Glutarimide Alkaloids via MCR Chemistry.

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Supporting Information Placeholder
ABSTRACT: The concise four step synthetic route for glutarimide alkaloids of high biological interest is presented. The scaffold is accessed via an Ugi four component reaction, hereby introducing two points of variation. This is followed by a hydrolysis, a cyclization under mild conditions and an amine deprotection. The diastereomers of the cyclized intermediate can be separated, thus leading to optically pure alkaloids. Via this route, four natural products and ten derivatives were synthesized.

The glutarimide moiety (2,6-piperidinedione) is present in a number of natural product scaffolds and is linked to diverse biological activities. In medicinal chemistry, the glutarimide scaffold is present in derivatives with antibiotic, antiviral, anti-inflammatory and neuroregenerative properties, just to name a few. Glutarimide – containing polyketides have shown cell migration inhibitory activity, and glutarimide macroketones are effective against cancer metastasis.

Glutarimide alkaloids are an important class of natural products. The scaffold is present in the structure of Julocrotine, which has shown antiproliferative effects in in vitro tests against the promastigote and amastigote forms of Leishmania amazonensis.

The Julocrotine structure was elucidated in 1961 with a series of degradation reactions and a report in 1974 showed the synthesis of a lower homologue using harsh conditions. In 2011, a six step synthesis starting from L-glutamic acid was described. Shortly afterwards, a four-step synthesis was described starting from Cbz-glutamine. In this case, the key amine intermediate was used as the amine component of an Ugi reaction, but with limited diversity. Moreover, a stereoselective synthesis for Julocrotine and structurally related glutarimide alkaloids was reported based on Boc-L-glutamine. (Figure 1)

![Figure 1. Comparison of previous works with the current approach.](image-url)

Previous works
- L-glutamic acid
- Cbz-glutamine
- Boc-L-glutamine

This work
- Chiral amine

All together, the previously reported methodologies are restricted to the synthesis of only one alkaloid, not allowing the efficient synthesis of derivatives. However, the establishment of a convenient synthetic route for structurally related natural products and derivatives is important for the further biological evaluation of this scaffold. Thus, we envisioned an efficient synthetic route with variation points, which was first established for the natural product Julocrotine. Multi-component reaction (MCR) chemistry allows the effective synthesis of complex scaffolds in a few steps having as starting points easily accessible and diverse building blocks.

Retrosynthetically, the scaffold can be accessed via a 4-component Ugi reaction, followed by an intramolecular cyclization (scheme 1).

![Scheme 1. Retrosynthesis](image-url)

The aldehyde was synthesized in two steps by applying previously described conditions with slight modifications, first the opening of γ-butyrolactone towards methyl 4-hydroxybutanoate, and then the oxidation to methyl 4-oxobutanoate (Scheme 2).

![Scheme 2. Aldehyde synthesis](image-url)

We found that the use of pyridinium chlorochromate (PCC) resulted in much higher yields compared to the Swern oxidation. Oxidation by Dess-Martin periodinane led to lower yields than PCC and it was more challenging to reproduce the same yields.

Regarding the amine component, the chiral amine (R)-(+-)-1-(4-methoxyphenyl)-ethylamine was chosen, in order to play also a protecting role during the intramolecular cyclization. The synthetic route was established as a mild four step synthesis; starting from a four-component Ugi reaction, then an ester hydrolysis, and followed by the intramolecular cyclization and the deprotection of the amine component (Scheme 3). From the Ugi reaction, a new chiral center is introduced; thus diastereomers are formed (in this case the diastereomeric ratio was 3:2). Interestingly, the diastereomers can be separated easily in the cyclization step with column chromatography. In the last step, the cyclized products were deprotected separately. The initial attempt with hydrogenation and Pd/C was unsuccessful, but deprotection with refluxing TFA resulted in quantitative yield.
It is noteworthy that the diastereomeric ratios \((S,S): (R,S)\) as determined by separation in the cyclization step varied significantly. More specifically for crotonimides A and B the ratio \((S,S): (R,S)\) was 4:5 and 3:2, respectively. The greatest difference was observed for crotonimide C with the ratio \((S,S): (R,S)\) being 1:5, thus the natural product was not the major one.

Next, we went on with the synthesis of a small library of derivatives. In the Ugi reaction, there are two points of variation: the carboxylic acid and the isocyanide component. The aldehyde was kept constant due to its role in the cyclization. To investigate the scope and limitation, 10 derivatives were synthesized by using the \((R)-(+)-1-(4-	ext{methoxyphenyl})\)-ethylamine and varying either the carboxylic acid or the isocyanide, as shown in the next scheme (scheme 5).

### Table 1. Isolated yields for the derivatives.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Isocyanide</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)_4</td>
<td>(7a)</td>
<td>53%</td>
<td>98%</td>
<td>62%</td>
<td>85%</td>
</tr>
<tr>
<td>(S)_5</td>
<td>(7b)</td>
<td>98%</td>
<td>62%</td>
<td>53%</td>
<td>98%</td>
</tr>
<tr>
<td>(S)_6</td>
<td>(7c)</td>
<td>62%</td>
<td>53%</td>
<td>98%</td>
<td>62%</td>
</tr>
<tr>
<td>(S)_7</td>
<td>(7d)</td>
<td>85%</td>
<td>53%</td>
<td>62%</td>
<td>98%</td>
</tr>
<tr>
<td>(S)_8</td>
<td>(8a)</td>
<td>52%</td>
<td>80%</td>
<td>20%</td>
<td>75%</td>
</tr>
<tr>
<td>(S)_9</td>
<td>(8b)</td>
<td>80%</td>
<td>20%</td>
<td>52%</td>
<td>80%</td>
</tr>
<tr>
<td>(S)_10</td>
<td>(8c)</td>
<td>20%</td>
<td>75%</td>
<td>52%</td>
<td>80%</td>
</tr>
<tr>
<td>(S)_11</td>
<td>(8d)</td>
<td>75%</td>
<td>80%</td>
<td>52%</td>
<td>80%</td>
</tr>
</tbody>
</table>
It should be noted that although the use of 1-adamantylisocyanide resulted in the Ugi and hydrolysis products as expected, in the cyclization step under these conditions only unreacted starting material was obtained, probably due to steric hindrance. Furthermore, the use of the indole moiety, either as carboxylic acid or isocyanide component, resulted into complicated reaction mixtures in the Ugi reactions and products with low purity, which could not be used further.

Interestingly, the use of meta-bromo-benzoic acid in the cyclization step gave only one diastereomer (16c) (as indicated by NMR data), which was deprotected towards an enantiomer with optical rotation of $\alpha_D = +13.57$ (16d). This unexpected result is in good agreement with the data from crotonimide C, where the observed ratio (S,S) : (R,S) was 1:5. Probably due to steric hindrance one diastereomer is significantly favored during the cyclization step of the meta-bromo-benzoic derivative and the other is probably formed in non-isolated traces.

Overall, we have established a straightforward, facile synthetic route for glutarimide alkaloids, allowing great diversity in the products, as well as the isolation of optically pure natural products. By our synthetic route, the biological evaluation of the glutarimide alkaloids scaffold for multiple targets will be significantly facilitated in the future.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures; compound characterization data; $^1$H and $^{13}$C spectra of all compounds, SFC, HRMS (ESI), crystal structure (PDF).

AUTHOR INFORMATION

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