Steric acceleration of activated ene reactions

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Steric buttressing has been used to effect ene reactions involving conjugated enoic esters under relatively mild conditions and with improved control of observed stereoselectivities.

Keywords: steric buttressing, ene reaction, trityl, kainic acid analogues, pyrrolidines

We recently described a sterically assisted ene-reaction that occurs at room temperature and related processes involving unactivated ene reactions.[1] For example, the ene precursor **1** cyclised to give an 88% yield of **2** at 140°C (xylene) for 102 hours, with only the *cis*-isomer being formed (>95%). It was of interest to see if steric acceleration could also be used to assist ene-reactions involving activated alkenes, since these normally tend to require less forcing conditions for cyclisation. In particular, systems of the type **3** were of interest in opening routes to the pyrrolidine **4a** and its congeners the kainic acids, *e.g.* **4b**.[2] Using synthetic routes to **4a**, as a model for the synthesis of kanoids has been reported previously by Kennewell *et al.*[2] and, more recently, by Greenwood and Parsons.[3]

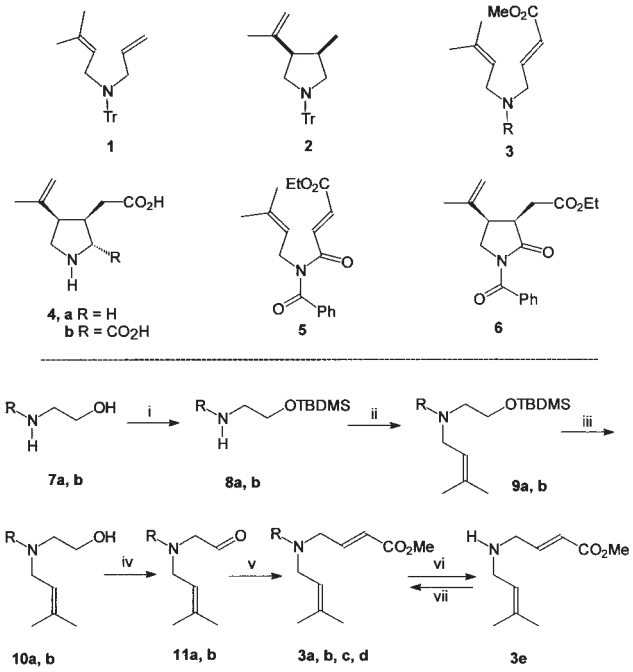
Pyrrolidines such as **4a** are also of interest as conformationally constrained analogues of the neurotransmitter γ-aminobutyric acid.[4] For such routes, a high degree of control of the relative stereochemistry about the pyrrolidine positions 3 and 4 is required in order to produce the normal *cis*-kainic acid stereochemistry or the isomeric *trans*-allokainic acid stereochemistry. Use of Lewis acid catalysts to promote the ene cyclisation under milder conditions generally affords mainly the cyclic 3,4-*trans* isomers,[5] although, using the pyrrolidone precursor **5**, Xia and Ganem showed that magnesium perchlorate catalysed the ene cyclisation to give mainly the *cis*-product **6**.[6] Ene-routes to kainic acid and its congeners have been described by Oppolzer[7], Kennewell *et al.*[2], Kirihata *et al*,[8] and Ogasawara and co-workers.[9]

Although the above studies involve reactions of systems similar to **3**, no model studies on the effect of the nitrogen buttress have been made. The successful synthetic route to the trifluoroacetyl derivative (series **a**) and t-boc derivative (series **b**) is outlined in Scheme 1. The ethanolamine derivatives **7a, b** required *O*-protection as their *t*-butyldimethylsilyl ethers **8a, b** before they could be selectively *N*-alkylated with prenyl bromide. Selective removal of the ether protecting group, to give **10**, followed by Swern oxidation to the aldehyde **11** and Wittig-Horner condensation, using methyl diethylphosphonoacetate, gave the conjugated esters **3a** and **3b**. A number of the intermediates in this sequence showed the presence of amide rotamers in their ^{1}H NMR spectra. The conjugated bond of the isolated product esters (**3**) was the (*E*)-isomer only.

Deprotection of the *N*-boc group in **3b** afforded the amine **3e**, which could then be *N*-reprotected thus allowing preparation of the *N*-tritylated derivative, **3c**, and *N*-benzyl derivative, **3d**.

Ene-cyclisations of the four esters **3a–d** into the corresponding pyrrolidines **12a–d**, were then carried out, following the reaction by ^{1}H NMR spectroscopy, using tetrachloroethane at 130°C, see Fig. 1. The results showed that the t-boc derivative **3b** cyclised the slowest followed by the trifluoroacetyl compound **3a**, then the benzyl derivative **3d**, with the trityl derivative **3c** very much the fastest. In tetrachloroethane the trityl compound cyclised within a few minutes so the reaction could not easily be followed by NMR; in Fig. 1 the rate shown was in deuteriotoluene at 98°C. Thus the trityl buttress exerts a major influence in enhancing the rate of the ene-reaction.

Models of the trifluoroacetyl and *t*-boc groups show that, in the former, the trifluoromethyl group is held nearer to the alkene branches than for the *t*-butyl group as, in the latter



Scheme 1 i, *t*-Butyldimethylsilyl chloride, DMF, imidazole, r.t.; ii, NaH. DMF, r.t., then 1-Bromo-3-methylbut-2-ene; iii, TBAF, DMF, r.t.; iv, oxalyl chloride, DCM, r.t., then DIPEA; v, NaH, THF, r.t., then methyl diethylphosphonoacetate on **11a**, **b**; vi, TFA, DCM on **3b**; viii, NEt_3, DCM then trityl chloride or BzBr.

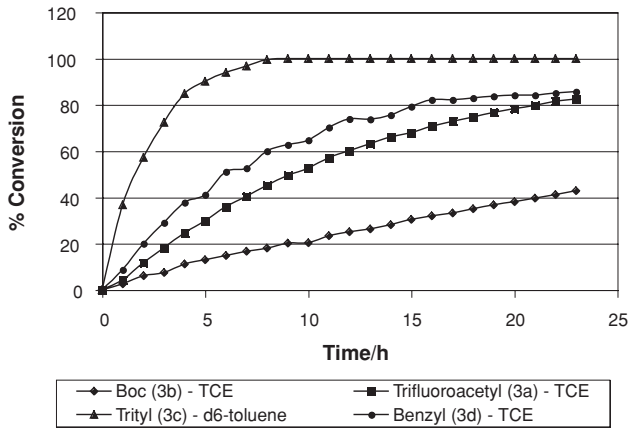


Fig. 1 Graph of percentage conversion of compounds **3** into pyrrolidines **12**.

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Table 1 Equilibration of thermal ene reactions on **3a–d**

Buttress	Conditions	**12**, ratio *cis*/*trans*	^{1}H NMR data (δ)					
			cis-isomer			*trans*-isomer		
			*H*CH=C	*H*CH=C	MeC=C	*H*CH=C	*H*CH=C	MeC=C
Boc (**3a**)[a]	TCE/142°C/66 h	76:24	4.64 br s	4.88 br s	1.43 s	4.79 br s	4.85 br s	1.44 s
CF_3CO (**3b**)[b]	TCE/142°C/46 h	82:18	4.67 br s	4.74 br s	1.68 s	4.90 br s	4.90 br s	1.66 s
Trityl (**3c**)[b]	Toluene/ 98°C/78 h	88:12	4.59 br s	4.78 br s	1.52 s	4.65 br s	4.66 br s	1.57 s
Benzyl (**3d**)[b]	Xylene/140oC/87 h	84:16	4.70 br s	4.87 br s	1.71 s	4.73 br s	4.75 br s	1.72 s

[a]NMR in d_2-tetrachloroethane, 500 MHz.
[b]NMR in $CDCl_3$, 300 MHz.

case, the carbamate oxygen atom allows the *t*-butyl group to be held in space further away from these alkene branches. It is likely, therefore, that, in comparing the cyclisation rates for these two groups, the steric buttressing effect outweighs any electronic factors.

The trityl **3c** and benzyl **3d** derivatives show faster reaction rates and greater stereoselectivity than their amide counterparts. This may well be the result of the lone pair of electrons on the now sp^3 hybridised nitrogen contributing to a slightly altered ene transition state. Given the similarity in electronic properties of the two 'alkyl' buttresses, the marked difference in their ability to promote the ene cyclisation can be considered to be entirely due to the massive steric requirements of the trityl group, compared to its benzyl analogue.

In contrast to the behaviour of the unactivated ene reaction involving compound **1**, all these ene reactions produced mixtures of the *cis*- and *trans* isomers (Table 1). The greater the buttressing effect the more selective was formation of the *cis*-isomer, the trityl derivative (series **c**) producing a ratio of 88:12 in favour of the *cis*-isomer. Presumably the presence of the extra ester group, allows some cyclisation of the transoid conformer,[8b] compared to that in **1**, where only the *cis*-isomer is observed.

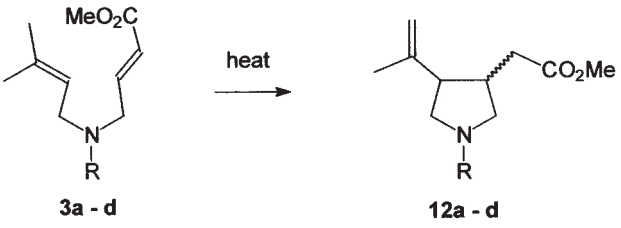
In order to check that the transoid isomer was not being formed by a subsequent thermal equilibration of the initially formed *cis*-isomer, a sample of the purified tritylated material, **12c**, (ratio *cis*:*trans*, 88:12) was heated for longer periods. In toluene (98°C) no equilibration was observed over 70 h. However, by heating in xylene (140°C) for longer periods (up to 70 h) some equilibration occurred to form more of the *trans*-isomer (ratio *cis*:*trans* 80:20). Thus the formation of the initial ratio of isomers is under kinetic control. Thermodynamic control can be observed at the higher temperature, yielding more of the *trans*-isomer. A similar thermal equilibration of the initial kinetic 3,4-*cis*-product **6** into the corresponding 3, 4-*trans*-isomer has been reported by Xia and Ganem.[5]

In conclusion, nitrogen buttressing groups have been studied for their ability to effect the ene cyclisation on a model system related to the natural product, kainic acid. The results obtained demonstrate that steric factors outweigh any electronic considerations, at least in terms of promoting cyclisation and controlling stereoselectivity. The sterically assisted ene cyclisations proceed under kinetic control.

Experimental

^{1}H NMR spectra were recorded on Bruker DPX 250 MHz, Bruker AM 300 MHz or Bruker DRX 500 MHz spectrometers in deuteriochloroform with tetramethylsilane as internal reference. Infrared spectra were run on a Perkin Elmer 2000 spectrometer as either liquid films or Nujol mulls. Merck silica gel (60°C) was used for column chromatography and thin layer chromatography was carried out on neutral silica gel (Merck GF60A, 0.25 mm). Solvents were purified and dried using reported methods.[1] Organic extracts were dried over anhydrous sodium sulfate.

General procedure for the NMR thermolysis study of **3a–d**: A sample of the ene precursor (10–20 mg) in d_2-tetrachloroethane (1 cm^3) (and d_8-toluene for **3c**) was placed in an NMR tube in the Bruker



3a - d **12a - d**

Scheme 2

Avance DPX-500. The temperature of the samples were raised to 130°C as rapidly as possible (within 15 minutes) and spectra recorded at hourly intervals for 24 h. For reaction progress, the disappearance of starting material peaks were measured by integration within each spectral subset and compared as a ratio with the initial integral reading.

N-(*Trifluoroacetyl*)-*N*-(2-*t*-*butyldimethylsilyloxyethyl*)*amine* **8a**: To a solution of the alcohol **7a** (10.02 g, 63.8 mmol) in dry DMF (100 cm^3) were added imidazole (5.2 g, 76.4 mmol) and *t*-butyldimethylsilyl chloride (11.51 g, 76.4 mmol). The resulting solution was stirred at room temperature under argon for 20 h before quenching in aqueous saturated sodium hydrogen carbonate solution (300 cm^3) and extracting with DCM (3 × 100 cm^3). The solvent was removed under reduced pressure and the residual pale yellow oil dissolved in ether (60 cm^3) and washed with water (3 × 50 cm^3), dried, filtered and the solvent removed under reduced pressure to give the *title compound* as a pale yellow liquid (17.01 g, 98.4%); ν_{max} (thin film)/cm^{-1}: 3317, 1709, 1259, 1167, 1108; δ_H (250 MHz, $CDCl_3$) 0.09 (6 H, s, 2 × CH_3), 0.91 (9 H, s,–$C(CH_3)_3$), 3.46–3.53 (2 H, m, N–CH_2), 3.75 (2 H, t, *J* 5.4, CH_2O), 6.71 (1 H, broad s, NH). Found: MH^+ (CI) 272.1304; $C_{10}H_{21}NO_2F_3Si$ requires 272.1288.

N-(*t-Butoxycarbonyl*)-*N*-(2-*t-butyldimethylsilyloxyethyl*)*amine* **8b**: To a solution of the alcohol **7b** (6.07 g, 37.7 mmol) in dry DMF (80 cm^3) were added imidazole (5.04 g, 75 mmol) and *t*-butyldimethylsilyl chloride (6.78 g, 45 mmol). The resulting solution was stirred at room temperature under argon for 20 h then poured onto saturated aqueous sodium hydrogen carbonate solution (200 cm^3) and extracted with DCM (3 × 50 cm^3). The combined organic extracts were dried, filtered and evaporated under reduced pressure before redissolving this in ether (50 cm^3) and washing with water (3 × 30 cm^3), redried, filtered and evaporated to dryness under reduced pressure to yield the *title compound* as a pale yellow liquid (9.82 g, 95%), ν_{max} (thin film/DCM)/cm^{-1} 3360, 2957, 2931, 2885, 2858, 1704, 1103; δ_H (250 MHz, $CDCl_3$) 0.09 (6 H, s, 2 × CH_3), 0.90 (9 H, s, –$C(CH_3)_3$), 1.45 (9 H, s, $C(CH_3)_3$), 3.22 (2 H, t, *J* 5.2, NCH_2), 3.65 (2 H, t, *J* 5.2, OCH_2), 4.85 (1H, br, NH). Found: MH^+ (CI) 276.1946; $C_{13}H_{30}NO_3Si$ requires 276.1989.

N-(*Trifluoroacetyl*)-*N*-(*2-t-butyldimethylsilyloxyethyl*)-*3-methylbut-2-enylamine* **9a**: To a suspension of sodium hydride (1.30 g, 32.5 mmol) in dry DMF (70 cm^3) was added the amide **8a** (8.04 g, 29.7 mmol) and the resulting mixture stirred at room temperature under argon for 1.5 h. After this time 1-bromo-3-methylbut-2-ene (5.71 g, 38.4 mmol) was added dropwise over 10 min and the mixture then stirred at room temperature for a further 22 h. The solution formed was poured into aqueous saturated sodium hydrogen carbonate solution (150 cm^3) and the product extracted with DCM (3 × 40 cm^3) . The organic extract was concentrated under redued presure and the liquid residue dissolved in ether (50 cm^3) and washed with water (3 × 50 cm^3), dried, filtered and the solvent removed under reduced pressure to give the *title compound* (9.02 g, 89.7%); ν_{max} (film)/cm^{-1}: 1694, 1258, 1144 and 1114; δ_H (300MHz; $CDCl_3$) 0.06 (6 H, s, 2 × CH_3), 0.91 (9 H, s, –$C(CH_3)_3$), 1.71–1.76

(6 H, m, 2 × CH_3), 3.43–3.51 (2 H, m, –NCH_2), 3.76–3.83 (2 H, m, NCH_2), 4.13–4.18 (2 H, m, OCH_2), 5.07–5.16 (1 H, m, HC=C). Found: MH^+ (CI) 340.1900; $C_{15}H_{29}NO_2F_3Si$ requires 340.1914.

N-(*t-Butoxycarbonyl*)-*N*-(2-*t-butyldimethylsilyloxyethyl*)-3-*methylbut*-2-*enylamine* **9b**. This was prepared in a similar manner to the trifluoroacetyl derivative **9a**. From the amide **8b** (9.5 g, 35 mmol) was obtained the *title compound* (10.13 g, 85.3%), ν_{max} (film)/ $cm.^{-1}$: 1698, 1103; δ_H (300 MHz, $CDCl_3$) 0.06 (6 H, s, 2 × CH_3), 0.90 (9 H, s, –$C(CH_3)_3$), 1.46 (9 H, s, –$C(CH_3)_3$), 1.67 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 3.24 (2 H, br s, NCH_2), 3.71 (2 H, br s, NCH_2), 3.88 (OCH_2), 5.19 (1 H, t, *J* 6.3 , HC=C). Found: M^+ (EI): 343.2407; $C_{18}H_{37}NO_3Si$ requires 343.2537.

Preparation of the alcohols **10a, b**: The silyl ethers **9a, b** (25 mmol) were dissolved in dry THF (50 cm^3) followed by tetrabutylammonium fluoride (1.0 M solution in THF, 30 mmol) and the resulting orange solution stirred at room temperature under argon for 3 h. The resulting solution was evaporated to small bulk under reduced pressure and the residue dissolved in DCM (25 cm^3), washed with water (3 × 25 cm^3), dried, filtered and evaporated to dryness under reduced pressure. The residue was passed through a plug of neutral silica gel (20 g) eluting with 1:19 methanol-ethyl acetate to afford the corresponding alcohols as the major fraction.

N-(*Trifluoroacetyl*)-*N*-(*2-hydroxyethyl*)-3-*methylbut*-2-*enylamin*e **10a**: (42%), obtained as a colourless oil; ν_{max} (film)/cm^{-1} 3408, 1678, 1204, 1138, 1082; δ_H (500MHz, D_6-DMSO)1.68 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 2.95 (2 H, t, *J* 5.3, NCH_2), 3.55 (2 H, d, *J* 7.4, NCH_2), 3.63 (2 H, dt, *J* 4.4, 5.3, OCH_2), 5.23 (1 H, t, *J* 7.4, HC=C), 5.28 (1 H, t, *J* 4.4, OH).

N-(*t-Butoxycarbonyl*)-*N*-(2-*hydroxyethyl*)-3-*methylbut*-2-*enylamine* **10b**: (57.5%), obtained as a colourless oil; ν_{max} (film)/cm^{-1} 3427, 1667, 1051; δ_H (500 MHz, D_6-DMSO, 353 K) 1.40 (9 H, s, $C(CH_3)_3$), 1.64 (3 H, s, CH_3), 1.69 (3 H, s, CH_3), 3.16 (2 H, t, *J* 6.4, NCH_2), 3.46 (2 H, t, *J* 6.4, OCH_2), 3.79 (2 H, d, *J* 6.8, NCH_2), 4.29 (1 H, br s, OH), 5.13 (1 H, t, *J* 6.8, HC=C). Found: M^+ (EI) 229.1641; $C_{12}H_{23}NO_3$ requires 229.1672.

Methyl (*2-E)*-4-*N*-(*Trifluoroacetyl*)-*N*-(3-*methylbut*-2-*enyl*) *aminobut*-2-*enoate* **3a**: A solution of oxalyl chloride (0.16 g, 1.3 mmol) in dry DCM (10 cm^3) under argon was cooled to –70°C and dry DMSO (0.21 g, 2.6 mmol) was added dropwise over 10 min. The resulting solution was stirred for a further 20 min. before adding the alcohol **10a** (0.16 g, 0.8 mmol) in dry DCM (10 cm^3) over 20 min, keeping the temperature below –60°C and the cloudy solution formed stirred at –70°C for 3.5 h, followed by the dropwise addition of ethyldiisopropylamine (0.51 g, 4.0 mmol) over 5 min and the mixture stirred for a further 30 min, allowing the mixture to warm to –10°C. The mixture was diluted with DCM (10 cm^3) and washed with 3% w/v aqueous ammonium chloride solution (2 × 20 cm^3), dried, filtered and the solvent removed under reduced pressure to form the corresponding aldehyde **11a** as a yellow gum (0.12 g, 67%) which was used without further purification.

To a suspension of sodium hydride (0.02 g, 0.5 mmol) in dry THF (10 cm^3) was added methyl diethylphosphonoacetate (0.13 g, 0.5 mmol) and the resulting clear solution stirred at room temperature under argon for 30 min before adding a solution of the aldehyde **11a** (0.12 g, 0.5 mmol) and the solution stirred for a further 3 h before pouring into water (50 cm^3) and extracting with DCM (3 × 50 cm^3). The organic extract was dried, filtered and the solvent removed under reduced pressure before column chromatography (neutral silica; 9:1 hexane-ethyl acetate) to give the *title ester* as a yellow oil (0.078 g, 46%); ν_{max} (film)/cm^{-1} 1728, 1695, 1278, 1200, 1145, 974; δ_H (300 MHz, $CDCl_3$) 1.67 (3 H, s, CH_3), 1.76 (3 H, s, CH_3), 3.75 (3 H, s, OCH_3), 4.00 (2 H, m, NCH_2), 4.10 (2 H, m, NCH_2), 5.11 (1 H, m, HC=C), 5.91 (1 H,m, HC=C), 6.82 (1 H, dt, *J* 15.7, 5.5, HC=C). Found *m/z* (EI), 279.1115; $C_{12}H_{16}NO_3F_3$ requires 279.1082.

Methyl (*2-E)*-4-*N*-(*t-Butoxycarbonyl*)-*N*-(3-*methylbut*-2-*enyl*) *aminobut*-2-*enoate*. **3b**:- Using the above described method, the alcohol **10b** (3.19 g, 13.7 mmol) was oxidised to the corresponding aldehyde **11b** (2.76 g, 88.6 %) as a yellow gum, which was used without further purification.

Using the above described method, the aldehyde **11b** (2.48 g, 10.9 mmol) was condensed with methyl diethylphosphonoacetate (2.29 g, 10.9 mmol) to afford the *title ester* (2.14 g, 70%) as a colourless oil; ν_{max} (film)/cm^{-1}: 1728, 1696, 1271, 987; δ_H (300 MHz, $CDCl_3$) 1.45 (9 H, s, $C(CH_3)_3$), 1.63 (3 H, s, CH_3), 1.72 (3 ,s, CH_3), 3.75 (3 H, s, OCH_3), 3.81 - 3.91 (4 H, m, 2 × NCH_2), 5.13 (1 H, t, *J* 6.4, HC=C), 5.86 (1 H, d, *J* 15.6, HC=C), 6.85 (1 H, dt, *J* 15.6, 4.8, HC=C). Found: C, 63.3; H, 9.1; N, 4.9. $C_{15}H_{25}NO_4$ requires C, 63.6; H, 8.9; N, 4.9%.

Methyl (2*E*)-*N*-(*3-Methylbut*-2-*enyl*)-4-*aminobut*-2-*enoate* **3f**: To a solution of the carbamate **3b** (0.61 g, 2.2 mmol) in dry DCM (4 cm^3) was added trifluoroacetic acid (2.97 g, 26 mmol) and the solution stirred at room temperature under nitrogen for 2.5 h. The solution was diluted with more DCM (6 cm^3) and washed with brine (10 cm^3), water (10 cm^3), then saturated aqueous sodium hydrogen carbonate solution (2 × 10 cm^3), dried, filtered and the solvent removed under reduced pressure to give a yellow oil. The oil was dissolved in a small quantity of DCM and filtered through a pad of silica gel, eluting with DCM to give, after removal of the solvent, the *title amine* as a pale yellow oil (0.26 g, 66%); ν_{max} (film)/cm^{-1}: 3391, 1725, 1661, 1273; δ_H (400 MHz, $CDCl_3$) 1.58 (1 H, br s, NH), 1.65 (3 H, s, CH_3), 1.73 (3 H, s, CH_3), 3.22 (2 H, d, *J* 7.0, NCH_2), 3.41 (2 H, d, *J* 8.7, NCH_2), 5.24 (1 H, t, *J* 8.7, HC=C), 5.99 (1 H, d, *J* 19.7, HC=C), 7.00 (1 H, dt, *J*19.7, 7.0, HC=C). Found: $(M-H)^+$ (CI)182.1160; $C_{10}H_{16}NO_2$ requires 182.1176.

Methyl (2*E*)-*N*-(3-methylbut-2-*enyl*)-*N*-(*trityl*)-4-*aminobut*-2-*enoate* **3c**: To a solution of the amine **3f** (0.85g, 4.6 mmol) in dry DCM (15 cm^3) were added triethylamine (0.66 g, 6.5 mmol) and triphenylmethyl chloride (1.55 g, 5.6 mmol). The solution was stirred under nitrogen at room temperature for 70 h before washing the solution with 3% w/v aqueous ammonium chloride solution (2 × 20 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 20 cm^3) and water (20 cm^3) before drying, filtering and removal of solvent under reduced pressure. The viscous oil produced was chromatographed through neutral silica gel (prewashed with 1:19 triethylamine/hexane), eluting with 4:1 hexane-diethyl ether to afford the *title amine* as a colourless, gummy oil (1.28 g, 65%); ν_{max} (film)/cm^{-1}: 3084, 3058, 3031, 2854, 1723, 1653, 1596, 1271, 984; δ_H (300 MHz, $CDCl_3$) 1.29 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 2.88 (2 H, d, *J* 6.8, NCH_2), 3.06 (2 H, d, *J* 5.6, NCH_2), 3.72 (3 H, s, OCH_3), 5.34 ((1 H, t, *J* 6.8, HC=C), 5.69 (1 H, d, *J* 15.7, HC=C), 7.14–7.53 (16 H, aromatic and HC=C); *m/z* (CI) 426 (MH^+).Found: C, 81.9; H, 7.6; N, 3.1. $C_{29}H_{31}NO_2$ requires C, 81.85; H, 7.3; N, 3.3%.

Methyl (2*E*)-*N*-*benzyl*-*N*-(3-*methylbut*-2-*enyl*)-4-*aminobut*-2-*enoate* **3d**: In a similar manner to that described above the amine **3f** (0.22 g, 1.2 mmol) was alkylated with benzyl bromide (0.23 g, 1.4 mmol). After isolation of the product by chromatography through neutral silica gel, the *title amine* was isolated as a colourless oil (0.23 g, 71%); ν_{max} (film)/cm^{-1}:2918, 1727, 1667, 1284, 982; δ_H (300 MHz, $CDCl_3$) 1.69 (3 H, s, CH_3), 1.84 (3 H, s, CH_3), 3.76 (3 H, s, OCH_3), 3.96 (2 H, m, NCH_2), 4.27 (2 H, m, NCH_2), 5.37 (1 H, t, *J* 7.5 ,HC=C), 6.12 (1 H, d, *J* 15.7, HC=C), 6.96 (1 H, dt, *J*15.7, 7.3, HC=C), 7.32–7.41 (5 H, m, aromatic H). Found (CI) M^+: 274.1782; $C_{17}H_{23}NO_2.H^+$ requires 274.1802.

Cyclisations of the esters **3a – 3d**: Solutions of the esters (100 mg) in the appropriate solvent (see Table 1; either d_2-1,1,2,2-tetrachloroethane or d_8-toluene; 3 cm^3) were heated under argon, following the progress of the reaction on samples by ^1H NMR spectroscopy, until cyclisation was > 95% complete. Solvent was removed under reduced pressure and the residue redissolved in the minimum volume of DCM before filtering through a short column of silica gel, eluting with DCM, and the solvent removed to give a mixture of the *cis*- and *trans*-pyrrolidine esters **12a–d**. The isomeric mixtures were not separated but characterised by ^1H NMR spectroscopy (see Table 1), the initial isopropylidene group in the starting materials **3** being replaced by the formed isopropenyl group in the products **12**.

Thermolysis of the tritylated pyrrolidine **12c**: A sample (30 mg) of the tritylated product **12c**, purified by preparative TLC (silica gel, 1:1 hexane:diethyl ether) (*cis*:*trans* ratio 88:12) was dissolved in d_{10}-*o*-xylene and heated under reflux under argon over 70 h. ^1H NMR spectroscopy indicated the ratio of isomers had changed to approximately 80:20. However, on further heating, for up to 200 h, extensive decomposition set in and further equilibration could not be observed.

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