Total synthesis of (−)-slaframine from (2*R*,3*S*)-3-hydroxyproline

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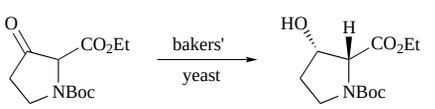
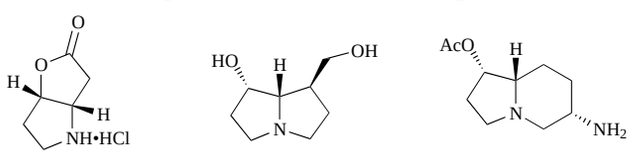
The yeast reduction products (2*R*,3*S*)-*N*-Boc-3-hydroxyproline esters 23 have been converted into the 3-methoxymethoxyprolinal 26 which undergoes an efficient Julia olefination with the L-serine-derived amino sulfone 29. Selective reduction of the resulting alkene 31 using diimide and cyclization leads to *N*-(benzyloxycarbonyl)slaframine 33c and thence to natural (−)-slaframine 5 and its more stable, crystalline *N*-acetyl derivative 34.

Despite the enormous advances that have been made during the past few years in the area of asymmetric synthesis, the chiral pool of reasonably readily available starting materials remains relatively small. With this in mind, we recently found that the easily prepared keto proline derivative **1**[1] could be reduced by



1 **2**



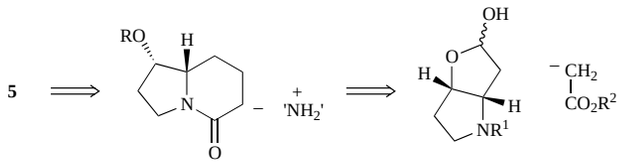
3 **4** **5**

fermenting Bakers' yeast to the corresponding (2*R*,3*S*)-hydroxyproline **2** with an enantiomeric excess of 80%.[2] Subsequent to this report, the method has been improved in terms of both chemical and optical yield either by using a different yeast species[3] or immobilized Bakers' yeast.[4] Illustrative of the synthetic utility of the 3-hydroxyproline **2** are its conversions into the (−)-Geissman–Waiss lactone **3**,[5] useful as a precursor to pyrrolizidines such as turneforcidine **4**,[6] and indolizidines such as castanospermine[3] and (1*S*,8a*S*)-1-hydroxyindolizidine.[4] We were attracted to the possibility of further demonstrating the utility of the hydroxyproline **2** in a synthesis of (−)-slaframine **5**, particularly because this potential precursor already possesses two of the three asymmetric centres present in this natural product. Herein, we report in full on the eventually successful outcome of this idea.[7]

(−)-Slaframine **5** is a unique aminoindolizidine produced by a mould, *Rhizoctonia leguminicola*, which usually infests members of the *Leguminosae* family, especially clover (*Trifolium*) when it is commonly known as 'black patch'.[8] This unstable metabolite was first identified in 1965[9] and originally assigned a 1-acetoxy-8-amino formulation,[10] which was subsequently revised to the alternative 6-amino structure **5**.[11] The compound was identified during a search for toxic materials present in cattle fodder and was traced to *Rhizoctonia* fungal infestations of the clover, rather than being a toxin present in the clover itself. The initial symptom of slaframine poisoning, excessive and uncontrolled salivation,[8] is the origin of its trivial name (Icel. *slafra*, to slaver);[10] continued exposure to the compound can cause extensive liver damage and eventual death. The mode of action is not known with certainty; it appears to hypersensitize smooth muscle to the action of acetylcholine, an effect which can be reversed by atropine.[8] It also appears that slaframine may not be the actual toxic principal but rather a 'pro-toxin'; as yet, the exact nature of the true toxic metabolite is unknown.[12] Slaframine can also stimulate pancreatic secretion and it has been proposed as a possible drug candidate for the alleviation of the symptoms of cystic fibrosis sufferers.[13]

The first synthesis of (±)-slaframine established the overall structure and featured pyridine hydrogenation and a Dieckmann cyclization to form the pyrrolidine ring.[14] An attempted asymmetric synthesis from L-glutamic acid foundered, in terms of providing optically active material, when racemization occurred during a similar cyclization step.[15] Other approaches to the racemic compound have featured an intramolecular imino-Diels–Alder cyclization,[16] pyridine reduction coupled with intramolecular amide acylation,[17] anodic oxidation to obtain a suitable aminopipecolinic acid ester,[18] an intramolecular Wittig olefination using a salt derived from thalidomide[19] and use of the selective chemistry of vicinal tricarbonyls,[20] a method which also provides 6-*epi*-slaframine.[21] The first asymmetric synthesis was based around cyclization of an amino epoxide derived from L-glutamic acid and required separation of intermediate epoxide stereoisomers.[22] Later approaches leading to an optically active product utilized azidoalkene cyclization,[23] homologation of a 3-hydroxyproline derivative and cyclization by attack of a free amino group onto an oxazolidinone,[24] a radical cyclization method,[25] conjugate addition of a chiral α-sulfinyl ketimine anion to an α-amidoacrylate[26] and, most recently, an intramolecular aldol cyclization using an *N*-substituted-3-oxopyrrolidine.[27]

Our first idea was to introduce the 6-amino group at a late stage by electrophilic amination of the enolate **6** (Scheme 1), for



6 **7** **8** **9**

Scheme 1

which a number of synthetic equivalents of the amine cation **7** are available. Molecular models indicated that there should be a preference for approach of the electrophile from the desired α-face. The required lactam would then be available by a two carbon homologation of the lactol **8**, derived by reduction of the Geissman–Waiss lactone **3**, using an acetic acid enolate

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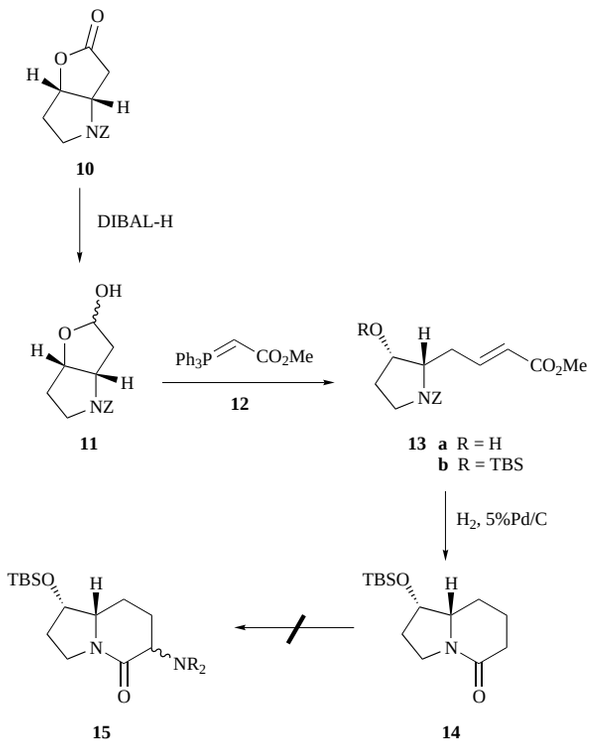
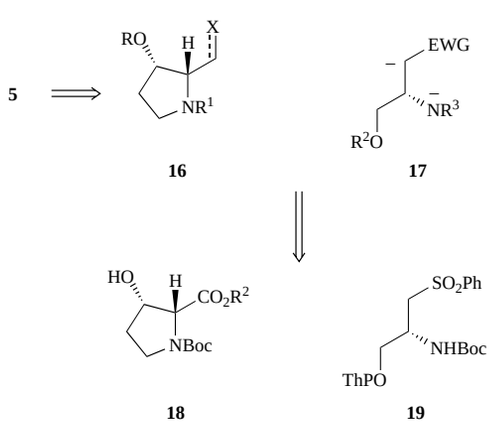
equivalent **9**; deprotection at nitrogen and a subsequent facile cyclization should lead to the lactam precursor of enolate **6**. For convenience, we first examined this idea using the racemic lactone **10**.[5] Reduction using diisobutylaluminium hydride (DIBAL-H) proceeded uneventfully to give the expected lactol **11** which subsequently underwent a smooth Wittig coupling with the phosphorane **12** to provide an excellent yield of the homologated compound **13a** (Scheme 2). Protection of the free



Scheme 2

hydroxy group as the *tert*-butyldimethylsilyl (TBS) ether **13b** followed by hydrogenation resulted in saturation of the alkene, removal of the *N*-benzyloxycarbonyl (Z) and cyclization to the lactam **14**. However, initial attempts to aminate the derived enolate (*cf.* **6**) using azodicarboxylates[28] were uniformly unsuccessful. We then became aware that Cha and his colleagues had attempted a similar tactic and had experienced the same lack of success.[23] We therefore abandoned this approach in favour of a more direct homologation of the initial yeast reduction product **2**.

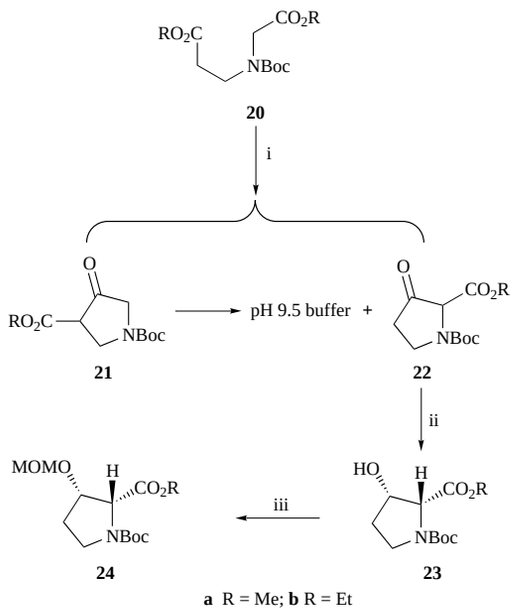
The plan is outlined in Scheme 3. If the hydroxyproline **18**



Scheme 3

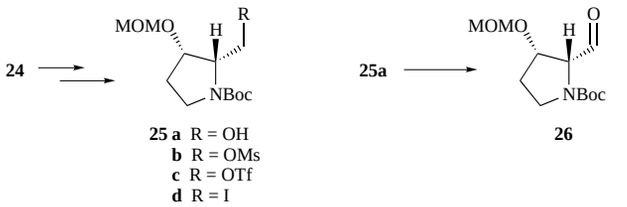
were to be suitably protected, reduced and derivatized, then the electrophilic intermediate **16** could be used to alkylate a dianion **17** which would introduce all of the carbons and other functionality necessary to complete a synthesis of slaframine **5**. An alternative electrophile would be the corresponding aldehyde (**16**; X = O), although use of this would add an extra degree of unsaturation which would probably have to be subsequently reduced. An advantage of using a three carbon nucleophile based on structure **17** is that the amino function will also be ionized, thus suppressing the likelihood of it acting as a β-leaving group, upon carbanion generation. The dianion obtainable from such a compound (**19**), derived from L-serine, has previously been used to prepare several non-natural α-amino acids;[29] we therefore initiated the plan shown in Scheme 3 by preparing potentially suitable electrophiles from the initial yeast reduction product **2**.[2–4]

The method of Rapoport[1] was used to prepare the required keto prolines **22** (Scheme 4). Thus, the protected amino diesters



Scheme 4 *Reagents and conditions:* i, KOBu^t, toluene, 0 °C, 0.5 h; ii, Bakers' yeast (dried or immobilized), sugar, water, 34 °C, 24–36 h; iii, MOMCl, Pr^i_2NEt, CH_2Cl_2, 20 °C, 15 h

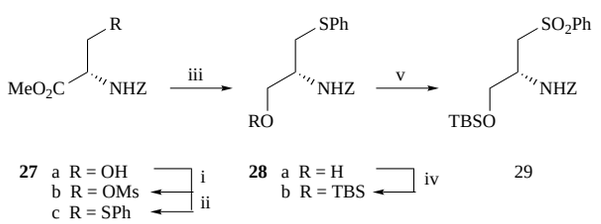
20 were obtained from the corresponding glycinate hydrochloride and 3-bromopropanoate followed by *N*-protection using di-*tert*-butyl dicarbonate (Boc anhydride).[30] Subsequent Dieckmann cyclization by brief exposure to potassium *tert*-butoxide in toluene gave a mixture of keto esters (**21** and **22**), enriched in the required kinetic products **22**; the ethyl esters **20b** gave a slightly higher yield. Longer reaction times or use of a protic solvent gave more or very largely the 4-oxo-3-carboxylates **21**, which fortunately were easily separated by extraction into pH 9.5 phosphate buffer.[1] Subsequent yeast reduction then gave the hydroxyprolines **23** as single diastereoisomers, as previously reported.[2] In our hands, both the direct method[31] and use of yeast immobilized on calcium alginate[4,32] gave essentially the same chemical and optical yields to those originally reported,[2] although the latter method involved a much easier and more rapid work-up as the immobilized yeast was much more amenable to filtration. There appeared to be little difference between the methyl and ethyl esters in this reduction step. The hydroxy group was then smoothly protected as the methoxymethyl (MOM) ether (**24**)[33] and the esters reduced to the corresponding alcohol **25a**, for which DIBAL-H in toluene, in the presence of boron trifluoride–diethyl ether,[34] proved to be the best reagent of those examined which included lithium aluminium hydride, Red-Al and sodium borohydride in methanol (Scheme 5). A number of electrophilic derivatives were then prepared by standard methods: the methanesulfonate **25b** proved to be rather unstable, the trifluoromethanesulfonate **25c**[35] even more so, to the extent that it could only be isolated in



Scheme 5

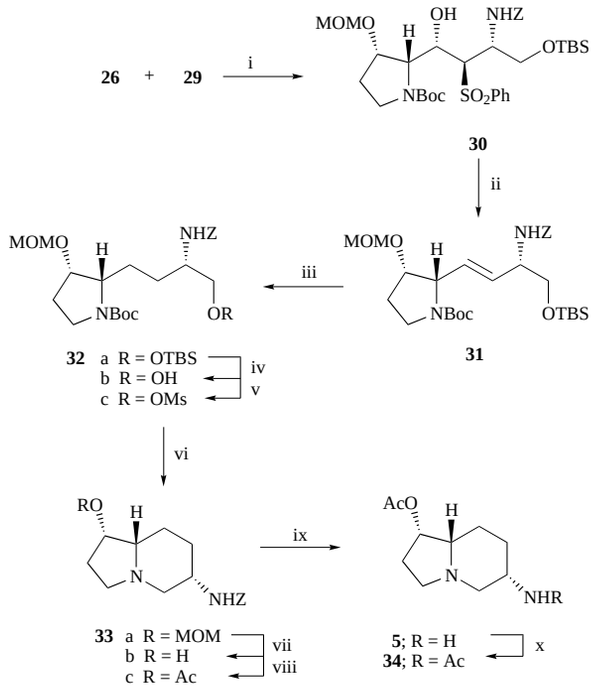
poor yield and then was too unstable to permit purification. Similarly, the bromide was not isolated after treatment of the alcohol **25a** with carbon tetrabromide–triphenylphosphine[36] while the corresponding iodide **25d** was obtained as an unstable oil in moderate yield from the alcohol **25a** using the I_2–Ph_3P–imidazole method[37] but not by Finkelstein exchange starting with the methanesulfonate **25b**. The corresponding aldehyde **26** was obtained by oxidation of **25a** using either the perruthenate (TPAP) method[38] or sulfur trioxide–pyridine and dimethyl sulfoxide in the presence of triethylamine,[39] although, in contrast, Swern oxidation gave low returns. Both methods gave good yields and, although the work-up was not quite so simple, we routinely used the latter method due to the relative instability and cost of the TPAP reagent.

We chose to use the sulfone **29**, modified with respect to the originally reported reagent **19**, so that the two protecting groups therein were orthogonal with respect to those already present in the electrophilic candidates **25** and **26**. This proved to be straightforward and efficient to prepare from methyl *N*-(benzyloxycarbonyl)-L-serinate **27a**[40] by sequential methanesulfonylation and displacement by thiophenolate (Scheme 6). The



Scheme 6 *Reagents and conditions:* i, MsCl, DMAP, CH_2Cl_2, pyridine, −18 °C, 16 h; ii, NaSPh, DMF, 20 °C, 16 h; iii, $NaBH_4$, MeOH, 20 °C, 5 h; iv, TBSCl, DMAP, Et_3N, CH_2Cl_2, 20 °C, 16 h; v, MCPBA, CH_2Cl_2, 20 °C, 2.5 h (Ms = $MeSO_2$)

resulting sulfide **27c** was reduced to the alcohol **28a**, using an excess of sodium borohydride in methanol,[41] which was then protected as its *tert*-butyldimethylsilyl (TBS) ether **28b** and oxidized to the key sulfone **29**. That this could be regioselectively metallated as desired was ascertained by treatment of a dry-ice cooled solution in THF with 2.1 equiv. of butyllithium followed by deuterium oxide; deuterium incorporation was observed only at nitrogen and α- to the sulfone function. However, as suggested by their relative instabilities, all attempts to alkylate the dianion derived from sulfone **29** by the electrophiles **25a–c** gave no more than traces of the desired homologue. We therefore turned our attention to coupling aldehyde **26** and sulfone **29** using a Julia olefination reaction[42] and were delighted to find that the required hydroxy sulfone **30** could be routinely obtained in around 60% isolated yield. After purification, the compound was obtained as essentially a single diastereoisomer with, we assume, the *anti* stereochemistry shown,[43] although this aspect was not rigorously proven. The second step of the Julia olefination typically involves conversion of the hydroxy function into the corresponding acetate or benzoate,[42] prior to reductive removal of the sulfone group,[44] although this is not always necessary.[42,45] This proved to be so in the present case: direct treatment of the hydroxy sulfone **30** with buffered 6% sodium–mercury amalgam, using the optimized procedure due to the Trost group,[44] gave an almost quantitative return of the



Scheme 7 *Reagents and conditions:* i, BuLi, THF, −78–0 °C, add **26**, −78–0 °C, 4 h; ii, 6% Na–Hg, KH_2PO_4, MeOH, 0–20 °C, 18 h; iii, 2,4,6-triisopropylbenzenesulfonyl hydrazide, Et_3N, CH_2Cl_2, 20 °C, 48 h; iv, TBAF, THF, 0–20 °C, 2 h; v, MsCl, Et_3N, DMAP, CH_2Cl_2, −18 °C, 16 h; vi, TFA, CH_2Cl_2, 20 °C, 0.5 h then 2 M aq. NaOH; vii, HCl, MeOH, 65 °C, 20 min; viii, Ac_2O, Et_3N, DMAP, CH_2Cl_2, 20 °C, 1 h; ix, H_2, 5% Pd–C, MeOH, AcOH, (9:1), 20 °C, 16 h; x, as viii for 2 h

alkene **31**. Much poorer yields of the esters derived from the hydroxy sulfone **30** were obtained if the initial condensation was worked up with an acid chloride.

All attempts to selectively hydrogenate the alkene **31** using a range of transition metal catalysts, hydrogen sources and solvents resulted in hydrogenolysis of the *N*-benzyloxycarbonyl function along with the desired saturation of the alkene link. Fortunately, the required selectivity was achieved using diimide, generated from 2,4,6-triisopropylbenzenesulfonyl hydrazide.[46] Although the reaction was rather sluggish, an excellent yield of the alkane **32a** was eventually realized, setting the stage for completion of the synthesis. Removal of the silicon protecting group proceeded smoothly using tetrabutylammonium fluoride (TBAF) and the resulting alcohol **32b** was then converted into the corresponding methanesulfonate **32c**. Acid-induced removal of the *N*-Boc function using trifluoroacetic acid (TFA) gave an intermediate salt which underwent rapid cyclization upon basification with 2 M aqueous sodium hydroxide to give the required indolizidine ring system **33a**. This compound, along with subsequent derivatives, proved to be rather air-sensitive and wherever possible, was handled and stored under an inert nitrogen atmosphere. The MOM ether was next hydrolysed by brief exposure to hot methanolic hydrogen chloride and the resulting alcohol **33b**[14,16] acetylated to provide *N*-(benzyloxycarbonyl)slaframine **33c**. Finally, hydrogenolysis provided a sample of the target, (−)-slaframine **5**, which displayed identical optical rotation, chromatographic behaviour and ^{1}H NMR spectral data to those previously reported.[22,23,25] The instability of the natural material led us to convert the sample into *N*-acetylslaframine **34** which also displayed an identical melting point,[11,22,25] ^{13}C NMR spectrum[22] and optical rotation[11,22,23,25] with those previously reported. As noted by Pearson,[22] there are some variations in the reported optical rotations of this derivative {*e.g.* $[\alpha]_D^{25}$ −11.2 (*c* 1.45, EtOH);[22] $[\alpha]_D^{25}$ −18.8 (*c* 0.4, EtOH);[23] $[\alpha]_D^{25}$ −15.9 (*c* 5, EtOH)[11]}, although his material, which displayed the lowest rotation, was optically pure according to independent Mosher's ester analysis.[22] We

assume that the minor amount of the (1*R*,8a*R*) enantiomer of slaframine which should be present in our sample, arising from the optically imperfect yeast reduction of the keto esters **22**, had been removed during chromatography, after the third asymmetric centre was introduced during the Julia olefination step.

This relatively brief approach to (−)-slaframine **5** should be applicable to the elaboration of other indolizidines, both natural and non-natural, and demonstrates that protected 3-hydroxyprolinals (*e.g.* **26**) can be successfully homologated using the Julia olefination reaction without significant racemization or β-elimination, a problem which has been encountered in reactions between aldehyde **26** and other nucleophilic species such as vinyllithiums.

Experimental

General

Infrared spectra were obtained using a Pye-Unicam SP3-100 or a Perkin-Elmer 1600 series 1 FTIR spectrometer using liquid films on sodium chloride plates unless otherwise stated. ^{1}H NMR spectra were obtained using a Perkin-Elmer R32a instrument operating at 90 MHz, a Bruker WM250 instrument operating at 250 MHz, a JEOL EX 270 spectrometer operating at 270 MHz or a Bruker AM-400 instrument operating at 400 MHz. The JEOL EX 270 spectrometer operating at 67.8 MHz or the Bruker AM-400 instrument operating at 100.1 MHz was used to obtain ^{13}C NMR spectra. All spectra were recorded using dilute solutions in deuteriochloroform, with tetramethylsilane as the internal standard, and assignments were made on the basis of COSY and ^{1}H–^{13}C correlation spectra. *J* Values are given in Hz. Mass spectra were obtained in the EI (70 eV) or fast atom bombardment modes (EI and FAB, respectively) using either an AEI MS 902 or a VG 7070E instrument, with the exception of high resolution FAB spectra, which were obtained using a VG Autospec instrument at the EPSRC MS Service, Swansea University. Optical rotations ($[a]_D$) were determined using an Optical Activity AA-10 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.

Solvents were purified and dried when necessary using standard procedures.[47] Unless stated otherwise, all reactions were performed under an atmosphere of dry nitrogen and all organic solutions from aqueous work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. CC refers to column chromatography using silica gel [SORBSIL C60-H (40–60 mm)] and the eluents specified. Petrol refers to light petroleum with bp 40–60 °C and ether refers to diethyl ether.

Methyl 1-(*tert*-butoxycarbonyl)-3-oxopyrrolidine-2-carboxylate 22a and methyl 1-(*tert*-butoxycarbonyl)-4-oxopyrrolidine-3-carboxylate 21a

Using the method of Rapoport and co-workers[1] on a 70 mmol scale, diester **20a**[30] was converted into a mixture of the two β-keto esters **21a** and **22a** (16.97 g, 98%) which were separated by extraction into pH 9.5 buffer.[1] Final purification by CC [EtOAc–CH_2Cl_2 (1:1)] gave the keto ester **22a** (10.32 g, 60%)[1] as a colourless oil; R_F 0.77; ν_{max}/cm^{-1} 1776, 1745 and 1709; δ_H(250 MHz; highly rotameric at 297 K) 1.43 (~3.5H, s, CMe_3), 1.49 (~5.5H, s, CMe_3), 2.70 (2H, app. t, *J* 8.1, 4-CH_2), 3.80 (3H, s, OMe), 3.84–3.89 (2H, m, 5-CH_2), 4.50 (~0.7H, m, 2-H) and 4.58 (~0.3 H, m, 2-H); δ_C(67.8 MHz) 28.0 and 28.2 (3 × Me), 36.3 and 37.0 (4-CH_2), 41.5 and 42.1 (5-CH_2), 52.3 (OMe), 65.2 and 65.6 (2-CH), 80.7 and 81.0 (CMe_3), 153.7 and 153.9 (NCO), 166.7 and 167.0 (CO_2) and 204.0 and 204.5 (3-CO); *m/z* (EI) 243 (M^+, 0.3%), 187 (14), 142 (21), 84 (62) and 57 (100).

The unwanted 4-oxo-3-carboxylate **21a** could be recovered from the aqueous fractions by acidification and extraction using ether or ethyl acetate.[1]

Ethyl 1-(*tert*-butoxycarbonyl)-3-oxopyrrolidine-2-carboxylate 22b

Using the foregoing method, the *N*-Boc diethyl diester **20b** (17.5 g, 57 mmol) gave the keto ester **22b** (11.12 g, 76%)[1] as a colourless oil; R_F 0.84; ν_{max}/cm^{-1} 1774, 1742 and 1711; δ_H(270 MHz; highly rotameric at 297 K) 1.22 (3H, t, *J* 6.9, OCH_2CH_3), 1.35 (~3H, s, CMe_3), 1.41 (~6H, s, CMe_3), 2.61 (2H, app. t, *J* 7.2, 4-CH_2), 3.74–3.93 (2H, m, 5-CH_2), 4.11–4.17 (2H, m, OCH_2CH_3), 4.39 (~0.7H, m, 2-H) and 4.45 (~0.3H, m, 2-H); δ_C(67.8 MHz) 13.9 and 14.0 (Me), 28.0 and 28.2 (3 × Me), 36.3 and 36.9 (4-CH_2), 41.5 and 42.1 (5-CH_2), 62.0 (OCH_2), 65.3 and 65.6 (2-CH), 80.6 and 80.9 (CMe_3), ~153 (NCO), ~166 (CO_2) and 204.6 (3-CO); *m/z* (FAB) 258 (M^+ + H, 18%), 202 (89), 184 (16), 158 (38), 130 (25), 84 (25) and 57 (100) (Found: C, 55.5; H, 7.6; N, 5.3. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.4%).

Methyl (2*R*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylate 23a

Direct yeast method. To a gently stirred mixture of the keto ester **22a** (4.0 g, 16.5 mmol), commercial sugar (80 g) in tap water (400 ml) was added freshly purchased dried Bakers' yeast [Sainsbury's 'Easy Bake Dried Bakers' Yeast' (red box), 48 g].[31] The resulting suspension was stirred at 34 °C for 24 h then filtered (water pump suction; filtration can be rather slow) and the semi-solid residue washed repeatedly with small aliquots of water. The combined filtrates were filtered through Kieselguhr (2 ×) and the resulting clear, yellow filtrate extracted with dichloromethane (5 × 100 ml). (Any emulsions were broken up by adding a little methanol followed by gentle swirling or by filtration through Kieselguhr.) The combined extracts were dried and evaporated to leave a pale yellow oil (~2.65 g); CC [EtOAc–CH_2Cl_2 (1:1)] gave the *hydroxy ester* **23a** (2.48 g, 61%) as a colourless oil; R_F 0.36; $[a]_D^{25}$ +29.6 (*c*, 1.0; CH_2Cl_2); ν_{max}/cm^{-1} 3442, 1746 and 1682; δ_H(400 MHz; rotameric at 297 K) 1.41 (~5.5H, s, CMe_3), 1.46 (~3.5H, s, CMe_3), 1.98–2.10 (2H, m, 4-CH_2), 2.90 (1H, br s, OH; disappears on D_2O shake), 3.41–3.49 (1H, m, 5-H_a), 3.56–3.68 (1H, m, 5-H_b), 3.74 (3H, s, OMe), 4.35 (~0.6H, d, *J* 6.7, 2-H), 4.41 (~0.4H, d, *J* 6.7, 2-H) and 4.54–4.63 (1H, m, 3-H); δ_H(400 MHz; 333 K) 1.43 (9H, s, CMe_3), 1.97–2.04 (2H, m, 4-CH_2), 3.43–3.50 (1H, m, 5-H_a), 3.60–3.63 (1H, m, 5-H_b), 3.75 (3H, s, OMe), 4.36 (1H, d, *J* 6.3, 2-H) and 4.55–4.60 (1H, m, 3-H); δ_C(100.1 MHz; 297 K) 28.3 and 28.4 (Me_3), 32.2 and 32.7 (4-CH_2), 43.9 and 44.3 (5-CH_2), 52.0 and 52.2 (OMe), 63.4 and 64.1 (2-CH), 71.4 and 72.3 (3-CH), 80.3 (CMe_3), 153.9 and 154.4 (NCO) and 171.0 (CO); δ_C(400 MHz; 333 K) 28.4 and 28.6 (Me_3), 32.6 (4-CH_2), 44.1 (5-CH_2), 51.9 (OMe), 64.0 (2-CH), 72.4 (3-CH), 80.3 (CMe_3), 153.6 (NCO) and 170.9 (CO); *m/z* (FAB) 246 (M^+ + H, 18%), 190 (7), 172 (9), 146 (100), 130 (19), 86 (37), 68 (7) and 57 (93) (Found: C, 54.0; H, 8.1; N, 5.5. $C_{11}H_{19}NO_5$ requires C, 53.9; H, 7.8; N, 5.7%).

Ethyl (2*R*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylate 23b

Immobilized yeast method. Sodium alginate (2 g) was added portionwise to rapidly stirred water (400 ml) maintained at 50 °C to give a homogeneous gel. After the addition, the gel was cooled to ambient temperature. During this time, dried Bakers' yeast (24 g) was suspended in water (100 ml) at ambient temperature.[32] The mixture was stirred to give a homogeneous slurry to which aqueous calcium chloride (6% w/v, 100 ml) was added. After 2 min stirring, the resulting slurry was poured, in a thin stream, into the rapidly stirred sodium alginate gel causing the formation of globules. These were filtered off and washed with water until the washings showed no turbidity and finally gave no precipitate when treated with aqueous acid [5 g of oxalic acid dihydrate in water (100 ml)] and drained of excess water.

The keto ester **22b** (2.0 g, 6.6 mmol) and commercial sugar were added to tap water (100 ml) and the mixture stirred at

ambient temperature until the sugar dissolved. All of the immobilized yeast prepared as above was then added in one portion and the whole gently stirred at 34 °C for 36 h. Work-up as above, but with much more rapid filtration and washing steps, gave the hydroxy ester **23b** (1.27 g, 64%) as a colourless oil; R_F 0.42; $[\alpha]_D^{25}$ +19.4 (*c*, 1.5; CH_2Cl_2) {lit.,[2] $[\alpha]_D^{25}$ +18.2 (*c*, 1.45; CH_2Cl_2)}; ν_{max}/cm^{-1} 3443, 1741 and 1682; δ_H(270 MHz; rotameric at 297 K) 1.22 (3H, t, *J* 6.7, OCH_2CH_3), 1.34 (~3.5H, s, CMe_3), 1.38 (~5.5H, s, CMe_3), 1.94–1.97 (2H, m, 4-CH_2), 2.75 (1H, br s, OH; disappears on D_2O shake), 3.36–3.45 (1H, m, 5-H_a), 3.53–3.60 (1H, m, 5-H_b), 4.12–4.16 (2H, m, OCH_2CH_3), 4.24 (~0.6H, d, *J* 6.9, 2-H), 4.30 (~0.4H, d, *J* 6.9, 2-H) and 4.51–4.54 (1H, m, 3-H); δ_C(67.8 MHz; 297 K) 13.0 and 14.2 (Me), 28.1 and 28.3 (Me_3), 31.9 and 32.5 (4-CH_2), 43.7 and 44.1 (5-CH_2), 60.9 and 61.0 (OCH_2), 63.3 and 63.8 (2-CH), 71.2 and 72.0 (3-CH), 79.7 and 80.0 (CMe_3), 153.8 and 154.2 (NCO) and 170.3 and 170.5 (CO); *m/z* (FAB) 260 (M^+ + H, 30%), 204 (100), 186 (23), 130 (37), 86 (59), 68 (21) and 57 (99) (Found: C, 55.7; H, 8.6; N, 5.4. $C_{12}H_{21}NO_5$ requires C, 55.6; H, 8.2; N, 5.4%).

Methyl (2*R*,3*S*)-1-(*tert*-butoxycarbonyl)-3-(methoxymethoxy)-pyrrolidine-2-carboxylate 24a

To an ice-cold solution of the hydroxy ester **23a** (2.24 g, 9.14 mmol) in dry dichloromethane (30 ml) was added *N*,*N*-diisopropylethylamine (4.0 ml, 22.85 mmol). The resulting solution was stirred for 5 min before the dropwise addition of chloromethyl methyl ether (3.5 ml, 45.7 mmol). The resulting solution was stirred without further cooling for 15 h then diluted with dichloromethane (100 ml). The resulting solution was washed with saturated aqueous sodium carbonate (50 ml), water (2 × 30 ml) and brine (30 ml), then dried and evaporated. The residue was purified by CC [EtOAc–CH_2Cl_2 (1:4)] to give the *methoxymethyl ether* **24a** (2.43 g, 92%) as a colourless oil; R_F 0.57; $[\alpha]_D^{25}$ +5.41 (*c*, 2.2; MeOH); ν_{max}/cm^{-1} 1748 and 1699; δ_H(250 MHz; rotameric at 297 K) 1.41 (~5.5H, s, CMe_3), 1.47 (~3.5H, s, CMe_3), 2.00–2.18 (2H, m, 4-CH_2), 3.34 (3H, s, CH_2OMe), 3.38–3.49 (1H, m, 5-H_a), 3.55–3.69 (1H, m, 5-H_b), 3.74 (3H, s, OMe), 4.48–4.55 (2H, m, 2- and 3-H) and 4.58–4.70 (2H, m, CH_2OMe); δ_C(100.1 MHz; 297 K) 28.1 and 28.2 (Me_3), 29.6 and 30.2 (4-CH_2), 43.5 and 44.0 (5-CH_2), 51.6 (OMe), 55.4 (OMe), 61.5 and 62.1 (2-CH), 75.3 and 76.2 (3-CH), 79.4 and 79.5 (CMe_3), 94.9 and 95.3 (OCH_2O), 153.5 and 154.0 (NCO) and 169.6 and 170.2 (CO); *m/z* (FAB) 290 (M^+ + H, 15%), 234 (45), 202 (24), 190 (39), 174 (18), 158 (38), 130 (17), 128 (18) and 57 (100) (Found: C, 54.1; H, 8.2; N, 4.8. $C_{13}H_{23}NO_6$ requires C, 54.0; H, 8.0; N, 4.8%).

Ethyl (2*R*,3*S*)-1-(*tert*-butoxycarbonyl)-3-(methoxymethoxy)-pyrrolidine-2-carboxylate 24b

By the foregoing method, the hydroxy ester **23b** (1.92 g, 7.4 mmol) was converted into the corresponding *methoxymethyl ether* **24b** (2.13 g, 95%), a colourless oil which showed R_F 0.54; $[\alpha]_D^{25}$ +7.26 (*c*, 0.83; MeOH); ν_{max}/cm^{-1} 1743 and 1702; δ_H(270 MHz; rotameric at 297 K) 1.31 (3H, t, *J* 7.3, OCH_2CH_3), 1.44 (~2H, s, CMe_3), 1.49 (~7H, s, CMe_3), 2.08–2.18 (2H, m, 4-CH_2), 3.38 (3H, s, CH_2OCH_3), 3.40–3.60 (2H, m, 5-CH_2), 3.64–3.78 (1H, m, 2-H), 4.20–4.41 (2H, m, OCH_2CH_3), 4.44–4.57 (1H, m, 3-H) and 4.62–4.72 (2H, m, OCH_2O); δ_C(67.8 MHz; 297 K) 14.0 and 14.2 (Me), 28.1 and 28.3 (Me_3), 29.6 and 30.3 (4-CH_2), 43.5 and 44.0 (5-CH_2), 55.3 and 55.5 (OMe), 60.6 and 60.7 (OCH_2), 61.5 and 62.0 (2-CH), 75.4 and 76.2 (3-CH), 79.8 and 79.9 (CMe_3), 95.2 and 95.4 (OCH_2O), 153.6 and 154.2 (NCO) and 169.6 and 169.8 (CO); *m/z* (FAB) 304 (M^+ + H, 22%), 248 (63), 230 (11), 216 (48), 204 (79), 172 (66), 142 (25), 68 (33) and 57 (100) (Found: C, 55.2; H, 8.6; N, 4.5. $C_{14}H_{25}NO_6$ requires C, 55.4; H, 8.3; N, 4.6%).

(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-(methoxymethoxy)-pyrrolidine-2-methanol 25a

From the methyl ester 24a. To a stirred solution of the methyl ester **24a** (0.41 g, 1.42 mmol) and boron trifluoride–diethyl ether (0.06 ml, 0.5 mmol) in dry toluene (5 ml) maintained at −78 °C was added diisobutylaluminiuim hydride (2.9 ml of a 1.5 M solution in toluene, 4.3 mmol).[34] The resulting solution was stirred at −78 °C for 1 h then allowed to warm to ambient temperature and stirred for an additional 4 h. Ethyl acetate (20 ml) and saturated aqueous potassium sodium tartrate (5 ml) were added carefully and the resulting two-phase mixture stirred for 10 min to give a semi-solid mass which was triturated with ethyl acetate (3 × 20 ml). The combined extracts were filtered and the solid washed thoroughly with ethyl acetate. The combined organic solutions were dried and evaporated and the residue separated by CC [EtOAc–CH_2Cl_2 (1:1)] to give the *alcohol* **25a** (0.29 g, 71%) as a colourless oil; R_F 0.52; $[\alpha]_D^{25}$ +10.57 (*c*, 1.3; MeOH); ν_{max}/cm^{-1} 3402 and 1693; δ_H(400 MHz; rotameric at 333 K) 1.47 (9H, s, CMe_3), 1.99–2.17 (2H, br m, 4-CH_2), 3.25 (1H, br s, OH), 3.39 (3H, s, CH_2OCH_3), 3.42–3.50 (2H, m, 5-CH_2), 3.76 (1H, dd, *J* 11.0 and 5.8, α-CH_a), 3.83–3.90 (1H, m, α-CH_b), 3.90–4.01 (1H, app. br s, 2-H), 4.28–4.43 (1H, app. br s, 3-H) and 4.57–4.75 (2H, m, OCH_2O); δ_C(67.8 MHz; 297 K) 28.5 (Me_3), 29.7 and 30.2 (4-CH_2), 43.7 and 44.9 (5-CH_2), 55.5 and 55.8 (OMe), 59.6 and 61.6 (2-CH), 62.6 and 63.1 (α-CH_2), 77.7 and 78.0 (3-CH), 80.1 and 80.2 (CMe_3), 95.9 and 96.2 (OCH_2O) and 154.6 and 156.4 (NCO); δ_C(100.1 MHz; 333 K) 28.6 (Me_3), 30.1 (4-CH_2), 44.4 (5-CH_2), 55.8 (OMe), 61.7 (2-CH), 63.2 (α-CH_2), 77.4 and 77.8 (3-CH), 80.2 (CMe_3), 96.2 (OCH_2O) and *ca.* 156.0 (NCO); *m/z* (FAB) 262 (M^+ + H, 37%), 206 (88), 174 (26), 162 (27), 144 (18), 130 (70), 100 (20), 82 (12), 68 (13), 57 (100) and 45 (83) (Found: M^+ + H, 262.1661. $C_{12}H_{23}NO_5$ requires *M*, 262.1661) (Found: C, 54.8; H, 9.1; N, 5.2. $C_{12}H_{23}NO_5$ requires C, 55.1; H, 8.9; N, 5.4%).

From the ethyl ester 24b. As in the foregoing method, the ethyl ester **24b** (2.66 g, 8.78 mmol) was reduced using boron trifluoride–diethyl ether (0.5 ml, 4.4 mmol) and diisobutylaluminium hydride (23.4 ml of a 1.5 M solution in toluene, 35.1 mmol) in toluene (20 ml) and gave the *alcohol* **25a** (1.51 g, 66%), which exhibited spectral data identical to those quoted above.

(2*R*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-(methoxymethoxy)-pyrrolidine-2-carbaldehyde 26

TPAP method. To a stirred solution of the alcohol **25a** (1.14 g, 4.37 mmol) in dry dichloromethane (9 ml) and dry acetonitrile (1 ml) was added dry *N*-methylmorpholine *N*-oxide (0.71 g, 6.1 mmol), powdered molecular sieves (2 g; freshly dried at 110 °C for 24 h) and tetrapropylammonium perruthenate (TPAP) (0.074 g, 0.21 mmol).[38] The resulting suspension was stirred at ambient temperature for 18 h then filtered through a small plug of silica which was subsequently washed with dichloromethane. The combined eluents were evaporated to leave the *aldehyde* **26** (0.90 g, 79%) as a colourless oil which was sufficiently pure to use in the next step. An analytical sample was obtained by CC [EtOAc–CH_2Cl_2 (1:4)] and showed R_F 0.73; ν_{max}/cm^{-1} 1704; δ_H(400 MHz; 333 K) 1.43 (9H, s, CMe_3), 1.92–2.03 (1H, m, 4-CH_a), 2.03–2.11 (1H, m, 4-CH_b), 3.31 (3H, s, CH_2OCH_3), 3.55–3.70 (2H, m, 5-CH_2), 4.08–4.20 (1H, m, 2-H), 4.54–4.60 (1H, m, 3-H), 4.57 (1H, d, *J* 6.8, OCH_aCH_bO), 4.61 (1H, d, *J* 6.8, OCH_aCH_bO) and 9.48 (1H, app. br s, CHO); δ_C(67.8 MHz; 297 K) 28.1 and 28.3 (Me_3), 30.5 and 31.0 (4-CH_2), 44.5 and 44.7 (5-CH_2), 55.7 (OMe), 67.5 and 67.8 (2-CH), 79.1 (3-CH), 80.4 and 80.8 (CMe_3), 95.2 (OCH_2O), 153.7 (NCO) and 200.1 (CHO); δ_C(100.1 MHz; 333 K) 28.4 (Me_3), 31.0 (4-CH_2), 44.7 (5-CH_2), 55.8 (OMe), 67.9 (2-CH), 79.2 (3-CH), 80.7 (CMe_3), 95.8 (OCH_2O), *ca.* 154.0 (NCO) and 199.5 (CHO); *m/z* (FAB) 260 (M^+ + H, 2%), 230 (38), 204 (12), 174 (74), 130 (72), 98 (9), 68 (14) and 57 (100) (Found: C, 55.7; H, 8.5; N, 5.1. $C_{12}H_{21}NO_5$ requires C, 55.6; H, 8.2; N, 5.4%).

Sulfur trioxide–pyridine complex method. To a stirred solution of the alcohol **25a** (0.27 g, 1.03 mmol) and triethylamine (0.72 ml, 5.2 mmol) in dry dichloromethane (10 ml) maintained

at 0 °C was added a solution of sulfur trioxide–pyridine complex (0.49 g, 3.1 mmol) in dry dimethyl sulfoxide (1.6 ml).[39] No additional coolant was added and the mixture was stirred overnight then diluted with dichloromethane (20 ml). The resulting solution was washed with 1.0 M hydrochloric acid (10 ml), water (10 × 20 ml) and brine (10 ml) then dried and the volatiles removed, finally at 1 mmHg. The residue was dissolved in dichloromethane (10 ml) and the solution filtered through silica, which was subsequently thoroughly washed with the same solvent. The filtrates were evaporated and the residue purified by CC, as above, to give the *aldehyde* **26** (0.19 g, 71%), identical to the foregoing sample.

Methyl (*S*)-2-benzyloxycarbonylamino-3-methylsulfonyloxypropanoate 27b

Freshly distilled methanesulfonyl chloride (9.0 ml, 116.3 mmol) was added dropwise to an ice-cold, stirred solution of methyl *N*-benzyloxycarbonyl-(L)-serinate **27a** (14.71 g, 58.14 mmol)[40] and 4-(dimethylamino)pyridine (0.50 g, 4.09 mmol) in dry dichloromethane (60 ml) and dry pyridine (9.7 ml, 116.3 mmol) and the resulting mixture stirred overnight at −18 °C. After dilution with dichloromethane (50 ml), the mixture was washed sequentially with 1.0 M hydrochloric acid (10 ml), water (3 × 50 ml) and brine (50 ml) then dried and evaporated, finally at 1 mmHg, to leave the crude methanesulfonate as a pale yellow oil which slowly crystallized. Recrystallization from dichloromethane–hexanes gave the *methanesulfonate* **27b** (15.01 g, 78%) as a colourless solid after drying at 1 mmHg, which showed mp 76–82 °C (decomp.); $[\alpha]_D^{20}$ −34.8 (*c*, 2.5; MeOH); $\nu_{max}(CHCl_3)$/cm^{-1} 3440, 1753, 1722, 1348 and 967; δ_H(250 MHz) 2.94 (3H, s, SO_2Me), 3.78 (3H, s, OMe), 4.50 (1H, dd, *J* 10.3 and 2.7, 3-H_a), 4.60 (1H, dd, *J* 10.3 and 2.7, 3-H_b), 4.66 (1H, ddd, *J* 7.4, 2.7 and 2.7, 2-H), 5.19 (2H, s, CH_2Ph), 5.90 (1H, d, *J* 7.4, disappears on D_2O shake, NH) and 7.34 (5H, app. br s, Ph); δ_C(67.8 MHz) 37.3 (SO_2Me), 53.2 (2-CH), 53.4 (OMe), 67.3 (CH_2), 68.6 (CH_2), 128.1, 128.3, 128.5 (all CH of Ph), 135.8 (C), 155.7 (NCO) and 168.7 (OCO); *m/z* (EI) 331 (M^+, 3%), 235 (10), 196 (5), 193 (9), 176 (61), 164 (7), 91 (93), 79 (100) and 42 (24) [Found: M^+ + H (FAB), 332.0804. $C_{13}H_{18}NO_7S$ requires *M*, 332.0801] (Found: C, 46.9; H, 5.2; N, 4.2. $C_{13}H_{17}NO_7S$ requires C, 47.1; H, 5.2; N, 4.2%).

Attempted purification by CC [EtOAc–CH_2Cl_2 (1:4)] resulted in extensive decomposition of the methanesulfonate; R_F 0.72, although the progress of the methanesulfonylation could be followed by TLC.

Methyl (*R*)-2-benzyloxycarbonylamino-3-phenylthiopropanoate 27c

A solution of the methanesulfonate **27b** (15.00 g, 45.3 mmol) in dry DMF (50 ml) was added dropwise to an ice-cold, stirred solution of sodium thiophenolate [freshly prepared by portionwise addition of sodium hydride (1.1 g, 46 mmol, washed with dry ether) to a solution of thiophenol (5.00 g, 45.3 mmol) in DMF (50 ml) until effervescence had ceased for 10 min, followed by filtration through glass wool]. After 1 h, no more coolant was added and the mixture stirred for 16 h then diluted with ethyl acetate (100 ml). The resulting solution was washed sequentially with water (10 × 50 ml), 2 M aqueous sodium hydroxide (2 × 50 ml) and water (2 × 50 ml) then dried and evaporated. CC of the residue (CH_2Cl_2) gave the *sulfide* **27c** (15.3 g, 98%) as a colourless, waxy solid; R_F 0.5; mp *ca.* 35 °C; $[\alpha]_D^{20}$ −17.2 (*c*, 1.8; MeOH); $\nu_{max}(CHCl_3)$/cm^{-1} 3429, 1732, 1698, 1348 and 1316; δ_H(250 MHz) 3.38–3.41 (2H, m, CH_2SPh), 3.51 (3H, s, OMe), 4.62 (1H, ddd, *J* 8.0, 8.0 and 4.8, 2-H), 5.07 (2H, s, CH_2Ph), 5.68 (1H, br, NH), 7.34 (5H, app. br s, Ph) and 7.20–7.41 (5H, m, SPh); δ_C(67.8 MHz) 36.9 (CH_2SPh), 52.3 (2-CH), 53.5 (OMe), 66.9 (CH_2), 127.0–129.0 (all CH of 2 × Ph), 134.3, 136.0 (both C), 155.4 (NCO) and 170.6 (OCO); *m/z* (EI) 345 (M^+, 6%), 194 (54), 178 (7), 123 (49), 91 (100) and 77 (8) [Found: M^+ + H (FAB), 346.1113 (10%). $C_{18}H_{20}NO_4S$ requires *M*, 346.1113] (Found: C, 62.7; H, 5.5; N, 4.0. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.1%).

(*R*)-2-Benzyloxycarbonylamino-3-phenylthiopropan-1-ol 28a

Sodium borohydride (16.8 g, 443 mmol) was added portionwise to a rapidly stirred, ice-cooled solution of the sulfide **27c** (15.25 g, 45.3 mmol) in methanol (300 ml) at such a rate that effervescence was under control and the temperature of the mixture remained below 30 °C. When the addition was complete (*ca.* 20 min), the resulting solution was stirred for 5 h, prior to the careful addition of water (50 ml). The product was extracted into dichloromethane (5 × 100 ml); evaporation of the combined extracts left the alcohol **28a** (13.87 g, 97%) as a pale yellow oil which was sufficiently pure (⩾95%) according to ^{1}H NMR data to utilize in the next step. An analytical sample was secured by CC [EtOAc–CH_2Cl_2 (1:1)] and gave the *alcohol* **28a** as a colourless oil; R_F 0.64; $[\alpha]_D^{20}$ −37.2 (*c*, 0.37; MeOH); $\nu_{max}(CHCl_3)$/cm^{-1} 3432, 1714, 1585, 1344 and 1325; δ_H(250 MHz) 2.65 (1H, br, OH), 3.00–3.25 (2H, m, 3-CH_2), 3.59–3.74 (1H, m, 2-H), 3.74–3.93 (2H, m, 1-CH_2), 5.09 (2H, s, CH_2Ph), 5.43 (1H, br, NH), 7.35 (5H, app. br s, Ph) and 7.10–7.52 (5H, m, SPh); δ_C(100.1 MHz) 34.5 (3-CH_2), 52.0 (2-CH), 62.8 (CH_2), 66.8 (CH_2), 126.2, 127.7, 128.0, 128.4, 128.9, 129.2 (all CH of 2 × Ph), 135.4, 136.1 (both C) and 156.2 (NCO); *m/z* (EI) 317 (M^+, 4%), 209 (46), 178 (9), 166 (16), 150 (10), 124 (99), 123 (83), 108 (100), 107 (52), 91 (87), 86 (32), 77 (12) and 45 (16) (Found: C, 64.4; H, 6.0; N, 4.4. $C_{17}H_{19}NO_3S$ requires C, 64.3; H, 6.0; N, 4.4%).

(*R*)-2-Benzyloxycarbonylamino-1-(*tert*-butyldimethylsilyloxy)-3-phenylthiopropane 28b

A solution of *tert*-butyldimethylsilyl (TBS) chloride (6.90 g, 45.8 mmol) in dichloromethane (10 ml) was added in a thin stream to a solution of the sulfide **28a** (13.19 g, 41.6 mmol), triethylamine (7.0 ml, 50.0 mmol) and 4-(dimethylamino)-pyridine (10 mg) in dichloromethane (25 ml). The resulting solution was stirred at ambient temperature overnight, diluted with dichloromethane (100 ml) and washed with water (3 × 30 ml) and brine (50 ml) then dried and evaporated. CC (CH_2Cl_2) gave the *silyl ether* **28b** (16.48 g, 92%) as a colourless oil; R_F 0.70; ν_{max}/cm^{-1} 3441, 3334, 1722, 1584, 1499, 1470, 1326 and 1252; δ_H(250 MHz) 0.19 (6H, s, 2 × SiMe), 0.99 (9H, s, $SiCMe_3$), 3.14 (1H, dd, *J* 13.6 and 8.1, 3-H_a), 3.30 (1H, dd, *J* 13.6 and 5.1, 3-H_b), 3.70–3.76 (1H, m, 2-CH), 3.89–3.95 (1H, m, 1-H_a), 4.01 (1H, dd, *J* 9.8 and 2.9, 1-H_b), 5.20 (2H, s, CH_2Ph), 5.36 (1H, br, NH), 7.42 (5H, app. br s, Ph) and 7.17–7.58 (5H, m, SPh); δ_C(100.1 MHz) −5.6 (2 × SiMe), 18.1 ($SiCMe_3$), 25.7 ($SiCMe_3$), 34.0 (3-CH_2), 51.6 (2-CH), 62.4 (CH_2), 66.6 (CH_2), 125.9, 128.0, 128.2, 128.4, 128.7, 128.8 (all CH of 2 × Ph), 135.7, 136.3 (both C) and 155.6 (NCO); *m/z* (FAB) 432 (M^+ + H, 24%), 374 (29), 324 (8), 297 (16), 232 (9), 149 (10), 123 (74), 115 (18), 102 (45), 91 (100), 77 (11), 75 (38) and 74 (27) (Found: C, 64.1; H, 7.9; N, 3.2. $C_{23}H_{33}NO_3SSi$ requires C, 64.0; H, 7.7; N, 3.2%).

(*R*)-2-Benzyloxycarbonylamino-1-(*tert*-butyldimethylsilyloxy)-3-phenylsulfonylpropane 29

A solution of the silyl ether **28b** (15.10 g, 35 mmol) in dichloromethane (70 ml) was added dropwise to an ice-cold, rapidly stirred solution of *m*-chloroperoxybenzoic acid (MCPBA) [25 g of a ~50–55% dispersion in water (Aldrich), *ca.* 70 mmol] in dichloromethane (100 ml). The solution was stirred at this temperature for 0.5 h then for a further 2 h without cooling, during which time a white precipitate appeared. Dichloromethane (200 ml) was added and the resulting solution washed sequentially with saturated aqueous sodium sulfite (3 × 50 ml), 2 M aqueous sodium hydroxide (3 × 50 ml), water (3 × 50 ml) and brine (50 ml), then dried and filtered through a short plug of silica, rinsing with dichloromethane. The filtrate was evaporated; CC (CH_2Cl_2) of the residue gave the *sulfone* **29**

(13.24 g, 87%) as a colourless oil; R_F 0.55; $[\alpha]_D^{20}$ −24.9 (*c*, 0.52; MeOH); ν_{max}/cm^{-1} 3349, 1714, 1532, 1402, 1306, 1253 and 1148; δ_H(250 MHz) 0.29 (6H, s, 2 × SiMe), 0.86 (9H, s, $SiCMe_3$), 3.42 (2H, d, *J* 5.9, 3-CH_2), 3.65 (1H, dd, *J* 10.2 and 4.9, 1-H_a), 3.83 (1H, dd, *J* 10.2 and 3.1, 1-H_b), 4.00–4.12 (1H, m, 2-CH), 5.04 (2H, s, CH_2Ph), 5.27 (1 H, br d, *J ca.* 7.5, NH), 7.30–7.37 (5H, m, Ph), 7.52 (2H, dd, *J* 7.4 and 6.7, 2 × *m*-H of SO_2Ph), 7.63 (1H, t, *J* 7.4, *p*-H of SO_2Ph) and 7.90 (2H, d, *J* 6.7, 2 × *o*-H of SO_2Ph); δ_C(100.1 MHz) −5.5 (2 × SiMe), 18.3 ($SiCMe_3$), 25.9 ($SiCMe_3$), 48.8 (2-CH), 56.3 (3-CH_2), 63.7 (CH_2), 67.0 (CH_2), 128.1, 128.2, 128.3, 128.6, 129.4, 133.9 (all CH of 2 × Ph), 136.3, 139.5 (both C) and 155.5 (NCO); *m/z* (FAB) 464 (M^+ + H, 54%), 448 (13), 406 (100), 356 (17), 332 (100), 330 (22), 288 (11), 266 (11) and 242 (10) [Found: M^+ + H (FAB), 464.1927. $C_{23}H_{34}NO_5SSi$ requires *M*, 464.1927] (Found: C, 59.2; H, 7.3; N, 2.8. $C_{23}H_{33}NO_5SSi$ requires C, 59.6; H, 7.2; N, 3.0%).

(2*S*,3*S*,1′*S*,2′*R*,3′*R*)-1-(*tert*-Butoxycarbonyl)-2-[3′-benzyloxycarbonylamine-4′-(*tert*-butyldimethylsilyloxy)-1′-hydroxy-2′-phenylsulfonylbutyl]-3-(methoxymethoxy)pyrrolidine 30

A 1.6 M solution of butyllithium in hexanes (4.55 ml, 7.29 mmol) was slowly added dropwise to a rapidly stirred solution of the sulfone **29** (1.69 g, 3.64 mmol) in THF (10 ml) maintained at −78 °C. The resulting orange solution was stirred at this temperature for 0.5 h then the cooling bath was removed and stirring continued for a further 0.5 h. The solution was then recooled to −78 °C and a solution of the aldehyde **26** (0.90 g, 3.74 mmol) in THF (5 ml) added dropwise during 0.25 h. After 2 h at −78 °C, the mixture was stirred without cooling for 2 h, then quenched by the addition of saturated aqueous ammonium chloride (5 ml). The resulting two-phase mixture was stirred for 5 min then diluted with ethyl acetate (20 ml), thoroughly mixed and the two phases separated. The aqueous phase was extracted with ethyl acetate (20 ml) and the combined organic solution dried and evaporated. CC [EtOAc–CH_2Cl_2 (1:4)] of the residue gave the *hydroxy sulfone* **30** (1.50 g, 60%) as a pale yellow oil; R_F 0.75; ν_{max}/cm^{-1} 3419, 1726 and 1683; δ_H(400 MHz) 0.22 (6H, s, 2 × SiMe), 0.86 (9H, s, $CH_2OSiCMe_3$), 1.48 (9H, s, NCO_2CMe_3), 1.96–2.18 (2H, m, 4-CH_2), 3.39 (3H, s, MeO), 3.32–3.51 (2H, m, 5-CH_2), 3.65 (1H, dd, *J* 6.8 and 3.6, 4′-H_a), 3.84 (1H, dd, *J* 6.8 and 3.9, 4′-H_b), 4.25–4.38 (1H, m, 3-H), 4.38–4.43 (1H, br m, 2′-H), 4.43–4.50 (1H, br m, 3′-H), 4.50–4.55 (1H, m, 2-H), 4.68 (2H, AB system, *J* 3.7, OCH_2O), 4.70–4.79 (1 H, m, 1′-H), 5.04 (2H, AB system, *J* 4.3, OCH_2Ph), 6.18 (1H, br s, NH), 7.27–7.37 (5H, m, Ph), 7.44 (2H, dd, *J* 7.7 and 7.5, *m*-H of $PhSO_2$), 7.53 (1H, t, *J* 7.5, *p*-H of $PhSO_2$) and 7.99 (2H, d, *J* 7.7, *o*-H of $PhSO_2$); δ_C(100.1 MHz) −5.5 (2 × SiMe), 18.4 ($SiCMe_3$), 25.9 ($SiCMe_3$), 28.5 (NCO_2CMe_3), 30.1 (4-CH_2), 45.1 (5-CH_2), 51.8 (β-CH), 55.8 (OMe), 62.8 (2-CH), 66.0 (α-CH_2), 66.6 (CH_2Ph), 67.1 (γ-CH), 67.7 (δ-CH), 75.7 (3-CH), 80.8 ($OCMe_3$), 96.4 (OCH_2O), 128.0, 128.1, 128.4, 128.9, 129.5, 133.5 (all CH of 2 × Ph), 136.9, 139.0 (both C), 155.8 (CO) and 157.1 (CO) (Found: C, 58.6; H, 7.7; N, 3.6. $C_{35}H_{54}N_2O_{10}SSi$ requires C, 58.2; H, 7.5; N, 3.9%).

(2*S*,3*S*,3′*S*)-2-[4′-(*tert*-Butyldimethylsilyloxy)-3′-(benzyloxycarbonylamino)but-1′-enyl]-1-(*tert*-butoxycarbonyl)-3-(methoxymethoxy)pyrrolidine 31

To an ice-cold, stirred solution of the hydroxy sulfone **30** (1.14 g, 1.48 mmol) in methanol (20 ml) was added potassium dihydrogen orthophosphate (5.0 g) and freshly prepared 6% sodium–mercury amalgam (5.67 g, equivalent to 14.8 mmol of sodium).[44] The cooling bath was removed and the mixture stirred for 18 h. Water (20 ml) and dichloromethane (100 ml) were added and stirring continued for 5 min. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 20 ml). The organic solutions were combined and washed with brine (20 ml) then dried and evaporated. CC [EtOAc–CH_2Cl_2 (1:4)] of the residue gave the *alkene* **31** (0.81 g, 97%) as a colourless oil; R_F 0.60; ν_{max}/cm^{-1} 3331, 1717 and 1697; δ_H(250 MHz) 0.07 (6H, s, 2 × SiMe), 0.89 (9H, s, $CH_2OSiCMe_3$), 1.42 (9H, s, NCO_2CMe_3), 1.79–1.99 (1H, m, 4-H_a), 2.02–2.19 (1H, m, 4-H_b), 3.25–3.49 (2H, m, 5-CH_2), 3.35 (3H, s, MeO), 3.62 (1H, dd, *J* 5.3 and 3.9, 4′-H_a), 3.72 (1H, dd, *J* 5.3 and 4.6, 4′-H_b), 4.12–4.25 (1H, m, 2-H), 4.25–4.40 (1H, br m, 3′-H), 4.62 (2H, s, OCH_2O), 4.98–5.10 (1H, m, 3-H), 5.13 (2H, s, OCH_2Ph), 5.51–5.78 (3H, m, 2 × =CH and NH) and 7.35 (5H, app. br s, Ph); δ_C(67.8 MHz) −4.8 (2 × SiMe), 18.7 ($SiCMe_3$), 26.3 ($SiCMe_3$), 29.1 (NCO_2CMe_3), 30.1 (4-CH_2), 42.9 (5-CH_2), 54.3 (3′-CH), 56.1 (OMe), 60.3 (2-CH), 65.8 (4′-CH_2), 67.1 (CH_2Ph), 77.0 (3-CH), 79.9 ($OCMe_3$), 96.2 (OCH_2O), 127.4, 128.0 (CH=CH), 128.5, 128.7, 130.4 (all CH of Ph), 137.0 (C), 154.9 (CO) and 156.2 (CO) [Found: M^+ + H (FAB), 565.3312. $C_{29}H_{49}N_2O_7Si$ requires *M*, 565.3309].

When obtained using CD_3OD as solvent, most resonances in the ^1H NMR spectrum appeared as complex multiplets; however, the alkene region appeared as two well-resolved signals: δ_H(400 MHz) 5.54 (1H, dd, *J* 15.4 and 4.7, =CH) and 5.69 (1H, dd, *J* 15.4 and 7.3, =CH).

(2*S*,3*S*,3′*S*)-2-[(4′-*tert*-Butyldimethylsilyloxy)-3′-(benzyloxycarbonylamino)butyl]-1-(*tert*-butoxycarbonyl)-3-(methoxymethoxy)pyrrolidine 32a

To a stirred solution of the alkene **31** (0.83 g, 1.48 mmol) and triethylamine (0.5 ml, 3.7 mmol) in dichloromethane (15 ml) at ambient temperature was added 2,4,6-triisopropylbenzenesulfonyl hydrazide (4.42 g, 14.83 mmol) in five equal portions during 2 days.[46] After the final addition, the mixture was stirred for 8 h and the resulting clear solution diluted with dichlorometane (10 ml) and washed sequentially with ice-cold 1 M hydrochloric acid (10 ml), water (3 × 25 ml) and brine (25 ml). The dried solution was evaporated to leave essentially pure alkane **32a** (0.65 g, 78%) as a pale yellow oil which was taken on to the next step. An analytical sample was obtained by CC [EtOAc–CH_2Cl_2 (1:4)] which gave the *alkane* **32a** as a colourless oil; R_F 0.53; $[\alpha]_D^{20}$ +5.94 (*c*, 1.3; MeOH); ν_{max}/cm^{-1} 3320, 1715 and 1690; δ_H(250 MHz) 0.12 (6H, s, 2 × SiMe), 0.94 (9H, s, $SiCMe_3$), 1.35–2.21 (6H, m), 2.87–3.20 (1H, m, 5-H_a), 3.42 (3H, s, MeO), 3.60–3.95 (2H, m), 3.95–4.06 (1H, m), 4.11–4.32 (2H, m, CH_2OSi), 4.65–4.74 (1H, m), 4.74 (2H, s, OCH_2O), 5.17 (2H, s, CH_2Ph), 6.04 (1H, br s, NH) and 7.42 (5H, app. br s, Ph) (Found: C, 61.3; H, 8.6; N, 4.7. $C_{29}H_{50}N_2O_7Si$ requires C, 61.5; H, 8.9; N, 4.9%).

(1*S*,6*S*,8a*S*)-1-Hydroxy-6-(benzyloxycarbonylamino)octahydroindolizine [*O*-deacetyl-*N*-(benzyloxycarbonyl)slaframine] 33b

Tetrabutylammonium fluoride (1.31 ml of a 1.0 M solution in THF, 1.32 mmol) was added dropwise to an ice-cold, stirred solution of the alkane **32a** (0.62 g, 1.1 mmol) in THF (5 ml). The cooling bath was removed and, after 1.5 h, TLC analysis indicated that desilylation was complete. The solution was diluted with dichloromethane (5 ml) and washed with water (3 × 5 ml) then dried and evaporated. CC [EtOAc–CH_2Cl_2 (1:1)] of the residue gave the *alcohol* **32b** (0.46 g, 92%), a colourless, viscous oil which showed R_F 0.39; $[\alpha]_D^{20}$ +7.22 (*c*, 1.3; MeOH); ν_{max}/cm^{-1} 3420 and 1710; δ_H(250 MHz) 1.22–1.33 (1H, m), 1.45 (9H, s, CMe_3), 1.48–1.98 (5H, m), 2.50–2.61 (1H, m), 3.37 (3H, s, OMe), 3.28–3.40 (1H, m), 3.56–3.68 (2H, m, CH_2OH), 3.68–3.80 (1H, m), 3.80–3.97 (1H, m), 4.11–4.22 (1H, m), 4.63 (2H, s, OCH_2O), 5.00 (2H, s, CH_2Ph) and 7.32–7.40 (5H, m).

Freshly distilled methanesulfonyl chloride (0.1 ml, 1.02 mmol) was added dropwise to an ice-cold solution of the alcohol **32b** (0.23 g, 0.51 mmol), triethylamine (0.13 ml, 1.02 mmol) and 4-(dimethylamino)pyridine (~2 mg) in dichloromethane (5 ml). The solution was then stirred at −18 °C for 16 h, diluted with dichloromethane (10 ml) and washed with 1 M hydrochloric acid (5 ml), water (3 × 5 ml) and brine (5 ml). The dried

solution was filtered through a plug of silica gel, which was then washed with EtOAc–CH_2Cl_2 (1:1). The filtrate was evaporated to leave the methanesulfonate **32c** contaminated with methanesulfonyl chloride. Exposure to high vacuum (~1 mmHg) for a few hours then gave the methanesulfonate **32c** (0.38 g) which was not further purified but taken immediately to the next step.

Trifluoroacetic acid (2.50 g, 21.7 mmol) was added dropwise to a stirred solution of the crude methanesulfonate **32c** (0.38 g, ~0.72 mmol) in dichloromethane (10 ml). After 0.5 h, TLC analysis showed complete reaction. The brown solution was evaporated and the glassy residue redissolved in dichloromethane (20 ml) and the resulting solution washed sequentially with 2 M aqueous sodium hydroxide (5 ml), water (5 × 2 ml) and brine (2 × 2 ml). The dried solution was then evaporated to leave a pale brown, viscous oil which was purified by CC [CH_2Cl_2–MeOH–saturated aq. NH_3 (9.5 ml:0.5 ml:10 drops)] to give the *indolizine* **33a** (0.076 g, 45% based on alcohol **32b**), as a colourless, viscous oil which rapidly turned brown upon exposure to air and which showed R_F 0.62; ν_{max}/cm^{-1} 1715; δ_H(250 MHz; poorly resolved) 1.55–2.36 (8H, m), 2.97–3.09 (2H, m, 5-CH_2), 3.12–3.22 (1H, m, 6-CH), 3.40 (3H, s, OMe), 3.85–4.36 (3H, m), 4.58–4.74 (2H, m, OCH_2O), 5.11 (2H, s, CH_2Ph) and 7.35 (5H, m, Ph); *m/z* (EI) 334 (M^+, <1%), 289 (1%), 242 (21), 197 (4), 142 (27), 137 (5), 136 (6), 108 (18), 107 (19), 100 (10), 91 (100), 86 (21), 79 (29) and 77 (14).

Acetyl chloride (45 μl) was added to methanol (1 ml). After 10 min, this was added to the indolizine **33a** (0.070 g, 0.21 mmol) and the solution heated at reflux for 20 min, then cooled and evaporated. The brown residue was dissolved in water (5 ml) and the resulting solution washed with dichloromethane (3 × 3 ml), then basified by the addition of 10 M aqueous sodium hydroxide (1 ml), saturated with sodium chloride. A white emulsion formed immediately and the mixture was extracted into ethyl acetate (3 × 5 ml). The combined extracts were washed with brine then dried and evaporated. CC [CH_2Cl_2–MeOH–saturated aq. NH_3 (9.5 ml:0.5 ml:10 drops)] separated O-*deacetyl*-N-(*benzyloxycarbonyl*)*slaframine* **33b** (0.058 g, 87%)[14,16] as a viscous, colourless oil which rapidly turned brown upon exposure to air; R_F 0.32; ν_{max}/cm^{-1} 3400 and 1715; δ_H(250 MHz; poorly resolved) 1.64–1.81 (1H, m), 1.88–2.41 (4H, m), 2.41–2.61 (1H, m), 2.61–2.90 (2H, m), 2.90–3.36 (1H, m), 3.60–3.82 (2H, m), 4.20–4.31 (1H, m), 4.37–4.49 (1H, m), 5.13 (2H, s, CH_2Ph) and 7.25–7.47 (5H, m, Ph); δ_C(67.8 MHz) 20.1 (7-CH_2), 28.3 (8-CH_2), 33.1 (2-CH_2), 45.7 (6-CH), 52.3 (3-CH_2), 57.3 (5-CH_2), 66.4 (CH_2Ph), 68.3 (8a-CH), 72.8 (1-CH), 128.0, 128.1, 128.4 (all CH), 136.6 (C) and 155.5 (NCO) (Found: C, 66.6; H, 7.7; N, 10.2. $C_{16}H_{22}N_2O_3$ requires C, 66.2; H, 7.6; N, 9.7%).

(1*S*,6*S*,8a*S*)-1-Acetoxy-6-(benzyloxycarbonylamino)octahydroindolizine [*N*-(benzyloxycarbonyl)slaframine] 33c, (1*S*,6*S*,8a*S*)-1-acetoxy-6-aminooctahydroindolizine [(−)-slaframine] 5 and (1*S*,6*S*,8a*S*)-1-acetoxy-6-acetylaminooctahydroindolizine (*N*-acetylslaframine) 34

O-Deacetyl-*N*-(benzyloxycarbonyl)slaframine **33b** (0.034 g, 0.12 mmol) was dissolved in dichloromethane (2 ml) and the stirred solution treated sequentially with triethylamine (0.25 ml), 4-(dimethylamino)pyridine (1 mg) and acetic anhydride (0.25 ml). After 1 h, TLC analysis showed the reaction to be complete. The solution was diluted with dichloromethane (5 ml) and washed with water (2 × 1 ml) and brine (1 ml) then dried and evaporated. CC [CH_2Cl_2–MeOH–saturated aq. NH_3 (9.5 ml:0.5 ml:10 drops)] of the pale brown, viscous residue gave N-(*benzyloxycarbonyl*)*slaframine* **33c** (0.038 g, 92%) as a colourless, viscous oil which rapidly turned brown in air and which showed R_F 0.73; ν_{max}/cm^{-1} 3306, 1745, 1696 and 1491; δ_H(250 MHz) 1.26–2.06 (6H, m), 2.05 (3H, s, OAc), 2.06–2.35 (3H, m), 3.00–3.11 (2H, m), 3.91–4.01 (1H, m, 8a-H), 5.12 (2H, AB system, *J* 12.0, C*H*$_2$Ph), 5.18–5.27 (1H, m, 1-CH), 5.70 (1H, br d, *J ca.* 6, NH) and 7.42 (5H, m, Ph).

A suspension of 5% palladium on carbon (0.5 g) in dry methanol and acetic acid (9:1, 4 ml) was stirred under an atmosphere of hydrogen for 1 h then a solution of *N*-(benzyloxycarbonyl)slaframine **33c** (0.030 g) in methanol–acetic acid (9:1, 1 ml) was added and hydrogenation continued at ambient temperature overnight. The suspension was filtered through Kieselguhr and the clear, colourless filtrate evaporated to give a pale brown, viscous oil which showed two close spots (R_F 0.48 and 0.50) on TLC analysis [CH_2Cl_2–MeOH–saturated aq. NH_3 (9.5 ml:0.5 ml:10 drops)]. CC in the same solvent system separated the major component, (−)-slaframine **5** (0.015 g, 78%), as a colourless, viscous oil which rapidly darkened upon exposure to air and which showed R_F 0.48; $[\alpha]_D^{19}$ −31.4 (*c* 1, $CDCl_3$) {lit.,[22] $[\alpha]_D^{25}$ −33 (*c* 1.6, $CHCl_3$); lit.,[25] $[\alpha]_D$ −32.3 (*c* 0.3, $CDCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3540, 1727, 1378, 1250 and 1114; δ_H(250 MHz) 1.50–1.71 (2H, m, 8-CH_2), 1.71–1.83 (2H, m, 2-CH_2), 1.85–2.35 (5H, m, 6-H, 3- and 7-CH_2), 2.08 (3H, s, OAc), 3.00–3.24 (2H, m, 5-CH_2), 3.28–3.43 (1H, m, 8a-H), 5.18–5.28 (1H, m, 1-H) and 6.16 (2H, br, NH_2). The instability of the sample prevented further meaningful characterization.

Acetic anhydride (0.5 ml) was added dropwise to an ice-cold, stirred solution of (−)-slaframine **5** (0.015 g), triethylamine (0.5 ml) and 4-(dimethylamino)pyridine (small crystal) in dry dichloromethane (2 ml). After 2 h, the volatiles were evaporated and the semi-solid residue purified by CC [$CHCl_3$–MeOH (9.5:5)] to give *N*-acetylslaframine **34** (0.014 g, 77%) as a colourless solid which slowly darkened in air; R_F 0.52 (lit.,[22] R_F 0.5 in the same solvent system); mp 138–140 °C (lit.,[11] mp 140–142 °C; lit.,[22] mp 139–141 °C; lit.,[25] mp 140–141 °C); $[\alpha]_D^{19}$ −15.7 (*c* 0.14, EtOH) {lit.,[11] $[\alpha]_D^{25}$ −15.9 (*c* 5, EtOH); lit.,[22] $[\alpha]_D^{25}$ −11.2 (*c* 1.45, EtOH); lit.,[23] $[\alpha]_D^{25}$ −18.8 (*c* 0.4, EtOH); lit.,[25] $[\alpha]_D$ −14.6 (*c* 0.3, EtOH)}; δ_C(67.8 MHz) 20.4, 20.9 (both CO*Me*), 23.3, 28.0 (7- and 8-CH_2), 30.3 (2-CH_2), 43.7 (6-CH), 52.8, 57.3 (3- and 5-CH_2), 67.2 (8a-CH), 74.6 (1-CH), 169.0 and 170.3 (both CO), the latter spectrum being in excellent agreement with that previously reported.[22]

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