Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7057

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PAPER

Claisen rearrangements of equilibrating allylic azides†

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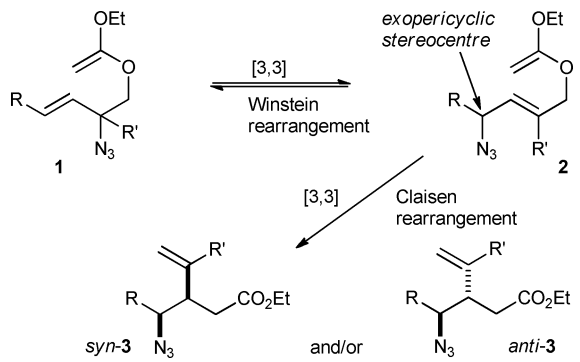
Received 13th April 2011, Accepted 30th June 2011
DOI: 10.1039/c1ob05972f

Equilibrating mixtures of allylic azide-containing allylic alcohols or allylic 2-tolylsulfonylacetic esters undergo Johnson–Claisen or Ireland–Claisen rearrangement reactions to give unsaturated γ-azidoesters and -acids, respectively. Decarboxylation of the acids under basic conditions gives azidosulfones, with moderate to high diastereoselectivity.

Introduction

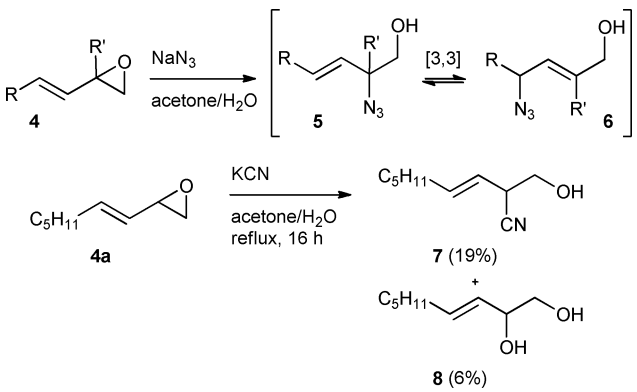
Allylic azides have seen limited use in synthesis,[1,2] because they exist as equilibrating mixtures of regioisomers,[3] which interconvert *via* [3,3]-sigmatropic rearrangement (Winstein rearrangement).[4–6] It occurred to us that Claisen rearrangement of allylic azide-containing substrates would take place regardless of the position of equilibrium if the isomers unreactive in the sigmatropic process were inert with respect to competing reaction pathways.[7] Thus, ketene acetals **1** and **2**, generated from allylic alcohols under Johnson–Claisen conditions, would react to give esters **3**. We were interested additionally in any 1,2-asymmetric induction associated with C–C bond formation (Scheme 1).[8]



Scheme 1 Proposed tandem rearrangement.

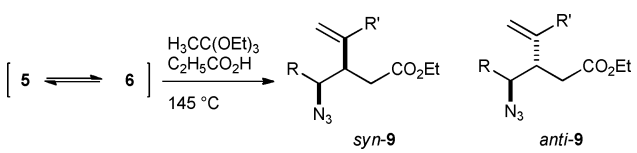
Results and discussion

Allylic azidoalcohol substrate mixtures **5** and **6** were prepared by reaction of vinylic oxiranes **4**[9] with sodium azide (Scheme 2).† That **5** and **6** were formed by initial attack on **4** by azide by an S_N2 mechanism, rather than in an S_N2' sense, followed by equilibration was suggested by the observation that only allylic nitrile **7** (together with hydrolysis product **8**[10]) was formed upon analogous treatment of **4a** with potassium cyanide (Scheme 2).[11]



Scheme 2 Preparation of allylic azidoalcohols **5**/**6**.

Mixtures of **5** and **6** were heated in the presence of triethyl orthoacetate (as solvent) and sub-stoichiometric propionic acid to give unsaturated γ-azidoesters **9** (Scheme 3, Table 1). Substrates bearing straight-chain and branched alkyl R groups reacted in high yield, although longer reaction times were required for the more sterically demanding congeners. Where R′ = Me (Table 1, entries b–d), moderate *syn* stereoselectivity was observed. This was assigned by NOESY-NMR of the derived lactam **10** (Scheme 4), and the



Scheme 3 Johnson–Claisen rearrangement reactions of **5**/**6**.

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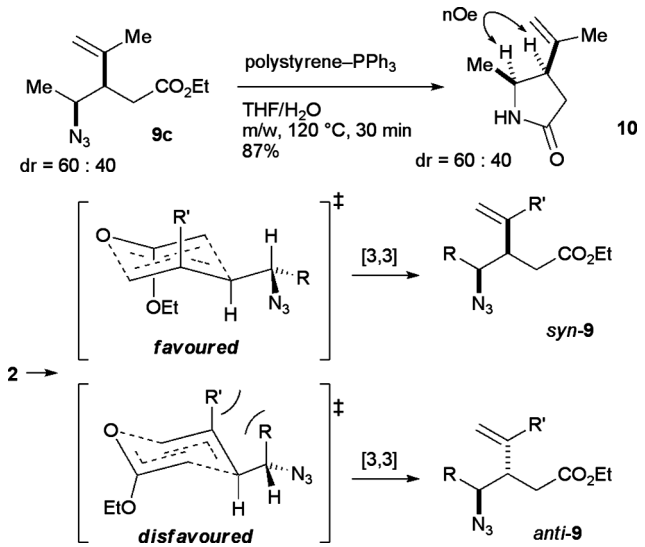
† Electronic supplementary information (ESI) available: Full experimental procedures and characterisation of compounds **4–12** and **14**. CCDC reference number 813338. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05972f

Table 1 Johnson–Claisen rearrangement reactions of **5/6**

Entry	R	R′	Ratio **5**:**6**	t (h)	Yield (%)	Ratio *syn*-: *anti*-**9**[a]
a	nC_5H_{11}	H	73 : 27	6	99	50 : 50
b	nC_5H_{11}	Me	61 : 39	24	72	59 : 41
c	Me	Me	64 : 36	12	86	60 : 40
d	*c*Hex	Me	63 : 37	26	94	63 : 37
e	Ph	H	100 : 0	48	0	—
f	2-Pyridyl	Me	100 : 0	48	<4	(77 : 23)
g	Me	Ph	0 : 100[b]	24	75	50 : 50

[a] Determined by ^{1}H NMR analysis; [b] **6g** was present as a 3 : 1 *E* : *Z* mixture



Scheme 4 Assignment of structures **9** and proposed origin of selectivity.

selectivities of the other rearrangements were inferred from this result. Where R or R′ was an aryl group (Table 1, entries e–g), the allylic azidoalcohols **5e**, **5f** and **6g** existed as single isomers, with the olefin in conjugation with the aryl group.[12–14] When R = Ph, the substrate existed solely as the conjugated allylic isomer **5e**, and no reaction was observed (Table 1, entry e). In the reaction of the less aromatic[15] pyridine **5f**, small amounts of impure **9f** were formed after extended reaction times (Table 1, entry f).[16] In contrast, the allylic azidoalcohol **6g** reacted efficiently, reflecting the inferred absence in the equilibrium mixture of the unreactive, less highly conjugated ketene acetal corresponding to **5g**. Selectivity for the 3,4-*syn* products where R′ = Me may result from unfavourable 1,3-diaxial interactions in the transition states leading to the 3,4-*anti* isomers. In this model, in line with our previous studies,[8h] internal approach of the ketene acetal takes place along a trajectory in proximity to the $\sigma^*_{C\text{–}N}$ orbital (Scheme 4).

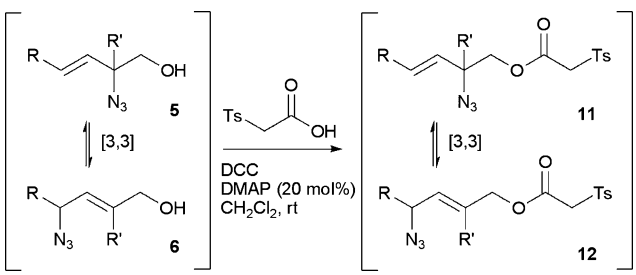
Our attention turned to the modest stereoselectivities observed for the rearrangement reactions described above. We had shown previously that analogous *Z*-allylic thioethers reacted in Johnson–Claisen rearrangements with higher *syn* stereoselectivity than the *E*-isomers.[8h] However, *Z*-allylic azides could isomerise to the more reactive[17] *E*-isomers by [3,3]-sigmatropic rearrangement, and therefore it was considered that changing olefin geometry would not result in an increase in stereoselectivity. However, it was anticipated that increased steric bulk at the terminal position of the ketene acetal would increase the diastereofacial selectivity

Table 2 Preparation and isomer ratios of esters **11/12**

Entry	R	R′	Ratio **5**:**6**[a]	Yield (%)	Ratio **11**:**12**[a]
a	nC_5H_{11}	H	73 : 27	99	58 : 42
b	nC_5H_{11}	Me	61 : 39	69	32 : 68
c	Me	Me	64 : 36	97	30 : 70
d	*c*Hex	Me	63 : 37	92	36 : 65
e	Ph	H	100 : 0	97	100 : 0
f	2-Pyridyl	Me	100 : 0	52	100 : 0
g	Me	Ph	0 : 100	75	0 : 100

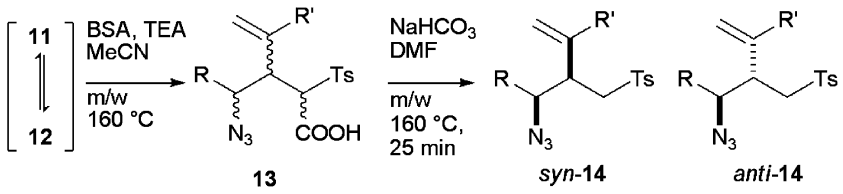
[a] Determined by ^{1}H NMR analysis

of attack on the allylic moiety.[8a] The recently developed[18] decarboxylative variant (dCr) of the Ireland–Claisen rearrangement reaction of α-tosyl esters was particularly attractive for this study, since the decarboxylation step obviated the incorporation of a third stereocentre. The required dCr substrates **11/12** were prepared by treatment of azidoalcohols **5/6** with tosylacetic acid–DCC–DMAP (Scheme 5, Table 2). Interestingly, in cases where the allylic azide could contain a trisubstituted olefin (entries b–d) inversion of the ratio to favour the 1,4-azidoesters **12** occurred. This effect was attenuated in substrate **11/12a**, where both isomers possess disubstituted olefins, and substrates **e** and **f** possessing conjugating aryl groups existed solely as isomers **11**. The decrease in the proportion of vicinal isomers may be a consequence of the removal upon esterification of the possibility of hydrogen-bonding between the azide and alcohol –OH groups.[19,20]



Scheme 5 Formation of ester substrates **11/12** from alcohols **5/6**.

Attempted dCr reactions of **11/12** using the BSA–KOAc conditions[18] gave low yields of **14**.[21] Carrying out the rearrangement and decarboxylation as two discrete steps improved the yield. Thus, microwave irradiation of **11/12** in the presence of BSA–TEA afforded acids **13**. After removal of residual BSA and TEA, decarboxylation with sodium hydrogencarbonate–DMF gave **14**. With the exception of **11/12f**, all esters **11/12** underwent rearrangement under these conditions (Scheme 6, Table 3). More hindered substrates required increased amounts of BSA and TEA to react. In contrast to the unreactive phenyl-bearing azidoalcohol **5e**, the single-regioisomer azidoester **11e** underwent dCr reaction to give **14e**, albeit in relatively low yield. Substrate **11f** decomposed under these conditions, possibly triggered by BSA-mediated pyridine *N*-silylation. X-Ray crystallographic analysis of *syn*-**14a** confirmed its structure (Fig. 1);[22] *syn* stereochemistry for the other major products was inferred from this result. In each case, the predominance of the *syn* product was more pronounced than that observed for Johnson–Claisen rearrangement of the corresponding allylic azidoalcohols.



Scheme 6 Formation of azidosulfones **14**.

Table 3 Claisen rearrangement and decarboxylation of esters **11/12**

Entry	R	R′	Conditions[a]	t (min)	Yield (%)	Ratio *syn*- : *anti*-**14**[b]
a	nC_5H_{11}	H	A	15	86	84 : 16
b	nC_5H_{11}	Me	B	30	68	68 : 32
c	Me	Me	A	30	82	91 : 9
d	*c*Hex	Me	B	30	44	82 : 18
e	Ph	H	B	90	22	75 : 25
f	2-Pyridyl	Me	A	30	0	—
g	Me	Ph	A	40	32	73 : 27

[a] Conditions A: BSA (3.0 equiv), TEA (1.2 equiv); conditions B: BSA (5.0 equiv), TEA (2.0 equiv). [b] Determined by ^{1}H NMR analysis

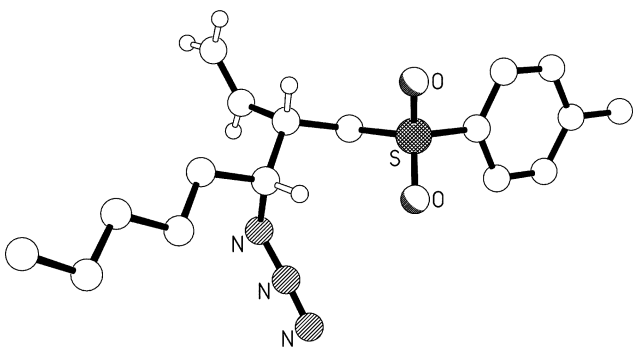


Fig. 1 The molecular structure of *syn*-**14a**.

Conclusions

In conclusion, equilibrating mixtures of allylic azides participate effectively in Claisen rearrangements, in most cases regardless of the position of equilibrium. Diastereoselectivity can be achieved by selection of the appropriate olefin substitution pattern and rearrangement type.

Experimental

Procedures for the preparation of **4a–g**, **7**, **8**, **10**,and characterisation data for all compounds are detailed in the ESI.† Representative procedures for the preparation of allylic azidoalcohols **5a/6a**, ester **9**, esters **11a/12a** and homoallylic sulfone **14a** are given below.

(*E*)-2-Azidonon-3-en-1-ol (5a) and (*E*)-4-azidonon-2-en-1-ol (6a)

To a solution of **4a** (31.5 mmol, 1.0 equiv) in acetone (45 mL) and water (19 mL) was added sodium azide (94.5 mmol, 3.0 equiv) in one portion. After heating the resulting solution under reflux for 8 h, the reaction mixture was cooled to rt and NH_4Cl (5.0 g) was added. Water (50 mL) was added and the reaction mixture was concentrated under reduced pressure to remove acetone. The remaining aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a 73 : 27 mixture of *(E)-2-azidonon-3-en-1-ol* **5a** and *(E)-4-azidonon-2-en-1-ol* **6a** respectively (4.04 g, 70%) as a colourless oil after purification over silica gel (30% TBME/petrol).

Data for the mixture: ν_{max} (film) 3352, 2101, 1667, 1462, 1240, 1072 cm^{-1}; *m/z* (CI) 201 $[MNH_4]^+$, 191, 158, 126 (Found: $[MNH_4]^+$, 201.1715. $C_9H_{17}N_3O$ requires $[MNH_4]^+$, 201.1715.

NMR data for **5a**: δ_H (500 MHz, $CDCl_3$) 5.85 (1H, dt, *J* 15.5, 6.5, H-4), 5.40 (1H, ddt, *J* 15.5, 8.0, 1.5, H-3), 4.03 (1H, dt, *J* 11.5, 5.0, H-2), [3.60 (1H, dd, *J* 11.5, 5.0) and 3.52 (1H, dd, *J* 11.5, 7.5), H-1], 2.09–2.11 (2H, m, H-5), 1.66 (2H, s (br), OH), 1.43–1.25 (12H, m, H-6,7,8), 0.89 (6H, t, *J* 7.0, H-9); δ_C (101 MHz, $CDCl_3$) 138.2, 123.4, 66.3, 65.0, 32.3, 31.2, 28.7, 22.4, 14.0.

NMR data for **6a**: δ_H (500 MHz, $CDCl_3$) 5.88 (1H, dt, *J* 15.0, 5.5, H-2), 5.66 (1H, ddt, *J* 15.5, 7.5, 1.5, H-3), 4.21 (2H, dd, *J* 5.5, 1.5, H-1), 3.85 (1H, dt, *J* 14.0, 7.5, H-4), 1.66 (2H, s (br), OH), 1.56–1.49 (2H, m, H-5), 1.43–1.25 (12H, m, H-6,7,8), 0.89 (6H, t, *J* 7.0, H-9); δ_C (101 MHz, $CDCl_3$) 132.9, 128.9, 64.0, 62.6, 34.5, 31.4, 35.5, 22.5, 14.0.

Ethyl 4-azido-3-ethenylnonanoate (9a)

To a solution of a 73 : 27 mixture of allylic azides **5a** and **6a** respectively (100 mg, 0.546 mmol, 1.0 equiv) in triethyl orthoacetate (20.4 mmol, 13.0 equiv) was added propionic acid (0.314 mmol, 0.2 equiv) dropwise *via* syringe. After heating under reflux for 6 h, the reaction mixture was cooled to rt and concentrated under reduced pressure to afford *ethyl 4-azido-3-ethenylnonanoate* **9a** (137 mg, 99%, 50 : 50 *syn*:*anti* mixture of diastereomers) as a colourless oil without further purification: ν_{max} (film) 2102, 1736, 1641, 1465, 1257, 923 cm^{-1}; δ_H (400 MHz, $CDCl_3$) [5.74 (1H, ddd, *J* 17.0, 10.0, 4.0), and 5.65 (1H, ddd, *J* 17.0, 10.0, 4.0), *syn*+*anti* C*H*CH_2), 5.19–5.13 (4H, m, *syn*+*anti* CHCH_2), [4.14 (2H, q, *J* 7.5) and 4.15 (2H, q, *J* 7.5), *syn*+*anti* OCH_2], [3.84–3.43 (1H, m) and 3.26–3.06 (1H, m), *syn*+*anti* H-4], 2.77–2.69 (2H, m, *syn*+*anti* H-3), [2.56 (2H, dd, *J* 15.0, 5.0) and 2.41 (2H, dd, *J* 15.0, 8.0), *syn*+*anti* H-2], 1.62–1.32 (16H, m, *syn*+*anti* H-5,6,7,8), [1.27 (3H, t, *J* 7.5), and 1.26 (3H, t, *J* 7.5), *syn*+*anti* OCH_2CH_3], 0.91 (6H, t, *J* 6.0 *syn*+*anti* H-9); δ_C (101 MHz, $CDCl_3$) 172.0 (C-1), [137.2 and 135.6, (*C*HCH_2)], [118.3 and 117.8, (CH*C*H_2)], [65.8 and 65.3, (C-4)], 60.5 (OCH_2), [44.9 and 44.5, (C-3)], [37.0 and 36.3, (C-2)], 32.2, 32.0, 31.5, 26.0, 25.8, 22.5, 14.2, 14.0; *m/z* (CI) 271 $[MNH_4]^+$, 254 $[MH]^+$, 226 (Found: $[MH]^+$, 254.1858. $C_{13}H_{23}N_3O_2$ requires $[MH]^+$, 254.1869).

(*E*)-2-Azidonon-3-enyl 2-tosylacetate (11a) and (*E*)-4-azidonon-2-enyl 2-tosylacetate (12a)

To a solution of a 73 : 27 mixture of allylic azides **5a** and **6a** respectively (1.00 g, 5.46 mmol, 1.0 equiv) in dichloromethane (10 mL) was added DMAP (0.546 mmol, 0.1 equiv), followed by a solution of DCC (6.01 mmol, 1.1 equiv) in dichloromethane (10 mL) at rt. The mixture was stirred for 5 min before addition of 2-*p*-toluenesulfonylacetic acid (1.29 g, 6.01 mmol, 1.1 equiv). After stirring the colourless suspension for 16 h, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford a 58 : 42 mixture of the esters (*E*)-*2-azidonon-3-enyl 2-tosylacetate* **11a** and (*E*)-*4-azidonon-2-enyl 2-tosylacetate* **12a** (2.05 g, 99%) respectively as a colourless oil after purification over silica gel (25% ether/petrol).

Data for the mixture: ν_{max} (film) 2932, 2099, 1747, 1598, 1455, 1330, 1152, 1085, 975, 814, 728, 646, cm^{-1}; δ_C (126 MHz, $CDCl_3$) 162.2, 162.1, 138.7, 133.2, 129.9, 128.5, 125.9, 128.5, 125.9, 122.3, 67.1, 65.5, 63.5, 62.0, 60.8, 34.2, 32.2, 31.4, 31.2, 28.5, 25.4, 22.5, 22.4, 21.7, 14.0; *m/z* (CI) 397 $[MNH_4]^+$, 352, 243 (Found: $[MNH_4]^+$, 397.1926. $C_{18}H_{25}N_3O_4S$ requires $[MNH_4]^+$, 397.1910).

^{1}H-NMR data for **11a**: δ_H (500 MHz, $CDCl_3$) 7.85–7.81 (2H, m, *o*-Ts), 7.39–7.37 (2H, m, *m*-Ts), 5.82 (1H, dt, *J* 15.0, 7.0, H-4), 5.31 (1H, ddt, *J* 15.0, 7.0, 1.5, H-3), 4.62 (2H, d, *J* 5.0, H-1), 4.13 (2H, d, *J* 5.0, CH_2Ts), 4.10–3.90 (1H, m, H-2), 2.47 (3H, s, TsMe), 2.10–2.15 (2H, m, H-5), 1.57–1.28 (6H, m, H-6,7,8), 0.89 (3H, t, *J* 7.5, H-9).

^{1}H-NMR data for **12b**: δ_H (500 MHz, $CDCl_3$) 7.85–7.81 (2H, m, *o*-Ts), 7.39–7.37 (2H, m, *m*-Ts), 5.74–5.65 (2H, m, H-2,3), 4.62 (2H, d, *J* 5.0, H-1), 4.13 (2H, d, *J* 5.0, CH_2Ts), 3.82 (1H, dt, *J* 14.0, 7.0, H-4), 2.47 (3H, s, TsMe), 1.57–1.28 (8H, m, H-5,6,7,8), 0.89 (3H, t, *J* 7.5, H-9).

1-[(3-Azido-2-ethenyloctane)sulfonyl]-4-methylbenzene (14a)

To a solution of a 58 : 42 mixture of allylic azides **11a** and **12a** respectively (50 mg, 0.132 mmol, 1.0 equiv) in acetonitrile (1.0 M) was added *N*,*O*-bistrimethylsilylacetamide (0.396 mmol, 3.0 equiv) and TEA (0.158 mmol, 1.2 equiv) in a capped microwave vial. The mixture was heated by microwave at 160 °C until TLC showed consumption of the starting material. The reaction mixture was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were passed though an SCX ion-exchange column (conditioned with 10% MeOH/dichloromethane) and concentrated under reduced pressure to afford the acid intermediate **13a** without further purification. To solution of the crude acid (1.0 equiv) in DMF (1.0 M) was added sodium hydrogencarbonate (1.2 equiv) in a microwave vial. The mixture was heated by microwave at 160 °C for 35 min and cooled to rt. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford *1-[(3-azido-2-ethenyloctane)sulfonyl]-4-methylbenzene* **14a** (38 mg, 86%, 84 : 16 *syn*:*anti* mixture of diastereomers) as a white solid after purification over silica gel (2–10% ether/petrol). Repeated purification over silica gel (2–10% ether/petrol) followed by recrystallisation (EtOAc/petrol) afforded an analytical sample of *syn*-**14a** for crystallography studies and an analytical sample enriched in *anti*-**14a**.

Data for *syn*-**14a**: m.p 72–74 °C; ν_{max} (film) 2902, 2100, 1456, 1142, 880, 771, 706, 670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.5, *o*-Ts), 7.39 (2H, d, *J* 8.5, *m*-Ts), 5.60 (1H, ddd, *J* 17.0, 10.0, 8.5, C*H*CH_2), 5.17 (1H, d, *J* 10.0, *trans*-CHC*H*$_2$), 5.12 (1H, d, *J* 17.0, *cis*-CHC*H*$_2$), 3.70 (1H, ddd, *J* 8.5, 5.5, 3.0, H-3), [3.40 (1H, dd, *J* 14.0, 7.0) and 3.15 (1H, dd, *J* 14.0, 6.0), H-1], 2.90 (1H, dddd, *J* 12.5, 9.5, 6.0, 3.0, H-2), 2.48 (3H, s, TsMe), 1.62–1.31 (8H, m, H-4,5,6,7), 0.92 (3H, t, *J* 6.0, H-8); δ_C (101 MHz, $CDCl_3$) 144.9 (Ts), 136.9 (Ts), 133.7 (*C*HCH_2), 130.0 (*m*-Ts), 128.0 (*o*-Ts), 119.5 (CH*C*H_2), 64.3 (C-3), 58.1 (C-1), 42.5 (C-2), 32.2 (C-4), 31.5 (C-5), 25.8 (C-6), 22.5 (C-7), 21.7 (TsMe), 14.0 (C-8); *m/z* (CI) 353 $[MNH_4]^+$, 310, 226, 174, 152; *m/z* (CI) 353 $[MNH_4]^+$, 310, 226, 152 (Found: $[MNH_4]^+$, 353.2020. $C_{17}H_{25}N_3O_2S$ requires $[MNH_4]^+$, 353.2011) (Found: C, 60.95; H, 7.47; N, 12.48. $C_{17}H_{25}N_3O_2S$ requires C, 60.87; H, 7.51; N, 12.53).

NMR data for *anti*-**14a**: δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0, *o*-Ts), 7.38 (2H, d, *J* 8.0, *m*-Ts), 5.68 (1H, ddd, *J* 17.5, 10.0, 8.5, C*H*CH_2), 5.17 (1H, d, *J* 10.0, *trans*-CHC*H*$_2$), 5.16 (1H, d, *J* 17.5, *cis*-CHC*H*$_2$), 3.41–3.36 (1H, m, H-3), [3.31 (1H, dd, *J* 14.5, 3.5) and 3.20 (1H, dd, *J* 14.5, 9.0), H-1], 2.80–2.74 (1H, m, H-2), 2.48 (3H, s, TsMe), 1.63–1.28 (8H, m, H-4,5,6,7), 0.91 (3H, t, *J* 7.0, H-8); δ_C (101 MHz, $CDCl_3$) 144.4 (Ts), 135.9 (Ts), 135.5 (*C*HCH_2), 129.9 (*m*-Ts), 128.1 (*o*-Ts), 118.9 (CH*C*H_2), 65.8 (C-3), 56.9 (C-1), 43.0 (C-2), 31.6 (C-4), 31.4 (C-5), 25.3 (C-6), 22.4 (C-7), 21.7 (TsMe), 13.6 (C-8).

Acknowledgements

We thank EPSRC and Pfizer for support (supported DTA studentship to A.G.O.).

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