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An Ireland–Claisen rearrangement approach to $\beta^{2,3}$-amino acids

Paul M. Ylioja, Alexander D. Mosley, Claire E. Charlot, David R. Carbery *

Department of Chemistry, University of Bath, Bath, BA2 7AY, UK

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Abstract

The first use of enamide substrates in an Ireland–Claisen [3,3]-sigmatropic rearrangement reaction is presented as a novel route to complex $\beta^{2,3}$-amino acids

β-Amino acids are important organic molecules[1] finding use in proteomics, medicinal chemistry and as valuable organic synthetic building blocks. Furthermore, β-amino acids feature in a number of important peptide natural products such as the potent protein phosphatase inhibitor Motuporin **1**[2] a constituent residue being the allylic β-amino acid, 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid, Adda **2** (Fig. 1).[3] Due to the importance of β-amino acids in organic synthesis a significant number of differing synthetic strategies to these compounds have been reported.[1] However, there have been very few approaches based upon a sigmatropic process.[4,5]

We envisaged a novel approach to disubstituted $\beta^{2,3}$-amino acids by utilising the Ireland–Claisen [3,3]-sigmatropic rearrangement reaction.[6,7] More specifically, γ,δ-unsaturated β-amino acids may be accessible through this route if nitrogen substitution was to be incorporated upon the allylic unit at C-3 (Scheme 1).

The rearrangement of such systems should lead to the transformation of the C_{sp^2}–N bond to a C_{sp^3}–N bond and importantly, the formation of a stereogenic centre at the β-amine centre. We reasoned that this approach to β-amino acids would benefit from the synthetically useful characteristics of this [3,3]-sigmatropic rearrangement, namely the predictable diastereocontrol, the chirality transfer via chair transition states and the formation of congested quaternary centres.

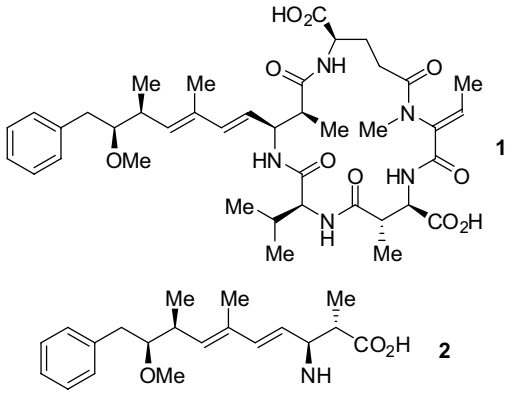
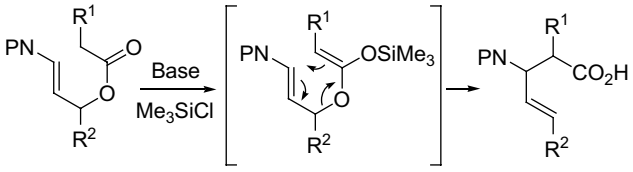


Fig. 1. Motuporin and Adda.



Scheme 1. Proposed Ireland–Claisen rearrangement of enamide substrates.

Investigations commenced with developing a suitable substrate synthesis. Two key requirements were identified from the initial model substrates. Firstly, a propionate

* Corresponding author. Tel.: +44 1225 386 144; fax: +44 1225 386 231.
E-mail address: d.carbery@bath.ac.uk (D. R. Carbery).

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ester would keep the model system simple yet allow for the study of diastereoselection. Secondly, the use of 2° allylic esters would offer asymmetric control with enantiopure substrates during later studies.

To this end it was reasoned that reduction of a suitable N-protected vinylogous amide would offer a feasible route to such alcohols. After some initial investigation, our developed substrate synthesis is summarised in Scheme 2. Oxazolidinone **4** was synthesised through a two step procedure of oxidation of but-3-yn-2-ol **3** and immediate conjugate addition of 2-oxazolidinone to the ynone in the presence of catalytic amounts of DABCO.[8] This allowed access to multigram quantities of **4**. Sodium borohydride reduction cleanly and chemoselectively reduced the ketone moiety to form alcohol **5**.[9,10] This alcohol was observed to be sensitive; however, good quantities of **5** could be accessed without the need for further purification. It was discovered that EDCi mediated coupling between alcohol **5** and propionic acid in the presence of catalytic amounts of DMAP allowed for an efficient coupling to form ester **6a**. Again, ester **6a** was sensitive to chromatography but was seen to be pure without recourse to further purification.

With propionate **6a** at hand, attention was turned to developing the key rearrangement. A focused period of investigation led to the key proof of principle being obtained. Accordingly, the use of LiHMDS and TMSCl in THF at −78 °C and subsequent warming to room temperature led to consumption of the starting propionate. The free acid was isolated in 60% yield after an aqueous acid work up and a subsequent base/acid extraction cycle. This initial reaction yielded a mixture of carboxylic acid diastereomers **7** in reasonable yield (Scheme 3).

Having demonstrated the feasibility of this β-amino acid synthesis, a process of reaction optimisation was undertaken with our observations depicted in Table 1. Key observations made from this study are the sensitivity of the reaction efficiency to the choice of base, with LiHMDS offering best reaction efficiency.[11] However, marginally the best diastereoselectivity was observed when using KHMDS (Table 1).

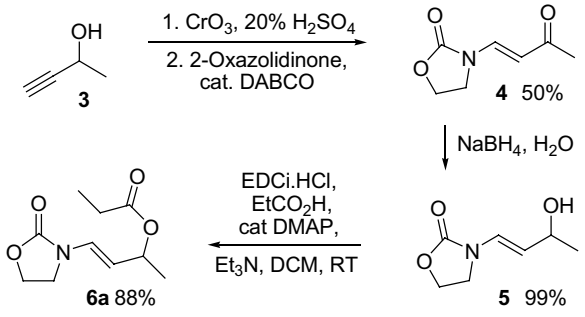
Table 1
Initial optimisation

Entry	Base	Solvent	T (°C)	R_3SiCl	Equiv	Yield (%)	dr
1	KHMDS[a]	Toluene	−78	TMSCl	1.5	0	na
2	KHMDS[a]	Et_2O	−78	TMSCl	1.5	0	na
3	KHMDS[b]	Et_2O	−78	TMSCl	1.5	17	10:3
4	KHMDS[b]	THF	−78	TMSCl	1.5	0	na
5	LiHMDS[b]	THF	−78	TMSCl	2	60	2:1
6	LiHMDS[b]	Tol	−78	TMSCl	1.2	13	3:2
7	LiHMDS[a]	THF	−100	TMSCl	2	40	1:1
8	LiHMDS[a]	THF	−78	TBSCl	2	0	na
9	LDA	Et_2O	−78	TMSCl	1.5	0	na
10	LDA	THF	−100	TMSCl	2	0	na

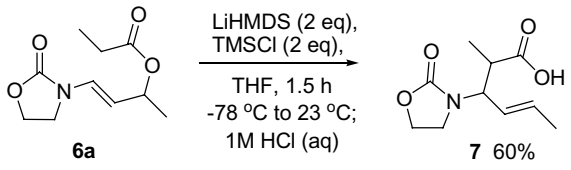
[a] 1 M in THF.
[b] 1 M in toluene.

Having initially investigated the propionate model, a number of substrates were synthesised with a view to demonstrating a level of substrate scope (Scheme 4). These substrates were synthesised in an analogous manner using the appropriate carboxylic acid and EDCi, in reasonable yields (Table 2).

The substrates prepared were examined using the LiHMDS rearrangement conditions as we wished to primarily determine the substrate tolerance. Whilst it is possible to isolate the carboxylic acid products cleanly, treatment of the crude reaction mixture with TMS–diazomethane[12] allows for the isolation of the readily handled methyl ester (Scheme 5). Pleasingly the range of ester substitution examined did not adversely effect the rearrangement reaction (Table 3).



Scheme 2. Model propionate substrate synthesis.

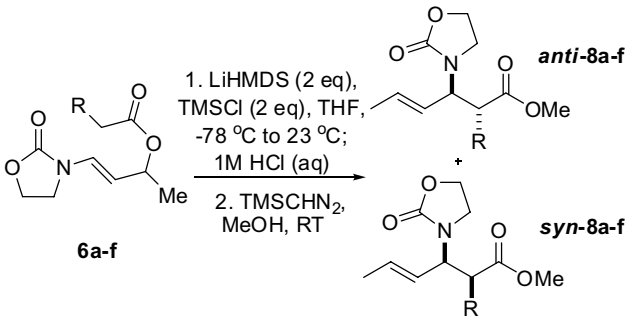


Scheme 3. Initial successful rearrangement.

Scheme 4. Substrate formation.

Table 2
Substrate synthesis

Entry	R	Product	Yield (%)
1	Me	**6a**	88
2	H	**6b**	55
3	*i*-Pr	**6c**	81
4	Allyl	**6d**	64
5	Phenyl	**6e**	35
6	OBn	**6f**	54



Scheme 5. Scope of rearrangement.

Table 3
Scope of rearrangement

Entry	R	Product	Yield (%)	dr (*anti:syn*)
1	Me	**8a**	55	2:1
2	H	**8b**	Trace	na
3	*i*-Pr	**8c**	48	3:2
4	Allyl	**8d**	79	3:2
5	Phenyl	**8e**	69	>95:5
6	OBn	**8f**	62	2:1

A trend is identifiable in that simple alkyl functionalities lead to little observed diastereoselectivty whereas the Ph substituent led only to a single diastereomer. A number of points deserve mentioning. Whilst the diastereoselection is disappointing in the alkyl substituted examples it is also noticeably lower from many Ireland–Claisen reactions of propionates where diastereomeric ratios of the order of ca. 85:15 are often observed.[13] A number of possible factors may be affecting the diastereoselectivity with poor *E*/*Z* enolate geometry control,[14] the enamide moiety effecting the preference of chair versus boat transition states[15] and post-rearrangement enolisation[16] all having deleterious effects. This discussion now places the excellent diastereoselectivity observed with phenyl substrate **6e** in stark contrast. The factors listed above can also be applied to **6e** as suggestions for the good diastereocontrol, that is, the possibility of good *E*/*Z* enolate control, a single transition state operating or selective protonation after post-rearrangement enolisation.[17] Understanding and improving upon these initial observations are key and are currently being examined in greater depth. The isolated yields of methyl esters **8a**,**c**–**f** are generally good. Complete consumption of starting material is observed in each instance with the mass balance being completed by elimination and silylation by-products as suggested by ^{1}H NMR analysis of crude reaction mixtures. Interestingly, we were unable to perform the rearrangement on the simple acetate substrate **6b**. An intractable mixture was always observed although crude NMR data suggested the existence of amino acid **8b** product. The reason for this substrate performing so poorly is not clearly understood and is part of our ongoing studies.

The assignment of relative stereochemistry was putatively based upon the observed coupling constants of the allylic methine signal. This signal is resolved in a number of the recorded ^{1}H NMR spectra. This proton is observed in both *anti*- and *syn*-diastereomers as a doublet of doublets. The major diastereomer in each instance offers a larger coupling constant and is consistent with an *anti*-periplanar open chain conformation of the product β-amino acid systems (Fig. 2) and therefore assigned as the *anti*-diastereomer.

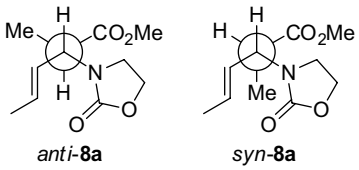


Fig. 2. Conformations of *anti*- and *syn*-diastereomers.

Of particular note are the conversion of substrates **6d** and **6f**, which form the α-allyl and the α-benzyloxy β-amino acid systems, respectively. Product **8d** will allow for the formation of cyclic β-amino acids such as the important antibiotic, cispentacin[18] via ring closing metathesis protocols. Notably, **8f** is a protected and functionalised β-amino α-hydroxy acid (isoserine), which feature in a number of highly significant natural products such as Paclitaxel.[19]

In conclusion, a novel entry to biologically important β-amino acids, which utilises an Ireland–Claisen rearrangement of enamido allylic esters, has been reported. This is the first report of an enamide in a [3,3]-sigmatropic rearrangement reaction. The reaction is general and may offer a powerful entry to important β-amino acids. Further studies of this reaction are currently ongoing in our laboratory.

Acknowledgements

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10. Hydroxy/methanol exchange was observed in this system, therefore the procedure from Ref. 8 was adapted to an aqueous $NaBH_4$ reduction.
11. *Representative procedure*: To a solution of **6e** (422 mg, 1.54 mmol, 1.0 equiv) and trimethylsilyl chloride (357 μl, 3.08 mmol, 2.0 equiv) in THF (5 ml) at −78 °C was added LiHMDS (1 M in THF, 2.31 ml, 2.31 mmol, 1.5 equiv). The reaction was stirred for 30 min before warming to room temperature and stirred for a further hour. The reaction was quenched with 1 M HCl (50 ml) and extracted with EtOAc (3 × 30 ml). The crude reaction product was dissolved in MeOH (5 ml) and TMS diazomethane was added (2 M in Et_2O, 1.55 ml, 3.08 mmol, 2.0 equiv) before stirring for 16 h. The solvent was then removed in vacuo and the crude methyl ester further purified by silica gel column chromatography (petroleum ether/ethyl acetate 10:1) to afford **8e** as a clear oil (292 mg, 1.06 mmol, 69%). FTIR (film/cm^{-1}) ν_{max}: 3062, 3031, 2952, 2918, 1738. δ_H (250 MHz; $CDCl_3$) ppm: 7.23–7.36 (5H, m, Ar*H*), 5.47 (1H, dqd, $J = 15.5$, 6.3, 0.6 Hz, CH=C*H*CH_3), 5.23 (1H, dqd, $J = 15.2$, 7.9, 1.3 Hz, NCHC*H*=$CHCH_3$), 4.71 (1H, dd, $J = 11.4$, 7.9 Hz, NC*H*), 4.21–4.37 (2H, m, OCH_2CH_2N), 4.14 (1H, d, $J = 11.4$ Hz, ArC*H*CO_2Me), 3.66 (3H, s, CO_2CH_3), 3.55–3.70 (2H, m, OCH_2CH_2N), 1.50 (3H, ddd, $J = 6.3$, 1.6, 0.6 Hz, CH=CHCH_3). δ_C (75 MHz; $CDCl_3$) ppm: 172.4, 157.6, 135.1, 131.5, 129.3, 128.9, 128.6, 127.9, 127.2, 124.3, 62.3, 58.7, 54.3, 52.3, 42.6, 17.7. HRMS (+ve ESI): calculated for $C_{16}H_{20}NO_4$ ($M+H^+$): 290.1392. Found: 290.1415.
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