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PAPER

Si-free enolate Claisen rearrangements of enamido substrates†

Wesley R. R. Harker,[a] Emma L. Carswell[b] and David R. Carbery*[a]

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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 enamide esters. Optimisation studies have probed the crucial role of the initial enolisation and the nature of the enamide 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.[1] The exact pharmacological role played by the protein phosphatase in these biochemical processes is still unknown, partly due to a scarcity of selective inhibitors to act as biological probes.[2] Accordingly, the development of efficient yet flexible syntheses of protein phosphatase inhibitors is of synthetic pertinence as crucial structure–activity relationship data for biological probing should therefore be attainable.

The natural cyclic peptide motuporin **1**[3] (Fig. 1) isolated form the marine sponge *Theonella swinhoei* (Gray) is a highly potent and selective protein phosphatase inhibitor. Motuporin inhibits protein phosphatase type 1 (PP1, IC_{50} < 1.0 nM) and displays cytotoxicity towards a number of human cancer cell lines.[4] The biological activity of **1** is closely linked to the presence of the unusual β-amino acid residue (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldecadenoic acid, ADDA, **2**.[5–6] This β-amino acid residue is also found in the structurally related cyclic peptides nodularin and the microcystins.[7]

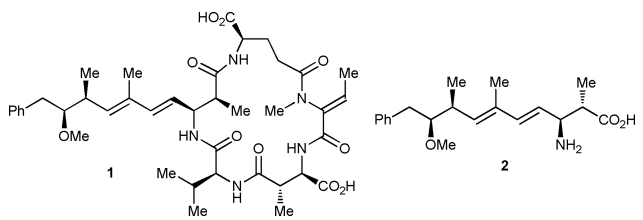
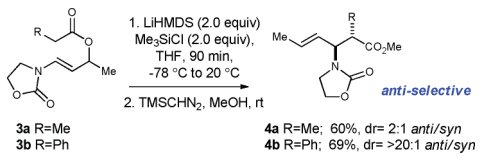


Fig. 1 Motuporin and ADDA.

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 enamide moiety (Scheme 1).[11] On [3,3]-sigmatropic rearrangement of a silylketene acetal derived from such enamides, *anti*-β[2,3]-amino esters are formed[12] with the flexible synthetic handle of an *N*-allylic moiety also present.



Scheme 1 Sensitivity of diastereoselectivity to substrate.

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 diastereocontrol 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 article. A more detailed level of optimisation failed to significantly improve upon the Ireland–Claisen substrate reported in Scheme 1. Employment of 1.3 equivalents of LiHMDS and Me_3SiCl 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 enamide 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]

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,

[a]*Department of Chemistry, University of Bath, Bath, United Kingdom, BA2 7AY. E-mail: d.carbery@bath.ac.uk; Tel: 44 1225 386144*
[b]*MSD, Newhouse, Motherwell, United Kingdom*

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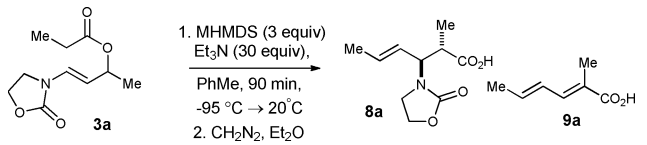
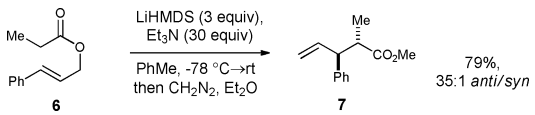
Table 1 Silicon-free rearrangement optimisation



Entry	M	**8a** (%)[a]	dr (*anti*/*syn*) **8a**	**9a** (%)[a]
1	Li	46[b]	>25 : 1	38
2	Li[c]	21	>25 : 1	40
4	Na	0	—	0
5	K	0	—	0
6	Li[d]	2	—	80
7	Li[e]	3	—	80
8	Li[f]	42[g]	2 : 1	0
9	Li[h]	0	—	0

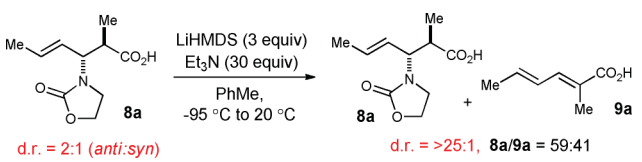
[a] Assayed by ^{1}H NMR analysis of crude reaction mixture. [b] Ester **4a** isolated (45%) after treatment with CH_2N_2 in Et_2O. [c] LiHMDS (4 equiv.), Et_3N (40 equiv.) used. [d] Base added to substrate and Me_3SiCl (6 equiv.). [e] Me_3SiCl (6 equiv.) added to base and substrate. [f] Warmed to quenching temperature of –10 °C. [g] Starting material **3a** recovered (35%). [h] Reaction conducted in THF, intractable mixture formed.



Scheme 2 Collum Si-free ester enolate Claisen rearrangement.

anti-**4a** was isolated after methylation in unexceptional yield however with excellent levels of diastereoselectivity (Entry 1, Table 1).

An increase in the loading of base proved detrimental with a reduction in the amount **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 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 diastereocontrol in Si-free rearrangement.

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 $NaBH_4$ mediated reduction of the corresponding ketone (Fig. 2).

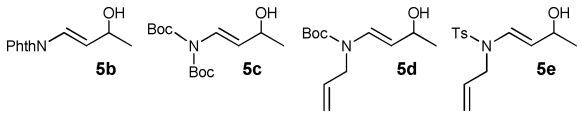


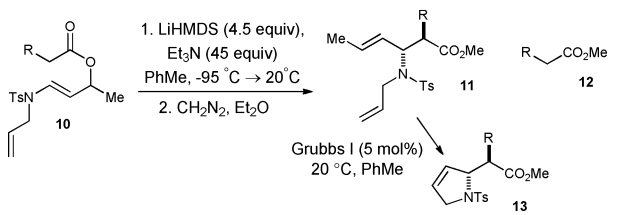
Fig. 2 Key enamido allylic alcohols studied.

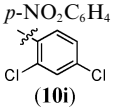
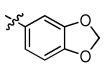
We were unable to prepare **5b** cleanly due to competing phthalimide carbonyl reduction. Enecarbamate alcohols **5c** and **5d** proved particularly prone to dehydration, with crotonaldehyde and the parent N–H carbamate observed in crude ^{1}H NMR analyses. In contrast, enesulfonamide **5e** proved 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 Et_3N (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).

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

Table 2 [3,3]-Sigmatropic rearrangements of *N*-allyl enesulfonamides



Entry	R	**11**	dr[a]	**12**	**13**
1	Me (**10a**)	51 (**11a**)	>25 : 1	0	71 (**13a**)
2[b]	Me	<5	1 : 1	53	—
3	^{i}Pr (**10b**)	65 (**11b**)	>25 : 1	0	86 (**13b**)
4	Allyl (**10c**)	70 (**11c**)	10 : 1	0	—
5	OBn (**10d**)	0	—	41	—
6	Ph (**10e**)	30 (**11d**)	>25 : 1	0	—
7[b]	Ph	67	>25 : 1	27	92 (**13c**)
8[b]	*o*-IC_6H_4 (**10f**)	67 (**11e**)	>25 : 1	21	51[c] (**13d**)
9[b]	*p*-$OMeC_6H_4$ (**10g**)	73 (**11f**)	>25 : 1	18	89 (**13e**)
10[b]	*p*-$NO_2C_6H_4$ (**10h**)	40 (**11g**)	20 : 1	15	96 (**13f**)
11[b]	 (**10i**)	68 (**11h**)	>25 : 1	22	83[c] (**13g**)
12[b]	 (**10j**)	55 (**11i**)	>25 : 1	25	89 (**13h**)

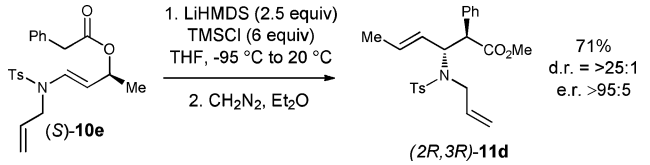
[a] *anti*/*syn* ratio measured by ^{1}H NMR analysis of crude reaction mixtures. [b] LiHMDS (2.5 equiv.), Me_3SiCl (6 equiv.), THF, –95 °C → 20 °C. [c] Ring closing diene metathesis conducted at 65 °C.

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.[17] 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 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.[18] Accordingly, such a metathesis ring-closure was smoothly achieved using Grubb's 1st generation catalyst 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 diastereocontrol suggest this strategy may offer some future synthetic value. For example, pyrroline **13d** was smoothly converted through an *intra*molecular Heck reaction, forming the tricyclic β-amino ester **14** in good yield (Scheme 4).[19]

Scheme 4 Heck elaboration to tricyclic β-proline systems.

Finally, the development and examination of new enamide substrates has allowed us to fulfil a long-term goal of preparing an enantioenriched substrate with a view to performing asymmetric versions of these enamide Ireland–Claisen rearrangements. The development of the *N*-allyl enamide class has allowed the transformation of commercial enantiopure butyn-2-ol through the protocol of Meyer.[20] It is worth mentioning the non-trivial matter of cleanly forming such a substrate. However, we have ascertained that high levels of diastereo- (dr > 25 : 1) and enantiocontrol (er > 95 : 5) are achievable in this proof-of-concept study by the rearrangement of phenylacetate (*S*)-**10f** to (2*R*,3*R*)-**11f** using the silylation protocol (Scheme 5).



Scheme 5 Absolute stereocontrol in [3,3]-sigmatropic rearrangement of enamides.

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 enesulfonamides 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-methylphenylsulfonamido)but-3-en-2-yl propionate (10a)

To a solution of EDCI (0.54 g, 2.81 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (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%, 2 × 30 mL), $NaHCO_3$ (sat., 3 × 30 mL), brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed *in vacuo* to afford (*E*)-4-(*N*-allyl-4-methylphenylsulfonamido)but-3-en-2-yl propionate **10a** as a yellow oil (0.40 g, 84%). FTIR (film/cm^{-1}) υ_{max}: 3082 (m), 3039 (m), 2980 (m), 2931 (m), 2861 (m), 1727 (s), 1656 (s), 1597 (s); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ: 1.10 (t, 3H, J = 7.6 Hz, C*H*$_3$CH$_2$–), 1.29 (d, 3H, J = 6.6 Hz, C*H*$_3$CH(CH–)O–), 2.25 (q, 2H, J = 7.6 Hz, CH$_3$C*H*$_2$–), 2.45 (s, 3H, –C$_6$H$_4$C*H*$_3$), 3.96 (qd, 2H, J = 15.0, 5.4 Hz, –NC*H*$_2$CHCH$_2$), 4.80 (dd, 1H, J = 14.2, 6.6 Hz, –NCHC*H*–), 5.09–5.17 (m, 2H, C*H*$_2$CHCH$_2$N–), 5.34 (app. quin, 1H, J = 6.6 Hz, CH$_3$C*H*(CH–)O–), 5.79 (ddt, 1H, J = 17.0, 10.3, 5.4 Hz, –NCH$_2$C*H*CH$_2$), 6.96 (d, 1H, J = 14.2 Hz, –NC*H*CH–), 7.29 (app. d, 2H, J = 7.6 Hz, Ar*H* Ts), 7.65 (d, 2H, J = 7.6 Hz, Ar*H* Ts); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.1, 21.0, 21.5, 27.9, 48.0, 69.8, 110.1, 117.9, 127.0, 129.5, 129.8, 131.3, 136.1, 143.9, 173.6; HRMS (ESI, +ve) m/z calcd. for $C_{23}H_{27}NNaO_4S$ 436.1558, found 436.1679 $(M + Na)^+$.

(*anti-E*)-Methyl 3-(*N*-allyl-4-methylphenylsulfonamido)-2-methylhex-4-enoate (11a)

To a solution of LiHMDS (1 M in toluene, 1.34 mL, 1.34 mmol) and triethylamine (1.81 mL, 13.4 mmol) at –95 °C was added **10a** (0.10 g, 0.30 mmol) in toluene (1 mL) *via* syringe (4 mL h^{-1}) down the side of the reaction vessel. The reaction was slowly warmed to room temperature over 1 h before the addition of HCl (1 M)/brine (1 : 1, 5 mL). The organics were extracted with Et_2O (5 × 15 mL) before immediate methylation with diazomethane (generated from *N*-nitrosomethyl urea in a diazomethane generator). Further purification by flash chromatography (EtOAc/petroleum ether 40–60 °C/triethylamine; 20 : 80 : 1 → 40 : 60 : 1) afforded (*anti-E*)-methyl 3-(*N*-allyl-4-methylphenylsulfonamido)-2-methylhex-4-enoate **11a** as a white solid (0.06 g, 55%, dr >25 : 1). M.p. 88–90 °C; FTIR (film/cm^{-1}) υ_{max}: 2966 (m), 2916 (m), 1735 (s), 165 s (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.06 (d, 3H, J = 6.9 Hz), 1.51 (dd, 3H, J = 6.4, 1.5 Hz),

2.39 (3H, s), 3.02 (ddt, 2H, J = 10.1, 7.8, 6.9 Hz), 2.83 (s, 3H), 3.69–3.85 (s, 2H), 4.27 (app. t, 1H, J = 10.1 Hz), 5.07–5.18 (m, 2H), 5.41 (ddq, 1H, J = 15.1, 10.1, 1.5 Hz), 5.55 (dq, 1H, J = 15.1, 6.4 Hz), 5.71 (ddt, 1H, J = 17.3, 10.2, 6.5 Hz), 7.26 (app. d, 2H, J = 8.2 Hz), 7.69 (app. d, 2H, J = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.6, 17.7, 21.4, 43.4, 49.4, 51.7, 64.1, 117.6, 126.2, 127.7, 129.1, 132.1, 135.3, 137.8, 142.9, 175.0; HRMS (ESI, +ve) m/z calcd. for $C_{18}H_{25}NO_4S$ 352.1582, found 352.1577 $(M + H)^+$.

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 CH_2Cl_2 (5 mL) was added Grubbs I catalyst (5 mol%) and stirred at room temperature for 6 h. When the reaction was judged complete by TLC, the reaction was concentrated *in vacuo* and further purified by flash chromatography (EtOAc/petroleum ether 40–60 °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}) υ_{max}: 2960 (m), 2928 (m), 2878 (m), 1730 (s), 1597 (m); ^{1}H NMR (500 MHz, $CDCl_3$) 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 (m, 2H), 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. d, 2H, J = 8.1 Hz), 7.74 (app. d, 2H, J = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.1, 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 $C_{15}H_{20}NO_4S$ 310.1130, found 310.1108 $(M + H)^+$.

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

To a solution of EDCI (0.54 g, 2.81 mmol) in CH_2Cl_2 (100 mL), was added triethylamine (0.39 mL, 2.81 mmol), DMAP (0.02 g, 0.14 mmol), 2-iodo phenylacetic acid (0.74 g, 2.81 mmol). This solution was cooled to 0 °C before adding **5e** (0.40 g, 1.41 mmol) in CH_2Cl_2 (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%, 2 × 30 mL), $NaHCO_3$ (sat., 3 × 30 mL), brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed *in vacuo* to afford **10f** as a yellow oil (0.64 g, 86%). FTIR (film/cm^{-1}) υ_{max}: 2978 (m), 2922 (m), 1727 (s), 1655 (s), 1596 (w); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ: 1.31 (d, 3H, J = 6.6 Hz), 2.44 (s, 3H), 3.77 (app. d, 2H), 3.97–4.08 (m, 2H), 4.91 (dd, 1H, J = 14.2, 6.6 Hz), 5.12 (app. dq, 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 = 7.8 Hz); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) 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 $C_{22}H_{24}INNaO_4S$ 548.0368, found 548.0407 $(M + Na)^+$.

(*anti-E*)-Methyl 3-(*N*-allyl-4-methylphenylsulfonamido)-2-(2-iodophenyl) hex-4-enoate (11e)

To a solution of LiHMDS (1 M 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^{-1}) down the side of the reaction vessel. The reaction was slowly warmed to room temperature over 1 h before the addition of HCl (1 M)/brine (1 : 1, 5 mL). The organics were extracted with Et_2O (5 × 15 mL) before immediate methylation with diazomethane (generated from *N*-nitrosomethyl urea in a diazomethane generator). Further purification by flash chromatography (EtOAc/petroleum ether 40–60 °C/triethylamine; 20 : 80 : 1 → 40 : 60 : 1) afforded (*anti-E*)-methyl 3-(*N*-allyl-4-methylphenylsulfonamido)-2-(2-iodophenyl)hex-4-enoate **11e** as a white solid (0.05 g, 67%, dr >25 : 1). M.p. 97–99 °C; FTIR (film/cm^{-1}) υ_{max}: 3179 (w), 2953 (m), 2922 (m), 1734 (s), 1597 (m); ^{1}H NMR (500 MHz, $CDCl_3$) 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 (m, 2H), 5.79 (ddt, 1H, J = 17.0, 10.8, 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.6, 21.4, 49.2, 52.2, 57.8, 64.2, 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 $C_{25}H_{32}NO_6S$ 474.1950, found 474.1948 $(M + H)^+$.

Methyl 2-(2-iodophenyl)-2-(1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (13d)

To a solution of **11e** (0.09 g, 0.17 mmol) in toluene (5 mL) was added Grubbs I catalyst (5 mol%) and stirred at 65 °C for 6 h. When the reaction was judged complete by TLC, the reaction was concentrated *in vacuo* and further purified by flash chromatography (EtOAc/petroleum ether 40–60 °C; 10 : 90 → 20 : 80) to afford **13d** as a white solid (0.04 g, 51%). M.p. 186–188 °C; FTIR (film/cm^{-1}) υ_{max}: 3026 (m), 2952 (m), 2878 (m), 1728 (s), 1597 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.66–3.75 (m, 1H), 3.75 (s, 3H), 3.97 (app. dq, 1H J = 15.7, 1.9 Hz), 4.78 (d, 1H, J = 5.6 Hz), 5.19–5.24 (m, 1H), 5.50–5.59 (m, 2H), 6.95 (app. t, 1H, J = 7.4 Hz), 7.24–7.34 (m, 4H), 7.73 (app. d, 2H, J = 8.3 Hz), 7.89 (app. d, 1H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5, 52.3, 55.5, 59.9, 68.7, 127.5, 127.6 (×2), 127.7, 129.1, 129.7, 129.9, 134.2, 136.3, 138.0, 140.2, 143.6, 172.2; HRMS (ESI, +ve) m/z calcd. for $C_{22}H_{21}INO_4S$ 498.0235, found 498.0259 $(M + H)^+$.

anti-Methyl 1-tosyl-1,2,8,8a-tetrahydroindeno[2,1-b]pyrrole-8-carboxylate (14)

To a solution of $Pd(OAc)_2$ (3.00 mg, 0.01 mmol, 0.2 eq.), PPh_3 (3.67 mg, 0.01 mmol, 0.2 eq.), Ag_2CO_3 (29.1 mg, 0.11 mmol, 1.5 eq.) in MeCN was added **11e** (35.0 mg, 0.07 mmol, 1.0 eq.). The reaction mixture was refluxed for 4 h, concentrated *in vacuo* before being subjected to flash column chromatography using ethyl acetate/petroleum ether 40–60 °C (20 : 80) to yield **14** as an amorphous clear solid (22.0 mg, 84%). FTIR (film/cm^{-1}) υ_{max}: 2958 (m), 2919 (m), 2849 (m), 1734 (s), 1597 (m); ^{1}H NMR (500 MHz, CD_3Cl) δ: 2.47 (s, 3H, –$C_6H_4CH_3$), 3.80 (s, 3H, –CO_2CH_3), 4.92 (br. d, 1H, J = 9.5 Hz, –NCH*H*CH–), 4.63 (br. s, 1H, –C*H*CO_2CH_3), 4.90 (dd, 1H, J = 9.5, 2.0 Hz, –NCH*H*CH–), 5.31 (app. dd, 1H, J = 4.1, 2.8 Hz, –NC*H*(CH–)CH–), 6.36 (app. dd, 1H, J = 4.1, 2.8 Hz, –NCH_2CH–), 7.10–7.15 (m, 1H, Ar*H*), 7.23–7.27 (m, 2H, Ar*H*), 7.36 (app. d, 2H, J = 8.2 Hz, Ar*H*, Ts), 7.45–7.51 (m, 1H, Ar*H*), 7.75 (app. d, 2H, J = 8.2 Hz, Ar*H*, Ts); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 52.5, 54.5, 58.3, 66.1, 112.9, 125.1, 126.1, 127.8, 127.9, 128.6, 129.9, 130.5, 132.9, 137.8, 142.9,

144.2, 172.3; HRMS (ESI, +ve) m/z calcd. for $C_{20}H_{20}N_1O_4S_1$ 370.1148, found 370.1113 $(M + H)^+$.

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