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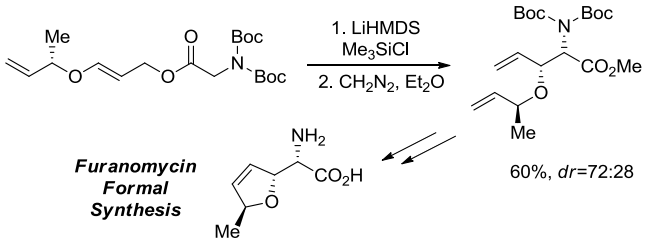

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Ireland-Claisen rearrangement of substrates bearing chiral enol ether units

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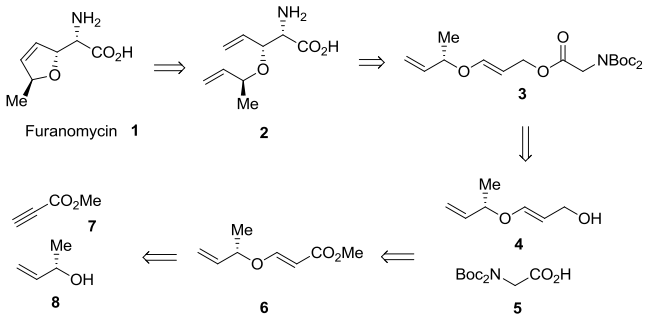
ABSTRACT

The Ireland-Claisen [3,3]-sigmatropic rearrangement of an allylic glycinate bearing a remote chiral enol ether has been studied. Remote *exo*pericyclic stereocontrol is achievable in this instance. The product from this rearrangement has been progressed through a formal total synthesis of the natural antibiotic, furanomycin.

l-(+)-Furanomycin (**1**) (Scheme 1) is a naturally occurring cyclic β-alkoxy α-amino acid isolated by Katagiri from the fermentation broth of *Streptomyces* L-803(ATCC15795).[1] The original report detailed that **1** significantly suppressed the growth of several bacterial species including strains of *Escherichia coli*, *Bacillus subtilis*, *Shigella paradysenteriae*, *Salmonella paratyphi and Mycobacterium tuberculosis*. A later report demonstrated that **1** acts as a substrate of isoleucyl aminoacyl tRNA synthetase (AARSIle) with *in vitro* replacement of isoleucine during protein translation.[2]



Scheme 1. Furanomycin **1** and Retrosynthetic Analysis.

Although **1** does not offer exceptional molecular complexity, the antibiotic activity and the compact nature of furanomycin has meant that significant synthetic attention has been paid as a vehicle for assessing new methodologies.[3,4]

We have recently reported the Ireland-Claisen [3,3]-sigmatropic rearrangement of glycinates[5] containing allylic enol ether units as part of a larger research programme into new applications of the Ireland-Claisen rearrangement.[6] After rearrangement of these glycinates, functionalized *syn*-β-alkoxy α-amino acids are formed with high levels of stereocontrol. The inherent *syn*-β-alkoxy α-amino acid structure embedded within furanomycin suggested **1** as a clear target for this Ireland-Claisen methodology.

A retrosynthetic analysis of **1** lent itself to a late-stage ring-closing diene metathesis approach to form the dihydrofuran ring from a suitable dienyl *syn*-β-alkoxy α-amino ester (Scheme 1). Diene **2** would in turn be accessed from an Ireland-Claisen rearrangement of glycinate **3**.[7] Key allylic alcohol **4** should be formed through a reduction of β-alkoxy acrylate **6**, with the ultimate introduction of chirality stemming from enantiopure allylic alcohol **8** (Scheme 1).[8]

The retrosynthetic strategy described in Scheme 1 asks two key questions. Firstly, we were unaware of the use of a chiral allyl vinyl ether, such as that present in **3**, which would act as a remote *exo*pericyclic stereocontrol element in an Ireland-Claisen rearrangement. Secondly, the silylketene acetal formed from glycinate **3** would bear *two* allyl vinyl ether fragments that could offer competing rearrangement (Figure 1). We were confident of chemoselective rearrangement based on our previous work on a simpler *O*-allyl enol ether.[5b] However, the relative stereocontrol offered by this *exo*pericyclic stereocentre was not as clear-cut and therefore offered an interesting methodological problem which could be answered through this attempted total synthesis.

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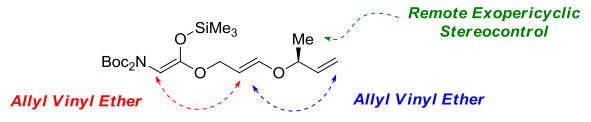
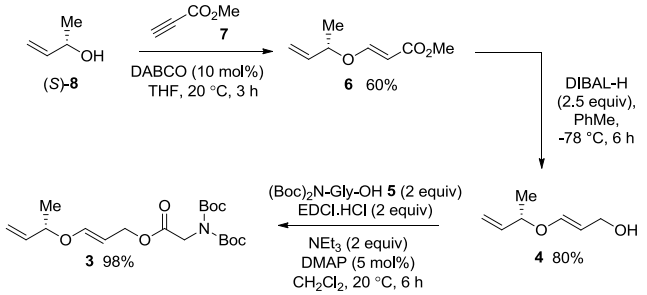


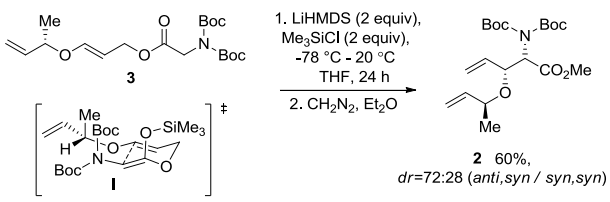
Figure 1. Postulated Silylketene Acetal Required for Rearrangement.

Our synthesis commenced with the construction of the requisite glycinate **3** (Scheme 2). Oxy-Michael reaction of allylic alcohol **8** to methyl propiolate, catalysed by DABCO, formed vinylogous carbonate **6** in 60% yield. DIBAL-H mediated reduction of the ester moiety (80%) and rapid EDCI mediated coupling of **5** with di-Boc-glycine formed **3** in excellent yield (98%).



Scheme 2. Synthesis of Rearrangement Substrate **3**.

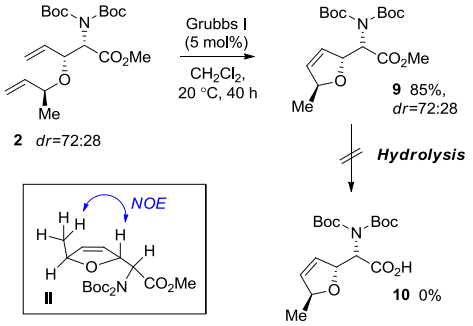
Application of the rearrangement protocol previously optimized for these di-Boc glycinate substrates[5b] resulted in smooth rearrangement, which after acid methylation, allowed isolation of *syn*-β-alkoxy α-amino ester **2** (Scheme 3). Two inseparable diastereomers were isolated from this reaction in a ratio of *anti,syn/syn,syn* = 72:28, with the major *anti,syn*-diastereomer displayed in Scheme 3. Efforts were made to improve the rearrangement selectivity by conducting the reaction at lower temperatures over extended periods of time. However, both reaction efficiency and selectivity were adversely affected. The levels of stereocontrol mirror the magnitude we reported for a structurally similar glycinate bearing a chiral enol ether derived from 1-phenylethanol.[5b] The sense of selectivity is still consistent with the π-facial selectivity proposed by Greene[9] for chiral enol ethers in asymmetric dichloroketene [2+2]-cycloadditions and is depicted as transition state geometry **I** (Scheme 3).



Scheme 3. Ireland-Claisen Rearrangement to Key Diallyl Ether **2**.

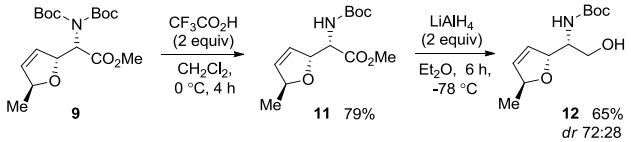
Our previous study with di-Boc glycinates demonstrated a comprehensively high level of *syn*-diastereoselectivity at the α- and β-stereocentres relative to the ester and this has been incorporated into our understanding in this instance. The sense of diastereocontrol relative to the original allylic stereocentre was assessed after ring formation (*vide supra*). Ring-closing metathesis[10] using the first generation Grubbs Ru-catalyst occurred smoothly at room temperature (Scheme 4) and preserved the observed level of diastereocontrol. The sense of relative stereocontrol offered by the *exo*pericyclic allylic stereocentre was determined through spectroscopic means with a pronounced NOE observable between the C(2) ring methine and the methyl group (**II**, Scheme 4). A similar NOE was not observed in the minor stereoisomer.

Our original plan had been to effect ester hydrolysis prior to acidic removal of the two *tert*-butyl carbamate protecting groups, allowing convergence with the penultimate intermediate in Standaert's efficient synthesis of furanomycin.[3d] However, this saponification proved unmanageable (Scheme 4). A number of conditions were studied with the bases KOTMS, LiOH, NaOH, KOH and CsOH all examined. It is clear that **9** is consumed during the saponification, as evidenced by TLC reaction monitoring. However, intractable mixtures form as a result, further confirming the base sensitivity of these β-alkoxy α-amino esters previously seen with the acyclic rearrangement products.



Scheme 4. Dihydrofuran Formation.

Therefore, a decision was made to alter the synthetic strategy and proceed with a formal total synthesis. We had previously demonstrated that clean mono-Boc deprotection was possible with these compounds. This was indeed the case with **9**, which was progressed to **11** on treatment with TFA. Subsequent $LiAlH_4$-mediated ester reduction formed *N*-Boc furanomycinol **12** which converged with the Standaert synthesis.[3d] Unfortunately, the mixture of diastereomers formed from the Ireland-Claisen rearrangement continued to be inseparable throughout the synthesis and therefore **12** was obtained as a 72:28 mixture of diastereomers.



Scheme 5. Completion of Formal Total Synthesis.

In conclusion, the first Ireland-Claisen rearrangement of a substrate bearing a chiral allylic enol ether as a stereocontrol element is reported. A reasonable level of relative stereocontrol is observed on consideration of the remote nature of the controlling stereocentre. The rearrangement product has in turn been transformed to a late-stage intermediate from a recent synthesis of furanomycin and hence constitutes a rapid formal total synthesis of **1**.

Acknowledgements

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