PERKIN 1

Design of potential new HIV protease inhibitors: enantioconvergent synthesis of new pyrrolidin-3-ol, and pyrrolidin-3-one peptide conjugates

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Novel potential HIV protease inhibitors are obtained by an enantioconvergent synthesis of mimicking Phe-Pro dipeptides, achieved through the coupling between Boc(L)Phe or Boc(L)Tyr and both enantiomers of *syn*-2-benzylpyrrolidin-3-ol and their corresponding pyrrolidin-3-one analogs. The stereochemistry and enantiopurity of intermediate 3-hydroxypyrrolidines **5a** and **5b** are determined through ^{1}H NMR analysis, and through the synthesis and ^{19}F NMR assignments of the corresponding Mosher's esters **13a** and **13b**. The enantiopure compounds **5a** and **5b** are obtained with 100% diastereoselectivity using specific experimental reductive conditions upon Meldrum's acid derivatives of activated aromatic amino acids.

Introduction

Chiral 2-substituted pyrrolidin-3-ols or pyrrolidin-3-ones have been widely used in the design of pseudopeptides as aspartyl,[1–3] serine,[4] cysteine[5,6] proteinase inhibitors, or non-peptidic neuraminidase inhibitors.[7] In the course of our studies directed towards the synthesis of new anti-HIV protease derivatives, we investigated the possibility of using the pyrrolidin-3-one and pyrrolidin-3-ol synthons as proline-mimicking moieties. Indeed it has been observed that HIV protease shows a preference for Tyr-Pro and Phe-Pro primary cleavages[8–12] at P1-P1′ residues (notation according to Schechter and Berger).[13] A representation of the interactions of one natural substrate with the native HIV-1 protease is given in Fig. 1.[10,12] These Tyr-Pro and Phe-Pro preferences are particularly interesting, because it is unusual for mammalian endopeptidases to cleave at the N-terminal proline residue position.[12,14] This cleavage specificity suggests that these new peptidomimicking derivatives will exhibit a high enzymatic selectivity against the HIV-1 protease. These enzymatic observations are the basis for the design of new HIV protease inhibitors. For this purpose, the proline moiety is replaced by a substituted pyrrolidine ring, which is also capable of interacting with both S1′ and S2′ enzyme pockets (Fig. 2). This new family of compounds interacts with the four hydrophobic pockets, which are surrounded by the enzyme catalytic site.

The tyrosinyl or phenylalanyl moieties interact with the S1 pocket (Ile 50, Ile 84, Leu 23) through the side chain of the aromatic amino acid and with the S2 pocket (Ile 47, Val 32) through the *tert*-butyl group. The substituted pyrrolidine ring, which replaces the proline residue in the substrates including Phe-Pro or Tyr-Pro sequences, interacts with the S1′ pocket (Ile 50′, Ile 84′, Leu 23′) and with the S2′ pocket (Ile 47′, Val 32′): the S1′ pocket through the methylene groups of the pyrrolidine ring, and the S2′ pocket through the benzyl substituent on the pyrrolidine ring. These new modified dipeptides mimicking **1**, **2** and **3**, **4** (Fig. 2) are also capable of maintaining a tight interaction with the two aspartic acid residues (25 and 25′) of the HIV protease active site through a water molecule.

In this paper, we report the total enantioconvergent synthesis of the target molecules: *N*-tyrosinyl- (or *N*-phenylalanyl)-2-substituted pyrrolidin-3-ols respectively, **1a**,**b** and **2a**,**b** and *N*-tyrosinyl- (or phenylalanyl)-2-substituted pyrrolidin-3-ones respectively, **3a**,**b** and **4a**,**b**.

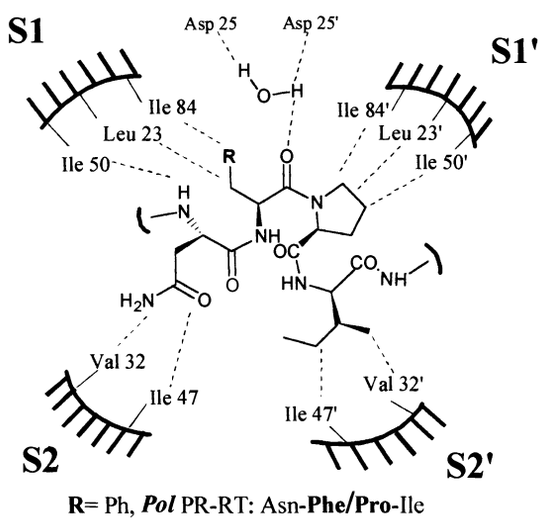
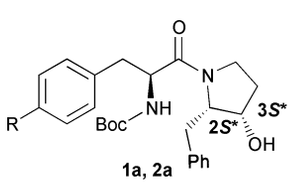


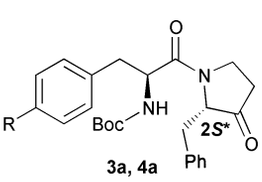
Fig. 1 Representation of one specific substrate of the HIV-1 protease (PR), situated between PR-RT in the *pol* polyprotein.[10,12]



1a, 2a

1a = 2*S*, 3*S*; R = H
1b = 2*R*, 3*R*; R = H

2a = 2*S*, 3*S*; R = OH
2b = 2*R*, 3*R*; R = OH

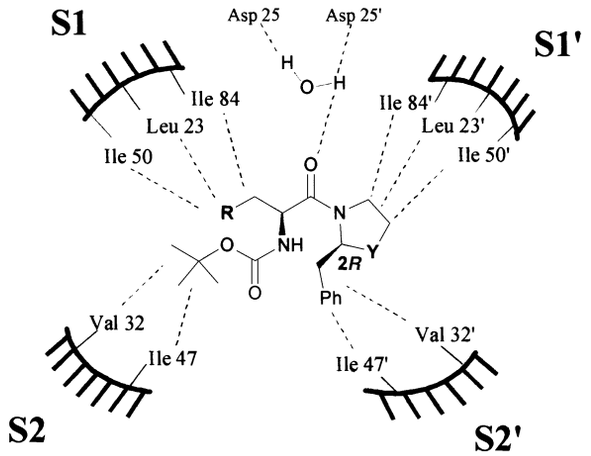


3a, 4a

3a = 2*S*; R = H
3b = 2*R*; R = H

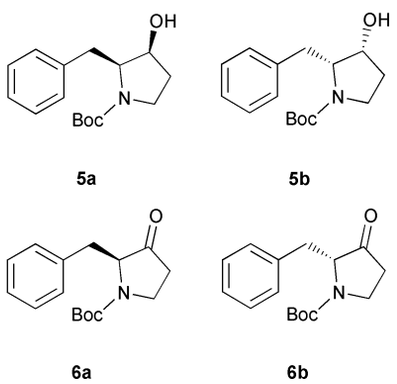
4a = 2*S*; R = OH
4b = 2*R*; R = OH

The versatile pyrrolidinol chiral building blocks **5a** and **5b** were first synthesised through an enantioconvergent strategy.



1b R: Ph, Y: (3*R*) CHOH
2b R: *para*-HO-Ph; Y: (3*R*) CHOH
3b R: Ph, Y: C=O
4b R: *para*-HO-Ph; Y: C=O

Fig. 2 Representation of the binding of the target molecules **1a**,**b**; **2a**,**b** and **3a**,**b**; **4a**,**b** within the different S1, S1′ and S2, S2′ pockets of the HIV protease active site.



5a **5b**

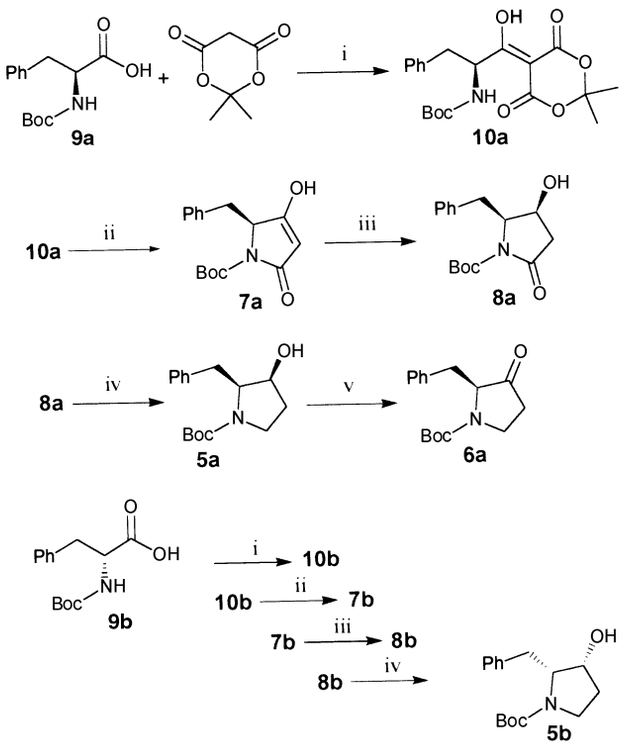
6a **6b**

Compounds **5a** and **5b** were then coupled to various aromatic amino acids (Phe and Tyr) using peptidic synthesis methods, which led to the final target molecules **1a**,**b** and **2a**,**b**. The *N*-tyrosinyl- (or phenylalanyl)-2-substituted pyrrolidin-3-ones, respectively **3a**,**b** and **4a**,**b**, were obtained from the corresponding pyrrolidin-3-ones **6a** and **6b**.

Results and discussion

In earlier studies, Jouin *et al.*[15,16] and more recently Peet *et al.*[6] described a total stereoselective synthesis of 5-alkylpyrrolidine-2,4-diones and 5-alkyl-4-hydroxypyrrolidin-2-ones. Other synthetic routes have also been described. For example, the pyrrolidin-2-one moiety was accessible *via* a 5-*exo*-cyclisation pathway described by Parsons and co-workers.[17] Unfortunately this synthetic strategy led to a mixture of stereoisomers. Reddy *et al.*[18] described a method allowing the synthesis of 5-alkyl-4-hydroxypyrrolidin-2-one intermediates, through a Wittig reaction on various oxazolidinones, coming from various α-amino acids. The olefination was followed by a rearrangement carried on under strongly acidic conditions, which led to *N*-substituted 5-alkylpyrrolidine-2,4-diones. These compounds were later reduced to their corresponding pyrrolidin-3-ols using sodium borohydride as reductive agent.

Among the proposed synthetic routes leading to enantiopure pyrrolidin-3-ol synthons, we selected the procedure described by Jouin *et al.*,[15,16] which involved tetramic acids **7a** and **7b** as intermediates, and which appeared to be a very efficient method. The first step required the addition of Meldrum's acid to selected activated amino acids **9a**,**b**. The resulting



Scheme 1 *Reagents*, *conditions*: i) DCC, DMAP, CH_2Cl_2, 0 °C to RT; ii) EtOAc, reflux; iii) $NaBH_4$, AcOH, CH_2Cl_2, −15 to −5 °C; iv) BH_3–DMS, THF, reflux; v) TPAP (5 mol%), NMO, CH_2Cl_2, 0 °C to RT.

adduct was used as a suitable precursor for the synthesis of the chiral *N*-substituted tetramic acids **7a** and **7b** (Scheme 1), which afforded the corresponding 4-hydroxypyrrolidin-2-ones **8a** and **8b** after stereoselective reduction. However, it should be underlined that the methodology described by Jouin *et al.*[15,16] did not lead to 100% diastereoselectivity, as claimed by the authors, for the synthesis of compounds **8a** and **8b**. Considering these contradictory results, we modified the experimental procedure in order to prepare **5a**, **5b** as diastereo- and enantio-pure compounds, and to increase the diastereoselectivity of the tetramic acid reduction step. Their purity was demonstrated by a ^{1}H NMR study of the 5-hydroxypyrrolidin-2-ones **8a**, **8b** and by a ^{19}F NMR study of the Mosher's esters **13a**, **13b** of the key synthons, *syn*-2-benzylpyrrolidin-3-ols **5a** and **5b** (Scheme 2).

Synthesis of pyrrolidin-3-ols and pyrrolidin-3-ones

Addition of Meldrum's acid to Boc(L)PheOH **9a** or Boc(D)-PheOH **9b** in the presence of DCC–DMAP (respectively, 1.18 and 1.5 equiv.) led to the corresponding adducts **10a** and **10b**, in excellent yields (Scheme 1). These results were inconsistent with previous observations reported by Jouin *et al.*[15,16] and by Joullié and co-workers,[19] who found that the DCC–DMAP activation system was not suitable for this reaction. Those authors recommended the use of isopropenyl chloroformate as activating agent for this reaction. The corresponding adducts **10a** and **10b**, when refluxed for 10 minutes in EtOAc, underwent a cyclisation reaction. After spontaneous decarboxylation, this step produced the corresponding tetramic acids **7a** and **7b**, which were directly purified by recrystallisation in ethanol–hexane. The next step was their diastereoselective reduction using sodium borohydride. Following the reduction conditions ($NaBH_4$ in a mixture of acetic acid–methylene dichloride) reported by Jouin *et al.*,[15,16] we found that the diastereoselectivity excess was not 100% but only 63% as measured by ^{1}H NMR (Fig. 3). Finally we found that the optimal reduction conditions leading to 100% diastereoisomeric excess for 1 equiv. of tetramic acid **7a** or **7b** were: $NaBH_4$ (4 equiv.), AcOH

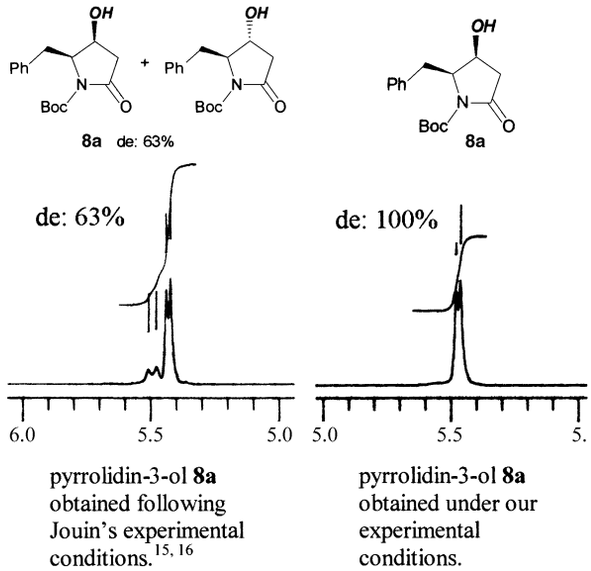
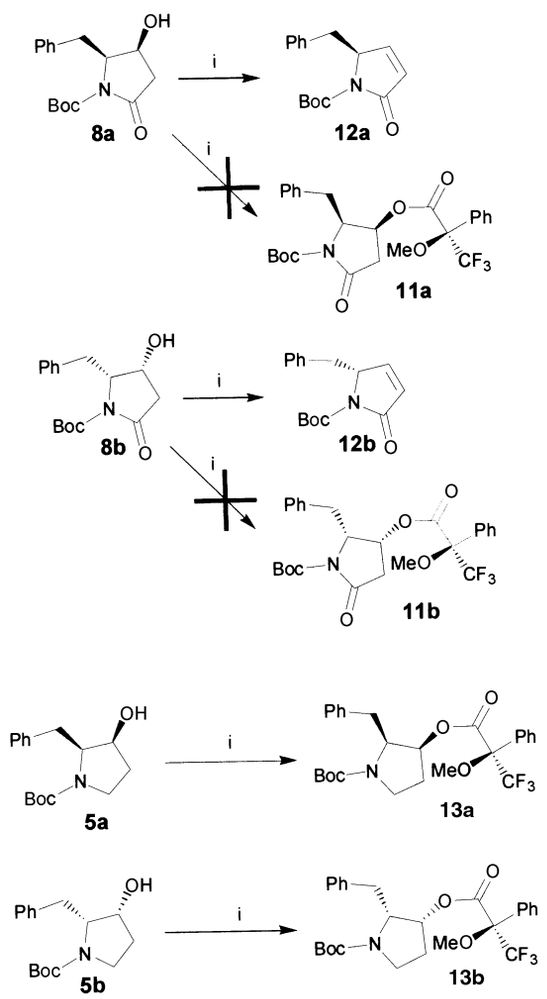


Fig. 3 ^{1}H NMR spectra of the pyrrolidin-3-ol **8a**.



Scheme 2 *Reagents*, *conditions*: i) (*R*)-(+)-Mosher's acid chloride, DMAP, CH_2Cl_2, 0 °C to RT.

(16 equiv.), at temperatures ranging from −15 to −5 °C. Under these conditions, compounds **8a** and **8b** were obtained in 92% yield. Reduction of lactams **8a** and **8b** using BH_3–DMS in THF[20,21] led to the enantio- and diastereo-pure key synthons pyrrolidin-3-ols **5a** and **5b**. These synthons were oxidised into their corresponding pyrrolidin-3-ones **6a** and **6b**, using Ley–Mardsen methodology[22] [TPAP 5 mol%, NMO (1.5 equiv.), in methylene dichloride, at temperatures ranging from 0 °C to RT]

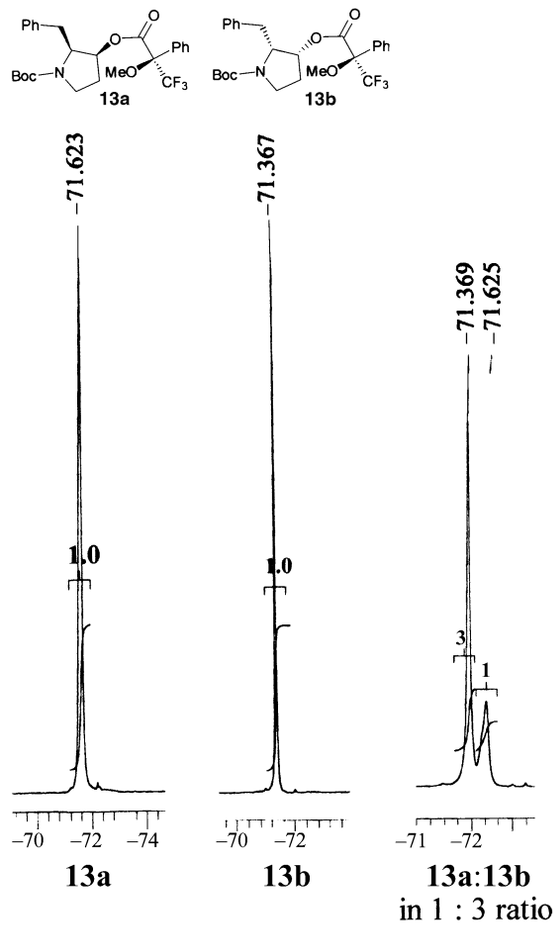


Fig. 4 ^{19}F NMR spectra of Mosher's esters **13a** and **13b**.

in 93% yield. This method led to better yields than did classical Swern oxidation conditions.[23]

In order to confirm the enantiopurity of the 4-hydroxypyrrolidin-2-ones **8a** and **8b** obtained from this enantioconvergent strategy, we attempted to synthesise their corresponding Mosher's esters[24] **11a** and **11b** using experimental conditions described in Scheme 2. Unfortunately only the β-elimination enelactam products **12a** and **12b** were obtained. These results led us to synthesise the Mosher's esters **13a** and **13b**, starting from the key synthons **5a** and **5b**. The Mosher's esters **13a** and **13b** were obtained in 95% yields using the following experimental conditions: (*R*)-(+)-Mosher's acid chloride reagent (1.1 equiv.), DMAP (2 equiv.), in methylene dichloride, at temperatures ranging from 0 °C to RT.

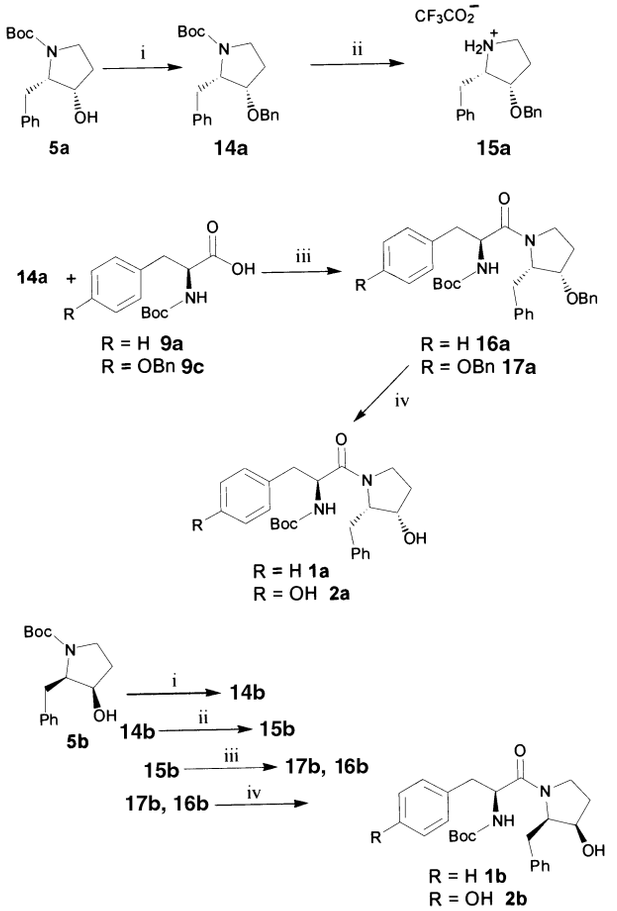
NMR studies

The diastereoisomeric excess of 4-hydroxypyrrolidin-2-ones **8a** and **8b** (Scheme 2) resulting from the reductive step was determined through ^{1}H NMR studies. The chemical shifts of the hydroxy proton were found respectively at δ 5.46 for the *syn* isomer, and at δ 5.56 for the *anti* isomer, in DMSO-d_6 (Fig. 3). These NMR measurements allowed us to confirm the diastereoselectivity of the reduction step of the tetramic acids **7a** and **7b**, and therefore the diastereoisomeric purity of the *syn*-5-benzyl-4-hydroxypyrrolidin-2-ones **8a** and **8b**.

The ^{19}F NMR study performed on the Mosher's esters **13a** and **13b** allowed us to evaluate the enantiomeric purity of key synthons **5a** and **5b**. ^{19}F NMR spectra represented in Fig. 4 showed respectively only one single peak for fluorine signals of compounds **13a** and **13b**, while two peaks were found for the mixture of compounds **13a** and **13b**. This ^{1}H and ^{19}F NMR study clearly demonstrated the diastereo- and enantio-purity of compounds **13a**, **13b** and **5a**, **5b**.

Synthesis of peptide conjugates

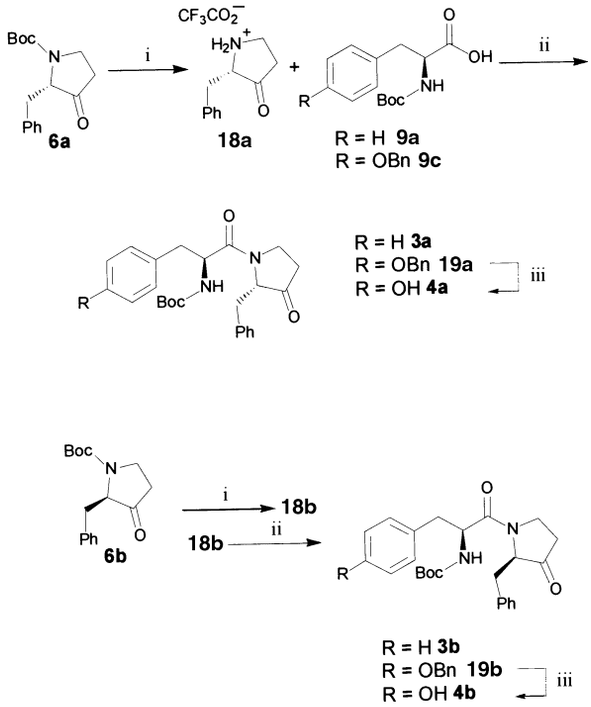
Starting from the key synthons, *viz*. the pyrrolidin-3-ols **5a**, **5b** and their counterparts **6a** and **6b** containing the pyrrolidin-3-one scaffold, two series of derivatives were synthesised following the sequences represented in Schemes 3 and 4. The synthesis of the first series containing the pyrrolidinol motif (Scheme 3)



Scheme 3 *Reagents*, *conditions*: i) NaH, TBAI (5 mol%), BnBr, THF, 0 °C to RT; ii) TFA–CH_2Cl_2; iii) PyBOP, Et_3N, CH_2Cl_2, 0 °C to RT; iv) H_2 (1 atm.), 20% $Pd(OH)_2$–C (10 mol%), EtOH, 25 °C.

involved the protection of the hydroxy function of pyrrolidin-3-ols **5a** and **5b** by a benzyl group. The resulting ethers **14a** and **14b** were isolated in quantitative yields. After *N*-Boc deprotection, the salts **15a** and **15b** were coupled to various *N*-Boc-protected aromatic amino acids, *i.e.* Boc(L)PheOH **9a**, and Boc(L)Tyr(OBn)OH **9c** using (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP)[25] in methylene dichloride, in the presence of Et_3N. The resulting compounds **16a**, **16b** and **17a**, **17b** were isolated in excellent yields. The last step was the deprotection of the benzyloxy group, achieved by hydrogenolysis in the presence of Pearlman's catalyst [20% $Pd(OH)_2$ on charcoal; 10 mol%] leading to the final compounds **1a**, **1b** and **2a**, **2b**.

The last series of final compounds **3a**,**3b** and **4a**,**4b** were isolated respectively from pyrrolidin-3-ones **6a** and **6b**, using a similar procedure (Scheme 4). After *N*-Boc deprotection, the corresponding salts **18a**, **18b** were coupled with *N*-Boc-protected aromatic amino acids, *i.e.* Boc(L)PheOH **9a** and Boc(L)Tyr-(OBn)OH **9c**. The pyrrolidinone–aromatic amino acid conjugates **3a**, **3b** and **4a**, **4b** were obtained in 98, 97% and 98, 99% yields, respectively. The tyrosinyl derivatives **19a** and **19b** were deprotected by classical hydrogenation with black palladium (Pd–C 10%, 4 mol%) leading to the tyrosinylpyrrolidin-3-ones **4a** and **4b** in quantitative yields. The two series of compounds, which have been fully characterised, will be later tested as HIV-1 protease inhibitors.



Scheme 4 *Reagents*, *conditions*: i) TFA–CH_2Cl_2; ii) PyBOP, Et_3N, CH_2Cl_2, 0 °C to RT; iii) H_2 (1 atm.), 10% Pd–C (4 mol%), EtOH, 25 °C.

Conclusions

We report the total enantioconvergent synthesis of new potential HIV protease inhibitors, which are based on proline substitution by mimicking pyrrolidinol or pyrrolidinone moieties in specific Phe-Pro or Tyr-Pro sequences found in various HIV protease substrates. Key synthon pyrrolidin-3-ols **5a**, **5b** and pyrrolidin-3-ones **6a**, **6b** were synthesised through an enantioconvergent synthesis, which led to the target compounds in diastereo- and enantio-pure forms, as demonstrated by ^1H NMR and ^{19}F NMR studies.

Experimental

General procedures

Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without purification. All the protected amino acids, and peptide-coupling reagents, were purchased from BACHEM. Tetrahydrofuran was distilled over sodium benzophenone ketyl immediately prior to use. Methylene dichloride was distilled over P_2O_5 and stored over molecular sieves 4 Å at +4 °C. Ethyl acetate was stored on molecular sieves 4 Å. NMR spectra were recorded at 250 MHz for ^1H, and 63 MHz for ^{13}C with a Brüker AC-250 apparatus. In some cases, the spectra are of poor resolution because of the presence of different conformers and rotamers. One drop of TFA was then added to the solution in the NMR tube to decrease the conformational flexibility of the molecules and to increase the resolution. ^{19}F NMR spectra were recorded at 282.4 MHz on a Brüker Avance 300. *J*-Values are given in Hz. IR spectra were recorded with an FT-IR apparatus. Optical rotations were measured at 25 °C using a Perkin-Elmer 241 polarimeter with a path length of 1.0 dm, at the sodium D-ray. All mps are uncorrected. Flash column chromatography was carried out on Merck $60F_{254}$ silica gel (230–400 mesh). Centrifugal radial chromatography was carried out with a Chromatotron,™ Model No 7924T, using plates coated with silica gel Merck 60 PF_{254}. Reactions were monitored by TLC using Merck $60F_{254}$ TLC plates. Mass spectra were recorded using fast atom bombardment (FAB > 0) in positive mode (Dr Astier, Laboratoire de Mesures Physiques-RMN, USTL,

Montpellier, France) on a JEOL DX-100 using a caesium ion source and glycerol–thioglycerol (1 : 1, GT) or *m*-nitrobenzyl alcohol (NOBA) as matrix.

5-[(2*S*)-2-(*tert*-Butoxycarbonylamino)-1-hydroxy-3-phenylpropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 10a

To a stirred solution of Boc(L)PheOH **9a** (3.00 g, 11.3 mmol), Meldrum's acid (1.79 g, 12.4 mmol), and DMAP (2.07 g, 17.0 mmol) in CH_2Cl_2 (30 mL) under nitrogen at 0 °C was added dropwise a solution of DCC (2.75 g, 13.3 mmol) in CH_2Cl_2 (15 mL) *via* a syringe over a period of 15 minutes. The resulting solution was then allowed to warm up to room temperature and was stirred during 4 hours. The slurry mixture was then poured rapidly into cold EtOAc (250 mL) according to the procedure described by Jouin *et al.*[15,16] and filtered. The layers were separated, and the organic layer was successively washed with cold 5% aq. citric acid (150 mL, 2×), cold water (150 mL, 2×), and cold brine (150 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated to yield **10a** (4.43 g, quantitative yield) as a white powder; mp 119 °C (lit.,[15] 120 °C); R_f 0.73 (EtOAc–cyclohexane–AcOH 7 : 3 : 1); δ_H (250 MHz; DMSO-d_6) 7.29–7.07 (6H, m), 5.41 (1H, br s), 2.91–2.61 (2H, m), 1.52 (6H, s), 1.16 (9H, s); *m*/*z* (FAB > 0, GT) 392 ([M + H]$^+$, 10%), 336 (30), 292 (28), 148 (18), 120 (21), 103 (10), 91 (28) (Found: C, 60.58; H, 6.55; N, 3.47. $C_{20}H_{25}NO_7$ requires C, 60.47; H, 6.46; N, 3.59%).

5-[(2*R*)-2-(*tert*-Butoxycarbonylamino)-1-hydroxy-3-phenylpropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 10b

A similar procedure, as used for the preparation of **10a**, led to **10b** (quantitative) as a white powder; mp 119 °C (lit.,[15] 120 °C); R_f 0.73 (EtOAc–cyclohexane–AcOH 7 : 3 : 1); ν_{max}(KBr)/cm^{-1} 3049; δ_H (250 MHz; DMSO-d_6) 7.44–7.26 (6H, m), 5.62 (1H, br s), 3.03–2.81 (2H, m), 1.71 (6H, s), 1.36 (9H, s); *m*/*z* (FAB > 0, GT) 414 ([M + Na]$^+$, 22), 392 ([M + H]$^+$, 21), 336 (57), 292 (7), 148 (7), 120 (19), 103 (8), 91 (31) (Found: C, 61.51; H, 6.52; N, 3.46. $C_{20}H_{25}NO_7$ requires C, 61.37; H, 6.44; N, 3.58%).

(5*S*)-5-Benzyl-1-*tert*-butyloxycarbonyl-4-hydroxy-1,5-dihydropyrrol-2-one 7a

A stirred solution of **10a** (4.43 g, 11.31 mmol) in dry nitrogen-bubbled EtOAc (300 mL) was refluxed for 10 minutes. The solution was concentrated under reduced pressure to yield 4.49 g of a yellowish powder which was then recrystallised in ethanol–hexane to provide **7a** (3.08 g, 94%) as a white powder; mp 141 °C (lit.,[15] 141 °C); R_f 0.48 (EtOAc–cyclohexane–AcOH 7 : 3 : 1); $[\alpha]_D^{25}$ +231.4 (*c* 1.02, MeOH) {lit.,[15] $[\alpha]_D^{25}$ +230 (*c* 1, MeOH)}; ν_{max}(KBr)/cm^{-1} 3327, 3031, 2988, 2928, 1761, 1649, 1629, 1573, 1478, 1362, 1310, 1155, 1085, 761, 704; δ_H (250 MHz; DMSO-d_6) 7.04 (3H, m), 6.80 (2H, m), 4.47 (1H, s), 4.43 (1H, br d, *J* 2.8 Hz), 3.17 (1H, dd, *J* 13.8, 5.1 Hz), 2.98–2.84 (1H, m), 1.31 (9H, s); δ_C (62.9 MHz; DMSO-d_6) 175.62, 168.81, 149.06, 134.58, 129.58, 127.98, 126.74, 94.87, 81.05, 59.80, 34.25, 27.91; *m*/*z* (FAB > 0, GT) 579 ([2M + H]$^+$, 8%), 290 ([M + H]$^+$, 36), 234 (100), 190 (12) (Found: C, 66.53; H, 6.47; N, 4.75. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%).

(5*R*)-5-Benzyl-1-(*tert*-butoxycarbonyl)-4-hydroxy-1,5-dihydropyrrol-2-one 7b

A similar procedure, as used for the preparation of **7a**, led to **7b** (92%) as a white powder; mp 142 °C (lit.,[15] 148 °C); R_f 0.48 (EtOAc–cyclohexane–AcOH 7 : 3 : 1); $[\alpha]_D^{25}$ −231.1 (*c* 1.04, MeOH) {lit.,[15] $[\alpha]_D^{25}$ −230 (*c* 1, MeOH)}; ν_{max}(KBr)/cm^{-1} 3327, 3028, 2932, 1757, 1644, 1577, 1477, 1367, 1297, 1154, 1083, 758, 703; δ_H (250 MHz; DMSO-d_6) 7.09 (3H, m), 6.84 (2H, m), 4.52 (1H, s), 4.47 (1H, br d, *J* 2.8 Hz), 3.20 (1H, dd, *J* 13.9, 5.3 Hz), 2.92 (1H, br d, *J* 13.7 Hz), 1.35 (9H, s); δ_C (62.9 MHz; DMSO-d_6) 175.67, 168.78, 149.06, 134.58, 129.55, 127.92, 126.67, 94.77, 81.01, 59.82, 34.27, 27.87; *m*/*z* (FAB > 0, GT) 579 ([2M + H]$^+$, 11%), 290 ([M + H]$^+$, 24), 234 (100), 190 (7) (Found: C, 66.32; H, 6.81; N, 4.72. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%).

(4*S*,5*S*)-2-Benzyl-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidin-2-one 8a

To a stirred solution of **7a** (2.60 g, 8.99 mmol) in CH_2Cl_2 (54 mL) was added acetic acid (8.2 mL, 144 mmol) at −5 °C, then $NaBH_4$ (1.36 g, 35.9 mmol) at −15 °C over a period of 30 minutes. The resulting mixture was stirred during 45 minutes, and then warmed to −5 °C during 9 hours. 150 mL of 5% aq. citric acid was then added at 0 °C, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL, 3×), and the combined organic layers were successively washed with 5% aq. citric acid (67 mL), water (67 mL, 2×) and brine (67 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatographic purification (EtOAc–DCM 6 : 4) gave **8a** (2.41 g, 92%) as a white powder; mp 119 (lit.,[15] 120–124 °C); R_f 0.42 (DCM–EtOAc 6 : 4); $[\alpha]_D^{25}$ 43.2 (*c* 1.15, MeOH) {lit.,[15] $[\alpha]_D^{25}$ 43 (*c* 1, MeOH)}; ν_{max}(CHCl$_3$)/cm^{-1} 3403, 3062, 2982, 2930, 1779, 1685, 1627, 1577, 1455, 1366, 1246, 1172, 1114, 1020, 751; δ_H (250 MHz; DMSO-d_6) 7.22–7.13 (5H, m), 5.46 (1H, d, *J* 4.0 Hz), 4.27–4.17 (2H, m), 3.03 (1H, dd, *J* 13.6, 6.5 Hz), 2.86 (1H, dd, *J* 13.5, 4.8 Hz), 2.41 (1H, dd, *J* 16.6, 7.0 Hz), 2.18 (1H, dd, *J* 16.5, 7.5 Hz), 1.29 (9H, s); δ_C (62.9 MHz; DMSO-d_6) 172.35, 150.22, 139.31, 130.77, 129.03, 126.97, 82.49, 64.88, 63.42, 40.92, 34.12, 28.42; *m*/*z* (FAB > 0, GT) 314 ([M + Na]$^+$, 41%), 292 ([M + H]$^+$, 16), 236 (100), 218 (9), 214 (31), 192 (9) (Found: C, 65.78; H, 7.16; N, 4.94. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%).

(4*R*,5*R*)-5-Benzyl-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-one 8b

A similar procedure, as used for the preparation of **8a**, led to **8b** (92%) as a white powder; mp 119 °C (lit.,[15] 119–120 °C); R_f 0.42 (DCM–EtOAc 6 : 4); $[\alpha]_D^{25}$ −43.1 (*c* 1.00, MeOH) {lit.,[15] $[\alpha]_D^{25}$ −43.5 (*c* 1, MeOH)}; ν_{max}(CHCl$_3$)/cm^{-1} 3064, 2984, 2933, 1781, 1684, 1647, 1627, 1579, 1506, 1457, 1364, 1249, 1154, 1088,1019, 761, 706; δ_H (250 MHz; CDCl$_3$) 7.24–7.12 (5H, m), 5.47 (1H, d, *J* 4.0 Hz), 4.28–4.16 (2H, m), 3.01 (1H, dd, *J* 13.5, 6.4 Hz), 2.88 (1H, dd, *J* 13.5, 4.7 Hz), 2.40 (1H, dd, *J* 16.6, 6.9 Hz), 2.19 (1H, dd, *J* 16.6, 7.4 Hz), 1.32 (s, 9H); δ_C (62.9 MHz; DMSO-d_6) 172.22, 149.71, 137.83, 129.92, 128.48, 126.53, 83.25, 65.47, 62.76, 40.02, 33.95, 27.90; *m*/*z* (FAB > 0, GT) 314 ([M + Na]$^+$, 11%), 292 ([M + H]$^+$, 7), 236 (100), 218 (11), 214 (15), 192 (13) (Found: C, 65.81; H, 7.34; N, 4.72. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%).

(2*S*,3*S*)-2-Benzyl-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ol 5a

To a stirred solution of **8a** (1.86 g, 6.39 mmol) in THF (48 mL) under nitrogen was added a solution of BH_3–DMS (1.96 mL, 19.2 mmol) dropwise *via* a syringe at room temperature. The solution was refluxed for 35 minutes. The reaction mixture was then cooled and poured into diethyl ether (300 mL). The borane reagent excess was neutralised with saturated aq. NH_4Cl (55 mL). The layers were separated, and the organic layer was successively washed with 5% aq. citric acid solution (100 mL), water (100 mL, 2×), and brine (100 mL). The resulting slurry mixture was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatographic purification (DCM–EtOAc 9 : 1, then 8 : 2) gave **5a** (1.70 g, 96%) as a white powder; mp 71 °C; R_f 0.47 (DCM–EtOAc 8 : 2); $[\alpha]_D^{25}$ −6.00 (*c* 1.00, CHCl$_3$); ν_{max}(CHCl$_3$)/cm^{-1} 3435, 3030, 2979, 2933, 1794, 1682, 1603, 1477, 1454, 1404, 1367, 1169, 1108; δ_H (250 MHz; CDCl$_3$ + TFA) 7.25–7.12 (5H, m), 4.29 (1H, dd, *J* 12.7, 6.2 Hz), 4.04 (1H, br dd, *J* 13.9, 5.7 Hz), 3.48–3.31 (2H, m), 3.01 (1H, dd, *J* 13.6, 5.2 Hz), 2.85 (1H, dd, *J* 13.57, 8.4 Hz),

2.02–1.60 (2H, m), 1.35 (9H, s); δ_C (62.9 MHz; DMSO-d_6) 154.95, 139.58, 129.72, 128.32, 126.03, 79.57, 71.59, 61.92, 43.46, 34.60, 31.29, 28.45; *m/z* (FAB > 0, GT) 555 ([2M + H]$^+$, 2%), 300 ([M + Na]$^+$, 3), 278 ([M+H]$^+$, 24), 222 (100), 204 (12), 186 (24), 178 (5), 160 (11) (Found: C, 69.37; H, 8.44; N, 5.18. $C_{16}H_{23}NO_3$ requires C, 69.29; H, 8.36; N, 5.05%).

(2*R*,3*R*)-2-Benzyl-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ol 5b

A similar procedure, as used for the preparation of **5a**, led to **5b** (94%) as a white powder; mp 71 °C; R_f 0.40 (DCM–EtOAc 8 : 2); $[\alpha]_D^{25}$ 6.00 (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3437, 3064, 2979, 2932, 1792, 1684, 1603, 1539, 1465, 1405, 1368, 1168, 1110, 1051, 651; δ_H (250 MHz; $CDCl_3$ + TFA) 7.11–7.01 (5H, m), 4.10 (1H, dd, *J* 12.7, 6.3 Hz), 3.90 (1H, br dd, *J* 13.9, 5.7 Hz), 3.27–3.15 (2H, m), 2.75 (1H, dd, *J* 13.5, 8.4 Hz), 1.86 (1H, m), 1.63–1.51 (2H, m), 1.25 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 154.95, 139.58, 129.69, 128.32, 126.03, 79.55, 71.61, 61.94, 43.42, 34.59, 31.31, 28.45; *m/z* (FAB > 0, GT) 555 ([2M + H]$^+$, 3%), 300 ([M + Na]$^+$, 3), 278 ([M + H]$^+$, 22), 222 (100), 204 (10), 186 (19), 178 (8), 160 (8) (Found: C, 69.46; H, 8.27; N, 5.16. $C_{16}H_{23}NO_3$ requires C, 69.29; H, 8.36; N, 5.05%).

(2*S*)-2-Benzyl-1-(*tert*-butoxycarbonyl)pyrrolidin-3-one 6a

To a stirred solution of **5a** (0.200 g, 0.721 mmol), NMO (0.127 g, 1.08 mmol), and powdered 4 Å molecular sieves in CH_2Cl_2 (2 mL) was added continuously TPAP (12.7 mg, 5 mol%) at 0 °C, under nitrogen. The solution was then allowed to warm to room temperature and was stirred during 20 minutes. The slurry mixture was filtered on a short silica column and washed with EtOAc. The product was concentrated under reduced pressure, and chromatotron purification (cyclohexane–EtOAc 7 : 3) gave **6a** (0.185 g, 93%) as a colourless oil; R_f 0.43 (cyclohexane–EtOAc 8 : 2); $[\alpha]_D^{25}$ 199.9 (*c* 1.00, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3019, 2980, 2931, 1757, 1701, 1691, 1478, 1454, 1406, 1215, 1148, 1116; δ_H (250 MHz; $CDCl_3$) 7.16–7.02 (3H, m), 6.88–6.84 (2H, m), 3.96 (1H, br s), 3.54–3.00 (2H, m), 2.93–2.82 (1H, m), 2.69–2.48 (1H, m), 2.27–2.07 (1H, m), 1.77–1.58 (1H, m), 1.33 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 213.68, 154.13, 136.18, 129.75, 128.41, 126.81, 80.18, 63.23, 41.47, 36.21, 36.11, 28.41; *m/z* (FAB > 0, GT) 551 ([2M + H]$^+$, 5%), 288 ([M + Na]$^+$, 7), 276 ([M + H]$^+$, 15), 220 (100), 202 (23), 176 (11), 91 (39) (Found: C, 69.63; H, 7.78; N, 4.93. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%).

(2*R*)-2-Benzyl-1-(*tert*-butoxycarbonyl)pyrrolidin-3-one 6b

A similar procedure, as used for the preparation of **6a**, led to **6b** (90%) as a colourless oil; R_f 0.43 (cyclohexane–EtOAc 8 : 2); $[\alpha]_D^{25}$ −198.4 (*c* 1.02, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3019, 2980, 2931, 1757, 1691, 1406, 1215, 1148, 1116; δ_H (250 MHz; $CDCl_3$) 7.40 (3H, m), 7.20 (2H, m), 4.35 (1H, br s), 3.91 (1H, m), 3.35 (1H, m), 3.29–3.20 (1H, m), 3.02–2.82 (1H, m), 2.70–2.48 (1H, m), 2.20–2.03 (1H, m), 1.70 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 213.80, 154.25, 136.28, 129.84, 128.51, 126.92, 80.30, 63.35, 41.71, 36.27, 36.14, 28.52; *m/z* (FAB > 0, GT) 551 ([2M + H]$^+$, 3%), 288 ([M + Na]$^+$, 7), 276 ([M + H]$^+$, 18), 220 (100), 202 (23), 176 (11), 91 (35) (Found: C, 69.61; H, 7.81; N, 5.00. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%).

(4*S*,5*S*)-2-Benzyl-1-(*tert*-butoxycarbonyl)-3-[(*R*)-α-methoxy-α-trifluoromethyl)phenylacetoxy]pyrrolidine 13a

To a stirred solution of **5a** (0.130 g, 0.469 mmol) and DMAP (0.116 mg, 0.442 mmol) in CH_2Cl_2 (4 mL) was added (*R*)-(+)-Mosher's acid chloride (98 μL, 0.516 mmol) dropwise at 0 °C, under nitrogen. The solution was then allowed to warm to room temperature and was stirred for 1.5 h. The slurry mixture was then diluted with 12 mL of diethyl ether and successively washed with 5% aq. $NaHCO_3$ (4 mL), water (4 mL, 2×), and brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatotron purification (cyclohexane–EtOAc 8.5 : 1.5) gave **13a** (0.104 g, 95%) as a colourless oil; R_f 0.44 (cyclohexane–EtOAc 8.5 : 1.5); $[\alpha]_D^{25}$ −26.5 (*c* 0.59, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3065, 2980, 2931, 1749, 1685, 1496, 1453, 1402, 1367, 1346, 1255, 1171, 1123, 1082, 1049, 980, 945, 858, 765, 699, 650; δ_H (250 MHz; $CDCl_3$) 7.44 (2H, m), 7.37 (3H, m), 7.06 (3H, m), 6.89 (2H, m), 5.22 (1H, q, *J* 6.5 Hz), 4.20 (1H, q, *J* 6.3 Hz), 3.41 (4H, br s), 3.24–2.71 (3H, m), 2.05 (1H, m), 1.66–1.51 (1H, m), 1.35 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 166.09, 154.48, 138.01, 131.78, 129.91, 129.60, 128.71, 128.31, 127.50, 126.26, 121.14, 84.77 (q, *J* 26.6 Hz), 79.99, 75.80, 59.78, 55.45, 43.02, 34.62, 29.42, 28.41; δ_F (282.4 MHz; $CDCl_3$) −71.62 (3F, s); *m/z* (FAB > 0, GT) 508 ([M + H]$^+$, 10%), 430 (45) (Found: C, 63.44; H, 6.26; N, 2.71. $C_{26}H_{30}F_3NO_5$ requires C, 63.28; H, 6.13; N, 2.84%).

(4*R*,5*R*)-2-Benzyl-1-(*tert*-butoxycarbonyl)-3-[(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetoxy]pyrrolidine 13b

A similar procedure, as used for the preparation of **13a**, led to **13b** (95%) as a colourless oil; R_f 0.46 (cyclohexane–EtOAc 8.5 : 1.5); $[\alpha]_D^{25}$ −67.9 (*c* 0.59, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3064, 3030, 2979, 2898, 1747, 1684, 1496, 1478, 1454, 1399, 1367, 1254, 1169, 1124, 1082, 1047, 1018, 994, 946, 858, 766, 700, 650; δ_H (250 MHz; $CDCl_3$) 7.49 (2H, m), 7.37 (3H, m), 7.05 (3H, m), 6.85 (2H, m), 5.22 (1H, q, *J* 6.4 Hz), 4.16 (1H, q, *J* 6.1 Hz), 3.50 (4H, s), 3.18 (1H, m), 2.58–2.98 (2H, m), 2.02 (1H, m), 1.67 (1H, m), 1.29 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 166.09, 154.60, 138.10, 132.09, 129.94, 129.64, 128.67, 128.34, 127.35, 126.30, 125.73, 84.48 (q, *J* 26.8 Hz), 80.06, 75.73, 60.47, 53.58, 43.06, 34.15, 29.32, 27.01; δ_F (282.4 MHz; $CDCl_3$) −71.37 (3F, s); *m/z* (FAB > 0, GT) 530 ([M + Na]$^+$, 100%), 475 (8), 430 (9) (Found: C, 62.44; H, 6.31; N, 2.69. $C_{26}H_{30}F_3NO_5$ requires C, 62.32; H, 6.13; N, 2.84%).

(2*S*,3*S*)-2-Benzyl-3-benzyloxy-1-(*tert*-butoxycarbonyl)-pyrrolidine 14a

To a stirred solution of **5a** (0.500 g, 1.80 mmol) in THF (7.5 mL), under nitrogen, were added successively tetrabutylammonium iodide (TBAI) (53.3 mg, 5 mol%) and benzyl bromide (653 μL, 5.41 mmol) *via* a syringe. The solution was cooled to 0 °C, and NaH (95%; 50.0 mg, 1.98 mmol) was added. After 10 minutes, the solution was allowed to warm to room temperature, and was stirred for 6 hours. 5% Aq. citric acid (30 mL) was then added, and the solution was extracted with EtOAc (12 mL, 3×). The layers were separated, and the organic layer was successively washed with water (12 mL, 2×) and brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatotron purification (cyclohexane, then cyclohexane–EtOAc 8 : 2) gave **14a** (0.656 g, 99%) as a clear yellow oil; R_f 0.41 (cyclohexane–EtOAc 9 : 1); $[\alpha]_D^{25}$ 17.7 (*c* 1.34, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3029, 2980, 1684, 1497, 1402, 1168, 1085; δ_H (250 MHz; $CDCl_3$ + TFA) 7.31–7.21 (5H, m), 7.19–7.10 (5H, m), 4.38 (1H, m, *J* 11.7 Hz), 4.32 (1H, d, *J* 11.8 Hz), 4.12 (1H, br dd, *J* 12.7, 6.4 Hz), 3.97 (1H, br dd, *J* 14.9, 6.4 Hz), 3.34–3.28 (2H, m), 2.89 (1H, dd, *J* 13.5, 6.8 Hz), 2.78 (1H, dd, *J* 13.4, 5.8 Hz), 2.00–1.93 (1H, m), 1.87–1.72 (1H, m), 1.27 (9H, m); δ_C (62.9 MHz; $CDCl_3$) 154.68, 139.61, 138.22, 129.98, 128.44, 128.13, 127.70, 127.58, 125.88, 79.39, 78.74, 71.94, 60.24, 42.77, 35.05, 28.46, 26.97; *m/z* (FAB > 0, GT) 735 ([2M + H]$^+$, 3%), 390 ([M + Na]$^+$, 4), 368 ([M + H]$^+$, 25), 312 (81), 294 (6), 268 (11), 220 (20), 176 (27), 91 (96) (Found: C, 74.29; H, 7.88; N, 3.92. $C_{23}H_{29}NO_3$ requires C, 74.17; H, 7.95; N, 3.81%).

(2*R*,3*R*)-2-Benzyl-3-benzyloxy-1-(*tert*-butoxycarbonyl)-pyrrolidine 14b

A similar procedure, as used for the preparation of **14a**, led to

14b (99%), as a colourless oil; R_f 0.43 (cyclohexane–EtOAc 9 : 1); $[\alpha]_D^{25}$ −18.90 (*c* 1.17, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3065, 2979, 1682, 1497, 1454, 1403, 1171, 1130, 1088; δ_H (250 MHz; $CDCl_3$ + TFA) 7.27–7.15 (10H, m), 4.30 (1H, d, *J* 11.8 Hz), 4.10 (1H, d, *J* 11.8 Hz), 4.11 (1H, br dd, *J* 12.7, 6.4 Hz), 3.92 (1H, br dd, *J* 14.8, 6.4 Hz), 3.38–3.22 (2H, m), 2.91 (1H, dd, *J* 13.5, 6.9 Hz), 2.80 (1H, dd, *J* 13.5, 5.8 Hz), 1.97–1.89 (1H, m), 1.82–1.71 (1H, m), 1.28 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 154.75, 139.67, 138.29, 130.03, 128.48, 128.20, 127.74, 127.66, 125.95, 79.48, 78.82, 71.92, 60.28, 42.84, 35.12, 28.53, 27.02; *m*/*z* (FAB > 0, GT) 735 ($[2M + H]^+$, 2%), 390 ($[M + Na]^+$, 5), 368 ($[M + H]^+$, 17), 312 (100), 294 (10), 268 (16), 220 (13), 176 (18), 91 (45) (Found: C, 74.98; H, 7.81; N, 3.93. $C_{23}H_{29}NO_3$ requires C, 75.17; H, 7.95; N, 3.81%).

(2*S*,3*S*)-2-Benzyl-3-(benzyloxy)pyrrolidinium trifluoroacetate 15a

To a stirred solution of **14a** (0.414 g, 1.13 mmol) in CH_2Cl_2 (1.7 mL) was added TFA (1.7 mL, 22.6 mmol) under nitrogen at 0 °C. The solution was then allowed to warm to room temperature and was stirred for 30 minutes. Coevaporation with toluene (12 mL) and concentration under reduced pressure gave the resulting salt **15a** (0.432 g, quantitative yield) as a colourless oil; δ_H (250 MHz; CD_3OD) 7.56–7.44 (10H, m), 4.85 (1H, d, *J* 11.5 Hz), 4.61 (1H, d, *J* 11.5 Hz), 4.26 (1H, br s), 3.93 (1H, br s), 3.78–3.46 (2H, m), 3.42–3.33 (1H, m), 3.26–3.13 (1H, m), 2.61–2.47 (1H, m), 2.29–2.17 (1H, m); δ_C (62.9 MHz; $CDCl_3$) 139.69, 138.64, 130.82, 130.72, 130.30, 129.98, 129.78, 128.98, 78.94, 72.74, 67.51, 44.98, 34.05, 30.54; *m*/*z* (FAB > 0, NBA) 535 ($[2M + H]^+$, 4%), 268 ($[M + H]^+$, 55), 176 (31), 91 (100).

(2*R*,3*R*)-2-Benzyl-3-(benzyloxy)pyrrolidinium trifluoroacetate 15b

A similar procedure, as used in the preparation of **15a**, led to **15b** (quantitatively) as a colourless oil; δ_H (250 MHz; CD_3OD) 7.59–7.32 (10H, m), 4.88 (1H, d, *J* 11.5 Hz), 4.64 (1H, d, *J* 11.5 Hz), 4.30 (1H, m), 3.94 (1H, m), 3.65–3.57 (1H, m), 3.50 (1H, m), 3.40 (1H, dd, *J* 13.8, 7.3 Hz), 3.24 (1H, dd, *J* 13.9, 7.8 Hz), 2.65–2.49 (1H, m), 2.34–2.19 (1H, m); δ_C (62.9 MHz; $CDCl_3$) 139.67, 138.62, 130.83, 130.75, 130.27, 129.95, 129.79, 128.95, 78.96, 72.74, 67.50, 44.99, 34.08, 30.57; *m*/*z* (FAB > 0, NBA) 535 ($[2M + H]^+$, 3%), 268 ($[M + H]^+$, 46), 176 (37), 91 (100).

(2*S*,3*S*)-2-Benzyl-3-benzyloxy-1-[*N*-(*tert*-butoxycarbonyl)-L-phenylalanyl]pyrrolidine 16a

To a stirred solution of TFA salt **15a** (0.190 g, 0.498 mmol), Boc(L)PheOH **9a** (0.132 g, 0.498 mmol), and PyBOP (0.311 g, 0.598 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (174 μL, 1.25 mmol) dropwise at 0 °C under nitrogen. The solution was then allowed to warm to room temperature and was stirred for 3 hours. After concentration under reduced pressure, the resulting slurry was diluted in EtOAc (12 mL) and successively washed with 5% aq. $NaHCO_3$ (4 mL), water (4 mL), 5% aq. citric acid (4 mL), water (4 mL, 2×), and brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatotron purification (cyclohexane–EtOAc 7 : 3) gave **16a** (0.243 g, 95%) as a colourless oil; R_f 0.45 (cyclohexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ 26.4 (*c* 1.01, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3290, 3051, 3028, 2975, 2929, 1702, 1635, 1496, 1454, 1365, 1250, 1169, 1114, 1019, 922; δ_H (250 MHz; $CDCl_3$) 7.13–6.77 (15H, m), 5.12 (1H, d, *J* 9.3 Hz), 4.41–4.29 (1H, m), 4.11–4.05 (3H, m), 3.52–3.35 (1H, m), 3.14–3.02 (1H, m), 2.90–2.67 (4H, m), 2.45–2.24 (1H, m), 1.51–1.30 (2H, m), 1.23 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 170.81, 155.19, 139.39, 137.98, 136.66, 130.07, 129.52, 128.46, 128.24, 128.10, 127.78, 127.65, 126.96, 126.04, 79.76, 78.59, 71.84, 60.08, 53.21, 43.54, 40.13, 33.57, 28.45, 26.97; *m*/*z* (FAB > 0, NBA) 537 ($[M + Na]^+$, 11%), 515 ($[M + H]^+$, 91), 459 (46), 415 (100), 307 (11), 268 (43), 176 (24), 164 (11), 176 (24), 120 (28), 91 (55) (Found: C, 74.87; H, 7.51; N, 5.37. $C_{32}H_{38}N_2O_4$ requires C, 74.68; H, 7.44; N, 5.44%).

(2*R*,3*R*)-2-Benzyl-3-benzyloxy-1-[*N*-(*tert*-butoxycarbonyl)-L-phenylalanyl]pyrrolidine 16b

A similar procedure, as used for the preparation of **16a**, led to **16b** (93%) as a colourless oil; R_f 0.46 (DCM–EtOAc 9 : 1); $[\alpha]_D^{25}$ −5.8 (*c* 1.00, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3293, 3053, 2981, 2931, 1703, 1634, 1495, 1455, 1368, 1248, 1170, 1117, 1029; δ_H (250 MHz; $CDCl_3$) 7.30–6.98 (15H, m), 5.23 (1H, d, *J* 8.6 Hz), 4.57 (1H, m), 4.29–4.15 (2H, m), 4.04 (1H, m), 3.78 (1H, m), 3.48–3.37 (1H, m), 3.21–3.05 (1H, m), 2.98–2.88 (2H, m), 2.76 (1H, m), 2.65–2.45 (1H, m), 1.76 (2H, m), 1.36 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 170.82, 155.18, 139.49, 138.06, 136.98, 129.83, 129.50, 128.44, 128.32, 128.09, 127.82, 127.62, 126.90, 125.94, 79.57, 78.29, 71.49, 59.58, 53.13, 44.23, 39.95, 33.18, 28.44, 26.59; *m*/*z* (FAB > 0, NBA) 537 ($[M + Na]^+$, 11%), 515 ($[M + H]^+$, 91), 459 (46), 415 (100), 307 (11), 268 (43), 176 (24), 164 (11), 176 (24), 120 (28), 91 (55) (Found: C, 74.81; H, 7.35; N, 5.39. $C_{32}H_{38}N_2O_4$ requires C, 74.68; H, 7.44; N, 5.44%).

(2*S*,3*S*)-2-Benzyl-1-*O*-benzyl-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]-3-benzyloxypyrrolidine 17a

To a stirred solution of TFA salt **15a** (0.236 g, 0.619 mmol), Boc(L)Tyr(Bn)OH **9c** (0.230 g, 0.619 mmol), and PyBOP (0.386 g, 0.743 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (216 μL, 1.55 mmol) dropwise at 0 °C under nitrogen. The solution was then allowed to warm to room temperature and was stirred for 3 hours. After concentration under reduced pressure, the resulting slurry was diluted in EtOAc (12 mL) and successively washed with 5% aq. $NaHCO_3$ (4 mL), water (4 mL), 5% citric acid (4 mL), water (4 mL, 2×), and brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatotron purification (cyclohexane–EtOAc 7 : 3) gave **17a** (0.365 g, 95%) as a colourless oil; R_f 0.52 (cyclohexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ 30.63 (*c* 1.02, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3434, 3065, 3031, 2979, 2931, 1749, 1701, 1636, 1511, 1497, 1454, 1367, 1289, 1241, 1175, 1111, 1026, 699; δ_H (250 MHz; $CDCl_3$) 7.31–7.12 (15H, m), 7.09–6.99 (2H, m), 6.86–6.70 (2H, m), 5.23 (1H, d, *J* 8.4 Hz), 4.93 (3H, m), 4.43 (1H, m), 4.25 (1H, m), 4.20 (2H, m), 3.63–3.52 (1H, m), 3.28–3.16 (1H, m), 2.93 (1H, m), 2.82 (1H, m), 2.59–2.37 (1H, m), 1.58–1.47 (3H, m), 1.35 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 170.90, 157.74, 155.19, 139.39, 137.95, 137.05, 130.52, 130.04, 129.01, 128.71, 128.53, 128.44, 128.09, 127.97, 127.77, 127.58, 126.03, 114.93, 79.69, 77.32, 71.84, 69.98, 60.16, 53.33, 43.58, 39.20, 33.53, 28.44, 26.97; *m*/*z* (FAB > 0, NBA) 1241 ($[2M + H]^+$, 3%), 643 ($[M + Na]^+$, 11), 621 ($[M + H]^+$, 95), 565 (58), 521 (49), 413 (20), 294 (6), 268 (59), 226 (25), 197 (7), 91 (100) (Found: C, 75.59; H, 7.20; N, 4.41. $C_{39}H_{44}N_2O_5$ requires C, 75.46; H, 7.14; N, 4.51%).

(2*R*,3*R*)-2-Benzyl-1-*O*-benzyl-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]-3-benzyloxypyrrolidine 17b

A similar procedure, as used for the preparation of **17a**, led to **17b** (96%) as a white powder; mp 37–38 °C; R_f 0.38 (DCM–EtOAc 7 : 3); $[\alpha]_D^{25}$ −5.00 (*c* 1.00, MeOH); $\nu_{max}(KBr)/cm^{-1}$ 3433, 3065, 3032, 2980, 2932, 1748, 1701, 1636, 1510, 1497, 1455, 1368, 1288, 1240, 1173, 1115, 1027, 700; δ_H (250 MHz; $CDCl_3$) 7.25–6.91 (17H, m), 6.74 (2H, m), 5.20 (1H, d, *J* 8.8 Hz), 4.85 (2H, m), 4.45 (1H, br d, *J* 8.8 Hz), 4.21 (1H, m), 4.10 (2H, m), 3.73 (1H, m), 3.38 (1H, m), 3.17 (1H, m), 3.01–2.85 (2H, m), 2.75–2.67 (1H, m), 2.55–2.39 (1H, m), 1.70 (2H, m), 1.26 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 170.90, 157.74, 155.19, 139.39, 138.07, 137.99, 137.05, 130.52, 130.04, 129.01, 128.71, 128.59,

128.53, 128.44, 128.09, 127.97, 127.77, 127.58, 127.35, 126.03, 114.93, 79.69, 77.32, 71.84, 69.98, 60.16, 53.33, 43.58, 39.20, 33.53, 28.68, 26.82; *m/z* (FAB > 0, NBA) 1241 ([2M + H]$^+$, 2%), 643 ([M + Na]$^+$, 4), 621 ([M + H]$^+$, 29), 565 (8), 521 (17), 413 (8), 294 (3), 268 (12), 226 (9), 197 (5), 91 (58) (Found: C, 75.30; H, 7.03; N, 4.62. $C_{39}H_{44}N_2O_5$ requires C, 75.46; H, 7.14; N, 4.51%).

(2*S*,3*S*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-phenylalanyl]-pyrrolidin-3-ol 1a

A stirred solution of **16a** (0.170 g, 0.330 mmol) in ethanol (2 mL) was bubbled with dry nitrogen during 10 minutes. Pearlman's catalyst (20% $Pd(OH)_2/C$) (57.9 mg, 10 mol%) was then added, and the slurry was again nitrogen bubbled during 5 minutes. The reaction mixture was stirred for 50 minutes under a flux of hydrogen (atmospheric pressure) at room temperature. The resulting slurry was then filtered over Celite,® concentrated under reduced pressure and chromatotron purified (cyclohexane–EtOAc 6 : 4) to obtain **1a** (0.138 g, 99%) as a white powder; mp 51 °C; R_f 0.30 (cyclohexane–EtOAc 6 : 4); $[a]_D^{25}$ 21.6 (*c* 1.00, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3631, 3434, 3051, 2975, 2932, 1766, 1733, 1700, 1630, 1558, 1509, 1493, 1433, 1389, 1247, 1165, 1050, 677; δ_H (250 MHz; $CDCl_3$) 7.17–7.00 (10H, m), 5.16 (1H, d, *J* 8.6 Hz), 4.40 (1H, m), 4.20 (1H, m), 3.81 (1H, m), 3.26–3.07 (2H, m), 2.82–2.65 (3H, m), 2.43–2.35 (1H, m), 1.47 (2H, br s), 1.27 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 170.90, 155.21, 139.46, 136.59, 129.71, 129.48, 128.52, 128.39, 127.00, 126.19, 79.81, 70.52, 61.97, 53.45, 44.05, 40.07, 33.24, 30.97, 28.41; *m/z* (FAB > 0, NBA) 447 ([M + Na]$^+$, 10%), 425 ([M + H]$^+$, 100), 369 (92), 351 (7), 325 (62), 307 (8), 248 (7), 204 (11), 178 (78), 160 (17), 120 (72), 91 (57) (Found: C, 70.88; H, 7.69; N, 6.48. $C_{25}H_{32}N_2O_4$ requires C, 70.73; H, 7.60; N, 6.60%).

(2*R*,3*R*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-phenylalanyl]-pyrrolidin-3-ol 1b

A similar procedure, as used for the preparation of **1a**, led to **1b** (99%) as a colourless oil; R_f 0.29 (cyclohexane–EtOAc 6 : 4); $[a]_D^{25}$ 9.83 (*c* 0.54, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3431, 3052, 2978, 2931, 1762, 1732, 1703, 1634, 1561, 1507, 1491, 1432, 1391, 1245, 1169, 1051, 678; δ_H (250 MHz; $CDCl_3$) 7.11–6.93 (10H, m), 5.23 (1H, d, *J* 8.5 Hz), 4.48 (1H, m), 3.99 (2H, m), 3.44 (1H, m), 3.15 (2H, m), 2.87–2.76 (2H, m), 2.54–2.38 (1H, m), 1.64 (1H, m), 1.46 (2H, m), 1.23 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 171.03, 155.33, 139.42, 136.90, 129.72, 129.52, 128.75, 128.59, 127.03, 126.35, 79.79, 70.60, 61.33, 53.40, 45.02, 40.14, 32.93, 28.52, 27.01; *m/z* (FAB > 0, GT) 447 ([M + Na]$^+$, 11%), 425 ([M + H]$^+$, 63), 369 (43), 351 (12), 325 (100), 307 (6), 204 (7), 178 (46), 160 (16), 91 (32) (Found: C, 70.94; H, 7.49; N, 6.66. $C_{25}H_{32}N_2O_4$ requires C, 70.73; H, 7.60; N, 6.60%).

(2*S*,3*S*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]-pyrrolidin-3-ol 2a

A stirred solution of **17a** (0.100 g, 0.161 mmol) in ethanol (2 mL) was nitrogen bubbled during 10 minutes. Pearlman's catalyst [$Pd(OH)_2/C$ 20%, moisture ≈ 60% (28.3 mg wet, 10 mol%)] was then added, and the slurry solution was again nitrogen bubbled during 5 minutes. The reaction mixture was stirred for 45 minutes under a flux of hydrogen (under atmospheric pressure) at room temperature. The resulting slurry was then filtered over Celite,® concentrated under reduced pressure, and purified by chromatotron (cyclohexane–EtOAc 6 : 4) to obtain **2a** (69.8 mg, 98%) as a white solid; mp 87–88 °C; R_f 0.45 (EtOAc–cyclohexane 6 : 4); $[a]_D^{25}$ 33.2 (*c* 1.00, MeOH); ν_{max}(KBr)/cm^{-1} 3429, 3052, 2981, 2932, 1700, 1629, 1516, 1508, 1497, 1453, 1369, 1289, 1249, 1170, 1103, 1048, 705; δ_H (250 MHz; $CDCl_3$) 7.28 (1H, br s), 7.11–6.94 (5H, m), 6.81 (2H, d, *J* 8.2 Hz), 6.52 (2H, d, *J* 8.2 Hz), 5.21 (1H, d, *J* 8.9 Hz), 4.31 (1H, m), 3.90 (1H, m), 3.74 (1H, m), 3.13 (1H, m), 2.97 (1H, m), 2.76–2.63 (2H, m), 2.41 (1H, m), 2.21 (1H, m), 1.85 (1H, m), 1.34 (1H, m), 1.24 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 171.38, 155.71, 155.53, 139.34, 130.65, 129.79, 128.48, 127.67, 126.34, 115.62, 80.26, 70.68, 61.91, 53.66, 44.13, 39.09, 33.34 28.50, 28.36; *m/z* (FAB > 0, NBA) 463 ([M + Na]$^+$, 4%), 441 ([M + H]$^+$, 13), 385 (6), 341 (4), 204 (5), 178 (5), 136 (60), 107 (16), 91 (14) (Found: C, 68.23; H, 7.41; N, 6.25. $C_{25}H_{32}N_2O_5$ requires C, 68.16; H, 7.32; N, 6.36%).

(2*R*,3*R*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]-pyrrolidin-3-ol 2b

A similar procedure, as used for the preparation of **2a**, led to **2b** (96%) as a colourless oil; R_f 0.31 (cyclohexane–EtOAc 6 : 4); $[a]_D^{25}$ 8.36 (*c* 1.35, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3428, 3051, 2982, 2932, 1705, 1628, 1515, 1494, 1455, 1363, 1294, 1249, 1152, 1110, 1052, 705; δ_H (250 MHz; $CDCl_3$) 7.40–7.24 (6H, m), 7.08 (2H, m), 6.76 (2H, m), 5.40 (1H, d, *J* 8.6 Hz), 4.64 (1H, m), 4.28 (1H, m), 3.89 (1H, m), 3.60 (1H, m), 3.33 (1H, m), 3.19 (1H, m), 3.04 (1H, m), 2.91 (1H, m), 2.65 (1H, m), 1.86–1.71 (2H, m), 1.47 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 171.37, 155.63, 155.53, 139.26, 130.78, 129.48, 128.59, 127.54, 126.41, 115.56, 80.24, 70.48, 63.11, 53.63, 45.10, 38.88, 32.95, 28.51, 28.45; *m/z* (FAB > 0, NBA) 463 ([M + Na]$^+$, 3%), 441 ([M + H]$^+$, 8), 385 (5), 341 (7), 204 (6), 178 (12), 136 (71), 107 (22), 91 (16) (Found: C, 68.33; H, 7.41; N, 6.28. $C_{25}H_{32}N_2O_5$ requires C, 68.16; H, 7.32; N, 6.36%).

(2*S*)-2-Benzyl-3-oxopyrrolidinium trifluoroacetate 18a

The same procedure as previously described for the synthesis of **15a**, led, when applied to **6a**, quantitatively to **18a**, as a colourless oil; δ_H (250 MHz; CD_3OD) 7.30–7.21 (5H, m), 3.97 (1H, dd, *J* 10.7, 4.0 Hz), 3.71–3.60 (1H, m), 3.49–3.36 (1H, m), 3.29–3.20 (2H, m), 2.83–2.59 (2H, m); δ_C (62.9 MHz; CD_3OD) 207.49, 136.63, 129.98, 129.44, 128.62, 67.45, 41.89, 34.55, 31.90; *m/z* (FAB > 0, GT) 351 ([2M + H]$^+$, 3%), 176 ([M + H]$^+$, 58).

(2*R*)-2-Benzyl-3-oxopyrrolidinium trifluoroacetate 18b

A similar procedure, as used for the preparation of **15a**, led to **18b** quantitatively, as a colourless oil; δ_H (250 MHz; CD_3OD) 7.62–7.48 (5H, m), 4.26 (1H, dd, *J* 10.4, 3.9 Hz), 4.01–3.88 (1H, m), 3.82–3.70 (1H, m), 3.63–3.54 (1H, m), 3.48 (1H, m), 3.13–3.07 (1H, m), 2.96–2.88 (1H, m); δ_C (62.9 MHz; CD_3OD) 207.51, 136.65, 130.01, 129.42, 128.64, 67.41, 41.93, 34.51, 31.87; *m/z* (FAB > 0, GT) 351 ([2M + H]$^+$, 4%), 176 ([M + H]$^+$, 53).

(2*S*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-phenylalanyl]-pyrrolidin-3-one 3a

To a stirred solution of the TFA salt **18a** (0.105 g, 0.363 mmol), Boc(L)PheOH **9a** (97.3 mg, 0.363 mmol), and PyBOP (0.234 g, 0.436 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (127 μL, 0.908 mmol) dropwise at 0 °C under nitrogen. The solution was then allowed to warm to room temperature and was stirred during 1.5 h. After concentration under reduced pressure, the resulting slurry was diluted in EtOAc (12 mL) and successively washed with 5% aq. $NaHCO_3$ (4 mL), water (4 mL), 5% aq. citric acid (4 mL), water (4 mL, 2×), and brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatotron purification (cyclohexane–EtOAc 7 : 3) gave **3a** (0.332 g, 98%) as a yellowish oil; R_f 0.40 (cyclohexane–EtOAc 7 : 3); $[a]_D^{25}$ 115.2 (*c* 1, MeOH); ν_{max}(KBr)/cm^{-1} 3305, 3065, 3030, 2980, 2930, 1759, 1705, 1644, 1495, 1455, 1368, 1247, 1168, 1080, 1055, 1030, 704; δ_H (250 MHz; $CDCl_3$) 7.19–7.00 (8H, m), 6.81 (2H, m), 5.27 (1H, d, *J* 8.7 Hz), 4.48 (1H, m), 4.12 (1H, m), 3.25 (1H, dd, *J* 13.4, 5.8 Hz), 2.96–2.69 (5H, m), 2.33 (1H, br

dd, *J* 18.9, 8.8 Hz), 1.47 (1H, m), 1.34 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 212.31, 171.21, 155.18, 136.32, 135.74, 129.95, 129.75, 129.35, 128.67, 128.48, 127.01, 79.80, 63.30, 52.27, 42.61, 39.87, 36.21, 35.08, 28.34; *m*/*z* (FAB > 0, GT) 845 ($[2M + H]^+$, 3%), 445 ($[M + Na]^+$, 5), 423 ($[M + H]^+$, 27), 376 (28), 323 (16), 202 (4), 176 (15), 120 (24), 91 (23) (Found: C, 70.28; H, 7.21; N, 6.52. $C_{25}H_{30}N_2O_4$ requires C, 70.37; H, 7.16; N, 6.63%).

(2*R*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-phenylalanyl]-pyrrolidin-3-one 3b

A similar procedure, as used for the preparation of **3a**, led to **3b** (97%) as a colourless oil; R_f 0.40 (cyclohexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ −24.01 (*c* 1.11, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3433, 3058, 3031, 2981, 2930, 1760, 1705, 1647, 1496, 1456, 1369, 1246, 1167, 1095; δ_H (250 MHz; $CDCl_3$) 7.15–7.01 (8H, m), 6.81 (2H, m), 5.29 (1H, d, *J* 8.6 Hz), 4.58–4.47 (1H, m), 4.12 (1H, m), 3.27–3.07 (1H, m), 2.99–2.61 (5H, m), 2.34 (1H, m), 1.28 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 212.43, 171.45, 155.29, 136.67, 135.84, 129.87, 129.80, 129.33, 128.74, 128.60, 127.12, 80.11, 63.07, 52.39, 42.77, 40.98, 36.78, 35.21, 28.34; *m*/*z* (FAB > 0, GT) 445 ($[M + Na]^+$, 4%), 423 ($[M + H]^+$, 26), 376 (27), 323 (25), 202 (4), 176 (12), 120 (18), 91 (22) (Found: C, 71.26; H, 7.09; N, 6.55. $C_{25}H_{30}N_2O_4$ requires C, 71.07; H, 7.16; N, 6.63%).

(2*S*)-2-Benzyl-1-*O*-benzyl-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]pyrrolidin-3-one 19a

To a stirred solution of the TFA salt **18a** (0.210 g, 0.726 mmol), Boc(L)Tyr(Bn)OH **9c** (0.270 g, 0.726 mmol), and PyBOP (0.454 g, 0.872 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (253 μL, 1.82 mmol) dropwise at 0 °C under nitrogen. The solution was then allowed to warm to room temperature and was stirred during 2 hours. After concentration under reduced pressure, the resulting slurry was diluted in EtOAc (12 mL) and successively washed with 5% aq. $NaHCO_3$ (4 mL), water (4 mL), 5% aq. citric acid (4 mL), water (4 mL, 2×), and brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatotron purification (cyclohexane–EtOAc 7 : 3) gave **19a** (0.369 g, 96%) as a colourless oil; R_f 0.35 (cyclohexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ 89.8 (*c* 1.00, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3434, 3338, 3065, 3032, 2981, 2931, 1758, 1705, 1643, 1611, 1541, 1498, 1455, 1240, 1174, 1094, 1017; δ_H (250 MHz; $CDCl_3$) 7.31–7.25 (4H, m), 7.19–7.01 (6H, m), 6.90 (2H, m), 6.77 (2H, d, *J* 8.6 Hz), 5.33 (1H, d, *J* 8.8 Hz), 4.95 (2H, m), 4.52 (1H, m), 4.20 (1H, m), 3.37 (1H, dd, *J* 13.43, 5.9 Hz), 3.02–2.78 (5H, m), 2.46 (1H, br dd, *J* 19.2, 9.0 Hz), 1.59 (1H, m), 1.43 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 212.40, 171.44, 157.86, 155.25, 136.86, 135.85, 130.47, 129.84, 128.67, 128.59, 128.09, 127.49, 127.39, 127.11, 115.05, 80.00, 69.98, 63.04, 52.47, 42.69, 39.20, 36.36, 35.19, 28.45; *m*/*z* (FAB > 0, GT) 551 ($[M + Na]^+$, 4), 529 ($[M + H]^+$, 38), 473 (33), 429 (21), 226 (19), 202 (7), 176 (18), 91 (63) (Found: C, 72.58; H, 6.79; N, 5.39. $C_{32}H_{36}N_2O_5$ requires C, 72.70; H, 6.86; N, 5.30%).

(2*R*)-2-Benzyl-1-*O*-benzyl-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]pyrrolidin-3-one 19b

A similar procedure, as used for the preparation of **19a**, led to **19b** (96%) as a white powder; mp 43 °C; R_f 0.37 (cyclohexane–EtOAc 7 : 3); $[\alpha]_D^{25}$ −72.9 (*c* 1.00, MeOH); $\nu_{max}(KBr)/cm^{-1}$ 3435, 3064, 3030, 2982, 2928, 1759, 1705, 1645, 1540, 1497, 1455, 1241, 1174, 1093, 1017, 651; δ_H (250 MHz; $CDCl_3$) 7.64–7.51 (4H, m), 7.46–7.17 (6H, m), 7.11 (4H, m), 6.36 (1H, d, *J* 8.6 Hz), 5.27 (2H, m), 4.78 (1H, m), 4.32 (1H, m), 3.84 (1H, m), 3.32–3.01 (5H, m), 2.78 (1H, m), 1.77 (1H, m), 1.52 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 212.32, 171.56, 158.17, 155.33, 136.90, 135.81, 130.57, 129.83, 128.94, 128.66, 128.33, 127.46, 127.39, 127.19, 115.04, 80.06, 69.94, 63.26, 52.28, 42.80, 39.98, 36.71, 35.66, 28.41; *m*/*z* (FAB > 0, GT) 551 ($[M + Na]^+$, 3%), 529 ($[M + H]^+$, 18), 473 (10), 429 (13), 226 (11), 202 (4), 176 (9), 91 (24) (Found: C, 72.62; H, 6.92; N, 5.19. $C_{32}H_{36}N_2O_5$ requires C, 72.70; H, 6.86; N, 5.30%).

(2*S*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]-pyrrolidin-3-one 4a

A stirred solution of **19a** (0.150 g, 0.284 mmol) in ethanol (2 mL) was nitrogen bubbled during 10 minutes. 10% Pd–C (12.1 mg, 4 mol%) was then added, and the slurry was again nitrogen bubbled during 5 minutes. The reaction mixture was stirred for 8 hours under a flux of hydrogen (under atmospheric pressure) at room temperature. The resulting slurry was then filtered over Celite,® concentrated under reduced pressure, and chromatotron purified (cyclohexane–EtOAc 6 : 4) to obtain **4a** (0.122 g, 98%) as a white powder; mp 71 °C; R_f 0.33 (cyclohexane–EtOAc 6 : 4); $[\alpha]_D^{25}$ 107.9 (*c* 1.00, MeOH); $\nu_{max}(KBr)/cm^{-1}$ 3428, 3331, 3064, 2982, 2932, 1759, 1701, 1641, 1614, 1594, 1516, 1499, 1455, 1369, 1248, 1170, 1103, 1046; δ_H (250 MHz; $CDCl_3$) 7.56 (1H, br s), 7.21–6.99 (4H, m), 7.00–6.89 (3H, m), 6.73 (1H, d, *J* 8.2 Hz), 6.65 (1H, d, *J* 8.3 Hz), 5.50 (1H, d, *J* 8.9 Hz), 4.51 (1H, m), 4.36 (1H, br s), 3.30 (1H, dd, *J* 13.4, 5.8 Hz), 3.01–2.76 (5H, m), 2.54–2.37 (1H, m), 1.76–1.53 (1H, m), 1.41 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 212.51, 171.80, 155.80, 155.47, 135.66, 130.53, 129.79, 128.63, 127.24, 127.16, 115.59, 80.31, 63.15, 52.55, 42.79, 39.01, 36.32, 35.20, 28.41; *m*/*z* (FAB > 0, NBA) 877 ($[2M + H]^+$, 3%), 461 ($[M + Na]^+$, 4), 439 ($[M + H]^+$, 15), 383 (12), 339 (11), 202 (4), 176 (11), 136 (11), 107 (23) (Found: C, 68.29; H, 7.02; N, 6.47. $C_{25}H_{30}N_2O_5$ requires C, 68.47; H, 6.90; N, 6.39%).

(2*R*)-2-Benzyl-1-[*N*-(*tert*-butoxycarbonyl)-L-tyrosinyl]-pyrrolidin-3-one 4b

A similar procedure to that used for the preparation of **4a**, led to **4b** (99%) as a white powder; mp 84 °C; R_f 0.41 (DCM–EtOAc 7 : 3); $[\alpha]_D^{25}$ −81.8 (*c* 1.00, MeOH); $\nu_{max}(KBr)/cm^{-1}$ 3430, 3058, 2982, 2931, 1759, 1704, 1641, 1614, 1593, 1498, 1455, 1370, 1169,1103, 1045; δ_H (250 MHz; $CDCl_3$) 7.06 (1H, br s), 6.94–6.84 (4H, m), 6.75 (3H, m), 6.57 (1H, d, *J* 8.3 Hz), 6.46 (1H, d, *J* 8.3 Hz), 5.30 (1H, d, *J* 8.8 Hz), 4.40 (1H, m), 4.36 (1H, m), 3.14 (1H, m), 2.90 (1H, m), 2.79–2.54 (4H, m), 2.36–2.09 (1H, m), 1.91 (1H, m), 1.23 (9H, s); δ_C (62.9 MHz; $CDCl_3$) 212.35, 171.60, 155.67, 155.42, 135.01, 130.63, 129.83, 128.64, 127.89, 127.19, 115.73, 80.42, 63.38, 54.06, 41.53, 38.23, 36.72, 35.70, 28.45; *m*/*z* (FAB > 0, NBA) 877 ($[2M + H]^+$, 2%), 461 ($[M + Na]^+$, 3), 439 ($[M + H]^+$, 15), 383 (12), 339 (11), 202 (4), 176 (11), 136 (71), 107 (23) (Found: C, 68.66; H, 6.82; N, 6.28. $C_{25}H_{30}N_2O_5$ requires C, 68.47; H, 6.90; N, 6.39%).

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