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![Chemical structure and reaction arrow]

80%, dr=72:28
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 exoercyclic stereocontrol is achievable in this instance. The product from this rearrangement has been progressed through a formal total synthesis of the natural antibiotic, furanomycin.

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

![Scheme 1. Furanomycin 1 and Retrosynthetic Analysis.](image)

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.

We have recently reported the Ireland-Claisen [3,3]-sigmatropic rearrangement of glycinites bearing a remote allylic enol ether units as part of a larger research programme into new applications of the Ireland-Claisen rearrangement. After rearrangement of these glycinites, 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. 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).

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 exoercyclic stereocentre 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 β-allyl enol ether. However, the relative stereocentre offered by this exoercyclic 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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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.](image)

Application of the rearrangement protocol previously optimized for these di-Boc glycinate substrates 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 both reaction efficiency and diastereomer displayed in Scheme 3.

![Scheme 3. Ireland-Claisen Rearrangement to Key Diallyl Ether 2.](image)

Our previous study with di-Boc glycinate 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 diastereoccontrol relative to the original allylic stereocentre was assessed after ring formation (vide supra). Ring-closing metathesis using the first generation Grubbs Ru-catalyst occurred smoothly at room temperature (Scheme 4) and preserved the observed level of diastereoccontrol. The sense of relative stereocontrol offered by the exopericyclic 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.

![Scheme 4. Dihydrofuran Formation.](image)

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 LiAlH₄-mediated ester reduction formed N-Boc furanomycinol 12 which converged with the Standaert synthesis. 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.](image)

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.

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References and notes