Studies on the Synthesis of Tedanolide: Synthesis of the C(5)–C(21) Segment via a Highly Stereoselective Fragment Assembly Aldol Reaction of a Chiral β , γ -Unsaturated Methyl Ketone

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Received April 9, 1999

ORGANIC LETTERS 1999 Vol. 1, No. 1

/ol. 1, No. 95–98

 $\begin{array}{c} \text{ABSTRACT} \\ & & & \\ &$

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Tedanolide, **1**, a highly cytotoxic macrolide, was isolated in 1984 from the Caribbean sponge *Tedania ignis*² (Figure 1). The structurally related macrolide 13-deoxytedanolide (**2**) was subsequently isolated from *Mycale adhaerens*, a sponge species from the western Pacific Ocean.³ Tedanolide displays significant cytotoxicity against KB and PS tumor cell lines in vivo, with ED_{50} 's of 16 pg/mL in the PS assay and 250 pg/mL in the KB assay.² 13-Deoxytedanolide is also highly cytotoxic, with a reported IC₅₀ of 94 pg/mL vs P388 murine leukemia cells.³ These potent biological properties have stimulated interest in the synthesis of these molecules, especially tedanolide, whose stereostructure has been determined by X-ray analysis.^{4–10} We report herein a highly

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stereoselective synthesis of the C(5)–C(21) segment **3** of tedanolide, via the fragment assembly aldol reaction of the chiral aldehyde **4** and the β , γ -unsaturated methyl ketone **5**.

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In planning this approach to the synthesis of **3**, we relied on earlier studies from our laboratory which indicated that the diastereofacial selectivity of **4** should favor production of the C(13,14)-syn (i.e., Felkin) stereochemistry of $3^{11,12}$ and that the intrinsic diastereofacial bias of **5**, although

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Figure 1. Retrosynthetic analysis.

expected to be relatively modest,13 should reinforce that of 4 in a matched double asymmetric¹⁴ fragment coupling process using the lithium enolate of 5. However, we also recognized that successful implementation of this strategy would be dependent on two critical issues. The first was whether the potentially sensitive C(10) stereocenter of β , γ unsaturated ketone 5 would survive the planned aldol coupling. The second concerned the definition of a suitable protecting group strategy for the C(15) hydroxyl group, since our earlier studies indicated that this unit would have a pronounced effect on the aldol reaction stereoselectivity.¹² While a C(15)-OTES ether was deemed appropriate for latestage manipulations in our projected total synthesis, our earlier studies suggested that a β -TES ether would not be suitable for the proposed fragment assembly sequence. Fortunately, as described herein, the aldol reaction of 4 and **5** proved to be a highly stereoselective and synthetically useful transformation.

Aldehyde 4 was synthesized starting from the readily available chiral aldehyde 6^{15} (Scheme 1). A Wittig reaction of **6** with $Ph_3P=CMeCO_2Et$ provided the targeted (*E*)-enoate in 85% vield following chromatographic separation of the minor Z isomer (97:3 selectivity). Reduction of the (E)-enoate with DIBAL then provided 7 in 83% yield from 6.16Diastereoselective epoxidation of 7 was performed using the Sharpless asymmetric epoxidation,¹⁷ and the resulting epoxy alcohol was oxidized to the aldehyde 8 in 65% overall yield by using the Parikh–Doering procedure.¹⁸ Epoxyaldehyde 8 was elaborated to the homoallylic alcohol 10 via aldol reaction with the chiral crotonate imide 9,19 protection of the aldol product as a TBS ether, and then reduction of the acyl oxazolidinone using LiBH₄ (5 equiv) in THF containing 3 equiv of H₂O.²⁰ Acylation of the primary hydroxyl group of **10** followed by oxidative cleavage of the terminal olefin and asymmetric crotylboration²¹ of the resulting aldehyde provided 12 with excellent stereoselectivity. Finally, protection of the C(15) alcohol as a TES ether followed by oxidative cleavage of the olefin completed the synthesis of 4.



The diastereofacial selectivity of **4** and the related aldehydes **13a** and **13b** was probed by studying their aldol reactions with enolates generated from methyl isopropyl ketone (3-methyl-2-butanone; Table 1 and Figure 2). The results of these reactions demonstrate once again that the

⁽¹³⁾ For example, the chiral methyl ketones employed in the studies summarized in refs 10 and 11, which are more structurally complex than 5 in the present work, exhibited diastereofacial preferences ranging from 60: 40 to 83:17, depending on the metal enolate employed (see footnote 10 in ref 11).

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 Table 1.
 Aldol Reactions of Aldehydes 4 and 13 with

 3-Methyl-2-Butanone
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entry no.	RCHO	aldol reaction conditions $(-78 \ ^{\circ}\text{C})^{a}$	yield (%) ^b	major product	14:15
1	4	LHMDS, THF, -78 °C	83	14a	≥97:03
2	4	TiCl₄, <i>i</i> -Pr₂NEt, CH₂Cl₂, −78 °C	60	14a	77:23
3	4	Bu ₂ BOTf, <i>i</i> -Pr ₂ NEt, CH ₂ Cl ₂ , -78 °C	86	14a	59:41
4	13a	LHMDS, THF, -78 °C	79	14b	$\geq 95:05$
5	13a	NaHMDS, THF, -78 °C	76	14b	90:10
6	13a	KHMDS, THF, -78 °C	26	14b	80:20
7	13a	TiCl₄, <i>i</i> -Pr₂NEt, CH₂Cl₂, −78 °C	55	14b	85:15
8	13a	Bu ₂ BOTf, <i>i</i> -Pr ₂ NEt, CH ₂ Cl ₂ , -78 °C	85	14b	55:45
9	13b	LHMDS, THF, -78 °C	74	14c	93:7
10	13b	NaHMDS, THF, -78 °C	54	14c	$\geq 95:05$
11	13b	Bu ₂ BOTf, <i>i</i> -Pr ₂ NEt, CH ₂ Cl ₂ , -78 °C	61	14c	33:67

^{*a*} Aldol reactions were performed at -78 °C by adding 1.0 equiv of 4 or 13 to the enolate generated from 3 equiv of isopropyl methyl ketone. ^{*b*} The combined yields (unoptimized) of 14 and 15 isolated chromatographically.

aldehyde diastereofacial selectivity is enolate metal dependent, with the best selectivity for the Felkin diastereomer **14** being obtained with the lithium enolate. The stereochemistry of **14a** ($R^1 = TBS$, $R^2 = TES$) was assigned following removal of the TES ether (TBAF, ClCH₂CH₂Cl) and conversion of the resulting 1,3-diol to the 1,3-anti acetonide **16**.^{22,23} However, in contrast to our earlier studies with aldehydes **17a** and **17b**, the reaction diastereoselectivity is not highly dependent on the identity of the C(15)-OR protecting group.¹² Our current working hypothesis is that the bulky C(7)-OTBDPS substituent of **17** induces the C(5)-OTBS group to adopt a conformation anti to the C(5,6)bond which, in turn, forces the C(3)-OTES unit to be anti to C(3,4). In this particular conformation, the TES ether is



Figure 2. Structures of products of aldol reactions of aldehydes 4 and 13 with 3-methyl-2-butanone.

positioned relatively close to the aldehyde, where it can destabilize the otherwise favored chairlike transition state.¹² However, the gearing effects that dominate the conformational preferences of **17** are not operational, or at least are not as prevalent in **4**, since the C(18-19)-epoxide unit is less sterically demanding than the C(8)-OTBDPS unit of **17** (the conformation of the backbone of **4** should be as shown in Figure 3 in order to minimize gauche interactions;



Figure 3. Conformational analysis of 4 and 17.

note also that **4** and **17** are in opposite absolute stereochemical series).²⁴ Consequently, the C(17)-OTBS ether can adopt a position anti to the C(15,16) bond, which in turn allows the C(15)-OTES ether to move away from aldehyde unit in the reaction transition state.

The synthesis of the chiral β , γ -unsaturated ketone **5** commenced with enal **19**, which was prepared by standard procedures from enoate **18** (Scheme 2). The diastereoselective aldol reaction of **19** with the D-valine derived acyl oxazolidinone **20**²⁵ provided **21** with excellent selectivity



(89% yield). Protection of the hydroxyl group as a TBS ether (96%) followed by reduction of the acyl unit (62%) and protection of the primary hydroxyl group as a TES ether then provided **22** in 95% yield. The BOM ether was then removed via reduction with lithium naphthalenide (87%).²⁶ The primary alcohol was oxidized to the sensitive β , γ unsaturated enal by using catalytic TPAP and NMO (96% yield),²⁷ which was dissolved in THF and added to a solution of MeLi in Et₂O at -78 °C. The resulting secondary alcohol was then oxidized, again by using the catalytic TPAP protocol,²⁷ to give the targeted methyl ketone **5** in 67% overall yield for this final four-step sequence.

To our considerable delight, treatment of 1.9 equiv of **5** with 2.1 equiv of LiHMDS in THF at -78 °C followed by addition of 1.0 equiv of aldehyde **4** provided aldol **3** in 53% yield, *as the only observed aldol diastereomer*. In addition, 28% of aldehyde **4** and 36% of β , γ -unsaturated ketone **5** were recovered, along with ca. 8% of a compound tentatively identified as the aldol dimer of **5**. The stereochemistry of the newly formed C(13) hydroxyl group of **3** was assigned by spectroscopic correlation with **14a**, using the characteristic and diagnostic^{11,23} ABX pattern for the C(12)–C(13) spin

system in the ¹H NMR spectrum as a specific point of comparison. Remarkably, both methyl ketone **5** and aldol **3** are stable to silica gel chromatography, and the potentially sensitive C(10) stereocenter exhibits no tendency to epimerize under normal handling conditions.²⁸

In conclusion, we have demonstrated that the aldol reaction of aldehyde **4** and the chiral β , γ -unsaturated methyl ketone **5** is a synthetically viable strategy for construction of the C(5)–C(21) segment of tedanolide. Further progress toward completion of a total synthesis of this highly bioactive marine macrolide will be reported in due course.

Acknowledgment. Support provided by the National Institutes of Health (Grant No. GM 38436) is gratefully acknowledged.

Supporting Information Available: Figures giving ¹H NMR spectra of **3**, **14a**–**c**, and **15a**–**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990572S

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