Si-Free Enolate Claisen Rearrangements of Enamido Substrates

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α-Alkyl β-amino esters are available in high diastereoselectivity through a silicon-free Claisen enolate [3,3]-sigmatropic rearrangement of enamido esters. Optimisation studies have probed the crucial role of initial enolisation and the nature of the enamido N-centre. The demonstration of chirality transfer and the formation of β-proline systems, is also presented.

Phosphatases are an important group of proteins with diverse biological roles. The exact pharmacological role played by the protein phosphatases in these biochemical processes is still unknown, partly due to a scarcity of selective inhibitors to act as biological probes. Accordingly, the development of efficient yet flexible syntheses of protein phosphatase inhibitors is of synthetic pertinence as crucial structure-activity relationship data for biochemical probing should therefore be attainable.

The natural cyclic peptide motuporin 1 (Figure 1) isolated from the marine sponge Theonella swinhoei (Gray) is a highly potent and selective protein phosphatase inhibitor. Motuporin inhibits protein phosphatase type 1 (PP1, IC₅₀ < 1.0 nM) and displays cytotoxicity towards a number of human cancer cell lines. The biological activity of 1 is closely linked to the presence of the unusual β-amino acid residue (2S,3S,8S,9S,4E,6E)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldecenoic acid, ADDA. 2,5 This β-amino acid residue is also found in the structurally related cyclic peptides nodularin and the microcystins. 7

With a view to developing a flexible route to motuporin, we have examined a novel Ireland-Claisen 8 substrate class 9–10 assembled around a key enamido moiety (Scheme 1). 11 On [3,3]-sigmatropic rearrangement of a silylketene acetal derived from such enamides, anti-β,3-amino esters are formed 12 with the flexible synthetic handle of an N-allylic moiety also present.

These initial studies uncovered a stark sensitivity of the levels of observed anti-diastereoselectivity to the nature of the substrate acyl fragment. Whilst poor levels of diastereorecontrol were seen with propionate 3a, excellent diastereoselectivity was obtainable with phenylacetate substrate 3b (Scheme 1).

With the targets of motuporin and ADDA in mind, the need to improve the levels of diastereoselectivity seen in the rearrangement of propionate substrates was imperative. Accordingly, we have returned to examine this reaction in greater detail and report our findings in this Letter. However a more detailed level of optimisation failed to significantly improve upon the Ireland-Claisen reported in Scheme 1. Employment of 1.3 equivalents of LiHMDS and Me₂SiCl allowed for a small improvement in yield (72%) but with an identical level of diastereoselectivity (anti/syn=2:1; see Supporting Information for full attempts at re-optimisation). This optimisation study had examined variables such as the loading of base and silylation additive, 13 nature of base, soft enolisation conditions 14 and phosphorylative conditions, 15 but this transformation was observed to be invariant.

Whilst this study did not appear to offer any particular hope for the development of a useful reaction, it did however mould our understanding of the problem at hand considerably. We initially hypothesised that increased stability of intermediate ester enolates and/or silylketene acetals offered by the presence of the conjugating phenyl group in 3b in contrast to propionate 3a was beneficial to the rearrangement of the enamido substrates. In the context of stabilising intermediate enolates, we became aware of Collum’s intriguing Si-free [3-3]-sigmatropic rearrangement of cinnamyl propionate 6 where a Li-enolate rearranges (Scheme 2). 16

Scheme 2 Collum Si-Free Ester Enolate Claisen Rearrangement

This protocol immediately offered itself as a potential solution to
the described synthetic problem. Using an adaptation of Collum’s conditions whereby the reaction was initiated at -95 °C, anti-4a was isolated after methylation in unexceptional yield however with excellent levels of diastereoselectivity (Entry 1, Table 1).

Table 1 Silicon-Free Rearrangement Optimisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>8a (%)</th>
<th>dr (anti/syn) 8a</th>
<th>9a (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>46</td>
<td>&gt;25:1</td>
<td>38</td>
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<td>2</td>
<td>Li’</td>
<td>21</td>
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<td>40</td>
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<tr>
<td>4</td>
<td>K</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Li’</td>
<td>2</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Li’</td>
<td>3</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>Li’</td>
<td>42</td>
<td>2:1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Li</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

*Assayed by 1H NMR analysis of crude reaction mixture. †Ester 4a isolated (45%) after treatment with CH3N2 in Et2O. ‡LHMDS (4 equiv), Et3N (40 equiv) used. §Base added to substrate and MeSiCl (6 equiv). ¶MeSiCl (6 equiv) added to base and substrate. ‖Warmed to quenching temperature of -10 °C. ††Starting material 3a recovered (35%). ‡‡Intractable mixture formed.

An increase in the loading of base proved detrimental with a lowering of 8a present in the crude mixture (Entry 2). The addition of silyl chloride to this protocol leads to an unfavourable outcome (Entries 6-7). The data presented suggests that a subsequent elimination of 2-oxazolidinone occurs after rearrangement. Furthermore, it had been noticed that a colour change occurred on warming to >-10 °C. When quenching a rearrangement at -10 °C a striking change in diastereoselectivity (Entry 8, dr=2:1 anti/syn) is observed. Therefore, we believe a kinetic resolution occurs with the syn-isomer preferentially eliminating to diene 9a after an initial poorly selective rearrangement. Further support for this hypothesis was obtained when isolated acid 8a was re-subjected to reaction conditions with dienyl acid 9a and an enrichment of the anti-diastereomer was observed (Scheme 3). The removal of the Lewis basic solvent THF from the system is seen to be important as shown by unsuccessfully attempting the rearrangement in this solvent (entry 9).

Scheme 3 Kinetic Resolution Mechanism for High Diastereorecontrol in Si-Free Rearrangement

d.r. = 2:1 (anti/syn) d.r. = >25:1, 8a/9a = 59:41

Whilst these studies were disappointing it in turn led us to examine the influence of the enamide nitrogen centre as this may affect leaving group ability and alter the electronic nature of the enamide. The preparation of alcohols 5b-e for subsequent acylation was attempted through a NaBH4 mediated reduction of the corresponding ketone.

We were unable to prepare 5b cleanly due to competing phthalimide carbonyl reduction. Enecarbarate alcohols 5c and 5d proved particularly prone to dehydration, with crotonaldehyde and the parent N-H carbamate observed in crude 1H NMR analyses. In contrast, enesulfonamide 5e proved stable enough to convert via EDCI-mediated esterification to the corresponding propionate.

When conducting these Si-free Claisen rearrangements using the Collum protocol on the ester derivatives of 5c, we have observed a minor improvement in recovered yield on utilising a higher loading of LiHMDS and Et3N (4.5 and 45 equivalents respectively), possibly due to competitive N-allyl lithiation.

These new conditions now lead to improved outcomes with high diastereoselectivity observed with no subsequent elimination (Entry 1, Table 2). The improvement when using the Collum-based protocol for this N-allyl enamide is unambiguous when compared with the silylation protocol which offers poor yield and diastereoselectivity (Entry 2).

Table 2 [3,3]-Sigmatropic Rearrangements of N-allyl enesulfonamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>11 (%)</th>
<th>dr (anti/syn)</th>
<th>12 (%)</th>
<th>13 (%)</th>
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<tr>
<td>1</td>
<td>Me</td>
<td>51</td>
<td>&gt;25:1</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>Pr</td>
<td>65</td>
<td>&gt;25:1</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>Allyl</td>
<td>70</td>
<td>10:1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Obn</td>
<td>2</td>
<td>41</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>30</td>
<td>&lt;25:1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>67</td>
<td>&gt;25:1</td>
<td>27</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>p-OMe</td>
<td>67</td>
<td>&gt;25:1</td>
<td>21</td>
<td>51</td>
</tr>
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<td>10b</td>
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<td>67</td>
<td>&gt;25:1</td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td>11b</td>
<td>68</td>
<td>67</td>
<td>&gt;25:1</td>
<td>22</td>
<td>83</td>
</tr>
</tbody>
</table>

*anti/syn ratio measured by 1H NMR analysis of crude reaction mixtures. †LHMDS (2.5 equiv), Me3SiCl (6 equiv), THF,-95 °C→20 °C. ‡Ring closing diene metathesis conducted at 65 °C.

On examining the substrate scope from the original communication, an improvement in dr is seen with the exception of the O-benzyl glycolate 10d. We feel the Si-free protocol for alkyl esters actually compliments a traditional silylation approach for arylacetate esters as we find a silylation approach is better for arylacetate substrates as seen when examining 10e (entries 6-7). It should be pointed out that methyl arylacetates 12 are also isolated and we believe this is due to methylation of the parent...
acid after hydrolysis of unconverted substrate at the end of the reaction. It is worth commenting on the sensitivity of these enamide esters. The substrates under discussion will not withstand chromatography and even the nature of the acyl fragment can have a profound effect. We endeavoured to study an α-amino ester substrate, with a view to synthesising α,β-diamino acid systems. However, attempted carbodiimide coupling of 5e with N-phthaloyl glycine proved unsuccessful, even though we have published the synthesis and rearrangement of structurally homologous enol ether substrates. Furthermore, these previous studies also support our belief that the inability to form a rearranged product from 10d is not due to a lack of reactivity but due to electronic issues with a substrate bearing multiple electron donating heteroatoms.

The amino dienes prepared through this sigmatropic approach lend themselves for subsequent elaboration, in particular a ring-closing diene metathesis to pyrrolines. Accordingly, such a metathesis ring-closure was smoothly achieved using Grubb’s 1st generation in a number of instances (Table 2, Entries 1,3, 7-12). The products from these metatheses offer themselves as intriguing exocyclic carboxyl β-prolines. The olefin synthetic handle and the excellent diastereocore suggest this strategy may offer some future synthetic value. For example, pyrroline 13d was smoothly converted through an intramolecular Heck reaction, forming the tricyclic β-amino ester 14 in good yield (Scheme 4).

Finally, the development and examination of new enamide substrates has allowed us fulfil a long-term goal of preparing an enantioenriched substrate with a view to performing asymmetric versions of these enamide Ireland-Claissen rearrangements. The development of the N-allyl enamide class has allowed the transformation of commercial enantiopure butyn-2-ol through the protocol of Meyer.

It is worth mentioning the non-trivial matter of clearly forming such a substrate. However, we have ascertained that high levels of diastereo- (>25:1) and enantiocontrol (er >95:5) are achievable in this proof-of-concept study by the rearrangement of phenylacacetate (S)-10f to (2R,3R)-11f using the silylation protocol (Scheme 5).

In conclusion, optimization studies have led to the development of new substrates for the [3,3]-sigmatropic rearrangements of enamido allylic esters. These developments include the use of N-allyl enesulfonanides for the highly diastereoselective rearrangement of alkyl esters using a Si-free, enolate Claisen protocol. The electronic control offered by the new enamide has also provided suitable substrate stability to allow the rearrangement of enantiopure substrates. We are currently looking to expand the synthetic application of these β-amino esters.

### Experimental procedures

(E)-4-((N- Allyl-4-methylphenylsulfonylamido)but-3-en-2-yl propionate (10a)

To a solution of EDCI (0.54 g, 2.81 mmol) in CH₂Cl₂ (100 mL), was added triethylamine (0.39 mL, 2.81 mmol), DMAP (0.02 g, 0.14 mmol) and propionic acid (0.22 mL, 2.81 mmol). This solution was cooled to 0 °C before adding 5e (0.40 g, 1.41 mmol) in CH₂Cl₂ (10 mL) and stirring for 15 h at room temperature. Citric acid (10%, 30 mL) was added and the organic layer separated before washing with further citric acid (10% 2x 30 mL), NaHCO₃ (sat. 3 x 30 mL), brine (30 mL). The organic layer was dried over MgSO₄, filtered and solvent removed in vacuo to afford (E)-4-((N-allyl-4-methylphenylsulfonylamido)but-3-en-2-yl propionate 10a as a yellow oil (0.40 g, 84%). FTIR (film/cm⁻¹)νmax: 3082 (m), 3039 (s), 2980 (m), 2931 (s), 2861 (m), 1656 (s), 1597 (s); ¹H NMR (500 MHz, (CD₃)₂CO) δ: 1.10 (t, 3H, J=7.6 Hz, CH₂(CH₃)₂), 1.29 (3H, J=6.6 Hz, CH₂(CH(CH₃)O-)), 2.25 (q, 2H, J=7.6 Hz, CH₂CH₂-), 2.45 (3H, J=6.9 Hz, CH₃CH₂-), 3.96 (qd, 2H, J=15.0, 5.4 Hz, -NCH₂CH₂CH₂-), 4.80 (dd, 1H, J=14.2, 6.6 Hz, -NCH₂CH₂-), 5.09–5.17 (m, 2H, CH₂CH₂CHN₂-), 5.34 (app. quin, 1H, J=6.6 Hz, CH₃CH₂CH(O)-), 5.79 (ddt, 1H, J=17.0, 10.3, 5.4 Hz, -NCH₂CH₂CH₂-), 6.96 (d, 1H, J=14.2 Hz, -NCH₂CH₂-), 7.29 (app. d, 2H, J=7.6 Hz, ArH Ts), 7.65 (d, 2H, J=7.6 Hz, ArH Ts); ¹³C NMR (125 MHz, CDCl₃) δ: 9.1, 21.0, 21.5, 27.9, 48.0, 69.8, 110.1, 117.9, 127.0, 129.5, 131.3, 136.1, 143.9, 173.6; HRMS (ESI +ve) m/z calcd. for C₂₃H₂₂NNaO₄S 436.1558, found 436.1679 (M+Na)⁺.

### Conclusions

In conclusion, optimization studies have led to the development of new substrates for the [3,3]-sigmatropic rearrangements of enamido allylic esters. These developments include the use of N-allyl enesulfonanides for the highly diastereoselective rearrangement of alkyl esters using a Si-free, enolate Claisen protocol. The electronic control offered by the new enamide has also provided suitable substrate stability to allow the rearrangement of enantiopure substrates. We are currently looking to expand the synthetic application of these β-amino esters.
Methyl 2-(1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)propanoate (13a)

To a solution of 11a (0.02 g, 0.05 mmol) in CH₂Cl₂ (5 mL) was added Grubbs I catalyst (5 mol%) and stirred at room temperature for 6 h. When reaction was judged complete by TLC, the reaction was concentrated in vacuo and further purified by flash chromatography (EtOAc/petroleum ether 40 °C-60 °C; 10:90→20:80) to afford 13a as a white solid (0.01 g, 79%). M.p. 95–97 °C; FTIR (film/cm⁻¹) νmax: 2960 (m), 2928 (m), 2876 (m), 1730 (s), 1597 (m); ¹H NMR (500 MHz, CDCl₃) δ: 1.12 (d, 3H, J = 7.1 Hz), 2.44 (s, 3H), 3.31 (qd, 1H, J = 7.1, 3.96 Hz), 3.72 (s, 3H), 4.06–4.19 (2H, m), 4.84–4.89 (m, 1H), 5.55 (app dq, 1H, J = 5.5, 2.2 Hz), 5.72 (app. dq, 1H, J = 5.5, 2.2 Hz), 7.33 (app. dq, 2H, J = 8.1 Hz), 7.74 (app. d, 2H, J = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ: 10.11, 21.5, 43.9, 51.8, 56.1, 67.9, 126.5, 126.8, 127.4, 129.8, 134.1, 143.6, 174.5; HRMS (ESI +ve) m/z calcd. for C₁₃H₂₂NO₃S 310.1310, found 310.1310 (M+H)⁺.

(E)-4-(N-Allyl-4-methylphenylsulfonamido)but-3-en-2-yl acetate (10f)

To a solution of EDCI (0.54 g, 2.81 mmol) in CH₂Cl₂ (100 mL), was added triethylamine (0.39 mL, 2.81 mmol), DMAP (0.02 g, 0.14 mmol), 2-iodophenylacetic acid (0.74 g, 2.81 mmol). This solution was cooled to 0 °C before adding 5e (0.40 g, 1.41 mmol) in CH₂Cl₂ (20 mL) and stirring for 15 h at room temperature. Citric acid (10%, 30 mL) was added and the organic layer separated before washing with further citric acid (10% 2x 30 mL), NaHCO₃ (sat. 3 x 30 mL), brine (30 mL). The organic layer was dried over MgSO₄, filtered and solvent removed in vacuo to afford 10f as a yellow oil (0.64 g, 86%). FTIR (film/cm⁻¹) νmax: 2978 (m), 2922 (m), 1727 (s), 1655 (s), 1596 (w); ¹H NMR (500 MHz, CDCl₃) δ: 1.31 (d, 3H, J = 6.6 Hz), 2.44 (s, 3H), 3.77 (app. d, 2H, J = 9.2, 6.6 Hz), 4.91 (dd, 1H, J = 14.2, 6.6 Hz), 5.12 (appdq, 1H, J = 10.4, 1.4 Hz), 5.20 (app dq, 1H, J = 17.3, 1.7 Hz), 5.39 (app. quin, 1H, J = 6.6 Hz), 5.65 (ddt, 1H, J = 17.3, 10.4, 5.0 Hz), 7.00–7.08 (m, 2H), 7.35–7.43 (m, 4H), 7.72 (app. d, 2H, J = 8.2 Hz), 7.88 (d, 1H, J = 1.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ: 20.4, 20.5, 46.0, 47.6, 70.6, 100.6, 109.9, 117.1, 127.0, 128.4, 128.8, 129.8, 129.9, 131.0, 131.8, 136.4, 138.5, 139.2, 144.0, 169.0; HRMS (ESI +ve) m/z calcd. for C₂₄H₂₄N₂O₅S 548.0368, found 548.0407 (M+Na)⁺.

(anti-E)-Methyl 3-(N-allyl-4-methylphenylsulfonamido)-2-(2-iodophenyl)hex-4-ene-1-one (11e)

To a solution of LiHMDS (1M in THF, 0.34 mL, 0.34 mmol), TMSCl (0.10 mL, 1.57 mmol) at -95 °C was added 10f (0.07 g, 0.26 mmol) in THF (0.7 mL) via syringe (4 mL/h) down the side of the reaction vessel. The reaction was slowly warmed to room temperature over 1 hour before the addition of HCl (1 M)/brine (1:1.5 mL). The organics were extracted with Et₂O (5 x 15 mL) before immediate methylation with diazomethane (generated from N-nitrosomethyl urea in a diazomethane generator). Further purification by flash chromatography (EtOAc/petroleum ether 40 °C-60 °C/triethylamine; 20:80:1→40:60:1) afforded (anti-E)-methyl 3-(N-allyl-4-methylphenylsulfonamido)-2-(2-iodophenyl)hex-4-ene-1-one 11e as a white solid (0.05 g, 67%, d.r. >25:1). M.p. 97–99 °C; FTIR (film/cm⁻¹) νmax: 3179 (w), 2953 (m), 2922 (m), 1734 (s), 1597 (m); ¹H NMR (500 MHz, CDCl₃) δ: 1.35 (d, 3H, J = 6.5 Hz), 2.41 (s, 3H), 3.63 (s, 3H), 3.83 (app. d, 1H, J = 17.3, 6.7 Hz), 3.93 (app. d, 1H, J = 7.3, 6.7 Hz), 4.75 (d, 1H, J = 11.7 Hz), 4.91 (d, 1H, J = 11.7 Hz), 5.14–5.23 (m, 2H), 5.25–5.37 (2H, 5.79 (ddt, 1H, J = 10.7, 6.7 Hz), 6.92 (app. t, 1H, J = 7.9 Hz), 7.26 (app. d, 2H, J = 8.7 Hz), 7.27–7.33 (m, 1H), 7.51 (app. d, 1H, J = 7.9 Hz), 7.74 (app. d, 2H, J = 8.7 Hz), 7.82 (d, 1H, J = 7.9 Hz); ¹³C NMR (125 MHz, CDCl₃) δ: 17.6, 21.4, 49.2, 52.2, 57.8, 68.4, 118.1, 124.7, 127.9, 128.5, 128.9, 129.0, 129.2, 129.3, 132.1, 135.0, 137.7, 138.9, 139.6, 143.1, 171.8; HRMS (ESI +ve) m/z calcd. for C₂₄H₂₄N₂O₅S 474.1950, found 474.1948 (M+H)⁺.
Notes and references

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