

Model Studies Directed Toward the Total Synthesis of 14-Membered Cyclopeptide Alkaloids: Synthesis of Prolyl Peptides *via* a Four-Component Condensation

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The general applicability of a four-component condensation for the formation of *N*-acyl- β -aryloxyprolines has been demonstrated in several model studies. The relative stereochemistry of the diastereoisomers obtained has been assigned from ^1H n.m.r. studies, and confirmed by an *X*-ray analysis of one of the stereoisomers.

As a continuation of investigations^{1d-4} into the total synthesis of the 14-membered cyclopeptide alkaloids,^{1a-f} more specifically those belonging to the amphibine-B family, we report the synthesis of diastereoisomeric prolyl dipeptides *via* a four-component condensation. Preliminary results to ascertain the feasibility of this novel approach have been reported earlier.^{2,3}

This strategy may now be considered a general method for the construction of appropriately functionalized linear precursors for the synthesis of naturally occurring cyclopeptide alkaloids and analogues thereof.⁵

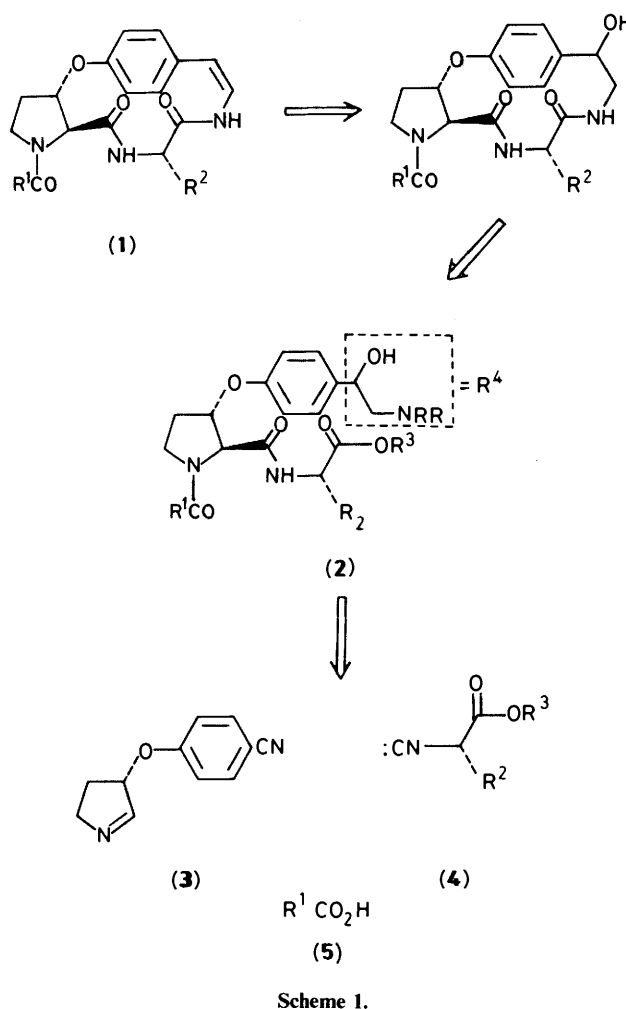
The four-component condensation (4CC), first proposed by Ugi,⁶ generates an *N*-acylated amino acid amide from an aldehyde, an amine, a carboxylic acid, and an isonitrile. The 14-membered cyclopeptide alkaloids of the amphibine-B family have the general structure (1) and the linear precursors (2) of these may be visualized as acylated cyclic secondary amino acid amides. A retrosynthetic analysis shows that compounds (3)—(5) are the intermediates needed for carrying out the 4CC (Scheme 1).

The key intermediate is the 3-aryloxy-4,5-dihydropyrrole (3), an intramolecular condensation product of the aldehyde and amine components. Compound (3) can then react with the isonitrile (4) derived from the required amino acid, and carboxylic acid (5) to afford the desired *N*-acylated- β -(aryloxy)prolyl peptide (2). This approach generates the *N*-acyl bond, the bond to the α -carbon of proline, the prolyl amide, and the desired *trans* stereochemistry, all in one reaction step. The synthesis of prolyl peptides by the four-component condensation is shown in Scheme 2.

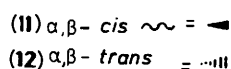
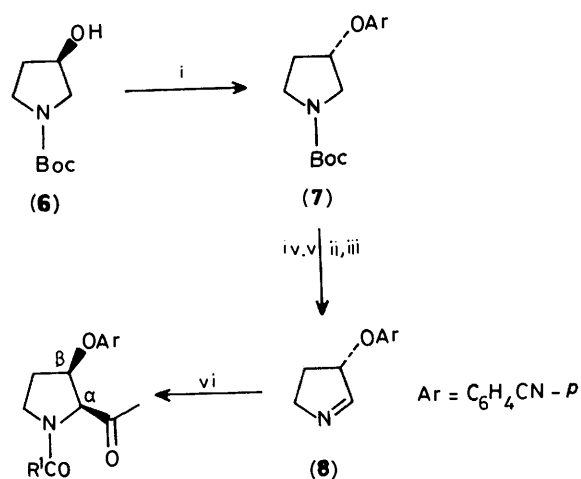
Results and Discussion

N-Butoxycarbonylpyrrolidin-3-ol (6)² was prepared from pyrrolidin-3-ol⁷ and di-*t*-butyl dicarbonate in 88% yield. The alkyl aryl ether (7) was prepared in 85% yield using equimolar ratios of (6) and *p*-cyanophenol and a slight excess of both diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) as described by Mitsunobu.⁸ Removal of the *t*-butoxycarbonyl group with trifluoroacetic acid (TFA) afforded the trifluoroacetate salt of the corresponding 3-(4-cyanophenoxy)pyrrolidine (82.4%). The free base was extracted from aqueous sodium carbonate and subsequently treated with *t*-butyl hypochlorite⁹ (Bu^tOCl), at 0°C, to give a quantitative yield of the corresponding *N*-chloro derivative. This was dehydrohalogenated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol, to afford the highly unstable 3-(4-cyanophenoxy)-4,5-dihydropyrrole (8). Careful handling permitted the isolation of derivative (8) allowing spectroscopic identification of this product (^1H and ^{13}C n.m.r.).

The isonitriles (10a)¹⁰⁻¹³ and (10b)^{10,11} were prepared according to published procedures. A model study incorpor-



ating two glycine derivatives was examined as these compounds closely resemble reagents that would be used in a cyclopeptide alkaloid synthesis. 3-(4-Cyanophenoxy)-4,5-dihydropyrrole (8) was prepared *in situ* as described and subjected to the 4CC conditions by addition of an ethanolic solution of *N*-butoxycarbonylglycine (9a) and ethyl 2-isocyanoacetate (10a) to afford a mixture of *cis* and *trans* isomers in a 55:45 ratio (11a) and (12a) (64%). ^1H N.m.r. spectroscopy allowed differentiation between the *cis* and *trans* isomers, the latter (12a) exhibiting a characteristic singlet for the α -proton of the substituted proline, while the α,β -proton coupling constant of the former, (11b), was 6.5 Hz in CDCl_3 .



- (9a) R¹ = Ph
 (9b) R¹ = CH₂NHBoc
 (10a) R¹ = CH(NHBoc) Prⁱ
 (10b) R¹ = CH₂CO₂Et
 (10c) R¹ = CH(CH₂Ph)CO₂Me



- (11a)(12a) R¹ = CH₂NHBoc; R² = CH₂CO₂Et
 (11b)(12b) R¹ = Ph; R² = CH₂CO Et
 (11c)(12c) R¹ = Ph; R² = (S) CH(CH₂Ph)
 (11d)(12d) R¹ = Ph; R² = (R) CH(CH₂Ph)

Scheme 2. Reagents and conditions: i, PPh₃, DEAD, THF, r.t., HOC₆H₄CN; ii, F₃CCO₂H, CH₂Cl₂, 0 °C; iii, 10% aq. Na₂CO₃, 0 °C; N, t-butyl hypochlorite, Et₂O, 0 °C; v, DBU, MeOH; vi, (9) R¹CO₂H/MeOH, and (10) R²NC/MeOH

A model study utilizing benzoic acid (9b), ethyl 2-isocyanoacetate (10a) and the key intermediate (8), formed *in situ* under 4CC conditions, produced two products, (11b) and (12b), in a 63:37 ratio (*cis*:*trans*). Consistent with the foregoing results, the *trans*-(12b) isomer exhibited a sharp singlet in its ¹H n.m.r. spectrum while the α, β -proton coupling constant of the *cis*-(11b) isomer was 5.2 Hz in CDCl₃.

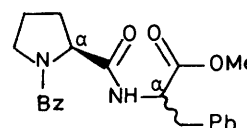
Another model study incorporated the racemic isonitrile derived from phenylalanine (10b), 3-(4-Cyanophenoxy)-4,5-dihydropyrrole (8), benzoic acid (9b), and the isonitrile (10b) afforded four enantiomeric pairs of diastereoisomers (11c, d) and (12c, d) that were separable by chromatography. The *cis*:*trans* isomeric ratio was 60:40 and the total yield for the 5-step reaction sequence was 50%. β -Elimination of *p*-cyanophenol was the major side reaction in all cases.

The four enantiomeric pairs of diastereoisomers were examined by ¹H n.m.r. spectroscopy as (see in Figure 1) and the relative stereochemical assignments for each stereogenic centre were made by comparison with two model dipeptides (13) and (14) of known absolute stereochemistry.

Compounds (13) and (14) had the same α - and *N*-substituents as the linear 4CC products [(11c, d) and (12c, d)], and were prepared by coupling *N*-benzoyl-L-proline¹⁴ with either L- or D-

Table 1. Relative stereochemical assignments for (11c, d) and (12c, d)

Compound number	Ring	Configuration
(11c)	<i>cis</i>	Pro α S, β R, Phe α S
(11d)	<i>cis</i>	Pro α S, β R, Phe α R
(12c)	<i>trans</i>	Pro α S, β S, Phe α S
(12d)	<i>trans</i>	Pro α S, β S, Phe α R



phenylalanine methyl ester using the water soluble carbodi-imide, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride, *N*-hydroxybenzotriazole and *N*-methylmorpholine, in dichloromethane, at 0 °C. The diastereoisomer (13) provided the Pro α S, Phe α R configuration. Each dipeptide was examined by ¹H n.m.r. spectroscopy (see Figure 2). The diastereotopic benzylic protons, labelled with an arrow in these spectra, exhibit distinctly different chemical shifts depending on the relative stereochemistry of the two stereogenic centres (*S,S* or *S,R*) in each dipeptide. This difference permitted the assignment of the relative stereochemistry of the diastereoisomeric products obtained in the 4CC. ¹H N.m.r. spectroscopy has been used for the detection of racemization in peptide synthesis and verification of configuration, based upon a shielding phenomenon seen in peptides containing adjacent aromatic and aliphatic amino acid residues.¹⁵ Figure 1 shows portions of the ¹H n.m.r. spectrum of each of the four isolated diastereoisomeric prolyl peptides. The diastereotopic benzylic protons are marked with an arrow and the identical trend, noted for the same protons in model peptides (13) and (14) is seen in this figure. The difference in chemical shift for each isomer are either large or small. The ¹H n.m.r. spectra of peptides (12c) and (11c) exhibit the largest comparative differences in chemical shifts for the diastereotopic benzylic protons. Therefore, the relative stereochemical assignments for the proline α -centre and the phenylalanine α -centre should be *S,S* in these isomers. The ¹H n.m.r. spectra of peptides (12d) and (11d) support the relative stereochemical assignment of the α -proline and α -phenylalanine carbons as *S,R*, respectively, because of the smaller comparative differences in chemical shifts for the diastereotopic benzylic protons.

The 4CC also produces *cis* and *trans* isomers with respect to the pyrrolidine ring. In cases where the ring substituents are *cis* to each other, the proline α -proton is split by the proline β -proton as seen in the spectra of (11d) and (11c). When the same substituents are *trans*, the proline α -proton is not split and exhibits a characteristic singlet. This arises because the dihedral angle between the planes containing the α - and β -protons is close to 90°, and therefore the coupling constant is essentially zero. Peptides (12c) and (12d) both exhibit this sharp diagnostic singlet, and may, therefore, each be assigned the *trans* configuration.

The ¹H n.m.r. data for each isomer was extremely useful in making relative stereochemical assignments and these are shown in Table 1 for each isomer.

The sharp diagnostic proline α -proton singlet is a valuable tool for determining whether cyclization, from a *trans* linear precursor, has occurred. In the ¹H n.m.r. spectrum of

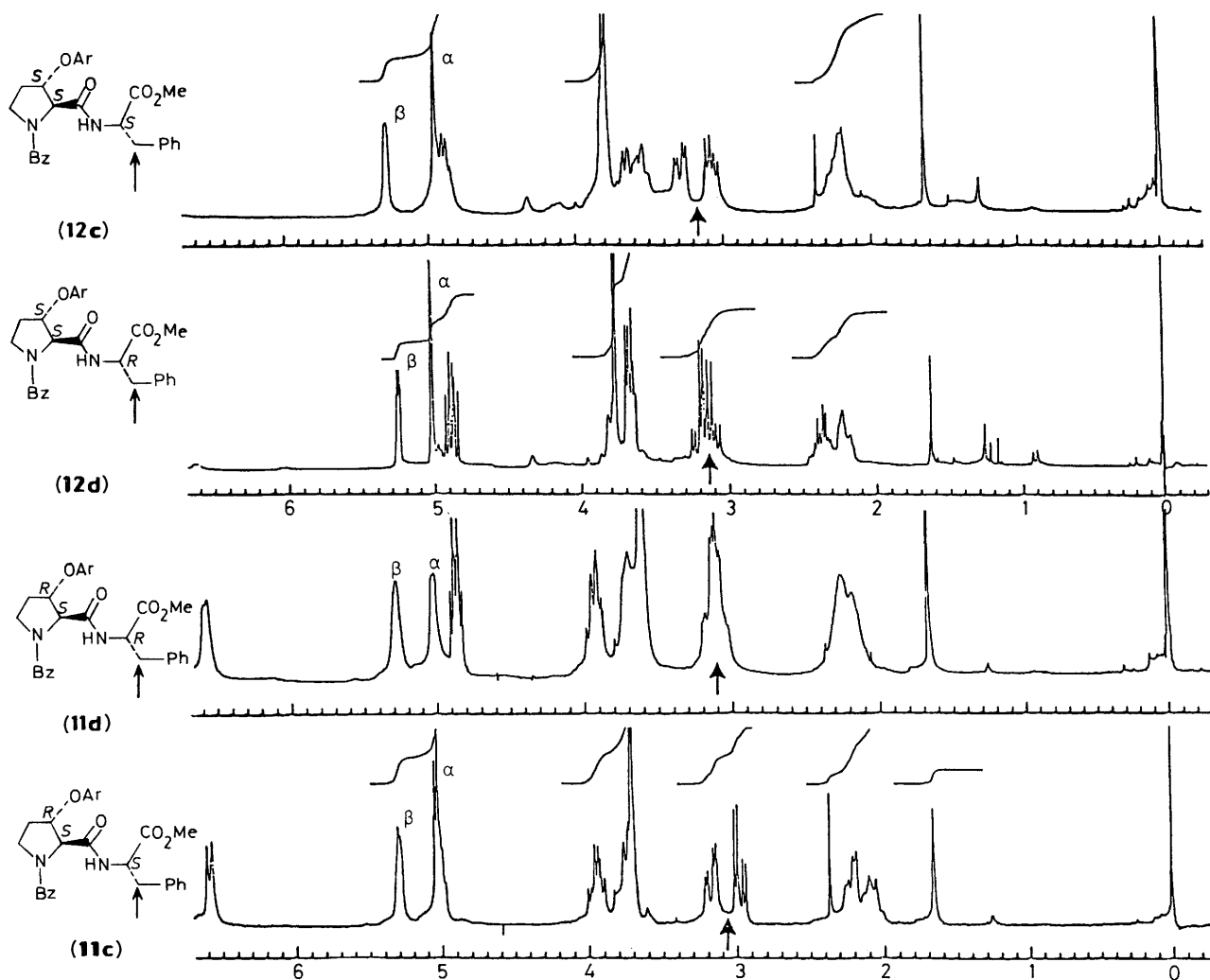


Figure 1. 250 MHz ^1H N.m.r. spectra of diastereoisomeric products: (11c), (11d), (12c), and (12d) (Ar = $\text{C}_6\text{H}_4\text{CN-}p$)

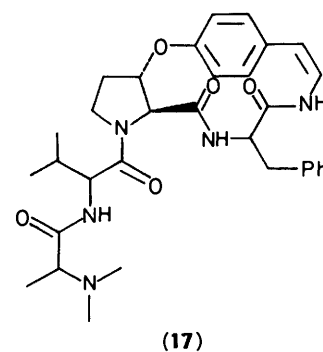
amphibine-B type alkaloids containing a *trans* β -hydroxyproline residue, the α,β -coupling constant can be measured.^{1,16}

The relative stereochemical assignments shown in Table 1 were confirmed by an X-ray crystal analysis obtained for the dipeptide (12c) (Figure 3 and Table 2). The dihedral angle between the planes containing the α - and β -protons was calculated to be 97.05° .

Finally, a further model 4CC was carried out using the 4,5-dihydropyrrole (8) butoxycarbonyl L-valine (9c) and the racemic isonitrile corresponding to phenylalanine (10b). In this case, 8 optically active diastereoisomers (15a–h) were obtained and these, after chromatographic separation using silica gel and a gradient solvent system, were identified by ^1H n.m.r. spectroscopy.

The diastereoisomer (15a) closely resembles a linear precursor that could be used in the synthesis of the cyclopeptide alkaloid mauritine-A (17). The optically active peptide (15a), $[\alpha]_D^{22} +28.0^\circ$ (*c* 0.31 in CHCl_3) was *N*-deblocked with TFA, and the valine residue was coupled with *N,N*-dimethyl-L-alanine^{17,18} utilizing 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride, *N*-hydroxybenzotriazole, and *N*-methylmorpholine to give the optically active peptide (16) $[\alpha]_D^{22} +31.4^\circ$ (*c* 0.23 in CHCl_3), a suitable linear precursor to mauritine-A (17).

The large number and sometimes complex mixtures of



(17)

enantiomeric diastereoisomers obtained from the 4CC [see, for example, the production of the eight isomers (15a–h)] made it important to utilize optically active starting materials. The synthesis of chiral pyrrolidin-3-ols has been reported and may be found in a recent review.¹⁹

With the *R*-enantiomer (18) in hand, *N*-*t*-butoxycarbonyl-(3*S*)-(4-cyanophenoxy)pyrrolidine (19), $[\alpha]_D +23.49^\circ$ (*c* 0.80 in CHCl_3) was prepared (84.4% yield) as described previously, using *p*-cyanophenol, triphenylphosphine (TPP), and diethyl azodicarboxylate (DEAD). The *N*-protecting group was removed by treatment with trifluoroacetic acid (TFA) to afford

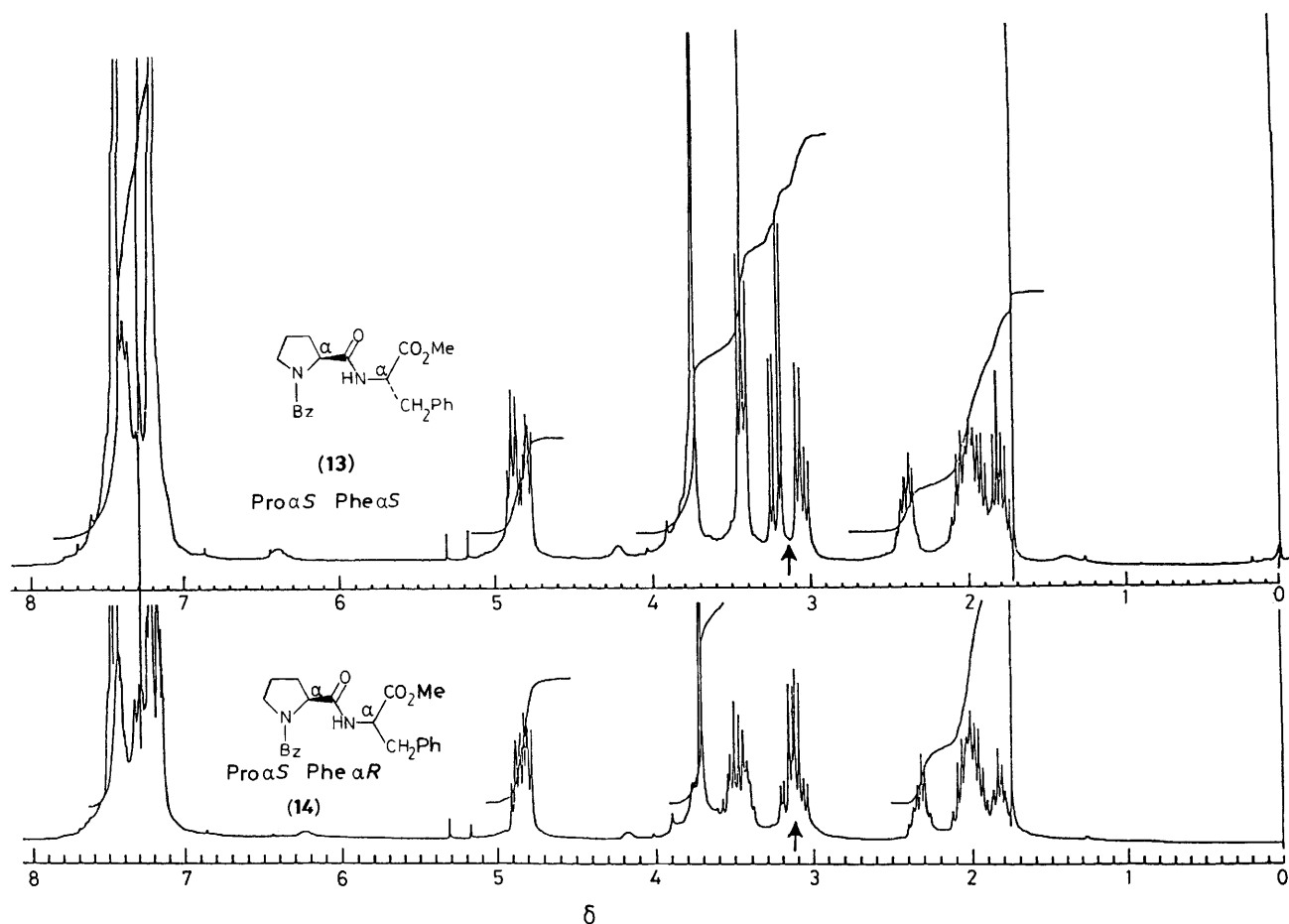


Figure 2. Comparison of the 250 MHz ^1H spectra of (13) and (14)

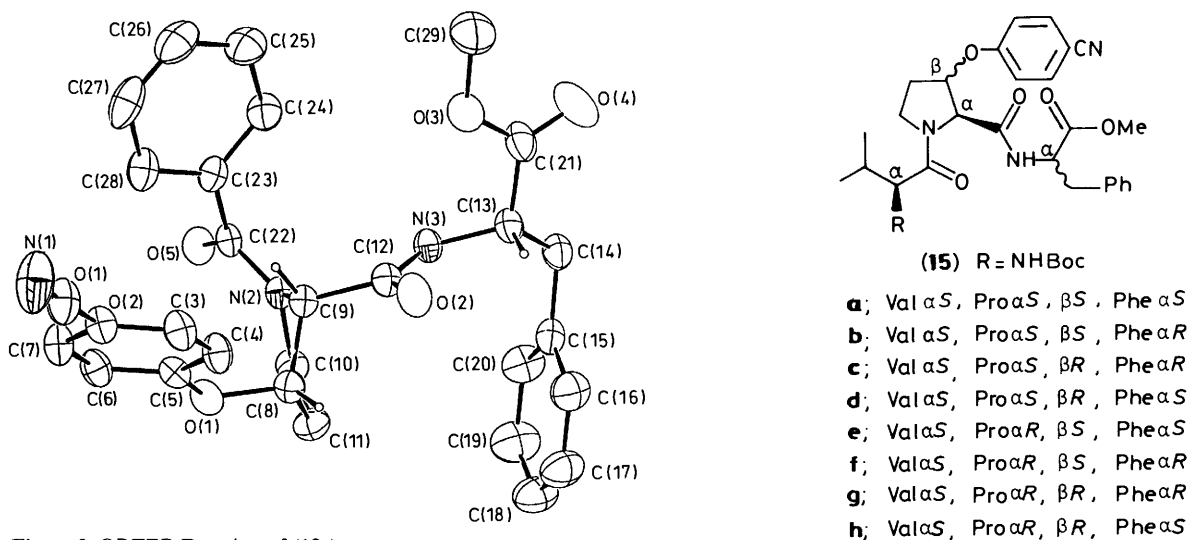
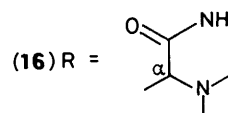


Figure 3. ORTEP Drawing of (12c)

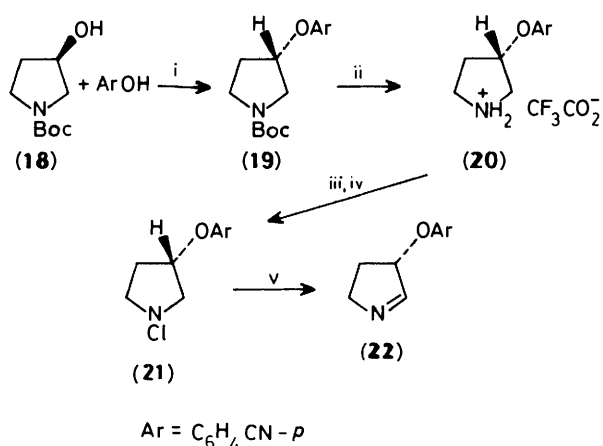
the trifluoroacetate salt (20), $[\alpha]_{\text{D}} + 17.58^\circ$ (c 0.62 in EtOH). This material was then available for the *in situ* formation of the unstable 4,5-dihydropyrrole intermediate (22), from the corresponding *N*-chloro compound (21) and DBU. The *N*-chloro compound was prepared *via* treatment of salt (20), with aqueous sodium carbonate, followed by *t*-butyl hypochlorite, as described previously (see Scheme 3).



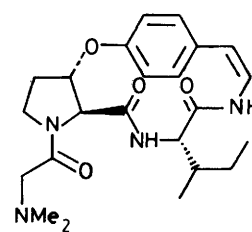
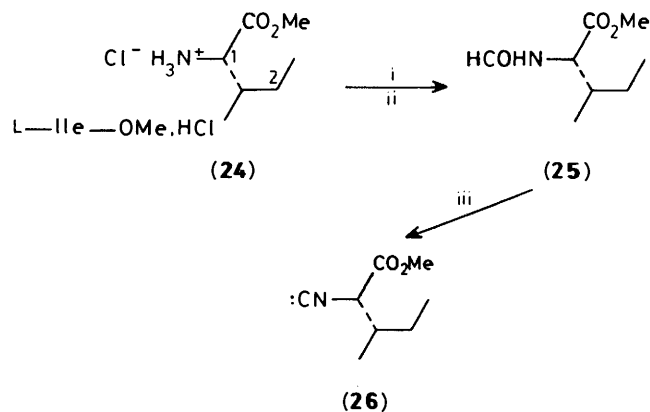
We then turned our attention towards the synthesis of the 14-membered cyclopeptide alkaloid nummularine-F (23). In this case, the ring bound amino acid is *L*-isoleucine. Based upon a

Table 2. Refined positional parameters for compound (12c)

Atom	x	y	z
C(1)	0.181 0(3)	0.609 2(2)	0.724 (3)
C(2)	0.271 0(2)	0.540 7(2)	0.754 1(3)
C(3)	0.366 2(2)	0.537 8(2)	0.710 3(3)
C(4)	0.453 8(2)	0.472 8(2)	0.738 9(3)
C(5)	0.447 4(2)	0.411 6(2)	0.814 6(2)
C(6)	0.353 9(2)	0.415 4(2)	0.806 3(2)
C(7)	0.265 0(2)	0.479 7(2)	0.830 2(3)
C(8)	0.615 9(2)	0.323 7(2)	0.777 1(2)
C(9)	0.545 7(2)	0.257 3(2)	0.611 9(2)
C(10)	0.641 4(2)	0.153 3(2)	0.760 9(2)
C(11)	0.706 1(2)	0.257 3(2)	0.854 3(3)
C(12)	0.612 1(2)	0.260 5(2)	0.515 4(2)
C(13)	0.704 8(2)	0.170 8(2)	0.341 7(2)
C(14)	0.809 5(2)	0.105 1(2)	0.371 4(3)
C(15)	0.897 2(2)	0.136 9(2)	0.536 4(3)
C(16)	0.959 2(3)	0.230 4(2)	0.613 7(3)
C(17)	1.038 1(3)	0.259 2(2)	0.765 4(3)
C(18)	1.057 1(3)	0.196 1(2)	0.842 4(3)
C(19)	0.996 5(3)	0.103 0(2)	0.767 8(3)
C(20)	0.917 6(3)	0.074 1(2)	0.616 4(3)
C(21)	0.621 5(2)	0.142 2(2)	0.174 7(3)
C(22)	0.428 9(2)	0.103 5(2)	0.564 6(2)
C(23)	0.322 3(2)	0.124 6(2)	0.442 8(2)
C(24)	0.312 8(2)	0.092 9(2)	0.294 8(3)
C(25)	0.207 7(3)	0.105 0(2)	0.179 6(3)
C(26)	0.113 2(3)	0.150 0(2)	0.211 6(3)
C(27)	0.122 7(2)	0.184 1(2)	0.357 4(4)
C(28)	0.226 2(2)	0.170 9(2)	0.475 5(3)
C(29)	0.429 7(3)	0.162 5(3)	-0.003 7(4)
N(1)	0.110 2(2)	0.663 3(2)	0.697 5(3)
N(2)	0.534 9(2)	0.161 6(1)	0.626 4(2)
N(3)	0.638 3(2)	0.175 4(1)	0.434 1(2)
O(1)	0.531 5(1)	0.346 1(1)	0.851 0(2)
O(2)	0.638 3(2)	0.341 5(1)	0.514 9(2)
O(3)	0.514 5(2)	0.178 6(2)	0.150 2(2)
O(4)	0.650 4(2)	0.094 6(2)	0.073 8(2)
O(5)	0.421 6(1)	0.034 7(1)	0.606 7(2)
C(30)	0.214 8(3)	0.428 1(2)	0.207 9(3)
C(31)	0.117 4(4)	0.468 0(4)	0.252 5(6)
C(32)	0.307 8(5)	0.385 0(3)	0.311 9(4)
O(6)	0.225 5(2)	0.433 0(2)	0.101 8(2)

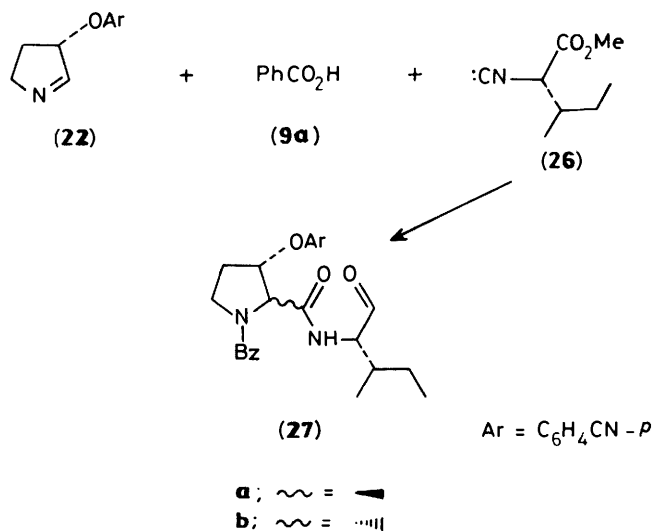
**Scheme 3.** Reagents and conditions: i, PPh₃, DEAD, THF; ii, F₃CCO₂H, CH₂Cl₂, 0 °C; iii, 10% aq. Na₂CO₃, 0 °C; iv, Bu'OCl, Et₂O, 0 °C; v, DBU, MeOH

reported synthesis of the optically active isonitrile derived from L-valine,²⁰ methyl α-isocyanoisovalerate, we successfully prepared methyl (2*S*,3*S*)-2-isocyano-3-methylpentanoate, [α]_D¹⁸

**(23)**
Nummularine - F**Scheme 4.** Reagents and conditions: i, HCO₂⁻Na⁺, HCO₂H; ii, Ac₂O; iii, Cl₃COCOCl, *N*-methylmorpholine, CH₂Cl₂, 0 °C

+ 34.2° (*c* 7.785 benzene), (see Scheme 4) from *N*-formyl-L-isoleucine methyl ester (24) in good yield.

In a model study for the synthesis of nummularine-F, utilizing the 4CC conditions, the optically active (3*S*)-(4-cyanophenoxy)-4,5-dihydropyrrole (22), was combined with benzoic acid (9a), and methyl (2*S*,3*S*)-2-isocyano-3-methylpentanoate (26) to give, on chromatography, two optically active diastereoisomeric condensation products (27a, b) (see Scheme 5). The *cis*-(27b),

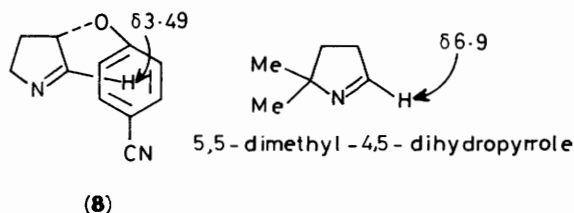
**Scheme 5.**

[α]_D + 51.1° (*c* 0.525 in CHCl₃), and the *trans*-(27a), [α]_D - 87.74° (*c* 0.155 in CHCl₃), stereoisomers were formed in a 57:43 ratio (47.7% yield) from the *N*-chloro derivative (21).

In all of the four-component reactions carried out so far, the

cis and *trans* product ratio always showed a predominance of the *cis* isomer and although the ratio was altered by changing the reaction temperature or concentration, the *trans* isomer was never obtained exclusively or as the major product.

The 3-(4-cyanophenoxy)-4,5-dihydropyrrole (**8**) was isolated (as discussed previously) and its ¹H n.m.r. spectrum examined. The aldimine proton resonance was seen to be shifted upfield (δ 3.49) from the expected value (δ 6.9) for a proton bonded to a non-aromatic *sp*² carbon atom as in 5,5-dimethyl-4,5-dihydropyrrole.²¹ This observation may be explained by assuming that the conformation of the molecule is such that the aromatic ring lies below the plane of the imine bond, thereby shielding the imine proton and causing an upfield shift.



Experimental

¹H N.m.r. and ¹³C n.m.r. spectra were recorded on a Bruker WM 250 (250 MHz) or an IBM WP 200 SY (200 MHz) Fourier transform spectrometer in the designated solvents, with SiMe₄ as internal reference. When deuterium oxide was used as the solvent, 3-(trimethylsilyl)propane-1-sulphonic acid sodium salt (TSS) was used as the internal standard. I.r. spectra were recorded on a Perkin-Elmer Model 281A spectrometer. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Centre. Either a Hitachi Perkin-Elmer RHM-2 high resolution double focussing electron impact spectrophotometer or a V.G. Micromass 7070-H high resolution mass spectrometer, both interfaced with a Kratos DS-50-S data system were used. Optical rotations were measured at the sodium D line with a Perkin-Elmer Model 241 polarimeter. M.p.s were determined with a Thomas Hoover melting point apparatus and are corrected. Analytical thin layer chromatography (t.l.c.) was performed on Merck silica gel 60 F₂₅₄ plates (0.2 mm). Visualization was effected with u.v. light, ninhydrin (3% w/v) in 95% ethanol containing 2% v/v acetic acid, phosphomolybdic acid reagent (7% w/v) reagent, and 2,4-dinitrophenylhydrazine reagent. Chromatography was carried out on E. Merck Silica Gel 60, particle size 0.040–0.63 mm, using the solvent systems listed in the individual experiments. Elemental analyses were performed by Mic Anal, Tucson, Az. Tetrahydrofuran (THF), diethyl ether, and 1,4-dioxane, were distilled from sodium-benzophenone; methanol was distilled from magnesium; and dichloromethane was distilled from calcium hydride.

Crystallographic Data.—C₂₉H₂₇N₃O₅·C₃H₆O, *M* = 555.64. Triclinic, space group P $\bar{1}$, *a* = 11.941(1), *b* = 14.496(1), *c* = 10.258(1) Å, α = 110.06(1), β = 113.83(1), γ = 86.60(1)°, *V* = 1 519 Å³, *Z* = 2, *D*_c = 1.215 g cm⁻³, graphite-monochromated Cu-K α radiation, λ = 1.54184 Å, μ = 6.5 cm⁻¹. A total of 4 820 reflections were measured on an Enraf-Nonius CAD4 diffractometer using the ω -2 θ scan technique over the ranges 4 ≤ 2 θ ≤ 120°, -13 ≤ *h* ≤ 13, -16 ≤ *k* ≤ 16, and -11 ≤ *l* ≤ 0. These yielded 4 232 unique reflections (*R* = 0.015) of which 3 514 reflections with *F*² > 3 σ (*F*²) were used during structure refinement. Hydrogen atom co-ordinates, refined thermal parameters, bond distances and bond angles have been deposited at the Cambridge Crystallographic Data Centre.*

The structure was solved by direct methods (MULTAN)

and refined by full-matrix least-squares techniques with non-hydrogen atoms anisotropic and hydrogen atoms included as non-refined contributions to the structure factors. The weighting scheme used was $w = 1/\sigma^2(F)$ and the final residuals, $R = \Sigma|F_o| - |F_c|/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$, were 0.059 and 0.079, respectively. All computer programs were from Enraf-Nonius SDP package and were run on a PDP 11/60 computer.²² The neutral atom scattering factors and complex anomalous dispersion corrections were taken from refs. 23 and 24.

***N*-t-Butoxycarbonyl-3-(4-cyanophenoxy)pyrrolidine (7).**—To a solution of *N*-t-butoxycarbonylpyrrolidin-3-ol (**6**)² (10.0 mmol), 4-cyanophenol (10.0 mmol), and triphenylphosphine (11.0 mmol) in anhydrous THF (50 ml) was added diethyl azodicarboxylate (11.0 mmol). The reaction mixture was stirred at ambient temperature overnight after which it was evaporated under reduced pressure and the residual oil triturated with diethyl ether–light petroleum (9:1) to give a white precipitate (consisting of triphenylphosphine oxide and diethyl diazene-1,2-dicarboxylate). The latter was filtered off and the filtrate evaporated under reduced pressure to give an oil which was filtered through silica gel and rinsed with an appropriate solvent mixture. The filtrate was again concentrated and the residue dissolved in diethyl ether and the solution treated sequentially with 5% aqueous sodium hydroxide, water, and saturated brine, and dried (MgSO₄). Concentration of the filtrate under reduced pressure afforded a residue which was chromatographed, using ethyl acetate–hexane (1:2) as eluant, to afford the product (85%); m.p. 116–119 °C; *R*_F 0.36 (EtOAc–hexane, 1:1); ν_{\max} (CHCl₃) 1 690, 1 610, 1 415, 1 255, and 1 170 cm⁻¹; δ_{H} (250 MHz, CDCl₃), 1.39, 1.40 (two s, 9 H), 1.95–2.25 (m, 2 H), 3.20–3.65 (m, 4 H), 5.13 (m, 1 H), 7.13 (d, 2 H, *J* = 8.9 Hz), and 7.78 (d, 2 H, *J* = 8.9 Hz); *m/z* (c.i.) 288.1508 (*M*⁺, Calc. for C₁₆H₂₀N₂O₃, 288.1474) (Found: C, 66.45; H, 7.05; N, 9.75. C₁₆H₂₀N₂O₃ requires C, 66.65; H, 6.99; N, 9.72%).

3-(4-Cyanophenoxy)pyrrolidine Trifluoroacetate.—*N*-t-Butoxycarbonyl-3-(4-cyanophenoxy)pyrrolidine (**7**) (2.06 g, 7.14 mmol) was dissolved in anhydrous dichloromethane (4.0 ml) and treated with trifluoroacetic acid (4.0 ml). After 1 h the mixture was evaporated under reduced pressure to give a viscous liquid which was treated with anhydrous diethyl ether to induce crystallization. Recrystallization of the product from isopropyl alcohol yielded the title compound (1.789 g, 82.4%), m.p. 127–129 °C; *R*_F 0.60 (CH₂Cl₂–MeOH–NH₄OH, 80:20:2); ν_{\max} (KBr) 3 000, 2 220, 1 660, 1 605, 1 500, 1 435, 1 260, 1 190, and 1 060 cm⁻¹; δ_{H} (250 MHz, D₂O) 2.38 (dt, 2 H, *J* 3.2, 7.9 Hz), 3.70 (m, 4 H), 5.35 (m, 1 H, *J* 3.2 Hz), 7.12 (d, 2 H, *J* 9.0 Hz), and 7.75 (d, 2 H, *J* 9.0 Hz); *m/z* (e.i.) 188.0985 (*M*⁺, Calc. for C₁₁H₁₂N₂O₁, 188.0950).

Ugi Four-Component Condensation: General Procedure.—3-(4-Cyanophenoxy)pyrrolidine trifluoroacetate (2.27 g, 7.52 mmol) was treated with cold 10% aqueous sodium carbonate (40 ml), then repeatedly extracted with diethyl ether. The combined ether layers were dried (Na₂CO₃), filtered, and volume of the ether solution containing 3-(4-cyanophenoxy)pyrrolidine [ν_{\max} (CHCl₃) 2 225, 1 605, 1 505, and 1 255 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 1.89–2.00 (m, 1 H), 2.07–2.22 (m, 1 H), 2.29 (s, 1 H), 2.89–3.00 (8 line m, 1 H), 3.04–3.23 (m, 3 H), 4.88 (m, 1 H), 6.92 (d, 2 H, *J* 9.0 Hz), 7.57 (d, 2 H, *J* 9.0 Hz); δ_{C} (50 MHz, CDCl₃) 33.2, 45.9, 53.5, 79.0, 104.0, 116.0, 118.8, 133.8, and 160.0] was reduced. The flask was flushed with

* For details see Instructions for Authors (1989) in *J. Chem. Soc., Perkin Trans. I*, 1989, Issue 1.

nitrogen and sealed with a rubber septum after addition of anhydrous sodium carbonate (150–200 mg). The flask was then immersed in an ice-bath and covered completely with foil to protect the reaction mixture from light. In a semi-darkened room, *t*-butyl hypochlorite (1.05 ml, 8.80 mmol) was added *via* a foil-wrapped syringe. After the mixture had been stirred at 0 °C for 45 min, t.l.c. (Et₂O and/or CH₂Cl₂–MeOH–NH₄OH, 90:10:1) indicated quantitative formation of *N*-chloro-3-(4-cyanophenoxy)pyrrolidine. The reaction mixture was then diluted with ether, washed quickly with cold water followed by saturated brine and dried (MgSO₄). It was then filtered and concentrated to pure white crystalline *N*-chloro-3-(4-cyanophenoxy)pyrrolidine (1.48 g, 6.65 mmol, 88.5%); m.p. 84.5 °C (decomp.); *R*_F 0.34 (Et₂O–light petroleum 1:1); *R*_F 0.67 (EtOAc); *R*_F 0.53 (Et₂O); *v*_{max}(CHCl₃) 3 000, 2 950, 2 860, 2 230, 1 610, 1 505, 1 365, 1 250, 1 200, 1 170, 1 115, 1 080, 835, and 710 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 2.08 (m, 1 H), 2.52 (m, 1 H), 3.24 (m, 1 H) 3.40–3.55 (m, 2 H) 3.61 (dd, 1 H, *J* 6.2, 12.2 Hz), 4.98 (m, 1 H), 6.89 (d, 2 H, *J* 8.9 Hz), and 7.59 (d, 2 H, *J* 8.9 Hz); *m/z* (c.i.) 222.0571 (*M*⁺, Calc. for C₁₁H₁₁N₂OCl, 222.0560).

The unstable chloro-3-(4-cyanophenoxy)pyrrolidine quickly transferred to a foil-wrapped flask and dissolved in methanol (24 ml), was then treated with DBU (1.5 ml, 10.03 mmol) for 1 h in an oil-bath to 90 °C. The progress of the reaction was followed by t.l.c. until the *N*-chloro compound had disappeared. The mixture was then treated with methanolic benzoic acid (**9b**) (10 ml, 1.2217 g, 10.004 mmol) and methyl 2-isocyano-3-phenylpropionate (**10b**) (1.3939 g, 7.366 mmol). The oil-bath temperature was held at 80 °C for 3.5 h and then at ambient temperature for 12 h after which the reaction mixture was chilled and filtered. The precipitate was rinsed with methanol, then air dried to afford the Pro α S, β R, Phe α S condensation product (**11c**) (380 mg 11.5%). The combined methanol filtrates were concentrated to an amber oil (5.81 g) which was then dissolved in ethyl acetate (125 ml) and washed successively with water, aqueous citric acid (0.5M) saturated aqueous sodium hydrogen carbonate, and saturated brine. The solution was then dried (MgSO₄) and concentrated to give an amber oil (2.46 g of crude material). Separation and isolation of the product diastereoisomers was effected by column chromatography. The crude residue was adsorbed onto silica gel and applied as a dry powder to the head of a silica gel column equilibrated with ethyl acetate–hexane (1:1) and eluted with the same solvent mixture. The initial fractions eluted contained unchanged isonitrile (**10b**) (532.8 mg, 38.2%) and *p*-cyanophenol that resulted from the elimination side reaction (326.6 mg, 41.3%). The remaining fractions consisted of the *trans* (**12c, d**) and *cis* (**11c, d**) stereoisomers in a 40:60 ratio with a 50% total yield from the *N*-chloro derivative.

The four diastereoisomeric condensation products had the following analytical and spectral characteristics.

(+)-*N*-[1-Benzoyl-*trans*-2-(4-cyanophenoxy)-L*-*prolyl*]-L*-phenylalanine methyl ester (**12c**), m.p. 165–166 °C; *R*_F 0.24 (EtOH–hexane, 1:1); *R*_F 0.62 (EtOAc); *v*_{max}(KBr) 3 305, 2 220, 1 750, 1 640, 1 605, 1 410, 845, and 700 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 2.10–2.36 (m, 2 H), 3.06 (dd, 1 H, *J* 7.2, 14.0 Hz), 3.27 (dd, 1 H, *J* 5.2, 14.0 Hz), 3.45–3.73 (m, 2 H), 3.78 (s, 3 H), 4.80–5.05 (m, 2 H), 4.94 (s, 1 H), 5.25–5.35 (m, 1 H), 6.90–7.70 (m, 15 H); *m/z* (e.i.) 497.1948 (*M*⁺, Calc. for C₂₉H₂₇N₃O₅, 497.1951) (Found: C, 70.25; H, 5.5; N, 8.55. C₂₉H₂₇N₃O₅ requires C, 70.01; H, 5.47; N, 8.44).

(+)-*N*-[1-Benzoyl-*trans*-3-(4-cyanophenoxy)-L*-*prolyl*]-D*-phenylalanine methyl ester (**12d**), m.p. 105–109 °C; *R*_F 0.11

(EtOAc–hexane, 1:1.3); *R*_F 0.51 (EtOAc); *v*_{max}(KBr) 2 220, 1 740, 1 670, 1 625, 1 605, 1 500, 1 420, and 1 250 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 2.15–2.44 (m, 2 H), 3.10 (dd, 1 H, *J* 6.9, 13.9 Hz), 3.20 (dd, 1 H, *J* 5.4, 13.9 Hz), 3.62–3.80 (m, 5 H), 3.76 (s, 3 H), 4.87 (m, 1 H), 5.01 (s, 1 H), 5.25 (d, 1 H, *J* 4.0 Hz), 6.9–7.7 (m, 15 H), 6.99 (d, 2 H, *J* 8.8 Hz), 7.59 (d, 2 H, *J* 8.8 Hz); *m/z* (e.i.) 497.1881 (*M*⁺, Calc. for C₂₉H₂₇N₃O₅, 497.1951).

(+)-*N*-[1-Benzoyl-*cis*-3-(4-cyanophenoxy)-L*-*prolyl*]-D*-phenylalanine methyl ester (**11d**), *R*_F 0.49 (EtOAc); *R*_F (EtOAc–hexane, 2:1); *v*_{max}(CHCl₃) 3 010, 2 230, 1 745, 1 680, 1 640, 1 607, 1 505, 1 385, 1 250, 1 173, and 830 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 2.14–2.40 (m, 2 H), 3.00–3.25 (m, 2 H), 3.55–3.85 (m, 4 H), 3.60 (s, 3 H), 3.85–4.00 (m, 1 H), 4.80–4.90 (m, 1 H), 4.90–5.05 (m, 1 H), 5.20–5.35 (m, 1 H), 6.45–6.65 (m, 1 H), and 6.90–7.75 (m, 15 H); *m/z* (e.i.) 497.1296 (*M*⁺, Calc. for C₂₉H₂₇N₃O₅, 497.1951).

(+)-*N*-[1-Benzoyl-*cis*-3-(4-cyanophenoxy)-L*-*prolyl*]-L*-phenylalanine methyl ester (**11c**), m.p. 101–103.5 °C; *R*_F 0.45 (EtOAc); *R*_F 0.20 (EtOAc–hexane, 2:1); *v*_{max}(KBr) 2 220, 1 743, 1 675, 1 603, 1 500, 1 425, and 1 250 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 2.05–2.25 (m, 2 H), 2.97 (dd, 1 H, *J* 5.5, 13.7 Hz), 3.17 (dd, 1 H, *J* 4.3, 13.7 Hz), 3.65–3.85 (m, 4 H), 3.88–4.00 (m, 1 H), 4.96–5.10 (m, 2 H), 5.03 (br d, 1 H, *J* 4.9 Hz), 5.28–5.35 (m, 1 H), 6.58 (d, 1 H, *J* 8.4 Hz), 6.85–7.03 (m, 7 H), and 7.44–7.65 (m, 7 H); *m/z* (e.i.) 497.1898 (*M*⁺, Calc. for C₂₉H₂₇N₃O₅, 497.1951).

(+)-*N*-[*trans*-3-(4-Cyanophenoxy)-1-{N-[(1,1-dimethyl-ethoxy)carbonyl]glycyl}-L*-*prolyl*]glycine ethyl ester (**12a**), *R*_F 0.38 (EtOAc); *v*_{max}(CDCl₃) 2 250, 1 745, 1 680, 1 605, 1 505, 1 250, and 1 175 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 1.29 (t, 3 H, *J* 7.2 Hz), 1.45 (s, 9 H), 2.24–2.57 (m, 2 H), 4.12–3.68 (m, 1 H), 4.21 (9, 2 H, *J* 7.7 Hz), 4.81 (s, 1 H), 5.20–5.39 (m, 1 H), 5.30 (d, 1 H, *J* 3.6 Hz), 7.04 (d, 2 H, *J* 8.9 Hz), 7.47 (t, 1 H, *J* 5.6 Hz), and 7.61 (d, 2 H, *J* 8.9 Hz); *m/z* (c.i.) 419.1662 (*M*⁺, Calc. for C₁₉H₂₃N₄O₇, 419.1567).

(+)-*N*-[*cis*-3-(4-Cyanophenoxy)-1-{N-[(1,1-dimethyl-ethoxy)carbonyl]glycyl}-L*-*prolyl*]glycine ethyl ester (**11a**), *R*_F 0.17 (EtOAc); *v*_{max}(CDCl₃) 1 690, 1 665, 1 605, 1 505, 1 250, and 1 170 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 1.26 (t, 3 H, *J* 7.2 Hz), 1.42, 1.43 (two s, 9 H), 2.26–2.54 (m, 2 H), 3.62–4.11 (m, 6 H), 4.16 (q, 2 H, *J* 7.2 Hz), 4.85 (d, 1 H, *J* 6.5 Hz), 5.07–5.24 (m, 1 H), 5.30–5.42 (m, 1 H), 6.61 (t, 1 H, *J* 5.1 Hz), 7.01 (d, 2 H, *J* 8.9 Hz), 7.60 (d, 2 H, *J* 8.9 Hz); *m/z* (c.i.) 475.2153 (*M*⁺, Calc. for C₂₉H₃₁N₄O₇, 475.2193).

(+)-*N*-[*trans*-3-(4-Cyanophenoxy)-*N*-benzoyl-L*-*propyl*]-glycine ethyl ester (**12b**), *R*_F 0.52 (EtOAc); *v*_{max}(CDCl₃) 2 230, 1 745, 1 670, 1 605, 1 410, 1 250, 1 175, and 835 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 1.29 (t, 3 H, *J* 7.1 Hz), 2.21–2.34 (m, 1 H), 2.40–2.57 (m, 1 H), 3.66–3.82 (m, 2 H), 3.98 (dd, 1 H, *J* 5.2, 18.1 Hz), 4.12 (dd, 1 H, *J* 5.2, 18.1 Hz), 4.23 (q, 2 H, *J* 7.1 Hz), 5.05 (s, 1 H), 5.40 (d, 1 H, *J* 3.9 Hz), 7.04 (d, 2 H, *J* 8.8 Hz), and 7.33–7.70 (m, 7 H); *m/z* (c.i.) 421.1673 (*M*⁺, Calc. for C₂₃H₂₃N₃O₅, 421.1638).

(+)-*N*-[*cis*-3-(4-Cyanophenoxy)-*N*-benzoyl-L*-*prolyl*]-glycine ethyl ester (**11b**), *R*_F 0.31 (EtOAc); *v*_{max}(CDCl₃) 3 005, 2 230, 1 745, 1 680, 1 640, 1 065, 1 505, 1 380, 1 250, 1 173, and 835 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 1.26 (t, 3 H, *J* 7.2 Hz), 2.05–2.38 (m, 2 H), 3.68–3.85 (m, 1 H), 3.91 (dd, 1 H, *J* 4.4, 18.5 Hz), 3.98–4.11 (m, 2 H), 4.18 (q, 2 H, *J* 7.2 Hz), 5.03 (d, 1 H, *J* 5.2 Hz), 5.30 (m, 1 H), 6.68 (s, 1 H), 7.02 (d, 2 H, *J* 8.7 Hz), and 7.42–7.75 (m, 7 H); *m/z* (c.i.) 421.1690 (*M*⁺, Calc. for C₂₃H₂₃N₃O₅, 421.1638).

(–)-*N*-Benzoyl-L-*prolyl*-L-phenylalanine methyl ester (**13**), m.p. 125–131 °C; *R*_F 0.44 (EtOAc); [α]_D²⁵ –48.94° (*c* 0.20, EtOH); *v*_{max}(CDCl₃) 3 015, 1 745, 1 680, 1 620, and 1 510 cm⁻¹; δ_{H} (250 MHz, CDCl₃) 1.75–2.15 (2 m, 3 H), 2.30–2.45 (m, 1 H), 3.04 (dd, 1 H, *J* 7.2, 13.9 Hz), 3.21 (dd, 1 H, *J* 5.3, 13.9 Hz), 3.42 (t, 2 H, *J* 6.6 Hz), 3.73 (s, 3 H), 4.78 (dd, 1 H, *J* 5.3, 7.2 Hz), 4.86

† The symbol * indicates that the relative configuration of the two centres is known, but not their absolute configuration; *Pure Appl. Chem.*, 1984, **56**, 595.

(dd, 1 H, J 7.0, 13.0 Hz), and 7.05—7.55 (m, 11 H); δ_C (50 MHz, CDCl_3) 22.52, 27.3, 37.9, 50.3, 52.2, 53.4, 59.8, 126.9, 127.1, 128.2, 128.4, 129.2, 130.1, 136.1, 136.2, 170.8, 171.0, and 171.7; m/z (c.i.) 380.1762 (M^+ , Calc. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$, 380.1736).

(-)-N-Benzoyl-L-prolyl-D-phenylalanine methyl ester (**14**), m.p. 103—107.5 °C; R_F 0.37 (EtOAc); $[\alpha]_D^{25}$ -52.17° (c 0.20, EtOH); ν_{max} (CDCl_3) 3 015, 1 745, 1 670, 1 625, and 1 510 cm^{-1} ; δ_H (250 MHz, CDCl_3) 1.75—2.15 (2 m, 3 H), 2.25—2.40 (2 m, 1 H), 3.07 (dd, 1 H, J 6.8, 13.8 Hz), 3.17 (dd, 1 H, J 5.5, 13.8 Hz), 3.40—3.65 (9 m, 2 H), 3.71 (s, 3 H), 4.75—4.95 (m, 2 H), and 7.10—7.60 (m, 1 H); δ_C (50 MHz, CDCl_3) 25.2, 27.4, 37.8, 50.1, 53.2, 59.7, 127.0, 128.2, 128.5, 129.1, 130.1, 136.0, 136.1, 170.8, 171.1, and 171.7; m/z (c.i.) 380.1700 (M^+ , Calc. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$, 380.1736).

(+)-N-{trans-3-(4-Cyanophenoxy)-1-[N-(1,1-dimethylethoxycarbonyl)-L-valyl]-L-prolyl]-L-phenylalanine methyl ester (**15a**), R_F 0.63 (EtOAc); $[\alpha]_D^{22}$ +28.0 (c 0.3, CHCl_3); ν_{max} (CDCl_3) 1 700, 1 695, 1 605, 1 500, 1 250, and 1 170 cm^{-1} ; δ_H (250 MHz, CDCl_3) 0.90 (d, 3 H, J 6.7 Hz), 1.01 (d, 3 H, J 6.7 Hz), 1.44 (s, 9 H), 1.92—2.08 (m, 1 H), 2.31—2.45 (m, 2 H), 3.00 (dd, 2 H, J 5.9, 13.7 Hz), 3.10 (dd, 2 H, J 4.7, 13.7 Hz), 3.61 (s, 3 H), 3.75—4.03 (m, 2 H), 4.32 (dd, 1 H, J 6.2, 9.2 Hz), 4.78—4.85 (m, 2 H), 5.07 (dd, 1 H, J 6.0, 12.4 Hz), 5.25 (d, J 9.3 Hz), 6.21 (d, 1 H, J 7.8 Hz), 6.92 (d, 2 H, J 8.9 Hz), 7.10—7.13 (m, 2 H), 7.22—7.30 (m, 3 H), and 7.54 (d, 2 H, J 8.9 Hz); m/z (c.i.) 592.2894 (M^+ , Calc. for $\text{C}_{32}\text{H}_{40}\text{N}_4\text{O}_7$, 592.2897).

(+)-N-{trans-3-(4-Cyanophenoxy)-1-[N-(N,N-dimethyl-L-alanyl)-L-valyl]-L-propyl]-L-phenylalanine methyl esters (**16**), R_F 0.45 (CH_2Cl_2 -MeOH- NH_4OH , 90:10:1); $[\alpha]_D^{22}$ +31.4 (c 0.23, in CHCl_3); ν_{max} (CDCl_3) 3 022, 3 018, 1 653, 1 605, 1 229, 1 215, 797, 795, 717, and 678 cm^{-1} ; δ_H (250 MHz, CDCl_3) 0.95 (d, 3 H, J 6.7 Hz), 1.02 (d, 3 H, J 6.7 Hz), 1.21 (d, 3 H, J 7.0 Hz), 2.00—2.20 (m, 1 H), 2.26 (s, 6 H), 2.28—2.45 (m, 2 H), 2.95—3.03 (m, 2 H), 3.11 (dd, 1 H, J 4.7, 16.0 Hz), 3.62 (s, 3 H), 3.90 (m, 1 H), 4.12 (9 m, 1 H), 4.53 (dd, 1 H, J 7.2, 8.9 Hz), 4.75—4.90 (m, 2 H), 4.80 (d, 1 H, J 6.6 Hz), 5.09 (m, 1 H), 6.20 (d, 1 H, J 7.8 Hz), 6.93 (d, 2 H, J 8.89 Hz), 7.10—7.14 (m, 2 H), 7.22—7.32 (m, 3 H), 7.55 (d, 2 H, J 8.9 Hz), and 7.75 (d, 2 H, J 8.9 Hz); m/z (c.i.) 592.3160 ($M + 1$, Calc. for $\text{C}_{32}\text{H}_{42}\text{N}_5\text{O}_6$, 592.3135).

(3R)-N-*t*-Butoxycarbonylpyrrolidin-3-ol (**18**),¹⁹ M.p. 62—64 °C $[\alpha]_D^{23}$ -22.2 (c 0.54 in CHCl_3); R_F 0.42 (EtOAc).

(3S)-N-*t*-Butoxycarbonyl-3-(4-cyanophenoxy)pyrrolidine (**19**), M.p. 105.5 °C; $[\alpha]_D^{18}$ +23.49° (c 0.80 in CHCl_3); R_F 0.22 (CH_2Cl_2 -acetone, 98:2); R_F 0.32 (CH_2Cl_2 -EtOH, 97:3); ν_{max} 2 980, 2 220, 1 680, 1 605, 1 420, 1 392, 1 362, and 1 165; δ_H (250 MHz, CDCl_3) 1.47 (s, 9 H), 2.18 (m, 2 H), 3.32—3.72 (two m, 4 H), 4.94 (m, 1 H), 6.92 (d, 2 H, J 8.6 Hz), and 7.60 (d, 2 H, J 8.6 Hz) (Found: C, 66.95; H, 7.15; N, 9.6. $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3$ requires C, 66.65; H, 6.99; N, 9.72%).

(3S)-3-(4-Cyanophenoxy)pyrrolidinium trifluoroacetate (**20**). M.p. 98—100 °C (isopropyl alcohol); $[\alpha]_D$ +17.58° (c 0.62 in EtOH); R_F 0.23 (CH_2Cl_2 -MeOH- NH_4OH , 90:10:1); ν_{max} (KBr) 2 220, 1 658, 1 608, 1 505, 1 435, 1 200, and 1 140; δ_H (250 MHz, D_2O) 2.39 (dt, 2 H, J 3.1, 7.8 Hz), 3.51—3.70 (m, 4 H), 5.36 (m, 1 H), 7.12 (d, 2 H, J 9.0 Hz), and 7.76 (d, 2 H, J 9.0 Hz) (Found: C, 51.85; H, 4.3; N, 9.25. $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3$ requires C, 51.66; H, 4.34; N, 9.27%).

Methyl (2S,3S)-2-isocyano-3-methylpentanoate (**26**). B.p. 36 °C/0.017 mmHg; $[\alpha]_D^{18}$ +34.2° (c 7.785 in benzene); R_F 0.74 (EtOAc); ν_{max} (neat) 2 980, 2 158, 1 755, 1 665, and 1 215 cm^{-1} ; δ_H (250 MHz, CDCl_3) 0.93 (t, 3 H, J 7.4 Hz), and 1.08 (d, 3 H, J 6.8 Hz); 1.26—1.56 (m, 2 H), 2.10 (m, 1 H), 3.82 (s, 3 H), and 4.21 (d, 1 H, J 4.5 Hz) (Found: C, 62.0; H, 8.6; N, 9.05. $\text{C}_8\text{H}_{13}\text{NO}_2$ requires C, 61.91; H, 8.44; N, 9.02%).

(-)-N-[1-Benzoyl-trans-3-(4-cyanophenoxy)-L-prolyl]-L-isoleucine methyl ester (**27a**). $[\alpha]_D^{22}$ -87.74° (c 0.155 in CHCl_3); R_F 0.27 (EtOAc-hexane, 1:1); ν_{max} (CHCl_3) 2 230, 1 740, 1 680, 1 608, 1 505, and 1 250 cm^{-1} ; δ_H (250 MHz, CDCl_3) 0.86—1.04

(m, 6 H), 1.13—1.30 (m, 1 H), 1.36—1.50 (m, 1 H), 1.92—2.05 (m, 1 H), 2.18—2.29 (m, 1 H), 2.46—2.52 (m, 1 H), 3.76, 3.77 (2 s, 3 H), 4.56 (dd, 0.5 H, J 4.8, 8.2 Hz), 4.69 (m, 0.3 H), 4.81 (dd, 0.2 H, J 3.9, 9.2 Hz), 5.00 (s, 0.6 H), 5.11 (s, 0.4 H), 5.34 (d, 0.6 H, J 3.7 Hz), 5.42 (d, 0.4 H, J 4.2 Hz), 6.00—6.28 (br m, 1 H), 7.00—7.08 (m, 2 H, J 8.9 Hz), and 7.42—7.68 (m, 7 H); m/z 463.20952 (M^+ , Calc. for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_5$, 463.2107).

(+)-N-[1-Benzoyl-cis-3-(4-cyanophenoxy)-D-prolyl]-L-isoleucine methyl ester (**27b**). $[\alpha]_D^{22}$ +51.05° (c 0.525 in CHCl_3); R_F 0.33 (hexane-acetone, 3:2); ν_{max} (CHCl_3) 3 015, 2 480, 2 235, 1 740, 1 685, 1 645, 1 608, 1 508, 1 385, 1 255, 1 175, and 835 cm^{-1} ; δ_H (250 MHz, CDCl_3) 0.78—0.90 (m, 6 H), 0.95—1.15 (m, 1 H), 1.24—1.46 (m, 1 H), 1.80—2.05 (m, 2 H), 2.10—2.35 (m, 1 H), 2.60—2.80 (m, 1 H), 3.72 (s, 3 H), 3.95—4.06 (m, 1 H), 4.58—4.70 (m, 1 H), 5.01 (d, 1 H, J 4.7 Hz), 5.29 (m, 1 H), 6.55—6.73 (m, 1 H), 7.00 (d, 2 H, J 8.6 Hz), and 7.43—7.75 (m, 7 H); m/z 463.209 53 (M^+ , Calc. for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_5$, 463.2107).

3-(4-Cyanophenoxy)-L-4,5-dihydropyrrole (**8**). ν_{max} (CHCl_3) 2 230, 1 605, 1 505, 1 255, 1 175, and 835 cm^{-1} ; δ_H (250 MHz, CDCl_3) 1.81 (m, 1 H), 2.49 (m, 1 H), 2.76 (dd, 1 H, J 8.3, 16.1 Hz), 3.15 (dt, 1 H, J 3.1, 8.6 Hz), 3.49 (d, 1 H, J 4.7 Hz), 4.69 (5 line m, 1 H), 6.93 (d, 2 H, J 8.9 Hz), and 7.59 (d, 2 H, J 8.9 Hz); δ_C (50 MHz, CDCl_3) 29.2, 45.0, 78.5, 85.8, 104.8, 116.0, 116.1, 118.8, 134.0, and 160.9.

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