ORGANIC LETTERS

2010
Vol. 12, No. 10
2342−2345

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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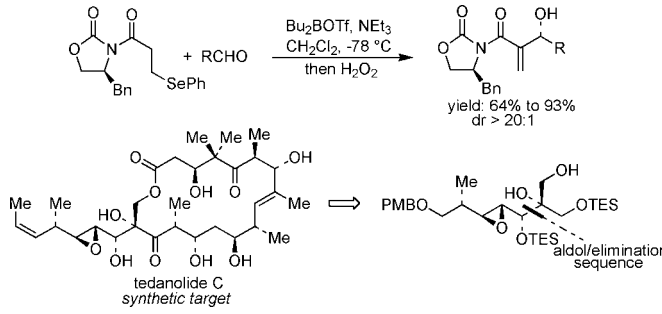
Received March 24, 2010

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-(phenylselenyl)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.

Tedanolide C (**1**) is the newest member of a family of marine natural products which include tedanolide (**2**), 13-deoxytedanolide (**3**), and the candidaspongiolides (**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 IC_{50} value of 0.057 μg/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 μg/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

(1) Tedanolide C (**1**): Chevallier, C.; Bugni, T. S.; Feng, X.; Harper, M. K.; Orendt, A. M.; Ireland, C. M. *J. Org. Chem.* **2006**, *71*, 2510.
(2) Tedanolide (**2**): Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Bilayet Hossain, M.; Van Der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.
(3) 13-Deoxytedanolide (**3**): Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971.
(4) Candidaspongiolide (**4**): Meragelman, T. L.; Willis, R. H.; Woldemichael, G. M.; Heaton, A.; Murphy, P. T.; Snader, K. M.; Newman, D. L.; van Soest, R.; Boyd, M. R.; Cardellina, J. H., II; McKee, T. C. *J. Nat. Prod.* **2007**, *70*, 1133.

10.1021/ol1006955
Published on Web 04/20/2010

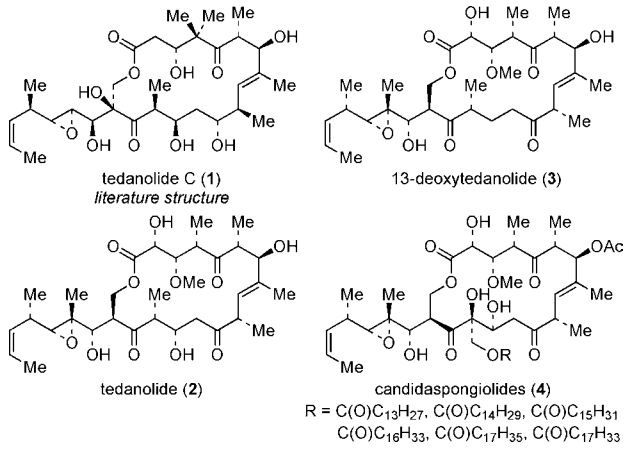
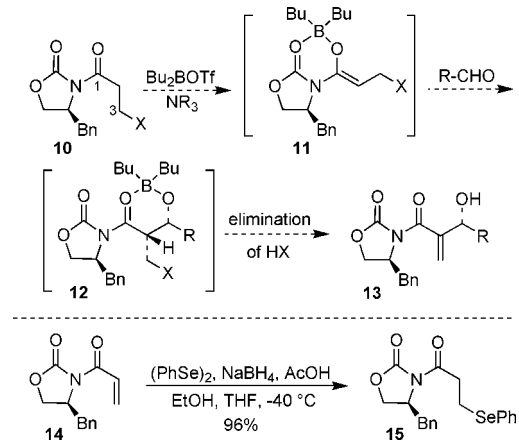


Figure 1. Family of tedanolide natural products.

Scheme 2. Rationale of Applying Aldol Chemisty for the Preparation of Baylis−Hillman-Type Products



proposed structure of tedanolide C (**1**);[1] the absolute configuration of tedanolide C has not been assigned. Therefore, we selected the enantiomeric stucture **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**. 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.[7] 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).[8,9] 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 workup. We anticipated that the phenylselenyl 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 recrystallization.[10]

Oxazolidinone **15** was readily converted into the corresponding boron enolate upon treatment with Bu_2BOTf and NEt_3 under standard conditions (c = 0.2 M in CH_2Cl_2, −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 H_2O_2 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 and 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

Scheme 1. Retrosynthetic Anaylsis of the C(15)−C(23) Fragment of Tedanolide C (Synthetic Target **5**)

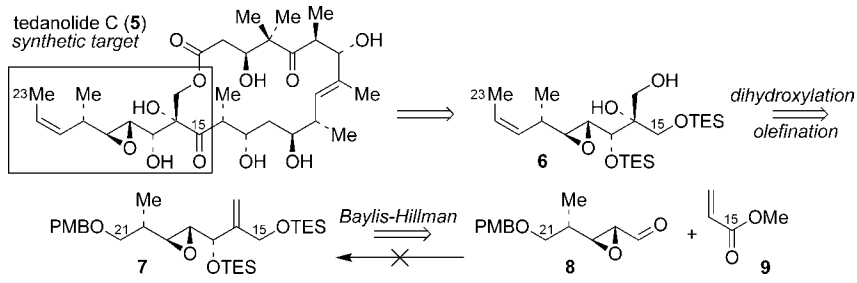
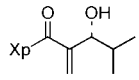
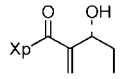
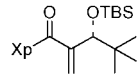
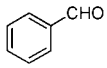
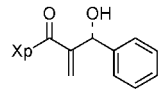
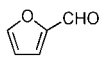
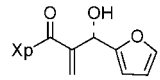
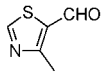
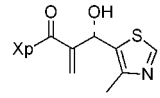
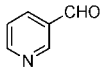
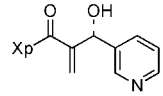
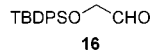
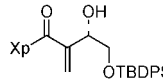
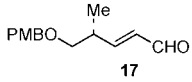
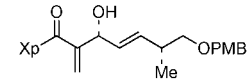


Table 1. Synthesis of α-Methylene-*β*-hydroxy Acyl Oxazolidinones **13a**−**i** via an Aldol/Elimination Sequence[a]

entry	aldehyde	product[b,c]	yield[d]
1		**13a** 	81%
2		**13b** 	93%
3		**13c** 	56%[e]
4		**13d** 	86%
5		**13e** 	86%
6		**13f** 	84%
7		**13g** 	88%
8	 **16**	**13h** 	88%
9	 **17**	**13i** 	76%

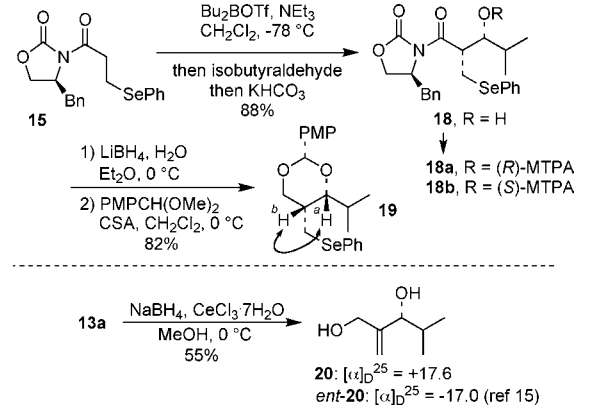
[a] General procedure for the aldol/elimination sequence: Formation of the boron enolate from imide **15** (1.0 equiv), Bu_2BOTf (1.2 equiv), and NEt_3 (1.8 equiv) in CH_2Cl_2 (c = 0.2 M) at −78 °C; addition of aldehyde (1.1 equiv) at −78 °C; oxidation of the aldol product in CH_2Cl_2 and pyridine (2.0 equiv) at 0 °C with H_2O_2 (approximately 3−5 equiv); all products were isolated by column chromatography. [b] Xp = (4*S*)-(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.

oxidative workup 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**−**i** were obtained as single diasteromers.

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 nonoxidative) workup. Treatment of **18** with $LiBH_4$ 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 ^{1}H NOE data provide the basis for this assignment (Scheme 3).

Scheme 3. Stereochemical Assignments



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, the 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 conditions[16]

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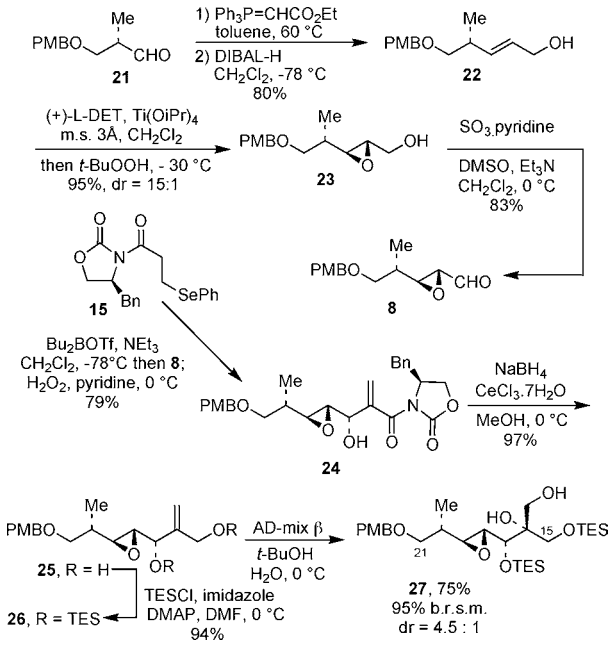
(14) (a) The reductive cleavage of the auxiliary with $LiBH_4$ gave a mixture of the 1,2- and the 1,4-reduced products in a 1:1 ratio. (b) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(15) Enders, D.; Voith, M. *Synthesis* **2002**, 1571.

(16) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

Scheme 4. Synthesis of the C(15)−C(21) Fragment **27** of Tedanolide C



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 distereoselectivity. 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** toward tedanolide C will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health (GM038436) is gratefully acknowledged. R.B. thanks the Austrian Science Fund (FWF) for a Schrödinger fellowship.

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

OL1006955

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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.