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# Stereoselective total synthesis of the *E*-isomer of putative lucentamycin A

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ABSTRACT

A synthesis of the *E*-isomer of the proposed structure of the novel tripeptide, lucentamycin A, was performed in an attempt to define the correct stereochemistry of this natural product. The synthetic route developed employs a stereoselective Rh-catalyzed reductive cyclization process to generate the key pyrrolidine residue in the target and a stereospecific inversion of the *Z*-olefin geometry to form desired *E*-isomer. Subsequent amide coupling reactions afforded the desired *E*-isomer of putative lucentamycin A. A comparison of the NMR data of synthetic *E*-**1a** with that of the naturally occurring lucentamycin A demonstrated that they are not identical substances and the ***E*-1a** was found to display no anti-proliferative activity on the colon cancer cell line HCT-116 in contrast to natural lucentamycin A.

Lucentamycins A–D are naturally occurring tripeptides isolated from the fermentation broth of a marine-derived *actinomycete Nocardiopsis lucentensis* by Fenical in 2007.[1] Among the four peptides, lucentamycin A was found to have significant in vitro cytotoxicity against HCT-116 human colon carcinoma with an $IC_{50}$ value of 0.20 μM. Owing to its high anti-proliferative activity against colon cancer cells, Lucentamycin A has received great attention. The gross structure and stereochemistry of this tripeptide, assigned as **1a** (Fig. 1) by using the NMR spectroscopic analysis and Marfey degradation, features a *cis* disubstituted exocyclic *Z*-alkene containing pyrrolidine core, and N-acylated homoarginine, and C-terminal leucine moieties.

The intriguing structural motif and biological properties of lucentamycin A prompted synthetic studies by Lindsley et al.[2] that culminated in the preparation of the proposed 8-*epi*-lucentamycin A (**1d**) instead of the natural product **1a**. Concurrently to this effort, Del Valle et al.[3] carried out the first total synthesis of the putative natural product but observed that NMR spectroscopic data of the synthetic compound did not match that reported for naturally occurring lucentamycin A. This finding suggested that the absolute stereochemistry of the proline residue in the putative structure of lucentamycin A (**1a**) needed revision.

Recently, we described the total syntheses of the stereoisomers (**1a**–**d)** corresponding to the four possible absolute configurations of the two contiguous C2 and C3 stereocenters in the pyrrolidine core of putative lucentamycin A. Our hope was that either the previously uncharacterized 8S,9S (**1b**) or 8*R*,9*S* (**1c**) stereoisomers (Fig. 1) would be the naturally occurring lucentamycin A.[4] The preparative routes used for the syntheses of **1a–d** employed stereoselective Rh-catalyzed reductive cyclization reactions[5,6] using (*S*)- and (*R*)-BINAP. These processes afforded four key optically active intermediates, **3a**, **3b**, **5a**, and **5b**, which served as building blocks for the four lucentamycin A isomers (Scheme 1). Prior to our report, Del Valle and his coworkers described[7] ester enolate-Claisen rearrangement based syntheses of the same four stereoisomers. Importantly, the data accumulated for the four synthetic substances did not match that reported for naturally occurring lucentamycin A, showing that the configurations of the pyrrolidine stereogenic centers are not the source of the structural mis-assignment of the natural product.

Careful examination of the $^1H$ NMR spectroscopic properties of synthetic **1b–d** revealed that significant differences exist between the chemical shifts of the pyrrolidine ring protons relative to those of natural lucentamycin A. In addition, the closeness of the

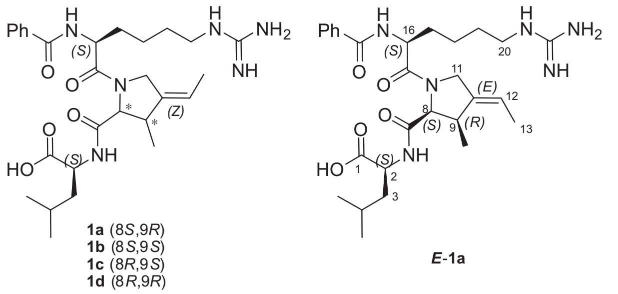

**Figure 1.** Proposed structures of putative lucentamycin A (**1a**), its isomers (**1b–d**), and *E*-isomer of **1a** (*E*-**1a**).

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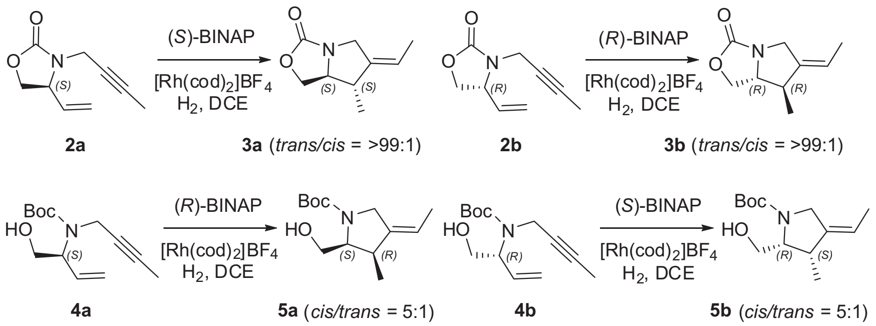


**Scheme 1.** Stereoselective synthesis of pyrrolidine isomers **3a**,**b** and **5a**,**b** via Rh-catalyzed reductive cyclization processes.

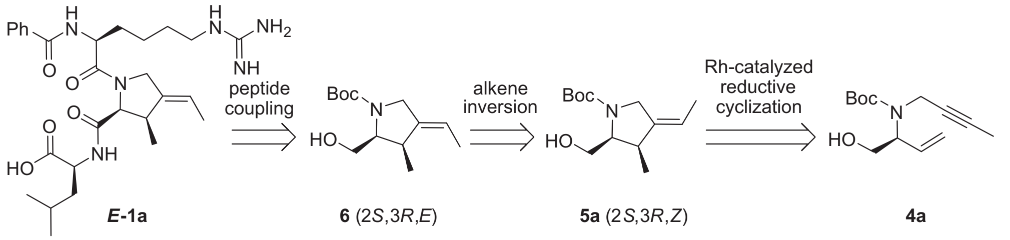
respective chemical shifts of H8 (4.36 vs 4.22 ppm), H9 (3.18 vs 3.21 ppm), H11a (4.58 vs 4.50 ppm), and H11b (4.44 vs 4.40 ppm) protons in the spectra of synthetic and isolated **1a**, suggest that the stereochemistry of the pyrrolidine ring in natural lucentamycin A is most likely 8*S*,9*R*, as was originally proposed.[4,7] When all of the current information is taken into account, it is reasonable to propose that mis-assignment of the structure of the natural product might be a consequence of a difference in the stereochemistry of the pyrrolidine exocyclic ethylidene moiety and/or the two other amino acid residues. To address one aspect of this issue, we have carried out a synthesis of the *E*-isomer of the (8S,9R)-stereoisomer (*E*-**1a**, Fig. 1) of putative lucentamycin A in order to determine if it is identical to naturally occurring substance.

As illustrated in a retrosynthetic manner in Scheme 2, the key steps in the synthesis of *E*-**1a** include a stereoselective construction of the *cis*-pyrrolidine core via a BINAP directed Rh-catalyzed reductive cyclization reaction of the optically active 1,6-enyne **4a** and stereochemical inversion of the ethylidene group in the *Z*-isomer **5a** to form (2*S*,3*R*,E)-(4-ethylidene-3-methylpyrrolidin-2-yl)methanol (**6**). The preparative route began with the transformation of (2*S*)-enyne **4a** to *cis*-(2*S*,3*R*)-pyrrolidine **5a** preferentially (5:1 dr, 92%, Scheme 2) utilizing reductive cyclization reaction promoted by the Rh-(*R*)-BINAP complex in 1,2-dichloroethane at room temperature under a hydrogen atmosphere.[4] Boc-deprotection of **5a** using HCl–dioxane, followed by oxazolidinone ring formation with carbonyldiimidazole in the presence of triethylamine afforded the bicyclic-pyrrolidine **7** in 60% yield and a 5:1 *cis*:*trans* ratio. These diastereomers were readily separated by using flash column chromatography.

Inversion of ethylidene group stereochemistry was accomplished employing a four step sequence involving dihydroxylation, mesylation, epoxide ring formation, and deoxygenation. Specifically, catalytic *cis*-dihydroxylation of **7** using osmium tetraoxide and *N*-methylmorpholine N-oxide at room temperature furnished the diol **8** as a single stereoisomer in 46% yield. However, when this reaction is performed at 0 °C the diol **8** is generated in 81% yield. Mesylation of the secondary hydroxyl group in **8** using MsCl in the presence of triethylamine at 0 °C gave mesylate **9**, which was subsequently treated with methanolic KOH to afford epoxide **10** in quantitative yield.[8] Because epoxide ring formation takes place by inversion of configuration, this epoxide should serve as a precursor of the targeted *E*-ethylidene derivative **11**. Relatively few general methods exist for stereocontrolled olefin forming through removal of oxygen from epoxides and most of the known procedures require the use of expensive reagents and harsh reaction conditions.[9] However, we observed that deoxygenation of epoxide **10** occurred under mild condition using diphosphorous tetraiodide ($P_2I_4$)[10] in refluxing pyridine-$CH_2Cl_2$ to afford **11** (58% yield, 15% recovery of **10**), which possesses the desired *E*-ethylidene stereochemistry. Moreover, when this reaction is carried out utilizing the higher boiling $CCl_4$ instead of $CH_2Cl_2$ as solvent, alkene **11** is produced in 69% yield in 10 h. The resulting alkene **11** was found to be a single diastereoisomer with *E*-stereochemistry (see below).

Hydrolysis of oxazolidinone ring in **11** followed by Boc-protection of the amine moiety afforded the (2*S*,3*R*,*E*)-alcohol **6** in 88% yield (Scheme 2). The configuration of the ethylidene moiety in **6** was determined by comparing the results of 1D NOE experiments with the (*Z*/*E*)-isomers **7** and **11** (Fig. 2). The, *E*-isomer **11** displayed a clear NOE between the methyl protons on the olefin moiety and the methine proton at C7. This NOE was absent in the spectrum of the *Z*-isomer **7**. However, a strong NOE was observed between the methyl protons on the olefin moiety in **7** and the methylene proton at C5. The stereochemical assignment also gained support from a comparison of the $^{13}$C NMR chemical shifts in the spectra of **7** and **11**. The strong shielding effect experienced by the olefinic methyl group in the *E*-isomer **11** results in an upfield shift of the C7 (36.3 ppm) resonance relative to that of *Z*-isomer 7 ($\delta$ = 40.4 ppm) and an upfield shift of the C5 ($\delta$ = 46.2 ppm) resonance of *Z*-isomer 7 relative to that of *E*-isomer **11** ($\delta$ = 48.5 ppm) was observed. The *cis*-relative stereochemistry of C7a and C7 in *E*-isomer **11** was also associated with a clear NOE correlation between the protons at C7a and C7.

With the aim of developing a shorter synthetic route, we explored a sequence for the preparation of the key intermediate **6** that does not require installation and removal of oxazolidinone ring. Accordingly, protection of the alcohol moiety in **5a** (*cis*/*trans* = 5:1) to form the silylated alcohol **12** was accomplished



**Scheme 2.** Retrosynthetic analysis of the *E*-isomer of proposed lucentamycin A.