A mild and efficient approach to enantioenriched α-hydroxyethyl α,β-unsaturated δ-lactams

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Abstract
A straightforward approach toward enantioenriched α-substituted α,β-unsaturated δ-lactams is described. Although a considerable number of approaches toward α,β-unsaturated δ-lactams have been reported, there are relatively few examples of enantioenriched α,δ-disubstituted α,β-unsaturated δ-lactams formation. The δ-stereocenter was formed by addition of allylmagnesium bromide to an N-tert-butylsulfinyl imine. The α,β-unsaturated δ-lactam was furnished by ring-closing metathesis. Although Baylis-Hillman chemistry failed on this cyclic compound, introduction of the hydroxyethyl group prior to ring-closing metathesis was successful. A Baylis-Hillman reaction was used to introduce the substituent at the α-position of the α,β-unsaturated lactam.

Abstract

Keywords
δ-Lactams; Ring-closing metathesis; Asymmetric allylation; Baylis-Hillman reaction

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Supplementary Material
Supplementary data associated with this article can be found, in the online version, at XXXXXXXXXXXX.
Unsaturated lactam derivatives are important building blocks for the synthesis of natural products, pharmaceutical compounds, and peptides.\textsuperscript{1} Accordingly, methods for preparing \(\alpha,\beta\)-unsaturated \(\delta\)-lactams are of interest to synthetic chemists.\textsuperscript{2} In particular, \(\delta\)-substituted \(\alpha,\beta\)-unsaturated \(\delta\)-lactams are widely encountered in biologically active molecules and thus, various methodologies have been developed for preparing enantioenriched \(\delta\)-substituted \(\alpha,\beta\)-unsaturated \(\delta\)-lactams.\textsuperscript{3} In addition, a considerable number of approaches to afford \(\alpha\)-substituted \(\alpha,\beta\)-unsaturated \(\delta\)-lactams have been reported.\textsuperscript{4} However, only few studies toward enantioenriched \(\alpha,\delta\)-disubstituted \(\alpha,\beta\)-unsaturated lactams have been reported.\textsuperscript{5} In this report, we describe a mild and efficient approach toward optically active \(\alpha\)-hydroxyethyl \(\delta\)-substituted \(\alpha,\beta\)-unsaturated lactams.

In the course of a synthesis project, we planned to prepare secondary alcohol 1 (Scheme 1). For the indicated research effort, we were in need of an enantiomerically enriched \(\delta\)-lactam, but the configuration of the hydroxyethyl group was inconsequential. The desired alcohol 1 was expected to be formed by a Baylis-Hillman reaction of \(\alpha,\beta\)-unsaturated \(\delta\)-lactam 2. We envisioned that lactam 2 could be produced by ring-closing metathesis of amide 3.

The synthesis commenced with the construction of amine 9, which was adapted from Ellman and Nelson protocols (Scheme 2). Protection of diol 4 with TBSCI furnished bis-silyl ether 5, which was converted to aldehyde 6 by ozonolysis. Condensation with (R)-tert-butanesulfinamide auxiliary produced tert-butylsulfinyl imine 7.\textsuperscript{6,7} \(1,2\)-addition of allylmagnesium bromide to tert-butylsulfinyl imine 7 generated adduct 8 in high diastereoselectivity. Cleavage of the silyl and tert-butanesulfinyl groups under acidic conditions afforded chiral amine 9.

With chiral amine 9 in hand, \(\alpha,\beta\)-unsaturated lactam formation was explored (Scheme 3). Silylation of amine 9 followed by acylation generated metathesis precursor 10. We were delighted to find that ring-closing metathesis of 10 with Hoveyda-Grubbs 2nd generation catalyst smoothly produced lactam 11.\textsuperscript{3a,8,9} Protection of the nitrogen of amide 11 with MeI or Boc\textsubscript{2}O afforded the corresponding intermediates 2a and 2b. Unfortunately, attempted Baylis-Hillman reactions to furnish alcohol 1a or 1b, respectively, were unsuccessful.\textsuperscript{10,11}

Alternatively, we decided to employ the Baylis-Hillman reaction at an earlier stage (Scheme 4). Reaction of methyl acrylate (12) with acetaldehyde and subsequent hydrolysis furnished acid 13. Coupling of acid 13 and amine 14 with EDCI and HOBt proceeded smoothly to provide amide 15. To our delight, ring-closing metathesis of 15 occurred with catalyst 16, delivering the desired 2:3 mixture of two diastereomers of lactam 1c.\textsuperscript{12}

In summary, the preparation of a potentially versatile \(\alpha\)-substituted \(\alpha,\beta\)-unsaturated lactam is described. The chirality at the \(\delta\)-position of the lactam was established by using a tert-butanesulfinamide auxiliary. The \(\alpha,\beta\)-unsaturated lactam was efficiently provided by ring-closing metathesis. Ultimately, a Baylis-Hillman reaction was used to deliver the substitution at the \(\alpha\)-position of the \(\alpha,\beta\)-unsaturated lactam but had to be incorporated prior to ring-closing metathesis. We believe that this method can be applied to synthesize various \(\alpha\)-substituted \(\alpha,\beta\)-unsaturated lactams, which could be valuable precursors toward natural products and pharmaceutical compounds.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References and notes


7. Although the Ellman group reported that allylmagnesium bromide was added from the Si-face of (S)-tert-butylsulfinyl imine \( \textit{17} \) to deliver \( \textit{18} \) (ref 3a), the opposite configuration was later confirmed by the Nelson group (ref 3b). The Nelson group prepared \( (R) \)-benzamide \( \textit{19} \) from both the commercially available \( (R) \)-2-amino-4-pentenoic acid \( \textit{20} \) and using Ellman’s method with \( (S) \)-tert-butanesulfinamide. Then, they discovered that the retention time of both benzamides \( \textit{19} \) was identical on chiral HPLC.


9. Acidic removal of the silyl and tert-butanesulfinyl groups of \( \textit{8} \) followed by carbamate formation with CDI afforded \( \textit{21} \). Although acylation of \( \textit{21} \) generated metathesis precursor \( \textit{22} \), attempted ring-closing metathesis with Hoveyda-Grubbs 2nd generation catalyst to form bicycle \( \textit{23} \) led only to double bond isomerization, generating \( \textit{24} \).


11. Although \( \alpha \)-bromination of lactam \( \textit{2a} \) produced bromide \( \textit{25} \), attempts to prepare the desired alcohol \( \textit{1a} \) from bromide \( \textit{25} \) were unsuccessful.

12. The same result of the ring-closing metathesis of amide \( \textit{15} \) was obtained with Hoveyda-Grubbs 2nd generation catalyst

\[ \text{Hoveyda-Grubbs 2nd generation catalyst} \]

\[ \text{ring-closing metathesis} \]

\[ \text{bicycle} \]

\[ \text{double bond isomerization} \]
Scheme I.
Retrosynthesis of secondary alcohol 1
Scheme 2.  
Synthesis of chiral amine 9
Scheme 3.
Synthesis of $\alpha,\beta$-unsaturated lactams 2
Scheme 4.
Synthesis of $\alpha$-substituted $\alpha,\beta$-unsaturated lactam $1c$