

Total Synthesis of the Marine Natural Product (–)-Clavosolide A. A Showcase for the Petasis–Ferrier Union/Rearrangement Tactic

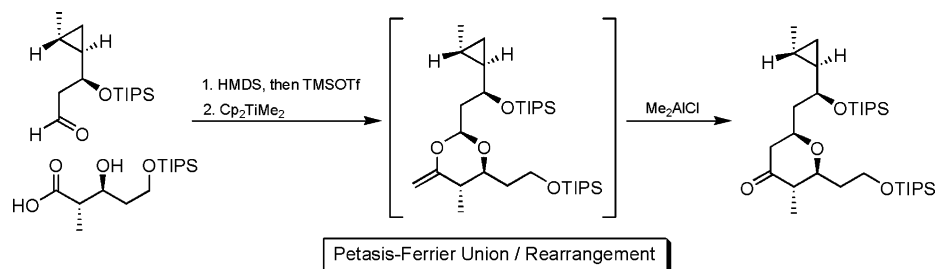
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ABSTRACT



The total synthesis of the marine diolide (–)-clavosolide A has been achieved in 17 steps (longest linear sequence) from commercially available crotonaldehyde exploiting the Petasis–Ferrier union/rearrangement tactic to construct the requisite aglycon monomer. A one-pot esterification/lactonization employing the Yamaguchi protocol, followed by bis-glycosidation, furnished (–)-clavosolide A.

In 2002, Faulkner et al.¹ disclosed the isolation and structural elucidation of clavosolides A and B, two novel marine diolide glycosides, the aglycons of which comprise a C_2 -symmetric 16-membered macrocycle punctuated with two *trans*-cyclopropylcarbinyl units (Figure 1). Erickson and co-workers² subsequently reported the structures of clavosolide C and D, two additional members of this family of marine natural products.

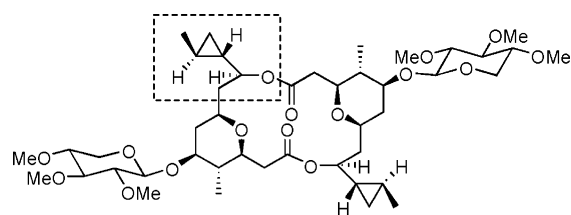
The unique architecture of the clavosolides has attracted considerable interest within the synthetic community.^{3–5} In

2005, Willis et al.³ disclosed the first total synthesis of the reported structure of clavosolide A (Figure 1). A discrepancy, observed in the ^1H NMR spectrum in the cyclopropyl region when compared to the ^1H NMR spectrum of the natural product, led to a proposed reassignment of the cyclopropylcarbinyl stereogenicity. A similar observation was made by Chakraborty and Reddy⁴ upon their synthesis of the initially assigned structure of (–)-clavosolide A. The relative stereochemistry of (+)-clavosolide A (**1**), and in particular the cyclopropylcarbinyl moiety, was subsequently secured by Lee and co-workers in their total synthesis of the natural product.⁵ Unfortunately, an error in the sign of the optical rotation led to an improbable assignment of the absolute stereochemistry.⁶

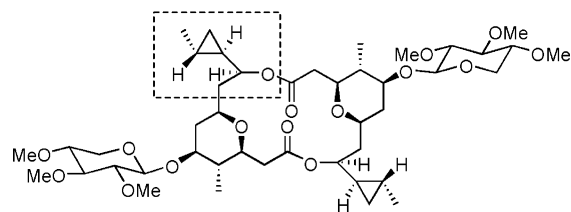
In this paper, we present a total synthesis of (–)-clavosolide A (**1**) exploiting the Petasis–Ferrier union/rearrange-

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- (3) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, *40*, 5097.
- (4) (a) Chakraborty, K. T.; Reddy, R. V. *Tetrahedron Lett.* **2006**, *13*, 2099. For an alternate synthesis of the initially assigned aglycon monomer, see: (b) Yakambram, P.; Puranik, V.; Gurjar, M. *Tetrahedron Lett.* **2006**, *22*, 3781.
- (5) Lee, H. D.; Kim, N. Y.; Kim, S. N.; Son, J. B. *Org. Lett.* **2006**, *8*, 661.

- (6) Addition and Correction: Lee, H. D.; Kim, N. Y.; Kim, S. N.; Son, J. B. *Org. Lett.* **2006**, *8*, 3411.



(-)-Clavosolide A (Proposed)



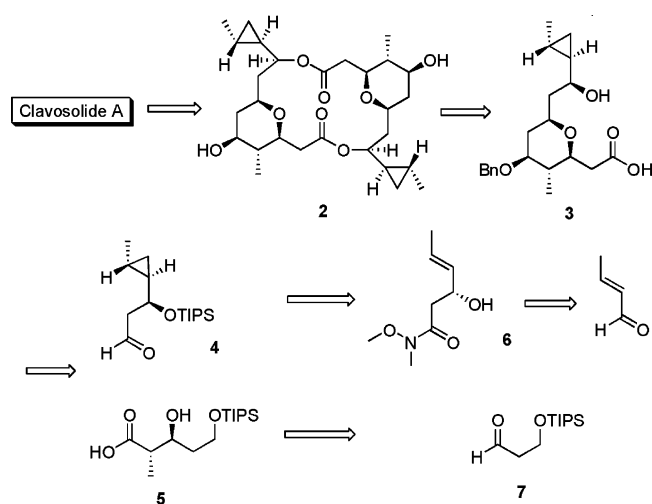
Clavosolide A (**1**) (Revised)

Figure 1. Original and revised structure of clavosolide A.

ment,^{7a,8} a tactic previously developed and successfully applied in our laboratory for the construction of a variety of architecturally complex natural products.^{7b} Our focus on (-)-clavosolide A (**1**) was to explore the viability of the Petasis–Ferrier union/rearrangement tactic in a system possessing a highly acid-labile functionality (i.e., a cyclopropylcarbinyl system). Establishment of the absolute stereochemistry was also a goal.

From the retrosynthetic perspective (Scheme 1), the aglycon of (-)-clavosolide A (**2**) was envisioned to arise

Scheme 1

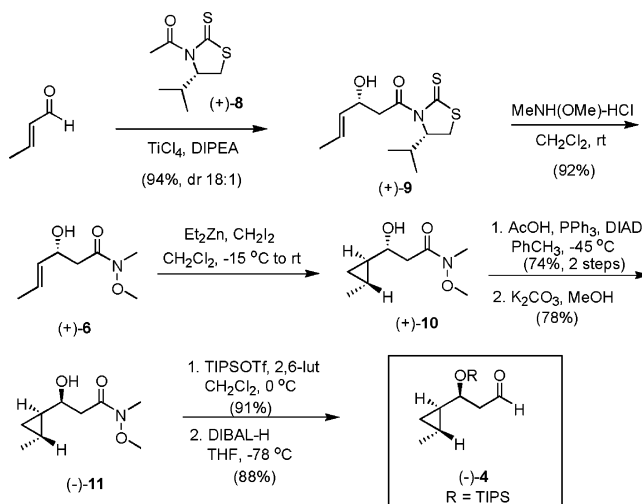


via a one-pot dimerization of monomer **3**, the product of a Petasis–Ferrier union/rearrangement, involving aldehyde **4** possessing the acid-labile cyclopropylcarbinyl moiety with hydroxy acid **5**. Aldehyde **4** in turn would derive from

commercially available crotonaldehyde exploiting a Nagao acetate aldol,¹⁰ followed by application of the Charette modification¹¹ of the Simmons–Smith cyclopropanation. The requisite β -hydroxy acid **5** was envisioned to arise via a Masamune boron-mediated anti-aldol⁹ involving aldehyde **7**.

We began the synthesis with construction of aldehyde **4** employing commercially available crotonaldehyde; seven steps were required (Scheme 2). A TiCl_4 -mediated Nagao

Scheme 2



acetate aldol reaction¹⁰ employing thiozolidinone (+)-**8** and crotonaldehyde gave allylic alcohol (+)-**9**; the yield was 94% (dr 18:1). Facile conversion to the Weinreb amide,¹² followed by the Charette modification¹¹ of the Simmons–Smith cyclopropanation, then led to *syn*-cyclopropylcarbinol (+)-**10** as a single diastereomer (NMR).

To correspond with the revised cyclopropylcarbinyl structure of (-)-clavosolide A (**1**), inversion of the stereogenicity at C9 was required.¹³ To this end, a Mitsunobu reaction¹⁴

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(8) Concurrent with our efforts, Willis et al. also achieved the total synthesis of (-)-clavosolide A; see: Barry, C. S.; Elsworth, J. D.; Sedan, T. P.; Bushby, N.; Harding, R. J.; Alder, W. R.; Willis, L. C. *Org. Lett.* **2006**, 8, 3319. We thank Professor Willis for helpful discussion during the course of this synthetic venture.

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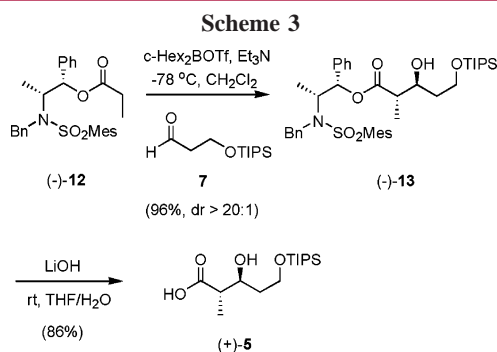
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(13) Anti-cyclopropanation of the TIPS-protected allylic alcohol led to a mixture (9:1) favoring the undesired *syn*-cyclopropylcarbinol (see: Charette, A. B.; Lacasse, M.-C. *Org. Lett.* **2002**, 20, 3351).

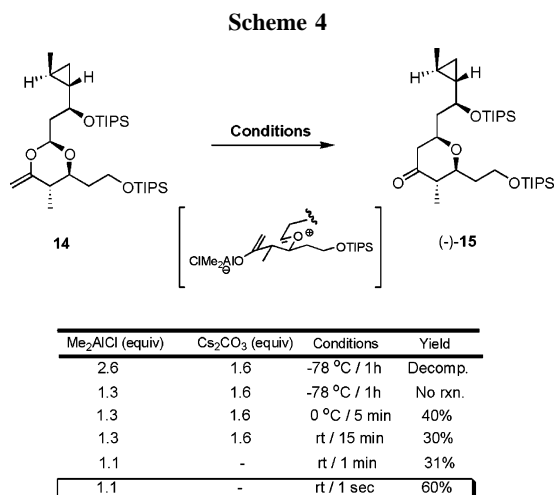
(14) Macor, J. E.; Wehner, J. M. *Heterocycles* **1993**, 35, 349.

with acetic acid furnished an inseparable diastereomeric mixture favoring the desired acetate (12:1, inversion vs retention).¹⁵ Ester hydrolysis followed by flash chromatography furnished the pure *anti*-cyclopropylcarbinol (–)-**11** in 58% yield for the three steps. Access to the first Petasis–Ferrier union/rearrangement component, aldehyde (–)-**4**, was then available via silyl protection of the hydroxyl group followed by DIBAL reduction.

The requisite β -hydroxy acid (+)-**5** was prepared in two steps. The proposed boron-mediated anti-aldol delivered alcohol (–)-**13** in 96% yield (dr > 20:1). Removal of the chiral auxiliary furnished hydroxy acid (+)-**5** in 86% yield (Scheme 3).



Conditions to effect the union/rearrangement via the Petasis–Ferrier tactic were initially developed and optimized employing enol acetal **14**,¹⁷ possessing the earlier assigned syn relationship in the cyclopropylcarbinyl moiety (Scheme 4). We were well aware of the potential risk of the

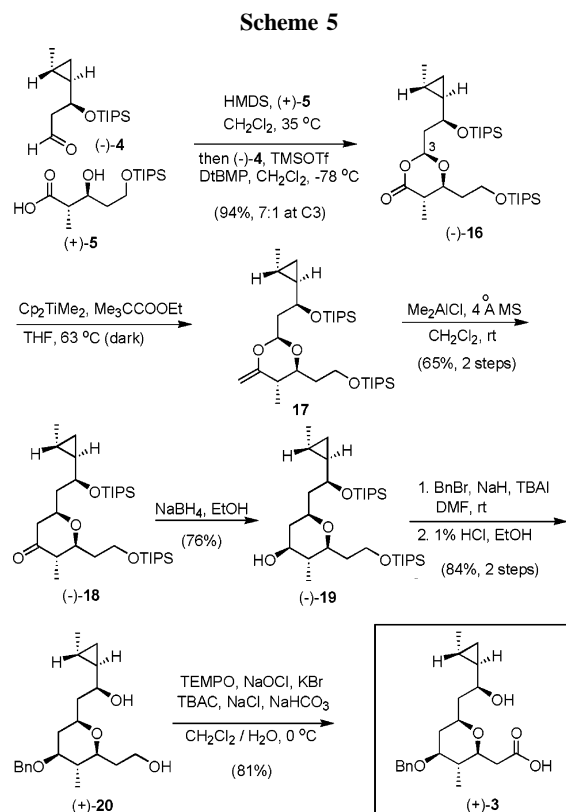


Me₂AlCl-promoted rearrangement due to the lability of the cyclopropylcarbinyl moiety to facile rearrangement¹⁶ under

(15) The order of addition (betaine formation) and temperature (–45 °C in toluene) in the Mitsunobu reaction proved to be critical to achieve high stereoselectivity.

Lewis acidic conditions. Although the union of the β -hydroxy acid and aldehyde proceeded smoothly, the Petasis–Ferrier rearrangement, not surprisingly, was highly dependent on the temperature, reaction time, and base additives employed. Best conditions proved to be extremely rapid addition of Me₂AlCl to enol acetal **14** at room temperature; a single diastereomer (–)-**15** resulted in 60% yield. Slower additions and/or inverse addition in conjunction with lower temperatures or prolonged reaction times resulted either in no reaction or complete decomposition. Other Lewis acids, as well as base additives such as Me₃Al and 2,6-di-*tert*-butyl-4-methylpyridine (DtBMP), were either incompatible or gave no reaction at room temperature.

With optimized conditions for the union/rearrangement in hand, we turned our attention to the revised structure of clavosolide A.^{3,5} Bis-silylation of β -hydroxy acid (+)-**5**, followed by TMSOTf-promoted¹⁸ condensation with aldehyde (–)-**4**, furnished dioxanone (–)-**16** as an inseparable mixture (7:1) of diastereomers at C3 in 94% yield. Petasis–Tebbe methylenation¹⁹ followed by immediate rearrangement of the unstable enol acetal **17**, employing the optimal conditions, led after purification by flash chromatography to tetrahydropyranone (–)-**18** in 65% yield for the two steps (Scheme 5).



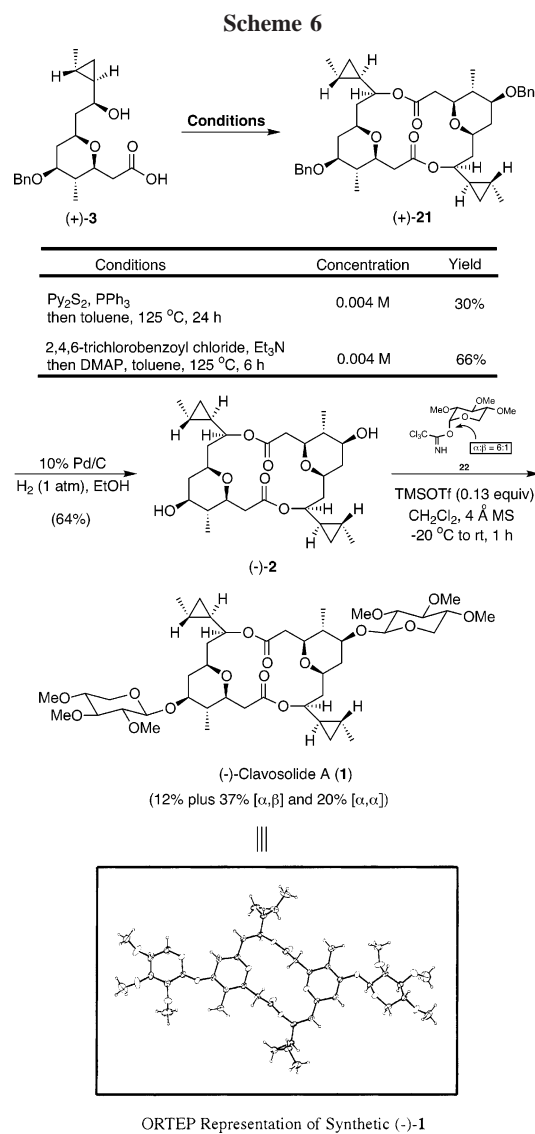
Completion of the aglycon monomer now required four steps. Sodium borohydride reduction²⁰ of tetrahydropyranone

(16) Poulter, D. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 3650.

(17) Enol acetal **14** was prepared in seven steps and 58% overall yield by a similar sequence as shown in Scheme 5 (excluding the Mitsunobu inversion).

(-)-**18** furnished the desired equatorial alcohol (-)-**19** in 76% yield (dr > 10:1), which was immediately protected as the corresponding benzyl ether. Removal of the silyl groups under acidic conditions then led to diol (+)-**20** in 84% yield for the two steps. Selective oxidation²¹ of the primary alcohol employing TEMPO, NaOCl, and tetrabutylammonium chloride (TBAC) completed construction of monomer (+)-**3** in 81% yield.

With monomer (+)-**3** in hand, we now faced the critical dimerization (Scheme 6). Several conditions were explored



(+)-**21** in 66% yield without noticeable formation of higher molecular weight congeners. Removal of the benzyl protecting groups by hydrogenolysis furnished aglycon (-)-**2** in 64% yield, identical in all respects including chiroptic properties to those reported by Lee and co-workers.⁵

Turning to the requisite bis-glycosidation, the challenge of high diastereoselectivity in the absence of anchimeric assistance would require an optimal acid (TMSOTf)²⁷ and solvent (e.g., acetonitrile)²⁵ for the glycosidation protocol. Unfortunately, such conditions only led to decomposition of both the aglycon and the glycosyl donor **22**,²⁶ presumably due to the nucleophilic nature of the solvent. Similar conditions with CH₂Cl₂ as the solvent did however furnish (-)-clavosolide A (**1**) in 12% yield, along with the expected α,β and α,α' anomers in 37% and 20% yield, respectively.

The ¹H NMR and ¹³C NMR data of (-)-clavosolide A (**1**) proved to be in excellent agreement with the corresponding data for both the natural and synthetic (-)-clavosolide A, as reported by Faulkner et al.¹ and by Lee and co-workers,⁵ respectively. However, upon measurement of the optical rotation, we obtained a value of -42.5 (*c* 0.10, CHCl₃), in contrast to the value of +52.0 (*c* 0.165, CHCl₃) reported by Lee and co-workers.⁵ To resolve this discrepancy, the relative and absolute stereochemistry of synthetic (-)-**1** were confirmed by X-ray crystallography, wherein the absolute stereochemistry was established based on the absolute configuration of D-(+)-xylose, employed to construct glycosyl donor **22**. We conclude therefore that the absolute stereochemistry of natural (-)-clavosolide A is as illustrated in Scheme 6.

In summary, an enantioselective total synthesis of (-)-clavosolide A has been achieved in 17 steps (longest linear sequence). Central to this venture was the highly convergent Petasis–Ferrier union/rearrangement to construct the *cis*-tetrahydropyran monomer (+)-**3**, demonstrating the viability of this tactic with an acid labile moiety. A one-pot dimerization then efficiently delivered aglycon (-)-**2**.

Acknowledgment. Financial support was provided by the National Institute of Health (National Institute of General Medical Screening) through Grant No. GM-29028. In addition, we thank Professor Lee (Sogang University, Korea) for his helpful resolution of the discrepancy concerning the sign of the optical rotation of their synthetic clavosolide A.

Supporting Information Available: Spectroscopic and analytical data for all new compounds, as well as experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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both with the original and revised clavosolide monomers.²² The Corey–Nicolaou “double activation” protocol²³ provided diolide (+)-**21** in 30% yield, albeit with low conversion. Pleasingly, the Yamaguchi conditions²⁴ cleanly afforded

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 (26) See the Supporting Information.
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