Enantioselective Synthesis of the C(1)-C(11) Fragment of Tedanolide C

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A convergent synthesis of the protected C(1)-C(11) fragment 6 of the targeted enantiomer of tedanolide C is described. The key step of the synthesis is the Felkin–Ahn addition of vinyl iodide 7 to aldehyde 8 that proceeds in 80% yield with 4:1 diastereoselectivity.

The isolation and structure determination of tedanolide C(1), a marine natural product isolated from a Papua New Guinea sponge of the *Ircinia* species, was reported by Ireland and co-workers in 2006.¹ Other members of the tedanolide family include tedanolide (2),² 13-deoxytedanolide (3),³ and the candidaspongiolides (4, Figure 1).⁴ The structure and relative stereochemistry of tedanolide C (1) was assigned by using NMR methods and DFT calculations, but the absolute stereochemistry remains unconfirmed.¹ Tedanolide C exhibits excellent potency against HCT-116 cells (colorectal cell line), with an IC₅₀ value of 0.057 μ g/mL (90 nM), and stops the growth of HCT-116 cells in the S-phase after 24 h of exposure at 0.2 μ g/mL.¹ It has been postulated that tedanolide C is a protein synthesis inhibitor, like its closely related congener, 13-deoxytedanolide. Surprisingly, however, the structure reported for 1 depicts the C(11)-C(23) fragment with an enantiomeric configuration



Figure 1. Tedanolide natural product family.

(except for the epoxide) relative to other members of the tedanolide family. The C(10)-C(23) fragment has been identified as the key pharmacophoric unit of 13-deoxy-tedanolide.⁵ Therefore, in planning a synthesis of tedanolide

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C (1) we decided to pursue the enantiomeric structure **5** as the synthetic target (Scheme 1) in anticipation that the configuration of the C(11)–C(23) unit of tedanolide C should be the same as that for the key C(10)–C(23) pharmacophore of 13-deoxytedanolide.

In 2010 our laboratory reported the synthesis of the C(15)-C(21) fragment of **5**.⁶ Kalesse et al. subsequently published their synthesis of the C(14)-C(23) fragment of a diastereomeric analog of tedanolide C using a Kiyooka aldol reaction.^{7,8} More recently still, a synthesis of the C(1)-C(12) fragment has been reported by Smith et al. by a route involving an asymmetric hydroformylation of a 1,3-diene.⁹ We report herein our synthesis of **6**, a protected version of the C(1)-C(11) fragment of the targeted enantiomer of tedanolide C.

Our strategy for the synthesis of fragment 6 (Scheme 1) involves the formation of the secondary C(7) hydroxyl group by addition of vinyl iodide 7 to aldehyde 8. We anticipated that the C(7) alcohol stereochemistry would be controlled by accessing a Felkin-Ahn transition state for the carbonyl addition.¹⁰ Aldehyde **8** was synthesized start-ing from the known aldehyde 9^{11} (Scheme 2). Subjection of 9 to an enantioselective Reformatsky-type reaction¹² with oxazolidinone 10^{13} in the presence of SnCl₂ afforded 11 in 56% yield with > 98:2 dr. The absolute configuration of the hydroxyl group at C(3) of **11** was confirmed by using the advanced Mosher ester method.¹⁴ Protection of alcohol 11 as a TBS ether using TBSOTf and 2,6-lutidine, followed by reduction of the acyl oxazolidinone with LiBH₄ and subsequent Parish-Doering oxidation¹⁵ of the primary alcohol, afforded aldehyde 12.¹⁶ The *syn* aldol reaction between 12 and propionyl oxazolidinone 13¹⁷ was performed in the presence of TiCl₄ and (-)-sparteine¹⁸ and gratifyingly afforded aldol 14 in 76% yield as a single diastereomer. The use of (-)-sparteine in this reaction was essential to obtain synthetically useful diastereoselectivity; the aldol reaction of the titanium enolate generated with diisopropylethyl amine (DIPEA) as the base afforded a 1:1 mixture of diastereomers. Protection of the

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Scheme 1. Strategy for the Synthesis of the Protected C(1)-C(11) Fragment of the Targeted Enantiomer of Tedanolide C







newly formed hydroxyl group of **14** as a TMS ether, followed by reduction of the acyl oxazolidinone with LiBH₄ and oxidation of the primary alcohol with SO₃·pyridine,¹⁵ completed this synthesis of aldehyde **8**.

The stereochemistry of aldol 14 was verified by the studies summarized in Scheme 3. Alcohol 15, obtained in two steps from 14, was elaborated into diol 16 in 62% yield by benzylation of the primary alcohol¹⁹ and deprotection of the two silyl ethers. Analysis of the ¹³C NMR spectrum of the derived acetonide 17 using Rychnovsky's method²⁰ confirmed the *syn* relationship between C(3)–OH and C(5)–OH. Independently, acetonide 18 was also generated in two steps from alcohol 15. The small H_a-H_b and H_a-H_c coupling constants (J < 2 Hz) observed in the ¹H NMR spectrum of 18 suggested that this compound

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Scheme 3. Stereochemical Assignments



adopts a chairlike conformation in which H_a is in an equatorial position. Furthermore, the ¹H NOE data obtained for **18** highlighted in Scheme 3 supported the assignment of *syn* stereochemistry between C(5)–OH and C(6)–CH₃ in aldol **14**.

Vinyl iodide 7 was synthesized from alkyne 19,²¹ which is available in five steps from commercial methyl (*R*)- β hydroxyisobutyrate (Scheme 4). We considered **19** to be a useful intermediate as the protecting group for the primary hydroxyl group can be easily removed and modified. Deprotection of the *p*-methoxybenzyl (PMB) ether was accomplished by treatment of **19** with DDQ at 0 °C in a 1:1 mixture of pH 7 phosphate buffer and CH₂Cl₂. The volatile propargyl alcohol was quickly treated with dimethoxytrityl chloride (DMTrCl) to give **20** in 88% yield over these two steps. Hydrostannylation of **20** using freshly distilled Bu₃SnH proceeded in 82% yield and with 93:7 regioselectivity. Treatment of the vinylstannane with I₂ afforded vinyl iodide **7** almost quantitatively.²²

In a first attempt toward the coupling of 7 and 8, treatment of 7 with *t*BuLi (2.2 equiv) at -78 °C, followed by addition of 8 at -78 °C, provided 21 as a 1:1 ratio of diastereomers. It has been reported that vinyl zincates provide higher diastereoselectivity upon addition to chiral aldehydes than the corresponding vinyl lithium reagents.²³ Thus, as shown in Scheme 4, treatment of vinyl iodide 7 with 2.2 equiv of *t*BuLi at -78 °C for 10 min, followed by addition of 1.1 equiv of ZnMe₂ at -78 °C for 5 min, afforded a solution of the vinyl zincate reagent. To this solution was added a solution of aldehyde 8, and the mixture was stirred for 3 h at -78 °C prior to workup.

Scheme 4. Synthesis of the C(1)-C(11) Fragment 6 of Tedanolide C



This procedure provided alcohol 21 in 80% yield as a 4:1 mixture of diastereomers that were not separated at this stage. The absolute configuration of the C(7) hydroxyl group of the major diastereomer was assigned by using the advanced Mosher ester method.¹⁴ Protection of the C(7) hydroxyl group of 21 as a TBS ether proceeded in 70% yield. In the next step, the DMTr protecting group was removed selectively by treatment of the fully protected intermediate with a 1:1:1 mixture of AcOH, trifluoroethanol, and CH₂Cl₂ without removal of the TMS ether.²⁴ Gratifyingly, this step enabled the separation of the two C(7)-diastereomers by standard column chromatography; the major diastereomer was isolated in 62% yield from this sequence (86% b.r.s.m.). The hindered C(5)-OTMS ether protecting group was removed in a subsequent step by using a solution of 40% HCO₂H in methanol, which afforded diol 22 in 81% yield.

For the final step of the synthesis of **6**, we expected the oxidation of the very hindered C(5)-hydroxyl group to be slower than the oxidation of the primary alcohol and were concerned that problems could arise with the β , γ -unsaturated aldehyde which in related systems is known to be sensitive toward epimerization at C(10). We selected the Dess-Martin periodinane reagent²⁵ for this step, since

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this reagent is known to be useful for oxidations that give aldehyde products that are highly prone to epimerization when other oxidation conditions are used.²⁶ However complete oxidation of **22** could not be achieved by using 5 equiv of the Dess–Martin periodinane even when the reaction was performed for 1 h at ambient temperature. The reaction had to be gently heated to 40 °C for 20 min to drive the oxidation of the C(5) alcohol to completion. In this way, the fully protected C(1)–C(11) fragment **6** of tedanolide C was obtained as a single isomer in almost quantitative yield, with no evidence of epimerization at C(10).

In summary, we developed a diastereoselective synthesis of the protected C(1)-C(11) fragment **6** of the targeted enantiomer of tedanolide C in 13 steps starting from the known aldehyde **9**. The synthesis involves a SnCl₂ mediated enantioselective Reformatsky-type reaction to set the C(3) stereocenter and an Evans–Crimmins aldol reaction to set the *syn* relationship between C(5) and C(6). The C(7) stereocenter was set by the Felkin–Ahn controlled addition of the vinylzincate derived from vinyl iodide 7 to aldehyde 8. The synthesis of **6** was completed by the Dess-Martin periodinane oxidation of the C(5)–C(11) diol unit. Further progress toward completion of a synthesis of tedanolide C will be reported in due course.

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Supporting Information Available. Experimental procedures and copies of ¹H and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.