Synthesis of cyanoformamides from primary amines and carbon dioxide under mild conditions. Synthesis of ceratinamine†

Eduardo García-Egido, Jairo Paz, Beatriz Iglesias and Luis Muñoz*

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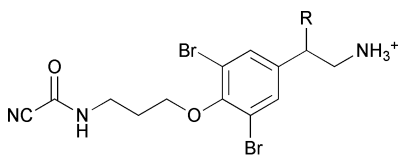
Treatment of primary amines with tetramethylphenylguanidine (PhTMG) and a cyanophosphonate at −10 °C under an atmosphere of carbon dioxide provides cyanoformamides in very high to excellent yields. The reaction proceeds efficiently within a short time. By-products were not detected in most runs and epimerization was not found when optically pure α-aminoesters were used as substrates. As an example, the reaction was applied to the synthesis of the marine natural product ceratinamine.

Introduction

Cyanoformamides, also called carbamoyl cyanides, are not very common compounds either in organic synthesis or in natural products chemistry. In fact, the first natural product with this functionality in its structure, ceratinamine (**1**) (Fig. 1), was isolated in 1996 by Fusetani and co-workers from the marine sponge *Pseudoceratina purpurea*[1] and was synthesized later by Ganem and Schoenfeld.[2] Ceratinamine is cytotoxic and has potent antifouling activity. A related compound, 7-hydroxyceratinamine (**2**) (Fig. 1), was isolated three years later from the marine sponge *Aplysinella* sp. by Schmitz.[3] Although *N*,*N*-dimethylcyanoformamide was isolated from several vegetables and fruits—such as tomatoes, oranges and apples—as a degradation metabolite of a pesticide,[4] other natural products with the cyanoformamide functionality have not been isolated to date.

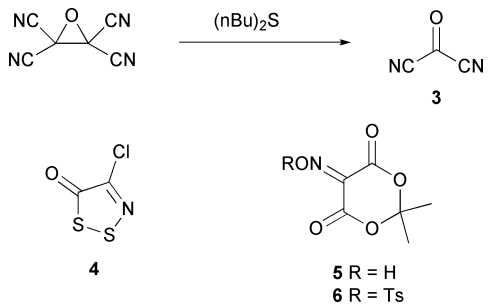


1 R = H
2 R = OH

Fig. 1

In spite of their potential use in the synthesis of complex molecules, there are only a few reports in the literature that describe the use of cyanoformamides for this purpose. Two outstanding examples are the synthesis of complex lactams by intramolecular cyanoamidation of unsaturated cyanoformamides[5] and the preparation of tetrazoles by reaction of cyanoformamides and aluminium azide.[6] Cyanoformamides have also been proposed as intermediates in the synthesis of symmetrical *N*,*N*′-dialkylureas.[7]

Only a few methods have been described in the literature to prepare cyanoformamides from amines. The most simple approaches make use of reagents like carbonyl cyanide **3** (prepared from tetracyanoethylene oxide and butylsulfide)[8] (Scheme 1) or triphosgene followed by treatment with the cyanide ion.[5b] Other methods use more sophisticated reagents like 4-chloro-5*H*-1,2,3-dithiazol-5-one (**4**),[7] isonitroso Meldrum's acid (**5**)[9] or its tosyl derivative 5-[(tosyloxy)imino]-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**) (Scheme 1).[10] The use of this type of compounds is not always desirable, not only because of their toxicity and complexity, but also because of the high reactivity of the system. Cyanoformamides can be potentially useful intermediates in organic synthesis and, as a result, new and simple methods for their preparation are necessary.



Scheme 1

In this paper we describe the preparation of carbamoyl cyanides under very mild conditions through the low temperature reaction of primary amines and carbon dioxide at atmospheric pressure with a cyanophosphonate. This methodology has been applied to the synthesis of the natural product ceratinamine. A similar method has previously been devised for the preparation of carbamoyl azides from primary amines[11] and 2-oxazolidinones from 1,2-amino alcohols.[12]

Results and discussion

The methodology described here relies on the formation of a stabilized carbamate anion by treatment of an amine with carbon dioxide in the presence of a pentasubstituted guanidine. Reaction of this carbamate anion with either diethylcyanophosphonate (DEPC) or diphenylcyanophosphonate (DPPC) cleanly gave the cyanoformamide (Scheme 2). The reaction conditions (temperature and solvent) previously optimized for the synthesis of

Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo, 36310 Vigo, Spain. E-mail: lmunoz@uvigo.es
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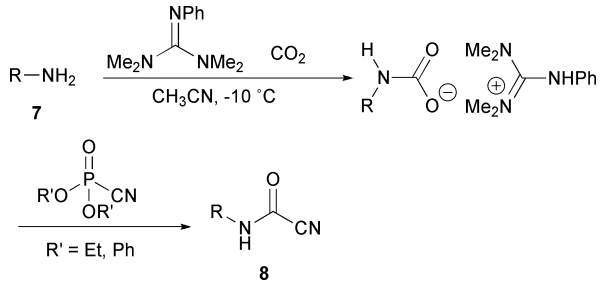


Scheme 2

carbamoyl azides were successfully applied to the preparation of cyanoformamides.[11]

The results of the reaction for several amines under different conditions are shown in Table 1. The yields are generally excellent and in all cases the data refer to isolated and purified products. By-products were not detected in most runs and, in cases where such compounds were detected, they were present at levels less than 5–10%.

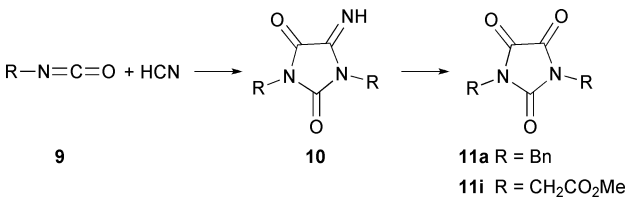
The spectroscopic characterization of carbamoyl cyanides **8** can be easily performed. These compounds have a weak IR band at 2230–2240 cm^{-1} and this is typical of the cyano group. The ^{13}C NMR spectra show signals for the carbonyl and the nitrile carbons in the region 142–143 ppm and at 111 ppm, respectively. These two chemical shifts are upfield compared to the expected values for both types of carbon when considered alone. This suggests a strong interaction between these two carbon atoms.

Although the methods for the preparation of carbamoyl azides[11] and cyanoformamides are almost identical in a formal sense, the outcomes of the reactions are dissimilar in several respects. Firstly, the reaction to form cyanoformamides proceeds quite rapidly and is normally complete within 1 hour. Indeed, we have observed that the yields can decrease markedly if the reaction time is extended unnecessarily. This means that longer reaction times lead to the formation of by-products by decomposition of the carbamoyl cyanides in the reaction medium. This type of behaviour could explain some of the problems described in the isolation of ceratinamine (**1**) and related compounds. As this is a rapid reaction that gives excellent yields it is not necessary to add an excess of nucleophile (*i.e.*, cyanide) to the reaction medium, a situation in contrast to that for azides.

Although most of the experiments described here were carried out using PhTMG as the base, the yields of cyanoformamides did not seem to be as base-dependent as the yields of carbamoyl azides. For example, significant differences were not found when DBU was used instead of PhTMG.

Another subtle difference between the two reactions concerns the by-products found in some experiments. The preparation of carbamoyl azides mainly yields symmetrical ureas as by-products. Surprisingly, ureas have not been detected in the preparation of cyanoformamides. In fact, only parabanic acid derivatives have been isolated from the reaction media, and even then only in very small amounts and in cases where the amine function is bound to a methylene group (**7a**, entry 2; **7i**, entry 10; Table 1). These compounds were identified by the absence of a signal for the amide proton in the ^1H NMR spectrum together with the shift of the carbonyl carbons to 152–156 ppm. The structures were also confirmed by mass spectrometry.

Parabanic acid derivatives **11** have been known in the literature for a long time.[13] These compounds were obtained by reaction of an isocyanate with cyanide followed by hydrolysis, as shown in Scheme 3. A possible mechanism has been proposed.[14]



Scheme 3

We have proposed isocyanates as possible intermediates in this kind of reaction and we therefore carried out several experiments to degrade cyanoformamides **8** in the presence of different bases. It was found that 5-imino-2,4-imidazolidinediones **10** were formed cleanly in variable yields depending on the base. For example, triethylamine promotes a slow reaction with the recovery of starting material but DBU leads to a more rapid reaction that goes to completion (see Experimental). This result is fully consistent with previous literature reports.[9]

In addition to the parabanic acid derivative **11a**, a phosphorylated by-product **12a** was isolated from benzylamine (**7a**) when diphenylcyanophosphonate was used as the electrophile (entry 2, Table 1). The reaction of L-tryptophan methyl ester (**7p**) (entry 19, Table 1) gave a similar result with DPPC, thus allowing the isolation of the phosphorylated compound **12p** together with a small amount of the bis-cyanoformamide **13** (Fig. 2).

Racemization was not detected when α-amino esters were used as substrates. The optical purity for valine derivatives was assessed by GC on a chiral support after derivatization of the carbamoyl cyanide as a urea with dimethylamine (>99.5%). In addition, evidence for the presence of diastereomers was not found by NMR for the cyanoformamide prepared from L-isoleucine.

Table 1 Yields of cyanoformamides from various amines

Entry	Amine (**7**)	Phosphorus reagent	**8** (%)
1	benzylamine (**a**)	DEPC	99
2	benzylamine (**a**)	DPPC	91
3	4-methoxybenzylamine (**b**)	DPPC	78
4	(*R*)-α-methylbenzylamine (**c**)	DEPC	96
5	2-(1-cyclohexenyl)ethylamine (**d**)	DEPC	99
6	cyclohexylamine (**e**)	DEPC	98
7	homoveratrylamine (**f**)	DEPC	99
8	2-amino-3-methylbutane (**g**)	DPPC	85
9	2-methoxyethylamine (**h**)	DPPC	78
10	glycine methyl ester (**i**)	DPPC	70
11	(*R*)-phenylglycine ethyl ester (**j**)	DEPC	89
12	L-Ala-OMe (**k**)	DPPC	79
13	L-Phe-OMe (**l**)	DEPC	95
14	L-Val-OMe (**m**)	DEPC	87
15	D-Val-OMe (**n**)	DEPC	96
16	L-Glu(OMe)-OMe (**o**)	DEPC	82
17	L-Glu(OMe)-OMe (**o**)	DPPC	82
18	L-Trp-OMe (**p**)	DEPC	85
19	L-Trp-OMe (**p**)	DPPC	81
20	L-Ile-OMe (**q**)	DEPC	96
21	L-Asp(OMe)-OMe (**r**)	DPPC	82

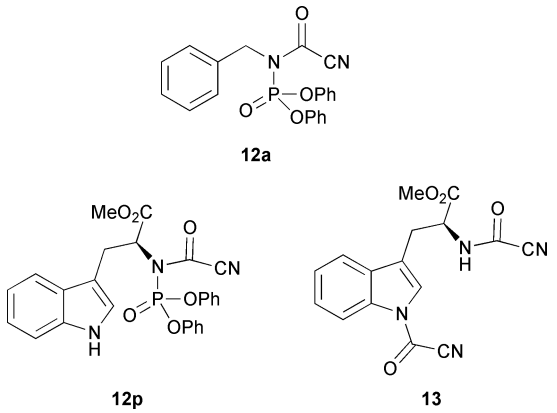


Fig. 2

In contrast to the situation in the reaction medium, evidence for instability of the carbamoyl cyanides was not found on handling these compounds in the laboratory. Indeed, these compounds could be purified by flash chromatography without substantial decomposition, whereas storage at −18 °C for several months did not have a significant effect on the purity of the compounds.

Attempts to prepare the corresponding cyanoformamides from aliphatic secondary amines produced a totally different outcome, which was similar to what happened in the case of carbamoyl azides.[11] Application of the optimized reaction conditions to dibutylamine produced the mixed anhydride (Fig. 3) in good yield (84%) as the only product after long reaction times (17 h). An extremely low yield of cyanoformamide (9%) could only be obtained after an extended reaction period (60 h). Similar results were found on applying the same procedure to other secondary amines.

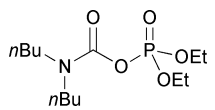
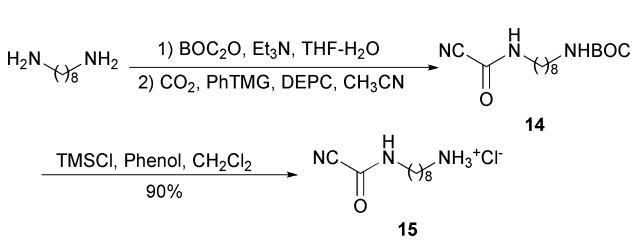


Fig. 3

In order to assess the viability of the method with more complex molecules, we decided to carry out the synthesis of ceratinamine (**1**). The main problem in this synthesis is the selective introduction of the cyanoformamide functionality on one of the amino groups. This requires the use of a protective group on the second amino function, which can be deprotected without affecting the carbamoyl cyanide moiety. The *tert*-butoxycarbonyl (BOC) group was assessed as shown in Scheme 4. Monoprotected octyl-1,8-diamine was transformed into the corresponding carbamoyl cyanide **14** in good yield. The BOC deprotection step was efficiently achieved under very mild acidic conditions (phenol, chlorotrimethylsilane), whereas typical deprotection conditions, such as TFA in dichloromethane, produced a small amount of decomposition by-products.



Scheme 4

The synthesis of ceratinamine (**1**) was carried out as shown in Scheme 5. Tyramine (**16**) was brominated in high yield and the amino group was protected in the standard way as the BOC derivative. Phenol **18** was alkylated with 1,3-dibromopropane in basic acetone, and the second amine functionality was introduced in the classical two-step procedure: substitution of bromide with azide followed by reduction. Although some problems were encountered in this reduction, it was efficiently carried out through the reaction with triphenylphosphine and subsequent hydrolysis of the iminophosphorane with water. Cyanoformamide **22** was formed in good yield under the conditions described here. Finally, deprotection under mild acidic conditions produced ceratinamine (**1**) in excellent yield. The spectra of the synthetic ceratinamine are identical to those of a natural sample. The overall yield of ceratinamine obtained using our synthetic route was 64% from tyramine (70% from dibromotyramine), which is slightly higher than the previously reported synthesis (52% from dibromotyramine).[2]

In summary, we have developed a convenient synthetic strategy for the preparation, under very mild conditions, of cyanoformamides from primary amines and carbon dioxide. The practical applicability of this methodology has been demonstrated by the efficient synthesis of ceratinamine, a natural product with biological activity.

Experimental

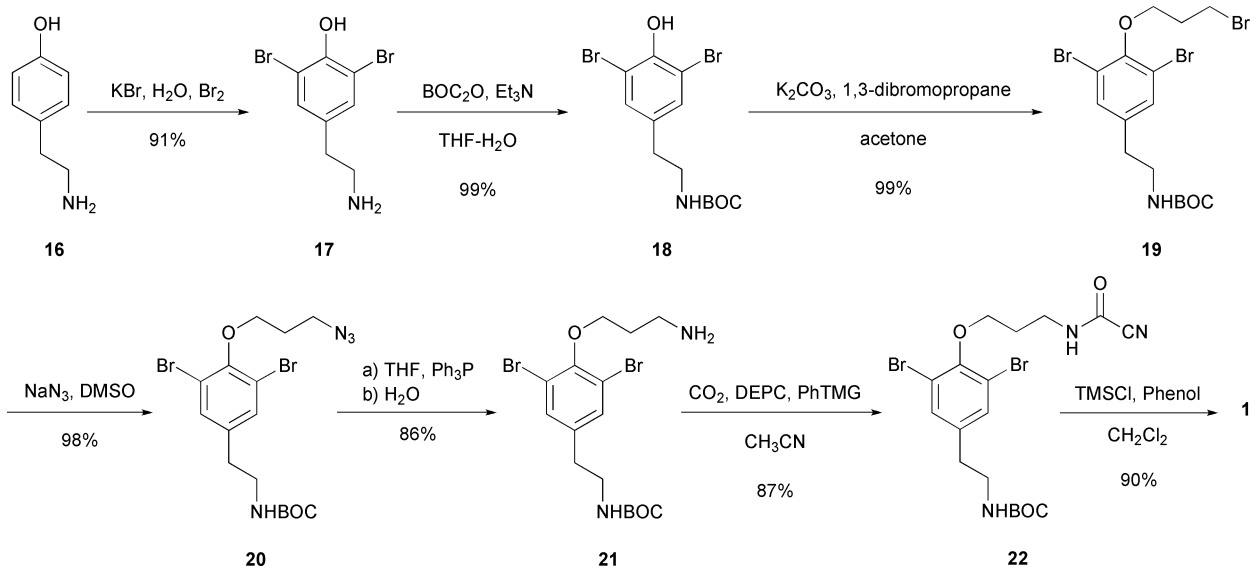
General methods

Dry acetonitrile was distilled from calcium hydride under an argon atmosphere. All the reagents were obtained from commercial suppliers and used as received unless otherwise indicated. Thin layer chromatography (TLC) was performed using plates coated with Kieselgel 60 F_{254}, and column chromatography was performed using Kieselgel 60 according to the method of Still *et al.*[15] NMR spectra were recorded on 400 MHz Bruker Instruments spectrometers. ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents (mostly $CDCl_3$) and were referred to the solvent residual peak. ^{31}P NMR spectra were externally referred to an 85% H_3PO_4 solution. *J* values are given in Hz.

General procedure for the synthesis of cyanoformamides

A solution of the amine and tetramethylphenylguanidine (PhTMG) (115 mol%; 215 mol% for hydrochlorides) in anhydrous acetonitrile (0.05 M) was chilled in a salt/ice bath and then dry CO_2 (g) was slowly bubbled through until saturation was achieved. DEPC (110 mol%) was added and CO_2 bubbling was continued for 10 min. The mixture was stirred for 1 hour at 0 °C under a CO_2 atmosphere. The mixture was poured onto EtOAc (150 mL) and the solution washed with water (3×) and 5% HCl (3×). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

Benzylcarbamoyl cyanide (8a). Following the general procedure and starting from benzylamine (0.214 g, 2.0 mmol),



Scheme 5

purification by flash chromatography (hexane/EtOAc 9:1 to 7:1) gave **8a** as a white crystalline solid (0.318 g, 99%). *Rf* 0.50 (hexane/EtOAc 1:1); mp 68.2–69.2 °C; ν_{max}(KBr)/cm^{-1} 3277br, 2240w, 1621br, 1554, 1452 and 695; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers, ratio 9:1) 4.52 (1.8 H, d, *J* 5.9), 4.69 (0.2 H, d, *J* 5.9), 6.48 (1 H, br s) and 7.29–7.42 (5 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 44.4, 111.4, 128.0, 128.4, 129.0, 135.1 and 143.1; *m/z* (EI) 160 (M^+, 100%), 133 (12), 104 (18), 91 (33), 79 (15); HRMS (EI) 160.0629 (M^+. $C_9H_8N_2O$ requires 160.0637).

When the reaction was carried out starting from the amine (1.099 g, 10.26 mmol) and DPPC (3.191 g, 12.31 mmol, 120 mol%), purification yielded the expected cyanoformamide **8a** (1.488 g, 91%), a white solid identified as **12a** (0.010 g, 0.3%) and a colourless oil identified as **11a** (0.140 g, 4.6%).

Diphenyl benzyl(cyanocarbonyl)phosphoramidate (12a). ν_{max}(NaCl)/cm^{-1} 3066, 2233, 1695 and 1591; δ_H (400 MHz; $CDCl_3$; Me_4Si) δ 4.98 (2 H, d, *J* 11.5) and 7.04–7.46 (15 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 49.5, 110.1, 119.9 (d, *J* 4.8), 126.1, 128.2, 128.4, 128.6, 129.9, 134.7, 144.9 and 149.2 (d, *J* 7.3); δ_P (160 MHz; $CDCl_3$) −10.82; HRMS (ESI) 393.1002 ([M + H]$^+$. $C_{21}H_{18}N_2O_4P$ requires 393.0999).

1,3-Dibenzylimidazolidine-2,4,5-trione (11a). ν_{max}(NaCl)/cm^{-1} 3032 and 1726; δ_H (400 MHz; $CDCl_3$; Me_4Si) 4.76 (2 H, s) and 7.16–7.50 (5 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 42.9, 128.6, 128.9 (2C), 134.3, 153.3 and 156.3; HRMS (ESI) 295.1083 ([M + H]$^+$. $C_{17}H_{15}N_2O_3$ requires 295.1077).

(4-Methoxybenzyl)carbamoyl cyanide (8b). Following the general procedure and starting from 4-methoxybenzylamine (1 g, 7.29 mmol) and DPPC (1.890 g, 7.29 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 10:1 to 5:1) yielded **8b** as a colourless oil that solidified on standing (1.080 g, 78%). ν_{max}(NaCl)/cm^{-1} 3293, 3056, 3007, 2941, 2839, 2235, 1686, 1612 and 1515; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.95:0.05) 3.82 (3 H, s), 4.40 (1.9 H, d, *J* 5.7), 4.58 (0.1 H, d, *J* 6.1), 6.91 (2 H, d, *J* 8.5), 7.23 (2 H, d, *J* 8.4) and 7.71 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 43.6, 55.1, 111.3, 114.1, 127.2, 129.3, 143.0 and 159.2; HRMS (ESI) 213.0642 ([M + Na]$^+$. $C_{10}H_{10}N_2NaO_2$ requires 213.0634).

(*R*)-(1-Phenylethyl)carbamoyl cyanide (8c). Following the general procedure and starting from amine **7c** (1 g, 8.25 mmol) and DEPC (1.37 mL, 8.25 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 8:1) gave compound **8c** as a colourless oil that solidified on standing (1.380 g, 96%). $[\alpha]_D^{25}$ +112.13 (*c* 0.92 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3286, 3059, 3039, 2982, 2935, 2877, 2801, 2236, 1678 and 1539; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.95:0.05) 1.53 (2.85 H, d, *J* 7.0), 1.61 (0.15 H, d, *J* 6.8), 5.08 (1 H, p, *J* 4 × 7.0), 7.28–7.45 (5 H, m) and 7.86 (1 H, br d, *J* 7.4); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 21.0, 50.5, 111.3, 126.0, 127.9, 128.7, 140.4 and 142.4; HRMS (ESI) 197.0681 ([M + Na]$^+$. $C_{10}H_{10}N_2NaO$ requires 197.0685).

(2-Cyclohexenylethyl)carbamoyl cyanide (8d). Following the general procedure and starting from 2-(1-cyclohexenyl)ethylamine (0.250 g, 2.0 mmol), purification by flash chromatography (hexane/EtOAc 19:1 to 9:1) gave the product **8d** as a white crystalline solid (0.352 g, 99%). *Rf* 0.645 (hexane/EtOAc 4:1); mp 48.5–49.0 °C; ν_{max}(KBr)/cm^{-1} 3278br, 2932br, 2238w, 1668br and 1559br; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 92:8) 1.53–1.67 (4 H, m), 1.91 (2 H, d, *J* 1.5), 2.02 (2 H, dd, *J* 2.2 and 1.3), 2.19 (2 H, t, *J* 6.7), 3.42 (1.8 H, q, *J* 6.2), 3.55 (0.08 H, q, *J* 6.2), 5.51 (1 H, br d, *J* 1.1), 6.47 (0.08 H, br s) and 6.52 (0.92 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 22.1, 22.6, 25.1, 27.7, 36.7, 38.2, 111.6, 124.8, 126.1, 133.2 and 143.0; *m/z* (EI) 178 (M^+, 6%), 108 (100), 95 (59), 93 (45), 79 (46), 69 (49); HRMS (EI) 178.1108 (M^+. $C_{10}H_{14}N_2O$ requires 178.1106).

Cyclohexylcarbamoyl cyanide (8e). Following the general procedure and starting from cyclohexylamine (0.198 g, 2.0 mmol), purification by flash chromatography (hexane/EtOAc 19:1 to 9:1) gave the product **8e** as a white solid (0.295 g, 98%). *Rf* 0.50 (hexane/EtOAc 9:1); mp 80.2–81.1 °C; ν_{max}(KBr)/cm^{-1} 3275br, 2935br, 2854, 2240w, 1663br and 1559; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers) 1.15–1.44 (5 H, m), 1.56–1.82 (3 H, m), 1.95

(2 H, m), 3.79–3.88 (1 H, m) and 6.16 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 24.4, 25.0, 32.0, 50.0, 111.7 and 142.3; *m/z* (EI) 152 (M^+, 0.02%), 109 (92), 96 (11), 82 (100), 67 (47); HRMS (EI) 152.0944 (M^+. $C_8H_{12}N_2O$ requires 152.0950).

(3,4-Dimethoxyphenethyl)carbamoyl cyanide (8f). Following the general procedure and starting from homoveratrylamine (0.362 g, 2.0 mmol), purification by flash chromatography (hexane/EtOAc 9:1 to 3:1) gave the product **8f** as a white solid (0.464 g, 99%). *Rf* 0.50 (hexane/EtOAc 1:1); mp 89.2–90.0 °C; ν_{max}(KBr)/cm^{-1} 3286br, 2229w, 1701, 1515 and 1265; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 19:1) 2.83 (2 H, t, *J* 6.9), 3.61 (0.95 H, q, *J* 6.8), 3.76 (0.05 H, q, *J* 6.8), 3.88 (3 H, s), 3.89 (3 H, s), 6.17 (1 H, br s), 6.69 (1 H, d, *J* 1.9), 6.73 (1 H, dd, *J* 8.1 and 1.9) and 6.85 (1 H, d, *J* 8.2); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 34.1, 41.5, 55.7, 55.8, 111.4, 111.5, 111.7, 120.6, 129.8, 143.2, 147.7 and 148.9; *m/z* (EI) 234 (M^+, 17%), 207 (11), 164 (11), 151 (100); HRMS (EI) 234.1002 (M^+. $C_{12}H_{14}N_2O_3$ requires 234.1004).

(3-Methylbutan-2-yl)carbamoyl cyanide (8g). Following the general procedure and starting from amine **7g** (1.5 g, 17.21 mmol) and DPPC (4.461 g, 17.21 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 12:1) gave compound **8g** as a colourless oil that solidified on standing (2.049 g, 85%). ν_{max}(NaCl)/cm^{-1} 3281, 3060, 2970, 2880, 2236, 1678 and 1543; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.89:0.11) 0.82–0.99 (6 H, m), 1.14 (2.67 H, d, *J* 6.8), 1.25 (0.33 H, d, *J* 6.6), 1.75 (1 H, m), 3.74 (0.11 H, m), 3.88 (0.89 H, m), 6.48 (0.11 H, br s) and 6.87 (0.89 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 16.8, 18.2 (2C), 32.5, 52.1, 111.7 and 142.7; HRMS (ESI) 141.1025 ($[M + H]^+$. $C_7H_{13}N_2O$ requires 141.1022).

(2-Methoxyethyl)carbamoyl cyanide (8h). Following the general procedure and starting from amine **7h** (0.786 g, 10.46 mmol) and DPPC (2.711 g, 10.46 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 6:1 to 4:1) gave compound **8h** as a yellowish oil (1.049 g, 78%). ν_{max}(NaCl)/cm^{-1} 3282, 3061, 2991, 2938, 2896, 2833, 2236, 1694 and 1544; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.92:0.08) 3.38 (3 H, s), 3.73–3.44 (4 H, m), 6.68 (0.08 H, br s) and 7.04 (0.92 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 39.8, 58.5, 69.5, 111.4 and 143.3; HRMS (ESI) 129.0660 ($[M + H]^+$. $C_5H_9N_2O_2$ requires 129.0658).

Methyl 2-(cyanocarbonylamino)acetate (8i). Following the general procedure and starting from amine **7i** (0.350 g, 3.93 mmol) and DPPC (1.019 g, 3.93 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 4:1 to 3:1) gave compound **8i** as a yellowish oil (0.389 g, 70%) together with a small amount of a white solid identified as **11i** (0.046 g, 9%). ν_{max}(NaCl)/cm^{-1} 3303, 3062, 3006, 2961, 2854, 2240, 1747, 1693 and 1544; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.97:0.03) 3.75 (3 H, s), 4.08 (1.94 H, d, *J* 5.6), 4.21 (0.06 H, d, *J* 6.4) and 7.86 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 41.3, 52.8, 111.0, 143.4 and 168.5; HRMS (ESI) 143.0450 ($[M + H]^+$. $C_5H_7N_2O_3$ requires 143.0451).

Dimethyl 2,2′-(2,4,5-trioxoimidazolidine-1,3-diyl)diacetate (11i). ν_{max}(NaCl)/cm^{-1} 3556, 3001, 2960, 2856 and 1748; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.76 (3 H, s) and 4.40 (2 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 39.5, 53.0, 152.2, 155.6 and 166.2; HRMS (ESI) 259.0571 ($[M + H]^+$. $C_9H_{11}N_2O_7$ requires 259.0561).

(*R*)-Ethyl 2-(cyanocarbonylamino)-2-phenylacetate (8j). Following the general procedure and starting from amine **7j** (2.090 g, 11.66 mmol) and DEPC (1.93 mL, 11.66 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 15:1 to 12:1) gave compound **8j** as a colourless oil that solidified on standing (2.411 g, 89%). $[\alpha]_D^{25}$ −37.60 (*c* 3.34 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3302, 3061, 3035, 2986, 2941, 2239, 1740, 1696 and 1528; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.97:0.03) 1.21 (3 H, t, *J* 2 × 7.1), 4.19 (1 H, dq, *J* 10.8, 3 × 7.1), 4.28 (1 H, dq, *J* 11.1, 3 × 7.3), 5.56 (0.03 H, d, *J* 8.6), 5.60 (0.97 H, d, *J* 7.4), 7.51–7.20 (5 H, m), 7.73 (0.03 H, br d, *J* 7.8) and 8.30 (0.97 H, br d, *J* 7.0); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 13.7, 56.9, 62.8, 111.0, 127.1, 129.0, 134.3, 142.3 and 169.3; HRMS (ESI) 233.0924 ($[M + H]^+$. $C_{12}H_{13}N_2O_3$ requires 233.0921).

(*S*)-Methyl 2-(cyanocarbonylamino)propanoate (8k). Following the general procedure and starting from amine **7k** (1.369 g, 13.28 mmol) and DPPC (3.442 g, 13.28 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 6:1 to 4:1) gave compound **8k** as a white solid (1.639 g, 79%). $[\alpha]_D^{25}$ +32.15 (*c* 1.32 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3310, 3059, 3002, 2958, 2852, 2238, 1747, 1701 and 1540; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.93:0.07) 1.49 (2.79 H, d, *J* 7.1), 1.72 (0.21 H, d, *J* 7.4), 3.78 (0.21 H, s), 3.81 (2.79 H, s), 4.61 (0.93 H, p, *J* 4 × 7.2), 4.91 (0.07 H, q, *J* 3 × 7.4), 6.74 (0.07 H, br s) and 7.24 (0.93 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 17.8, 49.1, 53.2, 111.1, 142.4 and 171.6; HRMS (ESI) 179.0430 ($[M + Na]^+$. $C_6H_8N_2NaO_3$ requires 179.0427).

(*S*)-Methyl 2-(cyanocarbonylamino)-3-phenylpropanoate (8l). Following the general procedure and starting from amine **7l** (1.299 g, 7.25 mmol) and DEPC (1.20 mL, 7.25 mmol, 100 mol%), purification by flash chromatography (silica gel, hexane/EtOAc 6:1 to 4:1) gave compound **8l** as a white solid (1.6 g, 95%). $[\alpha]_D^{25}$ +120.34 (*c* 0.9 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3298, 3032, 2955, 2854, 2237, 1744, 1695 and 1536; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 0.96:0.04) 3.13 (1 H, dd, *J* 14.1 and 5.7), 3.19 (1 H, dd, *J* 14.1 and 5.7), 3.79 (3 H, s), 4.75 (0.04 H, m), 4.88 (0.96 H, dt, *J* 7.8, 2 × 5.7), 6.51 (0.04 H, br s), 6.95 (0.96 H, br s), 7.03–7.12 (2 H, m) and 7.21–7.38 (3 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 37.2, 53.0, 54.0, 111.0, 127.7, 128.9, 129.1, 134.3, 142.4 and 170.1; HRMS (ESI) 255.0737 ($[M + Na]^+$. $C_{12}H_{12}N_2NaO_3$ requires 255.0740).

(*S*)-Methyl 2-(cyanocarbonylamino)-3-methylbutanoate [L-valine methyl ester carbamoyl cyanide] (8m). Following the general procedure and starting from L-valine methyl ester hydrochloride (0.168 g, 1.0 mmol), purification by flash chromatography (hexane/EtOAc 19:1 to 9:1) gave the product **8m** as a volatile colourless oil (0.159 g, 87%). *Rf* 0.25 (hexane/EtOAc 4:1); $[\alpha]_D^{25}$ +45.19 (*c* 1.41 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3309br, 2970, 2238w, 1748br, 1701br, 1540br and 1217; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers, ratio 96:4) 0.87 and 0.97 (5.96 H, d, *J* 6.9), 1.01 (0.12 H, d, *J* 7.3), 2.25 (1 H, m), 3.80 (2.88 H, s), 3.82 (0.12 H, s), 4.41 (0.04 H, dd, *J* 8.9 and 4.7), 4.60 (0.96 H, dd, *J* 8.8 and 4.7) and 7.47 (1 H, br d, *J* 7.4); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 17.5, 18.8, 31.3, 52.9, 58.0, 111.2, 143.0 and 170.8; *m/z* (EI) 234 (M^+), 142 (25%), 125 (100), 115 (11),

110 (46), 72 (10); HRMS (EI) 184.0856 (M^+. $C_8H_{12}N_2O_3$ requires 184.0848).

(*R*)-Methyl 2-(cyanocarbonylamino)-3-methylbutanoate [D-valine methyl ester carbamoyl cyanide] (8n). Following the general procedure and starting from D-valine methyl ester hydrochloride (0.168 g, 1.0 mmol), purification by flash chromatography (hexane/EtOAc 19:1 to 9:1) gave the product **8n** as a volatile colourless oil (0.175 g, 96%). *Rf* 0.25 (hex/EtOAc 4:1). $[\alpha]_D^{23}$ –43.63 (*c* 1.71 in $CHCl_3$). Spectroscopic data are identical to those of its enantiomer (**8m**).

(*S*)-Dimethyl 2-(cyanocarbonylamino)pentanedioate [L-glutamic acid dimethyl ester carbamoyl cyanide] (8o). Following the general procedure and starting from L-glutamic acid dimethyl ester hydrochloride (0.212 g, 1.0 mmol), purification by flash chromatography (hexane/EtOAc 9:1) gave the product **8o** as a yellowish oil (0.172 g, 82%). *Rf* 0.50 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ +21.40 (*c* 1.05 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3299br, 2958, 2238w, 1742br, 1700br, 1540br, 1440 and 1218br; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.04–2.15 (1 H, m), 2.25 (1 H, m), 2.37–2.47 (2 H, m), 3.70 (3 H, s), 3.79 (3 H, s), 4.64 (1 H, m, *J* 5.2) and 7.83 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.4, 29.7, 52.1, 52.5, 53.3, 111.1, 143.0, 170.3 and 173.2; *m/z* (EI) 228 (M^+), 169 (59%), 142 (41), 137 (100), 110 (28), 109 (89), 82 (47); HRMS (EI) 228.0755 (M^+. $C_9H_{12}N_2O_5$ requires 228.0746).

(*S*)-Methyl 2-(cyanocarbonylamino)-3-(1*H*-indol-3-yl)propanoate [L-tryptophan methyl ester carbamoyl cyanide] (8p). Following the general procedure and starting from L-tryptophan methyl ester hydrochloride (0.255 g, 1.0 mmol), purification by flash chromatography (hexane/EtOAc 4:1) gave the product **8p** as a yellowish solid (0.232 g, 85%). *Rf* 0.20 (hexane/EtOAc 2:1); mp 110.7–111.7 °C; $[\alpha]_D^{27}$ +82.08 (*c* 2.10 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3462, 3326br, 2237w, 1731br, 1679br, 1526br, 1370, 1253 and 744; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.24–3.34 (2 H, m), 3.67 (3 H, s), 4.85 (1 H, dt, *J* 7.8 and 5.3), 6.90 (1 H, d, *J* 2.2), 6.99 (1 H, br d, *J* 7.1), 7.03–7.20 (2 H, m), 7.29 (1 H, d, *J* 8.0), 7.43 (1 H, d, *J* 7.8) and 8.10 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.1, 53.0, 53.8, 108.6, 111.1, 111.5, 118.2, 120.1, 122.6, 123.0, 127.2, 136.1, 142.6 and 170.4; *m/z* (EI) 271 (M^+, 6%), 244 (10), 130 (100); HRMS (EI) 271.0964 (M^+. $C_{14}H_{13}N_3O_3$ requires 271.0957).

When the reaction was carried out starting from L-tryptophan methyl ester hydrochloride (0.410 g, 1.88 mmol) and DPPC (0.487 g, 1.88 mmol, 100 mol%), purification by flash chromatography gave, in addition to the cyanoformamide **8p** (0.415 g, 81%), a white solid identified as **13** (0.011 g, 2%) and a colourless oil identified as **12p** (0.024 g, 3%).

(*S*)-Methyl 3-[1-(cyanocarbonyl)-1*H*-indol-3-yl]-2-(cyanocarbonylamino)propanoate (13). ν_{max}(NaCl)/cm^{-1} 3303, 3110, 3032, 2955, 2853, 2236, 1745, 1698, 1606 and 1537; δ_H (400 MHz; acetone-d_6; Me_4Si) 3.36 (1 H, dd, *J* 15.1 and 8.3), 3.48 (1 H, dd, *J* 15.0 and 5.3), 3.74 (3 H, s), 4.99 (1 H, td, *J* 2 × 8.3, 5.2), 7.41–7.55 (2 H, m), 7.74 (1 H, m), 7.86 (1 H, s), 8.24 (1 H, m) and 9.33 (1 H, br d, *J* 8.0); δ_H (400 MHz; DMSO-d_6; Me_4Si) 3.15 (1 H, dd, *J* 14.9 and 9.2), 3.28 (1 H, dd, *J* 15.0 and 5.2), 3.66 (3 H, s), 4.77 (1 H, ddd, *J* 9.0, 7.5 and 5.2), 7.37–7.51 (2 H, m), 7.68 (1 H, br d, *J* 6.8), 7.77 (1 H, s), 8.15 (1 H, br d, *J* 7.7) and 10.51 (1 H, br d, *J* 7.4); δ_C (100 MHz; acetone-d_6; Me_4Si) 28.1, 54.1, 54.4, 112.3, 113.4, 118.3, 121.6, 122.8, 126.1, 127.9, 128.2, 133.3, 136.9, 142.6, 145.1 and 171.5; δ_C (100 MHz; DMSO-d_6; Me_4Si) 25.5, 52.3, 52.6, 110.7, 111.8, 116.0, 119.7, 120.2, 124.4, 125.7, 126.1, 130.9, 134.3, 140.7, 142.9 and 169.7; HRMS (ESI) 325.0928 ($[M + H]^+$. $C_{16}H_{13}N_4O_4$ requires 325.0931).

(*S*)-Methyl 2-[cyanocarbonyl(diphenoxyphosphoryl)amino]-3-(1*H*-indol-3-yl)propanoate (12p). ν_{max}(NaCl)/cm^{-1} 3412, 3062, 2952, 2235, 1748, 1695 and 1591; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.51 (1 H, dd, *J* 15.2 and 10.4), 3.55 (3 H, s), 3.71 (1 H, dd, *J* 15.3 and 5.6), 5.39 (1 H, m), 6.66–6.85 (2 H, m), 6.97 (1 H, s), 7.05–7.37 (11 H, m), 7.60 (1 H, d, *J* 7.2) and 8.00 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 24.7, 52.7, 60.5, 109.9, 110.0, 111.2, 118.7, 119.8, 120.0 (d, *J* 4.6), 120.2 (d, *J* 4.7), 122.2, 123.5, 126.0, 126.2, 126.9, 129.7, 129.8, 136.3, 144.4, 149.4 (d, *J* 8), 149.6 (d, *J* 7.7) and 168.4 (d, *J* 3.3); δ_P (160 MHz; $CDCl_3$) –11.34; HRMS (ESI) 504.1308 ($[M + H]^+$. $C_{26}H_{23}N_3O_6P$ requires 504.1319).

(2*S*,3*S*)-Methyl 2-(cyanocarbonylamino)-3-methylpentanoate [L-isoleucine methyl ester carbamoyl cyanide] (8q). Following the general procedure and starting from L-isoleucine methyl ester hydrochloride (0.182 g, 1.0 mmol), purification by flash chromatography (hexane/EtOAc 9:1 to 4:1) gave the product **8q** as a volatile yellowish oil (0.191 g, 96%). *Rf* 0.45 (hexane/EtOAc 4:1); $[\alpha]_D^{23}$ +51.72 (*c* 2.01 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3309br, 2968, 2237w, 1746br, 1700br, 1539br and 1216br; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers, ratio 96:4) 0.93–0.96 (6 H, m), 1.24 (1 H, m), 1.45 (1 H, m), 1.97 (1 H, m), 3.83 (2.88 H, s), 3.83 (0.12 H, s), 4.48 (1 H, dd, *J* 10.1 and 4.7), 4.64 (0.96 H, dd, *J* 8.5 and 4.6), 6.83 (0.04 H, br s) and 7.22 (0.96 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 11.5, 15.4, 25.1, 38.0, 52.8, 57.3, 111.2, 142.7 and 170.6; *m/z* (EI) 198 (M^+, 3%), 142 (83), 139 (100), 115 (58), 110 (83), 83 (13), 69 (90); HRMS (EI) 198.1001 (M^+. $C_9H_{14}N_2O_3$ requires 198.1004).

(*S*)-Dimethyl 2-(cyanocarbonylamino)succinate (8r). Following the general procedure and starting from amine **7r** (1.101 g, 6.83 mmol), PhTMG (1.371 g, 7.17 mmol, 105 mol%), DPPC (1.770 g, 6.83 mmol, 100 mol%) and CO_2 in CH_3CN (15 mL), purification by flash chromatography (silica gel, hexane/EtOAc 6:1→4:1) gave compound **8r** as a colourless oil (1.192 g, 82%). $[\alpha]_D^{25}$ +56.99 (*c* 2.94 in $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3308, 3042, 2958, 2854, 2240, 1743, 1699 and 1534; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers, ratio 0.98:0.02) 2.81 (1 H, dd, *J* 17.6 and 4.28), 2.94 (1 H, dd, *J* 17.6 and 4.9), 3.57 (3 H, s), 3.66 (3 H, s), 4.76 (1 H, dt, *J* 8.8 and 2 × 4.5), 7.45 (0.02 H, br d, *J* 10.0), 8.22 (0.98 H, br d, *J* 8.0); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 34.8, 48.7, 51.9, 52.9, 110.8, 142.8, 169.0 and 170.5; HRMS (ESI) 215.0672 ($[M + H]^+$. $C_8H_{11}N_2O_5$ requires 215.0662).

Treatment of carbamoyl cyanides with bases. Method 1 DBU (0.18 mL, 1.21 mmol, 100 mol%) was added to a solution of carbamoyl cyanide **8c** (0.21 g, 1.21 mmol) in CH_3CN (7 mL). The resulting mixture was stirred for 16 h, after which time the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc 10:1 to 2:1) yielded **10c** as a colourless oil (0.16 g, 81%), together with a white solid identified as 1,3-bis[(*R*)-1-phenylethyl]urea (0.02 g, 15%). **5-Imino-1,3-bis[(*R*)-1-phenylethyl]imidazolidine-2,4-dione (10c).** δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.89 (3 H, d, *J* 7.4), 1.94 (3 H, d, *J* 7.3), 5.42 (1 H, q, *J* 3 × 7.4), 5.61 (1 H, q, *J* 3 × 7.3), 7.29–7.42 (6 H, m), 7.45–7.57 (4 H, m) and 8.92 (1 H, br s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 17.0, 17.2, 51.2,

51.3, 127.2, 127.3, 127.8, 128.0, 128.4, 128.5, 139.1, 139.4, 152.0, 153.7 and 155.6; HRMS (ESI) 322.1543 ([M + H]$^+$. $C_{19}H_{20}N_3O_2$ requires 322.1550). **1,3-Bis[(*R*)-1-phenylethyl]urea.**[16] δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (6 H, d, *J* 6.8), 4.60 (2 H, br s), 4.76 (2 H, m), 7.10–7.16 (4 H, m) and 7.19–7.30 (6 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 23.4, 50.2, 125.7, 127.1, 128.6, 144.0 and 156.7.

Treatment of carbamoyl cyanides with bases. Method 2 Triethylamine (0.19 mL, 1.36 mmol, 400 mol%) was added to a solution of carbamoyl cyanide **8c** (0.06 g, 0.34 mmol) in CH_2Cl_2 (8 mL). The resulting mixture was stirred for 14 h, after which time the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexane/EtOAc 10:1) yielded **10c** (0.04 g, 71%), together with unreacted carbamoyl cyanide (0.01 g, 20%).

***tert*-Butyl 8-aminooctylcarbamate.** BOC_2O (2.18 g, 2.3 mL, 10.00 mmol, 100 mol%) and Et_3N (4.18 mL, 30.00 mmol, 300 mol%) were added to a solution of octane-1,8-diamine (2.00 g, 13.89 mmol) in THF/H_2O 4:1 (50 mL). The resulting mixture was stirred at room temperature for 23 h. THF was removed under reduced pressure, 2 M K_2CO_3 (15 mL) was added and the mixture was extracted several times with EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) gave *tert*-butyl 8-aminooctylcarbamate as a yellowish oil (0.435 g, 30%). ν_{max}(KBr)/cm^{-1} 3361br, 2971, 2927br, 2853, 1684br, 1521, 1365, 1249 and 1174br; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.27 (9 H, s), 1.41 (12 H, br s), 2.65 (2 H, t, *J* 7.0), 3.06 (2 H, t, *J* 6.2) and 4.61 (1 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.6, 26.7, 28.4, 29.2, 29.3, 30.1, 33.6, 40.5, 42.2, 78.9 and 155.9; *m*/*z* (EI) 244 (M$^+$, 28%), 187 (51), 171 (100), 159 (44), 143 (45), 114 (36), 100 (38), 86 (56); HRMS (EI) 244.2149 (M$^+$. $C_{13}H_{28}N_2O_2$ requires 244.2151).

***tert*-Butyl 8-(cyanocarbonylamino)octylcarbamate (14).** A solution of *tert*-butyl 8-aminooctylcarbamate (0.271 g, 1.11 mmol) in dry acetonitrile (5 mL) was added to a flask containing PhTMG (0.244 g, 1.28 mmol). Acetonitrile (10 mL) was added and the resulting solution was cooled with a salt/ice bath under an inert atmosphere. CO_2 (g) was bubbled through the solution for 10 min and DEPC (0.199 g, 0.185 mL, 1.22 mmol) was added dropwise. CO_2 (g) was bubbled through for a further 5 min and the solution was stirred under a CO_2 (g) atmosphere for 1 h, allowing the reaction to reach room temperature. The mixture was dissolved in EtOAc (100 mL) and the organic phase was washed with water (3×) and 5% HCl (3×). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1 to 4:1) gave **14** as a white crystalline solid (0.287 g, 90%). *Rf* 0.5 (hexane/EtOAc 2:1); mp 54.6–55.1 °C; ν_{max}(KBr)/cm^{-1} 3267br, 3278, 2933, 2859, 2234w, 1685br, 1526br, 1253 and 1171; δ_H (400 MHz; $CDCl_3$; Me_4Si) (two rotamers 92:8) 1.32 (9 H, s), 1.45 (8 H, br s), 1.51–1.61 (4 H, m), 3.11 (2 H, q, *J* 6.3), 3.35 (1.84 H, q, *J* 6.7), 3.49 (0.16 H, q, *J* 6.9), 4.13 (0.16 H, s), 4.54 (0.84 H, s), 6.20 (0.16 H, s) and 6.61 (0.84 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 26.5, 28.5, 28.8, 29.0, 30.0, 40.4, 40.5, 43.3, 79.2, 111.7, 142.3 and 156.2; *m*/*z* (EI) 297 (M$^+$, 0.2%), 211 (41), 197 (87), 171 (100), 169 (54), 154 (49), 86 (41), 74 (32), 69 (44); HRMS (EI) 297.2060 (M$^+$. $C_{15}H_{27}N_3O_3$ requires 297.2052).

8-(Cyanocarbonylamino)octan-1-amine hydrochloride (15). Compound **14** (0.060 g, 0.2 mmol) was dissolved in 5 mL of a CH_2Cl_2 solution that was 1 M TMSCl/3 M phenol (obtained by mixing 5 mL of a 4 M solution of TMSCl in CH_2Cl_2 with 15 mL of a 4 M solution of phenol in CH_2Cl_2). The mixture was stirred for 20 min at room temperature under an argon atmosphere. The solvent was removed under reduced pressure and phenol was removed by distillation in a Kugelrohr oven under high vacuum (1–2 mm Hg), with the temperature maintained below 70 °C. The residue was triturated and washed several times with ether, yielding **15** as a white crystalline solid (0.043 g, 90%). δ_H (400 MHz; MeOH-d_4; Me_4Si) 1.37 (8 H, m), 1.55 (2 H, m), 1.65 (2 H, m), 2.92 (2 H, t, *J* 7.6) and 3.25 (2 H, t, *J* 7.0); δ_C (100 MHz; MeOH-d_4; Me_4Si) 27.4, 27.8, 28.6, 29.7, 30.1, 31.1, 40.8, 41.0, 113.1 and 145.1; HRFABMS (positive, mNBA matrix) *m*/*z* 198.1600 ([M + H]$^+$. $C_{10}H_{20}N_3O$ requires 198.1606).

2,6-Dibromotyramine hydrobromide [4-(2-aminoethyl)-2,6-dibromophenol hydrobromide] (17). A solution of KBr (15 g) and bromine (3 mL) in water (50 mL) was added dropwise to a solution of tyramine hydrochloride (1.740 g, 10 mmol) in a mixture of ethanol/water 1:1 (10 mL) until a permanent yellow colour appeared. Water (20 mL) was added and the precipitate was filtered off and washed with saturated aqueous sodium bisulfite and water (3×). Compound **17** was obtained as a white crystalline solid (3.317 g, 91%). ν_{max}(KBr)/cm^{-1} 3310, 3205, 3137, 2987, 2915, 1473, 1145 and 868; δ_H (400 MHz; MeOH-d_4; Me_4Si) 2.86 (2 H, t, *J* 7.6), 3.14 (2 H, t, *J* 7.6) and 7.44 (2 H, s); δ_C (100 MHz; MeOH-d_4; Me_4Si) 32.9, 41.8, 112.6, 132.0, 133.8 and 151.6; *m*/*z* (EI) 293/295/297 (M$^+$, 45%/100%/49%), 268/266/264 (48/99/52), 185/187 (29/27), 155/157 (21/22), 105 (23), 80/82 (77/76); HRMS (EI) 294.9035 (M$^+$. $C_8H_9NO^{79}Br^{81}Br$ requires 294.9030).

4-(2-*tert*-Butoxycarbonylaminoethyl)-2,6-dibromophenol [*tert*-butyl 3,5-dibromo-4-hydroxyphenethylcarbamate] (18). BOC_2O (1.310 g, 1.38 mL, 6.00 mmol) and triethylamine (1.214 g, 1.67 mL, 12.00 mmol) were added to a stirred solution of **17** (1.128 g, 3.00 mmol) in THF/H_2O 1:1 (12 mL). The resulting mixture was stirred at room temperature for 14 h. THF was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was washed with 5% HCl (3×). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc 9:1 to 3:1). Compound **18** was obtained as a white crystalline solid (1.174 g, 99%). *Rf* 0.40 (hexane/EtOAc 4:1); mp 108.6–111.6 °C; ν_{max}(KBr)/cm^{-1} 3362, 1681, 1533, 1475, 1365, 1273, 1252, 1163 and 738; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.68 (2 H, t, *J* 6.6), 3.28 (2 H, q, *J* 6.6), 4.56 (1 H, br s), 5.92 (1 H, s) and 7.25 (2 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 28.5, 34.7, 41.6, 79.5, 109.8, 132.2, 133.6, 148.0 and 155.8; *m*/*z* (EI) 393/395/397 (M$^+$), 337/339/341 (31%/61%/30%), 276/278/280 (51/100/50), 263/265/267 (13/25/13); HRMS (EI) 394.9711 (M$^+$. $C_{13}H_{17}NO_3{}^{79}Br^{81}Br$ requires 394.9555).

***tert*-Butyl 3,5-dibromo-4-(3-bromopropoxy)phenethylcarbamate (19).** Compound **18** (0.500 g, 1.27 mmol) and K_2CO_3 (0.876 g, 6.35 mmol, 500 mol%) were added to a solution of 1,3-dibromopropane (2.56 g, 1.3 mL, 12.7 mmol, 1000 mol%) in dry acetone (10 mL). The resulting mixture was stirred at room

temperature under an argon atmosphere for 15 h. The solvents were removed under reduced pressure and the residue was dissolved in EtOAc (100 mL) and washed with water (3×). The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification of the crude product by chromatography (hexane/EtOAc 9:1 to 7:1) yielded **19** as a white crystalline solid (0.648 g, 99%). *Rf* 0.50 (hexane/EtOAc 4:1); mp 72.6–73.6 °C; ν_{max}(KBr)/cm^{-1} 3365br, 1684, 1528, 1456, 1364, 1277, 1250 and 1162br; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.44 and 1.45 (9 H total, two s), 2.41 (2 H, q, *J* 5.9), 2.72 (2 H, t, *J* 6.7), 3.33 (2 H, q, *J* 6.5), 3.73 (2 H, td, *J* 6.6 and 1.0), 4.12 (2 H, t, *J* 5.7), 4.57 (1 H, br s) and 7.34 (2 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) 28.3 (q), 29.9 (t), 33.3 (t), 34.9 (t), 41.3 (t), 70.6 (t), 79.3 (s), 118.0 (s), 132.9 (d), 137.9 (s), 151.2 (s), 155.7 (s); *m/z* (EI) 513/515/517/519 (M^+, 1%/3%/3%/1%), 457/459/501/503 (33/100/98/33), 396/398/400/402 (28/83/81/27), 276/278/280 (26/51/25), 263/265/267 (29/55/28); HRMS (EI) 514.9133 (M^+. $C_{16}H_{22}NO_3{}^{79}Br_2{}^{81}Br$ requires 514.9129).

***tert*-Butyl 4-(3-azidopropoxy)-3,5-dibromophenethylcarbamate (20).** A 0.5 M solution of NaN_3 in DMSO (1.06 mL, 35 mg, 0.53 mmol) was added to **19** (0.250 g, 0.49 mmol). The mixture was stirred at room temperature under an argon atmosphere for 23 h. Water (10 mL) was added and the mixture was extracted with ether (3×). The organic layer was washed with water (2×) and brine (1×). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure, yielding **20** as a white crystalline solid (0.224 g, 98%). *Rf* 0.50 (hexane/EtOAc 4:1); mp 64.3–65.5 °C; ν_{max}(KBr)/cm^{-1} 3346br, 2093br, 1674, 1539, 1288 and 1253; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s), 2.11 (2 H, q, *J* 6.3), 2.72 (2 H, t, *J* 6.9), 3.33 (2 H, q, *J* 6.7), 3.67 (2 H, t, *J* 6.7), 4.08 (2 H, t, *J* 5.8), 4.55 (1 H, br s) and 7.35 (2 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 28.1, 29.7, 35.1, 41.4, 48.2, 69.9, 79.5, 118.1, 132.9, 137.9, 151.4 and 155.7; *m/z* (EI) 476/478/480 (M^+, 2%/4%/2%), 420/422/424 (51/100/50), 359/361/363 (21/40/20), 313/315 (14/15), 276/278/280 (27/52/25), 263/265/267 (33/63/30), 240/242 (15/13); HRMS (EI) 476.0048 (M^+. $C_{16}H_{22}N_4O_3{}^{79}Br_2$ requires 476.0059).

***tert*-Butyl 4-(3-aminopropoxy)-3,5-dibromophenethylcarbamate (21).** A mixture of **20** (0.200 g, 0.42 mmol) and Ph_3P (0.100 g, 0.42 mmol) was stirred in dry THF (2 mL) at room temperature under an argon atmosphere for 3.5 h. Water (0.011 g, 0.63 mmol, 150 mol%) was added and the mixture was stirred for a further 19 h. The mixture was concentrated to dryness and the residue was dissolved in 5% citric acid (30 mL). The resulting white mixture was washed with hexane/EtOAc 1:1 (3×). The aqueous phase was basified to pH > 12 with 2 M NaOH and extracted with CH_2Cl_2 (4×). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **21** as a yellowish viscous oil (0.165 g, 86%), which was used without further purification. δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s), 1.99 (2 H, q, *J* 6.3), 2.72 (2 H, t, *J* 6.8), 3.02 (2 H, q, *J* 6.6), 3.33 (2 H, t, *J* 6.6), 4.07 (2 H, t, *J* 6.0), 4.57 (1 H, br s) and 7.34 (2 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 28.2, 33.6, 34.8, 39.1, 41.4, 71.1, 79.2, 118.0, 132.8, 137.7, 151.5 and 155.7.

***tert*-Butyl 3,5-dibromo-4-[3-(cyanocarbonylamino)propoxy]phenethylcarbamate (22).** PhTMG (0.074 g, 0.39 mmol) was added to a solution of **21** (0.150 g, 0.31 mmol) in acetonitrile (5 mL). The resulting mixture was diluted with more acetonitrile (10 mL) and was cooled with a salt/ice bath under an inert atmosphere. CO_2 was slowly bubbled through the mixture for 10 min. DEPC (0.058 g, 0.054 mL, 0.36 mmol) was added dropwise and the stream of CO_2 was maintained for a further 5 min. The reaction was stirred and the temperature was allowed to rise to room temperature over 1.5 h. The mixture was dissolved in EtOAc (100 mL) and was washed with water (3×) and 5% HCl (2×). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 9:1 to 3:1) gave **22** as a white crystalline solid (0.125 g, 87%). *Rf* 0.25 (hexane/EtOAc 3:1); mp 107.7–108.7 °C; ν_{max}(KBr)/cm^{-1} 3359br, 3223, 3056, 2237w, 1666br, 1534br, 1471, 1456, 1368, 1269, 1256 and 1168br; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s), 2.13 (2 H, q, *J* 5.4), 2.75 (2 H, t, *J* 6.9), 3.34 (2 H, q, *J* 6.6), 3.72 (2 H, q, *J* 6.0), 4.13 (2 H, t, *J* 5.4), 4.57 (1 H, br s), 7.07 (1 H, br s) and 7.37 (2 H, s); δ_C (100 MHz; $CDCl_3$; Me_4Si) (major rotamer) 28.3, 28.4, 35.0, 38.7, 41.4, 71.5, 79.6, 111.7, 117.9, 133.0, 138.4, 143.2, 150.8 and 155.8; *m/z* (FAB+) 504/506/508 ([M + H]$^+$, 15%/33%/16%); HRFABMS (positive, mNBA matrix) 506.0120 ([M + H]$^+$. $C_{18}H_{24}N_3O_4{}^{79}Br^{81}Br$ requires 506.0113).

Ceratinamine hydrochloride (1). Compound **22** (0.060 g, 12 mmol) was added to a CH_2Cl_2 solution (2.5 mL) that was 1M in TMSCl and 3M in phenol. The mixture was stirred at room temperature under an inert atmosphere for 20 min. The solvent was removed under reduced pressure and the phenol was distilled off in a Kugelrohr oven under high vacuum (1–2 mm Hg), with the temperature maintained below 70 °C. The solid residue was triturated and washed several times with ether to give **1** as a white crystalline solid (0.047 g, 90%). Mp 188.1 °C (dec.); ν_{max}(KBr)/cm^{-1} 3277, 3044, 2941, 2240w, 1668, 1457 and 1259; δ_H (400 MHz; MeOH-d_4; Me_4Si) 2.10 (2 H, q, *J* 6.6), 2.93 (2 H, t, *J* 7.6), 3.17 (2 H, t, *J* 7.2), 3.57 (2 H, t, *J* 7.1), 4.04 (2 H, t, *J* 5.9) and 7.56 (2 H, s); δ_H (400 MHz; DMSO-d_6; Me_4Si) 2.00 (2 H, q, *J* 6.5), 2.84 (2 H, t, *J* 7.2), 3.07 (2 H, t, *J* 7.2), 3.42 (2 H, q, *J* 6.6), 3.96 (2 H, t, *J* 6.0), 7.60 (2 H, s), 7.91 (3 H, br s) and 9.97 (1 H, br s); δ_C (100 MHz; MeOH-d_4; Me_4Si) 30.1, 33.2, 38.4, 41.5, 71.7, 113.1, 119.5, 134.5, 137.3, 142.3 and 153.6; δ_C (100 MHz; DMSO-d_6; Me_4Si) 28.5, 31.3, 38.8, 39.2, 70.5, 112.3, 117.4, 133.1, 136.9, 142.9 and 151.0; *m/z* (FAB+) 404/406/408 ([M + H]$^+$, 6%/12%/6%); HRFABMS (positive, mNBA matrix) 405.9590 (M^+. $C_{13}H_{16}N_3O_2{}^{79}Br^{81}Br$ requires 405.9589).

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