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Expedient synthesis of α,α-dimethyl-β-hydroxy carbonyl scaffolds via Evans' aldol reaction with a tertiary enolate

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ABSTRACT

An efficient synthetic methodology for 3-hydroxy-2,2-dimethyloctynoic acid (DHOYA) and several variants, which are increasingly common fragments encountered in bioactive marine cyanobacterial metabolites, was developed. These fragments were obtained in three steps via a tertiary aldol reaction utilizing an Evans' chiral auxiliary to afford the desired stereochemistry at the β-hydroxy carbon. Thus far, this methodology has been successfully applied in determination of the absolute stereochemistry of eight cyanobacterial natural products, including the VGSC activator palymramide A.

The α,α-dimethyl-β-hydroxy carbonyl functionality is a unique structural feature of a number of bioactive natural products, including the epothilones,[1] mycalamide A,[2] and peloruside A.[3] Recently a number of marine cyanobacterial natural products possessing an α,α-dimethyl-β-hydroxy carbonyl functionality in the form of a 3-hydroxy-2,2-dimethyloctynoic acid (DHOYA, **1**) fragment, or a derivative thereof, have been described (Fig. 1). Naturally occurring modifications of the structural motif represented by **1** include varying degrees of saturation, chain shortening, replacement of the β-hydroxy group by an amine, and mono-methylation at the α-carbon. Other derivatives of **1** feature multiple modifications; examples include antanapeptin B,[4] onchidin,[5] and malevamide B.[6] Natural products featuring **1** or a variant on this motif display a variety of biological activities including cytotoxicity to a number of cancer cell lines,[7–9] anti-microbial activity to mycobacteria,[8] anti-parasitic activity[10], and brine shrimp toxicity.[11,12] Given the range of biological activities of these molecules and the diversity of the modifications observed for fragment **1**, there is a compelling need for efficient synthetic methodologies to access this structural class as well as produce synthetic analogues for drug development purposes.

Moreover, one of the more difficult aspects of the structure elucidation of depsipeptides containing **1** is the determination of absolute configuration of the β-hydroxy ester linkage of fragment **1**. Chiral GCMS comparison of the hydrogenated and methyl esterified derivative of **1** (i.e. methyl 3-hydroxy-2,2-dimethyloctanoate) to synthetic standards affords a pragmatic approach for determining the absolute configuration of this stereocenter.[9] However, a critical requirement for this methodology is the availability of enantiomerically pure synthetic standards.

Fragment **1** has previously been synthesized in 9 steps using an asymmetric Kiyooka–Mukaiyama aldol reaction during total synthesis of yanucamide A[13] and pitipeptolide A[14] and to provide standards for chiral GCMS analysis of the wewakpeptins.[9] Additional approaches for construction of the α,α-dimethyl-β-hydroxy carbonyl backbone via a tertiary enolate have been applied in partial and total syntheses of peloruside A,[15,16] and in the total synthesis of pasteurestins A and B;[17] in the latter case, a Reformatsky reaction employing a bromoacyl derivative of Evans' chiral auxiliary and a TMS-protected terminal alkyne was employed.

However, we conceived a more efficient synthetic route in which fragment **1** could be achieved enantioselectively via a tertiary aldol reaction with an acylated Evans' chiral auxiliary and an aldehyde possessing an unprotected terminal alkyne. As the terminal alkyne of fragment **1** is unstable to acid hydrolysis, which is usually the first step in the stereochemical determination of depsipeptides, saturated 3-hydroxy-2,2-dimethyloctanoic acid (DHOAA, **2**) is preferred for chiral GCMS analysis.[7,9] Thus, our initial studies focused on the synthesis of fragment **2**.

Since the key reaction step in this scheme requires an Evans' chiral auxiliary that is not commercially available, the desired starting material was obtained via acylation of (*R*)-4-benzyl-2-oxazolidinone with isobutyryl chloride to give (*R*)-4-benzyl-3-isobutyryloxazolidin-2-one (**3**) in good yield (86%). Initially, we attempted

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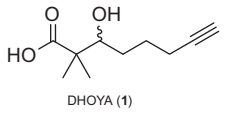


Figure 1. 3-Hydroxy-2,2-dimethyloctynoic acid (DHOYA, **1**).

the aldol reaction of (4′*R*)-**3** and hexanal using LDA alone; however, the expected aldol product was not formed based on LR-ESI-LCMS and ^{1}H NMR analyses. We suspected that a stronger Lewis acid was required for formation and stabilization of the tertiary enolate. We initially selected a titanium Lewis acid as we thought the titanium enolate would best facilitate the coordination of the aldehyde via the Zimmerman–Traxler transition state (see Table 1).[18,19] A similar strategy has been employed previously by the Kobayashi group in which LDA was used in combination with TiCl(O-*i*-Pr)$_3$ to form the titanium enolate in preparation of a 1,2-diol with a quaternary chiral center.[19]

Thus, we attempted the aldol addition of hexanal (1.2 equiv) and (4′*R*)-**3** using LDA (1.5 equiv) and TiCl(O-*i*-Pr)$_3$ (4 equiv). The reaction was stirred for 1.5 h at −40 °C and proceeded favorably to give (3*R*,4′*R*)-**4** in 35% yield (Table 1, entry 1). The configuration of the β-alcohol in this intermediate was confirmed as *R* by Mosher's analysis, which was consistent with the predicted Zimmerman–Traxler transition state model.[19] The Evans' chiral auxiliary was removed via hydrolysis to furnish (3*R*)-**2** with an overall yield of 29%. The synthesis was also conducted starting with (*S*)-4-benzyl-2-oxazolidinone. The aldol reaction with (4′*S*)-**3** gave (3*S*,4′*S*)-**4** with a 32% yield (Table 1, entry 2), while hydrolysis afforded the final product (3*S*)-**2** with an overall yield of 24%.

These initial results verified that this three step synthesis was indeed a viable route for the generation of (3*R*)-**2** and (3*S*)-**2**. These products are invaluable for use as standards in the chiral GCMS analysis of the β-hydroxy chiral center of marine natural products featuring **1** or a saturated derivative. One such application was in the case of mantillamide A (Fig. 2) where 5.2 mg was isolated from

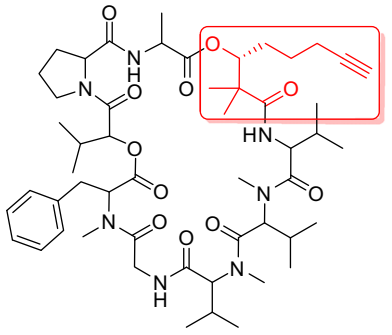
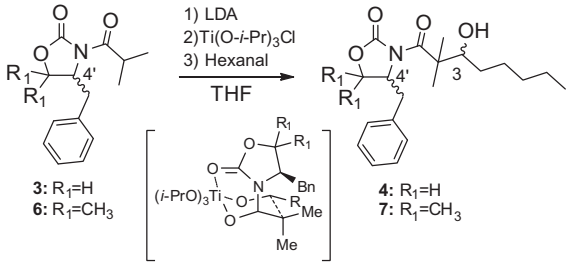


Figure 2. Mantillamide A, a secondary metabolite featuring fragment **1** (highlighted in red).

field collections; however, only 0.2 mg of the natural product was required for chiral GCMS analysis. Comparison of the methyl esterified fragment derived from mantillamide A to methyl esterified (3*R*)-**2** and (3*S*)-**2** obtained using the described synthetic route revealed that mantillamide A possesses an *R*-DHOYA unit. The retention time for the natural product was 53.67, while the retention time for the *R*-enantiomer was 53.64 and the retention time for the *S*-enantiomer was 52.08. Co-injections of the natural product with the *R*- and *S*-enantiomers confirmed the assignment as *R*. While the route was efficient for preparation of standards for stereochemical analyses, the overall yield was quite low. Thus, we investigated optimization of the aldol reaction to improve the overall yield making the route more attractive for utilization in total syntheses.

Suspecting that an additional deprotonation may be occurring on C-5, resulting in decomposition of the starting material and, therefore, contributing to the observed low yield, an Evans' chiral auxiliary [(4′*S*)-**5**], featuring *gem*-dimethyl substitution at C-5, was employed as the starting material in subsequent reactions.[20] Acylation of (4′*S*)-**5** gave (4′*S*)-**6** (97% yield), which was then uti-

Table 1
Optimization of aldol reaction in the synthesis of **2**



Entry	S.M.[a]	Scale[b]	Aldehyde (equiv)	Temperature conditions	Product	Yield[c] (%)
1	(4′*R*)-**3**	3.8	1.2	−40 °C, 1.5 h	(3*R*,4′*R*)-**4**	35
2	(4′*S*)-**3**	1.7	1.2	−40 °C, 1 h	(3*S*,4′*S*)-**4**	32
3	(4′*S*)-**6**	0.2	1.2	−40 °C, 3 h	(3*S*,4′*S*)-**7**	41
4	(4′*S*)-**6**	0.1	1.2	−78 °C→22 °C, 18 h	(3*S*,4′*S*)-**7**	9
5	(4′*S*)-**6**	0.2	3.0	−40 °C, 3 h	(3*S*,4′*S*)-**7**	58
6	(4′*S*)-**6**	0.2	3.0	−40 °C, 3 h; 0 °C, 2 h	(3*S*,4′*S*)-**7**	98[d]
7	(4′*S*)-**6**	0.2	3.0	−40 °C, 3 h; 0 °C, 2 h	(3*S*,4′*S*)-**7**	91
8	(4′*R*)-**6**	0.2	3.0	−40 °C, 3 h; 0 °C, 2 h	(3*R*,4′*R*)-**7**	82

[a] S.M.: Starting material.
[b] Scale based on mmol of starting material.
[c] Isolated yield following flash column chromatography.
[d] Enantiomeric ratio ⩾ 50:1 according to ^{1}H NMR and chiral GCMS analyses.