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# An Efficient Formal Synthesis of (−)-Clavosolide A Featuring a "Mismatched" Stereoselective Oxocarbenium Reduction

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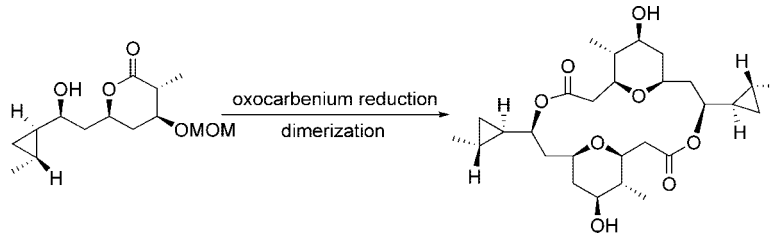
## ABSTRACT




**The enantioselective formal synthesis of the polyketide marine natural product (−)-clavosolide A is presented. The construction of the *β*-*C*-glycoside subunit is highlighted by a one-pot oxocarbenium cation formation/reduction sequence. Yamaguchi dimerization afforded the diolide aglycon in 18 steps (longest linear sequence).**

Secondary metabolites of marine origins continue to garner significant attention from the synthetic, as well as, medicinal community. The dimeric marine glycoside (−)-clavosolide A and related structures were recently isolated from the marine sponge *M. clavosa* in 2002 by Faulkner and co-workers who initially proposed the relative and absolute configuration of all clavosolides based on the extensive usage of 2-D NMR techniques.[1] Thus, the initial absolute configuration of the stereocenters surrounding the cyclopropyl subunit were described as 9*S*,9′*S*,10*S*,10′*S*,11*S*,11′*S* as shown in Scheme 1. A second disclosure by Erickson independently confirmed the absolute and relative configuration of (−)-clavosolides A and B as originally proposed by Faulkner and also described the presence of two subsequent class members, clavosolides C and D.[2]

This novel, highly functionalized 16-membered dimeric polyketide macrocyclic has attracted considerable interest from the synthetic community. The first synthesis of the proposed clavosolide A structure was reported by the Willis group. However, the synthesized compound was a diastereomer of the originally proposed structure.[3] Close inspection of the cyclopropyl region of the $^1$H NMR spectrum revealed the origin of the discrepancy between the synthesized structure and that of the natural product. This observation subsequently led to an amended structure (**1**) being proposed by Willis with the 9*S*,9′*S*,10*R*,10′*R*,11*R*,11′*R* absolute stereochemistry for the cyclopropane rings. The synthesis of **1** by Lee and co-workers yielded material that was spectroscopically identical to the originally described structure and hence constituted the first total synthesis of **1**.[4] The initial efforts of Chakraborty also yielded a synthesis of a diastereomer of **1**. However, a follow-up report provided the

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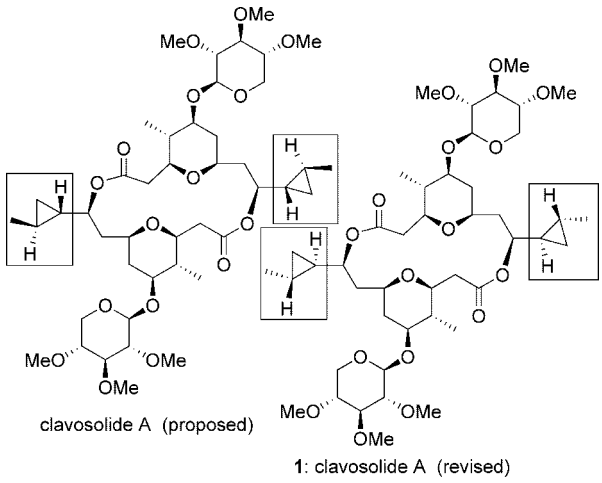
**Scheme 1.** Original and Revised Structures of (−)-Clavosolide A




correct structure.[5] Similarly, Gurjar and co-workers synthesized the incorrect monomeric subunit of **1**.[6] The efforts of Smith confirmed the relative and absolute stereochemistry of **1** through total synthesis and ultimately via X-ray analysis.[7] A revised total synthesis of **1** by the Willis group also reconfirmed Smith's preceding efforts.[8] While **1** has no reported biological activity, the polyfunctionality of the monomeric subunit made it an attractive target to investigate a "mismatched" oxocarbenium cation formation/reduction protocol.[9] We have successfully demonstrated this synthetic strategy in a variety of previous total synthetic endeavors.[10]

Our retrosynthetic analysis of **1** followed previous disconnections in that the carbohydrate moiety, a permethylated derivative of D-xylose, would be attached at the last step as shown in Scheme 2. Completion of the dimerized aglycon **2** would be contingent upon a successful synthesis of the monomeric subunit **3** which would be obtained from a bis-Yamaguchi macrolactonization reaction process. Thus, seco acid **3** would be derived from a functionalization of the alkylation product of lactone **4** followed by a stereoselective mismatched oxocarbenium cation formation/reduction sequence to afford the necessary $\beta$-*C*-glycoside precursor. We envisaged the generation of lactone **4** from a functionalized Evans' aldol adduct which, in turn, would be produced from

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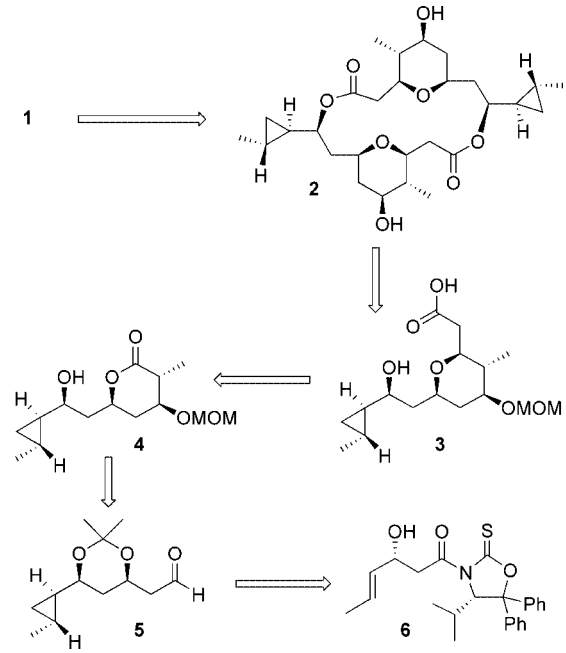
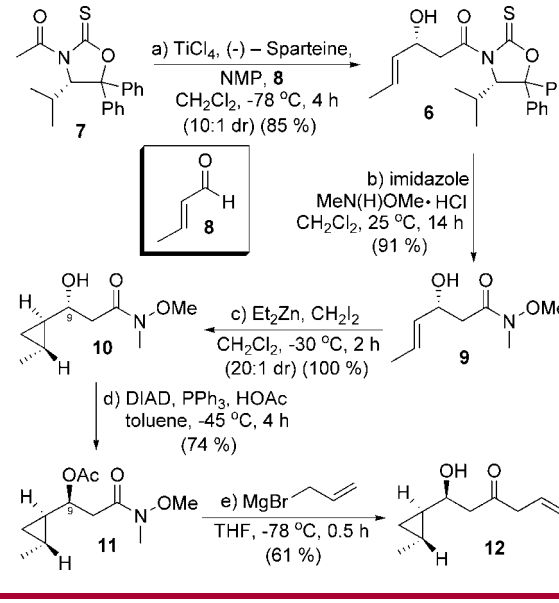
**Scheme 2.** Retrosynthetic Analysis of (−)-Clavosolide A



the *syn*-dioxolane aldehyde **5**. The required aldehyde **5** could, in principle, be derived in eight steps from **6** by means of an asymmetric acetate aldol reaction with (*E*)-crotonaldehyde.

**Scheme 3.** Synthesis of the $\beta$-Hydroxy Ketone **12**

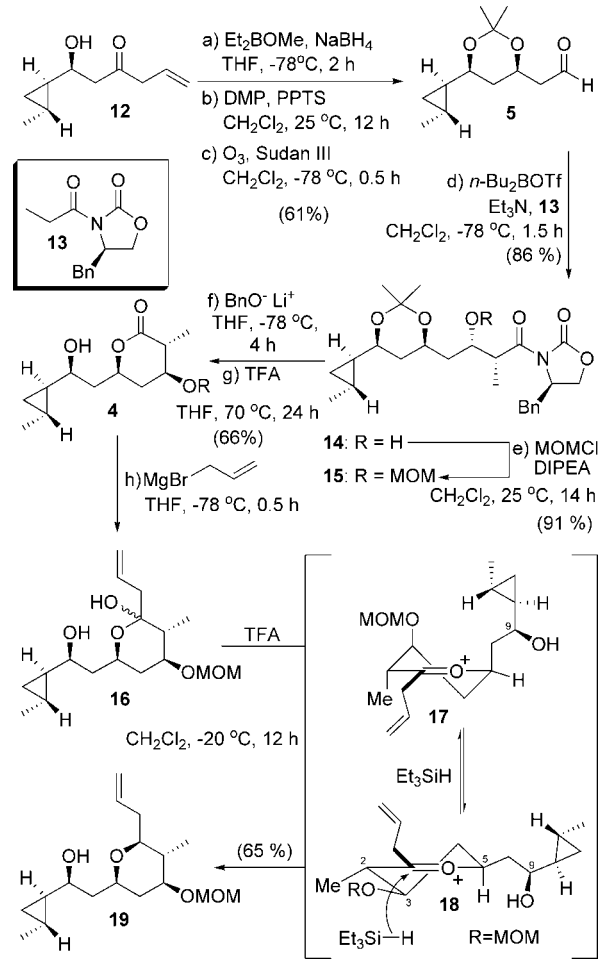



With this initial retrosynthetic plan in mind, focus was placed on the synthesis of the $\beta$-hydroxy-$\beta,\gamma$-unsaturated ketone **12**. As shown in Scheme 3, the synthesis of the required aldol adduct **6** relied on the treatment of the oxazolidinethione **7** with $TiCl_4$ to afford the necessary enolate which upon quenching with *E*-crotonaldehyde (**8**) at −78

°C provided the desired aldol adduct in 85% yield as a 10:1 ratio of inseparable diastereomers as described by Phillips.[11] An ensuing transamidation of **6** to the Weinreb amide under standard condition of the MeN(H)OMe•HCl salt and imidazole furnished chiral amide **9** in 91% yield.[12] With amide **9** in hand, a directed Simmons−Smith cyclopropanation under the Charette protocol afforded cyclopropyl carbinol **10** in 91% over two steps from **6** as a 20:1 ratio of diastereomers.[13] A subsequent Mitsunobu inversion of the free hydroxyl moiety of **10**, parallel to the efforts of Smith, afforded the correct $C_9$ acetate **11** in 74% yield as a 12:1 mixture of diastereomers. Careful treatment of **11** with excess allyl magnesium bromide concomitantly alkylated the Weinreb amide moiety and deprotected the secondary alcohol to afford the necessary $\beta$-hydroxy-$\beta,\gamma$-unsaturated **12** in 61% over the two transformations within the same reaction flask. With the necessary substrate for directed reduction in hand, our focus turned toward the construction of the necessary dioxolane aldehyde **5**.

Hence, treatment of ketone **12** under the method of Prasad ($Et_2BOMe$ and $NaBH_4$) afforded the required 1,3-*syn*-diol as a 10:1 mixture of inseparable diastereomers.[14] The crude diol was then dissolved in $CH_2Cl_2$ and treated under standard ketalization conditions with DMP and PPTS to afford the acetonide-protected alkene. An ensuing buffered ozonolysis of the olefinic moiety afforded dioxolane aldehyde **5** in 61% yield over three steps from **12** and set the stage for a reagent-controlled Evans aldol reaction.[15] Thus, stereoselective (*Z*)-enolate formation of the propionyl oxazolidinone **13** was accomplished under the standard Evans conditions (*n*-$Bu_2BOTf$, $Et_3N$); quenching with aldehyde **5** readily afforded aldol adduct **14** in 86% yield (12:1 dr by $^1H$ NMR) as shown in Scheme 4. Ensuing protection of the resulting secondary alcohol **14** was attempted under a variety of conditions. Treatment of **14** under standard protection conditions with silyl chlorides and imidazole led to no conversion, even with heating. The use of silyl triflates and 2,6-lutidine, unfortunately, did not allow for silicon ether formation. However, the protection of **14** was successful with MOMCl; it afforded acetal **15** in 91% yield after extensive optimization. Conversion of the oxazolidinone aldol adduct **15** into the desired lactone **4** was initiated by initially transforming **15** to the benzyl ester followed by hydrolysis of the acetonide and subsequent lactonization.[16] Along this line, the lithium alkoxide of benzyl alcohol led to the formation of the corresponding ester which was used immediately without

**Scheme 4.** Synthesis of the $\beta$-*C*-Glycoside **19**




purification. Subsequent lactonization was accomplished under standard hydrolysis conditions by treating the crude product with aqueous trifluoroacetic acid (TFA) in THF. The hydroxy lactone **4** was obtained in 66% yield from **15**.

With the synthesis of **4** complete, focus shifted toward the construction of the $\beta$-*C*-glycoside subunit. Hence, alkylation of lactone **4** with allylmagnesium bromide afforded the intermediate hemiketal **16** which readily underwent tandem stereoselective oxocarbenium cation formation/reduction with TFA and $Et_3SiH$ to afford the $\beta$-*C*-glycoside (as determined by NOE) **19** in 65% yield over the three step sequence from **4** (in >20:1 dr). Presumably, reductions of oxocarbenium cations occur via axial addition of $Et_3SiH$ to afford the $\beta$-*C*-glycoside.[17] Of the two possible reactive conformers, and based on the isolated $\beta$-*C*-glycoside, the proposed conformer **18** places all of the substituents at $C_2$, $C_3$, and $C_5$ in the pseudoequatorial positions. A majority of our stereoselective endocyclic oxocarbenium reductions have placed the $C_3$ hydroxyl moiety in the axial position and the $C_5$ substituent in the pseudo equatorial geometry. Typically, these oxocarbenium formation/reduction reactions are com-

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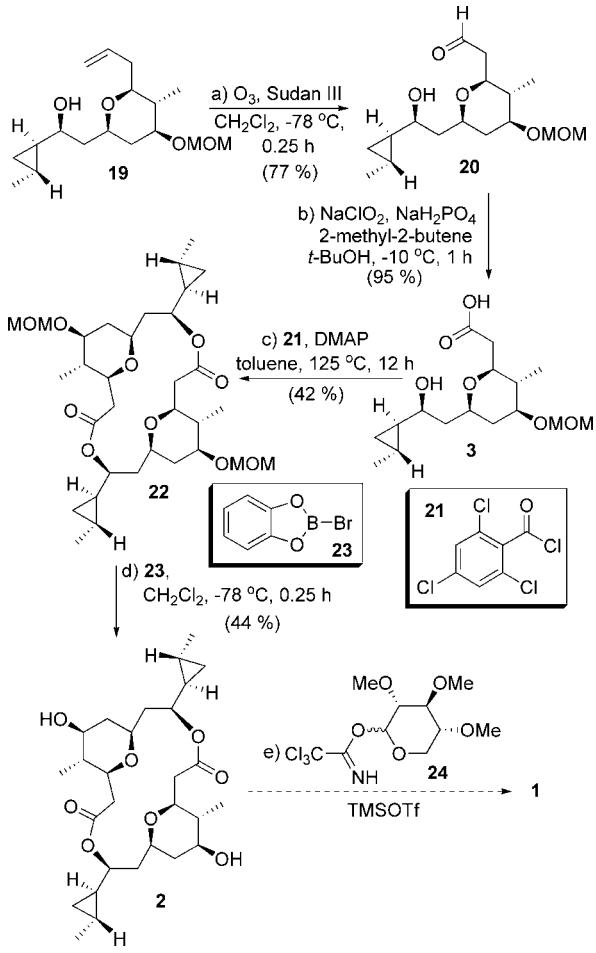
**Scheme 5.** Synthesis of **2** via a Yamaguchi Dimerization




plete at −78 → −40 °C within 0.25−0.5 h. Based on Woerpel's observations and our prior investigations, these $C_3$ axial and $C_5$ pseudoequatorial oxocarbenium conformations represent a "matched" geometry. However, the reactive oxocarbenium conformer **18** places the $C_3$ and $C_5$ substituents in the pseudoequatorial positions. Interestingly, the stereoselective oxocarbenium formation/reduction reaction required >12 h for completion at −20 °C. Hence, it is suggested that conformer **18** represents a "mismatched" geometry that nonetheless allowed for a highly stereoselective oxocarbenium reduction.

Previous efforts in our group have demonstrated the ability to silylate the axial alcohol moiety in the $C_3$ position of a six membered endocyclic oxocarbenium cation.[10] In this specific case regarding the reduction of the oxocarbenium cation **18**, no possibility existed that would allow for such a silylation process due to the protected pseudoequatorial $C_3$ hydroxyl moiety. Interestingly, no silicon ether formation at the $C_9$ alcohol of the *ansa* chain was observed. Thus, the concomitant directing effect and intramolecular silicon capture seems to be confined to hydroxyl functionality exclusively on the six-membered ring.[10]

With the functionalized *β-C*-glycoside in hand, our focus turned toward completion of the formal synthesis of **1** as delineated in Scheme 5. Consequently, buffered ozonolysis of the olefin moiety resident in **19** afforded aldehyde **20** in 77% yield. Subsequently, a Pinnick oxidation provided the necessary *seco* acid **3** in 95% yield which was used without further purification.[18] Dimerization of the monomeric acid **3** was completed under the previously reported Yamaguchi macrolactonization conditions to afford the protected glycon **22** in a modest 42% yield.[19] Final, deprotection of the bis-MOM acyclic acetals was accomplished using bromocatechol borane to afford the aglycon **2** in a 44% yield over two deprotection steps, thus constituting a formal synthesis of **1**.[20] The spectral data ($^1$H NMR, 600 MHz; $^{13}$C NMR, 125 MHz), optical rotation, and HRMS data of synthetic **2** were in complete agreement with those previously reported.[7,8] Given the challenges of diastereoselective glycosylation of **2** with **24**, the final reaction was not attempted.[7,8]

In summary, an efficient formal synthesis of **1** has been successfully achieved in 18 transformation sequences (23 total reactions) with an overall yield of ∼1% from commercially available (*E*)-crotonaldehyde. Additionally, we have observed a "mismatched" stereoselective oxocarbenium reduction to afford the *β-C*-glycoside subunit leading to an efficient synthesis of **2**.

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**Supporting Information Available:** Full experimental procedures and 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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