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Enantioselective Synthesis of α -Methylene- β -hydroxy Carboxylic Acid Derivatives via a Diastereoselective Aldol- β -Elimination Sequence: Application to the C(15)–C(21) Fragment of Tedanolide C

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Abstract

An enantioselective synthesis of α -methylene- β -hydroxy carboxylic acid derivatives via a highly diastereoselective, one-pot syn-aldol and β -elimination sequence utilizing the chiral β -(phenylselenenyl)propionyl imide **15** is described. This new method, which constitutes an alternative to the Baylis-Hillman reaction, has been applied to the synthesis of the C(15)–C(21) fragment of tedanolide C.

Tedanolid C (**1**) is the newest member of a family of marine natural products which include tedanolide (**2**), 13-deoxytedanolide (**3**) and the candidaspongionolides (**4**, Figure 1).^{1–4} Tedanolide C was isolated from a Papua New Guinea marine sponge of the *Ircinia* species, and its structure and relative stereochemistry were assigned by NMR methods in conjunction with molecular modeling and DFT calculations. Tedanolide C displays an IC₅₀ value of 0.057 μ g/mL (95 nM) against HCT-116 cells (colorectal cancer cell line), and also arrests growth of HCT-116 cells in the S-phase after 24 h exposure at 0.2 μ g/mL. It has been suggested that tedanolide C, like 13-deoxytedanolide (**3**), may be a protein synthesis inhibitor.¹

In planning a synthesis of tedanolide C (**1**), we elected to target the enantiomeric structure **5** (Scheme 1). The C(10)–C(23) fragment has been identified as the key pharmacophoric unit of 13-deoxytedanolide,⁵ but the stereochemistry of the corresponding fragment has been given the enantiomeric configuration (except for the epoxide) in the proposed structure of tedanolide C (**1**);¹ the absolute configuration of tedanolide C has not been assigned. Therefore, we selected

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

the enantiomeric structure **5** as the synthetic target in anticipation that this will lead to the biologically active, naturally occurring enantiomer.

Our retrosynthetic analysis (Scheme 1) of target **5** focuses on the formation of the tertiary hydroxy group at C(16) by a dihydroxylation reaction of alkene **7**. In order to synthesize **7**, we considered using the Baylis-Hillman reaction between epoxyaldehyde **8** and methyl acrylate (**9**).^{6,7} However, this reaction failed (Scheme 1), presumably because the valuable, synthetically advanced aldehyde intermediate **8** could not be used in large excess—as is generally required for bimolecular Baylis-Hillman reactions.^{6,7}

We therefore considered the possibility of using an aldol reaction to prepare Baylis-Hillman type products in an enantioselective fashion.⁸ Specifically, we anticipated that an acyl oxazolidinone like **10**, equipped with a leaving group at C(3) of the propionyl fragment, would be a suitable substrate for a boron-mediated Evans *syn*-aldol reaction (Scheme 2).⁹ This approach would have the advantage that both the masked Michael acceptor **10** and the aldehyde could be used in stoichiometric amounts.

As additional design criteria, the leaving group “X” in **10** was required to be stable under the aldol reaction conditions but to undergo β -elimination during reaction work-up. We anticipated that the phenylselenenyl group, as in **15**, would satisfy these criteria.⁸ Accordingly, acyl oxazolidinone **15** was synthesized in high yield by 1,4-addition of PhSeH to known acryloyl imide **14** and subsequent re-crystallization.¹⁰

Oxazolidinone **15** was readily converted into the corresponding boron enolate upon treatment with Bu₂BOTf and NEt₃ under standard conditions (*c* = 0.2 M in CH₂Cl₂, –78 °C).^{9a} Addition of isobutyraldehyde to the enolate solution at –78 °C to promote the aldol reaction (6 h at up to 0 °C), followed by oxidative workup with H₂O₂ and pyridine at 0 °C resulted in the oxidation of the phenylselenide to the selenoxide which underwent a subsequent β -elimination to give the allylic alcohol **13a** in 81% yield.

A wide variety of aldehydes are compatible with this methodology (Table 1). Simple aliphatic aldehydes such as isobutyraldehyde and propionaldehyde gave α -methylene- β -hydroxy imides **13a** and **13b** in 81–93% yield (entries 1, 2). Use of the stereochemically demanding pivaldehyde as substrate gave product **13c** in 56% yield after conversion to the TBS ether (entry 3).

Various aromatic aldehydes were excellent substrates: aldol-elimination reactions of benzaldehyde, 2-furaldehyde, 4-methylthiazole-5-carboxaldehyde and 3-pyridinecarboxaldehyde gave products **13d** (86%), **13e** (86%), **13f** (84%), and **13g** (88%), respectively (entries 4 – 7). Due to the mild oxidative work-up conditions, pyridine-*N*-oxide formation was not observed in the latter case.

Finally, the silyl-protected α -hydroxyaldehyde **16**¹¹ gave **13h** in 88% yield (entry 8). In addition, α,β -unsaturated aldehydes such as **17**¹² could also be used as substrate (76% yield; entry 9); unsaturated aldehydes are typically avoided in Baylis-Hillman reactions.⁶ The only substrate that worked poorly in our hands was acrolein, which gave a multitude of side products that were difficult to separate (data not shown). In all cases, the isolated allylic alcohols **13a**–**13i** were obtained as single diastereomers.

We expected from the outset that acyl oxazolidinone **15** would undergo aldol reaction via the corresponding Z(O)-boron-enolate **11** (X = SePh) and provide *syn*-aldol products prior to oxidative workup. This was confirmed in the case of aldol **18**, which was isolated from an aldol reaction of **15** and isobutyraldehyde following mild basic (but non-oxidative) work-up. Treatment of **18** with LiBH₄ and protection of the resulting 1,3-diol gave p-methoxyphenyl

(PMP) acetal **19**. The H_a-H_b coupling constant of **19** ($^3J = 1.9$ Hz) as well as 1H NOE data provide the basis for this assignment (Scheme 3).

The absolute configuration of aldol **18** was determined independently via the advanced Mosher ester method,¹³ as well as by reduction of the derived allylic alcohol **13a** to the known diol **20** upon treatment with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$.^{14,15}

Application of this new methodology to the synthesis of the C(15)–C(21) fragment **27** of tedanolide C is presented in Scheme 4. Aldehyde **8** was synthesized starting from the known aldehyde **21**. Thus, standard Wittig reaction of **21** with $Ph_3P=CHCO_2Et$ followed by DIBAL reduction of the ester provided allylic alcohol **22** (80%). Subjection of **22** to the Sharpless asymmetric epoxidation conditions¹⁶ followed by a Parikh-Doering oxidation of epoxyalcohol **23** provided the epoxyaldehyde **8** in 79% yield from **22**. Use of epoxyaldehyde **8** as the substrate for aldol reaction with **15**, followed by oxidative workup, provided allylic alcohol **24** in 79% yield with > 20:1 diastereoselectivity. Treatment of **24** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ ^{14b} and subsequent protection of the bis-allylic alcohol **25** with 2 equiv of TESCl gave the bis-silyl ether **26** in 91% yield for the two steps. Finally, asymmetric dihydroxylation of **26** by using Sharpless' AD-mix β ¹⁷ gave diol **27** (75%, 95% b.r.s.m.) as the major component of a 4.5:1 mixture of diastereomers.^{18,19}

In summary, we developed an efficient and highly stereoselective procedure for synthesis of α -methylene- β -hydroxy acyl oxazolidinones - so-called Baylis-Hillman adducts - via an enantioselective *syn*-aldol/ β -elimination sequence using β -(phenylselenyl)propionyl imide **15** as the key reagent. This method allows for the use of **15** and the aldehyde reaction partner in stoichiometric amounts—which is not possible in conventional Baylis-Hillman reactions. This new sequence has been applied to the synthesis of the C(15)–C(21) fragment **27** of tedanolide C (target structure **5**). Further elaborations of **27** towards tedanolide C will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18. The stereochemistry of the C(16) hydroxy group was assigned based on the usual sense of asymmetric induction in Sharpless asymmetric dihydroxylation reactions, and was not rigorously determined at this stage.
19. The two diastereomers were inseparable by standard column chromatography. Purification of the major diastereomer was performed by HPLC.

tedanolide C (**1**)
literature structure

13-deoxytedanolide (**3**)

tedanolide (**2**)

candidaspongiolides (**4**)

R = C(O)C₁₃H₂₇, C(O)C₁₄H₂₉, C(O)C₁₅H₃₁
C(O)C₁₆H₃₃, C(O)C₁₇H₃₅, C(O)C₁₇H₃₃

Figure 1.
Family of tedanolide natural products

Scheme 1. Retrosynthetic analysis of the C(15)–C(23) fragment of tedanolide C (synthetic target **5**).

Scheme 2.

Rationale of applying aldol chemistry for the preparation of Baylis-Hillman type products.

Scheme 3.
Stereochemical assignments

Scheme 4.
Synthesis of the C(15)–C(21) fragment **27** of tedanolide C

Table 1Synthesis of α -methylene- β -hydroxy acyl oxazolidinones **13a–i** via an aldol-elimination sequence^a

entry	aldehyde	
1		13a
2		13b
3		13c

entry	aldehyde	
4		13d

5		13e
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entry	aldehyde	
6		13f
7		13g
8	16	13h

entry	aldehyde	
9		13i

^a General procedure for the aldol-elimination sequence: Formation of the boron enolate from imide **15** (1.0 equiv), Bu₂BOTf (1.2 equiv) and NEt₃ (1.8 equiv) in CH₂Cl₂ (*c* = 0.2 M) at -78 °C; addition of aldehyde (1.1 equiv) at -78 °C; oxidation of the aldol product in CH₂Cl₂ and pyridine (2.0 equiv) at 0 °C with H₂O₂ (approx. 3–5 equiv); all products were isolated by column chromatography;

^b Xp = (4S)-(4-benzyloxazolidinone)-5-yl;

^c dr >20:1;

^d Isolated yields of the indicated products;

^e **13a** was isolated after protection as the TBS ether.