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Enantioselective Total Synthesis of (−)-Clavosolide B

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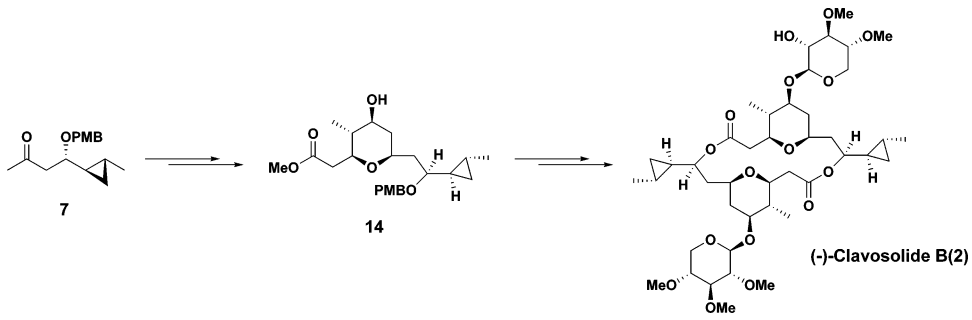
ABSTRACT



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 ^{1}H 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 *Myriastra clavosa* from the Philippines.[1] Another independent research by Erickson[2] also allowed the isolation of clavosolides A and B and confirmed the structures proposed by Faulkner and Rao. However, comparison of the ^{1}H NMR spectra of the isolated clavosolide A and synthetic compound of the proposed structure obtained by Willis[3] 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, Smith[7] and Willis[8] unambiguously determined the absolute stereochemistry of (−)-clavosolide A (**1**) by comparison of the optical rotation values, and Chakraborty[9] 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

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(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.

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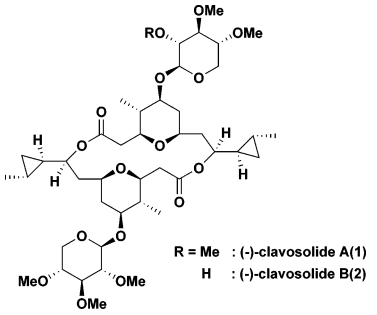
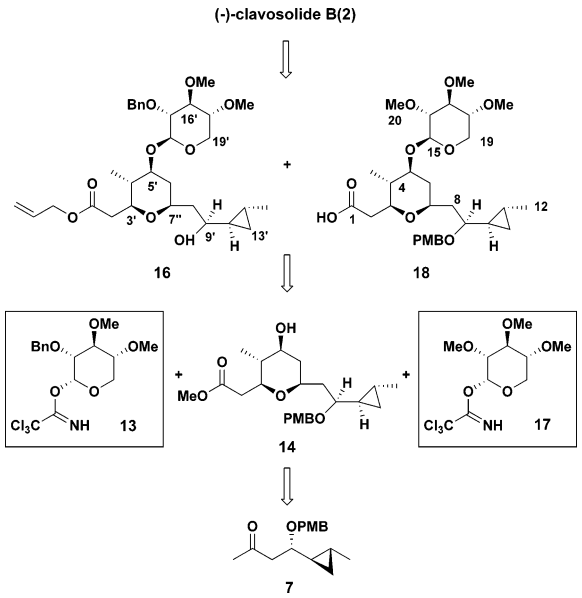


Figure 1. Revised structures for clavosolide A (**1**) and B (**2**).

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**

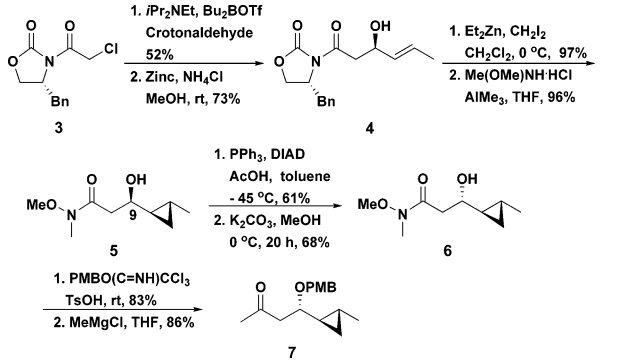
Scheme 1. Retrosynthesis of Clavosolide B (**2**)



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 Bu_2BOTf 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**

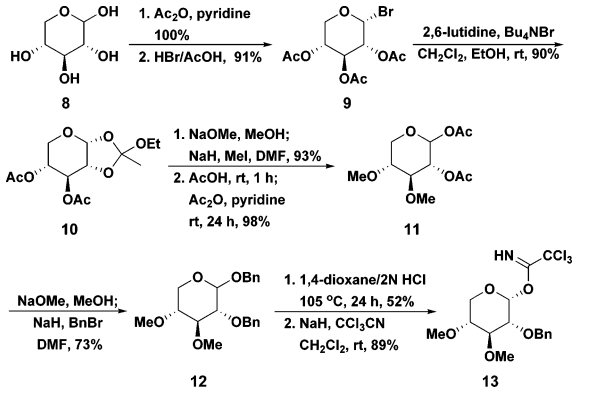
Scheme 2. Synthesis of Methyl Ketone **7**



proceeded with good selectivity (*syn*/*anti* = 11:1) in 97% yield, which was then treated with *N*,*O*-dimethylhydroxylamine hydrochloride and $AlMe_3$ to give Weinreb amide **5** in excellent yield. Mitsunobu inversion at the C9-stereogenic center using DIAD-PPh_3−AcOH[7] and removal of the acetate by K_2CO_3−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 pyridine[12] 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.

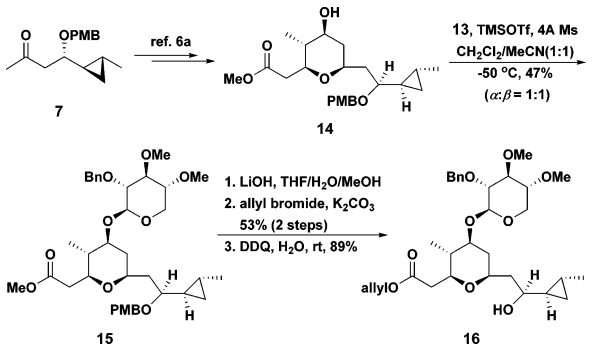
(11) Crich, D.; Jiao, X. Y.; Bruncko, M. *Tetrahedron* **1997**, *53*, 7127−7138.

(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 (α/β = 5:1) in 89% yield.

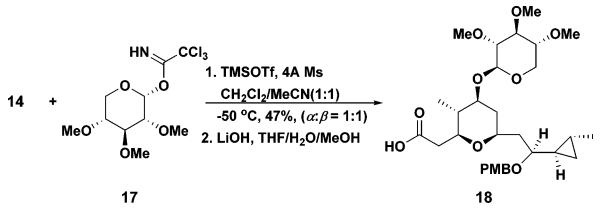
The synthesis of top half segment **16** was achieved following the sequence summarized in Scheme 4. Transformation of methyl ketone **7** into the key intermediate **14** was accomplished following the same procedure reported earlier in the synthesis of (−)-clavosolide A (**1**).[6a] Schmidt-type glycosylation[16] 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 α/β = 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.

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



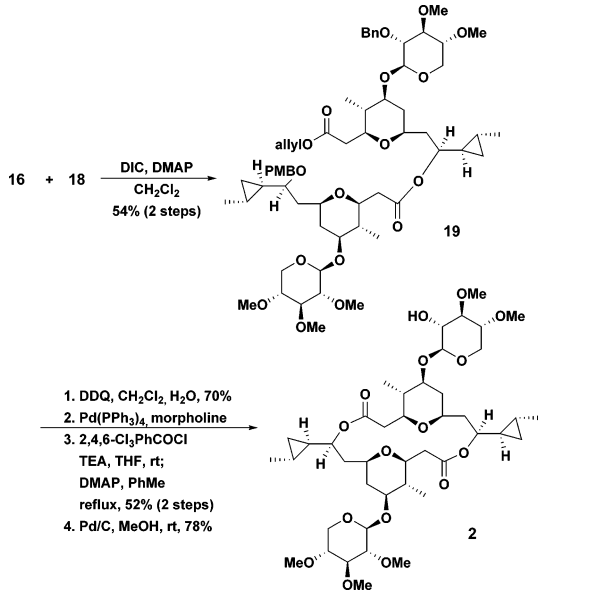
Bottom half segment **18** was also synthesized in a similar manner (Scheme 5). Schmidt-type glycosylation[16] of **14** with activated sugar imidate **17**, prepared following the literature procedure by us,[6a] was accomplished in 47% isolated yield, and subsequent hydrolysis produced another key intermediate **18**, which was used without further purification in the next step.

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



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

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



Comparison of the ^{1}H 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.

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(17) See Supporting Information for details.

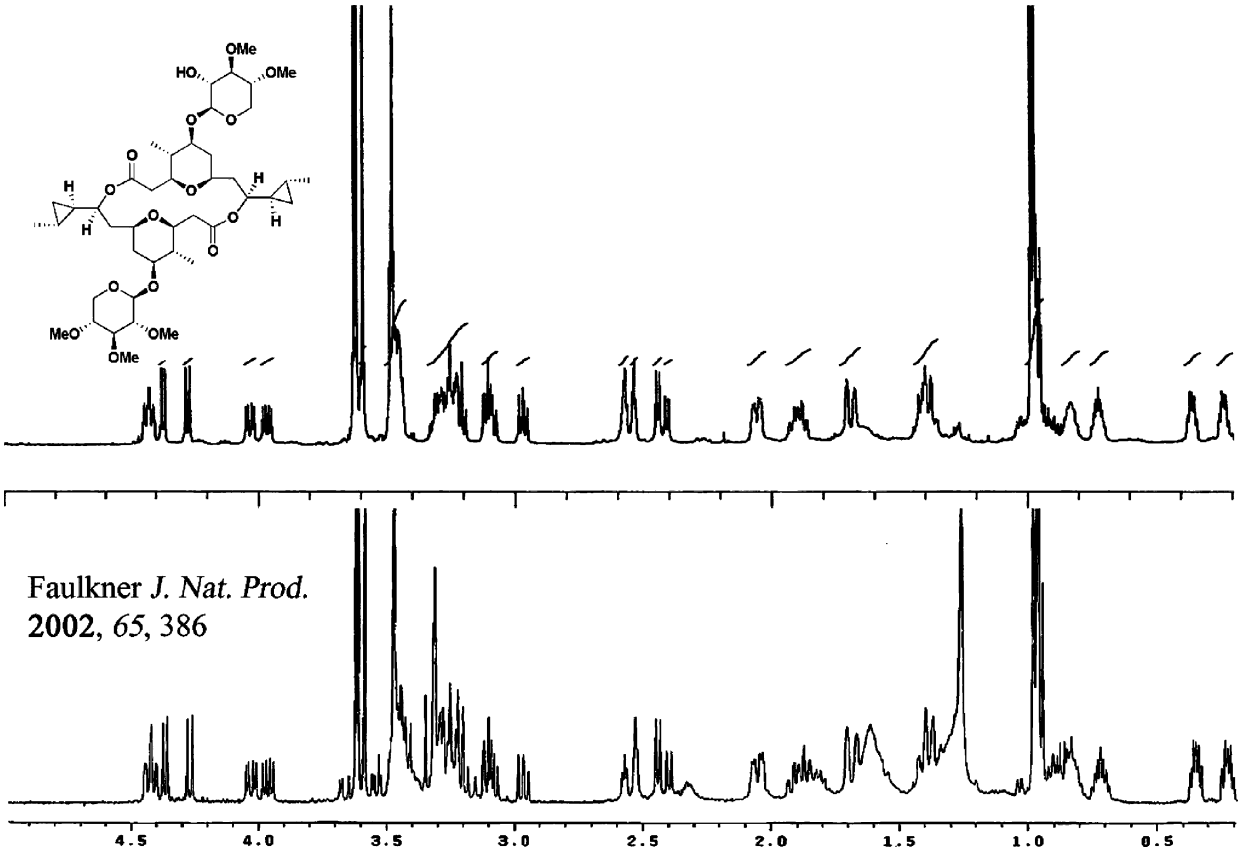

Figure 2. ^{1}H NMR spectra of the synthetic and isolated clavosolide B.

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 ^{1}H 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.

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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.

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