Remote Stereocontrol in [3,3]-Sigmatropic Rearrangements: Application to the Total Synthesis of the Immunosuppressant Mycestericin G

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ABSTRACT

The Ireland-Claisen [3,3]-sigmatropic rearrangement has been used to access biologically important β,β'-dihydroxy α-amino acids. The rearrangement reported is highly stereoselective and offers excellent levels of remote stereocontrol. This strategy has been used to synthesize the natural immunosuppressant mycestericin G and ent-mycestericin G, allowing for a revision of absolute configuration of this natural product.

The realization that naturally-occurring immunosuppressants, such as cyclosporin A, greatly reduce the likelihood of host rejection has made human organ transplantation a viable medical process. Arguably, this medical advance has profoundly changed society with heart, kidney, lung, liver and bone-marrow transplants now routinely successful. A large range of natural products have now been demonstrated to possess immunosuppressive activity with recently reported examples seeking to improve biological activity or diminish side-effects. One of the most potent immunosuppressant natural products is myriocin, (1, Figure 1) which has been isolated from three different fungal sources. Impressively, myriocin displays a 10-

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100 fold increase in immunosuppressant potency compared with cyclosporin A.\textsuperscript{6}

Figure 1. Myriocin and \( \beta,\beta' \)-Dihydroxy \( \alpha \)-Amino Acids

Structure-activity studies have strongly supported the crucial structural feature of 1 with respect to biological activity is the polar \( \beta,\beta' \)-dihydroxy \( \alpha \)-amino acid head group.\textsuperscript{7} Accordingly, flexible and efficient synthetic entries to such \( \beta,\beta' \)-dihydroxy \( \alpha \)-amino acids\textsuperscript{8} (2, Figure 1) are potentially important for the discovery of new immunosuppressive treatments and related chemical biology studies.\textsuperscript{9} In addition, the structurally related natural products, sphingofungin E\textsuperscript{10} and mycystericins A-G\textsuperscript{11}, contain this key \( \beta,\beta' \)-dihydroxy \( \alpha \)-amino acid moiety, and high levels of immunosuppressant activity have also been noted for both molecules.\textsuperscript{12}

In recent years we have been developing a programme of research directed toward the synthesis of novel amino acids through Ireland-Claisen rearrangements of substrates rich in heteroatom substitution.\textsuperscript{13} The Ireland-Claisen [3,3]-sigmatropic rearrangement is a key \( C-C \) bond forming reaction used in modern organic synthesis\textsuperscript{14,15} and is therefore ideally suited to such research effort. The rearrangement offers predictable diastereoccontrol, chirality transfer and the ability to form congested quaternary stereocentres. These three key attributes stem from the preference of acrylic substrates to rearrange via a highly ordered chair transition state.

Complex serine congeners, suitable for further elaboration to the natural product classes discussed above, might become accessible through sigmatropic rearrangements on serine-derived silylketene acetals. The employment of an Ireland-Claisen strategy for the synthesis of substituted serine analogues would require the generation of an unstable serine enolate. To avert this anticipated synthetic problem, the use of a serine-derived oxazolidine has been considered. Such a strategy would not only protect the sensitive \( \beta \)-hydroxy by circumventing degradative E1Cb elimination\textsuperscript{16}, it would also offer the potential to control absolute stereochemistry via the chiral relay strategy pioneered by Seebach.\textsuperscript{17} To examine this proposal, model ester substrate 3a was readily synthesized\textsuperscript{18} and subjected to standard Ireland-Claisen conditions used in our laboratory.\textsuperscript{19}

Table 1. Ireland-Claisen Rearrangement of Oxazolidine Enol Ester Substrates.


For examples of Ireland-Claiken rearrangements in natural product synthesis using substrates bearing cyclic \( \beta \)-etheral oxygen centres, see: (a) Ireland, R. E.; Armstrong, J. D.; Lebreton, J.; Meissner, R. S.; Rizzacassa, M. A. J. Am. Chem. Soc. 1993, 115, 7152. (b) Bunte, J. O.; Cuzzupe, A. N.; Daly, A. M.; Rizzacassa, M. A. Angew. Chem. Int. Ed. 2006, 45, 6376.


(18) See Supporting Information for details of substrate synthesis.
On treatment with LiHMDS and MeSiCl at -78 °C, the silylketene acetal derived from methyl enol ether 3a was found to rearrange smoothly, after warming to room temperature, with β-methoxy product 4a isolated as a single stereoisomer in 78% yield (Table 1, entry 1). The stereoselectivity is notable, not only for its magnitude, but also because the controlling stereocentre is two atoms from the forming C-C bond. This stereocontrol strategy has previously shown limited efficacy in asymmetric synthesis.14,19

The Ireland-Claisen rearrangement reaction of enol ethers 3a-n is general and leads to the formation of β-alkoxy and β-aryloxy α-amino acid products, isolated as methyl esters 4a-n in good yield and excellent diastereoselectivity. The absolute and relative stereochemistry has been confirmed by XRD of iodoaryl ether 4i (Figure 2).

The observed sense of stereoselectivity is consistent with transition state geometry I (Figure 2) whereby the enol ether fragment approaches the silylketene acetal anti to the oxazolidine tert-butyl group and agrees with reported stereoselective transformations using this regeneration of stereocentres tactic.20 Notably, the rearrangement of substrates bearing O-functional handles (entries 4-5, 9, 13) and O-protecting groups (entries 4, 7, 10, 12) suggest that this strategy may be of future synthetic value. This sigmatropic transformation is highly stereoselective in each case. In three instances, however, the substrate proved to be particularly unstable, necessitating it being used without purification for conversion to the rearranged aliphatic ether products in yields of 47-55% over two steps (entries 13-15). It is unclear exactly why these substrates have proven to be so sensitive, however, we can speculate that the substantial steric cost of these alky groups (β-iodobenzyl, β-butyl and cyclohexyl) promotes a conformational restriction of the enol ether oxygen, improving O₂ donation into the enol ether π-system, ultimately leading to increased sensitivity. However, it was found that these systems rearrange as efficiently as that seen in entries 1-12 (70-80%), when the yield of ester formation is taken into account. The Ireland-Claisen rearrangement products 4a-n are equivalent to O-alkyl and O-aryl aldos and, when placed in this context, the power of this rearrangement becomes apparent. Low levels of diastereoselectivity (dr ≤ 2:1) are observed when serine-derived oxazolidine esters are used in aldol reactions in conjunction with simple achiral aldehydes.21

The rearrangement is amenable to streamlined preparative scale (4 mmol of 6) manipulations. For example, when EDCI mediated coupling of 512 and 6,12a Ireland-Claisen rearrangement and carboxyl benzylidation are conducted without intermediate purification, ent-4k is isolated in 81% over three steps (Scheme 2).

This rearrangement reaction offers a rapid access to complex and functionalized β,β′-dihydroxy α-amino

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**Table 1. Diastereomeric Ratio of Claisen Rearrangements.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>d.r.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>98:2</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>98:2</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>98:2</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>98:2</td>
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<tr>
<td>5</td>
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<td>6</td>
<td>3f</td>
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<td>55</td>
</tr>
<tr>
<td>14</td>
<td>3n</td>
<td>98:2</td>
<td>47</td>
</tr>
</tbody>
</table>

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**Diagram 2. ORTEP Plot of XRD analysis of 4i (at 30% probability).** Structure deposited with CCDC (CCDC 812147) and proposed Ireland-Claisen rearrangement geometry I.

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acids motifs. To demonstrate the synthetic potential, a synthesis of mycestericin G (8, Scheme 2) has been examined. This natural product features a polyhydroxy α-amino acid head group and lipophilic tail, offering a potential entry from the cross-metathesis union of a rearrangement product 7 and a suitable lipophilic olefin partner, such as 9 (Scheme 2). Our envisioned strategy was to examine olefin homodimer 9 in combination with the 2nd generation Hoveyda-Grubbs Ru-carbene catalyst 24 as Grubbs has previously demonstrated the improved performance of homodimers 25 and the stated catalyst in sterically congested allylic alcohols 26 in cross-metathesis reactions.

Scheme 2. Mycestericin G Synthetic Strategy

The synthesis of mycestericin G was completed after PMB deprotection of 7, cross metathesis and hydrogenation, with final N-Boc oxazolidine cleavage furnishing mycestericin G after chromatography. The 1H NMR data was in excellent agreement with that reported, but the optical rotation was opposite in sign, yet of a similar magnitude to that quoted (Scheme 3). In contrast, the parallel synthetic sequence from L-serine produced ent-8, now with the same sense of optical rotation and comparable magnitude to that reported for mycestericin G.

Figure 3. Effect of alkene on sense of optical rotation.

To explain this discrepancy, we offer the following analysis. Hydrogenation of 1 forms dihydromyriocin 10 (Scheme 3). Key is the realisation that hydrogenation of the seemingly innocuous olefin in 1 leads to a reversal in the sense of optical rotation i.e. myriocin 1 is dextrorotatory whilst 10 is levorotatory.

The absolute configuration of mycesterin E (11) has been determined through the total synthesis. 28 This report also demonstrated that mycestericin G (8) was obtained from synthetic 11, forming material which was observed to have identical spectroscopic data. However, no optical rotation data was reported for this synthetic mycestericin G. Therefore, there is not an unequivocal demonstration that the configuration of the stereocenters in mycestericin G is the same as the two stereocenters in mycestericin E. The recent elegant synthesis of mycestericin G by Kumagai and Shibasaki is of particular interest. 12i This effort resulted in the synthesis of the structure originally reported; however, with an opposite sense of optical rotation to that in the original isolation paper. We feel that this observation offers further credence to a reassignment.

(26) Sterically demanding allylic alcohols have displayed efficacy in cross-metathesis reactions using Hoveyda-Grubbs II metathesis catalysts, see: Stewart, I. C.; Douglas; C. J.; Grubbs, R. H. Org. Lett. 2008, 10, 441.

of configuration of the natural immunosuppressant mycestericin G.
In conclusion, an Ireland-Claisen route to polyhydroxyamino acids, using a self-regeneration of stereocenters strategy, has been developed. It has also been applied in a succinct synthesis of mycestericin G and ent-mycestericin G, allowing a reassignment of configuration of this immunosuppressant natural product.

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Supporting Information Available For full experimental details and data for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.