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Synthesis of the BC/DE ring model of brevisin for confirmation of the structure around the acyclic junction

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ABSTRACT

Synthesis of the BC/DE ring model of brevisin, a polycyclic ether isolated from the red tide dinoflagellate *Karenia brevis*, is reported. Comparison of the NMR data of the BC/DE ring model with those corresponding to the same region of brevisin led to the confirmation of its structure around the acyclic juncture.

Polycyclic ethers, such as brevetoxins and ciguatoxins, are a group of the most representative secondary metabolites produced by dinoflagelates.[1] These compounds have been of great interest to many scientific groups because of their biological activity, their unusual structures, unique aspects of their biosynthesis, and because of the synthetic challenges that they present.[2] A new polycyclic ether, brevisin[3] (**1**, Fig. 1), was isolated from the red tide dinoflagellate, *Karenia brevis* that produces cyclic ether compounds, the brevetoxins,[2,4] brevenal,[5] and brevisamide.[6,7] Its unique structure consists of two tricyclic ether ring assemblies bridged by a methylene group. One of the ring assemblies contains a conjugated aldehyde side chain, which is similar to brevenal and brevisamide. The separated polycyclic ether skeleton in the center of **1** is unusual among marine polycyclic ethers.[1] Although the stereochemistry of each tricyclic ether moiety could be elucidated separately by NMR experiments, the stereochemical correlation between the ABC ring and the DEF ring portions in **1** could not be elucidated. The absolute configuration of **1** was determined as shown in Figure 1 by esterification of the hydroxy groups at C10 and C31 in **1** with the MTPA reagents.[8,9] Interestingly, even though **1** does not have flexible nine- or eight-membered ether rings in the middle of the molecule, **1** inhibited the binding of [^{3}H]-PbTx-3 to the voltage-sensitive sodium channels (VSSCs) analogous with other marine polycyclic ethers.[10] The methylene-linked structure is presumed to generate molecular flexibility which plays an important role in an interaction with VSSC. In order to elucidate the interaction of **1** with VSSC, structural and stereochemical confirmation of the linked methylene portion in **1** is essential. Comparison of NMR chemical shifts of a synthetic model with those of a corresponding domain of a naturally occurring compound is a well-recognized approach in the structural confirmation and stereochemical assignment of complex molecules.[11–13] Herein we report the chemical synthesis of the BC/DE ring model **2** (Fig. 1) and comparison of its NMR chemical shifts with those corresponding to the same region of natural brevisin for confirmation of the structure around the acyclic junction in **1**.

The synthetic plan employed was to build up the BC ring fragment **4** from the lactone **6**[14] and the E ring fragment **5** from the oxepane **7**,[15] couple these fragments by means of an aldol reaction, and then construct the D ring by a reductive etherification (Scheme 1).[16]

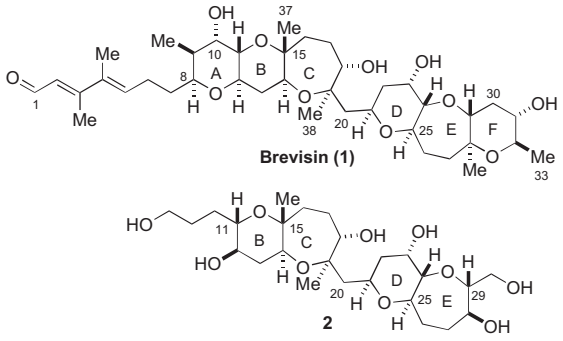

Figure 1. Structures of **1** and **2**.

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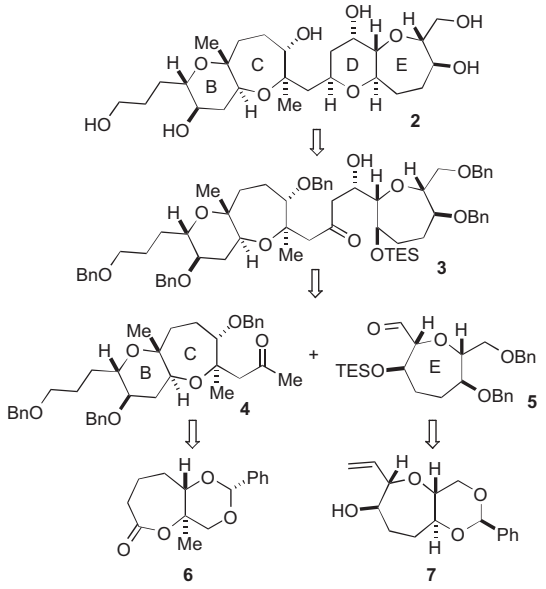
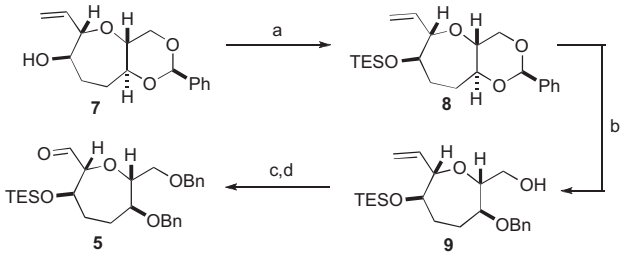


Scheme 1. Retrosynthetic analysis of **2**.

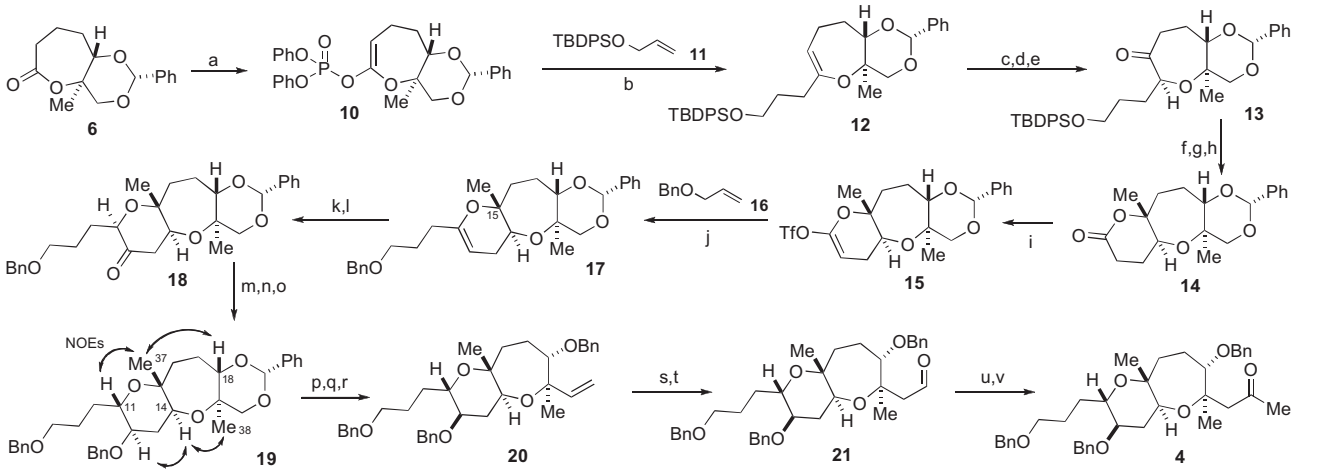
The synthesis of the E ring fragment **5** started from the TES protection of oxepane **7** with TESOTf to provide the TES ether **8**, and regioselective DIBALH reduction[17] of **8** gave alcohol **9**. Benzylation of **9** and subsequent ozonolysis gave the E ring aldehyde **5** in 51% yield for the four steps (Scheme 2).

The synthesis of the BC ring fragment **4** is summarized in Scheme 3. Treatment of lactone **6** with KHMDS and $(PhO)_2P(O)Cl$ gave the corresponding ketene acetal phosphate **10**. Hydroboration of the allyl TBDPS ether **11** gave an alkylborane which was reacted in situ with **10** under the Suzuki–Miyaura coupling condition[2c,18] to generate the enol ether **12**. Hydroboration of the enol ether **12** with $BH_3{\cdot}SMe_2$ gave a mixture of the stereoisomers, and subsequent oxidation of the mixture using TPAP–NMO[19] followed by treatment with DBU led to the ketone **13** as a single stereoisomer in 69% yield for three steps. Steric hinderance arising from the axial methyl group caused the low stereoselectivity in the hydroboration of **12**. The methylation of **13** with MeMgBr in toluene at



Scheme 2. Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 94%; (b) DIBALH, CH_2Cl_2, 0 °C to rt, 67%; (c) BnBr, ^{t}BuOK, TBAI, THF; (d) O_3, CH_2Cl_2, −78 °C; then PPh_3, 81% (two steps).

−78 °C[20] followed by the removal of TBDPS group with TBAF afforded the diol in 77% yield. The 1,5-diol was directly oxidized to lactone **14** by TEMPO/$PhI(OAc)_2$.[21] Treatment of the lactone **14** with KHMDS, Tf_2NPh, and DMPU gave the corresponding ketene acetal triflate **15**. Hydroboration of the allyl benzyl ether **16** gave the alkylborane which was reacted in situ with **15** under the Suzuki–Miyaura coupling condition to generate the enol ether **17**. Hydroboration of **17** with $BH_3{\cdot}SMe_2$ gave the unwanted stereoisomer as the sole product, and oxidation of the resulting alcohol with TPAP–NMO afforded the ketone **18** in 62% yield for two steps. It is likely that the undesired stereoselectivity following hydroboration of **17** was caused by the presence of an axial methyl group on C-15, as observed with **12**.[22] The ketone **18** was treated with DBU, reduced with $NaBH_4$, and the resulting alcohol was protected with the benzyl group to furnish the BC ring **19** as a single stereoisomer in 77% yield for three steps. The relative configurations of **19** were confirmed by the observed NOE correlations H-11/H_3-37, H-18/ H_3-37, H-12/H-14, and H-14/ H_3-38, and by the large proton coupling constant of 8.8 Hz between H-11 and H-12. After the regioselective DIBALH reduction of **19**, oxidation in CH_2Cl_2–DMSO with $SO_3{\cdot}$pyridine and subsequent Wittig reaction of the resulting aldehyde generated the olefin **20**. Hydroboration of **20** with 9-BBN-H followed by oxidation with $SO_3{\cdot}$pyridine/Et_3N/DMSO afforded the aldehyde **21**, which was treated with MeMgBr followed by oxidation of the resulting alcohol with TPAP/NMO to furnish the BC ring-methyl ketone fragment **4**.

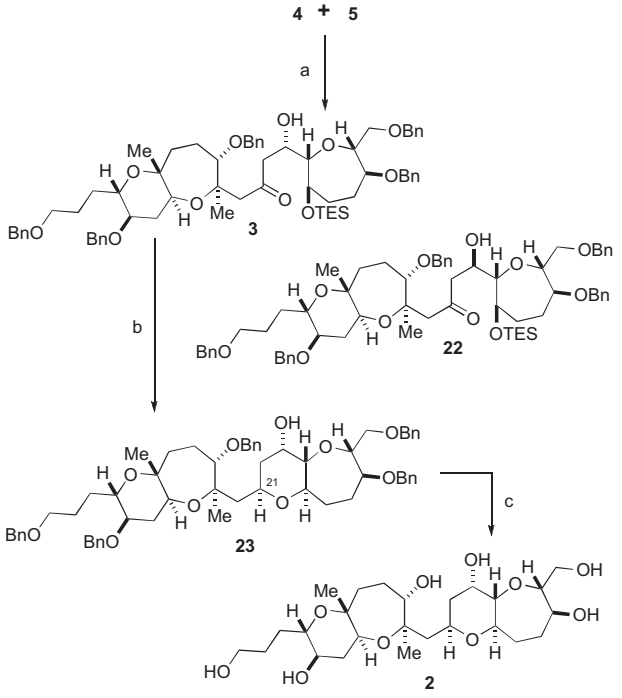


Scheme 3. Reagents and conditions: (a) KHMDS, $(PhO)_2P(O)Cl$, HMPA, THF, −78 °C, 97%; (b) **11**, 9-BBN-H, THF; then **10**, 3 M Cs_2CO_3 aq, $Pd(PPh_3)_4$, DMF, 50 °C, 87%; (c) $BH_3{\cdot}SMe_2$, THF, 45 °C; then satd $NaHCO_3$ aq, H_2O_2; (d) TPAP, NMO, MS4A, CH_2Cl_2; (e) DBU, toluene, 110 °C, 69% (three steps); (f) MeMgBr, toluene, −78 °C; (g) TBAF, THF; (h) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 61% (three steps); (i) KHMDS, Tf_2NPh, DMPU, THF, −78 to 0 °C; (j) **16**, 9-BBN-H, THF; then **15**, 3 M Cs_2CO_3 aq, $Pd(PPh_3)_4$, DMF, 88% (two steps); (k) $BH_3{\cdot}SMe_2$, THF; then satd $NaHCO_3$ aq, H_2O_2; (l) TPAP, NMO, MS4A, CH_2Cl_2, 62% (two steps); (m) DBU, CH_2Cl_2; (n) $NaBH_4$, MeOH, CH_2Cl_2, −78 °C; (o) ^{t}BuOK, BnBr, TBAI, THF, 77% (three steps); (p) DIBALH, CH_2Cl_2, 0 °C to rt; (q) $SO_3{\cdot}$pyridine, Et_3N, DMSO, CH_2Cl_2; (r) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 76% (three steps); (s) 9-BBN-H; then satd $NaHCO_3$ aq, H_2O_2; (t) $SO_3{\cdot}$pyridine, Et_3N, DMSO, CH_2Cl_2, 85% (two steps); (u) MeMgBr, THF, 0 °C; (v) TPAP, NMO, MS4A, CH_2Cl_2, 99% (two steps).

Coupling of the BC ring fragment **4** and the E ring fragment **5** and subsequent construction of the D ring were accomplished, as shown in Scheme 4. Treatment of the lithium enolate derived from **4** with aldehyde **5** furnished a separable 1:1 mixture of C-23 diastereomers **3** and **22**.[23] The ketone **3** was reduced stereoselectively[16] with Et_3SiH in the presence of TMSOTf to afford the benzyl-protected BC/DE ring **23**. The orientation of H-21 in **23** was confirmed by a ROESY cross-peak H-21/H-25. Finally, removal of the benzyl groups of **23** furnished the BC/DE ring model **2**.[24]

The NMR chemical shifts from CH-14 to CH-25 of **2** were compared with those of brevisin (**1**), as listed in Table 1. The observed chemical shifts of **2** agreed well with those of **1**, although there are relatively large differences in the B ring and the E ring regions (C-15, C-37, C-24, and C-25) which are to be expected due to the absence of the A ring and the F ring. The maximum difference of ^{13}C NMR chemical shifts around the methylene juncture (C-18, C-19, C-38, C-20, C-21, and C-22) is 0.3 ppm. The NMR spectral data of the synthetic BC/DE ring model bore a strong similarity to the data for the same region of brevisin, supporting the unique structure of brevisin around the methylene juncture.

The BC/DE ring model of brevisin was synthesized based on a convergent strategy by means of aldol coupling and the subsequent construction of the D ring. We already succeeded in the synthesis of the ABC ring of **1** via the Suzuki–Miyaura cross-coupling.[25] Therefore, this result will accelerate the total synthesis of this intriguing molecule.



Scheme 4. Reagents and conditions: (a) LDA, THF, −78 °C, 42% (82% br sm), 20% for **3**, 21% for **22**, 50% for recovered **4**; (b) Et_3SiH, TMSOTf, CH_2Cl_2, −78 °C, 62%; (c) Pd/C, H_2, THF, 99%.

Table 1
NMR chemical shifts (δ) from the CH-14 to CH-25 of brevisin (**1**), the BC/DE ring model **2**, and their differences ($\Delta\delta$) in pyridine-d_5

Pos.	^1H			^{13}C		
	2	**1**	$\Delta\delta$	**2**	**1**	$\Delta\delta$
14	4.42	4.42	0.00	71.6	71.6	0.0
15				77.0	78.8	−1.8
37	1.49	1.54	−0.05	16.4	16.7	−0.3
16a	2.70	2.70	0.00	35.7	35.8	−0.1
16b	1.75	1.75	0.00			
17a	2.06	2.05	0.01	26.7	26.8	−0.1
17b	2.06	2.04	0.02			
18	4.47	4.45	0.02	73.2	73.5	−0.3
19				80.9	81.1	−0.2
38	1.68	1.66	0.02	21.9	21.8	0.1
20a	1.97	1.96	0.01	48.0	48.0	0.0
20b	1.75	1.72	0.03			
21	4.46	4.40	0.06	68.9	68.9	0.0
22ax	2.01	2.03	−0.02	41.1	40.8	0.3
22eq	1.67	1.69	−0.02			
23	4.48	4.37	0.11	67.7	67.9	−0.2
24	3.62	3.33	0.29	84.9	83.8	1.1
25	4.10	4.03	0.07	75.4	74.8	0.6

Acknowledgments

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22. The carbon numbering corresponds to that of brevisin **1** (Fig. 1).
23. The stereochemistry of the newly generated hydroxy group at the C-23 of **3** and **22** was assigned after the construction of the D ring. The proton coupling constant (3 Hz) between H-23 and H-24 in **23** indicated the axial orientation of the hydroxy group at C-23.
24. *Data for* **2**: $[\alpha]_D^{18}$ − 3.1 (*c* 0.091, MeOH); ^{1}H NMR (500 MHz, pyridine-d_5) δ 4.54–4.45 (m, 3H), 4.42 (dd, *J* = 12.2, 4.6 Hz, 1H), 4.34–4.28 (m, 1H), 4.21 (dd, *J* = 10.5, 2.9 Hz, 1H), 4.15–4.03 (m, 3H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.77–3.60 (m, 3H), 2.70 (dd, *J* = 13.5, 10.1 Hz, 1H), 2.62–2.51 (m, 1H), 2.49–2.32 (m, 2H), 2.27–1.95 (m, 10H), 1.92–1.64 (m, 7H), 1.49 (s, 3H), 1.42–1.16 (m, 6H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 88.7, 84.9, 80.9, 77.0, 75.4, 74.9, 73.2, 71.6, 70.6, 70.4, 68.9, 67.7, 64.9, 62.5, 48.0, 41.1, 39.1, 35.7, 30.4, 30.1, 29.5, 27.6, 26.7, 21.9, 16.4; HRMS (FAB) calcd for $C_{25}H_{44}O_{10}Na$ $[M+Na]^+$ 527.2827, found 527.2823.
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