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Total Synthesis, Structural Revision, and Absolute Configuration of (+)-Clavosolide A

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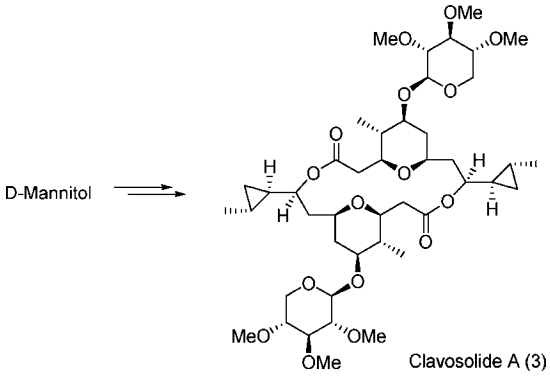
ABSTRACT



Enantioselective synthesis of 3, a revised structure for clavosolide A, was completed. Both ^{1}H and ^{13}C NMR spectra of the natural and synthetic compounds were identical, and optical rotation measurements identified the absolute configuration of the natural clavosolide A as the enantiomer of 3.

Marine sponges have provided an inexhaustible supply of bioactive metabolites.[1] There was a report by Fu[2] that the crude extract of the sponge *Myriastra clavosa* collected from Palau in 1998 contains clavosines A−C, a potent cytotoxin and inhibitor of protein phosphatase 1 and 2A. However, Faulkner and Rao[3] isolated a suite of unusual metabolites, clavosolides A (**1**) and B (**2**), from the crude extract of the sponge *M. clavosa* from the Philippines in 2002 and proposed the structure of these two compounds based on the extensive spectroscopic data. These structures, further supported by Erickson's report in 2002,[4] are quite unique because they are not related to any known sponge metabolites so far. We completed an enantioselective synthesis of the proposed structure of clavosolide A (**1**);[5] however, we found that the ^{1}H and ^{13}C NMR spectra of synthetic **1** were different around the cyclopropyl region from that of proposed structure of **1**. Based on this discrepancy, we proposed that the correct structure of clavosolide A should be **3**, which was further corroborated by an independent synthesis of **1** by Willis.[6] While this manuscript was in preparation, Willis and co-workers reported the synthesis of **1** and have reached the same conclusion that the correct structure of clavosolide A should be its diastereomer **3** (Figure 1).

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49.
(2) Fu, X.; Schmitz, F. J.; Kelly-Borges, M.; McCready, T. L.; Holmes, C. F. B. *J. Org. Chem.* **1998**, *63*, 7957−7963.
(3) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386-388.
(4) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303−1306.
(5) (a) Lee, D. H.; Son, J. B.; Kim, N. Y. *Abstracts of Papers*, 229th national Meeting of the American Chemical Society, San Diego, Mar 13−17, 2005; American Chemical Society: Washington, DC, 2005; ORGN-592. (b) For a review on the misassigned natural products, see: Nicolaou, K. C.; Snyder, S. A. Chasing molecules that were never there: Misassigned natural products and the role of chemical synthesis in modern structure elucidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.
(6) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, *40*, 5097−5099.

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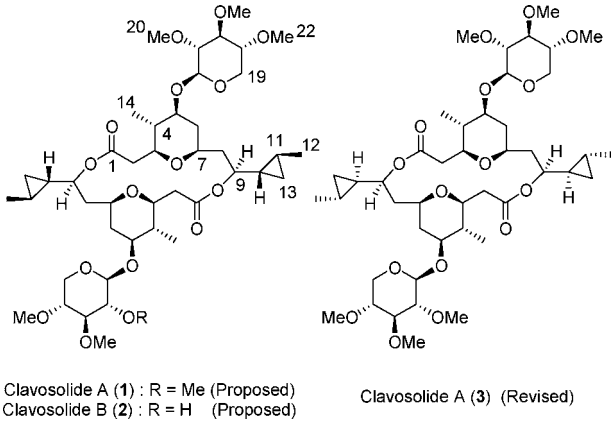
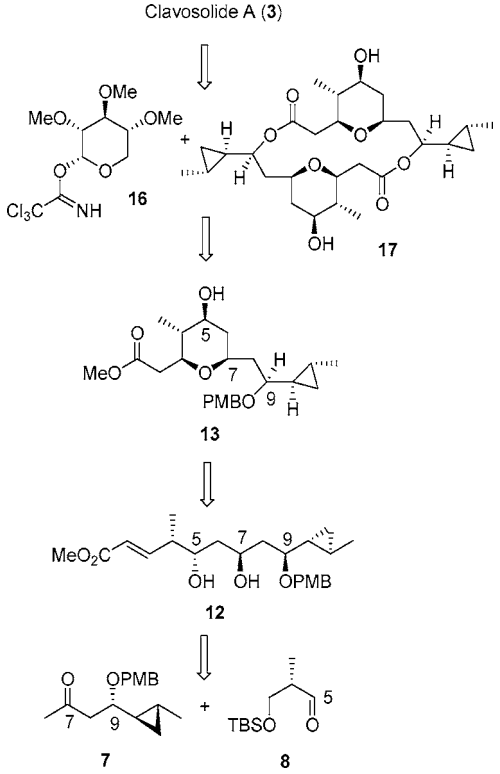


Figure 1. Proposed structure **1** and revised structure **3**.

We report herein the enantioselective synthesis of **3** and the determination of the absolute configuration of (+)-clavosolide A.

Retrosynthetic analysis for **3** is illustrated in Scheme 1. We envisioned that completion of the synthesis of **3** relied

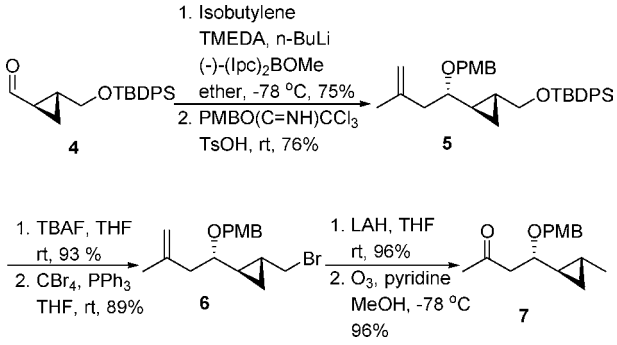
Scheme 1. Retrosynthesis of Clavosolide A (**3**)



on the coupling of diol **17** and the activated sugar moiety **16**, which was expected to be derived from D-xylose, via a Schmidt-type glycosylation. The C_2-symmetric nature of diol **17** allowed us to disconnect two ester linkages at the same time, making this strategy highly convergent from a simple precursor **13**. Intermediate **13**, with all the substituents at the equatorial position in the tetrahydropyran ring, would be constructed via intramolecular 1,4-addition of hydroxyl group at C7 to the conjugated ester moiety at C2−C3 of **12**. Subsequent stereoselective aldol reaction between ketone **7** and aldehyde **8** was expected to provide the desired (5*S*)-configuration in **12**.

The synthesis of methyl ketone **7** is summarized in Scheme 2. Brown's asymmetric methallylation[7] of aldehyde **4**, which

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



was prepared from D-mannitol according to the literature report,[8] produced homoallylic alcohol **5** (>97:3 by ^{1}H NMR) in 75% yield.

Protection of the corresponding secondary alcohol with PMB imidate provided the PMB ether **5**. Methyl ketone **7** was prepared in four steps from **5** via deprotection of the primary silyl ether, bromination of the primary alcohol, reduction[9] of the bromide **6** by lithium aluminum hydride, and ozonolysis of the double bond in the presence of pyridine.

1,5-Anti-selective aldol reaction of dibutylboron enolate of **7** with aldehyde **8**[10] in ether at −78 °C proceeded successfully to give the β-hydroxy ketone **9** (>96:4 by ^{1}H NMR) in 93% yield (Scheme 3).[11] 1,3-*Anti*-selective reduction of **9** using tetramethylammonium triacetoxyborohydride[12] in CH_3CN−AcOH was followed by treatment of the resulting *anti*-1,3-diol with 2,2-dimethoxypropane to produce acetonide **10**. The primary silyl ether group of **10** was

(7) (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439. (b) Akiyama, S.; Hooz, J. *Tetrahedron Lett.* **1973**, *14*, 4115−4118. (c) Brown, H. C.; Jadhav, P. K.; P. Perumal, P. T. *Tetrahedron Lett.* **1984**, *25*, 5111−5114.

(8) (a) Hong, J. H.; Oh, C. H.; Cho, J. H. *Tetrahedron Lett.* **2003**, *59*, 6103−6108. (b) Morikawa, T.; Sasaki, T.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97−103.

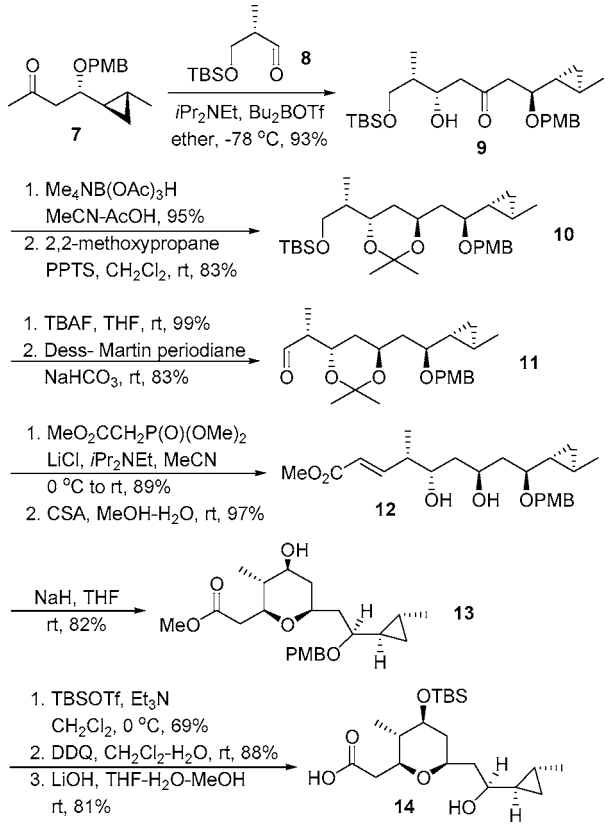
(9) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849−856. (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1982**, *47*, 276−280.

(10) For the preparation of aldehyde **8**, see: (a) Hosakawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S. I. *J. Org. Chem.* **1995**, *60*, 6159−6167. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron.* **2002**, *58*, 5909−5922. (c) Paterson, I.; Flarence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544.

(11) (a) Evans, D. A.; Colleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893−10898.

(12) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

Scheme 3. Synthesis of Hydroxyl Acid **14**



unmasked by TBAF, and subsequent Dess−Martin oxidation of the primary hydroxyl group afforded aldehyde **11** in 76% yield.

Aldehyde **11** was then converted to the (*E*)-α,*β*-conjugated ester using the Horner−Wadsworth−Emmons protocol,[13] and the acetonide protecting group was removed under acidic conditions to provide 1,3-diol **12**. Finally, key intermediate **13** was prepared by stereoselective intramolecular conjugate addition reaction[14] of the C_7-hydroxyl group under strong basic conditions with moderate diastereoselectivity (3,7-*syn*/3,7-*anti* = 11:1) in 82% yield. After an unambiguous structural confirmation by NOESY experiment,[15] secondary alcohol **13** was converted to hydroxyl acid **14**, a key intermediate for the cyclization, via a three-step sequence: protection of the secondary hydroxyl group with TBSOTf (69%), deprotection of PMB group by DDQ in CH_2Cl_2 (88%), and basic hydrolysis of ester group in THF−H_2O−MeOH (81%).

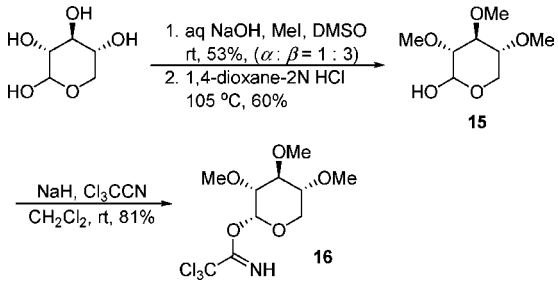
(13) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

(14) (a) Evans, D. A.; Ripin, D. H.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816−6826. (b) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 177−180. (c) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730−8736. (d) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481−484. (e) Schneider, C.; Schuffehauer, A. *Eur. J. Org. Chem.* **2000**, *65*, 73−82. (f) Edmunds, A. J. F.; Trueb W. *Tetrahedron Lett.* **1997**, *38*, 1009−1012. (g) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 6816−6826.

(15) See the Supporting Information for the 2D-NOESY spectrum.

Activated sugar moiety **16** was prepared as follows (Scheme 4). D-Xylose was treated with excess MeI in DMSO

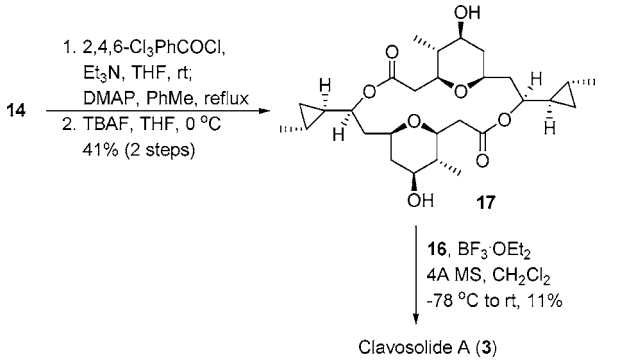
Scheme 4. Synthesis of Imidate **16**



to give per-methylated derivative[16] as a mixture of epimers (*β*/α = 3:1), which was subsequently brought to hemiacetal **15** under strongly acidic conditions.

The free hydroxy group in **15** was then converted to corresponding imidate, thereby delivering **16**[17] with the same epimeric ratio (α/*β* = 3:1) in 81% yield. With key building blocks **14** and **16** in hand, we are now in the final stage for the completion of **3** (Scheme 5). Dimerization of monomer

Scheme 5. Total Synthesis of Clavosolide A (**3**)



14 proceeded cleanly using the macrolactonization protocol of Yamaguchi in slightly modified conditions.[18] Removal of the TBS-protecting groups by TBAF in THF provided diol **17** in 41% overall yield in two steps. Finally, BF_3-assisted glycosylation between donor **16** and acceptor **17** in the presence of molecular seives provided the target compound **3** as a white solid[19] in 11% yield.

The ^{1}H NMR spectra of the compound isolated by Faulkner[3] and synthetic compound **3** are identical in all respects, including chemical shifts, coupling constants, and

(16) (a) Wang, H.; Sun, L.; Glazebnik, S.; Zhao, K. *Tetrahedron Lett.* **1995**, *36*, 2953−2956. (b) J. Schraml, E. Petrakova, O. Pihar, J. Hirsch, V. Chvalovsky, *Chem. Commun.* **1983**, *48*, 1829−1841.

(17) Furstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132−13142.

(18) Inanaga, J.; Hirata, K.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(19) Clavosolide A and B were isolated as a slightly greenish viscous oil, probably due to some impurities.

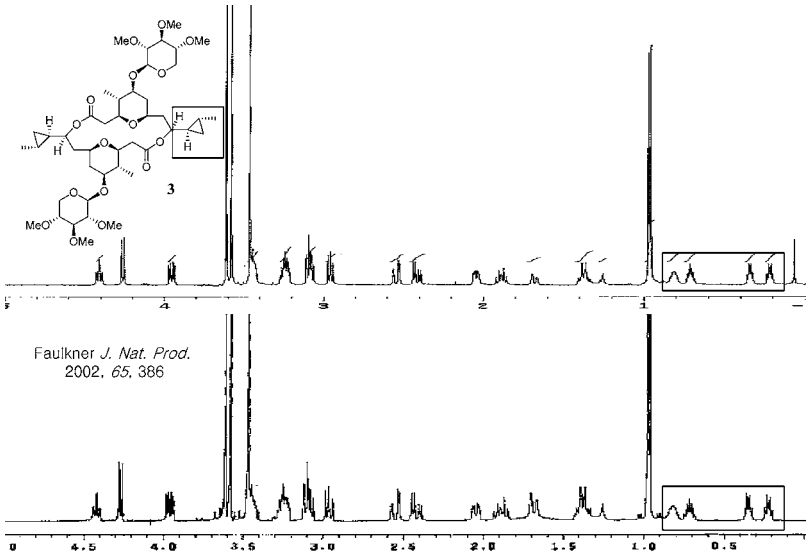


Figure 2. ^{1}H NMR spectra of synthetic compound **3** and isolated compound **1**. Reprinted with permission from Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386−388.

patterns (Figure 2). Also, the chemical shifts in ^{13}C NMR spectra of the natural and the synthetic materials are indistinguishable.[20]

Finally, the optical rotation of synthetic compound **3** was measured to be $[\alpha]_D$ +52.0 (*c* 0.165, $CHCl_3$),[3] which is in contrast to the reported value of $[\alpha]_D$ −48.5 (*c* 1, $CHCl_3$)[3] for the isolated compound **1**. Therefore, we concluded that natural (−)-clavosolide A must be an antipode of **3**.

In summary, the enantioselective synthesis of **3** was accomplished in 20 steps, in which 1,5-*anti*-selective aldol reaction of **7** with **8** and stereoselective intramolecular conjugate addition of **12** were utilized as key transformations. Structural revision of clavosolide A and determination of the absolute configuration of natural (−)-clavosolide A followed accordingly.

(20) See the Supporting Information.

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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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