ORGANIC LETTERS

2006
Vol. 8, No. 15
3315−3318

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

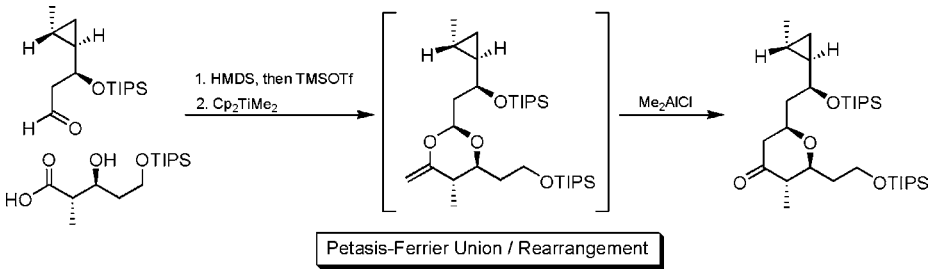
Amos B. Smith, III* and Vladimir Simov

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received May 12, 2006

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.

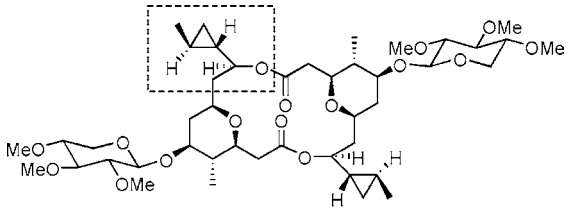
In 2002, Faulkner et al.[1] disclosed the isolation and structural elucidation of clavosolides A and B, two novel marine diolide glycosides, the aglycons of which comprise a C_2-symmetric 16-membered macrocycle punctuated with two *trans*-cyclopropylcarbinyl units (Figure 1). Erickson and co-workers[2] 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 ^{1}H NMR spectrum in the cyclopropyl region when compared to the ^{1}H NMR spectrum of the natural product, led to a proposed reassignment of the cyclopropylcarbinyl stereogenicity. A similar observation was made by Chakraborty and Reddy[4] 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-

(1) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386.
(2) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod.* **2002**, *65*, 1303.
(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.

10.1021/ol0611752 CCC: $33.50
Published on Web 06/28/2006



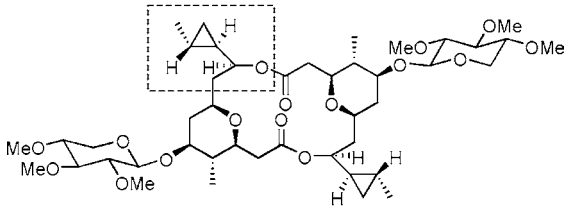
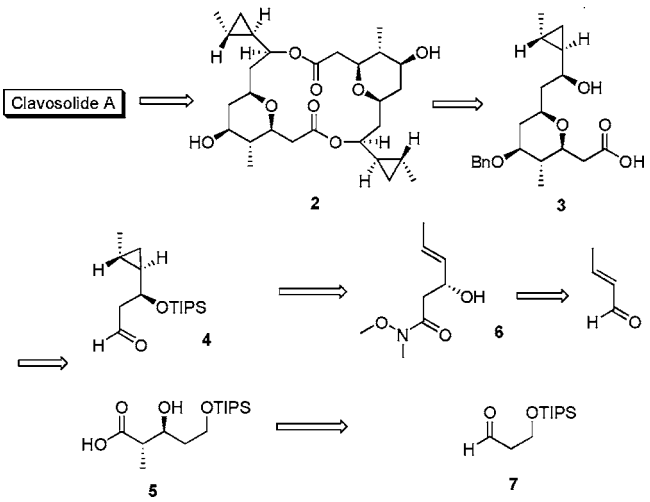


Figure 1. Original and revised structure of clavosolide A.

ment,[7a,8] a tactic previously developed and successfully applied in our laboratory for the construction of a variety of architectually 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

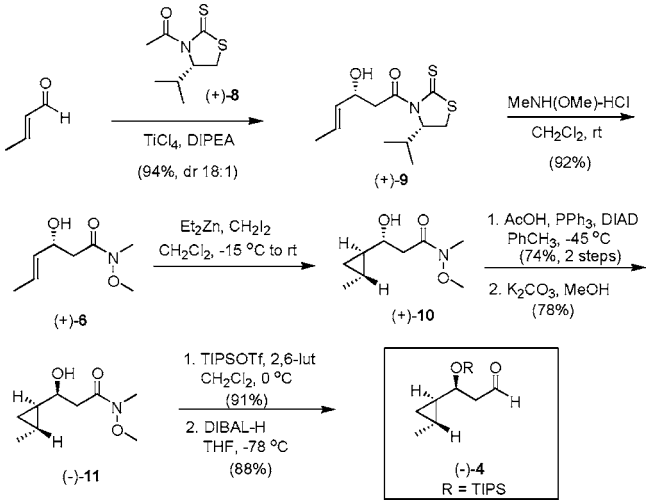
Scheme 1



via a one-pot dimerization of monomer **3**, the product of a Petasis−Ferrier union/rearrangement, involving aldehyde **4** possesing 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 modification[11] of the Simmons−Smith cyclopropanation. The requisite β-hydroxy acid **5** was envisioned to arise via a Masamune boron-mediated anti-aldol[9] 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 reaction[10] employing thiozilidinone (+)-**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 modification[11] 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 reaction[14]

(7) (a) Petsis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *37*, 141. (b) (+)-Phorboxazole A: Smith, A. B, III.; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. Smith, A. B., III; Razler, M. T.; Ciavarri, P. J.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *20*, 4399. (+)-Spongistatin 1: Smith, A. B., III; Sfouggatakis, C.; Gotchev, B. D.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *20*, 3637. (+)-Zampanolide and (+)-dactylolide: Smith, A. B., III; Safonov, I. G.; Corbett, M. R. *J. Am. Chem.* Soc. **2002**, *124*, 11102. (−)-Kendomycin: Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948. (+)-Sorangicin A: Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *14*, 3099.

(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.

(9) Abiko, A.; Buske, D. C.; Liu, J.; Inoue, T. *J. Org. Chem.* **2002**, *67*, 5250.

(10) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M. *J. Org. Chem.* **1986**, *51*, 2391.

(11) Charette, A.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966.

(12) Rychnovsky, S. D.; Sinz, C. J. *Tetrahedron* **2002**, *58*, 6561

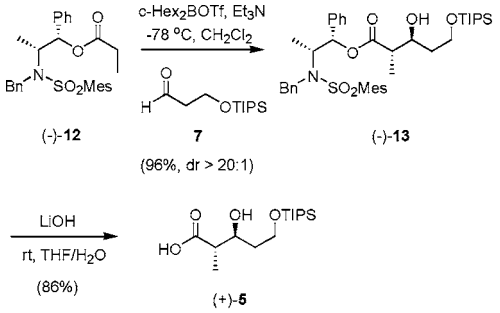
(13) Anti-cyclopropanation of the TIPS-protected allylic alcohol led to a mixture (9:1) favoring the undesired *syn*-cyclopropylcarbinol (see: Charette, A. B.; Lacasse, M.-C. *Org. Lett.* **2002**, *20*, 3351)

(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.

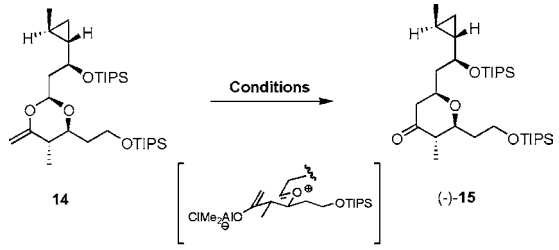
The requisite β-hydroxy acid (+)-**5** was prepared in two steps. The proposed boron-mediated anti-aldol delivered alcohol (−)-**13** in 96% yield (dr > 20:1). Removal of the chiral auxiliary furnished hydroxy acid (+)-**5** in 86% yield (Scheme 3).

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 moeity (Scheme 4). We were well aware of the potential risk of the

Scheme 4

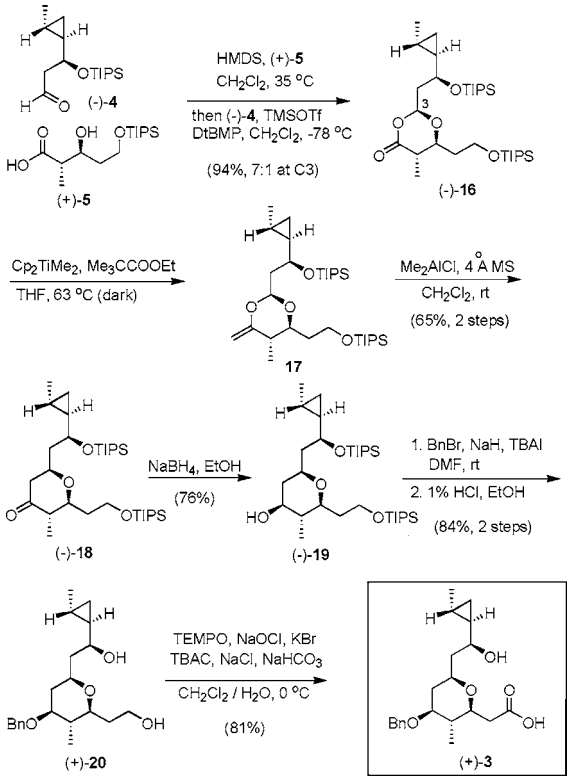


Me_2AlCl (equiv)	Cs_2CO_3 (equiv)	Conditions	Yield
2.6	1.6	-78 °C / 1h	Decomp.
1.3	1.6	-78 °C / 1h	No rxn.
1.3	1.6	0 °C / 5 min	40%
1.3	1.6	rt / 15 min	30%
1.1	-	rt / 1 min	31%
1.1	-	rt / 1 sec	60%

Me_2AlCl-promoted rearrangement due to the lability of the cyclopropylcarbinyl moiety to facile rearrangement[16] under 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 Me_2AlCl 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 Me_3Al 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-promoted[18] condensation with aldehyde (−)-**4**, furnished dioxanone (−)-**16** as an inseparable mixture (7:1) of diastereomers at C3 in 94% yield. Petasis−Tebbe methylenation[19] 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).

Scheme 5



Completion of the aglycon monomer now required four steps. Sodium borohydride reduction[20] of tetrahydropyranone

(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.

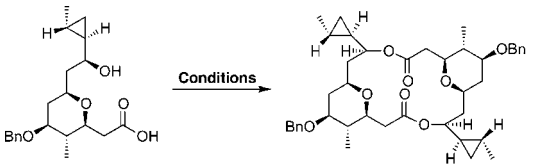
(16) Poulter, D. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *13*, 3650.

(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).

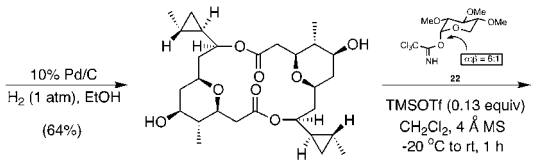
(−)-**18** furnished the desired equatorial alcohol (−)-**19** in 76% yield (dr > 10:1), which was immediately protected as the corresponding benzyl ether. Removal of the silyl groups under acidic conditions then led to diol (+)-**20** in 84% yield for the two steps. Selective oxidation[21] of the primary alcohol employing TEMPO, NaOCl, and tetrabutylammonium chloride (TBAC) completed construction of monomer (+)-**3** in 81% yield.

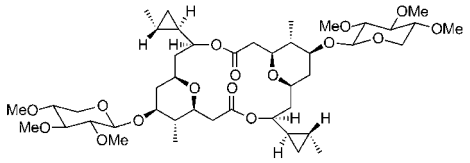
With monomer (+)-**3** in hand, we now faced the critical dimerization (Scheme 6). Several conditions were explored

Scheme 6

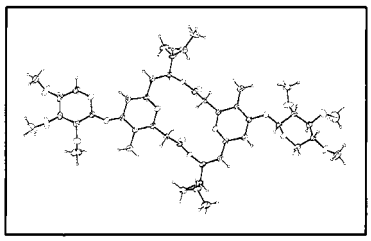


Conditions	Concentration	Yield
Py_2S_2, PPh_3 then toluene, 125 °C, 24 h	0.004 M	30%
2,4,6-trichlorobenzoyl chloride, Et_3N then DMAP, toluene, 125 °C, 6 h	0.004 M	66%





(-)-Clavosolide A (**1**)
(12% plus 37% [α,β] and 20% [α,α])



ORTEP Representation of Synthetic (-)-**1**

both with the original and revised clavosolide monomers.[22] The Corey−Nicolaou "double activation" protocol[23] provided diolide (+)-**21** in 30% yield, albeit with low conversion. Pleasingly, the Yamaguchi conditions[24] cleanly afforded (+)-**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 CH_2Cl_2 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 ^{1}H NMR and ^{13}C 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, $CHCl_3$), in contrast to the value of +52.0 (*c* 0.165, $CHCl_3$) 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.

OL0611752

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(26) See the Supporting Information.
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