A stereoselective synthesis *via* a 5-*exo-trig* cyclisation of *trans*-2-oxohexahydro-2*H*-furo[3,2-*b*]pyrroles (pyrrolidine-*trans*-lactones)—potent, novel elastase inhibitors

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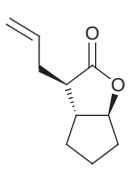
trans-2-Oxohexahydro-2*H*-furo[3,2-*b*]pyrroles (such as **2**) are conformationally strained 5,5-fused ring systems and are potent human neutrophil elastase (HNE) inhibitors. A stereoselective synthesis is described based on intramolecular *5-exo-trig* cyclisations of aldehyde acrylates **4** and **5** mediated by samarium(II) iodide to give predominantly *trans*-products **9** and **15**. The *n*-propyl group in **15** is also generated with stereoselectivity for the desired β-isomer.

Introduction

Human neutrophil elastase (HNE)[1] is a serine protease stored in the azurophilic granules of neutrophils. It is released in response to inflammatory stimuli and has a major role in protein digestion following phagocytosis. Excessive elastase release has been implicated in respiratory diseases such as acute respiratory distress syndrome, cystic fibrosis, emphysema[1] and chronic bronchitis.[2] Inhibitors of HNE are actively being investigated[3] as potential therapies for these diseases.

As part of our programme to develop low molecular weight non-peptide inhibitors of HNE for the treatment of chronic bronchitis, we are pursuing compounds developed from a lead triterpene identified by high throughput screening.[4] Our initial development of this lead led us to strained cyclopentane-*trans*-lactones typified by **1** which are micromolar inhibitors of



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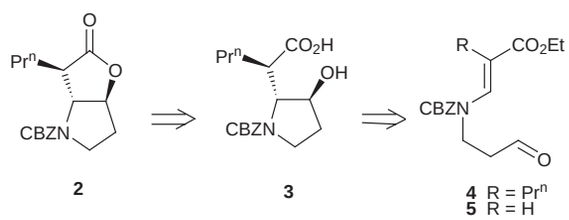
HNE.[5] These compounds inhibit HNE by acylating the nucleophilic hydroxy of serine-195† in the active site of the enzyme.

To enhance the potency of these inhibitors we designed, with the aid of computer modelling, a second generation of inhibitors based on *trans*-oxohexahydro-2*H*-furo[3,2-*b*]pyrroles, called colloquially pyrrolidine-*trans*-lactones **2**. We believe such compounds were unknown until our studies;[6] they now represent an important new class of heterocycles characterised by their inhibitory activity against serine proteases including HNE, chymotrypsin, cathepsin G and thrombin. We attribute their potency to a combination of conformational ring strain (from the *trans*-fused ring system) and molecular fit in the active site of the enzyme.[6] We describe here a synthetic approach which gives the desired stereocontrol over the three contiguous stereocentres *via* a samarium iodide mediated *5-exo-trig* cyclisation.

The retrosynthesis is shown in Scheme 1. Concern for the

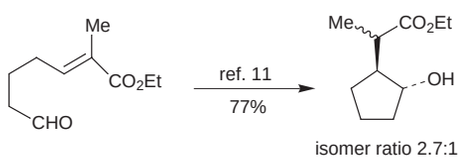


2 **3** **4** R = Pr^n **5** R = H

Scheme 1

potential reactivity of the strained *trans*-lactone led us to postpone lactone formation to the end of the synthesis: hence the initial disconnection to the hydroxy acid **3**. This in turn is disconnected *via* the 5-*exo-trig* cyclisation to the aldehyde **4** which we envisaged being available readily from ethyl propiolate and 3-aminopropanal diethyl acetal. From previous structure–activity relationships,[5,6] it was clear that the β-stereochemistry of the propyl group (*i.e.* drawn up as for **2**) gave increased inhibitory activity against HNE when compared with the α-propyl group. Thus stereocontrol in the cyclisation was critical to the success of this approach.

The literature contains examples of intramolecular reductive cyclisations of aldehydes with electron deficient olefins for the preparation of cyclopentanes by electro-reduction,[7] treatment with Bu_3SnH,[8] SmI_2[9,10] or VCl_2[11] and for the preparation of oxacycles[10,12,13] and pyrrolidines.[10,14–16] However at the time of this work we were unaware of any precedent for reductive cyclisations of aldehydes onto urethane acrylates (as in **4** or **5**) and only a single example (Scheme 2)[11] with substitution α to the



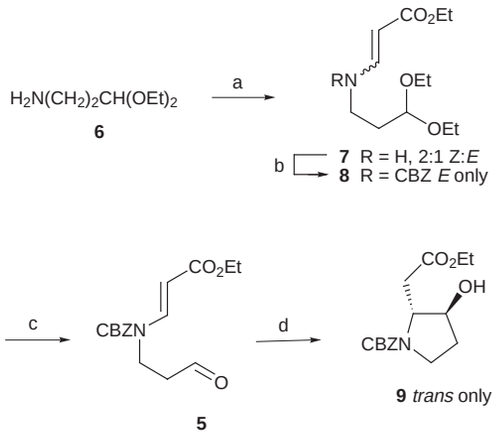
Scheme 2

ester (as in **4**). Since this work was completed, an example of this type of cyclisation has been described for the formation of a piperidine.[14]

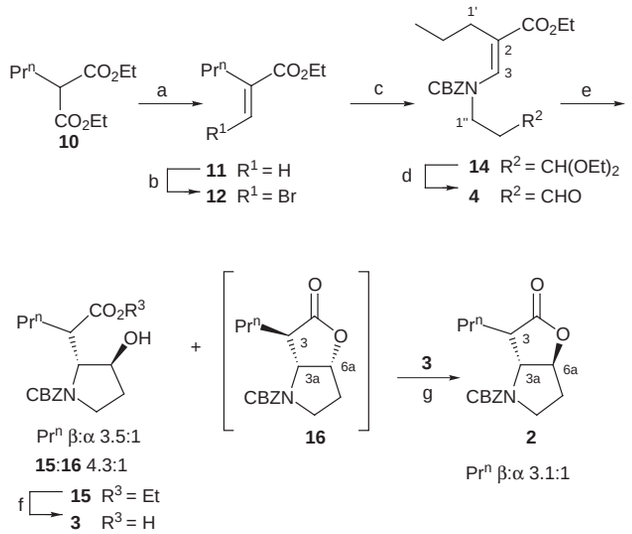
Results

We explored initially the des-propyl series (Scheme 3). The

† Numbered according to chymotrypsin.



Scheme 3 *Reagents and conditions*: (*a*) $HC{\equiv}CCO_2Et$, Et_2O, rt, 3 days, 100% crude; (*b*) *n*-BuLi, THF, −78 °C, 30 min, then CBZCl, warm to rt, 45 min, 100% crude; (*c*) TsOH·py, H_2O, Me_2CO, reflux, 7 h, 30%; (*d*) SmI_2, THF, HMPA, MeOH, 0 °C, 90 min, 53%.



Scheme 4 (all compounds racemic) *Reagents and conditions*: (*a*) KOH, EtOH, rt, 17 h; c HCl; $(HCHO)_n$, pyridine, piperidine, reflux, 90 min, 56%; (*b*) Br_2, $CHCl_3$, AcOH, 5 °C, 2 h, 100% crude; then DBU, THF, reflux, 75 min, 60%; (*c*) $CBZNH(CH_2)_2CH(OEt)_2$ **13**, NaH, DMF, rt, 2.5 h, 15%; (*d*) TsOH·py, H_2O, Me_2CO, reflux, 3 h, 100% crude; (*e*) SmI_2, THF, MeOH, HMPA, 5 °C, 90 min, 48%; (*f*) LiOH, EtOH, H_2O, reflux, 6 h, 100% crude; (*g*) 2,4,6-trichlorobenzoyl chloride, Et_3N, CH_2Cl_2 rt, 1 h; then DMAP, PhMe, reflux 3.5 h, 35%.

commercially available 3-aminopropanal diethyl acetal **6** was readily converted into the protected aldehyde **8** by 1,4-addition with ethyl propiolate[17] giving a 2:1 *E*:*Z* ratio of olefins **7** which upon deprotonation with *n*-butyllithium‡ and treatment with benzyl chloroformate gave only the (*E*)-product **8** with an olefinic coupling constant $J = 14.5$ Hz. Deprotection of the acetal **8** with pyridinium toluene-*p*-sulfonate in aqueous acetone gave the stable crystalline aldehyde **5**. Reductive cyclisation with excess samarium iodide in the presence of HMPA and using methanol as the proton source, gave a 53% yield of racemic *trans*-hydroxy ester **9**.§ Neither the *cis*-isomer of hydroxy ester **9** nor the anticipated more stable product the *cis*-lactone, were observed. Other conditions such as Bu_3SnH,[8] VCl_2,[11] $TiCl_3$ and a Zn–Cu couple,[18] zinc dust and TMSCl,[19] or Mg in MeOH[13] failed to give significant, if any, *trans*-hydroxy ester **9**.

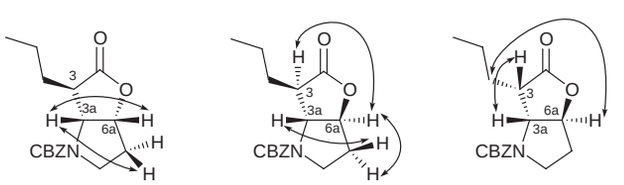
We next investigated cyclisation of the propyl aldehyde **4** (Scheme 4). Diethyl propylmalonate **10** was converted into the propylacrylate **11** under standard conditions.[20] Dibromination followed by dehydrobromination with DBU in THF gave the (*E*)-bromoacrylate **12** in 60% yield after distillation.¶ This was subjected to an addition–elimination reaction with the sodium salt of benzyl carbamate **13** to give a 15% yield of the unsaturated acetal **14**.¶ Alternative conditions [$PdCl_2(MeCN)_2$, CuCl, $CH_2C(Me)CO_2Me$,[13] DME] for a similar transformation failed to give any identifiable products.[21] This acetal **14** was deprotected smoothly to afford the crude (*E*)-acrylate aldehyde **4**. The (*E*)-geometry was determined by an NOE between H1′ and H1″. No NOE was observed between H1′ and H3. This acrylate aldehyde **4** underwent a SmI_2 mediated cyclisation to give a 48% yield of *trans*-hydroxy ester **15** (Pr^n β:α = 3.8:1) and an 11% yield of the β-propyl *cis*-lactone **16** (all racemic products). A repeat cyclisation on a larger scale gave a 62% yield of **15** with similar stereoselectivity. The ^{1}H-NMR spectra of the ester **15** correlate with those of a sample (Pr^n β:α = 1:1.5) prepared by a different route (unpublished results) giving confidence in the stereochemical assignment of this material.

Saponification of the ethyl ester **15** under standard conditions, followed by a Yamaguchi cyclisation[22] of the resulting hydroxy acid **3** under dilute conditions, gave the desired *trans*-lactone **2** (35% yield) as a 3.1:1 β:α mixture of isomers which were not separated readily by flash chromatography. The stereochemistries of the β- and α-isomers were determined by ^{1}H-NMR, and by correlation of the corresponding β- and α-allyl isomers which were separable and available *via* a different route.[6] We believe there is minimal epimerisation of the carbon bearing the *n*-propyl in transforming **15** to the *trans*-lactone **2**.

The ^{1}H-NMR spectra of **16**, **2**β and **2**α are complicated by peak broadening due to *cis–trans* isomerisation of the benzyl carbamates. However warming to 50 °C (or higher) sharpens many of the resonances and allowed structural assignments based on NOE, COSY and HMQC experiments. Table 1 shows clearly the difference in the diagnostic coupling constant between H6a and H3a in the *cis*-lactone **16** (5 Hz) and in the *trans*-lactones **2**β and **2**α (10 Hz). These values are in good agreement with those predicted by Macromodel.[23] Additional evidence for a difference in ring fusion stereochemistry is that a strong NOE is observed between H6a and H3a in the *cis*-lactone **16** where none is observed between H6a and H3a in **2**β or **2**α (Table 1).

The coupling constants between H3a and H3 in these systems are also of diagnostic use in differentiating between the β and α *n*-propyl groups (12 and 7 Hz respectively). These are

Table 1 Key NOE's and observed (obs.) and predicted[a] (pred.) ^{1}H coupling constants (Hz) for the *cis*- and *trans*-lactones **16**, **2**β and **2**α



	16		**2**β		**2**α	
	Obs.	Pred.	Obs.	Pred.	Obs.	Pred.
J_{3a-6a}	5	5.3	10	9.9	10	9.9
J_{3a-3}	<2[b]	0.6	12	11.9	7	6.7

[a] Predicted values were calculated using Macromodel (ref. 23). [b] Line broadening due to *cis–trans* isomerisation of the carbamate prevented accurate determination of this coupling constant even after warming.

‡ The sodium salt of **7** is highly insoluble in DMF. The lithium salt is preferred due to its solubility in THF.

§ This material **9** is identical to that prepared by other routes (ref. 6 and unpublished results).

¶ The olefin geometry is supported by the lack of an NOE between the olefinic proton and the *n*-propyl protons.

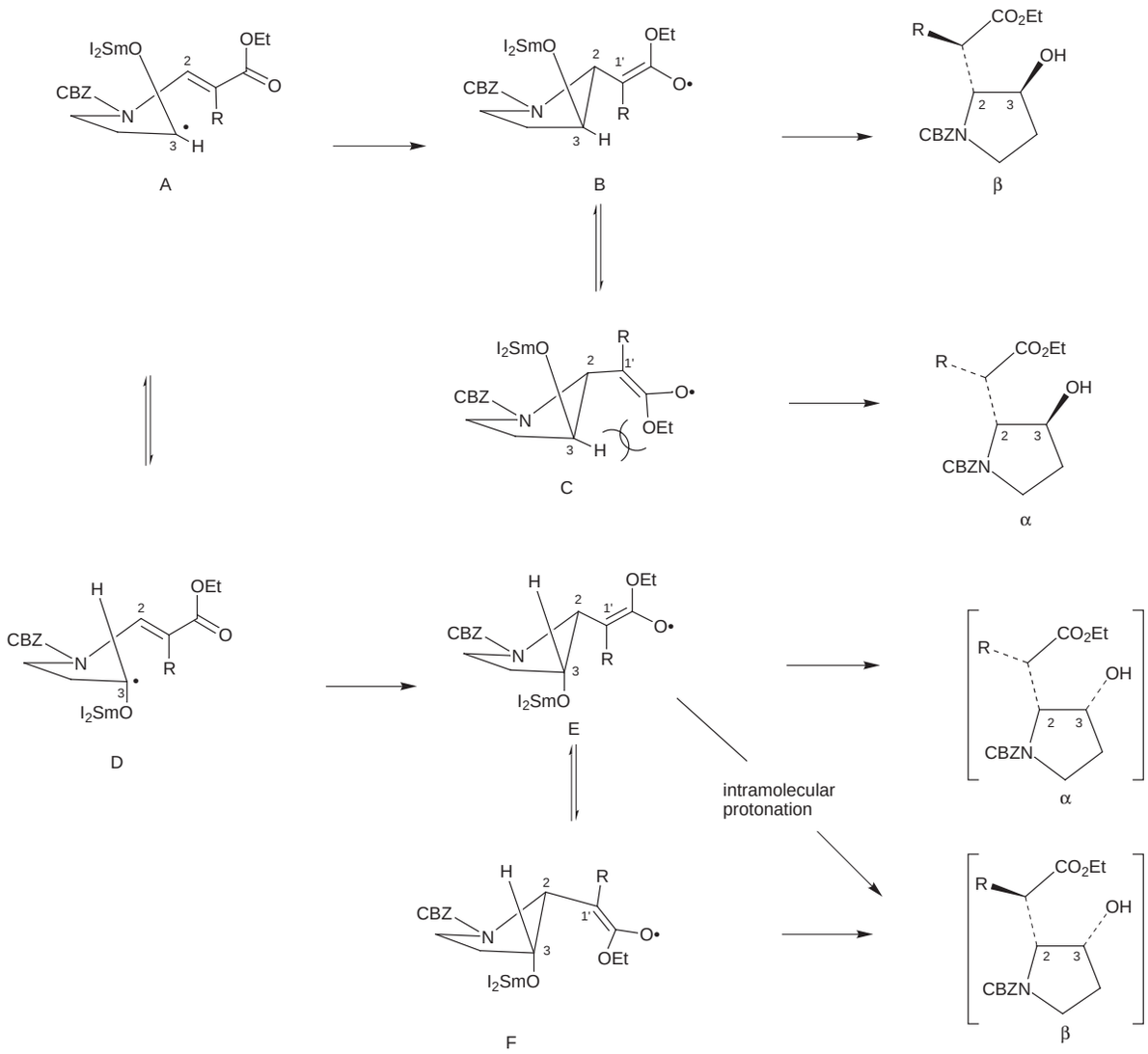


Fig. 1 Possible transition states for the *5-exo-trig* cyclisations of **4** and **5**. Unless shown otherwise protonation of B, C, E and F is assumed to occur from the most open (*exo*) face (from the back face as drawn). The *cis*-products from E and F are shown as hydroxy esters, although in fact only the *cis*-lactone **16** was isolated.

also in good agreement with those predicted by Macromodel.[23] Again, NOE's between H3 and H6a for **2**β and between H3 and H3a for **2**α confirm the propyl stereochemistries. The difference in coupling between H3a and H3 in **16** (<2 Hz) and **2**β (12 Hz) illustrates some of the structural differences between *cis* and *trans*-lactones.

Discussion

Although there have been considerable advances in the use of samarium(II) iodide mediated transformations, there is still only a hazy understanding of the mechanistic details involved.[24] However some suggestions and comments can be made. The formation of 5-membered carbocycles by intramolecular reductive cyclisation of aldehydes onto electron deficient (*E*)-olefins are known to give predominantly *trans* products and the olefin geometry (*E* or *Z*) has been noted as playing a critical role in affecting the *cis*- or *trans*-geometry of the products.[11,13] As mentioned previously however, there is little precedent for stereocontrol of substituents α to the ester (Scheme 2).[11]

The various transition states for the SmI_2 cyclisations of **4** and **5** are depicted in Fig. 1. These have been drawn as radical intermediates although they could be anionic intermediates. However as these radicals behave as nucleophiles, similar steric or electronic effects should apply.[25] The preference for the formation of *trans*-products (across C2–C3) **9** and **15** from transition state A (rather than D) may be explained in terms of minimising electronic repulsion between the developing methylene radical centre and the negatively charged aldehyde oxygen.[9b,11,26,27] Our results show the preference for A over D is less pronounced for R = propyl than R = H which is not easily rationalised.

Following cyclisation, the resultant radical species is then proposed to undergo further reduction by SmI_2 to give an anionic species (not shown) which is then rapidly protonated.[27] We assume that the stereochemistry of the *n*-propyl group is either determined by the facial preference for O to C proton transfer in the ketene acetal species or the facial preference for protonation of C1′. The results suggest that B is preferred to C. If one assumes that protonation occurs from the more open face (*exo*), this can be rationalised as minimising interactions between the OEt and H3 (as shown in C) leading to a preference for the β-propyl product. However application of this argument for preferring F over E is less clear cut. The F intermediate leads to the thermodynamically more stable β-propyl product (the product that is actually isolated) but is the less preferred conformation because the OEt is underneath the pyrrolidine ring. If however C3 alkoxide protonation occurs first, then an intramolecular protonation from the C3 hydroxy may occur. This would appear to be more facile in E than F and would lead to the desired β-propyl product (Fig. 1).

There are distinct physicochemical and biochemical differ-

ences[6] between the *trans*-lactone **2** and the *cis*-lactone **16** (*vide supra*). The pyrrolidine *trans*-lactones **2** are characterised by the infra-red lactone carbonyl stretching frequency at ν_{max} 1795 cm^{-1} in contrast to that of the *cis*-lactone **16** at 1778 cm^{-1}.[6] This may indicate increased ring strain. Additionally, the β-propylpyrrolidine *trans*-lactone of **2**β is a potent inhibitor of HNE with an IC_{50} of 45 nM (after a 15 min preincubation) in contrast to **16** which is inactive (up to 100 μM).[6] This is entirely consistent with the different molecular shapes of **2** and **16**; **2** exists in a 'pseudo-planar' conformation and **16** in an 'envelope' conformation. These molecular shapes explain the lack of 'molecular fit' of **16** in the active site of HNE. The difference in ring strain is also believed to contribute to the acylating power of the *trans*-fused molecule over the *cis*-fused analogue.

We have briefly explored these *5-exo-trig* cyclisations for the preparation of the analogous pyrrolidine *trans*-lactams.[6] Pyrrolidine products were not obtained although some recent protocols from Aurrecoechea and Fernandez–Acebes[28] have not been investigated.

Experimental

General methods

Unless otherwise indicated, δ_H NMR spectra were recorded on a 250 MHz Bruker spectrometer. 400 MHz and 750 MHz spectra were recorded on a Varian VXR 400 and Inova 750 MHz Varian spectrometers respectively. Spectra are referenced internally to residual proton solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, b = broad, m = multiplet, d = doublet, t = triplet, q = quartet), coupling constant (J in Hz), and assignment. Proton assignments were aided by COSY, HMQC, NOE and ROESY experiments. Infra-red spectra were recorded on a Perkin-Elmer 1700 series spectrometer. Thermospray mass spectra were recorded on an HP5989B Engine, using ammonia as carrier gas, with the filament on and in positive ion mode. Electrospray mass spectra were recorded on a Micromass Autospec Voltage Spec in positive ion mode using PEG/PEG-NH_3 conditions. Thin layer chromatography (TLC) was performed on Polygram Sil G/UV_{254} pre-coated plastic sheets and visualised by UV or potassium permanganate in dilute aqueous sodium carbonate. Flash chromatography was carried out on Merck 9385 silica gel 60.

(*E*)-3-[Benzyloxycarbonyl(3-oxopropyl)amino]acrylic acid ethyl ester 5

The enamine **7** (2:1 *Z*:*E*) was prepared according to ref. 15. The enamine **7** (24.17 g, 98.5 mmol) was dissolved in THF (200 cm^3) under N_2 and cooled to −70 °C. Bu^{n}Li (1.6 M in hexanes) (62 cm^3, 99.3 mmol) was added dropwise over 90 min to give a yellow–green solution. After 30 min, benzyl chloroformate (14.2 cm^3, 99.5 mmol) in THF (20 cm^3) was added over 60 min and the cooling bath removed immediately and the reaction allowed to warm to room temperature. After 45 min TLC showed absence of starting material. The reaction was quenched with saturated NH_4Cl solution (200 cm^3) and extracted with ethyl acetate (3 × 150 cm^3). The combined extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to afford (*E*)-3-[benzyloxycarbonyl(3,3-diethoxypropyl)amino]acrylic acid ethyl ester **8** as a yellow oil (41.68 g). A portion of this crude carbamate **8** (3.27 g, 8.62 mmol), pyridinium toluene-*p*-sulfonate (2.17 g, 8.62 mmol), water (10 cm^3) and acetone (40 cm^3) were heated at reflux for 7 h. The acetone was removed *in vacuo* and the residue diluted with EtOAc (50 cm^3) and water (40 cm^3). The aqueous layer was separated and extracted with EtOAc (2 × 25 cm^3). The combined organic extracts were washed with brine (25 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford an orange oil which solidified on standing. Trituration with EtOAc–hexane 1:1 (8 cm^3) at 5 °C followed by filtration and washing of the filter cake with Et_2O (5 cm^3) gave the aldehyde **5** (0.795 g, 30%) as a white solid. (Further material was available from the residue by chromatography.) (Found: C, 63.2; H, 6.4; N, 4.5. $C_{18}H_{19}NO_5$ requires C, 62.9; H, 6.3; N, 4.6%); TLC R_f = 0.24 (3:1 hexane–Et_2O); δ_H($CDCl_3$, 250 MHz) 9.78 (1 H, s, C*H*O), 8.18 (1 H, d, *J* 14.5, NC*H*CH), 7.37 (5 H, br s, *Ph*), 5.26 (2 H, s, PhCH_2), 5.20 (1 H, d, *J* 14.5, NCHC*H*), 4.19 (2 H, q, *J* 6.5, $CO_2CH_2CH_3$), 3.93 (2 H, t, *J* 7, NCH_2), 2.76 (2 H, t, *J* 7, 2H, CH_2CHO), 1.28 (3 H, t, *J* 6.5, $CO_2CH_2CH_3$); ν_{max} (Nujol mull)/cm^{-1} 2924, 2853, 1741, 1716, 1689, 1634, 1454 and 1411.

trans-3-Hydroxy-2-ethoxycarbonylmethylpyrrolidine-1-carboxylic acid benzyl ester 9

To samarium(II) iodide in THF (0.1 M) (10 cm^3, 1 mmol) and methanol (2 drops) at −5 °C was added with stirring the aldehyde **5** (50 mg, 0.164 mmol) in THF (1 cm^3) over 5 min. After 30 min, TLC showed no reaction. HMPA (CARCINOGEN) (0.2 cm^3) was then added causing the deep blue–green colour to rapidly change to purple and then to colourless. After a further 30 min TLC showed almost complete consumption of starting material. After addition of 2 M HCl (10 cm^3), the crude product was extracted with EtOAc (3 × 10 cm^3). The combined extracts were washed with brine (10 cm^3), 5% sodium thiosulfate solution (10 cm^3), brine (2 × 10 cm^3) and dried ($MgSO_4$). Solvent removal *in vacuo* followed by flash chromatography on silica (9385 Merck) eluting with 80:20 ether–hexane afforded recovered starting material **5** (0.009 g) and the desired product **9** (0.022 g, 44%; 53% based on consumed starting material). This material was identical to samples prepared by an alternative route;[6] TLC R_f = 0.40 (Et_2O); δ_H($CDCl_3$, 250 MHz) 7.40–7.24 (5 H, m, *Ph*), 5.18–5.10 (2 H, m, PhCH_2), 4.26 (1 H, br s, NC*H*CHOH), 4.20–3.99 (3 H, m, C*H*OH, OCH_2CH_3), 3.78–3.58 (1 H, m, N*H*CH), 3.51–3.40 (1 H, m, NHC*H*), 3.12 (0.6 H, dd, *J* 16 and 3, *H*CHCO$_2$Et), 2.87 (0.4 H, dd, *J* 16 and 3, *H*CHCO$_2$Et), 2.76 (0.6 H, s, O*H*), 2.55 (0.4 H, s, O*H*), 2.36 (0.6 H, d, *J* 16, HC*H*CO$_2$Et), 2.20 (0.4 H, d, *J* 16, HC*H*CO$_2$Et), 2.06 (1 H, m, NCH$_2$*H*CH), 1.92 (1 H, m, NCH$_2$HC*H*), 1.26 (3 H, t, *J* 7, $CO_2CH_2CH_3$); ν_{max}(thin film)/cm^{-1} 3443, 2978, 1731, 1701 and 1415.

(*E*)-3-Bromo-2-propylacrylic acid ethyl ester 12

A solution of bromine (2.26 cm^3, 43.75 mmol) in chloroform (20 cm^3) was added over 2 h to a solution of the ethyl 2-methylenepentanoate **11** (6.0 g, 42.0 mmol) (prepared according to ref. 20) in chloroform (15 cm^3) and acetic acid (3 cm^3) at 5 °C. After a further 2 h, the mixture was diluted with 2 M aqueous sodium carbonate (200 cm^3) and sufficient solid sodium metabisulfite to decolourise the mixture. This was then extracted with chloroform (2 × 40 cm^3). After drying ($MgSO_4$), concentration *in vacuo* gave a colourless oil (13.0 g). The oil (13.0 g, 43 mmol) was dissolved in dry THF (45 cm^3) and DBU (11.7 cm^3, 78 mmol) in THF (30 cm^3) was added over 5 min. The mixture was then heated at reflux for 75 min, cooled, and then diluted with water (500 cm^3) and 2 M hydrochloric acid (25 cm^3). After extraction with hexane (2 × 50 cm^3), the combined extracts were washed with brine (2 × 100 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to afford a yellow oil (7.8 g). This was distilled *in vacuo* to give the bromoacrylate **12** (5.75 g, 60%), bp 58.5–61 °C/4 mm Hg (Found: C, 43.7; H, 6.1. $C_8H_{13}BrO_2$ requires C, 43.45; H, 5.9%); δ_H($CDCl_3$, 250 MHz) 7.51 (1 H, s, BrC*H*), 4.21 (2 H, q, *J* 6.5, $CO_2CH_2CH_3$), 2.46 (2 H, t, *J* 8, CH_2CH$_2$CH$_3$), 1.50 (2 H, sextet, *J* 8, CH$_2$CH_2CH$_3$), 1.31 (3 H, t, *J* 6.5, $CO_2CH_2CH_3$), 0.96 (3 H, t, *J* 8, CH$_2$CH$_2$CH_3); ν_{max}(thin film)/cm^{-1} 2964, 1719, 1607 and 1464.

(*E*)-3-[Benzyloxycarbonyl(3,3-diethoxypropyl)amino]-2-propylacrylic acid ethyl ester 14

To the benzyl carbamate **13** (0.560 g, 2 mmol) and bromo-

acrylate **12** (0.480 g, 2.2 mmol) in dry DMF (7 cm^3) under N_2 was added sodium hydride (60% in oil) (0.090 g, 2.2 mmol). After 40 min, evolution of hydrogen was complete and the solution was orange–brown. After a further 2 h the mixture was diluted with water (100 cm^3) and brine (50 cm^3). Citric acid (2 g) was added. Extraction with EtOAc (2 × 60 cm^3) followed by washing of the combined extracts with brine (3 × 50 cm^3) and drying ($MgSO_4$) and concentration *in vacuo* gave a pale yellow oil (0.9 g). This was purified by flash column chromatography on silica gel eluting with hexane–ether 2:1 to afford the desired product **14** (0.130 g, 15%); TLC $R_f = 0.48$ (1:1 hexane–Et_2O); δ_H($CDCl_3$, 400 MHz) 7.64 (1 H, s, NC*H*), 7.40–7.30 (5 H, m, *Ph*), 5.21 (2 H, s, PhCH_2), 4.49 (1 H, t, *J* 5, C*H*($OEt)_2$), 4.19 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 3.68 (2 H, m, NCH_2CH_2), 3.60 (2 H, m, 2H, $CH(OCH_2CH_3)_2$), 3.43 (2 H, m, $CH(OCH_2CH_3)_2$), 2.28 (2 H, m, $CH_2CH_2CH_3$), 1.92 (2 H, m, NCH_2CH_2), 1.45 (2 H, m, $CH_2CH_2CH_3$), 1.28 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 1.08 (6 H, t, *J* 7, $CH(OCH_2CH_3)_2$), 0.91 (3H, t, *J* 7, $CH_2CH_2CH_3$); ν_{max}(KBr diffuse reflectance)/cm^{-1} 2963, 2934, 2882, 1724, 1709 and 1637; *m*/*z* (thermospray NH_3) MNH_4^+ 439 (20%), M − OEt 371 (20); *m*/*z* (thermospray, NH_3) [Found: M − OEt^+, 376.211. $C_{21}H_{30}NO_5$ requires 376.212 (1.3 ppm error)].

(*E*)-3-[Benzyloxycarbonyl(3-oxopropyl)amino]-2-propylacrylic acid ethyl ester 4

A mixture of the acetal **14** (0.048 g, 0.12 mmol), pyridinium toluene-*p*-sulfonate (0.050 g, 0.20 mmol), water (0.5 cm^3) and acetone (5 cm^3) were stirred at reflux for 3 h under nitrogen. After removal of most of the acetone *in vacuo*, the mixture was diluted with brine (25 cm^3) and 2 M sulfuric acid (2 cm^3) and extracted with EtOAc (2 × 20 cm^3). The combined extracts were washed with 8% $NaHCO_3$ solution (10 cm^3) and brine (15 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the aldehyde **4** as a colourless oil (0.040 g, 100%). A small sample for analysis was purified by flash chromatography on silica gel 9385 eluting with 30:70 ether–hexane; TLC $R_f = 0.24$ (1:1 ether–hexane); δ_H($CDCl_3$, 400 MHz) 9.77 (1 H, t, *J* 1.5, C*H*O), 7.54 (1 H, s, NC*H*), 7.38–7.31 (5 H, m, *Ph*), 5.20 (2 H, s, PhCH_2), 4.20 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 3.90 (2 H, t, *J* 7, NCH_2), 2.79 (2 H, m, CH_2CHO), 2.21 (2 H, m, $CH_2CH_2CH_3$) 1.44 (2 H, m, $CH_2CH_2CH_3$), 1.28 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 0.90 (3 H, t, *J* 7.5, $CH_2CH_2CH_3$); ν_{max}(KBr diffuse reflectance)/cm^{-1} 2975, 1730, 1715 and 1632; *m*/*z* (thermospray, NH_3) Found MH^+: 348.180. $C_{19}H_{26}NO_5 \cdot H^+$ requires 348.181 (2 ppm error).

rel-(2*R*,3*S*)-3-Hydroxy-2-[(1*S*)-1-ethoxycarbonylbutyl]-pyrrolidine-1-carboxylic acid benzyl ester 15β, *rel*-(2*R*,3*S*)-3-hydroxy-2-[(1*R*)-1-ethoxycarbonylbutyl]pyrrolidine-1-carboxylic acid benzyl ester 15α and *rel*-(3*R*,3a*R*,6a*R*)-3-propyl-2-oxohexahydro-2*H*-furo[3,2-*b*]pyrrole-4-carboxylic acid benzyl ester 16

To aldehyde **4** (0.038 g, 0.11 mmol) in dry THF (2 cm^3) was added dropwise over 2 min samarium iodide in THF (0.1 M, 8 cm^3, 0.8 mmol) at 5 °C. After 20 min HMPA (0.05 cm^3) was added and after 90 min TLC showed absence of starting material. The reaction was quenched with brine (100 cm^3), 2 M HCl (5 cm^3) and water (50 cm^3) and extracted with EtOAc (2 × 60 cm^3). The combined extracts were washed with brine ($MgSO_4$). Solvent removal *in vacuo* gave a yellow oil (56 mg); analytical HPLC, column: Inertsil M at 215 nm, eluting at 1.0 cm^3 min^{-1} with 100% "A" and 0% "B" for 2 min, to 100% "B" for 40 min and 100% "B" for 10 min. Solvent "A" = H_2O + 0.1% H_3PO_4 and solvent "B" = 95% MeCN–H_2O + 0.1% H_3PO_4), **15**β (27.58 min), **15**α (27.35 min) and **16** (27.17 min) in a ratio of 3.9:1.1:1.0 plus unidentified material. Flash chromatography on silica gel 9385 eluting with hexane–Et_2O 1:1 then 1:2 afforded the β-propyl *cis*-lactone **16** (4.3 mg, 11%) and a mixture of the β- and α-propyl esters **15** (18.5 mg, 48%).

Data for the β-propyl *cis*-lactone 16. TLC $R_f = 0.61$ (Et_2O); the resonances for the two rotamers are described separately for clarity; δ_H($CDCl_3$, 400 MHz, 30 °C) *rotamer 1*: 7.40–7.30 (5 H, br s, *Ph*), 5.18 (1 H, d, *J* 12, PhC*H*CH), 5.10 (1 H, d, *J* 12, PhHC*H*), 5.04 (1 H, ddd, *J* 5, 5 and 1, NCH_2CH_2CH), 4.24 (1 H, dd, *J* 5 and <2, NC*H*), 3.80 (1 H, m, N*H*CH), 3.41 (1 H, m, NHC*H*), 2.86 (1 H, ddd, *J* 7, 7 and <2, PrC*H*CO), 2.31 (1 H, ddd, *J* 14, 6 and 1, NCH_2HCH), 2.01(1 H, br s, NCH_2-HC*H*), 1.80–1.43 (2 H, m, $CH_2CH_2CH_3$), 1.38–1.25 (2 H, m, $CH_2CH_2CH_3$), 0.82 (3 H, br t, $CH_2CH_2CH_3$); *rotamer 2*: 7.40–7.30 (5 H, s, *Ph*), 5.18 (1 H, d, *J* 12, PhC*H*CH), 5.10 (1 H, d, *J* 12, PhHC*H*), 5.04 (1 H, ddd, *J* 5, 5 and 1, NCH_2CH_2CH), 4.24 (1 H, dd, *J* 5 and <2, NC*H*), 3.89 (1 H, m, N*H*CH), 3.41 (1 H, m, NHC*H*), 2.67 (1 H, ddd, *J* 7, 5 and <2, PrC*H*CO), 2.31 (1 H, ddd, *J* 14, 6 and 1, NCH_2HCH), 2.01 (1 H, br s, NCH_2-HC*H*), 1.80–1.43 (2 H, m, $CH_2CH_2CH_3$), 1.38–1.25 (2 H, m, $CH_2CH_2CH_3$), 0.99 (3 H, br t, $CH_2CH_2CH_3$); ν_{max}(KBr diffuse reflectance)/cm^{-1} 2961, 2940, 2865, 1778, 1704 and 1416; *m*/*z* (thermospray, NH_3) MNH_4^+ at 321 (30%); *m*/*z* (thermospray, NH_3) Found: MH^+: 304.154. $C_{17}H_{22}NO_4$ requires 304.154 (0.2 ppm error).

Data for the propyl ester 15. TLC $R_f = 0.52$ (Et_2O); δ_H($CDCl_3$, 400 MHz, 30 °C) 7.32–7.20 (5 H, m, *Ph*), 5.20–4.98 (2 H, br m, PhCH_2) 4.42–4.24 (1 H, br d), 4.04 (2 H, q, *J* 7), 3.96–3.84 (1 H, br m), 3.74–3.54 (1 H, br m), 3.38–3.24 (1 H, br m), 3.17–2.43 (1 H, br m), 2.07–1.90 (1 H, br m), 1.83–1.74 (1 H, br m), 1.74–1.43 (3 H, br m), 1.38–1.05 (5 H, br m), 0.87–0.66 (3 H, br m); *m*/*z* (thermospray, NH_3) MNH_4^+ at 350 (95%); analytical HPLC (system as described above) **15**β and **15**α co-eluted with material of a different α:β ratio prepared by a different route (unpublished results).

trans-2-(1-Carboxybutyl)-3-hydroxypyrrolidine-1-carboxylic acid benzyl ester 3

To the ester **15** (0.0153 g, 0.04 mmol) in THF (2 cm^3) was added lithium hydroxide monohydrate (0.018 g, 0.4 mmol) in water (0.2 cm^3) and the mixture heated at reflux for 18 h. TLC showed limited reaction. The THF was removed *in vacuo* and replaced with EtOH (2 cm^3) and water (1 cm^3). Further lithium hydroxide monohydrate (0.010 g) was added. After heating at reflux for 6 h, TLC showed absence of starting material. The ethanol was then removed *in vacuo*. The residue was diluted with 1 M hydrochloric acid (10 cm^3) and extracted with EtOAc (3 × 5 cm^3). The combined extracts were washed with brine (5 cm^3) and dried ($MgSO_4$). Solvent removal *in vacuo* afforded a colourless oil (0.015 g, >100%); TLC $R_f = 0.29$ (streak) (Et_2O); δ_H($CDCl_3$, 250 MHz) 7.40–7.22 (5 H, br s, *Ph*), 5.82–5.30 (1 H, br s), 5.30–4.97 (2 H, br m), 4.42–4.25 (1 H, br m), 4.18–3.94 (1H, br m), 3.81–3.60 (1H, br m), 3.52–3.30 (1 H, br m), 3.07–2.84 (0.3 H, br m), 2.59–2.39 (0.7 H, br m), 2.15–1.82 (2 H, br m), 1.80–1.08 (5 H, br m), 0.97–0.72 (3 H, br m); *m*/*z* (thermospray, NH_3) MH^+ at 322 (100%).

rel-(3*R*,3a*R*,6a*S*)-3-Propyl-2-oxohexahydro-2*H*-furo[3,2-*b*]-pyrrole-4-carboxylic acid benzyl ester 2β and *rel*-(3*S*,3a*R*,6a*S*)-3-propyl-2-oxohexahydro-2*H*-furo[3,2-*b*]pyrrole-4-carboxylic acid benzyl ester 2α

The hydroxy acid **3** (0.015 g, 0.047 mmol), triethylamine (10 μl, 0.071 mmol), 2,4,6-trichlorobenzoyl chloride (10 μl, 0.061 mmol) and DCM (5 cm^3) were stirred at room temperature in a stoppered flask. After 1 h, TLC showed absence of starting material. The reaction mixture was then diluted with PhMe (30 cm^3) and added over 1 h to a refluxing solution of DMAP (0.034 g, 0.28 mmol) in PhMe (25 cm^3). After refluxing for a further 2.5 h, the solvent was removed *in vacuo* and the residue treated with 1 M HCl (5 cm^3). The mixture was extracted with EtOAc (3 × 5 cm^3). The combined extracts were washed with brine (2 × 5 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to

give the crude product (0.0243 g). This material was purified by preparative TLC on silca eluting three times with 62.5:62.5:1 hexane–EtOAc–AcOH to afford the desired product as a colourless oil (0.005 g, 35%); TLC $R_f = 0.24$ (1:1 hexane–Et_2O + 2 drops AcOH); **2**β and **2**α were not readily separable by flash chromatography but their δ_H data is described separately for clarity (the ratio by integration is β:α = 3:1); **2**β: δ_H (d_6-DMSO, 750 MHz, 75 °C) 7.39–7.32 (5H, m, *Ph*), 5.10 (1H, d, *J* 12.5, Ph*H*CH), 5.08 (1H, d, *J* 12.5, PhHC*H*), 4.02 (1H, ddd, *J* 12, 10 and 5.5, NCH_2CH_2CH), 3.83 (1H, dd, *J* 11 and 10, N*H*CH), 3.63 (1H, m, NHC*H*), 3.33 (1H, dd, *J* 12 and 10, NC*H*), 2.95 (1H, ddd, *J* 12, 7 and 3, PrC*H*CO), 2.27 (1H, m, NCH_2HCH), 2.01 (1H, m, NCH_2HCH), 1.84 (1H, br m, $HCHCH_2CH_3$), 1.71 (1H, br m, $HCHCH_2CH_3$), 1.46 (1H, br m, CH_2HCHCH_3), 1.18 (1H, br m, CH_2HCHCH_3), 0.76 (3H, br t, CH_3); **2**α: δ_H (d_6-DMSO, 750 MHz, 75 °C) 7.39–7.32 (5H, m, *Ph*), 5.14 (1H, d, *J* 12.5, Ph*H*CH), 5.04 (1H, d, *J* 12.5, PhHC*H*), 4.31 (1H, ddd, *J* 11, 10.5 and 5.5, NCH_2CH_2CH), 3.83 (1H, dd, *J* 11 and 10, N*H*CH), 3.66 (1H, dd, 10.5 and 7, NC*H*), 3.57 (1H, m, NHC*H*), 2.84 (1H, br m, PrC*H*CO), 2.27 (1H, m, NCH_2HCH), 2.04 (1H, m, NCH_2HCH), 1.52 (2H, br m, $CH_2CH_2CH_3$), 1.41 (1H, br m, CH_2HCHCH_3), 1.28 (1H, br m, CH_2HCHCH_3), 0.81 (3H, br t, CH_3); comparison of this spectrum with that of a 2:1 α:β propyl sample prepared by a different route (unpublished results) gives good agreement; comparison with the α- and β-allyl-*trans*-lactone analogues[6] (which are separable) gives excellent agreement of the relevant coupling constants; ν_{max}(KBr diffuse reflectance)/cm^{-1} 2960, 2930, 2865, 1796, 1715, 1454, 1433, 1390, 1356, 1324, 1109 and 1026; *m*/*z* (thermospray, NH_3), MH^+ at 304 (100%); *m*/*z* (electrospray) Found M^+: 303.147. $C_{17}H_{21}NO_4$ requires M^+: 303.147; analytical HPLC (system as described above) **3**α (28.83 min), **3**β (29.17 min) in a ratio of 1:3.1; this material co-eluted with a 2:1 α:β sample prepared by a different route (unpublished results).

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