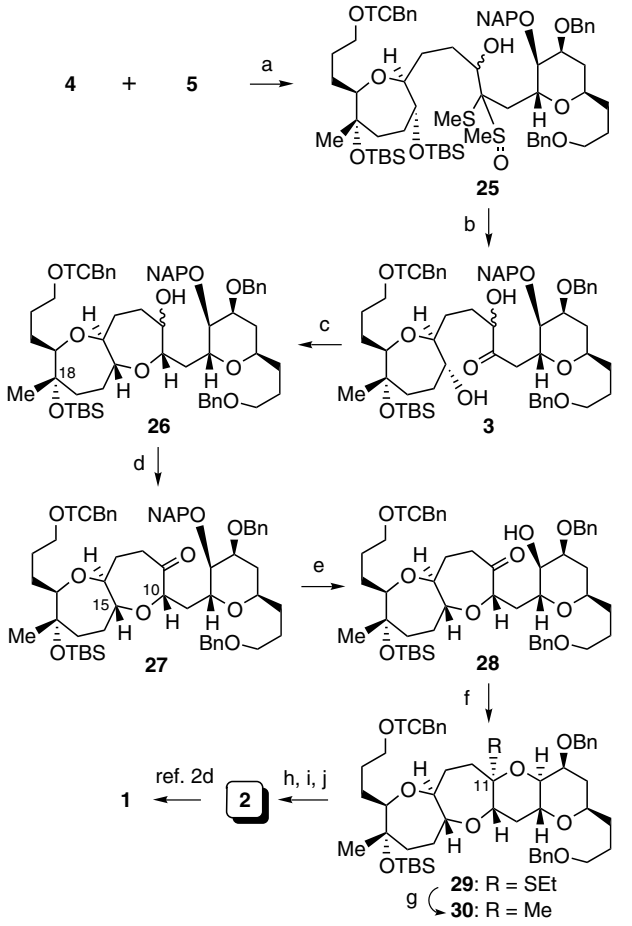
afford **14** in 93% yield for three steps. The TBS group of **14** was removed and the resulting alcohol was treated with Tf_2O to give **15** (99%), which was converted to **5** by a substitution reaction with lithiated methyl methylthiomethyl sulfoxide in 96% yield. Thus, the A-ring segment **5** was obtained in 14 steps in 20% overall yield from **8**.

In the preparation of **6**, depicted in Scheme 3, we employed Sharpless asymmetric epoxidation for kinetic resolution of **17** in order to construct the stereocenters at C18 and C19 of **6**.[10] The allyl alcohol **17** was provided by a four-step process from **7** [Weinreb amidation,[11] 2,4,6-trichlorobenzyl (TCBn) protection, addition of isopropenyl magnesium bromide, and Luche reduction][12] in 81% overall yield. When **17** was treated with (−)-diisopropyl tartrate and *tert*-butyl hydroperoxide in the presence of $Ti(O^iPr)_4$ at −25 °C, the desired epoxide **18** was obtained in 88% ee (44% yield) along with recovered (−)-**17** as an optically active form in 97% ee (47% yield).[13] The antipodal (−)-**17** was also convertible to **18** through a three-step process including Mitsunobu reaction,[14] benzoyl deprotection, and diastereoselective epoxidation[15] (92% ee and 60% overall yield).[13,16] The optically active **18**[17] was protected as a benzyl ether and treated with a higher-order divinylcyanocuprate in the presence of $BF_3 \cdot OEt_2$[18] to give **6** in 99% yield for two steps.

Construction of the D-ring **4** from **6** is shown in Scheme 4. Transformation of **6** into **19** (87% overall yield) through a three-step process [protection of the tertiary alcohol with a TBS group, removal of the benzyl group, and formation of an acryloyl ester] followed by a ring-closing olefin metathesis reaction using the second-generation Grubbs' catalyst[19] produced α,β-unsaturated lactone **20** (89% from **19**), which was reduced to **21** in quantitative yield. The lactone **21** was converted to cyclic vinyl triflate **22**, which was treated in situ with a



Scheme 4. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 → 23 °C, 9 h, 99%; (b) DDQ, CH_2Cl_2–H_2O (10:1), 23 °C, 14.5 h, 93%; (c) acryloyl chloride, $^iPr_2NEt$, CH_2Cl_2, 0 → 25 °C, 4 h, 94%; (d) $[(MesNCH_2)_2C](Cy_3P)Cl_2Ru{=}CHPh$ (cat.), $(CH_2Cl)_2$, reflux, 14 h, 89%; (e) H_2, 5% Pt/C, EtOAc, 23 °C, 5 h, 100%; (f) KHMDS, HMPA, THF, −78 °C, 2 h, then $PhNTf_2$, −78 °C, 1 h, then EE-$OCH_2CH_2CH_2MgBr$, CuI, Me_2S, −78 → −40 °C, 13.5 h; (g) thexylborane, THF, 0 °C, 13.5 h, then 3 M NaOH, TBHP, 0 → 23 °C, 1.5 h, 65% from **21**; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 → 23 °C, 6 h, 100%; (i) PPTS (cat.), MeOH, 23 °C, 8 h, 87%; (j) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 → 0 °C, 30 min, 100%.



Scheme 5. Reagents and conditions: (a) **5**, LDA (1 equiv), THF, −78 °C, 15 min, then **4** (0.37 equiv), −78 °C, 15 min, 86%; (b) TFA–THF–H_2O (1:5:5), 0 → 23 °C, 7.5 h, 71%; (c) TMSOTf, Et_3SiH, MS4A, CH_2Cl_2, −20 °C, 10 min, 65%; (d) DMPI, CH_2Cl_2, 25 °C, 1 h, 100%; (e) DDQ, CH_2Cl_2–MeOH–H_2O (40:10:1), 0 → 25 °C, 1 h, 93%; (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, 0 → 23 °C, 6.5 h, 85% (after three cycles); (g) *m*CPBA, CH_2Cl_2, 0 °C, 30 min, then $AlMe_3$, 0 °C, 1 h, 92%; (h) DDQ, CH_2Cl_2–H_2O (10:1), 25 °C, 5 h, 65%; (i) TIPSOTf, 2,6-lutidine, DMF, 70 °C, 5 h; (j) H_2, 10% Pd/C, EtOH, 25 °C, 2 h, 83% (two steps).

Grignard reagent, prepared from protected 3-bromopropanol, in the presence of copper iodide to afford cyclic vinyl ether **23**.[20] Hydroboration of **23** with thexylborane and the subsequent oxidation provided **24** stereoselectively in 65% overall yield from **21**. Deprotection followed by Swern oxidation[8] gave **4** in 87% yield for two steps.[17] The D-ring **4** was, thus, synthesized in 20 steps including the stereochemical inversion process in 20% overall yield from **7**.

Assembly of the ABCD-ring part is outlined in Scheme 5. Deprotonation of **5** with LDA followed by the reaction with **4** (0.37 equiv) produced **25** as a mixture of diastereomers (86% yield from **4**, 57% recovery of **5**). The TBS and methylthio methysulfinyl acetal groups of **25** were removed under less acidic conditions to give **3** (71% yield), which was cyclized by short-time (within 10 min) treatment with Et_3SiH in the presence of TMSOTf at −20 °C to produce **26** as a mixture of two diastereomers in 65% yield.[3,4,17,21] The alcohol **26** was oxidized with Dess–Martin periodinane[22] to give the desired **27** as a single stereoisomer (100% yield), the stereochemistry of which was confirmed by the presence of NOE between H10 and H15. The NAP group of **27** was removed with DDQ to afford **28** in 93% yield.[9]

Reaction of **28** with EtSH and $Zn(OTf)_2$ in CH_2Cl_2 did not complete even after 27 h and gave cyclic *S,O*-acetal **29** in 56% yield along with recovered **28** (42%); therefore, the process was repeated twice in order to obtain a reasonable amount of **29** (85% yield after three cycles).[23] Introduction of an angular methyl group at C11 was performed by oxidation of **29** with *m*CPBA followed by in situ treatment with $AlMe_3$ according to the Nicolaou procedure to produce **30** in 92% yield.[5] The tetracyclic **30** was converted to **2** $\{[\alpha]_D^{25}$ +23.6 ($CHCl_3$, *c* 0.29)$\}$ in 54% total yield through a three-step process including selective debenzylation, TIPS protection, and TCBn deprotection. The spectral data (^1H and ^{13}C NMR as well as IR) and optical rotation of the resulting **2** agreed well with those of the literature.[2d,h] Thus, the A- and D-ring segments (**5** and **4**) were convergently assembled into the ABCD-ring part **2** (16% overall yield for 10 steps from **4**), which was already converted to **1** by the Yamamoto group,[2d] thereby completing the formal total synthesis of **1**.

In conclusion, the concise construction of the *trans*-fused 7/7/6/6 tetracyclic ether (ABCD-ring) part **2** of hemibrevetoxin B (**1**) from the A- and D-ring segments (**5** and **4**) was achieved by a convergent process including coupling reaction of the acyl anion equivalent **5** with **4**, reductive cyclization of α,ε-dihydroxyketone **3**, and introduction of a methyl group at the central ring junction of **29** by the Nicolaou method.

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16. Slight lowering of the enantiomeric purity was observed in the Mitsunobu reaction step.
17. Since epoxide **18** was used as it stood (88–92% ee), the optical purity of **4** was same as that of **18**. Although the minor enantiomer of **4** produced small amounts of undesired diastereomers, which were inseparable from **25**, in the connection reaction with **5**, these were facilely separated from **26** at the C-ring cyclization step.
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23. The cyclic *S,O*-acetal formation reaction of **28** usually stopped at about 50% conversion after 6 h. Several attempts to improve the yield (changing solvent to MeCN or $MeNO_2$, heating, or changing concentration of **28** and reagents) showed no effect.