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Total Synthesis of the Marine Natural Product (−)-Clavosolide A

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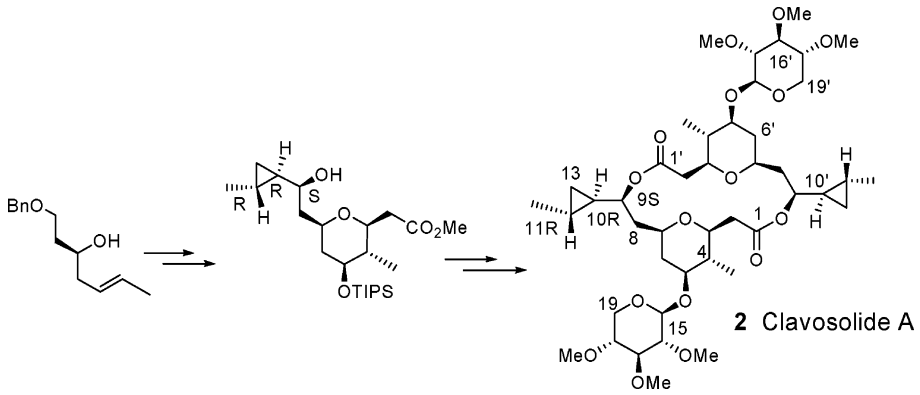
ABSTRACT



The total synthesis of the marine metabolite clavosolide A is reported which confirms the structure and absolute configuration of the natural product as the symmetrical diolide glycosylated by permethylated D-xylose moieties, 2.

The clavosolides A−D are a family of unusual diolides isolated from extracts of the marine sponge *Myriastra clavosa* collected in the Phillipines.[1] The structure of clavosolide A was assigned originally as diolide **1** on the basis of extensive spectroscopic studies combined with molecular modeling (Figure 1). It is an unusual symmetrical 16-membered ring dilactone assembled on a functionalized tetrahydropyran core with a permethylated xylose moiety which was assumed to have the more usual D-configuration. The macrocycle is further adorned by two cyclopropyl-containing side chains which were assigned the configuration 9*S*,9′*S*,10*S*,10′*S*,11*S*,11′*S*.

We recently completed the first total synthesis of the proposed structure of clavosolide A (**1**).[2] However, from the spectral data it was apparent that while the synthetic material

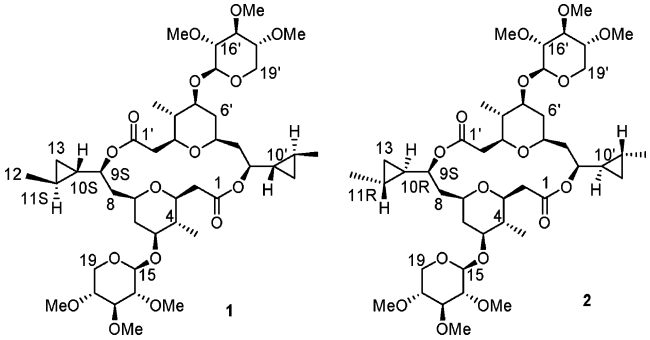


Figure 1. Originally proposed structure of clavosolide A (**1**)[1] and proposed revised structure **2**[2] for the natural product.

was closely related to the natural product, they were not the same. Following extensive NMR studies combined with evidence from the X-ray structure of a diastereomer, we

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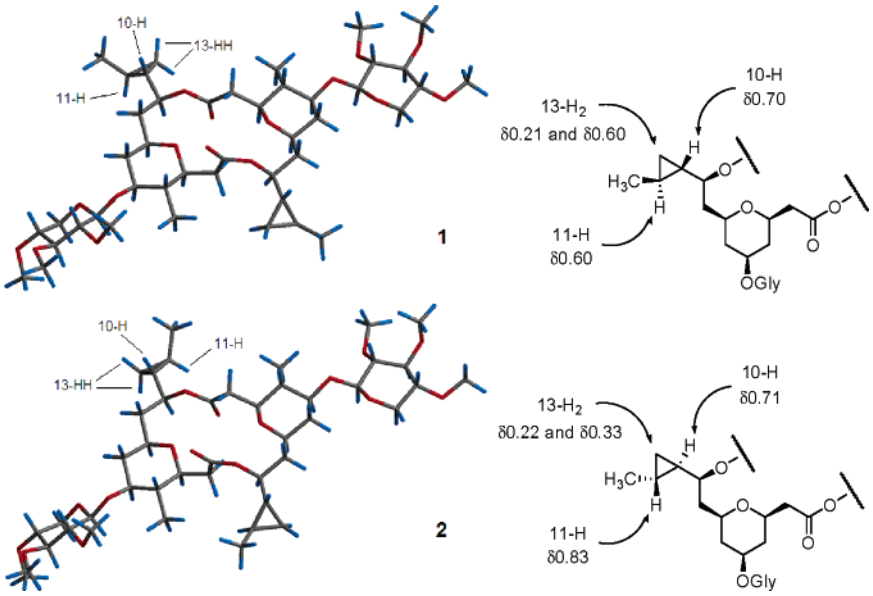

Figure 2. Models of (9*S*,10*S*,11*S*)-diastereomer **1** and (9*S*,10*R*,11*R*)-diastereomer **2** with NMR assignments.

proposed that **1** is in fact a diastereomer of the natural product and that clavosolide A has the 9*S*,9′*S*,10*R*,10′*R*,11*R*,11′*R* side chain **2** (Figure 1).[2]

Recently, Charkaborty and Reddy have completed a total synthesis of **1** using a radical-mediated strategy to assemble the tetrahydropyran ring,[3] while Gurjar and co-workers have reported the synthesis of the monomeric unit toward clavosolide A.[4] Furthermore Lee and co-workers[5] have described the first total synthesis of the proposed revised structure **2** for clavosolide A. Interestingly, while their spectral data were in good agreement with that reported for the natural product, the optical rotation was $[\alpha]_D$ +52.0 (*c* 0.165, $CHCl_3$), whereas for clavosolide A $[\alpha]_D$ −48.5 (*c* 1, $CHCl_3$)[1a] was reported; hence, Lee concluded that **2** is the antipode of clavosolide A. This would imply that, rather unexpectedly, clavosolide A must be derived from L-xylose.

Herein, we describe the total synthesis of **2**. The spectral data for **2** are in accord with the literature for clavosolide A[1a] and that reported by Lee.[5] However, in contrast to Lee, we found that the optical rotation is in agreement with that for the natural product. Hence we conclude that clavosolide A has structure **2** with the permethylated glycoside moieties derived from D-xylose.

Prior to embarking on the synthesis of diolide **2**, molecular modeling using Spartan was undertaken to gain further support for the proposed assignment[2] of the stereochemistry of the cyclopropyl side chains of the natural product and to rationalize the NMR data. A conformational search of the symmetrical dimers **1** and **2** was conducted using molecular mechanics energy minimization calculations (Figure 2). The ring adopts a similar conformation in both cases with an elongated diolide ring with the tetrahydropyrans and cyclopropyl groups lying almost in the plane of the ring. In the model of the synthetic diolide **1**, one of the cyclopropyl protons (13-H) is considerably closer to the carbonyl group of the ring than the other 13-H, which would account for the difference in their chemical shifts ($\Delta\delta$ = 0.39 ppm) in the ^{1}H NMR spectrum of **1**.

In contrast in the proposed structure **2** of the natural product, neither of the 13-protons comes within the deshielding region of the carbonyl group; hence, as expected, they have similar chemical shifts ($\Delta\delta$ = 0.11 ppm). Furthermore, the chemical shifts of the signals assigned to 11-H in diolides **1** and **2** are consistent with the models. In the model of **2**, 11-H points toward the diolide ring and resonates downfield (at δ 0.83) compared with the signal assigned to 11-H in **1** which resonates at δ0.60 and is directed away from the ring. Thus, these in silico studies are entirely consistent with the proposed revised structure **2** for clavosolide A.

Our synthetic approach to diolide **2** involved assembly of the tetrahydropyran core **6** via a stereoselective Prins cyclization, introduction of the cyclopropyl side chain, then dimerization, and finally glycosidation. We have previously reported[6] the enantioselective synthesis of **6** using a Nokami crotyl transfer reaction with the menthone-derived tertiary alcohol **3**[7] and 3-benzyloxypropanal to prepare the (*S*)-homoallylic alcohol **4** (Scheme 1). Treatment of **4** with methyl propiolate and catalytic *N*-methylmorpholine gave

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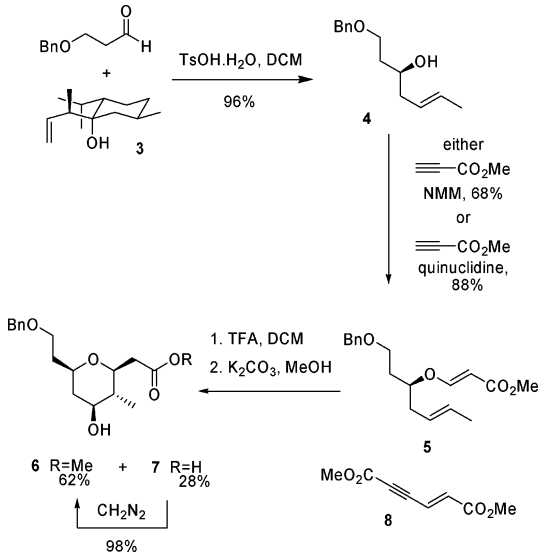
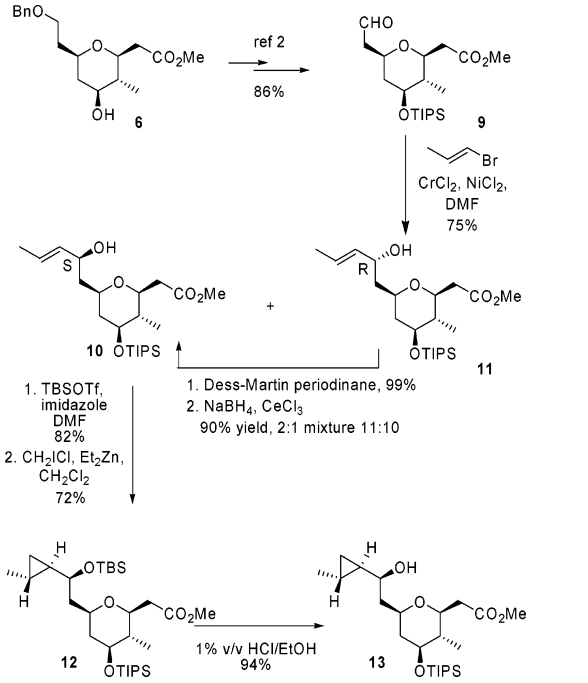
Scheme 1. Synthesis of Tetrahydropyran **6**



Scheme 2. Synthesis of Monomer **13**



enol ether **5**. The pivotal cyclization was achieved by a TFA-mediated Prins reaction to create the three new asymmetric centers in tetrahydropyran **6** with complete stereocontrol in a single pot process. Some ester hydrolysis occurred, but acid **7** was readily methylated with diazomethane giving ester **6** in 88% overall yield from **5**.

While the synthesis of enol ether **5** from alcohol **4** gave reasonable yields (68%), it proved problematic on a large scale. The reaction took several days to reach completion at room temperature and required an excess of methyl propiolate resulting in the formation of an unwanted byproduct **8**,[8] which proved difficult to remove. Hence, we have reinvestigated this reaction. Aggarwal and co-workers have used quinuclidine to good effect in the Baylis−Hillman reaction,[9] and indeed, we found that it proved to be an excellent catalyst in the synthesis of **5**. Slow addition of methyl propiolate to alcohol **4** in the presence of catalytic quinuclidine gave the required enol ether **5** in 88% isolated yield after just 5 h at room temperature. Since formation of enol ether **5** and subsequent Prins cyclization to tetrahydropyran **6** are both conducted in CH_2Cl_2 and quinuclidine is used in only catalytic amounts, it proved possible to telescope the two reactions into a single step by simply adding TFA to the mixture containing alcohol **4**, methyl propiolate, and quinuclidine once enol ether formation was complete (monitored by TLC).

With gram quantities of tetrahydropyran **6** in hand, it was next converted to aldehyde **9**, and then a Nozaki−Hiyama−Kishi coupling[10] of **9** with (*E*)-1-bromo-1-propene in the presence of $CrCl_2$ and catalytic $NiCl_2$ gave a 1:1 mixture of allylic alcohols **10** and **11** (Scheme 2). The assignment of the stereochemistry of these alcohols was reported previously.[2] The (*R*)-alcohol **11** could be converted to the required (*S*)-isomer **10** by a straightforward two-step oxidation/reduction using Dess−Martin periodinane[11] followed by standard Luche reduction conditions. To establish the required configuration of the side chain of **2**, a stereoselective anti cyclopropanation of (*S*)-alcohol **10** was required. This was achieved using a bulky protecting group on the secondary alcohol. Thus, allylic alcohol **10** was first protected as the TBS ether and then treatment with Et_2Zn and CH_2ICl[12] gave a 4:1 mixture of diastereomers (91% total yield of the diastereomers) in favor of the required anti product **12**. Following purification of **12** by column chromatography, the TBS ether was removed selectively under mild conditions leaving the TIPS protecting group intact giving **13** in 55% yield from **10**.

Having prepared the monomer **13**, then the key dimerization to diolide **15** was investigated. Methyl ester **13** was hydrolyzed under mild conditions using TMSONa followed by AcOH to give hydroxy acid **14** in 99% yield. For the synthesis of **1** we had used the Corey−Nicolaou protocol[13] to effect dimerization, which gave the required product in 53% yield.[2] However, on treatment of hydroxy acid **14** under similar conditions using 2,2′-bipyridyl disulfide and Ph_3P followed by heating the resultant thiol ester in toluene, a significant amount of the cyclic tetramer, ESI *m*/*z* 1665.1306 $[MNa]^+$ was formed along with the required dimer, ESI *m*/*z* 843.5614 $[MNa]^+$. Even using very dilute solutions, formation of the tetramer proved problematic. Both Chakraborty[3] and Lee[5] had effected the dimerization of analogous TBS-

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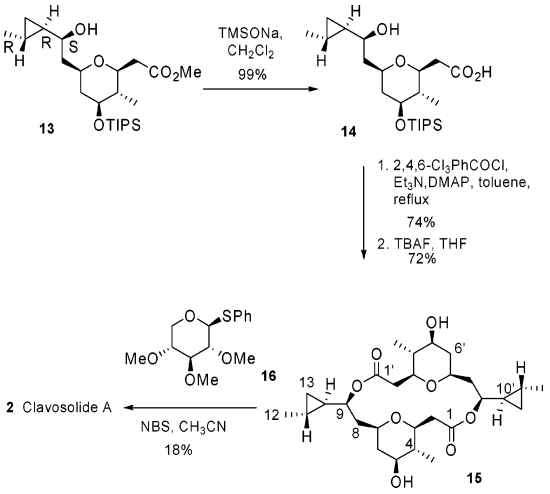
protected hydroxy acids by a modified Yamaguchi procedure[14] in their syntheses of **1** and **2**, respectively. Treatment of **14** with 2,4,6-trichlorobenzoyl chloride and Et_3N followed by heating in toluene with DMAP gave the dimer. Removal of the TIPS protecting group using TBAF gave the aglycone **15** in 53% overall yield from hydroxy acid **14**. To complete the synthesis of clavosolide A, glycosidation of **15** was investigated using a modification of the Nicolaou NBS glycosylation protocol.[15] Ratcliffe and Fraser-Reid[16] have reported that addition of CH_3CN leads to enhanced β-selectivity in glycosidation reactions, and hence, **15** was reacted with thioether **16** (prepared in good yield from D-xylose[2]) in the presence of NBS and CH_3CN. This gave the expected mixture of [α,α]- and [α,β]-anomers as well as the required [β,β]-anomer **2**, which was isolated in 18% yield. In the ^{1}H NMR spectrum of **2**, the signal assigned to 15-H (and 15′H) appeared as a doublet (J 8 Hz) at δ 4.27 consistent with the axial−axial relationship of 15-H and 16-H. There was an excellent correlation of the spectral data of the synthetic clavosolide A **2** with those reported for the natural product by Rao and Faulkner[1a] and by Lee and co-workers.[5] Our product was a white solid with $[\alpha]_D$ −38.0 (*c* 1, $CHCl_3$), while the natural product had been isolated as a greenish oil (the color was ascribed to the high chlorophyll content of the extract) from *M. clavosa*, $[\alpha]_D$ −48.5 (*c* 1, $CHCl_3$),[1a] and hence, we concluded that the natural product is indeed **2**, (−)-clavosolide A. Concurrent with this work, Smith and Simov[17] completed the total synthesis of **2**, and Lee[18] amended the value for their optical rotation from that given previously[5] to −39.7 (*c* 0.055, $CHCl_3$) in accord with (−)-clavosolide.

In conclusion, the studies described herein confirm the structure and absolute configuration of the marine natural product (−)-clavosolide A which is the symmetrical diolide **2** glycosylated with permethylated D-xylose moieties. The total synthesis of clavosolide A was achieved via an efficient assembly of the tetrasubstituted tetrahydropyran core from 3-benzyloxypropanal in 76% yield and with complete stereocontrol. Following the stereoselective creation of the required cyclopropyl side chain, dimerization and glycosidation gave the target compound **2**.

Scheme 3. Completing the Synthesis of (−)-Clavosolide A



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Supporting Information Available: Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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