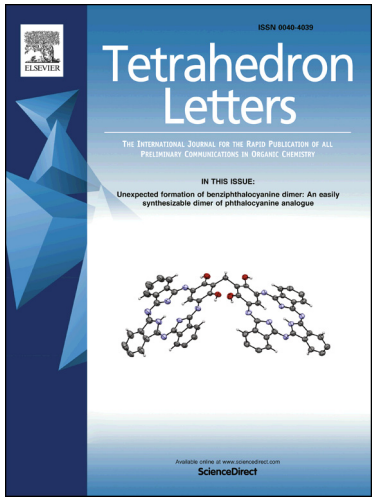

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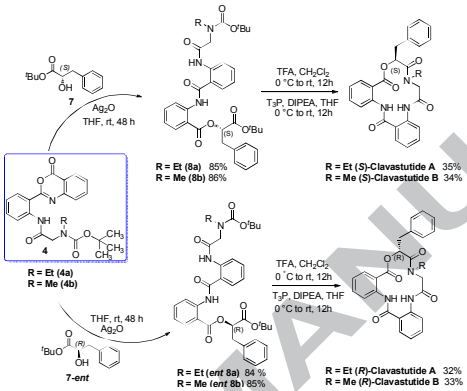

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ABSTRACT

Ag_2O mediated esterification of (*R*)-*tert*-butyl 2-hydroxy-3-phenylpropanoate has been realized *via* the effective ring opening of benzoxazinones that resulted in the efficient synthesis of cyclodepsipeptides clavutustides A and B and their enantiomers in very good overall yields

1. Introduction

Cyclodepsipeptides with a broad spectrum of biological activities including anti-plasmodial, antiviral, insecticidal, cytotoxic and anti-proliferative activities[1] also serve as lead compounds/templates for more pharmacologically potent and toxicologically safe derivatives.[2] With the latest advancements in the structural and pharmacological characterization of naturally occurring cyclic peptides and depsipeptides,[3] these compounds plays an important role in the development of novel therapeutics.

While cyclic peptides with unique biological activities are ubiquitous in nature,[4] anthranilic acid unit are rare in nature and anthranilic acid dimers with micromolar affinity for the CCK1 receptors were considered to be an important molecular scaffold in medicinal chemistry[5] Cyclodepsipeptides clavatustides A and B (Figure 1) containing an anthranilic acid dimer and D-phenyllactic acid are such molecules that were isolated by Bin Wu and co-workers from cultured mycelia and broth of Aspergillus clavatus C2WU isolated from Xenograpsus testudinatus.[6] Clavatustide B, the product isolated from clavatus C2WU, exhibited a potent anti-cancer activity in various human cancer cell lines, including liver, pancreatic, gastric, colorectal, and prostate cancers and retinoblastoma.[6] Clavatustide B is a promising anti-cancer agent against chemo- and radio-therapy resistant cancers[6a] as it has shown a potent inhibition of cell growth in chemo- and radio therapy resistant cell lines, pancreatic cancer cell line (panc-1)[6b] and prostate cancer cell line (PC3)[6c]. Its anti-cancer property is due to the delaying of G1-S phase cell cycle transition[7]. The G1-S cell cycle checkpoint-associated molecules including cyclin E2 played key roles in the clavatustide B-induced cell cycle blocking.

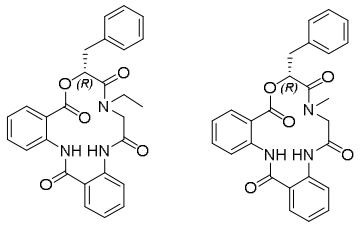
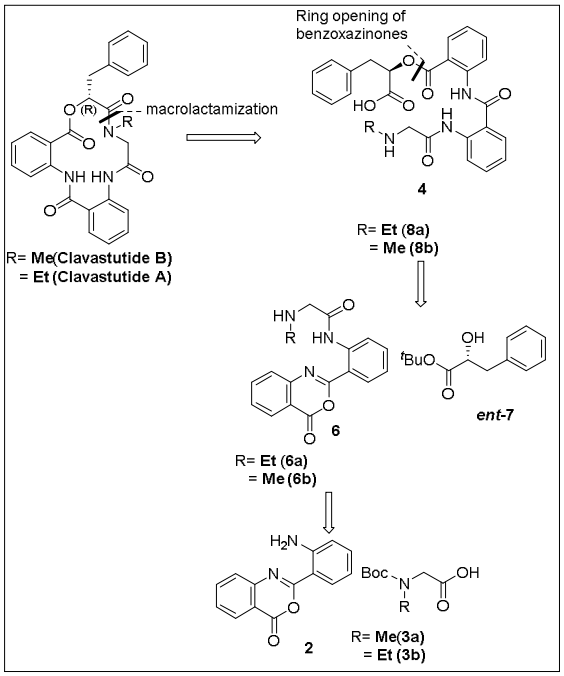


Figure 1. Clavatustides A & B

One of the challenges associated with the synthesis of depsipeptides is the limited availability of coupling reagents for the ester formation using α-hydroxyacid/esters.[8] It has been reported in the literature that benzoxazinones undergo nucelophilic ring opening with alcohols and amines and are intermediates for the synthesis of various molecules such as benzoxazinethiones, benzothiazinethiones, substituted amidobenzoates, 4-hydorxyquinolinones and quinazolinones.[9] This prompted us to explore the possibility of ring opening of benzoxazinone for the formation of the ester as an alternative method for the synthesis of clavatustides A and B. We have recently reported the first total synthesis of clavatustides A and B and its analogues that has established the correct values of optical rotation for these compounds in pure form.[10]

In continuation of our efforts towards the improved synthesis of clavatustides A and B, here in we report the ring opening of

benzoxazinone as an alternate route for the efficient synthesis of clavatustides A and B and its analogues.

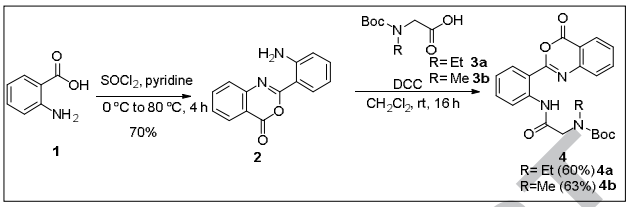


Scheme 1

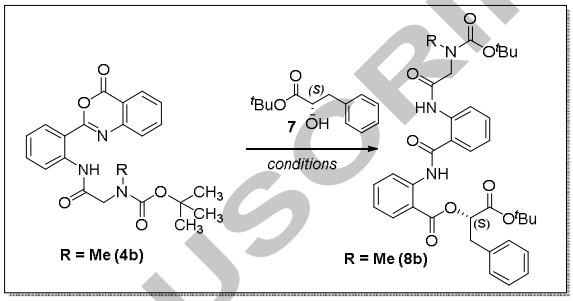
Retrosynthesis

Retro synthetically, macro lactamization was our preferred mode of cyclization. From the disconnection of ester functionality of **4** (scheme 1) it was envisioned that the nucleophilic ring opening of benzaxazinone **6** with methyl phenyllactate **5** would provide us the key compound **4** that would be set up for macro lactamizaton. Further disconnection of **6** gave rise to benzoxazinone **2** and N-alkyl glycine derivatives. The forward synthesis commenced with the synthesis of benzoxazinone **2** in 70% yields as per the reference protocol.[11] The benzoxazinone **2** was then coupled using the standard amide formation using DCC in CH_2Cl_2 with N-Boc-N-methylglycine **3a** to afford **4a** in 60 % yields while N-Boc-N-ethylglycine **3b** afforded **4b** in 63% yields (Scheme-2).

With compounds **4a** and **4b** in hand, we turned our attention to the ring opening of benzoxazinones with (***S***)-*tert*-butyl 2-hydroxy-3-phenylpropanoate (Scheme 3). A potential issue considered during the ring opening was the racemization of the phenyl lactate under the reaction conditions. Table-1 illustrates the optimization table for the esterification of α-hydroxyesters via ring opening of benzoxazinones. A short screen for the optimal conditions revealed that benzoxazinone **4a** could be opened with (*S*)-*tert*-butyl 2-hydroxy-3-phenylpropanoate in the presence of Ag_2O in THF to afford the desired ester **8a** as a single isomer in 82% isolated yield. While conditions shown in entries 1 and 2 (DBU/DMF/0 ^{0}C and NaH/DMF/0 °C) indicated the formation of ester by LCMS in 10 and 15% respectively, conditions shown in entries 3 and 4 (pyridine/DMF) did not indicate any product formation



Scheme 2. Synthesis of compounds **4a** & **4b**:

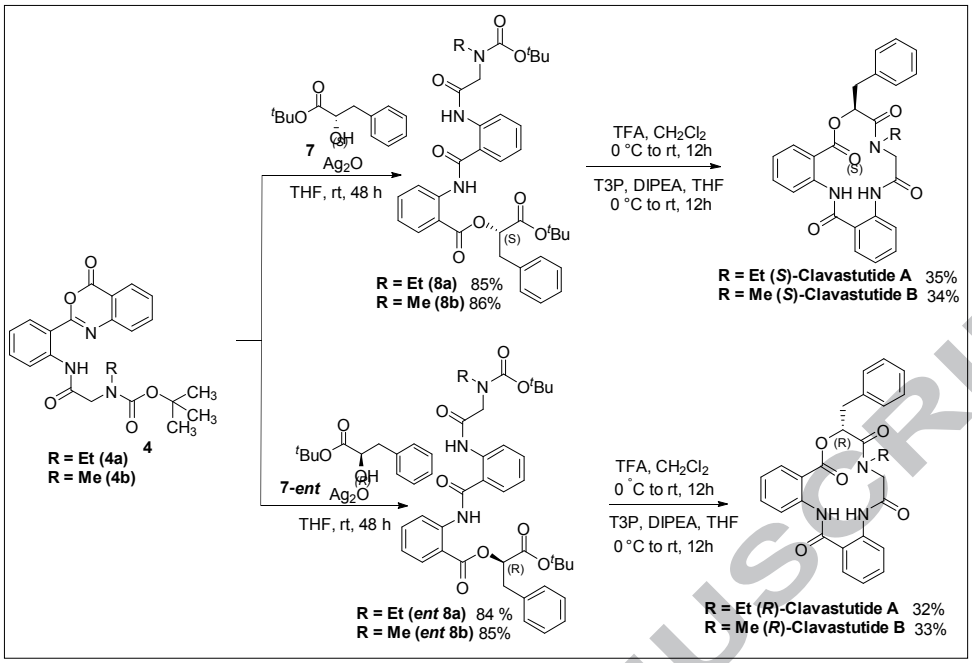


Scheme 3: Synthesis of Compound **8b**:

Sr.No	conditions[a]	yield[b]
1	DBU/DMF/0 °C	10%
2	NaH/DMF/0 °C	15%
3	Pyridine/DMF/120 °C	No product
4	Pyridine/rt	No product
5	Ag_2O/THF	82%[c]

Table 1: [a]reactions were run on **4b** (1 mmol), **7** (1 mmol); [b] conversion based on LCMS; [c] isolated yield

Gratifyingly, using the conditions optimized for the ring opening of benzoxazinones, treatment of **4a** and **4b** with (*S*)-tert-butyl 2-hydroxy-3-phenylpropanoate (scheme-4) in the presence of Ag_2O in THF resulted in the clean conversion to **8a** and **8b** as a single isomer. Compounds **8a** and **8b** were isolated in 85% and 86% respectively. Similarly, treatment of benzoxazinones **4a** and **4b** with (*R*)-tert-butyl 2-hydroxy-3-phenylpropanoate afforded *ent*-**8a** and *ent*-**8b** as single isomers in 84% and 85% respectively. Compounds **8a**, **8b** were then subjected to boc-deprotection using TFA and the obtained crude product was treated with T_3P to obtain *S*-clavatustides A and B in 35 % and 34 % respectively. Similarly, Compounds *ent*-**8a** and *ent*-**8b** were subjected to boc-deprotection followed by treatment with T3P to obtain *R*-clavatustides A and B in 32% and 33% respectively. Thus, the direct ring opening of benzoxazinones allowed us to synthesize clavatustides A and B in an overall yield of 12.5% and 12.9% respectively which is an improvement over the previously reported 9.1 % overall yield for the same.



Scheme 4: Total synthesis of (S)-Clavastutide A & (R)-Clavastutide A:

Conclusion:

An effective and an alternative method for the esterification of α-hydroxyesters in the synthesis of depsipeptides have been identified and its utility was demonstrated by the synthesis of clavatustides A & B. A short and efficient synthesis of clavatustides A and B was achieved in 4 steps with an overall yield 12.5 and 12.9 respectively.

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Supplementary Material

Supplementary data and experimental procedures (Spectroscopic data for compounds clavatustides **A** and **B** associated with this article can be found in the online

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Highlights:

1. An alternative method for the esterification of α-hydroxyesters has been developed.
2. Ring opening of benzoxazinones with α-hydroxy esters was demonstrated
3. Synthesis of clavatustides A and B was achieved in 4 steps with good overall yield
4. Both enantiomers or clavatustides A and B synthesized using the newly developed method