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## **Total Synthesis of the Proposed Structure of Brevenal**

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Brevenal is a pentacyclic polyether natural product isolated from the red tide-forming dinoflagellate, *Karenia brevis*.<sup>1</sup> Its gross structure and relative stereochemistry have been determined based on extensive NMR experiments. The biological profile of brevenal is of interest in that it competitively displaces tritiated dihydrobrevetoxin-B ([<sup>3</sup>H]PbTx-3) from voltage-sensitive sodium channels in a dose-dependent manner and acts as a natural brevetoxin antagonist in vivo.<sup>1</sup> More importantly, brevenal improved tracheal mucus velocity in picomolar concentrations in an animal model of asthma, and thus may be a source of agents for treating mucociliary dysfunction associated with cystic fibrosis and other lung disorders.<sup>2</sup> Herein, we describe the first total synthesis of the proposed structure **1** of brevenal.

Our synthetic strategy toward 1 was to build up the pentacyclic polyether core of 1 from the AB and DE ring fragments (2 and 3, respectively) by means of our developed Suzuki–Miyaura coupling-based methodology (Scheme 1).<sup>3–5</sup>

## Scheme 1. Synthetic Strategy



The synthesis of the AB ring fragment **2** started with Evans' *syn*-aldol reaction of aldehyde **4** with oxazolidinone **5**.<sup>6</sup> Subsequent reductive removal of the chiral auxiliary provided 1,3-diol **6** as a single stereoisomer (Scheme 2). Protection of **6** as its *p*-methoxy-benzylidene acetal followed by regioselective DIBALH reduction



gave alcohol **7**, which was then converted to allylic alcohol **9** via nitrile **8** by standard chemistry. Asymmetric epoxidation of **9** led to hydroxyl epoxide **10** as a single stereoisomer. Oxidation and ensuing methylenation of the resulting aldehyde gave vinyl epoxide **11**. Upon treatment of **11** with DDQ, removal of the PMB group and concomitant 6-*endo* ring closure smoothly took place,<sup>7</sup> giving rise to pyran **13** in 89% yield after TES protection. At this stage, the stereochemistry of **12** was confirmed by NOE experiments as shown. Pyran **13** was converted to enoate **14** in a four-step sequence. Hydrogenation/hydrogenolysis of **14** followed by Yamaguchi lactonization<sup>8</sup> gave lactone **15**, which was then transformed to the AB ring enol phosphate **2**.<sup>9</sup>

The synthesis of the DE ring fragment 3 is summarized in Scheme 3. Benzylation of the known oxepane 16,<sup>10</sup> corresponding to the D ring, followed by ozonolysis/reductive workup gave alcohol 17. The primary alcohol of 17 was benzylated, and the benzylidene acetal was removed to provide diol 18. One-pot triflation/TBS protection<sup>11</sup> and subsequent alkylation with allylMgBr/ CuBr<sup>12</sup> gave olefin **19**. Oxidative cleavage of the double bond, thioacetalization of the derived aldehyde, and removal of the TBS group led to alcohol 20. Hetero-Michael reaction with methyl propiolate followed by hydrolysis of the thioacetal afforded aldehvde 21, which upon exposure to SmI<sub>2</sub> (MeOH/THF) furnished tricyclic lactone 22 as a single stereoisomer after acidic treatment.<sup>13</sup> DIBALH reduction and Wittig reaction, followed by oxidation,14 led to ketone 23. The C26 equatorial methyl group was introduced by treating 23 with MeLi (THF, -78 to 0 °C), giving 24 stereoselectively (dr > 10:1).<sup>15</sup> The C26 and C27<sup>16</sup> stereochemistries were confirmed by NOEs. The tertiary alcohol was silvlated to give TBS ether 25. Hydroboration, hydrogenolysis of the benzyl groups, and ensuing acetal formation led to 26. Benzylation followed by regioselective cleavage of the acetal moiety provided alcohol 27. Finally, iodination followed by base treatment furnished the DE fragment 3.



<sup>*a*</sup> Reagents and conditions: (a) *n*-Bu<sub>2</sub>BOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 to 0 °C; (b) NaBH<sub>4</sub>, THF/H<sub>2</sub>O, 0 °C to rt, 90% (two steps); (c) *p*-MeOC<sub>6</sub>H<sub>4</sub>CH(OMe)<sub>2</sub>, PPTS, CH<sub>2</sub>Cl<sub>2</sub>, rt; (d) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78 to -40 °C, 94% (two steps); (e) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (f) NaCN, DMSO, 60 °C, 96% (two steps); (g) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 90%; (h) Ph<sub>3</sub>P=C(Me)CO<sub>2</sub>Et, toluene, 80 °C, 97%; (i) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, quant; (j) (+)-DET, Ti(O*i*-Pr)<sub>4</sub>, *t*-BuOOH, CH<sub>2</sub>Cl<sub>2</sub>, -40 °C, 88%; (k) SO<sub>3</sub>•pyridine, Et<sub>3</sub>N, DMSO/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (l) Ph<sub>3</sub>PCH<sub>3</sub>Br, NaHMDS, THF, 0 °C, 90% (two steps); (m) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, rt; (n) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 89% (two steps); (o) (Sia)<sub>2</sub>BH, THF, 0 °C; then aq. NaHCO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, rt, 92%; (p) SO<sub>3</sub>•pyridine, Et<sub>3</sub>N, DMSO/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (q) Ph<sub>3</sub>P=CHCO<sub>2</sub>Bn, toluene, 80 °C, 86% (two steps); (r) aq. HCl, THF, rt, 95%; (s) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, 2:1 THF/MeOH, rt, 90%; (t) 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl, Et<sub>3</sub>N, THF, 0 °C to rt; then DMAP, toluene, 110 °C, 98%; (u) KHMDS, (PhO)<sub>2</sub>P(O)Cl, HMPA/THF, -78 °C, 96%.

9648 J. AM. CHEM. SOC. 2006, 128, 9648-9650

Scheme 3. Synthesis of the DE Ring Fragment<sup>a</sup>



<sup>*a*</sup> Reagents and conditions: (a) NaH, BnBr, DMF, 0 °C to rt; (b) O<sub>3</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; then NaBH<sub>4</sub>, -78 to 0 °C, 96% (two steps); (c) KO*t*-Bu, BnBr, THF, rt; (d) *p*-TsOH, MeOH/CHCl<sub>3</sub>, rt, quant. (two steps); (e) Tf<sub>2</sub>O, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; then TBSOTf, -78 to 0 °C; (f) allylMgBr, CuBr, ether, 0 °C, 85% (two steps); (g) OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O, rt; then NaIO<sub>4</sub>, rt; (h) 1.3-propanedithiol, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 to 0 °C; (i) TBAF, THF, rt, 88% (three steps); (j) methyl propiolate, NMM, CH<sub>2</sub>Cl<sub>2</sub>, rt; (k) MeI, NaHCO<sub>3</sub>, MeCN/H<sub>2</sub>O, rt, 99% (two steps); (l) Sml<sub>2</sub>, MeOH, THF, rt; then *p*-TsOH, toluene, 80 °C, 84% (two steps); (m) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (n) Ph<sub>3</sub>PCH<sub>3</sub>Br, NaHMDS, THF, 0 °C to rt, 94% (two steps); (o) TPAP, NMO, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>, rt, 97%; (p) MeLi, THF, -78 to 0 °C, 97% (dr > 10:1); (q) TBSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, quant.; (r) 9-BBN, THF, rt; then aq. NaHCO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, 0 °C to rt; (s) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, rt; (t) *p*-MeOC<sub>6</sub>H<sub>4</sub>CH(OMe)<sub>2</sub>, PTS, CH<sub>2</sub>Cl<sub>2</sub>, rt, 80% (three steps); (u) KO*t*-Bu, BnBr, THF, rt; (v) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78 to -40 °C, 85% (two steps); (w) I<sub>2</sub>, PPh<sub>3</sub>, inidazole, THF, rt; (x) KO*t*-Bu, THF, 0 °C, 99% (two steps).

Scheme 4. Synthesis of the Pentacyclic Polyether Core<sup>a</sup>



<sup>*a*</sup> Reagents and conditions: (a) 9-BBN, THF, rt; then 3 M aq.  $Cs_2CO_3$ , Pd(PPh<sub>3</sub>)<sub>4</sub>, DMF, 50 °C; (b) BH<sub>3</sub>·SMe<sub>2</sub>, THF, 0 °C to rt; then aq. NaHCO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, 0 °C to rt, 84% (two steps); (c) TPAP, NMO, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 98%; (d) LHMDS, TMSCl, Et<sub>3</sub>N, THF, -78 °C; (e) OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O, rt, 87% (two steps); (f) DIBALH, THF, -78 °C, 76% (diastereomer: 7%; **31**: 12%); (g) TESOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (h) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/pH 7 buffer, rt; (i) TPAP, NMO, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 88% (three steps); (j) EtSH, Zn(OTf)<sub>2</sub>, THF, rt, 79%; (k) TBSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 97%; (l) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; then AlMe<sub>3</sub>, -78 to 0 °C, 92%.



<sup>*a*</sup> Reagents and conditions: (a) LiDBB, THF, -78 °C, 99%; (b) TBSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 98%; (c) TBAF, AcOH, THF, rt, 78% after three recycles; (d) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt; (e) Bestmann reagent, K<sub>2</sub>CO<sub>3</sub>, MeOH, rt; (f) *n*-BuLi, THF/HMPA, -78 °C; then MeI, rt, 99% (three steps); (g) HF•pyridine, THF, 0 °C to rt, 96%; (h) TESOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 99%; (i) PhMe<sub>2</sub>SiLi, CuCN, THF, -78 to 0 °C; (j) NIS, CH<sub>3</sub>CN/THF, 0 °C to rt, 99% (two steps); (k) **42**, Pd<sub>2</sub>(dba)<sub>3</sub>, Ph<sub>3</sub>As, CuTC, 1:1 DMSO/THF, rt, 63%; (l) TBDPSCl, imidazole, DMF, 0 °C; (m) PPTS, 4:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 0 °C, 74% (two steps); (n) SO<sub>3</sub>•pyridine, Et<sub>3</sub>N, DMSO/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (o) BrPh<sub>3</sub>PCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SePh, *n*-BuLi, THF/HMPA, -78 °C to rt, 97% (two steps); (p) H<sub>2</sub>O<sub>2</sub>, NaHCO<sub>3</sub>, THF, rt, 77%; (q) TASF, DMF/THF, 0 °C to rt, 79%; (r) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, quant.

With the requisite fragments in hand, the crucial fragment coupling and subsequent ring closing events were executed, as depicted in Scheme 4. Stereoselective hydroboration of the DE ring exocyclic enol ether 3 with 9-BBN delivered the corresponding alkylborane, which was in situ reacted with the AB ring enol phosphate 2 [Cs<sub>2</sub>CO<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>] to afford the cross-coupled product 28. Hydroboration of 28 with BH<sub>3</sub>·SMe<sub>2</sub> generated alcohol 29 as a single stereoisomer, which was then oxidized<sup>14</sup> to ketone **30**. The stereochemistries of C16 and C18 were confirmed by NOE experiments. Conversion to the corresponding enol silvl ether followed by dihydroxylation delivered  $\alpha$ -hydroxy ketone 31 as a single stereoisomer. Subsequent DIBALH reduction afforded diol 32 in good selectivity (dr = ca. 10:1).<sup>15</sup> Protection as the TES ethers, removal of the PMB group, and ensuing oxidation provided ketone **33**. Exposure of **33** to EtSH/Zn(OTf)<sub>2</sub> in THF effected deprotection of the TES groups and concomitant mixed thioacetal formation to furnish 34 in 79% yield. After TBS protection, oxidation with mCPBA at -78 °C followed by in situ treatment with excess AlMe<sub>3</sub> resulted in one-pot oxidative activation of the sulfide and stereoselective methylation, giving rise to pentacyclic polyether 36 as a single stereoisomer in excellent yield.<sup>17</sup> The stereochemistry of **36** was confirmed by NOEs and  ${}^{3}J_{H,H}$  as shown.

Having constructed the polycyclic ether skeleton, we next turned our attention to introduction of the left-hand side chain. The benzyl group of 36 was replaced with the TBS ether, and selective deprotection of the TBDPS group<sup>18</sup> produced alcohol 38 (Scheme 5). Oxidation,<sup>19</sup> Bestmann alkynylation,<sup>20</sup> and subsequent methylation led to alkyne 39. At this stage, the robust TBS groups were replaced with the TES groups. Treatment of 40 with Fleming's silylcuprate reagent (PhMe2SiLi, CuCN)21 effected syn-selective silylcupration of the internal alkyne (regioselectivity = ca. 9:1). Subsequent iododesilylation with NIS<sup>22</sup> afforded vinyl iodide 41 (E:Z = ca. 6:1)<sup>15</sup> Stille coupling<sup>23</sup> of **41** with vinyl stannane **42** was best accomplished by using the Pd2(dba)3/Ph3As catalyst system in the presence of copper(I) thiophene-2-carboxylate (CuTC),24 giving allylic alcohol 43 in 63% yield as a single isomer.<sup>15</sup> After conversion to alcohol 44, oxidation and Wittig reaction, followed by peroxide treatment,<sup>25</sup> afforded diene 45. Finally, global deprotection of the silvl groups followed by selective oxidation of the C1 alcohol with MnO<sub>2</sub> furnished synthetic **1**. Unfortunately, <sup>1</sup>H and <sup>13</sup>C NMR data for 1 were not identical to those reported for the natural sample. Especially, the observed chemical shifts around the DE ring of 1 significantly deviated from those reported for the natural product. Additionally, we observed a set of intense crosspeaks between 26-Me and 27-H in a ROESY spectrum of 1, while such a correlation has not been reported for the natural brevenal (for details, see Supporting Information). On the basis of these NMR variations, along with the proposed biosynthetic pathway for marine polycyclic ethers,<sup>26</sup> we think that the correct structure of brevenal is most likely represented by the C26 epimer of the originally proposed 1.

In conclusion, we have accomplished the first total synthesis of the proposed structure of brevenal. The pentacyclic polyether core was constructed in a highly convergent and stereocontrolled manner based on our Suzuki-Miyaura coupling strategy. Stereoselective synthesis of the left-hand multi-substituted dienal side chain was

achieved by CuTC-mediated modified Stille reaction. Continuous efforts toward structural determination and total synthesis of brevenal are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds 29, 36, 43, and synthetic 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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