



An enantioselective route to pyrrolidines: removal of the chiral template from homochiral pyrroloimidazoles

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ABSTRACT

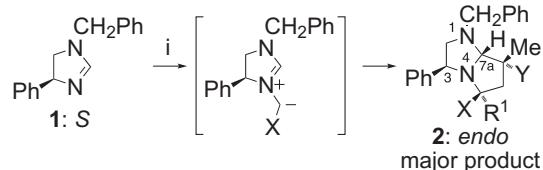
Two-step reductive removal of the chiral template from optically active pyrroloimidazoles, available from 1,3-dipolar cycloaddition of homochiral 4,5-dihydroimidazolium ylides, gives optically active substituted pyrrolidines. Selective manipulation of the substituents affords, e.g., naturally occurring and other optically active proline derivatives, and optically active pyrrolizidines and indolizidines.

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1. Introduction

We have previously reported the synthesis of pyrrolo[1,2-*a*]imidazoles by the 1,3-dipolar cycloaddition of 4,5-dihydroimidazolium (imidazolinium) ylides to alkenes, forming three of the five bonds of the new pyrrolidine ring in one pot.¹ In a subsequent paper we reported the extension of our methodology to afford enantiomerically pure pyrrolo[1,2-*a*]imidazoles **2** from 4,5-dihydroimidazole **1**, incorporating a phenyl substituent at the 4-position (e.g., Scheme 1; S-series illustrated).² The original dihydroimidazolium ylides provide a chiral template for the new pyrrolidine ring, so that if the templating atoms can be removed, the pyrroloimidazoles should serve as precursors for optically active pyrrolidines and derivatives, and we have sought to realise this strategy.

Removal of the templating atoms to reveal the pyrrolidine ring requires cleavage of the C(7a)–N(1) and C(3)–N(4) bonds of the pyrroloimidazole **2** (Scheme 1). It was envisaged that this could be accomplished by a two-step reductive sequence. Previous studies in



Scheme 1. Cycloaddition of chiral dihydroimidazolium ylides. Reagents: i, BrCHR¹X, CH₂=C(Me)Y, THF reflux, then DBU.

the achiral series indicated that step 1, reduction of the aminal function (NaBH₃CN, pH 1), should occur exclusively with C(7a)–N(1) bond cleavage.¹ It was anticipated that step 2, removal of the benzylic N-substituent, could be effected by hydrogenolysis. We now report in full the results of our investigations in this area, including a revised evaluation of the stereochemical course of some of the reactions when compared with our preliminary report³ along with manipulations of the optically active pyrrolidines to illustrate their potential as building blocks towards natural products and potentially biologically active molecules.^{4,5}

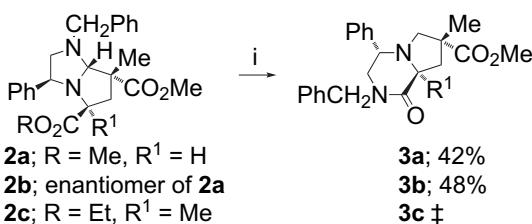
2. Results and discussion

Aminal reduction (NaBH₃CN, 2 M HCl aq, EtOH) of the 5-methoxycarbonylpyrroloimidazole **2a** or its enantiomer **2b**,

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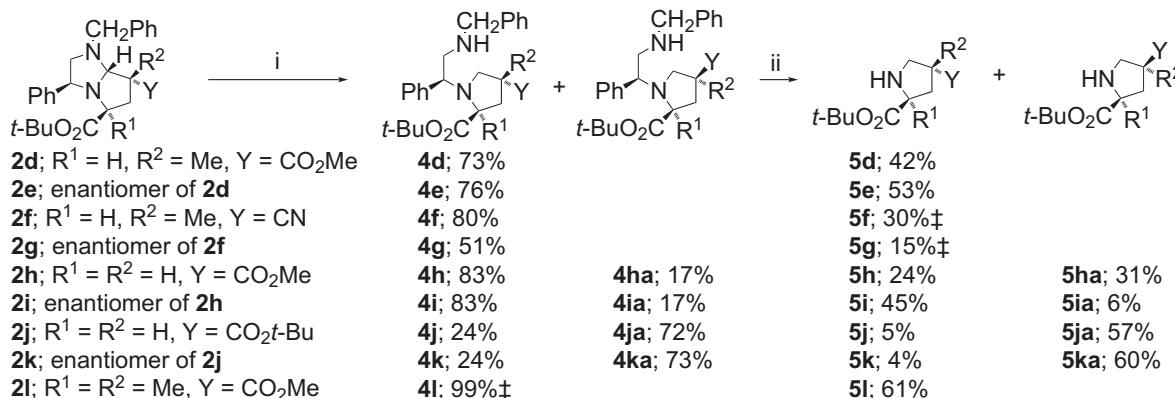
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prepared as reported in our earlier paper,² resulted solely in lactamisation to pyrrolo[1,2-*a*]pyrazines **3a** and **3b**, respectively (Scheme 2). The 5-ethoxycarbonyl bicyclic **2c** also afforded a pyrrolopyrazine **3c**, although this was not fully purified and characterised. Formation of these pyrrolopyrazines is undesirable and complicates template removal. Earlier work had demonstrated that lactamisation could be suppressed by performing the reduction in acetic acid with the inclusion of acetic anhydride to acylate the incipient secondary amine.⁶ It was, however, necessary to employ a large excess of acetic anhydride, and the resulting multi-component product mixture complicated purification. Reduction in a medium of TFA/TFAA also proved unsuccessful. Reversing the order of the steps, i.e., performing the hydrogenolysis first, could potentially circumvent this problem. However, several attempts at the hydrogenolysis of **2a** yielded an intractable mixture, and this approach was not pursued further.



Scheme 2. Reduction of 5-methoxy- or 5-ethoxycarbonyl pyrrolimidazoles. Reagents: i, NaBH₃CN, 2 M HCl aq, THF (‡not fully characterised).

We proposed that increasing the steric hindrance of the pyrrolimidazole C-5 ester would hinder attack on the ester carbonyl group by the secondary amine group liberated during the aminal reduction step, and pleasingly this tactic was found to suppress completely the undesired lactamisation. Thus 5-*tert*-butoxycarbonyl cycloadducts **2d–l** were reduced (NaBH₃CN, 2 M HCl aq, THF) in good total yields to the corresponding *N*-substituted pyrrolidines **4d–l** (Scheme 3). Attempted purification by column chromatography proved difficult, resulting in extensive loss of material; fortunately the crude pyrrolidines could be employed directly in the hydrogenolysis step.



Scheme 3. Reduction of 5-*tert*-butoxycarbonylpyrroloimidazoles. Reagents: i, NaBH₃CN, 2 M HCl aq, THF; ii, H₂, Pd(OH)₂, TFA, MeOH (‡not fully characterised).

Cleavage of the benzylic C–N bond in **4** completes template removal to reveal the pyrrolidines **5**. Hydrogenolysis of **4d** with palladium on charcoal as catalyst and acetic acid as solvent under 1 atm of hydrogen, or treatment with 1-chloroethyl chloroformate⁷ resulted in extensive decomposition and none of the expected product. Changing to Pearlman's catalyst (Pd(OH)₂) with methanol as solvent smoothly cleaved the benzylic *N*-substituent in **4** to give pyrrolidines **5d–l**.⁸ Although these experiments were successful, problems of

reproducibility were encountered in later reductions, possibly due to the presence of trace impurities or variability between catalyst batches. This led to the development of a more robust standard set of conditions employing Pearlman's catalyst shaken in methanol under 60 psi of hydrogen in a Parr apparatus; the inclusion of 1 mol equiv of trifluoroacetic acid was found to accelerate the reduction in certain instances. In the nitrile (7-cyanopyrroloimidazole) series (**4f,g**) the hydrogenolysis was poor, e.g., **4g** giving **5g** in 15% crude yield; further purification was not possible. Alternative reductive (Na, liq. NH₃) or oxidative [Pb(OAc)₄] protocols for the benzylic C–N cleavage were unsuccessful.⁸

Confirmation of the stereochemical identity of the product pyrrolidines came from the single-crystal X-ray analysis of the 4-bromobenzamide **6** from **5d** (Fig. 1). This derivative had the expected 2*S*,4*R* configuration resulting from retention of stereochemistry throughout the synthesis.

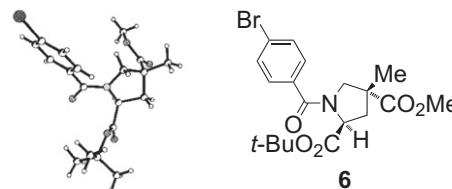
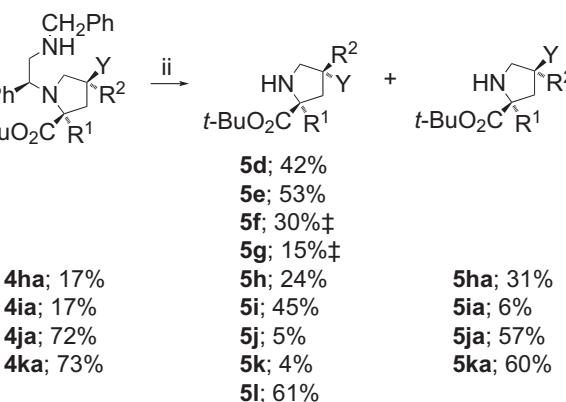


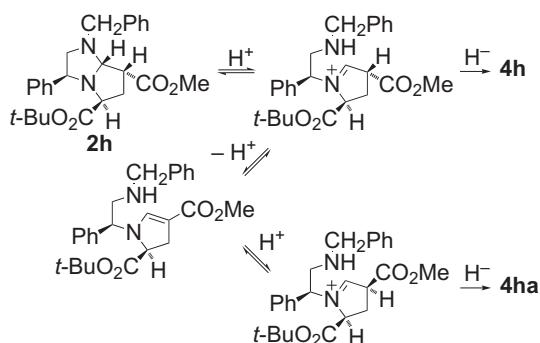
Fig. 1. X-ray crystal structure of 4-bromobenzamide **6**.

Despite the fact that they were uncontaminated with any other isomer, pyrroloimidazoles **2h** and **2i** monosubstituted with a methoxycarbonyl substituent at C-7 (R² = H), yielded pyrrolidines, which had undergone partial epimerisation at C-4. Evidence for this came in the NMR spectra of the corresponding *N*-substituted pyrrolidines **4h/4ha** and **4i/4ia** directly from the reductive aminal cleavage, in which diastereoisomeric products could clearly be identified. Based on the stereochemistry of the product (vide infra) it was assumed that the trans diastereoisomer dominated. It was found that use of a large excess (10 mol equiv) of acid, followed immediately by rapid addition of exactly 1 mol equiv of NaBH₃CN gave acceptable epimer ratios in favour of the 2,4-*trans* isomers.



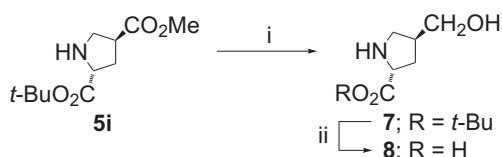
Thus, for example, reduction of **2h** produced a 5:1 *trans/cis* mixture of C-4 epimers **4h** and **4ha**, respectively (Scheme 3). Due to the difficulties encountered in purifying these *N*-substituted pyrrolidines the epimer mixture was carried directly through to the hydrogenolysis step. Epimerisation at C-4 most probably occurs by deprotonation–reprotonation at C-4 of the intermediate iminium ion before hydride trapping (Scheme 4). Excess NaBH₃CN was found to promote epimerisation, possibly due to the reaction

medium becoming basic. Similarly, slow addition of the reducing agent gave a much poorer epimer ratio, presumably by providing time for the deprotonation–reprotonation to occur. Hydrogenolysis of crude epimer mixtures **4h/4ha** and **4i/4ia** afforded the epimeric pyrrolidine mixtures **5h/5ha** and **5i/5ia**, respectively. It was pleasing to observe a considerable improvement in epimer ratio in the products **5** over the starting materials **4** in one case, possibly suggesting that the 2,4-*cis*-substituted pyrrolidines are less stable to the reaction conditions than the 2,4-*trans* diastereomers.



Scheme 4. Epimerisation at C-4 of pyrrolidines **4**.

Separation of the epimeric pyrrolidines proved straightforward by column chromatography. Although we were unable to obtain crystalline derivatives of any of these pyrrolidines, confirmation of the *trans* stereochemistry came from the conversion of **5i** into a natural product. Thus, reduction of the C-4 methyl ester using LiBH₄ in methanol to give alcohol **7** (Scheme 5), followed by cleavage of the C-2 *tert*-butyl ester with trifluoroacetic acid and ion-exchange purification afforded the naturally occurring (2*R*,4*S*)-4-hydroxymethylproline **8**,⁹ with an optical rotation in excellent agreement with that reported in the literature for the enantiomer, except of course for the opposite sign.¹⁰



Scheme 5. Synthesis of naturally occurring 4-hydroxymethyl-D-proline **8**. Reagents: i, LiBH₄, MeOH; ii, TFA, then Dowex 50W.

Surprisingly however, and contrary to our preliminary report,³ aminal reduction and hydrogenolysis of the C-7 monosubstituted 7-*tert*-butoxycarbonylpyrroloimidazoles **2j** and **2k** yielded pyrrolidines **5j/5ja** and **5k/5ka**, where the major products were now **5ja** and **5ka**, respectively, i.e., those having undergone the inversion of stereochemistry at the pyrrolidine C-4. By implication, the aminal reductions products **4j/4ja** and **4k/4ka** must also have had the C-4 inverted diastereoisomers as the major components (Scheme 3). This stereochemical observation was confirmed by single-crystal X-ray analysis of the 4-bromobenzamide **9** derived from pyrrolidine **5ja**, showing it to have 2*S*,4*S* configuration (Fig. 2) and thus demonstrating that C-4 and not C-2 had undergone inversion. Although we were unable to obtain crystals of the starting pyrroloimidazole **2j** of quality adequate for X-ray diffraction studies, ¹H NOE studies and spectra almost superimposable with those of **2h**, for which single-crystal X-ray data were available,² confirmed that the starting material was indeed 5,7-*trans*. Further, reduction of both 7-methoxycarbonylpyrroloimidazole **2h** and 7-*tert*-butoxycarbonyl derivative **2j** using LiAlH₄ (which does not cleave the aminal) afforded the same diol, the 5,7-bis(hydroxymethyl)pyrroloimidazole **10**, which had retained the

5,7-*trans* stereochemistry as evidenced by ¹H NOE studies. Two key NOE enhancements are illustrated. Confirmation that the single crystal of 4-bromobenzamide **9** was representative of the bulk material came from comparison of the powder X-ray and single-crystal diffraction data. Thus, the simulated powder pattern produced from the single-crystal diffraction data matched exactly the experimental powder data obtained from the remainder of the bulk sample of **9**. It is possible that the steric demands of the two *tert*-butyloxycarbonyl functions at C-5 and C-7 in the enantiomers **2j** and **2k** drive the epimerisation during aminal reduction over to the thermodynamically more stable 2,4-*cis* pyrrolidines **4ja** and **4ka** as the major components, a factor which is less pronounced in the analogous 7-methoxycarbonyl compounds. In addition, it is possible slower reduction of the intermediate iminium ions allows time for the epimerisation.

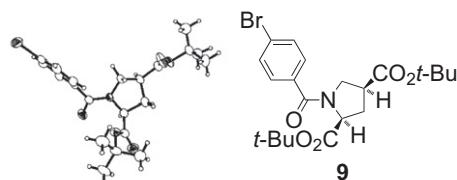
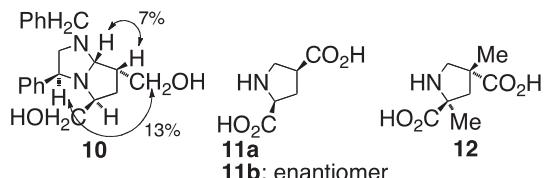
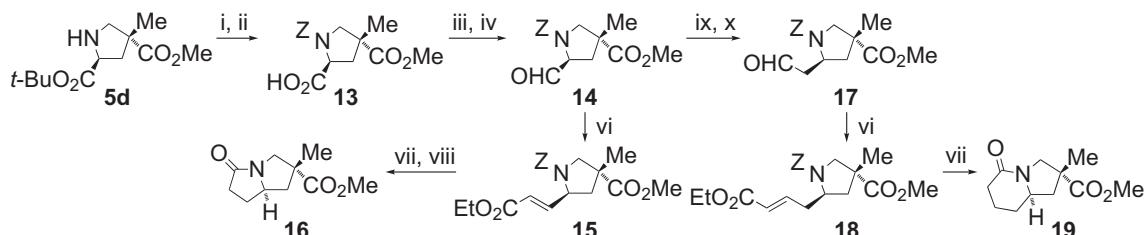


Fig. 2. X-ray crystal structure of 4-bromobenzamide **9**.



Pyrrolidines **5ja** and **5ka** were deprotected using trifluoroacetic acid followed by ion-exchange purification to yield the 2,4-*cis* amino diacids **11a** and **11b** with optical rotations in agreement with the reported values.¹¹ All four stereoisomers of the pyrrolidine 2,4-dicarboxylic acids have been reported as being competitive glutamate transport inhibitors;¹¹ the 2*S*,4*R* *trans*-diastereoisomer is a natural material.¹² Pyrrolidine **5l** was similarly deprotected using trifluoroacetic acid, followed by saponification of the methyl ester and ion-exchange chromatography to afford the 2,2,4,4-tetrasubstituted analogue **12**, as its hydrochloride salt.

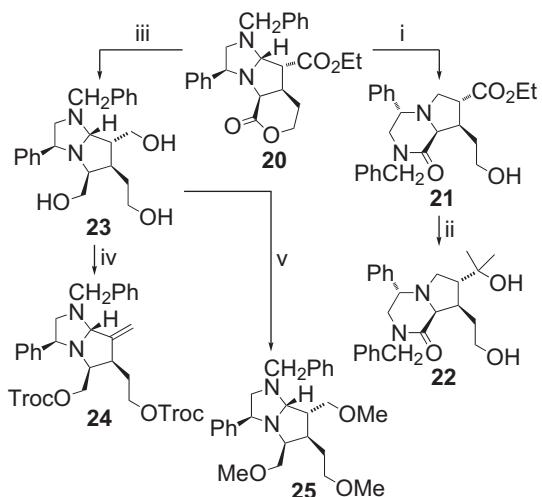
Selective manipulation of the C-2 substituent of our pyrrolidines provides an entry into pyrrolizidines and indolizidines (Scheme 6), ring systems present in a wide range of natural products.⁵ Thus amino diester **5d** was first protected on nitrogen with a benzyloxycarbonyl group to give a carbamate, followed by cleavage of the *tert*-butyl ester using trifluoroacetic acid to afford the acid **13**. Formation of the active ester with *N*-hydroxysuccinimide permitted reduction of the C-2 carboxy function to the corresponding alcohol using sodium borohydride, leaving the C-4 ester untouched. Oxidation of this alcohol to the aldehyde **14** with catalytic tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide permitted chain extension by Wadsworth–Emmons chemistry. Hence reaction with triethyl phosphonoacetate (NaH, 20 °C) yielded α,β -unsaturated ester **15**, installing the extra two carbon atoms required for cyclisation to the pyrrolizidine skeleton. Treatment with hydrogen over palladium on charcoal served to cleave the benzyloxycarbonyl group and to reduce the alkene to afford an amino ester; heating at reflux in xylene effected cyclisation to the pyrrolizidine **16**. Attempts to chain extend aldehyde **14** by three carbons using a variety of Wittig and Wadsworth–Emmons reagents proved unsuccessful. Instead aldehyde **14** was homologated via a Wittig reaction with the ylide formed from methoxymethyl-triphenylphosphonium chloride (KO^tBu, –15 °C) to yield an enol ether, which underwent hydrolysis to afford aldehyde **17**. This unstable compound was chain-extended by two carbon atoms by



Scheme 6. Pyrrolizidine and indolizidine synthesis. Reagents: i, $\text{PhCH}_2\text{OCOCl}$ (ZCI), Et_3N ; ii, TFA; iii, SuOH , DCC; iv, NaBH_4 ; v, Pr_4NRuO_4 , *N*-methylmorpholine-*N*-oxide; vi, $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH ; vii, H_2 , 60 psi, Pd-C ; viii, xylene reflux; ix, $\text{Ph}_3\text{P}^+\text{CH}_2\text{OMeCl}^-$, t-BuOK , THF; x, HCl aq, THF; xi, $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, $\text{LiN}(\text{SiMe}_3)_2$.

reaction with triethyl phosphonoacetate ($\text{LiN}(\text{SiMe}_3)_2$, 20 °C) to give α,β -unsaturated ester **18** (*E*-alkene illustrated). This time catalytic hydrogenation resulted in spontaneous lactamisation to afford the indolizidine **19**.

Formation of the tricyclic cycloadduct **20** from an intramolecular cycloaddition was reported in the preceding paper.² Unsurprisingly, aminal reduction in compound **20** (NaBH_3CN , 2 M HCl aq, THF) resulted in spontaneous opening of the lactone by the liberated secondary amine, to afford the bicyclic lactam **21**, isolated in 70% yield (Scheme 7). It was our aim to convert the ethyl ester into an isopropenyl group, a substituent found at the C-4 of natural 2,3,4-trisubstituted pyrrolidines in the kainoid family.¹³ Thus ester **21** was smoothly reacted with 2 mol equiv of methyl lithium, affording carbinol **22** in 50% yield. Unfortunately, further manipulation of this compound was not possible. Hydrogenolysis yielded an intractable mixture, whilst the lactam proved resistant to hydrolytic cleavage.



Scheme 7. Reagents: i, NaBH_3CN , 2 M HCl aq, THF; ii, 2 mol equiv MeLi , THF, -78 °C; iii, LiAlH_4 , THF; iv, 3 mol equiv $\text{Cl}_3\text{CCH}_2\text{OCOCl}$, pyridine; v, 3.5 mol equiv $\text{KN}(\text{SiMe}_3)_2$, 3.5 mol equiv MeI .

In an attempt to circumvent aminal opening resulting in lactamisation, tricycle **20** was treated with an excess of LiAlH_4 to afford the triol **23** in quantitative yield. To proceed further it was necessary to mask the hydroxyl groups of this highly polar triol, and we first examined protection of the alcohols as their trichloroethyl carbonates. Surprisingly, the product of treating **23** with 2,2,2-trichloroethyl chloroformate was the alkene **24**, presumably as a result of formation of the trichloroethyl carbonate at the C-7 hydroxymethyl group, and its subsequent elimination. To avoid this elimination the alcohols were protected as the corresponding methyl ethers using potassium hexamethyldisilazide and methyl iodide, affording **25** in quantitative yield. Disappointingly, attempted aminal cleavage under the standard conditions, followed by hydrogenolysis afforded a complex mixture of products.

3. Conclusion

We have illustrated the successful removal of the templating atoms from optically active pyrroloimidazoles prepared from optically active imidazolinium ylides, and some manipulations of the pyrrolidines so formed. There is clearly scope for much further application and elaboration of the cycloadducts, and work to this end is ongoing.

4. Experimental

4.1. General

Melting points were obtained on a Gallenkamp capillary or a Reichert hot stage and are uncorrected. IR spectra were recorded using a Perkin–Elmer 1820X FT spectrometer. Mass spectra were recorded using AEI MS902 or VG 7070E or VG Autospec spectrometers. ^1H NMR spectra were obtained using the following spectrometers: Bruker WM250 at 250 MHz; Jeol EX270 at 270 MHz; Bruker AM400 or Jeol EX400 at 400 MHz; Bruker DRX500 at 500 MHz. ^{13}C NMR spectra were recorded using the following instruments: Bruker WM250 spectrometer at 62.9 MHz; Jeol EX270 at 68 MHz; Bruker AM400 or Jeol EX400 spectrometer at 100.6 or 100.4 MHz, respectively. ^1H NMR spectra were determined in deuteriochloroform solution unless indicated, and chemical shifts are quoted in parts per million (ppm) from tetramethylsilane as internal standard; coupling constants are quoted in hertz. ^{13}C NMR spectra were determined in deuteriochloroform solution unless indicated and chemical shifts quoted in ppm from tetramethylsilane as internal standard or from tetramethylsilane using CDCl_3 as internal standard. Optical rotations were obtained using a Jasco DIP-370 polarimeter and a 50 mm cell. Column chromatography was carried out at medium pressure using Merck Kieselgel 60 (Art. 7729). Thin layer chromatography (TLC) was carried out on silica plates (Kieselgel 60, F254, Merck Art. 5554). Solvent extracts were dried over anhydrous magnesium sulfate or sodium sulfate for at least 10 min. Ether refers to diethyl ether and petroleum ether corresponds to the fraction with bp 40–60 °C. Tetrahydrofuran (THF) and ether were distilled from lithium aluminium hydride or potassium immediately prior to use. Other dry solvents were prepared as described in Perrin and Armarego¹⁴.

4.2. Reduction of pyrroloimidazole cycloadducts 2

4.2.1. (4S,7R,8aS)-2-Benzyl-7-methoxycarbonyl-7-methyl-4-phenyloctahydropyrrolo[1,2-*a*]pyrazin-1-one (3a). (3S,5S,7R,7aS)-1-Benzyl-5,7-bis(methoxycarbonyl)-7-methylhexahydropyrrolo[1,2-*a*]imidazole (**2a**, 0.24 g, 0.59 mmol) in ethanol (20 mL) was made acidic (determined using methyl green indicator) by the dropwise addition of 2 M hydrochloric acid. Sodium cyanoborohydride (40.8 mg, 0.65 mmol) was added in portions while maintaining the acidity, and the resultant mixture was stirred at room temperature for 3 h. The mixture was basified to pH 8 by the portionwise addition of solid potassium hydrogen carbonate, and partitioned between chloroform (2×50 mL) and water (50 mL). The organic phase

was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/hexane/triethylamine (50:49:1 v/v/v) and on standing this yielded the *title compound* as a colourless oil (93 mg, 42%): ν_{max} (film)/ cm^{-1} 2952, 1731, 1655, 1454, 1068, 701; δ_{H} (270 MHz; CDCl_3) 1.32 (3H, s, CCH_3), 2.14 (1H, dd, $J=9.2, 13.2, 8-\text{CHH}$), 2.37 (1H, d, $J=9.6, \text{NCHHC}$), 2.88 (1H, dd, $J=8.0, 13.2, 8-\text{CHH}$), 3.15 (1H, dd, $J=3.5, 13.1, \text{PhCHCHH}$), 3.30–3.40 (2H, m, NCHH and PhCHCHH), 3.67 (1H, dd, $J=3.5, 10.2, \text{PhCHCH}_2$), 3.71 (3H, s, OCH_3), 4.11 (1H, dd, $J=8.0, 9.2, 8-\text{aCH}$), 4.56, 4.73 (each 1H, d, $J=14.5, \text{PhCH}_2$), 7.24–7.35 (10H, m, Ar–H); δ_{C} (68 MHz; CDCl_3) 22.4 (CH_3), 38.5 (CHCH_2), 49.1 (CCH_3), 49.7 (PhCH_2), 52.2 (OCH_3), 52.8 (PhCHCH_2), 60.6 (PhCHCH_2), 63.1 (NCH_2C), 63.8 (CHCH_2), 127.1, 127.7, 127.8, 128.2, 128.5, 128.7 (6 \times Ar–CH), 136.7, 140.05 (2 \times Ar–C), 171.6 (CO_2), 176.7 (CON); m/z 378 (M^+ , 8%), 350 (23), 308 (26), 249 (22), 105 (100), 104 (24), 91 (86). HRMS: M^+ 378.1957; $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ requires M^+ 378.1943.

4.2.2. (*4R,7S,8aR*)-2-Benzyl-7-methoxycarbonyl-7-methyl-4-phenyloctahydropyrrolo[1,2-*a*]pyrazin-1-one (3b). Prepared from (*3R,5R,7S,7aR*)-1-benzyl-5,7-bis(methoxycarbonyl)-7-methylhexahydropyrrolo[1,2-*a*]imidazole (**2b**, 0.50 g, 1.22 mmol) by the method described above for the preparation of **3a** but using sodium cyanoborohydride (84.3 mg, 1.34 mmol) to afford the *title compound* as a pale yellow oil (220 mg, 48%); spectroscopic data were identical within experimental error to that recorded above for enantiomer **3a**.

4.2.3. (*2S,4R*)-1-[*(S*)-2-Benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (4d). Prepared from (*3S,5S,7R,7aS*)-1-benzyl-5-tert-butoxycarbonyl-7-methoxycarbonyl-7-methyl-3-phenylhexahydropyrrolo[1,2-*a*]imidazole (**2d**, 0.37 g, 0.82 mmol) by the method described above for the preparation of **3a** but using sodium cyanoborohydride (56.8 mg, 0.90 mmol). Purification by column chromatography, eluting with ethyl acetate yielded the *title compound* as a pale yellow oil (0.27 g, 73%): ν_{max} (film)/ cm^{-1} 3026, 2974, 1734, 1453, 1367, 1150, 1118, 700; δ_{H} (400 MHz; CDCl_3) 1.35 (3H, s, CH_3), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.67 (1H, dd, $J=4.5, 13.3, 3-\text{CHH}$), 2.68 (1H, dd, $J=9.7, 13.3, 3-\text{CHH}$), 2.81 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 2.87 (1H, d, $J=9.1, \text{NCHH}$), 2.95 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 3.05 (1H, d, $J=9.1, \text{NCHH}$), 3.61 (3H, s, OCH_3), 3.58–3.68 (2H, m, PhCHH and CHCO), 3.77 (1H, d, $J=13.3, \text{PhCHH}$), 4.01 (1H, t, $J=6.8, \text{PhCHCH}_2$), 7.21–7.29 (10H, m, Ar–H); δ_{C} (68 MHz; CDCl_3) 23.7 (CH_3), 27.9 ($\text{C}(\text{CH}_3)_3$), 40.5 (CHCH_2), 47.4 (CCH_3), 51.9 (OCH_3), 52.3 (PhCHCH_2), 53.8 (PhCH_2), 60.4 (NCH_2), 60.8 (CHCO), 64.3 (PhCHCH_2), 80.5 ($\text{C}(\text{CH}_3)_3$), 126.7, 127.4, 128.0, 128.1, 128.2, 128.5 (6 \times Ar–CH), 139.6, 140.2 (2 \times Ar–C), 174.1, 177.0 (2 \times CO); m/z 351 ($\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$, 2%), 332 (25), 276 (100), 91 (52). HRMS: $\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$ 351.2076; $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4$ requires $\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$ 351.2072. Found: C, 71.6; H, 8.3; N, 6.2%; $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4$ requires C, 71.7; H, 8.0; N, 6.2%.

4.2.4. (*2R,4S*)-1-[*(R*)-2-Benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (4e). Prepared from (*3R,5R,7S,7aR*)-1-benzyl-5-tert-butoxycarbonyl-7-methoxycarbonyl-7-methyl-3-phenylhexahydropyrrolo[1,2-*a*]imidazole (**2e**, 106 mg, 0.24 mmol) by the method described above for the preparation of **3a** but using sodium cyanoborohydride (16.3 mg, 0.26 mmol). Purification by column chromatography, eluting with ethyl acetate yielded the *title compound* as a pale yellow oil (81 mg, 76%): ν_{max} (film)/ cm^{-1} 3028, 2977, 2840, 1734, 1455, 1368, 1151, 1118, 734, 702; δ_{H} (400 MHz; CDCl_3) 1.35 (3H, s, CH_3), 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.67 (1H, dd, $J=4.5, 13.3, 3-\text{CHH}$), 2.68 (1H, dd, $J=9.8, 13.3, 3-\text{CHH}$), 2.81 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 2.87 (1H, d, $J=9.1, \text{NCHH}$), 2.95 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 3.05 (1H, d, $J=9.1, \text{NCHH}$), 3.61 (3H, s, OCH_3), 3.62–3.65 (2H, m, PhCHH and CHCO), 3.77 (1H, d, $J=13.2, \text{PhCHH}$), 4.01 (1H, t, $J=6.8, \text{PhCHCH}_2$), 7.21–7.30 (10H, m, Ar–H); δ_{C} (68 MHz; CDCl_3) 23.2 (CH_3), 27.5 ($\text{C}(\text{CH}_3)_3$), 40.1

(CHCH_2), 47.0 (CCH_3), 51.4 (OCH_3), 52.0 (PhCHCH_2), 53.5 (PhCH_2), 60.0 (NCH_2), 60.5 (CHCO), 63.9 (PhCHCH_2), 80.0 ($\text{C}(\text{CH}_3)_3$), 126.3, 127.0, 127.6, 127.8, 128.0, 128.1 (6 \times Ar–CH), 139.7, 139.95 (2 \times Ar–C), 173.55, 176.4 (2 \times CO); m/z 351 ($\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$, 4%), 332 (37), 276 (100), 91 (70). HRMS: $\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$ 351.2052; $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4$ requires $\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$ 351.2072.

4.2.5. (*2S,4R*)-1-[*(S*)-2-Benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-cyano-4-methylpyrrolidine (4f). Prepared from (*3S,5S,7R,7aS*)-1-benzyl-5-tert-butoxycarbonyl-7-cyano-7-methyl-3-phenylhexahydropyrrolo[1,2-*a*]imidazole (**2f**, 0.20 g, 0.48 mmol) by the method described above for the preparation of **3a** but using sodium cyanoborohydride (33 mg, 0.53 mmol). Purification by column chromatography, eluting with eluting with petroleum ether/ethyl acetate/triethylamine (60:19.5:0.5 v/v/v) yielded the *title compound* as a colourless oil (0.16 g, 80%): ν_{max} (film)/ cm^{-1} 3029, 2977, 2825, 2241, 1715, 1453, 1368, 1151, 732, 701; δ_{H} (400 MHz; CDCl_3) 1.45 (10H, s, NH and $\text{C}(\text{CH}_3)_3$), 1.47 (3H, s, CH_3), 1.90 (1H, dd, $J=4.6, 13.5, 3-\text{CHH}$), 2.67 (1H, dd, $J=9.7, 13.5, 3-\text{CHH}$), 2.90 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 2.96 (1H, d, $J=9.3, \text{NCHH}$), 3.01 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 3.08 (1H, d, $J=9.3, \text{NCHH}$), 3.71, 3.79 (each 1H, d, $J=13.3, \text{PhCH}_2$), 3.83 (1H, dd, $J=9.7, 4.6, \text{CHCO}$), 4.09 (1H, t, $J=6.8, \text{PhCHCH}_2$), 7.30–7.36 (10H, m, Ar–H); δ_{C} (68 MHz; CDCl_3) 23.75 (CH_3), 28.0 ($\text{C}(\text{CH}_3)_3$), 35.5 (CCH_3), 42.6 (CHCH_2), 52.4 (PhCHCH_2), 53.9 (PhCH_2), 60.4 (CHCO), 61.1 (NCH_2), 63.7 (PhCHCH_2), 81.4 ($\text{C}(\text{CH}_3)_3$), 125.0 (CN), 127.0, 127.9, 128.1, 128.3, 128.4, 128.7 (6 \times Ar–CH), 139.5, 139.93 (2 \times Ar–C), 173.15 (CO); m/z 345 (M^+ , 6%), 299 (53), 243 (88), 210 (30), 120 (41), 104 (56), 91 (100). HRMS (FAB): MH^+ 420.2657; $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_2$ requires MH^+ 420.2645.

4.2.6. (*2R,4S*)-1-[*(R*)-2-Benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-cyano-4-methylpyrrolidine (4g). Prepared from (*3R,5R,7S,7aR*)-1-benzyl-5-tert-butoxycarbonyl-7-cyano-7-methyl-3-phenylhexahydropyrrolo[1,2-*a*]imidazole (**2g**, 0.33 g, 0.79 mmol) by the method described above for the preparation of **3a** but using sodium cyanoborohydride (55 mg, 0.87 mmol) and ethanol (20 mL). Purification by column chromatography, eluting with eluting with petroleum ether/ethyl acetate/triethylamine (60:19.5:0.5 v/v/v) yielded the *title compound* as a colourless oil (0.17 g, 51%): ν_{max} (film)/ cm^{-1} 2976, 2236, 1714, 1452, 1368, 1154, 752, 702; δ_{H} (400 MHz; CDCl_3) 1.44 (10H, s, NH and $\text{C}(\text{CH}_3)_3$), 1.46 (3H, s, CH_3), 1.89 (1H, dd, $J=4.6, 13.4, 3-\text{CHH}$), 2.64 (1H, dd, $J=9.7, 13.4, 3-\text{CHH}$), 2.89 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 2.94 (1H, d, $J=9.3, \text{NCHH}$), 3.00 (1H, dd, $J=6.8, 11.7, \text{PhCHCHH}$), 3.07 (1H, d, $J=9.3, \text{NCHH}$), 3.68, 3.73 (each 1H, d, $J=13.3, \text{PhCH}_2$), 3.80 (1H, dd, $J=9.7, 4.6, \text{CHCO}$), 4.09 (1H, t, $J=6.8, \text{PhCHCH}_2$), 7.28–7.36 (10H, m, Ar–H); δ_{C} (100 MHz; CDCl_3) 23.7 (CH_3), 28.0 ($\text{C}(\text{CH}_3)_3$), 35.0 (CCH_3), 42.7 (CHCH_2), 51.7 (PhCHCH_2), 53.9 (PhCH_2), 60.3 (CHCO), 61.1 (NCH_2), 64.0 (PhCHCH_2), 81.3 ($\text{C}(\text{CH}_3)_3$), 125.0 (CN), 128.0, 128.3, 128.4, 128.7, 128.8, 128.9 (6 \times Ar–CH), 139.4, 139.8 (2 \times Ar–C), 173.2 (CO); m/z 345 ($\text{M}^+ - \text{C}_4\text{H}_{10}\text{O}$, 7%), 299 (28), 243 (87), 210 (11), 120 (27), 104 (52), 91 (100). HRMS: $\text{M}^+ - \text{C}_4\text{H}_{10}\text{O}$ 345.1870; $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_2$ requires $\text{M}^+ - \text{C}_4\text{H}_{10}\text{O}$ 345.1841. Found: C, 73.6; H, 8.1; N, 9.9%; $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_2 \cdot 0.3\text{H}_2\text{O}$ requires C, 73.5; H, 8.0; N, 9.9%.

4.2.7. (*2S,4R*)- and (*2S,4S*)-1-[*(S*)-2-Benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-methoxycarbonylpyrrolidines (4h) and (4ha). Sodium cyanoborohydride solution (1 M in THF; 0.23 mL, 0.23 mmol) was added in one portion to (*3S,5S,7R,7aS*)-1-benzyl-5-tert-butoxycarbonyl-7-methoxycarbonyl-3-phenylhexahydropyrrolo[1,2-*a*]imidazole (**2h**, 98 mg, 0.23 mmol) and hydrochloric acid (2 M; 2 mL) in THF (10 mL) and the resultant mixture was stirred at room temperature for 2 h. Workup as described for compound **3a** afforded a mixture of the *trans* pyrrolidine (**4h**) and the *cis* pyrrolidine (**4ha**) as a colourless oil (97 mg, 99%): ν_{max} (film)/ cm^{-1} 3027, 2974, 2951, 1734, 1149, 701; δ_{H} (400 MHz; CDCl_3 ; both diastereoisomers present, *cis*-isomer A/*trans*-isomer B 1:5) 1.38, 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$) isomers A

and B), 2.02–2.05, 2.24–2.27 (1H, m, CHCH_2CH isomers A and B), 2.88–2.94 (4H, m, PhCHCH_2 both isomers, NCHH both isomers and CH_2CHCH_2 isomer B), 3.12–3.22 (2H, m, CH_2CHCH_2 isomer A and NCHH both isomers), 3.60, 3.62 (3H, s, OCH_3 isomers B and A), 3.69–3.74 (3H, m, PhCH_2 both isomers and NCHCO both isomers), 3.97 (1H, t, $J=6.9$, PhCHCH_2 isomer A), 4.08 (1H, t, $J=6.6$, PhCHCH_2 isomer B), 7.20–7.30 (10H, m, Ar–H both isomers); δ_c (100 MHz; CDCl_3 ; both diastereoisomers present, *cis*-isomer A/*trans*-isomer B 1:5) 28.0 ($\text{C}(\text{CH}_3)_3$ both isomers), 32.4, 33.2 (CHCH_2CH isomers B and A), 41.1 (CH_2CHCH_2 both isomers), 51.7 (OCH_3 both isomers), 52.4 (PhCHCH_2 both isomers), 53.6 (PhCH_2 both isomers), 53.7, 54.0 (NCH_2 isomers B and A), 60.8, 61.5 (NCHCO isomers B and A), 64.0 (PhCHCH_2 both isomers), 80.7, 80.8 ($\text{C}(\text{CH}_3)_3$ isomers A and B), 126.9, 127.6, 128.1, 128.3, 128.4, 128.4, 128.5 (6× Ar–CH both isomers), 139.6, 139.8, 140.0 (2× Ar–C both isomers), 173.5, 173.8, 174.0, 174.3 (2× CO both isomers); m/z 438 (M^+ , 1%), 365 (4), 364 (15), 318 (56), 263 (35), 262 (80), 210 (19), 128 (23), 104 (56), 91 (100). HRMS: M^+ 438.2497; $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_4$ requires M^+ 438.2518.

4.2.8. (2R,4S)- and (2R,4R)-1-[(*R*)-2-Benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-methoxycarbonylpyrrolidines (4i**) and (**4ia**).** Prepared from (*3R,5R,7S,7aR*)-1-benzyl-5-tert-butoxycarbonyl-7-methoxycarbonyl-3-phenylhexahydrodipyrrolo[1,2-*a*]imidazole (**2i**, 0.80 g, 1.83 mmol) by the method described above for the preparation of **4h** but using sodium cyanoborohydride solution (1 M in THF; 1.83 mL, 1.83 mmol) and THF (80 mL). This yielded a mixture of the *trans* pyrrolidine (**4i**) and the *cis* pyrrolidine (**4ia**) as a colourless oil (0.80 g, 100%): ν_{max} (film)/ cm^{-1} 3028, 2975, 1732, 1454, 1367, 1149, 701; δ_{H} (270 MHz; CDCl_3 ; both diastereoisomers present, *cis*-isomer A/*trans*-isomer B 1:5) 1.39, 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$ isomers A and B), 2.02–2.05, 2.25–2.28 (1H, m, CHCH_2CH isomers A and B), 2.90–2.96 (4H, m, PhCHCH_2 both isomers, NCHH both isomers and CH_2CHCH_2 isomer B), 3.10–3.12 (1H, m, CH_2CHCH_2 isomer A), 3.19–3.22 (1H, m, NCHH both isomers), 3.59, 3.61 (1.2H, s, OCH_3 isomers B and A), 3.69–3.74 (3H, m, PhCH_2 both isomers and NCHCO both isomers), 4.00 (1H, t, $J=6.9$, PhCHCH_2 isomer A), 4.11 (1H, t, $J=6.7$, PhCHCH_2 isomer B), 7.25–7.35 (10H, m, Ar–H both isomers); δ_c (68 MHz; CDCl_3 ; both diastereoisomers present, *cis*-isomer A/*trans*-isomer B 1:5) 27.8 ($\text{C}(\text{CH}_3)_3$ both isomers), 32.3, 33.1 (CHCH_2CH isomers B and A), 41.0 (CH_2CHCH_2 both isomers), 51.7 (OCH_3 both isomers), 52.1 (PhCHCH_2 both isomers), 53.4 (PhCH_2 both isomers), 53.6, 54.0 (NCH_2 isomers B and A), 60.5, 61.2 (NCHCO isomers B and A), 63.7 (PhCHCH_2 both isomers), 80.6, 80.7 ($\text{C}(\text{CH}_3)_3$ isomers A and B), 126.9, 127.5, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4 (6× Ar–CH both isomers), 139.3, 139.3, 139.7, 139.7 (2× Ar–C both isomers), 173.5, 173.8, 173.9, 174.1 (2× CO both isomers); m/z 438 (M^+ , 1%), 365 (6), 364 (22), 318 (21), 263 (14), 262 (70), 128 (27), 104 (71), 91 (100). HRMS: M^+ 438.2544; $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_4$ requires M^+ 438.2518.

4.2.9. (2S,4S)- and (2S,4R)-1-[(*S*)-2-Benzylamino-1-phenethyl]-2,4-bis(tert-butoxycarbonyl)pyrrolidines (4ja**) and (**4j**).** Prepared from (*3S,5S,7R,7aS*)-1-benzyl-5,7-bis(tert-butoxycarbonyl)-3-phenylhexahydrodipyrrolo[1,2-*a*]imidazole (**2j**, 0.60 g, 1.25 mmol) by the method described above for the preparation of **4h** but using sodium cyanoborohydride solution (1 M in THF, 1.25 mL, 1.25 mmol) and hydrochloric acid (2 M; 12 mL). This yielded a mixture of the *cis* pyrrolidine (**4ja**) and the *trans* pyrrolidine (**4j**) as a colourless oil (0.58 g, 96%): ν_{max} (film)/ cm^{-1} 3062, 3028, 2977, 2930, 1725, 1654, 1367, 1150, 701; δ_{H} (270 MHz; CDCl_3 ; both diastereoisomers present, *trans*-isomer A/*cis*-isomer B 1:3) 1.37, 1.38, 1.39, 1.44 (18H, s, $\text{C}(\text{CH}_3)_3$ both isomers), 1.96–1.98 (2H, m, CHCH_2CH isomer A), 2.24 (2H, t, $J=6.9$, CHCH_2CH isomer B), 2.81–2.85 (4H, m, PhCHCH_2 both isomers, NCHH both isomers and CH_2CHCH_2 both isomers), 3.16–3.18 (1H, m, NCHH both isomers), 3.76–3.81 (3H, m, PhCH_2 both isomers and NCHCO both isomers), 3.94–3.96, 4.12–4.14 (1H,

m, PhCHCH_2 isomers A and B), 7.25–7.34 (10H, m, Ar–H both isomers); δ_c (68 MHz; CDCl_3 ; both diastereoisomers present, *trans*-isomer A/*cis*-isomer B 1:3) 27.9, 27.9 ($\text{C}(\text{CH}_3)_3$ isomers B and A), 32.5, 33.1 (CHCH_2CH isomers B and A), 41.8, 42.1 (CH_2CHCH_2 isomers B and A), 51.9 (PhCHCH_2 both isomers), 53.1 (NCH_2 isomer A), 53.3 (PhCH_2 both isomers), 53.5 (NCH_2 isomer B), 60.2, 61.2 (NCHCO isomers B and A), 63.2, 64.6 (PhCHCH_2 isomers B and A), 80.3, 80.4, 80.5, 80.6 (2× $\text{C}(\text{CH}_3)_3$ both isomers), 126.9, 127.0, 127.4, 127.5, 127.9, 127.9, 128.1, 128.5 (6× Ar–CH both isomers), 139.2, 139.4, 139.4 (2× Ar–C both isomers), 172.6, 173.0, 173.3, 174.0 (2× CO both isomers); m/z 407 ($\text{M}^+ - \text{C}_4\text{H}_9\text{O}$, 4%), 406 (7), 360 (32), 304 (32), 248 (67), 114 (30), 104 (38), 91 (100). HRMS: $\text{M}^+ - \text{C}_4\text{H}_9\text{O}$ 407.2325; $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_4$ requires $\text{M}^+ - \text{C}_4\text{H}_9\text{O}$ 407.2335.

4.2.10. (2R,4R)- and (2R,4S)-1-[(*R*)-2-Benzylamino-1-phenethyl]-2,4-bis(tert-butoxycarbonyl)pyrrolidines (4ka**) and (**4k**).** Prepared from (*3R,5R,7S,7aR*)-1-benzyl-5,7-bis(tert-butoxycarbonyl)-3-phenylhexahydrodipyrrolo[1,2-*a*]imidazole (**2k**) (118 mg, 0.25 mmol) by the method described above for the preparation of **4h** but using sodium cyanoborohydride solution (1 M in THF, 0.25 mL, 0.25 mmol) and hydrochloric acid (2 M; 2.5 mL). This yielded a mixture of the *cis* pyrrolidine (**4ka**) and the *trans* pyrrolidine (**4k**) as a colourless oil (114 mg, 97%): ν_{max} (film)/ cm^{-1} 2979, 1732, 1368, 1156; δ_{H} (270 MHz; CDCl_3 ; both diastereoisomers present, *trans*-isomer A/*cis*-isomer B 1:3) 1.30, 1.31, 1.36 (18H, 3×s, 2× $\text{C}(\text{CH}_3)_3$ both isomers), 1.91–1.93, 2.18–2.20 (2H, m, CHCH_2CH isomers A and B), 2.80–2.84 (4H, m, PhCHCH_2 both isomers, NCHH both isomers and CH_2CHCH_2 both isomers), 3.08–3.10 (1H, m, NCHH both isomers), 3.60–3.65 (3H, m, PhCH_2 both isomers and NCHCO both isomers), 3.87 (1H, dd, $J=6.3$, 7.3, PhCHCH_2 isomer A), 4.02 (1H, t, $J=6.6$, PhCHCH_2 isomer B), 7.15–7.23 (10H, m, Ar–H both isomers); δ_c (68 MHz; CDCl_3 ; both diastereoisomers present, *trans*-isomer A/*cis*-isomer B 1:3) 27.9, 28.0 ($\text{C}(\text{CH}_3)_3$ isomers B and A), 32.4, 33.1 (CHCH_2CH isomers B and A), 42.1, 42.2 (CH_2CHCH_2 isomers B and A), 52.4 (PhCHCH_2 both isomers), 53.6 (NCH_2 isomer A), 53.7 (PhCH_2 both isomers), 54.1 (NCH_2 isomer B), 60.7, 61.7 (NCHCO isomers B and A), 63.9, 65.2 (PhCHCH_2 isomers B and A), 80.3, 80.4, 80.5, 80.5 (2× $\text{C}(\text{CH}_3)_3$ both isomers), 126.7, 127.4, 128.0, 128.0, 128.2, 128.3, 128.5, 128.8 (6× Ar–CH both isomers), 139.9, 140.0, 140.1, 140.3 (2× Ar–C both isomers), 172.7, 173.2, 173.5, 173.8 (2× CO both isomers); m/z 480 (1%), 407 (7), 406 (19), 360 (68), 304 (65), 248 (96), 114 (90), 104 (95), 91 (100). HRMS: M^+ 480.2999; $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_4$ requires M^+ 480.2988.

4.3. N-Debenzylation of pyrrolidines 4

4.3.1. (2S,4R)-2-tert-Butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (5d**).** A suspension of (2S,4R)-1-[(*S*)-2-benzylamino-1-phenethyl]-2-tert-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (**4d**, 0.48 g, 1.06 mmol) and Pearlman's catalyst (moisture content 50%; palladium content 20%, dry weight basis; 100 mg) in methanol (25 mL) was stirred under an atmosphere of hydrogen at room temperature for 16 h. The suspension was filtered through a pad of kieselguhr and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the *title compound* as a colourless oil (107 mg, 42%), $[\alpha]_{\text{D}}^{22} +6.2$ (*c* 0.96 in CHCl_3): ν_{max} (KBr)/ cm^{-1} 2977, 1730, 1250, 1157; δ_{H} (270 MHz; CDCl_3) 1.29 (3H, s, CH_3), 1.47 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.68 (1H, dd, $J=6.6$, 13.2, CHCHH), 1.97 (1H, br s, NH), 2.70 (1H, dd, $J=9.2$, 13.2, CHCHH), 2.90, 3.31 (each 1H, d, $J=11.1$, NHCH_2), 3.71 (3H, s, OCH_3), 3.79 (1H, dd, $J=6.6$, 9.2, CHCO); δ_c (68 MHz; CDCl_3) 22.7 (CH_3), 27.9 ($\text{C}(\text{CH}_3)_3$), 41.5 (CHCH_2), 50.1 (CCH_3), 52.1 (OCH_3), 57.7 (NCH_2), 60.5 (CHCO), 81.2 ($\text{C}(\text{CH}_3)_3$), 174.0, 176.8 (2× CO); m/z 142 ($\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$, 100%), 82 (78). HRMS: $\text{M}^+ - \text{C}_4\text{H}_9\text{CO}_2$ 142.0840;

$C_{12}H_{21}NO_4$ requires $M^+ - C_4H_9CO_2$ 142.0868. Found: C, 59.6; H, 9.0; N, 5.8%; $C_{12}H_{21}NO_4$ requires C, 59.2; H, 8.7; N, 5.8%.

4.3.2. (2*R*,4*S*)-2-*tert*-Butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (5e). Prepared from (2*R*,4*S*)-1-[(*R*)-2-benzylamino-1-phenethyl]-2-*tert*-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (4e, 226 mg, 0.50 mmol) by the method described above for 5d but using Pearlman's catalyst (40 mg) and methanol (15 mL). This yielded the *title compound* as a colourless oil (65 mg, 53%), $[\alpha]_D^{22} -6.6$ (*c* 1.24 in $CHCl_3$): ν_{max} (KBr)/cm⁻¹ 2977, 1730, 1156; δ_H (270 MHz; $CDCl_3$) 1.29 (3H, s, CH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.67 (1H, dd, *J*=6.6, 13.2, $CHCHH$), 2.46 (1H, br s, NH), 2.69 (1H, dd, *J*=9.0, 13.2, $CHCHH$), 2.89, 3.29 (each 1H, d, *J*=11.0, $NHCH_2$), 3.71 (3H, s, OCH_3), 3.80 (1H, dd, *J*=6.6, 9.0, $CHCO$); δ_C (68 MHz; $CDCl_3$) 22.6 (CH_3), 27.9 ($C(CH_3)_3$), 41.4 ($CHCH_2$), 50.0 (CCH_3), 52.0 (OCH_3), 57.7 (NCH_2), 60.5 ($CHCO$), 81.1 ($C(CH_3)_3$), 173.9, 176.8 (2 \times CO); *m/z* 142 ($M^+ - C_4H_9CO_2$, 100%), 82 (51). HRMS: $M^+ - C_4H_9CO_2$ 142.0856; $C_{12}H_{21}NO_4$ requires $M^+ - C_4H_9CO_2$ 142.0868. Found: C, 59.6; H, 9.0; N, 5.8%; $C_{12}H_{21}NO_4$ requires C, 59.2; H, 8.7; N, 5.8%.

4.3.3. (2*S*,4*R*)- and (2*S*,4*S*)-2-*tert*-Butoxycarbonyl-4-methoxycarbonylpyrrolidines (5h) and (5ha). Prepared from a mixture of (2*S*,4*R*)- and (2*S*,4*S*)-1-[(*S*)-2-benzylamino-1-phenethyl]-2-*tert*-butoxycarbonyl-4-methoxycarbonylpyrrolidines (4h/4ha, 1.28 g, 2.92 mmol) by the method described above for the preparation of 5d but using Pearlman's catalyst (0.26 g) and methanol (60 mL). The residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the *cis* pyrrolidine (5ha) as a colourless oil (0.21 g, 31%): ν_{max} (film)/cm⁻¹ 2977, 1731, 1368, 1155; δ_H (250 MHz; $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 1.89 (1H, br s, NH), 2.07–2.10, 2.39–2.41 (each 1H, m, $CHCH_2CH$), 2.91–2.94 (1H, m, CH_2CHCH_2), 3.07 (1H, dd, *J*=6.7, 11.0, $NHCHH$), 3.36 (1H, dd, *J*=7.6, 11.0 $NHCHH$), 3.64 (1H, dd, *J*=7.3, 8.5, $NHCH$), 3.70 (3H, s, OCH_3); δ_C (68 MHz; $CDCl_3$) 28.4 ($C(CH_3)_3$), 34.3 ($CHCH_2CH$), 43.9 (CH_2CHCH_2), 51.0 (NCH_2), 52.3 (OCH_3), 61.0 (NCH), 81.7 ($C(CH_3)_3$), 174.1, 175.0 (2 \times CO); *m/z* 128 ($M^+ - C_4H_9CO_2$, 100%), 68 (74), 57 (20). HRMS: $M^+ - C_4H_9CO_2$ 128.0714; $C_{11}H_{19}NO_4$ requires $M^+ - C_4H_9CO_2$ 128.0711; and the *trans* pyrrolidine (5h) as a colourless oil (0.16 g, 24%): ν_{max} (film)/cm⁻¹ 2978, 1731, 1368, 1156; δ_H (250 MHz; $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 2.11–2.13 (1H, m, $CHCHHCH$), 2.30 (1H, br s, NH), 2.38–2.41 (1H, m, $CHCHHCH$), 2.99–3.01 (1H, m, CH_2CHCH_2), 3.12 (1H, dd, *J*=7.6, 10.8, $NHCHH$), 3.30 (1H, dd, *J*=5.9, 10.8, $NHCHH$), 3.66–3.69 (4H, m, OCH_3 and $NHCH$); δ_C (68 MHz; $CDCl_3$) 27.9 ($C(CH_3)_3$), 33.8 ($CHCH_2CH$), 43.7 (CH_2CHCH_2), 50.3 (NCH_2), 51.9 (OCH_3), 60.8 (NCH), 81.4 ($C(CH_3)_3$), 173.2, 174.6 (2 \times CO); *m/z* 128 ($M^+ - C_4H_9CO_2$, 91%), 68 (99), 57 (44), 56 (51). HRMS: $M^+ - C_4H_9CO_2$ 128.0706. $C_{11}H_{19}NO_4$ requires $M^+ - C_4H_9CO_2$ 128.0711.

4.3.4. (2*R*,4*S*)- and (2*R*,4*R*)-2-*tert*-Butoxycarbonyl-4-methoxycarbonylpyrrolidines (5i) and (5ia). Prepared from a mixture of (2*R*,4*S*)- and (2*R*,4*R*)-1-[(*R*)-2-benzylamino-1-phenethyl]-2-*tert*-butoxycarbonyl-4-methoxycarbonylpyrrolidines (4i/4ia, 1.89 g, 4.31 mmol) by the method described above for the preparation of 5d but using Pearlman's catalyst (0.38 g) and methanol (100 mL). The residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the *cis* pyrrolidine (5ia) as a colourless oil (60 mg, 6%): ν_{max} (film)/cm⁻¹ 3347, 2977, 1730, 1156; δ_H (250 MHz; $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 2.07–2.10 (1H, m, $CHCHHCH$), 2.40–2.42 (2H, m, NH and $CHCHHCH$), 2.92–2.95 (1H, m, CH_2CHCH_2), 3.06 (1H, dd, *J*=6.6, 10.8, $NHCHH$), 3.36 (1H, dd, *J*=7.6, 10.8, $NHCHH$), 3.70 (3H, s, OCH_3), 3.79 (1H, dd, *J*=5.6, 8.6, $NHCH$); δ_C (68 MHz; $CDCl_3$) 27.9 ($C(CH_3)_3$), 33.8 ($CHCH_2CH$), 43.4 (CH_2CHCH_2), 50.5 (NCH_2), 51.9 (OCH_3), 60.5 (NCH), 81.3 ($C(CH_3)_3$), 173.5, 174.5 (2 \times CO); *m/z* 128 ($M^+ - C_4H_9CO_2$, 100%), 68 (52), 57 (14). HRMS: $M^+ - C_4H_9CO_2$ 128.0710; $C_{11}H_{19}NO_4$ requires $M^+ - C_4H_9CO_2$ 128.0711; and the *trans* pyrrolidine (5i) as

a colourless oil (0.45 g, 45%): ν_{max} (film)/cm⁻¹ 3342, 2979, 1733, 1369, 1157; δ_H (250 MHz; $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 2.12–2.14 (1H, m, $CHCHHCH$), 2.38–2.41 (2H, m, NH and $CHCHHCH$), 2.98–3.00 (1H, m, CH_2CHCH_2), 3.12 (1H, dd, *J*=7.6, 10.7, $NHCHH$), 3.30 (1H, dd, *J*=5.9, 10.7, $NHCHH$), 3.66–3.69 (4H, m, OCH_3 and $NHCH$); δ_C (68 MHz; $CDCl_3$) 27.7 ($C(CH_3)_3$), 33.6 ($CHCH_2CH$), 43.5 (CH_2CHCH_2), 50.1 (NCH_2), 51.7 (OCH_3), 60.5 (NCH), 81.2 ($C(CH_3)_3$), 172.9, 174.4 (2 \times CO); *m/z* (FAB) 230 (MH^+ , 4%), 129 (100), 128 (84), 68 (75), and 57 (55). HRMS (FAB): MH^+ 230.1375; $C_{11}H_{19}NO_4$ requires MH^+ 230.1387. Found: C, 57.65; H, 8.5; N, 6.1%; $C_{11}H_{19}NO_4$ requires C, 57.6; H, 8.35; N, 6.1%.

4.3.5. (2*S*,4*R*)- and (2*S*,4*S*)-2,4-Bis(tert-butoxycarbonyl)pyrrolidines (5j) and (5ja). Prepared from a mixture of (2*S*,4*R*)- and (2*S*,4*S*)-1-[(*S*)-2-benzylamino-1-phenethyl]-2,4-bis(tert-butoxycarbonyl)pyrrolidines (4j/4ja, 100 mg, 0.21 mmol) by the method described above for the preparation of 5d but using Pearlman's catalyst (20 mg) and methanol (5 mL). The residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the *trans* pyrrolidine (5j) as a colourless oil (3 mg, 5%): ν_{max} (film)/cm⁻¹ 3342, 2979, 2934, 1729, 1368, 1152; δ_H (270 MHz; $CDCl_3$) 1.45, 1.46 (each 9H, s, $C(CH_3)_3$), 1.97 (1H, br s, NH), 2.02–2.04, 2.33–2.35 (each 1H, m, $CHCH_2CH$), 2.81–2.84 (1H, m, CH_2CHCH_2), 3.01 (1H, dd, *J*=6.9, 10.9, $NHCHH$), 3.33 (1H, dd, *J*=7.6, 10.9, $NHCHH$), 3.75 (1H, dd, *J*=5.6, 8.6, $NHCH$); δ_C (68 MHz; $CDCl_3$) 27.4 (2 \times $C(CH_3)_3$), 33.3 ($CHCH_2CH$), 44.4 (CH_2CHCH_2), 49.9 (NCH_2), 60.3 (NCH), 79.8, 80.4 (2 \times $C(CH_3)_3$), 172.6, 172.8 (2 \times CO); *m/z* 170 ($M^+ - C_4H_9CO_2$, 24%), 114 (100), 68 (34), 57 (43). Found: C, 61.7; H, 9.4; N, 5.0%; $C_{14}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2%; and the *cis* pyrrolidine (5ja) as a colourless oil (32 mg, 57%): ν_{max} (film)/cm⁻¹ 2977, 2933, 1728, 1368, 1251, 1151; δ_H (270 MHz; $CDCl_3$) 1.44, 1.47 (each 9H, s, $C(CH_3)_3$), 2.03–2.06 (1H, m, $CHCHHCH$), 2.28 (1H, br s, NH), 2.34–2.37 (1H, m, $CHCHHCH$), 2.87–2.89 (1H, m, CH_2CHCH_2), 3.07 (1H, dd, *J*=7.9, 10.9, $NHCHH$), 3.25 (1H, dd, *J*=5.9, 10.9, $NHCHH$), 3.64 (1H, dd, *J*=7.3, 8.5, $NHCH$); δ_C (68 MHz; $CDCl_3$) 28.0 (2 \times $C(CH_3)_3$), 34.0 ($CHCH_2CH$), 45.1 (CH_2CHCH_2), 50.5 (NCH_2), 61.0 (NCH), 80.6, 81.3 (2 \times $C(CH_3)_3$), 173.2, 173.5 (2 \times CO); *m/z* 170 ($M^+ - C_4H_9CO_2$, 40%), 114 (100), 68 (24), 57 (34). Found: C, 62.05; H, 9.4; N, 5.1%; $C_{14}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2%.

4.3.6. (2*R*,4*S*)- and (2*R*,4*R*)-2,4-Bis(tert-butoxycarbonyl)pyrrolidines (5k) and (5ka). Prepared from a mixture of (2*R*,4*S*)- and (2*R*,4*R*)-1-[(*R*)-2-benzylamino-1-phenethyl]-2,4-bis(tert-butoxycarbonyl)pyrrolidines (4k/4ka, 0.40 g, 0.83 mmol) by the method described above for the preparation of 5d but using Pearlman's catalyst (80 mg) and methanol (40 mL). The residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the *trans* pyrrolidine (5k) as a colourless oil (10 mg, 4%): ν_{max} (film)/cm⁻¹ 3318, 2978, 2934, 1729, 1368, 1152; δ_H (270 MHz; $CDCl_3$) 1.45, 1.46 (each 9H, s, $C(CH_3)_3$), 1.91 (1H, br s, NH), 2.01–2.03, 2.34–2.36 (each 1H, m, $CHCH_2CH$), 2.81–2.84 (1H, m, CH_2CHCH_2), 3.01 (1H, dd, *J*=6.9, 10.9, $NHCHH$), 3.33 (1H, dd, *J*=7.6, 10.9, $NHCHH$), 3.75 (1H, dd, *J*=5.3, 8.6, $NHCH$); δ_C (68 MHz; $CDCl_3$) 28.0 (2 \times $C(CH_3)_3$), 34.0 ($CHCH_2CH$), 44.8 (CH_2CHCH_2), 50.8 (NCH_2), 60.8 (NCH), 80.7, 81.3 (2 \times $C(CH_3)_3$), 173.2, 173.5 (2 \times CO); *m/z* 170 ($M^+ - C_4H_9CO_2$, 45%), 114 (100), 68 (51), 57 (42). HRMS: $M^+ - C_4H_9CO_2$ 170.1161; $C_{14}H_{25}NO_4$ requires $M^+ - C_4H_9CO_2$ 170.1181; and the *cis* pyrrolidine (5ka) as a colourless oil (136 mg, 60%): ν_{max} (film)/cm⁻¹ 3335, 2978, 1729, 1368, 1152; δ_H (250 MHz; $CDCl_3$) 1.44, 1.47 (each 9H, s, $C(CH_3)_3$), 1.94 (1H, br s, NH), 2.02–2.05, 2.34–2.37 (each 1H, m, $CHCH_2CH$), 2.88–2.90 (1H, m, CH_2CHCH_2), 3.05 (1H, dd, *J*=7.7, 10.9, $NHCHH$), 3.25 (1H, dd, *J*=5.9, 10.9, $NHCHH$), 3.64 (1H, dd, *J*=7.2, 8.4, $NHCH$); δ_C (68 MHz; $CDCl_3$) 27.8 (2 \times $C(CH_3)_3$), 33.7 ($CHCH_2CH$), 44.8 (CH_2CHCH_2), 50.2 (NCH_2), 60.7 (NCH), 80.4, 81.0 (2 \times $C(CH_3)_3$), 173.0, 173.2 (2 \times CO); *m/z* 170 ($M^+ - C_4H_9CO_2$, 79%), 114 (100), 68 (70), 57 (63). HRMS: $M^+ - C_4H_9CO_2$ 170.1166; $C_{14}H_{25}NO_4$

requires $M^+ - C_4H_9CO_2$ 170.1181. Found: C, 62.05; H, 9.6; N, 5.0%; $C_{14}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2%.

4.3.7. (2S,4R)-2-tert-Butoxycarbonyl-2,4-dimethyl-4-methoxycarbonylpyrrolidine (5i). To (3S,5S,7R,7aS)-1-benzyl-5-tert-butoxycarbonyl-7-methoxycarbonyl-5,7-dimethyl-3-phenylhexahydropyrrolo[1,2-a]imidazole (2i) (740 mg, 1.59 mmol) in THF (75 mL) was added hydrochloric acid (2 M; 15 mL) followed immediately by sodium cyanoborohydride (1 M in THF, 1.59 mL, 1.59 mmol). After stirring for 2.5 h the mixture was neutralised by the addition of solid potassium bicarbonate and partitioned between chloroform (3×75 mL) and water (100 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was taken up in methanol (100 mL), followed by the addition of trifluoroacetic acid (100 μ L) and Pearlman's catalyst (moisture content 50%; palladium content 20%, dry weight basis; 600 mg). The suspension was shaken under hydrogen (60 psi) in a Parr apparatus for 20 h. After filtration through kieselguhr the solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 mL), washed with saturated sodium bicarbonate solution (3×50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the title compound (230 mg, 56%) as a colourless oil, $[\alpha]_D^{22} +8.3$ (*c* 1.48 in CH_2Cl_2); ν_{max} (film)/cm⁻¹ 3343, 2976, 2876, 1725, 1458, 1369, 1256, 1135; δ_H (270 MHz; $CDCl_3$) 1.20, 1.31 (each 3H, s, CH_3), 1.42 (9H, s, $C(CH_3)_3$), 2.05, 2.27 (each 1H, d, *J*=13.7, CH_2), 2.53 (1H, br, NH), 2.74, 3.32 (each 1H, d, *J*=10.5, $NHCH_2$), 3.65 (3H, s, OCH_3); δ_C (68 MHz; $CDCl_3$) 23.1, 26.2 (2× CH_3), 27.7 ($C(CH_3)_3$), 47.4 (CH_2), 50.2 (4-C), 52.0 (OCH_3), 57.1 (NCH₂), 66.3 (2-C), 81.0 ($C(CH_3)_3$), 176.1, 177.2 (2× CO); *m/z* (FAB) 258 (MH^+ , 63%), 214 (74), 202 (100), 156 (71), 96 (36), 57 (34). HRMS (FAB): MH^+ 258.1702; $C_{13}H_{23}NO_4$ requires MH^+ 258.1700.

4.3.8. (2S,4R)-1-(4-Bromobenzoyl)-2-tert-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (6). To (2S,4R)-2-tert-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (5d) (400 mg, 1.65 mmol) in dry dichloromethane (20 mL) was added triethylamine (0.23 mL, 167 mg, 1.65 mmol), followed by 4-bromobenzoyl chloride (362 mg, 1.65 mmol). After stirring for 48 h, the solution was washed with water (2×30 mL), saturated sodium bicarbonate solution (2×30 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue purified by column chromatography, eluting with petroleum ether/ethyl acetate (2:1 v/v), to yield the title compound (600 mg, 86%) as a colourless oil. A portion was crystallised from pentane and dichloromethane to afford colourless prisms, mp 114–115 °C; ν_{max} ($CHCl_3$)/cm⁻¹ 2982, 2956, 2879, 1734, 1635, 1423, 1224, 1157; δ_H (400 MHz; ($CD_3)_2SO$, 85 °C) 1.30 (3H, s, CH_3), 1.39 (9H, s, $C(CH_3)_3$), 1.83 (1H, dd, *J*=8.1, 12.9, $CHCHH$), 2.77 (1H, dd, *J*=8.5, 12.9, $CHCHH$), 3.39 (1H, d, *J*=10.3, NCHH), 3.64 (3H, s, OCH_3), 3.85 (1H, br, NCHH), 4.41 (1H, dd, *J*=8.1, 8.5, $CHCH_2$), 7.38, 7.64 (each 2H, d, *J*=7.8, Ar–H); δ_C (100.4 MHz; $CDCl_3$; mixture of rotamers) 20.9 and 21.7 (CH_3), 27.3 and 27.8 ($C(CH_3)_3$), 39.1 and 41.0 (3-C), 46.9 and 49.3 (4-C), 52.65 (OCH_3), 56.0 and 58.0 (5-C), 59.0 and 60.9 (2-C), 81.0 and 81.7 ($C(CH_3)_3$), 123.5 and 124.0 (Ar–C), 129.4, 131.4, 131.7 (2× Ar–CH), 135.0 and 135.4 (Ar–C), 167.4 and 168.4, 170.2 and 170.8, 174.9 and 175.2 (3× CO); *m/z* 427 (M^+ , ^{81}Br , <1%), 425 (M^+ , ^{79}Br , <1%), 326 (36), 324 (37), 185 (96), 183 (100), 57 (25). HRMS: M^+ 425.0838; $C_{19}H_{24}BrNO_5$ requires M^+ 425.0838. Found: C, 53.54; H, 5.76; N, 3.26%; $C_{19}H_{24}BrNO_5$ requires C, 53.5; H, 5.7; N, 3.3%.

Crystal data for 6: $C_{19}H_{24}BrNO_5$, $M=426.3$, colourless block, $0.69 \times 0.25 \times 0.20$ mm; orthorhombic, $P2_12_12_1$; $a=9.816(3)$, $b=11.821(3)$, $c=19.271(4)$ Å, $U=2104(1)$ Å³, $T=298$ K, $\mu(Mo K\alpha)=1.98$ mm⁻¹, $D_c=1.35$ g cm⁻³, $Z=4$, $F(000)=880$, $2\theta_{max}=50^\circ$, 236

parameters, $wR=0.077$ for all 2117 data, $R=0.034$ for 779 data with $F_0 > 4\sigma(F_0)$.

4.4. Synthesis of naturally occurring proline derivative 8

4.4.1. (2R,4S)-2-tert-Butoxycarbonyl-4-hydroxymethylpyrrolidine (7). Lithium borohydride solution (2 M in THF; 1.06 mL, 2.11 mmol) was added dropwise to stirred (2R,4S)-2-tert-butoxycarbonyl-4-methoxycarbonylpyrrolidine (5i, 0.44 g, 1.92 mmol) and dry methanol (67.5 mg, 0.085 mL, 2.11 mmol) in dry ether (12 mL). The resulting mixture was stirred at room temperature for 0.5 h, when hydrochloric acid (2 M; 6 mL) was added dropwise and stirring was continued for 0.5 h. The mixture was basified to pH 8 by the portionwise addition of solid potassium hydrogen carbonate and extracted with dichloromethane (3×20 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate/triethylamine (99.5:0.5 v/v) to yield the title compound as a colourless oil (0.16 g, 41%): ν_{max} (film)/cm⁻¹ 3388, 3227, 2978, 2933, 1729, 1370, 1259, 1156; δ_H (400 MHz; $CDCl_3$) 1.42 (9H, s, $C(CH_3)_3$), 1.72–1.74 (1H, m, $CHCHHCH$), 2.48–2.53 (3H, m, $CHCHHCH$, CH_2CHCH_2 and NH), 2.97–2.99, 3.21–3.23 (each 1H, m, NHCH₂), 3.52–3.56 (3H, m, OCH_2 and NHCH); δ_C (68 MHz; $CDCl_3$) 27.9 ($C(CH_3)_3$), 32.8 ($CHCH_2CH$), 39.4 (CH_2CHCH_2), 57.2 (NCH₂), 63.8 (OCH_2), 67.4 (NCH), 83.4 ($C(CH_3)_3$), 170.6 (CO); *m/z* 100 ($M^+ - C_4H_9CO_2$, 100%), 82 (36), 57 (29). HRMS: Found: $M^+ - C_4H_9CO_2$ 100.0755; $C_{10}H_{19}NO_3$ requires $M^+ - C_4H_9CO_2$ 100.0762.

4.4.2. (2R,4S)-4-Hydroxymethylpyrrolidine-2-carboxylic acid (8). (2R,4S)-2-tert-Butoxycarbonyl-4-hydroxymethylpyrrolidine (7) (53 mg, 0.26 mmol) in trifluoroacetic acid (3 mL) was stirred at room temperature under nitrogen for 10 h. The solvent was removed under reduced pressure and the residue was purified by ion-exchange chromatography (Dowex 50X2-100 acid form). The column was washed with deionised water to pH 7 and then the product was eluted with aqueous ammonia (2 M). This yielded the title compound as a colourless gum (19 mg, 50%), $[\alpha]_D^{22} +47.8$ (*c* 0.49 in H_2O) (lit.¹⁰ –48.0, in H_2O , for the enantiomer): ν_{max} (KBr)/cm⁻¹ 3280, 2923, 1630, 1560, 1383, 1091; δ_H (270 MHz; D_2O) 1.70–1.72 (1H, m, $CHCHHCH$), 2.47–2.51 (2H, m, $CHCHHCH$ and CH_2CHCH_2), 3.09–3.12 (1H, m, NCHH), 3.46–3.52 (3H, m, NCHH and OCH_2), 4.09 (1H, t, *J*=8.6, NCH); δ_C (68 MHz; D_2O) 31.3 ($CHCH_2CH$), 39.9 (CH_2CHCH_2), 47.7 (NCH₂), 61.2 (NCH), 61.9 (OCH_2), 174.1 (CO); *m/z* (FAB) 146 (MH^+ , 58%), 89 (22), 77 (21). HRMS (FAB): MH^+ 146.0829; $C_6H_{11}NO_3$ requires MH^+ 146.0812.

4.4.3. (2S,4S)-2,4-Bis(tert-butoxycarbonyl)-1-(4-bromobenzoyl)pyrrolidine (9). To (2S,4S)-2,4-bis(tert-butoxycarbonyl)pyrrolidine (5ja) (81 mg, 0.30 mmol) in dry dichloromethane (10 mL) was added triethylamine (0.042 mL, 30.3 mg, 0.30 mmol) followed by 4-bromobenzoyl chloride (66 mg, 0.30 mmol). After stirring for 16 h, the solution was washed with saturated aqueous ammonium chloride (2×30 mL), water (50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford the title compound as a waxy amorphous solid (128 mg, 94%). Careful crystallisation from hexane afforded a very small sample of crystalline material, all of which was subjected to X-ray crystallographic analysis: ν_{max} ($CDCl_3$)/cm⁻¹ 2959, 2928, 2855, 1728, 1635, 1593, 1460, 1425, 1371, 1155; δ_H (400 MHz; $CDCl_3$) 1.44, 1.50 (each 9H, s, $C(CH_3)_3$), 2.13–2.22, 2.56–1.65 (each 1H, m, 3-CH₂), 2.92–3.01 (1H, m, 4-CH), 3.64–3.70 (1H, m, 5-CHH), 3.82 (1H, t, *J*=10.3, 5-CHH), 4.58 (1H, t, *J*=8.5, 2-CH), 7.52 (4H, 2×d, *J*=8.3, Ar–H); δ_C (100.4 MHz; $CDCl_3$; mixture of rotamers) 28.0, 29.7, 32.0, 41.7, 44.3, 49.0, 51.7, 59.6, 61.4, 81.8, 124.9, 128.7, 129.1, 131.6, 134.5, 168.4, 170.2, 170.3; *m/z* (Cl) 456 (MH^+ , ^{81}Br , 38%), 454 (MH^+ , ^{79}Br ,

36%), 417 (38), 415 (38), 400 (96), 398 (100), 376 (43), 320 (97). HRMS (Cl): MH^+ 454.1229; $C_{21}H_{28}BrNO_5$ requires MH^+ , 454.1224.

A crystal was encapsulated in an epoxy film and mounted on a glass fibre before transfer to the diffractometer. *Crystal data for 9*: $C_{21}H_{28}BrNO_5$, $M=454.35$, colourless tablet, monoclinic, $P2_1$ (No. 4); $a=5.759(2)$, $b=16.624(2)$, $c=12.098(3)$ Å, $\beta=98.74(2)$, $U=1144.7(3)$ Å 3 , $T=298(2)$ K, $\mu(Mo K\alpha)=1.824$ mm $^{-1}$, $D_c=1.318$ g cm $^{-3}$, $Z=2$, $F(000)=472$, $2\theta_{\text{max}}=32^\circ$; 2995 unique absorption-corrected reflections ($R_{\text{int}} 0.042$) were used in all calculations, $wR(\text{all } F^2)=0.0868$, $R_1=0.0434$ for all 2514 data with $F>4\sigma(F)$. Disorder of the Br atom and in one of the $\text{Me}_3\text{COC(O)}$ groups was successfully modelled. The Flack absolute structure parameter refined to 0.000(12).

4.4.4. (3S,5S,7R,7aS)-1-Benzyl-5,7-bis(hydroxymethyl)-3-phenylhexahydropyrrolo[1,2-a]imidazole (10). Method A: to a stirred solution of (3S,5S,7R,7aS)-1-benzyl-5,7-bis(*tert*-butoxycarbonyl)-3-phenylhexahydropyrrolo[1,2-a]imidazole (**2j**, 48 mg, 0.1 mmol) in THF (10 mL) under nitrogen was added lithium aluminium hydride solution (1 M in THF, 0.22 mL, 0.22 mmol). Stirring was continued for 16 h, after which time water (20 mL) was cautiously added and the mixture extracted with ether (3 \times 30 mL). The combined organic extracts were washed with water (2 \times 50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford the *title compound* (30 mg, 88%) as a colourless oil, $[\alpha]_D^{22} +114.2$ (c 0.39 in CH_2Cl_2); ν_{max} (KBr)/cm $^{-1}$ 3365 (br), 2930, 2874, 1496, 1455, 1075, 929; δ_{H} (400 MHz; CDCl_3) 1.87–2.04, 2.09–2.14 (each 1H, m, 6-CH $_2$), 2.40–2.44 (1H, m, 7-CH), 2.53 (1H, t, $J=9.8$, NCHHCH), 3.14–3.36 (5H, m, 5-CH, 5-CHCHH–OH, NCHHCH, NCH $_2$ Ph), 3.75–3.82 (1H, m, 7-CHCHH–OH), 4.02–4.08 (2H, m, 3-CH, 7-CHCHHOH), 4.13 (1H, d, $J=12.2$, 5-CHCHH–OH), 4.52 (1H, d, $J=6.4$, 7a-CH), 7.22–7.40 (10H, m, Ar–H); δ_{C} (100.4 MHz; CDCl_3) 31.7 (6-C), 41.7 (7-C), 59.6 (5-CHCH $_2$ OH), 63.0 (NCH $_2$ Ph), 63.6 (7-CHCH $_2$ OH), 64.4 (2-C), 65.5 (5-C), 68.6 (3-C), 89.5 (7a-C), 126.8, 127.5, 127.7, 128.6, 128.8, 128.9 (6 \times Ar–CH), 137.2, 141.5 (2 \times Ar–C); m/z (EI) 338 (M $^+$, 14%), 307 (2), 263 (18), 249 (25), 235 (13), 201 (44), 91 (100). HRMS: M^+ 338.1994; $C_{21}H_{26}N_2O_2$ requires M^+ 338.1994.

Method B: identical to the above except employing (3S,5S,7R,7aS)-1-benzyl-5-*tert*-butoxycarbonyl-7-methoxycarbonyl-3-phenylhexahydropyrrolo[1,2-a]imidazole (**2h**, 39 mg, 0.089 mmol) and lithium aluminium hydride solution (1 M in THF, 0.20 mL, 0.20 mmol) to afford a quantitative yield (30 mg) of the *title compound*, data identical to the above.

4.5. Synthesis of proline derivatives 11 and 12

4.5.1. (2S,4S)-2,4-Pyrrolidinedicarboxylic acid (11a). Prepared from (2S,4S)-2,4-bis(*tert*-butoxycarbonyl)pyrrolidine (**5ja**, 65 mg, 0.24 mmol) using the method described above for the preparation of **8**. Purification by ion-exchange chromatography yielded the *title compound* as a pale yellow oil (34 mg, 89%), $[\alpha]_D^{20} -46.6$ (c 0.09 in H_2O) (lit.,¹² $[\alpha]_D^{25} -40.0$, c 1.02 in H_2O); δ_{H} (400 MHz; D_2O) 2.14–2.16, 2.66–2.69 (each 1H, m, 3-CH $_2$), 3.19–3.21 (1H, m, 4-CH), 3.54 (2H, d, $J=8.2$, 5-CH $_2$), 4.17 (1H, t, $J=8.7$, 2-CH); δ_{C} (68 MHz; D_2O) 33.0 (3-CH $_2$), 45.0 (4-CH), 48.2 (5-CH $_2$), 61.6 (2-CH), 174.1, 178.2 (2 \times CO); δ_{H} (400 MHz; D_2O and $\text{CF}_3\text{CO}_2\text{D}$) 2.54, 2.79 (each 1H, m, 3-CH $_2$), 3.5 (1H, m, 4-CH), 3.7 (2H, dd, $J=8.4, 12.2$, 5-CHH), 3.88 (1H, d, $J=6.0, 12.2$, 5-CHH), 4.59 (1H, dd, $J=7.6, 8.5$, 2-CH); δ_{C} (68 MHz; D_2O and $\text{CF}_3\text{CO}_2\text{D}$) 33.7 (3-CH $_2$), 44.3 (4-CH), 50.2 (5-CH $_2$), 62.2 (2-CH), 173.5, 177.6 (2 \times CO).

4.5.2. (2R,4R)-2,4-Pyrrolidinedicarboxylic acid (11b). This compound was prepared from (2R,4R)-2,4-bis(*tert*-butoxycarbonyl)pyrrolidine (**5ka**, 100 mg, 0.37 mmol) using the method described above for the preparation of **8**. Purification by ion-exchange chromatography yielded the *title compound* as a pale yellow oil (47 mg, 80%), $[\alpha]_D^{20} +46.4$ (c 0.67 in H_2O) (lit.,¹² $[\alpha]_D^{24} +37.0$, c 1.01 in H_2O); δ_{H} (400 MHz; D_2O) 2.12–2.14, 2.66–2.69 (each 1H, m, 3-CH $_2$),

3.17–3.20 (1H, m, 4-CH), 3.53 (2H, d, $J=8.3$, 5-CH $_2$), 4.17 (1H, t, $J=8.8$, 2-CH); δ_{C} (68 MHz; D_2O) 32.6 (3-CH $_2$), 44.7 (4-CH), 47.7 (5-CH $_2$), 61.0 (2-CH), 173.7, 178.0 (2 \times CO); m/z (FAB) 160 (MH $^+$, 23%), 91 (22), 89 (21), 77 (23). HRMS (FAB): MH^+ 160.0602; $C_6H_9NO_4$ requires MH^+ 160.0604.

4.5.3. (2S,4R)-2,4-Dimethylpyrrolidine-2,4-dicarboxylic acid hydrochloride (12). (2S,4R)-2-*tert*-Butoxycarbonyl-2,4-dimethyl-4-methoxycarbonylpyrrolidine (**51**, 140 mg, 0.54 mmol) was dissolved in trifluoroacetic acid (5 mL) and the solution stirred for 16 h. The solvent was evaporated under reduced pressure and the residue taken up in sodium hydroxide solution (1 M, 10.8 mL, 10.8 mmol) and heated at reflux for 18 h. The solution was cooled to room temperature and neutralised with 1 M hydrochloric acid. Purification by ion-exchange chromatography (Dowex W50), eluting with water yielded the *title compound* (97 mg, 81%) as a colourless oil, $[\alpha]_D^{22} -15.2$ (c 0.52 in H_2O); ν_{max} (film)/cm $^{-1}$ 3441 (br), 1732; δ_{H} (250 MHz; D_2O) 1.75, 2.03 (each 3H, s, CH $_3$), 2.85–3.05 (2H, AB system, 3-CH $_2$), 3.68, 4.31 (each 1H, d, $J=12.4$, 5-CH $_2$); δ_{C} (68 MHz; D_2O , 80 °C) 22.9, 23.3 (2 \times CH $_3$), 46.6 (3-CH $_2$), 49.3 (4-C), 54.4 (5-CH $_2$), 70.8 (2-C), 175.3, 178.5 (2 \times CO); m/z (FAB) 188 (MH $^+$, 100%), 154 (83), 136 (75), 69 (71), 57 (91), 55 (97). HRMS: MH^+ 188.0916; $C_8H_{13}NO_4$ requires MH^+ 188.0917.

4.6. Synthesis of pyrrolizidine 16

4.6.1. (2S,4R)-1-Benzylloxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine-2-carboxylic acid (13). To (2S,4R)-2-*tert*-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (**5d**, 1.56 g, 6.42 mmol) stirred in dry dichloromethane (40 mL) at 0 °C under nitrogen was added triethylamine (648 mg, 893 μ L, 6.42 mmol) followed by benzyl chloroformate (1.095 g, 917 μ L, 6.42 mmol). The solution was allowed to warm to room temperature, stirred for 72 h then washed with water (2 \times 50 mL) and brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to yield (2S,4R)-1-benzylloxycarbonyl-2-*tert*-butoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine (2.35 g, 97%) as colourless crystals, mp 50–52 °C, $[\alpha]_D^{22} -45.2$ (c 1.08 in CH_2Cl_2); ν_{max} (film)/cm $^{-1}$ 3033, 2978, 2880, 1736, 1708; δ_{H} (400 MHz; CDCl_3 ; mixture of rotamers 1:1) 1.30–1.40 (9H, m, C(CH $_3$) $_3$), 1.47 (3H, s, CH $_3$), 1.78–1.84, 2.78–2.88 (each 1H, m, 3-CH $_2$), 3.32, 3.35 (each 0.5H, d, $J=10.8$, NCHH), 3.68, 3.70 (each 1.5H, s, OCH $_3$), 4.09, 4.15 (each 0.5H, d, $J=10.8$, NCHH), 4.28–4.33 (1H, m, 2-CH), 5.09–5.17 (2H, m, PhCH $_2$), 7.38–7.48 (5H, m, Ar–H); δ_{C} (100.4 MHz; CDCl_3 ; mixture of rotamers 1:1) 22.0 and 22.2 (CH $_3$), 27.8 and 27.9 (C(CH $_3$) $_3$), 39.8 and 40.7 (3-CH $_2$), 48.0 and 48.8 (4-C), 52.5 (OCH $_3$), 55.7 and 56.2 (NCH $_2$), 59.2 and 59.6 (2-CH), 67.0 and 67.1 (PhCH $_2$), 81.5 and 81.6 (C(CH $_3$) $_3$), 127.7, 127.8, 128.3, 128.4 (3 \times Ar–CH), 136.3 and 136.6 (Ar–C), 154.1 and 154.4 (C=O), 171.3 and 171.5 (CO), 175.5 (CO); m/z (FAB) 378 (MH $^+$, 5%), 322 (15), 278 (24), 232 (14), 91 (100). Found: C, 63.48; H, 7.38; N, 3.86%; $C_{20}H_{27}NO_6$ requires C, 63.44; H, 7.21; N, 3.71%.

A solution of the carbamate (1 g, 2.65 mmol) was stirred in trifluoroacetic acid (20 mL) at 0 °C for 1 h. The solvent was evaporated under reduced pressure to yield the *title compound* (850 mg, quantitative) as a colourless oil, $[\alpha]_D^{22} -64.5$ (c 0.66 in CH_2Cl_2); ν_{max} (film)/cm $^{-1}$ 2956, 2561, 2360, 1787, 1732 (br); δ_{H} (400 MHz; CDCl_3 ; mixture of rotamers 1:1) 1.39, 1.40 (each 1.5H, s, CH $_3$), 1.92 (0.5H, dd, $J=8.3$, 13.3, 3-CHH), 2.01 (0.5H, dd, $J=7.9, 13.4$, 3-CHH), 2.87–2.99 (1H, m, 3-CHH), 3.33 (0.5H, d, $J=11.2$, NCHH), 3.36 (0.5H, d, $J=12.0$, NCHH), 3.72, 3.73 (each 1.5H, s, OCH $_3$), 4.15 (0.5H, d, $J=11.2$, NCHH), 4.19 (0.5H, d, $J=12.0$, NCHH), 4.47–4.49, 4.50–4.52 (each 0.5H, m, 2-CH), 5.15–5.23 (2H, m, PhCH $_2$), 7.30–7.40 (5H, m, Ar–H), 9.55 (1H, br s, CO $_2$ H); δ_{C} (100.6 MHz; CDCl_3 ; mixture of rotamers 1:1) 21.1 and 21.3 (CH $_3$), 39.1 and 40.1 (3-CH $_2$), 47.9 and 48.6 (4-C), 52.4 (OCH $_3$), 55.3 and 55.8 (NCH $_2$), 58.3 and 58.6 (2-CH), 67.7 (PhCH $_2$), 127.3, 127.4, 127.8, 127.9, 128.1,

128.2 (3 \times Ar–CH), 135.3 and 135.5 (Ar–C), 154.7 and 155.3 (CO), 175.2 (CO), 175.7 and 176.2 (CO); m/z 321 (M $^+$, 4%), 276 (21), 232 (86), 186 (60), 142 (100), 108 (28). HRMS: M $^+$ 321.1225; C₁₆H₁₉NO₆ requires M $^+$ 321.1212.

4.6.2. (2S,4R)-1-Benzylloxycarbonyl-2-formyl-4-methoxycarbonyl-4-methylpyrrolidine (14). To a solution of (2S,4R)-1-benzylloxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine-2-carboxylic acid (13, 850 mg, 2.65 mmol) and N-hydroxysuccinimide (305 mg, 2.65 mmol) in dry THF (50 mL) was added dicyclohexylcarbodiimide (546 mg, 2.65 mmol) and the mixture left at –15 °C for 20 h. The solvent was evaporated under reduced pressure and the residue taken up in dichloromethane (50 mL), washed with water (2 \times 50 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure to afford the crude N-hydroxysuccinimide ester, which was used immediately. To the crude ester in dry THF (40 mL) was added sodium borohydride (262 mg, 6.9 mmol) and the solution stirred for 5 h before being poured cautiously into 1 M citric acid solution. The aqueous solution was extracted with ethyl acetate (3 \times 50 mL) and the combined organic extracts were washed with water (50 mL), saturated sodium bicarbonate solution (50 mL) and brine (50 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue purified by column chromatography, eluting with ethyl acetate/petroleum ether (3:2 v/v) to yield (2S,4R)-1-benzylloxycarbonyl-2-hydroxymethyl-4-methoxycarbonyl-4-methylpyrrolidine (400 mg, 49%) as a colourless oil, $[\alpha]_D^{22}$ –50.9 (c 1.45 in CH₂Cl₂): ν_{max} (CDCl₃)/cm^{–1} 3402 (br), 2954, 2882, 1732, 1683, 1419, 1338, 1317, 1226, 1198, 1049, 1028; δ_{H} (270 MHz; CDCl₃) 1.32 (3H, s, CH₃), 1.49 (1H, dd, J =10.1, 12.5, 3–CHH), 2.57 (1H, dd, J =7.1, 12.5, 3–CHH), 3.10 (1H, d, J =11.5, NCHH), 3.66 (3H, s, OCH₃), 3.70–3.80, 3.98–4.10 (each 1H, m, CH₂OH), 4.21 (1H, d, J =11.5, NCHH), 4.60 (1H, d, J =6.3, OH), 5.14 (2H, s, PhCH₂), 7.35 (5H, s, Ar–H); δ_{C} (68 MHz; CDCl₃) 36.5 (CH₃), 39.0 (3–CH₂), 47.7 (4–C), 52.3 (OCH₃), 56.1 (NCH₂), 60.6 (2–CH), 66.1 (CH₂OH), 67.2 (PhCH₂), 127.6, 127.9, 128.4 (3 \times Ar–CH), 136.2 (Ar–C), 156.6, 175.6 (CO); m/z 307 (M $^+$, <1%), 276 (53), 232 (87), 91 (100). HRMS: M $^+$ 307.1412; C₁₆H₂₁NO₅ requires M $^+$ 307.1420.

A solution of (2S,4R)-1-benzylloxycarbonyl-2-hydroxymethyl-4-methoxycarbonyl-4-methylpyrrolidine (200 mg, 0.65 mmol) in dry dichloromethane (2 mL) was purged with nitrogen for 15 min. To the stirred solution were added N-methylmorpholine-N-oxide (118 mg, 1 mmol), powdered 4 Å molecular sieves (310 mg) and tetrapropylammonium perruthenate (11 mg, 0.03 mmol). The flask was stoppered and the solution stirred for 30 min before being diluted with dichloromethane (6 mL) and loaded onto a column of silica gel. The product was eluted with ethyl acetate and the solvent evaporated under reduced pressure to yield the title compound (149 mg, 75%) as a colourless low-melting solid: ν_{max} (CDCl₃)/cm^{–1} 2959, 2873, 1732, 1715, 1265; δ_{H} (270 MHz; CDCl₃; mixture of rotamers 1:1) 1.28, 1.30 (each 1.5H, s, CH₃), 1.77–1.84, 2.56–2.66 (each 1H, m, 3–CH₂), 3.27 (1H, d, J =11.2, NCHH), 3.64, 3.65 (each 1.5H, s, OCH₃), 4.05, 4.11 (each 0.5H, d, J =11.2, NCHH), 4.22–4.34 (1H, m, 2–CH), 5.03–5.15 (2H, m, PhCH₂), 7.25–7.35 (5H, m, Ar–H), 9.45 (0.5H, d, J =1.5, CHO), 9.57 (0.5H, d, J =2.0, CHO); δ_{C} (68 MHz; CDCl₃; mixture of rotamers 1:1) 21.9 and 22.1 (CH₃), 36.6 and 37.5 (3–CH₂), 47.5 and 48.5 (4–C), 52.4 (OCH₃), 55.5 and 56.1 (NCH₂), 64.2 and 64.5 (2–CH), 67.2 (PhCH₂), 127.7, 127.9, 128.3 (3 \times Ar–CH), 135.7 and 138.0 (Ar–C), 153.9 and 154.9 (CO), 174.7 (CO), 199.2 and 199.4 (CHO); m/z (M $^+$ not found) 276 (M $^+$ –CHO, 32%), 232 (51), 91 (100). HRMS: M $^+$ –CHO 276.1232; C₁₆H₁₉NO₅ requires M $^+$ –CHO 276.1236.

4.6.3. (2S,4R)-1-Benzylloxycarbonyl-2-(2-ethoxycarbonyl-E-ethenyl)-4-methoxycarbonyl-4-methylpyrrolidine (15). To a stirred suspension of sodium hydride (60% dispersion in oil, 13 mg, 0.33 mmol) in dry THF (20 mL) under nitrogen was added triethyl phosphonoacetate (74 mg, 66 μ L, 0.33 mmol). After 20 min (2S,4R)-1-

benzyloxycarbonyl-2-formyl-4-methoxycarbonyl-4-methylpyrrolidine (16, 100 mg, 0.33 mmol) was added to the clear solution, and stirring continued for 16 h. The solvent was evaporated and the residue taken up in dichloromethane (50 mL), washed with saturated ammonium chloride solution (2 \times 30 mL), water (2 \times 30 mL) and brine (30 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue purified by column chromatography, eluting with petroleum ether/ethyl acetate (2:1 v/v) to yield the title compound (70 mg, 57%) as a colourless oil, $[\alpha]_D^{22}$ –49.2 (c 0.61 in CH₂Cl₂): ν_{max} (CDCl₃)/cm^{–1} 2959, 2873, 1730, 1712, 1414, 1265; δ_{H} (270 MHz; CDCl₃) 1.21 (3H, t, J =7.3, CH₂CH₃), 1.27 (3H, s, CH₃), 1.57, 2.65 (each 1H, d, J =8.2, 13.1, 3–CH₂), 3.12 (1H, d, J =11.2, NCHH), 3.59 (3H, s, OCH₃), 4.06–4.17 (3H, m, CH₂CH₃, NCHH), 4.40–4.50 (1H, m, 2–CH), 4.95–5.15 (2H, m, PhCH₂), 5.81 (1H, d, J =15.6, 31.1, CH=CHCO), 6.70–6.85 (1H, m, CH=CHCO), 7.20–7.30 (5H, m, Ar–H); δ_{C} (68 MHz; CDCl₃; mixture of rotamers) 14.1 (CH₂CH₃), 22.0 (CH₃), 42.0 and 42.9 (3–CH₂), 47.9 and 48.6 (4–C), 52.4 (OCH₃), 55.8 and 56.2 (NCH₂), 57.9 and 58.0 (2–CH), 60.4 (CH₂CH₃), 67.1 (PhCH₂), 121.1 (CH=CHCO), 127.8, 128.1, 128.4 (3 \times Ar–CH), 135.9 and 136.2 (Ar–C), 147.5 and 148.1 (CH=CHCO), 154.65, 166.1, 175.4 (3 \times CO); m/z 375 (M $^+$, <1%), 276 (5), 240 (42), 91 (100). HRMS: M $^+$ 375.1671; C₂₀H₂₅NO₆ requires M $^+$ 375.1682.

4.6.4. (2R,8R)-2-Methoxycarbonyl-2-methylpyrrolizidin-5-one (16). To a solution of (2S,4R)-1-benzylloxycarbonyl-2-(2-ethoxycarbonyl-E-ethenyl)-4-methoxycarbonyl-4-methylpyrrolidine (15, 65 mg, 0.27 mmol) in methanol (100 mL) was added palladium on charcoal (10% w/w; 40 mg) and the mixture shaken under a hydrogen atmosphere (60 psi) in a Parr apparatus for 20 h. After filtration through kieselguhr the solvent was removed from the filtrate under reduced pressure to afford (2R,4R)-2-(2-ethoxycarbonyl-E-ethenyl)-4-methoxycarbonyl-4-methylpyrrolidine (65 mg, quantitative), which was not further characterised but used immediately. A portion of this residue (22 mg) was heated at reflux in xylenes (1 mL) for 16 h and then distilled in a kugelrohr apparatus (22 mmHg, oven temperature 250 °C) to yield the title compound (10 mg, 50%) as a colourless oil, $[\alpha]_D^{22}$ –43.3 (c 0.09 in CH₂Cl₂): ν_{max} (CDCl₃)/cm^{–1} 2955, 1729, 1682, 1436, 1422, 1290, 1213, 1159; δ_{H} (500 MHz; CDCl₃) 1.32 (1H, dd, J =9.6, 12.6, 1–CHH), 1.38 (3H, s, CH₃), 1.72–1.79, 2.30–2.35 (each 1H, m, 7–CH₂), 2.46 (1H, ddd, J =2.0, 9.5, 16.7, 6–CHH), 2.55 (1H, dd, J =5.9, 12.6, 1–CHH), 2.67–2.76 (1H, m, 6–CHH), 3.44, 3.56 (each 1H, d, J =11.9, NCH₂), 3.74 (3H, s, OCH₃), 4.02–4.08 (1H, m, 8–CH); δ_{C} (100.4 MHz; CDCl₃) 24.3 (CH₃), 27.3 (7–CH₂), 34.6 (6–CH₂), 44.1 (1–CH₂), 51.1 (NCH₂), 52.2 (2–C), 52.5 (OCH₃), 61.1 (8–CH), 174.8, 176.3 (2 \times CO); m/z 197 (M $^+$, 38%), 169 (28), 156 (26), 138 (56), 97 (100), 82 (48), 69 (61), 55 (73). HRMS: M $^+$ 197.1055; C₁₀H₁₅NO₃ requires M $^+$ 197.1052.

4.7. Synthesis of Indolizidine 19

4.7.1. (2R,8aR)-2-Methoxycarbonyl-2-methylindolizidin-5-one (19). To a slurry of methoxymethyltriphenylphosphonium chloride in dry THF (20 mL) cooled to –15 °C under nitrogen was added potassium *tert*-butoxide (336 mg, 3.0 mmol) and the mixture stirred for 10 min. A solution of (2S,4R)-1-benzylloxycarbonyl-2-formyl-4-methoxycarbonyl-4-methylpyrrolidine (14, 290 mg, 0.95 mmol) in dry THF (10 mL) was added dropwise and the mixture stirred for 2 h whilst warming to 20 °C. The solution was diluted with diethyl ether (50 mL), washed with brine (3 \times 100 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure, the residue taken up in THF (30 mL) and hydrochloric acid (2 M; 30 mL) and stirred for 1 h. The biphasic mixture was extracted with diethyl ether (3 \times 50 mL) and the combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 \times 50 mL), water (100 mL), brine (100 mL) and dried (Na₂SO₄). The

solvent was evaporated under reduced pressure to yield crude *(2S,4R)-1-benzyloxycarbonyl-4-methoxycarbonyl-4-methyl-2-(2-oxoethyl)pyrrolidine* (**17**) as a colourless semi-solid (170 mg, 56%), which decomposed so was used directly. NMR data for crude material were complex due to rotamers, but included: δ_H (400 MHz; $CDCl_3$) 9.62 and 9.76 (CHO).

To a stirred solution of lithium hexamethyldisilazide (1 M in THF, 533 μ L, 0.533 mmol) in dry THF (25 mL) under nitrogen was added triethyl phosphonoacetate (119 mg, 106 μ L, 0.53 mmol). After 80 min a solution of *(2S,4R)-1-benzyloxycarbonyl-4-methoxycarbonyl-4-methyl-2-(2-oxoethyl)pyrrolidine* (**17**, 170 mg, 0.53 mmol) in THF (10 mL) was added dropwise over 15 min and the solution stirred for a further 4 h. The solution was diluted with diethyl ether (100 mL), washed with saturated ammonium chloride solution (2 \times 50 mL), water (50 mL) and brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to yield *(2R,4R)-1-benzyloxycarbonyl-2-(3-ethoxycarbonylprop-2-enyl)-4-methoxycarbonyl-4-methylpyrrolidine* (**18**) (180 mg, 87%) as an oil. The NMR data for ester (**18**) were complex, presumably due to rotamers and/or geometric isomers, but included: δ_C (100.4 MHz; $CDCl_3$) 155, 166, 176 (each br, 3 \times CO). The compound was used immediately without further characterisation.

To a solution of crude *(2R,4R)-1-benzyloxycarbonyl-2-(3-ethoxycarbonyl-E-prop-2-enyl)-4-methoxycarbonyl-4-methylpyrrolidine* (**18**, 90 mg, 0.23 mmol) in methanol (15 mL) was added palladium on charcoal (10% w/w; 40 mg) and the mixture shaken under a hydrogen atmosphere (60 psi) in a Parr apparatus for 20 h. After filtration through kieselguhr the solvent was removed from the filtrate under reduced pressure and the residue distilled in a kugelrohr apparatus (2 mmHg, oven temperature 180 °C) to yield the *title compound* (40 mg, 82%) as a colourless oil, $[\alpha]_D^{22} -56.5$ (*c* 0.23 in CH_2Cl_2): ν_{max} ($CDCl_3$)/cm⁻¹ 2954, 2931, 2876, 1730, 1625, 1466, 1437, 1209; δ_H (400 MHz; $CDCl_3$) 1.20–1.42 (5H, m, CH_3 , 1-CHH, 8-CHH), 1.62–1.70, 1.85–1.94 (each 1H, m, 7-CHH), 2.02–2.08 (1H, m, 8-CHH), 2.20–2.30 (1H, m, 6-CHH), 2.40 (1H, dd, *J*=6.3, 18.0, 6-CHH), 2.54 (1H, dd, *J*=4.9, 12.2, 1-CHH), 3.44 (1H, d, *J*=12.7, NCHH), 3.51–3.59 (1H, m, 8a-CH), 3.69 (3H, s, OCH_3), 3.94 (1H, d, *J*=12.7, NCHH); δ_C (100.4 MHz; $CDCl_3$) 20.9 (7-CH₂), 23.7 (CH₃), 28.9 (8-CH₂), 30.7 (6-CH₂), 44.5 (1-CH₂), 52.5 (OCH₃), 54.5 (NCH₂), 54.8 (2-C), 58.8 (8a-CH), 168.8, 176.4 (2 \times CO); m/z 211 (M⁺, 61%), 155 (67), 152 (100), 124 (30), 111 (43), 96 (50), 83 (61), 82 (64), 55 (73). HRMS: M⁺ 211.1208; $C_{11}H_{17}NO_3$ requires M⁺ 211.1208.

4.7.2. (4S,7R,8R,8aS)-2-Benzyl-7-ethoxycarbonyl-8-(2-hydroxyethyl)-4-phenyloctahydropyrrolo[1,2-a]pyrazin-1-one (**21**). To a solution of *(1S,3aS,4R,4aR,8aS)-3-benzyl-4-ethoxycarbonyl-8-oxo-1-phenyldecahydropyrano[3,4-b]pyrrolo[1,2-a]imidazole* (**20**, 750 mg, 1.79 mmol) in THF (75 mL) was added hydrochloric acid (2 M; 12 mL) followed immediately by sodium cyanoborohydride (1 M solution in THF; 1.79 mL, 1.79 mmol). After stirring for 3 h the mixture was neutralised by the addition of solid potassium hydrogen carbonate and partitioned between chloroform (3 \times 75 mL) and water (100 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography, eluting with ethyl acetate yielded the *title compound* (400 mg, 70%) as a colourless foam, $[\alpha]_D^{22} +1.9$ (*c* 3.80 in CH_2Cl_2): ν_{max} ($CDCl_3$)/cm⁻¹ 3623, 3155, 3088, 3067, 3031, 2984, 2939, 2879, 1726, 1647, 1587, 1495, 1455, 1446, 1378, 1370, 1354, 1285; δ_H (400 MHz; $CDCl_3$) 1.23 (3H, t, *J*=7.1, CH₃), 1.54–1.63, 2.18–2.26 (each 1H, m, CH_2CH_2OH), 2.85–2.91 (1H, m, 7-CH), 2.97–3.05 (3H, m, 6-CH₂, 8-CH), 3.20 (1H, dd, *J*=3.8, 12.3, 3-CHH), 3.36 (1H, dd, *J*=9.6, 12.3, 3-CHH), 3.70–3.80 (2H, m, CH_2CH_2OH), 3.85 (1H, dd, *J*=3.8, 9.6, 4-CH), 4.08–4.16 (3H, m, 8a-CH, CH_2CH_3), 4.55, 4.75 (each 1H, d, *J*=14.5, PhCH₂), 7.22–7.35 (10H, m, Ar–H); δ_C (100.4 MHz; $CDCl_3$) 14.1 (CH₃), 35.9 (CH_2CH_2OH), 43.6 (8-CH), 47.4 (7-CH), 49.6 (PhCH₂),

53.3 (3-CH₂), 54.4 (6-CH₂), 60.6 (4-CH), 61.0 (CH_2CH_3), 61.7 (CH_2CH_2OH), 65.8 (7-CH), 127.7, 127.8, 128.3, 128.7 (6 \times Ar–CH overlapping), 138.3, 138.7 (2 \times Ar–C), 168.2 (CON), 174.2 (COO); m/z 422 (M⁺, 64%), 377 (9), 331 (50), 230 (15), 104 (41), 91 (100). HRMS: M⁺ 422.2209; $C_{25}H_{30}N_2O_4$ requires M⁺ 422.2205.

4.8. Transformations of cycloadduct **20**

4.8.1. (4S,7R,8R,8aS)-2-Benzyl-8-(2-hydroxyethyl)-7-(1-hydroxy-1-methylethyl)-4-phenyloctahydropyrrolo[1,2-a]pyrazin-1-one (**22**). A solution of *(4S,7R,8R,8aS)-2-benzyl-7-ethoxycarbonyl-8-(2-hydroxyethyl)-4-phenyloctahydropyrrolo[1,2-a]pyrazin-1-one* (**21**, 350 mg, 0.83 mmol) in dry THF (50 mL) under nitrogen was cooled to –78 °C and a solution of methyl lithium (1 M solution in THF; 2.74 mL, 2.74 mmol) added dropwise. The golden-yellow solution was allowed to warm to 20 °C over 16 h and then the reaction quenched by addition of saturated ammonium chloride solution (5 mL). The THF was evaporated under reduced pressure and the residue partitioned between water (50 mL) and dichloromethane (3 \times 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with dichloromethane/methanol (90:10 v/v) to yield the *title compound* (170 mg, 50%) as a colourless foam, $[\alpha]_D^{22} -30.5$ (*c* 0.62 in CH_2Cl_2): ν_{max} (KBr)/cm⁻¹ 3402, 3062, 3030, 2968, 2928, 1631, 1495, 1455, 1356, 1268, 1209, 1155, 1060, 1029, 702; δ_H (400 MHz; $CDCl_3$) 1.09, 1.11 (each 3H, s, CH₃), 1.62–1.72, 2.03–2.10 (each 1H, m, CH_2CH_2OH), 2.25 (1H, dt, *J*=3.5, 8.4, 7-CH), 2.48 (1H, dd, *J*=8.4, 11.9, 6-CHH), 2.70–2.77 (1H, m, 8-CH), 2.87 (1H, dd, *J*=8.4, 11.9, 6-CHH), 3.30 (2H, d, *J*=6.1, 3-CH₂), 3.75–3.80 (3H, m, 8a-CH, CH_2CH_2OH), 4.00 (1H, t, *J*=6.1, 4-CH), 4.58, 4.75 (each 1H, d, *J*=14.5, PhCH₂), 7.20–7.35 (10H, m, Ar–H); δ_C (100.4 MHz; $CDCl_3$) 24.8, 29.1 (CH₃), 36.4 (CH_2CH_2OH), 41.0 (8-CH), 49.5 (PhCH₂), 52.6 (7-CH), 53.2 (3-CH₂), 53.3 (6-CH₂), 59.5 (4-CH), 61.3 (CH_2CH_2OH), 66.1 (8a-CH), 72.1 (CCH₃), 127.6, 127.9, 128.0, 128.3, 128.5, 128.6 (6 \times Ar–CH), 136.2, 138.2 (2 \times Ar–C), 168.65 (CO); m/z 408 (M⁺, 75%), 317 (76), 177 (76), 104 (61), 91 (100). HRMS: M⁺ 408.2399; $C_{25}H_{32}N_2O_3$ requires M⁺ 408.2413.

4.8.2. (3S,5S,6R,7R,7aS)-1-Benzyl-5,7-bis(hydroxymethyl)-6-(2-hydroxyethyl)-3-phenylhexahydropyrrolo[1,2-a]imidazole (**23**). To a solution of *(1S,3aS,4R,4aR,8aS)-3-benzyl-4-ethoxycarbonyl-8-oxo-1-phenyldecahydropyrano[3,4-b]pyrrolo[1,2-a]imidazole* (**20**, 127 mg, 0.30 mmol) in dry THF (30 mL) under nitrogen was added dropwise a solution of lithium aluminium hydride (1 M solution in THF; 0.66 mL, 0.66 mmol). After stirring for 2 h the excess lithium aluminium hydride was quenched by the addition of diethyl ether saturated with water (20 mL) and the solution partitioned between water (30 mL) and dichloromethane (2 \times 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to yield the *title compound* (116 mg, quantitative) as a colourless polar oil, $[\alpha]_D^{22} +37.0$ (*c* 1.00 in CH_2Cl_2): ν_{max} ($CDCl_3$)/cm⁻¹ 3689, 3624, 2930, 2858, 1603; δ_H (400 MHz; $CDCl_3$) 1.38–1.48, 1.70–1.88 (each 1H, m, CH_2CH_2OH), 1.95–2.00 (1H, m, 7-CH), 2.46 (1H, t, *J*=9.8, 2-CHH), 2.72–2.80 (1H, m, 6-CH), 3.08–3.16 (2H, m, 5-CH, 2-CHH), 3.23 (1H, t, *J*=10.0, 5-CHCHHOH), 3.38 (1H, d, *J*=12.4, PhCHH), 3.44 (1H, dd, *J*=5.6, 10.0, 5-CHCHHOH), 3.69 (2H, t, *J*=6.4, CH_2CH_2OH), 3.81 (1H, dd, *J*=2.8, 12.4, 7-CHCHHOH), 3.98 (1H, dd, *J*=5.2, 9.8, 3-CH), 4.18–4.22 (2H, m, 7-CHCHHOH, PhCHH), 4.46 (1H, d, *J*=6.8, 7a-CH), 7.22–7.38 (10H, m, Ar–H); δ_C (100.4 MHz; $CDCl_3$) 30.2 (CH_2CH_2OH), 34.5 (6-CH), 48.8 (7-CH), 59.3 (7-CHCH₂OH), 60.3 (5-CHCH₂OH), 60.7 (PhCH₂), 61.6 (CH_2CH_2OH), 62.3 (2-CH₂), 65.2 (5-CH), 67.8 (3-CH), 87.1 (7a-CH), 127.3, 127.7, 127.9, 128.6, 128.7, 129.2 (6 \times Ar–CH), 137.1, 140.6 (2 \times Ar–C); m/z 382 (M⁺, 2%), 381 (2), 365 (3), 280 (12), 263 (21), 249

(30), 120 (13), 104 (18), 91 (100). HRMS: M^+ 382.2256; $C_{23}H_{30}N_2O_3$ requires M^+ 382.2256.

4.8.3. (3S,5S,6R,7aS)-1-Benzyl-6-(2,2,2-trichloroethoxycarbonyloxy-methyl)-5-(2,2,2-trichloroethoxycarbonyloxyethyl)-7-methylene-3-phenylhexahydropyrrolo[1,2-a]imidazole (**24**). To a stirred solution of (3S,5S,6R,7R,7aS)-1-benzyl-5,7-bis(hydroxymethyl)-6-(2-hydroxyethyl)-3-phenylhexahydropyrrolo[1,2-a]imidazole (**23**, 60 mg, 0.16 mmol) in dry dichloromethane (15 mL) under nitrogen was added pyridine (37 mg, 38 μ L, 0.47 mmol) followed by 2,2,2-trichloroethyl chloroformate (100 mg, 65 μ L, 0.47 mmol). After stirring for 16 h the solution was diluted with a further 25 mL of dichloromethane and washed with saturated ammonium chloride solution (2 \times 30 mL), water (30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and evaporated to yield the *title compound* (75 mg, 67%) as a colourless oil: ν_{max} ($CDCl_3$)/cm⁻¹ 2961, 2929, 2856, 1759, 1676, 1638, 1604, 1455; δ_H (400 MHz; $CDCl_3$) 1.54–1.61, 2.00–2.08 (each 1H, m, 6-CH₂CH₂O), 2.24 (1H, t, J =9.7, 2-CHH), 2.90–2.96 (1H, m, 5-CHCH₂O), 2.99–3.05 (1H, m, 6-CH₂CH₂HO), 3.11–3.20 (3H, m, 6-CH, 2-CHH, PhCHH), 3.21–3.26 (1H, m, 5-CHCH₂O), 3.96–4.03 (3H, m, PhCHH, 7a-CH, 3-CH), 4.18–4.26 (1H, m, 5-CH), 4.24–4.30 (1H, m, 6-CH₂CH₂HO), 4.69, 4.72 (each 2H, s, CH_2Cl_3), 4.91, 5.11 (each 1H, d, J =2.4, C=CH₂), 7.15–7.30 (10H, m, Ar–H); δ_C (100.4 MHz; $CDCl_3$) 24.9 (6-CH₂), 37.2 (6-CH), 60.7 (CH_2O), 62.0 (2-CH₂), 67.8 (5-CH), 68.0 (CH_2O), 70.5 (3-CH), 76.4 (2 \times CH_2Cl_3), 76.8 (2 \times CH_2Cl_3), 87.6 (7a-CH), 94.6 (7-C), 109.9 (C=CH₂), 127.3, 127.9, 128.5, 128.9, 128.9, 129.1 (6 \times Ar-CH), 138.4, 142.2 (2 \times Ar-C), 152.35, 154.2 (2 \times CO); m/z (ESI) 719 (MH^+ , $^{37}Cl_3^{35}Cl_3$, 40%), 717 (MH^+ , $^{37}Cl_2^{35}Cl_4$, 85%), 715 (MH^+ , $^{37}Cl_1^{35}Cl_5$, 100%), 713 (MH^+ , $^{35}Cl_6$, 50%). HRMS: M^+ – $CO_2CH_2Cl_3$ 537.1115; $C_{29}H_{30}Cl_6N_2O_6$ requires M^+ – $CO_2CH_2Cl_3$ 537.1115.

4.8.4. (3S,5S,6R,7R,7aS)-1-Benzyl-5,7-bis(methoxymethyl)-6-(2-methoxyethyl)-3-phenylhexahydropyrrolo[1,2-a]imidazole (**25**). To a stirred solution of (3S,5S,6R,7R,7aS)-1-benzyl-5,7-bis(hydroxymethyl)-6-(2-hydroxyethyl)-3-phenylhexahydropyrrolo[1,2-a]imidazole (**23**, 96 mg, 0.25 mmol) in dry THF (30 mL) under nitrogen was added potassium hexamethyldisilazide (0.5 M solution in toluene; 1.67 mL, 0.83 mmol). After 1 h iodomethane (117.8 mg, 52 μ L, 0.83 mmol) was added and stirring continued for 16 h before the solution was diluted with diethyl ether (100 mL), washed with water (3 \times 50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to yield the *title compound* (107 mg, quantitative) as a colourless oil, $[\alpha]_D^{22}$ –18.2 (c 0.44 in CH_2Cl_2); ν_{max} (film)/cm⁻¹ 2924, 2873, 2809, 1495, 1453, 1381, 1358, 1193, 1170, 1114; δ_H (400 MHz; $CDCl_3$) 1.72–1.78 (2H, m, 6-CH₂CH₂O), 2.23–2.28 (2H, m, 6-CH, 2-CHH), 2.39 (1H, t, J =6.6, 7-CH), 3.05–3.35 (14H, m, 3 \times OCH_3 , 2-CHH, PhCHH, 5-CH₂O, 5-CH), 3.41–3.47 (3H, m, 6-CH₂CH₂O, 7-CHCH₂O), 3.81–3.86 (1H,

m, 7-CHCH₂O), 3.95 (1H, dd, J =5.4, 9.8, 3-CH), 4.12 (1H, d, J =12.7, PhCHH), 4.32 (1H, d, J =5.9, 7a-CH), 7.15–7.40 (10H, m, Ar–H); δ_C (100.4 MHz; $CDCl_3$) 28.4 (6-CH₂CH₂O), 39.7 (6-CH), 46.6 (7-CH), 58.6 (PhCH₂, 3 \times OCH_3), 64.0 (2-CH₂), 65.2 (5-CH), 69.3 (3-CH), 72.0, 73.7 (CH₂O), 87.0 (7a-CH), 126.8, 126.9, 127.9, 128.0, 128.2, 128.6 (6 \times Ar–CH), 139.2, 142.9 (2 \times Ar-C); m/z 424 (M^+ , 14%), 410 (11), 393 (25), 294 (17), 265 (22), 263 (80), 249 (21), 120 (23), 91 (100). HRMS: M^+ 424.2726; $C_{26}H_{36}N_2O_3$ requires M^+ 424.2726.

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Supplementary data

X-ray crystallographic data tables for compounds **6** and **9**. Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the numbers CCDC 787232, 787233. These data can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1RZ, England, or via www.ccdc.cam.ac.uk/data-request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.099.

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