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 9S,9'S,10S,10'S,11S,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 ¹H 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 9S,9'S,10R,10'R,11R,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 β -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 β -Hydroxy Ketone 12



With this initial retrosynthetic plan in mind, focus was placed on the synthesis of the β -hydroxy- β , γ -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 TiCl₄ 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 C₉ 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 β -hydroxy- β , γ -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 (Et₂BOMe and NaBH₄) afforded the required 1,3-syn-diol as a 10:1 mixture of inseparable diastereomers.¹⁴ The crude diol was then dissolved in CH₂Cl₂ 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 reagentcontrolled Evans aldol reaction.¹⁵ Thus, stereoselective (Z)enolate formation of the propionyl oxazolidinone 13 was accomplished under the standard Evans conditions (n-Bu₂BOTf, Et₃N); 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





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 β -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 Et₃SiH to afford the β -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 Et₃SiH to afford the β -C-glycoside.¹⁷ Of the two possible reactive conformers, and based on the isolated β -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 C₃ 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 $-78 \rightarrow -40$ °C within 0.25–0.5 h. Based on Woerpel's observations and our prior investigations, these C₃ axial and C₅ pseudoequatorial oxocarbenium conformations represent a "matched" geometry. However, the reactive oxocarbenium conformer **18** places the C₃ and C₅ 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 (¹H NMR, 600 MHz; ¹³C 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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