J|A|C|S
COMMUNICATIONS

Published on Web 07/11/2006

Total Synthesis of the Proposed Structure of Brevenal

Haruhiko Fuwa, Makoto Ebine, and Makoto Sasaki*

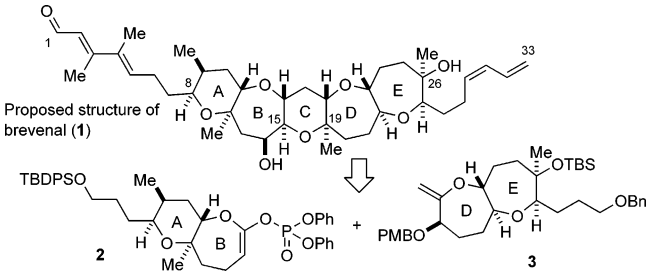
Laboratory of Biostructural Chemistry, Graduate School of Life Sciences, Tohoku University, Tsutsumidori-amamiya, Aoba-ku, Sendai 981-8555, Japan

Received April 12, 2006; E-mail: masasaki@bios.tohoku.ac.jp

Brevenal is a pentacyclic polyether natural product isolated from the red tide-forming dinoflagellate, *Karenia brevis*.[1] 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 ([^{3}H]PbTx-3) from voltage-sensitive sodium channels in a dose-dependent manner and acts as a natural brevetoxin antagonist in vivo.[1] 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.[2] 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).[3−5]

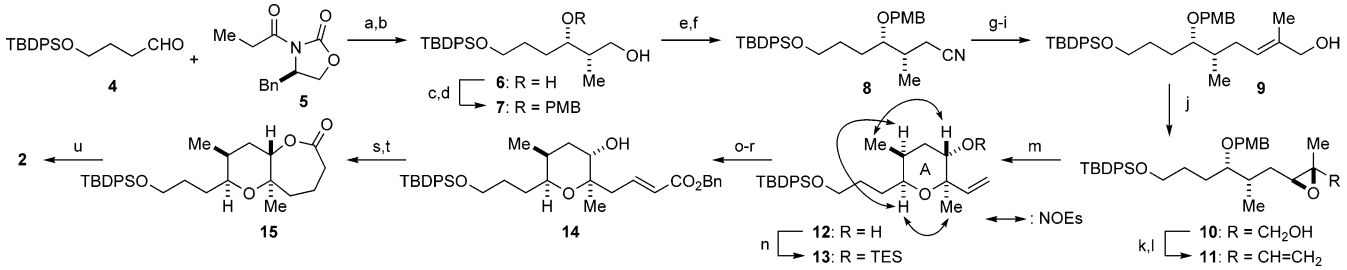
Scheme 1. Synthetic Strategy



The synthesis of the AB ring fragment **2** started with Evans' *syn*-aldol reaction of aldehyde **4** with oxazolidinone **5**.[6] Subsequent reductive removal of the chiral auxiliary provided 1,3-diol **6** as a single stereoisomer (Scheme 2). Protection of **6** as its *p*-methoxybenzylidene 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,[7] 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[8] gave lactone **15**, which was then transformed to the AB ring enol phosphate **2**.[9]

The synthesis of the DE ring fragment **3** is summarized in Scheme 3. Benzylation of the known oxepane **16**,[10] 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[11] and subsequent alkylation with allylMgBr/CuBr[12] 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 aldehyde **21**, which upon exposure to SmI_2 (MeOH/THF) furnished tricyclic lactone **22** as a single stereoisomer after acidic treatment.[13] 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).[15] The C26 and C27[16] stereochemistries were confirmed by NOEs. The tertiary alcohol was silylated 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**.

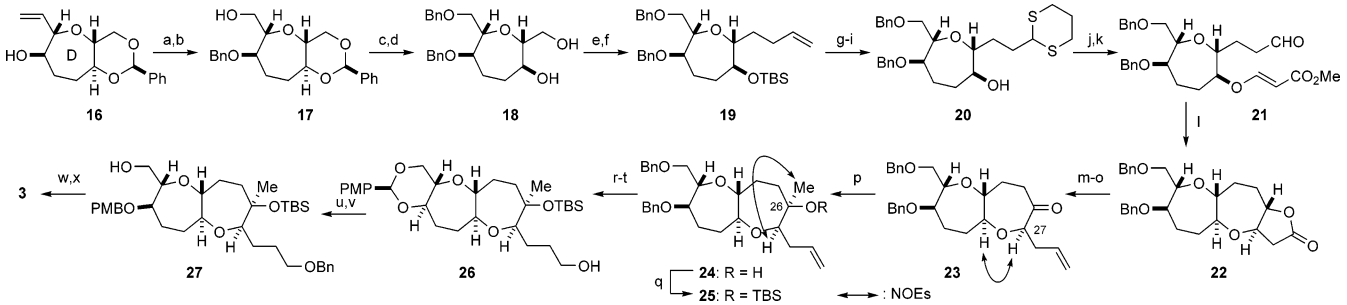
Scheme 2. Synthesis of the AB Ring Fragment[a]



[a] Reagents and conditions: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C; (b) $NaBH_4$, THF/H_2O, 0 °C to rt, 90% (two steps); (c) *p*-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, rt; (d) DIBALH, CH_2Cl_2, −78 to −40 °C, 94% (two steps); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C; (f) NaCN, DMSO, 60 °C, 96% (two steps); (g) DIBALH, CH_2Cl_2, −78 °C, 90%; (h) $Ph_3P{=}C(Me)CO_2Et$, toluene, 80 °C, 97%; (i) DIBALH, CH_2Cl_2, −78 °C, quant.; (j) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −40 °C, 88%; (k) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; (l) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 90% (two steps); (m) DDQ, CH_2Cl_2/H_2O, rt; (n) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 89% (two steps); (o) $(Sia)_2BH$, THF, 0 °C; then aq. $NaHCO_3$, H_2O_2, rt, 92%; (p) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; (q) $Ph_3P{=}CHCO_2Bn$, toluene, 80 °C, 86% (two steps); (r) aq. HCl, THF, rt, 95%; (s) H_2, $Pd(OH)_2$/C, 2:1 THF/MeOH, rt, 90%; (t) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C to rt; then DMAP, toluene, 110 °C, 98%; (u) KHMDS, $(PhO)_2P(O)Cl$, HMPA/THF, −78 °C, 96%.

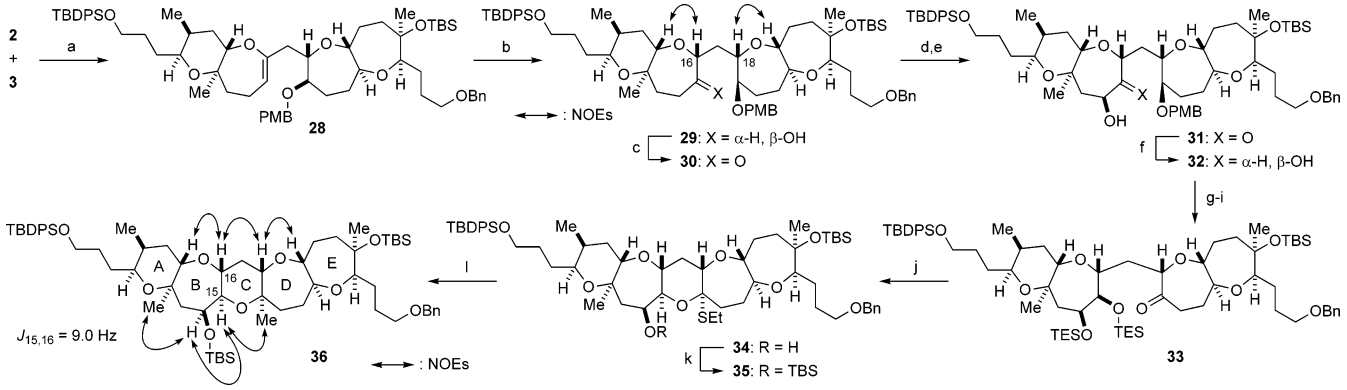
10.1021/ja062524q CCC: $33.50

Scheme 3. Synthesis of the DE Ring Fragment[a]



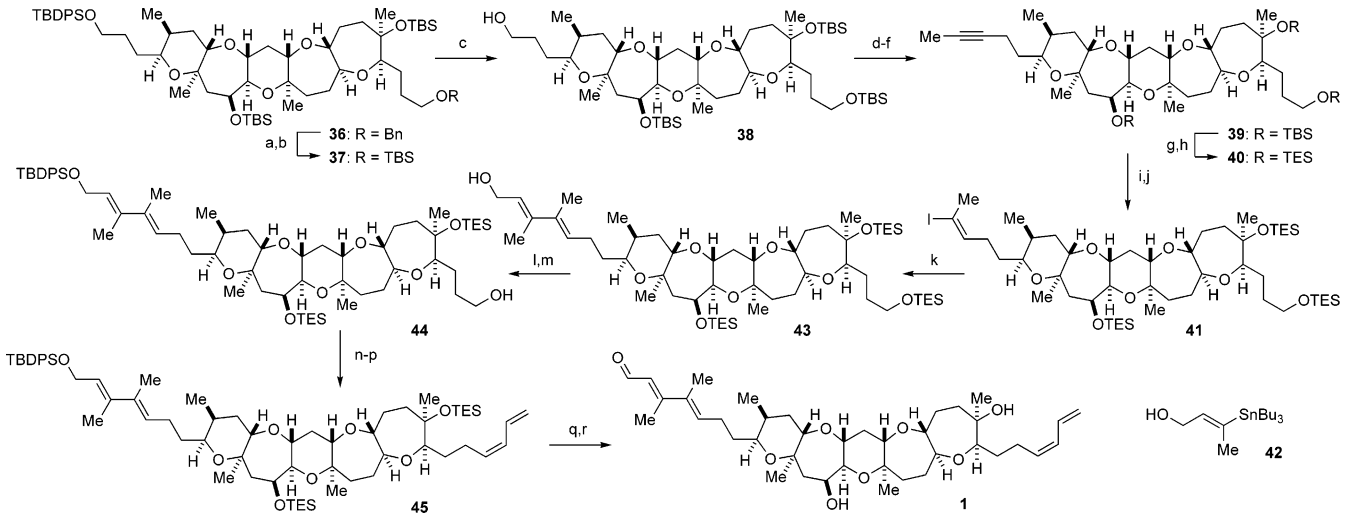
[a] Reagents and conditions: (a) NaH, BnBr, DMF, 0 °C to rt; (b) O_3, MeOH/CH_2Cl_2, −78 °C; then $NaBH_4$, −78 to 0 °C, 96% (two steps); (c) KO*t*-Bu, BnBr, THF, rt; (d) *p*-TsOH, MeOH/$CHCl_3$, rt, quant. (two steps); (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; then TBSOTf, −78 to 0 °C; (f) allylMgBr, CuBr, ether, 0 °C, 85% (two steps); (g) OsO_4, NMO, THF/H_2O, rt; then $NaIO_4$, rt; (h) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to 0 °C; (i) TBAF, THF, rt, 88% (three steps); (j) methyl propiolate, NMM, CH_2Cl_2, rt; (k) MeI, $NaHCO_3$, MeCN/H_2O, rt, 99% (two steps); (l) SmI_2, MeOH, THF, rt; then *p*-TsOH, toluene, 80 °C, 84% (two steps); (m) DIBALH, CH_2Cl_2, −78 °C; (n) Ph_3PCH_3Br, NaHMDS, THF, 0 °C to rt, 94% (two steps); (o) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 97%; (p) MeLi, THF, −78 to 0 °C, 97% (dr > 10:1); (q) TBSOTf, Et_3N, CH_2Cl_2, rt, quant.; (r) 9-BBN, THF, rt; then aq. $NaHCO_3$, H_2O_2, 0 °C to rt; (s) H_2, $Pd(OH)_2$/C, MeOH, rt; (t) *p*-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, rt, 80% (three steps); (u) KO*t*-Bu, BnBr, THF, rt; (v) DIBALH, CH_2Cl_2, −78 to −40 °C, 85% (two steps); (w) I_2, PPh_3, imidazole, THF, rt; (x) KO*t*-Bu, THF, 0 °C, 99% (two steps).

Scheme 4. Synthesis of the Pentacyclic Polyether Core[a]



[a] Reagents and conditions: (a) 9-BBN, THF, rt; then 3 M aq. Cs_2CO_3, $Pd(PPh_3)_4$, DMF, 50 °C; (b) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt; then aq. $NaHCO_3$, H_2O_2, 0 °C to rt, 84% (two steps); (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C, 98%; (d) LHMDS, TMSCl, Et_3N, THF, −78 °C; (e) OsO_4, NMO, THF/H_2O, rt, 87% (two steps); (f) DIBALH, THF, −78 °C, 76% (diastereomer: 7%; **31**: 12%); (g) TESOTf, Et_3N, CH_2Cl_2, 0 °C; (h) DDQ, CH_2Cl_2/pH 7 buffer, rt; (i) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C, 88% (three steps); (j) EtSH, $Zn(OTf)_2$, THF, rt, 79%; (k) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 97%; (l) *m*CPBA, CH_2Cl_2, −78 °C; then $AlMe_3$, −78 to 0 °C, 92%.

Scheme 5. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) LiDBB, THF, −78 °C, 99%; (b) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 98%; (c) TBAF, AcOH, THF, rt, 78% after three recycles; (d) Dess−Martin periodinane, CH_2Cl_2, rt; (e) Bestmann reagent, K_2CO_3, 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_3N, CH_2Cl_2, 0 °C, 99%; (i) $PhMe_2SiLi$, CuCN, THF, −78 to 0 °C; (j) NIS, CH_3CN/THF, 0 °C to rt, 99% (two steps); (k) **42**, $Pd_2(dba)_3$, Ph_3As, CuTC, 1:1 DMSO/THF, rt, 63%; (l) TBDPSCl, imidazole, DMF, 0 °C; (m) PPTS, 4:1 CH_2Cl_2/MeOH, 0 °C, 74% (two steps); (n) $SO_3{\cdot}$pyridine, Et_3N, DMSO/CH_2Cl_2, 0 °C; (o) $BrPh_3PCH_2CH_2CH_2SePh$, *n*-BuLi, THF/HMPA, −78 °C to rt, 97% (two steps); (p) H_2O_2, $NaHCO_3$, THF, rt, 77%; (q) TASF, DMF/THF, 0 °C to rt, 79%; (r) MnO_2, CH_2Cl_2, 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_2CO_3, $Pd(PPh_3)_4$] to afford the cross-coupled product **28**. Hydroboration of **28** with $BH_3 \cdot SMe_2$ generated alcohol **29** as a single stereoisomer, which was then oxidized[14] to ketone **30**. The stereochemistries of C16 and C18 were confirmed by NOE experiments. Conversion to the corresponding enol silyl ether followed by dihydroxylation delivered α-hydroxy ketone **31** as a single stereoisomer. Subsequent DIBALH reduction afforded diol **32** in good selectivity (dr = ca. 10:1).[15] Protection as the TES ethers, removal of the PMB group, and ensuing oxidation provided ketone **33**. Exposure of **33** to $EtSH/Zn(OTf)_2$ in THF effected deprotection of the TES groups and concomitant mixed thioacetal formation to furnish **34** in 79% yield. After TBS protection, oxidation with *m*CPBA at −78 °C followed by in situ treatment with excess $AlMe_3$ 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.[17] The stereochemistry of **36** was confirmed by NOEs and $^3J_{H,H}$ 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[18] produced alcohol **38** (Scheme 5). Oxidation,[19] Bestmann alkynylation,[20] 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 ($PhMe_2SiLi$, CuCN)[21] effected *syn*-selective silylcupration of the internal alkyne (regioselectivity = ca. 9:1). Subsequent iododesilylation with NIS[22] afforded vinyl iodide **41** (*E*:*Z* = ca. 6:1).[15] Stille coupling[23] of **41** with vinyl stannane **42** was best accomplished by using the $Pd_2(dba)_3/Ph_3As$ catalyst system in the presence of copper(I) thiophene-2-carboxylate (CuTC),[24] giving allylic alcohol **43** in 63% yield as a single isomer.[15] After conversion to alcohol **44**, oxidation and Wittig reaction, followed by peroxide treatment,[25] afforded diene **45**. Finally, global deprotection of the silyl groups followed by selective oxidation of the C1 alcohol with MnO_2 furnished synthetic **1**. Unfortunately, ^1H and ^{13}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 cross-peaks 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,[26] 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.

Acknowledgment. We thank Prof. D. G. Baden and Dr. A. J. Bourdelais for providing copies of ^1H and ^{13}C NMR of an authentic sample of brevenal, and Mr. R. Watanabe (Tohoku University) for NMR measurements. This work was financially supported by the Naito Foundation, a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and JSPS (postdoctoral fellowship for H.F.).

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}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.

References

(1) (a) Bourdelais, A. J.; Campbell, S.; Jacocks, H.; Naar, J.; Wright, J. L. C.; Carsi, J.; Baden, D. G. *Cell. Mol. Neurobiol.* **2004**, *24*, 553. (b) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M., Jr.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2.
(2) Abraham, W. M.; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. G. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 26.
(3) (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.
(4) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (c) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889. (d) Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851.
(5) (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (c) Tsukano, M.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294. (d) Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326.
(6) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(7) Uehara, H.; Oishi, T.; Inoue, M.; Shoji, M.; Nagumo, Y.; Kosaka, M.; Le Brazidec, J.-M.; Hirama, M. *Tetrahedron* **2002**, *58*, 6493.
(8) Yamaguchi, M.; Inanaga, J.; Hirata, K.; Sasaki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(9) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.
(10) Kadota, I.; Ohno, A.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6373.
(11) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158.
(12) Kotsuki, H.; Kadota, I.; Masamitsu, O. *Tetrahedron Lett.* **1990**, *31*, 4609.
(13) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099.
(14) Ley, S. V.; Normann, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(15) For stereochemical confirmation, see Supporting Information.
(16) The carbon numbering corresponds to that of brevenal.
(17) (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371. (c) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019.
(18) Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306.
(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(20) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.
(21) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (b) See also: Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.
(22) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 4609.
(23) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(24) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
(25) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558.
(26) For an example, see: Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476.

JA062524Q