ORGANIC LETTERS

2009
Vol. 11, No. 12
2531−2534

Total Synthesis of Brevenal

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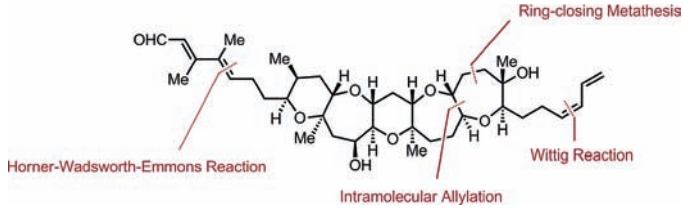
Received April 9, 2009

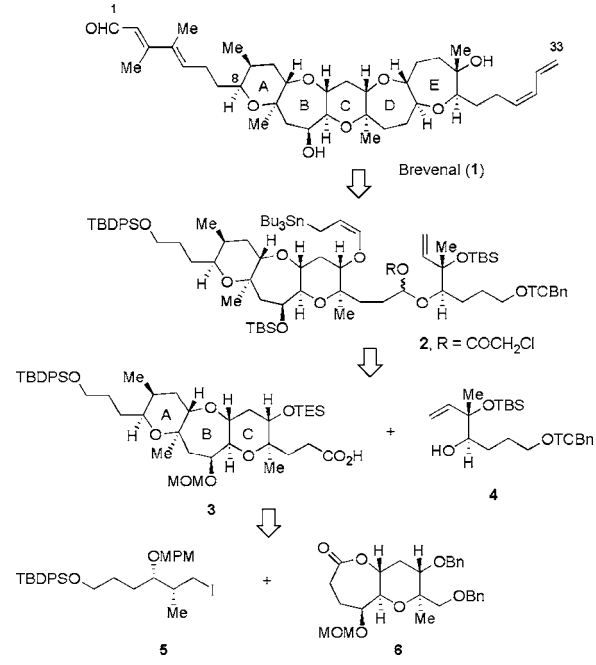
ABSTRACT



A total synthesis of brevenal is described. The pentacyclic ether core was constructed by the intramolecular allylation of α-acetoxy ether and subsequent ring-closing metathesis. Both of the diene side chains were introduced by Wittig olefination and a Horner−Wadsworth−Emmons reaction, respectively, in a highly stereoselective manner.

Brevenal (**1**), a new family of marine polycyclic ethers, was isolated from *Karenia brevis* in 2004.[1] This compound inhibits the binding of tritiated dihydrobrevetoxin-B to voltage-sensitive sodium channels in a concentration dependent manner and acts as a nontoxic brevetoxin antagonist.[1,2] Moreover, a significant improvement of tracheal mucus velocity was observed in an animal model of asthma.[3] As well as the novel biological activities, the unique structural features have attracted attention of synthetic chemists. In 2006, the first total synthesis and structure revision of **1** were reported by Sasaki and co-workers.[4] In this paper, we wish to report the recent results of our efforts on the total synthesis of brevenal (**1**).

Scheme 1. Retrosynthetic Analysis of Brevenal (**1**)



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(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*, 553–563. (b) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M., Jr.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2–6.

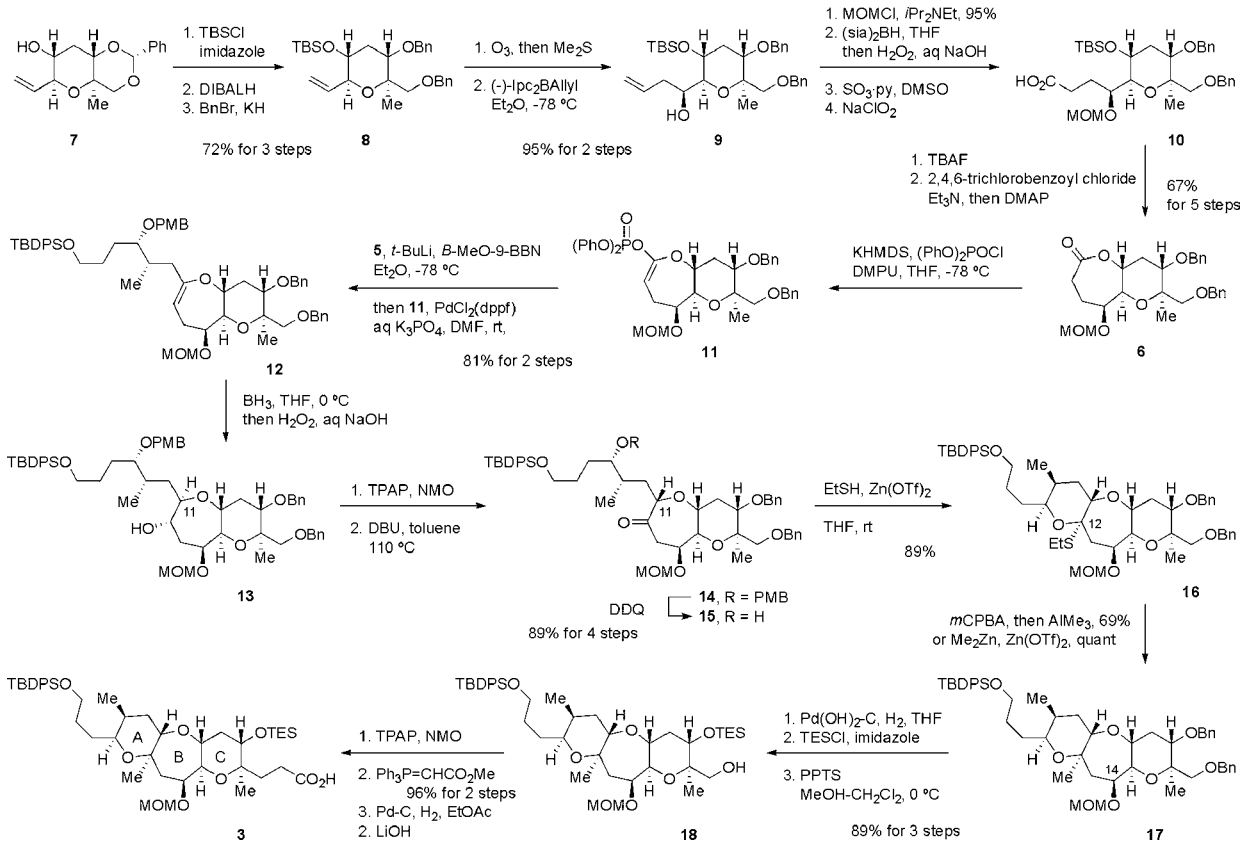
(2) The antagonistic effect of brevenal on brevetoxin-induced DNA damage is reported, see: Sayer, A.; Hu, Q.; Bourdelais, A. J.; Baden, D. G.; Gibson, J. E. *Arch. Toxicol.* **2005**, *79*, 683–688.

(3) 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*, 26–34.

(4) (a) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648–9650. (b) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989–16999. (c) Ebine, M.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2275–2278.

10.1021/ol900769d CCC: $40.75
Published on Web 05/14/2009

Scheme 2



Scheme 1 illustrates our retrosynthetic analysis of **1**. Both of the side chains would be constructed by Wittig-type olefination at a later stage. The pentacyclic ether core would be synthesized from **2** via the intramolecular allylation followed by ring-closing metathesis.[5] The cyclization precursor **2** was retrosynthetically broken down into the ABC ring segment **3** and the E ring precursor **4**. The tricycle **3** would be prepared from **5** and **6**.

The synthesis of the ABC ring segment **3** is described in Scheme 2. TBS protection of the known compound **7**[6] followed by reductive cleavage of the benzylidene acetal with DIBALH gave the corresponding primary alcohol, which was protected with BnBr/KH to furnish the bis-benzyl ether **8** in 72% yield. Ozonolysis of the olefin **8** followed by Brown's asymmetric allylboration provided **9** as a single stereoisomer in 95% yield.[7] MOM protection of the alcohol **9** followed by hydroboration-oxidation afforded the corresponding alcohol, which was subjected to stepwise oxidation leading to the carboxylic acid **10**. Removal of the TBS group with TBAF and the Yamaguchi lactonization provided **6** in 64% yield over 6 steps.[8] Treatment of the lactone **6** with $(PhO)_2POCl$/KHMDS provided the enol phosphate **11**. The Suzuki-Miyaura coupling of **11** and an alkyl borate, prepared from the iodide **5**[4c] by known procedure,[9] was carried out with $PdCl_2$(dppf) to furnish the enol ether **12** in 81% yield over 2 steps.[10] Hydroboration of **12** with BH_3 followed by oxidative workup gave the undesired stereoisomer **13** as the sole product. Since several attempts failed to obtain the desired product from **12** directly, stereoinversion at C11 position was carried out. TPAP oxidation of **13** followed by treatment of the resulting ketone with DBU in toluene at 110 °C provided **14** as a single stereoisomer. Deprotection of the PMB group of **14** using DDQ furnished the alcohol **15** in 89% yield over 4 steps. Treatment of **15** with EtSH/$Zn(OTf)_2$ gave the mixed thioacetal **16** in 89% yield.[4] Installation of the C12 angular methyl group was initially examined by a reported procedure. Thus, oxidation of **16** with *m*CPBA followed by treatment with $AlMe_3$ provided **17** as a single steroisomer in 69% yield.[4,11] However, the yield was not reproducible, and significant amounts of unidentified byproduct, presumably generated from the unstable sulfoxide intermediate, were formed in large-scale experiment. After several examinations, we found that the reaction of **16** with $Me_2Zn/Zn(OTf)_2$ furnished **17**, directly, in quantitative yield. The MOM ether at C14 position was

(5) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 3562–3566.

(6) (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517–4552. (b) Kadota, I.; Kadowaki, C.; Park, C.-H.; Takamura, H.; Sato, K.; Chan, P. W. H.; Thorand, S.; Yamamoto, Y. *Tetrahedron* **2002**, *58*, 1799–1816.

(7) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–404.

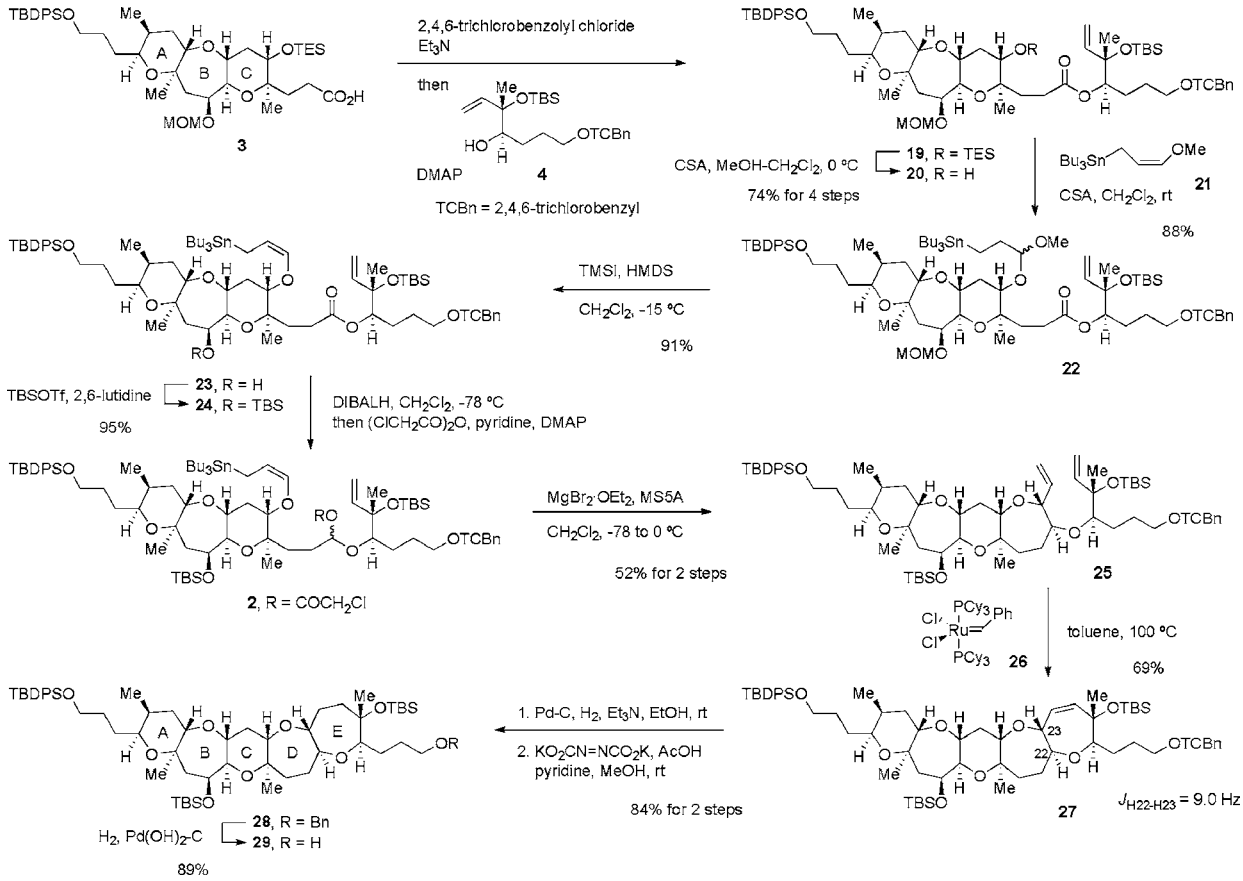
(8) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(9) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885–7892.

(10) Sasaki and co-workers have reported the same C-C bond formation with this alkyl borate: see ref 4.

(11) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321–5330.

Scheme 3



totally inert under the reaction conditions. Debenzylation of **17** with H_2/Pd(OH)$_2$-C, protection of the resulting diol with TESCl/imidazole, and selective cleavage of the primary TES ether under acidic conditions afforded **18** in 89% yield over 3 steps. TPAP oxidation of the alcohol **18** followed by Wittig reaction with $Ph_3P{=}CHCO_2Me$ gave the corresponding unsaturated ester (96% by 2 steps) which was subjected to hydrogenation and saponification leading to the ABC ring segment **3**.

Scheme 3 describes the key segment coupling. Thus, esterification of the carboxylic acid **3** and the known alcohol **4**[12] under the Yamaguchi conditions gave the ester **19**.[8] Selective removal of the TES protective group was performed with CSA to provide **20** in 74% yield over 4 steps. Acetalization of **20** with γ-methoxyallylstannane **21** in the presence of CSA provided the acetal **22** as a mixture of diastereoisomers in 88% yield. Treatment of **22** with TMSI/HMDS gave allylic stannane **23** in 91% yield.[13] Since the MOM protection was cleaved under the reaction conditions, the resulting hydroxyl group of **23** was protected as a TBS ether to furnish **24** in 95% yield. Modified Rychnovsky acetylation of the ester **24** provided the α-chloroacetoxy ether **2**.[14,15] Intramolecular allylation of **2** was carried out with $MgBr_2{\cdot}OEt_2$ to give **25** as a single stereoisomer in 52% yield over 2 steps.[16] Ring-closing metathesis of the diene **25** was carried out with the Grubbs' catalyst **26** leading to the pentacyclic ether **27** in 69% yield.[17,18] At this stage, the *trans* relationship between H22 and H23 was confirmed by the coupling constant, $J_{H22-H23} = 9.0$ Hz. Having synthesized the pentacyclic ether core, we next examined the construction of the right-hand side chain. However, deprotection of the TCBn group was very slow under the standard hydrogenation conditions such as H_2 and Pd catalysts, and decomposition of the substrate was observed when a prolonged reaction time was employed.[19] Finally, this problem was solved by the Sajiki's dechlorination procedure. Thus, the reaction of **27** with H_2/Pd−C in the presence of Et_3N proceeded smoothly

(12) (a) Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243–5246. (b) Kadota, I.; Abe, T.; Ishitsuka, Y.; Touchy, A. S.; Nagata, R.; Yamamoto, Y. *Heterocycles* **2007**, *74*, 617–627.

(13) Kadota, I.; Sakaihara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3195–3198.

(14) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46–47.

(15) For the original conditions, see: (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317–8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191–198. (c) Kopecky, D. J.; Rychnovsky, S. D. *Org. Synth.* **2003**, *80*, 177–183.

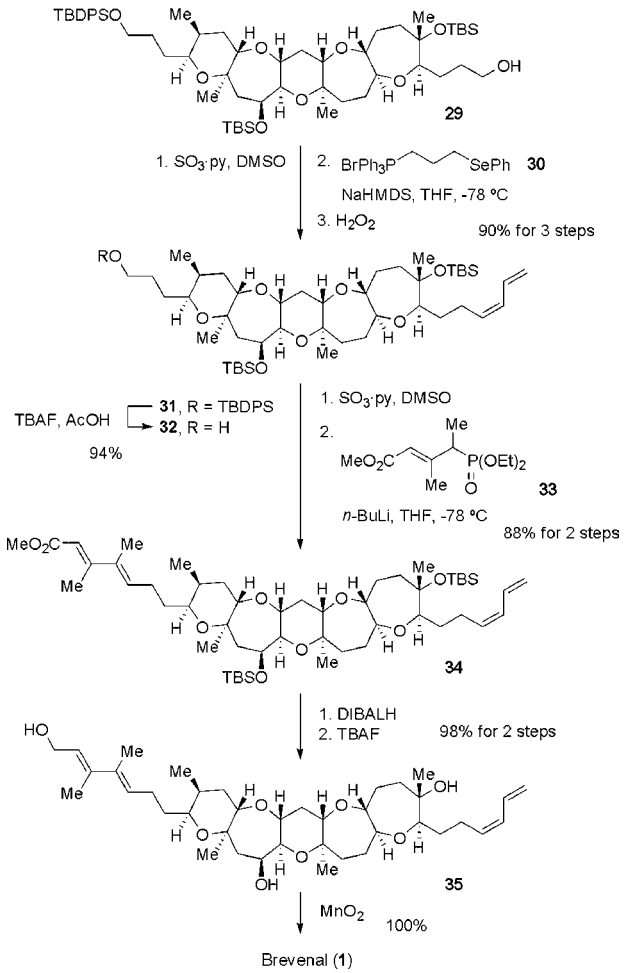
(16) None of the other stereoisomers were detected. Although the reaction conditions were optimized, partial decompsition of the substrate **2** was observed in this reaction.

(17) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

(18) The reaction of **25** required 3 equiv of **26** for the completion, and the formation of unidentified by-products was observed.

(19) For successful examples of the deprotection of TCBn group in similar cases, see ref 12.

Scheme 4



to give the corresponding benzyl ether in quantitative yield.[20] Hydrogenation of the E ring olefin with diimide afforded **28**, a synthetic intermediate of Sasaki's total synthesis,[4a,b,21] in 84% yield over 2 steps. Debenzylation of **28** was carried out with H_2/Pd(OH)$_2$-C leading to **29** in 89% yield.

Construction of the right-hand (*Z*)-diene moiety was carried out according to Nicolaou's procedure (Scheme 4).[22] Thus, oxidation of **29** with SO_3·py/DMSO followed by Wittig reaction using a ylide generated from **30** and NaHMDS, and subsequent oxidation with H_2O_2 provided **31** as a single stereoisomer in 90% yield over 3 steps. Selective removal of the TBDPS group was carried out with TBAF/AcOH to give the alcohol **32** in 94% yield. As well as the synthesis of the pentacyclic ether framework, the stereoselective construction of the left-hand side chain, highly substituted (*E*,*E*)-diene moiety, was of the challenging problems inherent in the total synthesis of brevenal. We chose the Horner-Wadsworth-Emmons reaction as a possible route to the diene system. Thus, after oxidation of **32**, the resulting aldehyde was treated with an anion generated from the phosphonate **33** and *n*-BuLi to provide **34** as a single steroisomer in 88% yield over 2 steps.[23] Reduction of the ester **34** with DIBALH followed by desilylation with TBAF afforded the triol **35** in 98% yield. Finally, selective oxidation of the allylic alcohol **35** with MnO_2 furnished brevenal (**1**) in quantitative yield. The synthetic **1** exhibited physical and spectroscopic data identical with those reported previously.

In conclusion, we have achieved a total synthesis of brevenal (**1**) via the intramolecular allylation of an α-chloroacetoxy ether and ring-closing metathesis. The longest linear sequence leading to **1** was 57 steps with 0.84% overall yield. Novel methods for the direct methylation of *O*,*S*-acetal (Scheme 2) and the stereoselective synthesis of the left-hand (*E*,*E*)-diene system (Scheme 4) are also deserving of attention.

Acknowledgment. This work was financially supported by the Nagase Science and Technology Foundation, the Wesco Scientific Promotion Foundation, the Naito Foundation, the Sumitomo Foundation, and the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details and full spectral data. Copies of ^{1}H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900769D

(20) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7247–7250.

(21) ^{1}H and ^{13}C NMR spectra of **28** were identical with those reported previously.

(22) (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935–7936. (b) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558–3575.

(23) For the preparation of the phosphonate **33**, see Supporting Information.