

Enantioselective Total Synthesis of
(–)-Clavosolide B

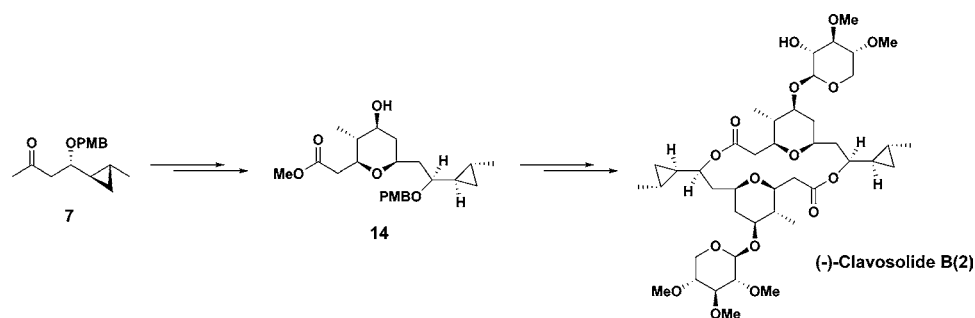
Jung Beom Son, Min-ho Hwang, Wonsun Lee, and Duck-Hyung Lee*

Department of Chemistry, Sogang University, Shinsoo-dong 1, Mapo-gu,
Seoul 121-742, Korea

dhlee@sogang.ac.kr

Received June 26, 2007

ABSTRACT



Enantioselective synthesis of **2**, a revised structure for (–)-clavosolide B, was accomplished by a convergent approach, where *syn*-selective aldol, hydroxy-directed cyclopropanation, Mitsunobu inversion, Schmidt-type glycosylation, and macrolactonization reactions were utilized as key reactions. Comparison of ^1H and ^{13}C NMR spectra and optical rotation measurement confirmed the relative and absolute stereochemistry of clavosolide B (**2**).

Clavosolides A and B were isolated by Faulkner and Rao in 2002 from the crude extract of the sponge *Myriastrea clavosa* from the Philippines.¹ Another independent research by Erickson² also allowed the isolation of clavosolides A and B and confirmed the structures proposed by Faulkner and Rao. However, comparison of the ^1H NMR spectra of the isolated clavosolide A and synthetic compound of the proposed structure obtained by Willis³ showed unequivocal discrepancies in the spectral region around the cyclopropane signals, which were later supported by Chakraborty^{4,5} and

us.⁶ Willis also proposed a revised structure **1** for clavosolide A,³ and our group confirmed the relative stereochemistry of clavosolide A (**1**) by stereoselective total synthesis.^{6a} Subsequently, Smith⁷ and Willis⁸ unambiguously determined the absolute stereochemistry of (–)-clavosolide A (**1**) by comparison of the optical rotation values, and Chakraborty⁹ confirmed it again.

On the basis of the previous work, we proposed the revised structure **2** for natural (–)-clavosolide B (**2**) (Figure 1). Herein, we report the first enantioselective total synthesis and structural revision of clavosolide B (**2**). Both (–)-clavosolide A (**1**) and B (**2**) are 16-membered diolides with two highly substituted tetrahydropyrans, two *trans*-disubstituted cyclopropyl rings, and 22 stereogenic centers. They

(1) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, 65, 386–388.(2) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, 65, 1303–1306.(3) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 40, 5097–5099.(4) Chakraborty, T. K.; Reddy, V. R. *Tetrahedron Lett.* **2006**, 47, 2099–2102.(5) For synthetic investigations of the originally proposed clavosolide A, see: (a) Yakambram, P.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, 47, 3781–3783. (b) Lee, D. H.; Son, J. B.; Kim, N. Y. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, March 13–17, 2005; American Chemical Society: Washington, DC, 2005; ORGN-592.(6) (a) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, 8, 661–664. (b) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, 8, 3411.(7) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, 8, 3315–3318.(8) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, 8, 3319–3322.(9) Chakraborty, T. K.; Reddy, V. R.; Chattopadhyay, A. K. *Tetrahedron Lett.* **2006**, 47, 7435–7438.

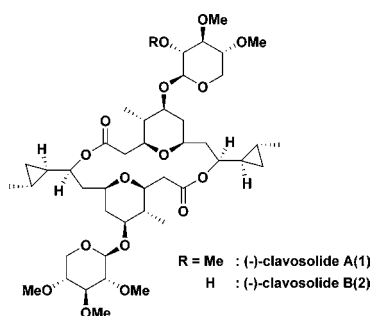
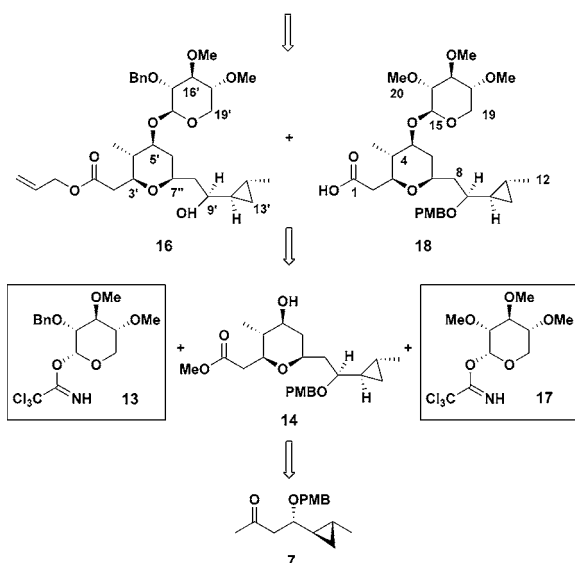


Figure 1. Revised structures for clavosolide A (1) and B (2).

differ only in the substitution pattern on the one sugar moiety (–OMe for clavosolide A vs –OH for clavosolide B).

The retrosynthetic analysis is illustrated in Scheme 1. Sequential disconnection of the two ester linkages in 2

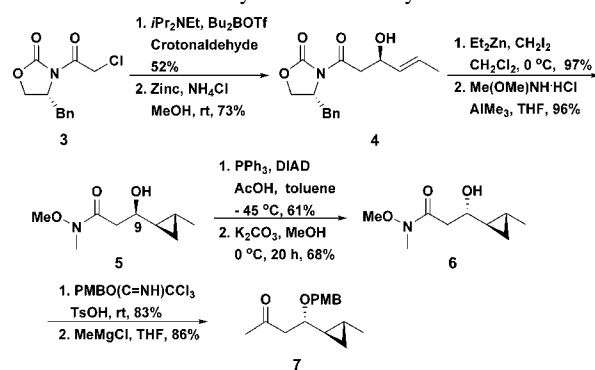
Scheme 1. Retrosynthesis of Clavosolide B (2)
(-)-clavosolide B(2)



requires an esterification and a macrolactonization as key reactions in the synthesis. Segments **16** and **18** are expected to derive from the coupling of common intermediate **14** and two activated sugar moieties **13** and **17** via a Schmidt-type glycosylation. Although pyran **14** was previously prepared from methyl ketone **7** by us,^{6a} a new and simpler sequence has been implemented to synthesize the ketone **7** based on the Smith procedure.⁷

A new synthetic route to methyl ketone **7** is summarized in Scheme 2. Treatment of the Evans chiral oxazolidinone derivative **3** with Bu₂BOTf and Hunig's base was followed by reaction with crotonaldehyde to provide the *syn*-selective aldol product (95:5 by ¹H NMR) in 52% yield.¹⁰ Subsequent dechlorination of the aldol product with zinc powder in MeOH provided the allylic alcohol **4** in 73% yield.¹¹ Hydroxy-directed cyclopropanation of allylic alcohol **4**

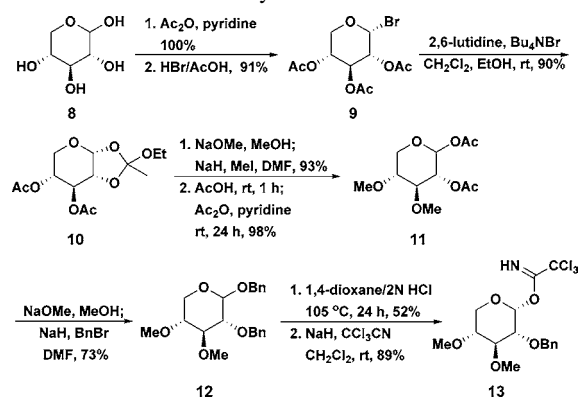
Scheme 2. Synthesis of Methyl Ketone **7**



proceeded with good selectivity (*syn/anti* = 11:1) in 97% yield, which was then treated with *N,O*-dimethylhydroxylamine hydrochloride and AlMe₃ to give Weinreb amide **5** in excellent yield. Mitsunobu inversion at the C9-stereogenic center using DIAD-PPh₃–AcOH⁷ and removal of the acetate by K₂CO₃–MeOH yielded the cyclopropyl carbinol **6**. The hydroxy group was converted to PMB ether using a standard protocol, and the product was treated with methylmagnesium chloride to provide the desired ketone **7**.

The synthesis of activated sugar moiety **13** is summarized in Scheme 3. Treatment of D-xylose (**8**) with acetic anhydride

Scheme 3. Synthesis of Imidate **13**



in pyridine¹² gave a per-acetylated derivative, and the product was subsequently reacted with hydrogen bromide in glacial acetic acid to provide the bromo derivative **9** in 91% overall yield. The reaction of bromide **9** with ethanol in the presence of tetrabutylammonium bromide and 2,6-lutidine gave the corresponding orthoester **10**.¹³ The remaining acetates were cleaved by the deacetylation method of Zemplén,¹⁴ and the resulting hydroxy groups were subjected to methylation using

(10) (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157. (b) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42.

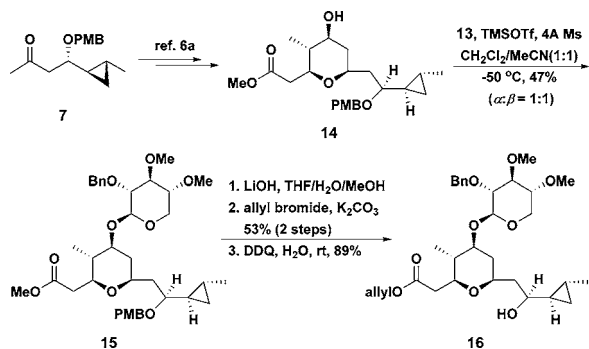
(11) Crich, D.; Jiao, X. Y.; Bruncko, M. *Tetrahedron* **1997**, *53*, 7127–7138.

(12) (a) Hudson, C. S.; Johnson, J. M. *J. Am. Chem. Soc.* **1915**, *37*, 2748–2753. (b) Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1976**, *52*, 95–101.

NaH and MeI in 93% overall yield. Finally, the product was treated with glacial acetic acid and an acetic anhydride–pyridine system to provide the diacetate **11** in 90% yield.¹⁵ Removal of two acetyl groups in the 3- and 4-position of **11** using NaOMe in MeOH and subsequent benzylation of two hydroxy groups by NaH–BnBr allowed the synthesis of dibenzyl ether **12**. Selective hydrolysis of the acetal moiety in **12** under acidic condition and activation of the resulting free hydroxy group provided the activated sugar imidate **13** as a mixture of epimers ($\alpha/\beta = 5:1$) in 89% yield.

The synthesis of top half segment **16** was achieved following the sequence summarized in Scheme 4. Transfor-

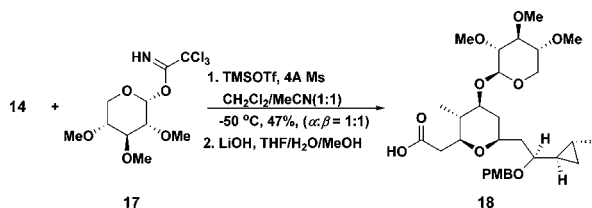
Scheme 4. Synthesis of Top Half Segment **16**



mation of methyl ketone **7** into the key intermediate **14** was accomplished following the same procedure reported earlier in the synthesis of (–)-clavosolide A (**1**).^{6a} Schmidt-type glycosylation¹⁶ of *sec*-alcohol **14** with an activated sugar imidate **13** in the presence of TMSOTf and molecular sieves produced a mixture of products with an $\alpha/\beta = 1:1$ ratio, and the desired β -isomer **15** was separated by silica gel column chromatography in 47% yield. Alcohol **16** was then prepared in a three-step sequence from **15**, via hydrolysis of methyl ester, esterification of carboxylic acid with allyl bromide and K_2CO_3 , and deprotection of PMB ether.

Bottom half segment **18** was also synthesized in a similar manner (Scheme 5). Schmidt-type glycosylation¹⁶ of **14** with

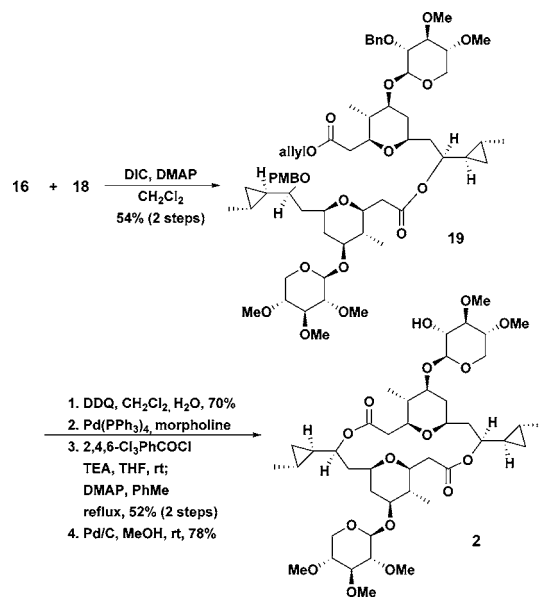
Scheme 5. Synthesis of Bottom Half Segment **18**



activated sugar imidate **17**, prepared following the literature procedure by us,^{6a} was accomplished in 47% isolated yield, and subsequent hydrolysis produced another key intermediate **18**, which was used without further purification in the next step.

With two key intermediates **16** and **18** in our hands, total synthesis of clavosolide B (**2**) was pursued immediately (Scheme 6). Alcohol **16** and carboxylic acid **18** were coupled

Scheme 6. Synthesis of (–)-Clavosolide B (**2**)



with the aid of DIC and DMAP to provide the ester **19** in 54% yield over two steps from the glycosylation reaction of **17**. Selective cleavage of the PMB protecting group by DDQ in CH_2Cl_2 – H_2O and of the allyl ester protecting group with $Pd(PPh_3)_4$ furnished the hydroxy acid. Macrolactonization of the hydroxy acid using a protocol of Yamaguchi in slightly modified conditions proceeded smoothly, and final deprotection of the benzyl group with Pd/C in MeOH provided the target compound **2** as a white solid in 78% yield.

Comparison of the 1H NMR spectra of the isolated and synthetic compounds turns out to be identical except for the signals from the impurities contained in the isolated natural product (Figure 2).¹⁷ This result leads to the revision of relative stereochemistry of clavosolide B (**2**) around the cyclopropyl system, which was already implied from the enantioselective total synthesis of clavosolide A (**1**).^{6–9} Optical rotation of the synthetic compound was also measured to be $[\alpha]_D -47.2$ (c 0.4, $CHCl_3$), which is similar to the reported value of $[\alpha]_D -41.0$ (c 0.5, $CHCl_3$) for the natural compound, therefore establishing the absolute stereochemistry of clavosolide B (**2**) as shown in Figure 1.

(13) (a) Zhang, J.; Zhu, Y.; Kong, F. *Carbohydr. Res.* **2001**, *336*, 229–235. (b) Mach, M.; Schlueter, U.; Mathew, F.; Reid, B. F.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345–7354. (c) Suhr, R.; Thiem, J. J. *Carbohydr. Chem.* **2004**, *23*, 261–276.

(14) Czifrák, K.; Hadady, Z.; Docsa, T.; Gergely, P.; Schmidt, J.; Wessjohann, L.; Somsák, L. *Carbohydr. Res.* **2006**, *341*, 947–956.

(15) Chu, J.; Guo, H.; Wang, S. *Tianjin Daxue Xuebao* **2004**, *37*, 434–437.

(16) (a) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731–732. (b) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694–696. (c) Furstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; Declercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142.

(17) See Supporting Information for details.

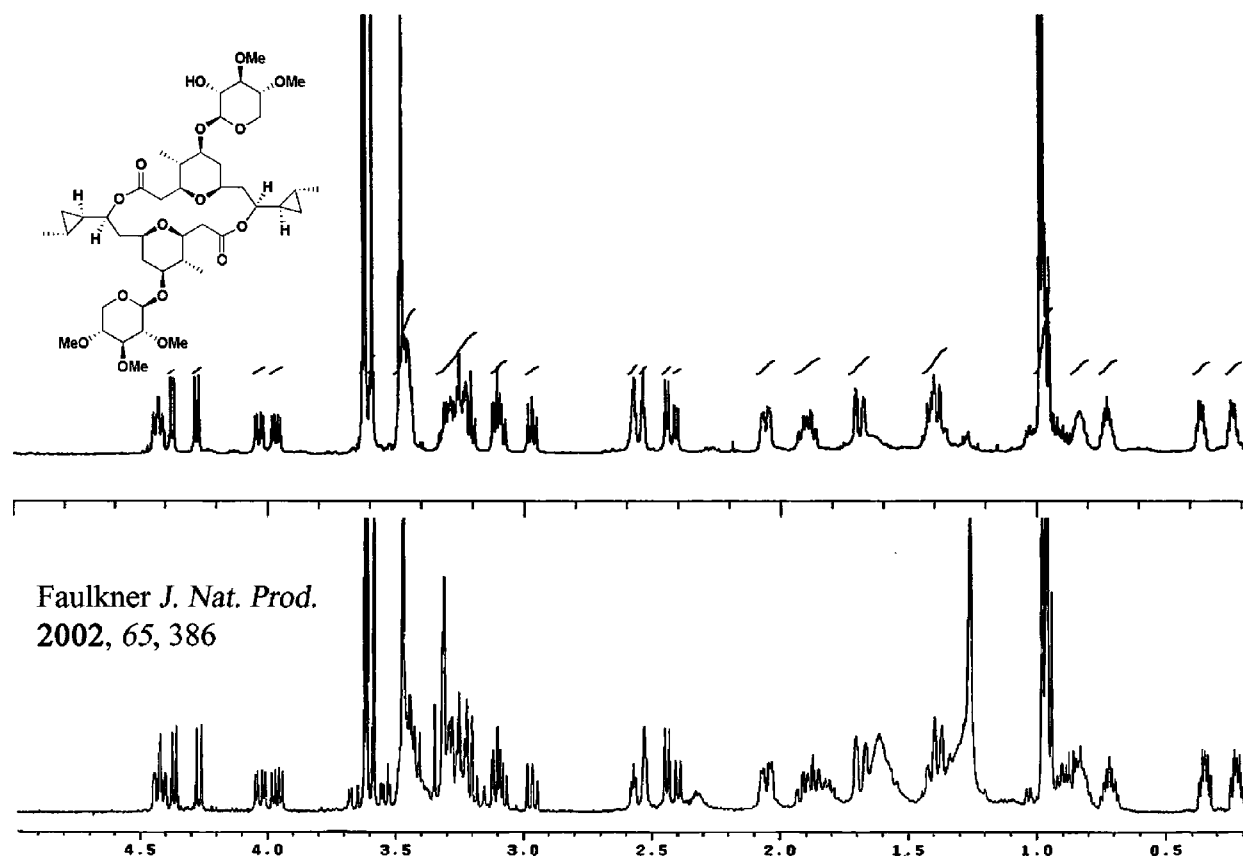


Figure 2. ^1H NMR spectra of the synthetic and isolated clavosolide B.

In summary, we have successfully synthesized clavosolide B (**2**) starting from Evans chiral oxazolidinone derivative **3** via *syn*-selective aldol, hydroxy-directed cyclopropanation, Mitsunobu inversion at the C9 position, a Schmidt-type glycosylation, and macrolactonization reactions as key steps. Comparison of ^1H and ^{13}C NMR spectra of the synthetic and natural clavosolide B has led to the revision of the relative stereochemistry of clavosolide B (**2**), and the optical rotation value confirmed the absolute stereochemistry of (–)-clavosolide B (**2**) as well.

Acknowledgment. This research was assisted financially by the Korea Research Foundation (KRF-203-C00057). A

BK21 postdoctoral fellowship grant to J. B. Son, BK21 graduate fellowship grants to M. Hwang and W. Lee, and a Seoul Science Fellowship grant to M. Hwang are gratefully acknowledged. The instrument facilities of the Organic Chemistry Research Center (OCRC) in the chemistry department of Sogang University were also helpful.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL7015115