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Asymmetric synthesis of (2*R*,3*S*)-4-halo-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitriles as precursors for the synthesis of β-hydroxy-α-amino acids

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Abstract

(2*R*,3*S*)-4-Halo-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitriles have been prepared through an efficient three-step sequence from (2*R*,3*S*)-2-benzylamino-3-benzyloxy-4-(*tert*-butyldimethylsilyloxy)butyronitrile, which is readily available in diastereomerically pure form by a Strecker-type reaction of the *N*-benzylimine, derived from selectively protected (*R*)-glyceraldehyde, and trimethylsilyl cyanide. These compounds enable the facile synthesis of chiral β-hydroxy-α-amino acids containing virtually any nucleophile capable of substituting the γ-halogen atom. As an illustration of their synthetic potential, the 4-bromo derivative has been successfully converted into (1*R*,2*R*)-2-benzyloxy-1-(*N*-methoxycarbonyl-*N*-benzylamino)-cyclopropanecarboxamide, which is a new conformationally restricted serine analogue, in two steps: base-induced cyclisation and subsequent hydrolysis of the nitrile group.

1. Introduction

β-Hydroxy-α-amino acids are an important class of compounds due to their inherent biological activities[1] and their role as structural components of more complex organic compounds[2] that possess a wide range of biological activities, such as antifungals, antibiotics and immunosuppresants (e.g. pneumocandins, nostofungicidine, vancomycin, echinocardin D, cyclosporin, polyoxin D, enpedopeptin and other peptide conjugates). They are also useful intermediates in the synthesis of other compounds, such as β-lactams,[3] aminosugars,[4] chiral ligands[5] and β-fluoro amino acids.[6]

A number of elegant approaches, including addition of organometallic reagents to aldehydes,[7] electrophilic amination,[8] nucleophilic ring opening of epoxides and azidirines,[9] dihydroxylation or aminohydroxylation of α,β-unsaturated carboxylic acid derivatives,[10] β-functionalisation of α-amino acids[11]

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and diastereoselective or chemo-enzymatic aldol condensation,[12] among others,[13] have been described for the asymmetric synthesis of various β-hydroxy-α-amino acids in enantiomerically pure form.

In this context, we have recently described a new route for the stereoselective synthesis of two α-epimers of the important β-hydroxy-α-amino acid 3,4-dihydroxy-2-aminobutanoic acid,[14] which is a key intermediate in the synthesis of β-lactam antibiotics and phytosiderophores. In our synthetic strategy, treatment of 3,4-di-*O*-benzyl-D-glyceraldehyde **1**, or its corresponding *N*-benzylimine, with trimethylsilyl cyanide in the presence or absence of Lewis acids, respectively, gave the corresponding double-bond addition compounds with high yields and diastereoselectivities with the 2*R* diastereoisomer favoured in both cases. Major compounds can be efficiently converted into the enantiomerically pure amino acids described above.

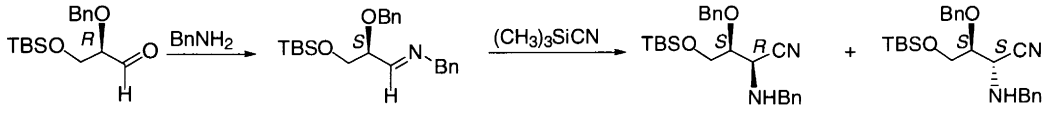
In this paper we wish to report the preparation of two new versatile building blocks, namely (2*R*,3*S*)-4-chloro- and (2*R*,3*S*)-4-bromo-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitrile (**8** and **9**). These compounds can act as synthetic precursors of β-hydroxy-α-amino acids due to the fact that the halogen at the γ-position can be displaced by a nucleophile late in the synthesis to provide the desired side-chain functionality. Our methodology for the synthesis of these compounds is based on the diastereoselective Strecker-type reaction between the inexpensive and easily available 2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-D-glyceraldehyde **2** and trimethylsilyl cyanide. In contrast to **1**, compound **2** has two different protecting groups, which means that chemoselective manipulation following nucleophilic additions is possible if desired (Fig. 1).

1 **2**

Fig. 1.

2. Results and discussion

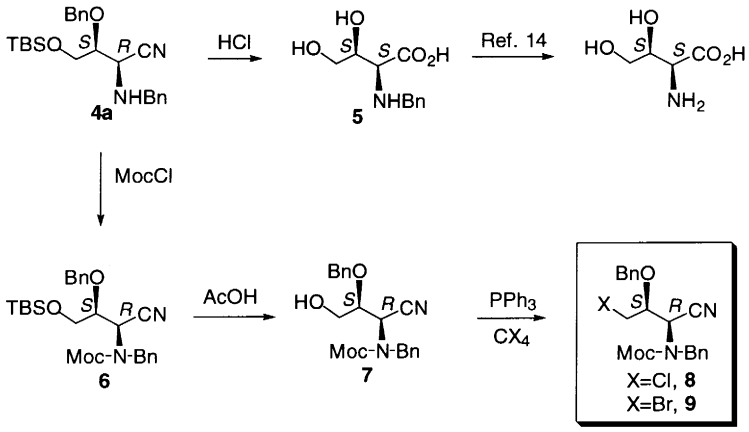
2-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-D-glyceraldehyde **2** is accessible from 1,3:4,5-di-*O*-benzylidenemannitol in four steps.[15] The reaction between imine **3**, obtained from aldehyde **2** and benzylamine, with trimethylsilyl cyanide in methylene chloride at room temperature, in the absence of Lewis acid, afforded the corresponding aminonitriles **4a** and **4b** in 75% yield and with an 85:15 diastereomeric ratio (Scheme 1).



2 **3** **4a** **4b**

Scheme 1.

The diastereomeric ratio was determined by integration of the corresponding *tert*-butyl group protons in the ^{1}H NMR spectrum of the crude reaction mixture. The major diastereoisomer **4a** could be easily isolated by column chromatography. The absolute configuration of the newly-formed stereogenic centre at C2 was unambiguously assigned as 2*R* by hydrolysis of this compound in an acid medium to give the known *N*-benzylamino acid **5**, which is an intermediate product in our previously reported synthetic route to (2*S*,3*S*)-3,4-dihydroxy-2-aminobutanoic acid (Scheme 2).



Scheme 2.

According to our previously proposed model, supported by ab initio calculations,[14] the stereochemical course of the reaction can be explained by assuming that the trimethylsilyl moiety coordinates to the imine nitrogen and that the glyceraldehyde moiety preferentially adopts an anti-Felkin–Anh conformation in which the α-C–OBn bond is oriented perpendicular to the imine group. The cyanide group should now preferentially attack from the re-side and give the observed major product (Fig. 2).

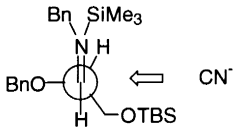


Fig. 2.

Next the conversion of aminonitrile **4a** into the desired intermediate products, (2*R*,3*S*)-4-halo-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitriles **8** (chloro) and **9** (bromo), was accomplished through the following sequence: protection of the amino function, selective deprotection of the primary hydroxy group and nucleophilic substitution of this group by a halogen (chloro or bromo), as shown in Scheme 2.

Initial protection of the amino function in compound **4a** with the Moc group was necessary to ensure that the subsequent selective deprotection of the primary hydroxy group took place successfully. This reaction was carried out smoothly in the presence of potassium carbonate and using methyl chloroformate in THF as the reagent to give compound **6** in 98% yield. Subsequent removal of the *O*-*tert*-butyldimethylsilyl group was readily performed with acetic acid and compound **7** was obtained in 99% yield. Finally, treatment of this compound with a mixture of the appropriate CX_4 (X=Cl or Br) and triphenylphosphine provided the target 4-haloaminonitriles **8** or **9** in quantitative and 92% yield, respectively.

Cyclopropylamino acid derivatives possess, as single molecules, a wide spectrum of biological properties.[16] Moreover, the incorporation of these amino acids into peptides is of great interest because the cyclopropyl ring increases their rigidity as a result of the bond stretching imposed by the methylene bridge.[17] The three-membered ring also hinders the rotation around the C_α–C_β bond and leads to two possible isomers (*cis* and *trans*) for cyclopropylamino acids substituted at C2. For this reason, interest in the synthesis of these products is growing, but it is worth noting that known synthetic procedures are lacking in terms of the preparation of cyclopropylamino acids substituted with an oxygen atom at C2.

As a straightforward illustration of the synthetic potential of such halo derivatives, compounds **8** and **9**

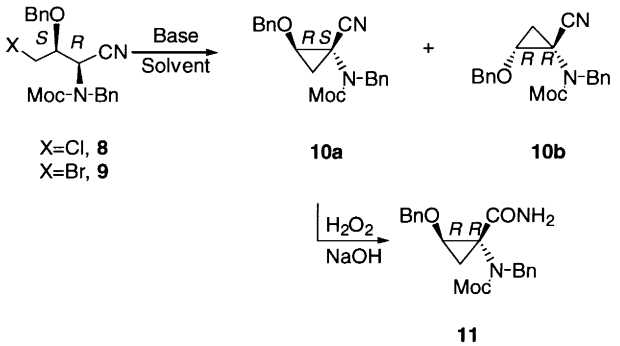
were converted into (1*R*,2*R*)-2-benzyloxy-1-(*N*-methoxycarbonylbenzylamino)cyclopropanecarboxamide **11**, a fully protected cyclopropylserine analogue whose introduction into a bioactive peptide could generate changes in the peptide conformation and thus modulate its interaction with the reactive site of an enzyme or bioreceptor.

Among the numerous different methodologies reported to date for the asymmetric synthesis of cyclopropylamino acid derivatives substituted at C2,[18] one of the most suitable for large-scale preparations is that reported by Salaün et al.[19] based on the base-induced cyclisation of (3*R*)-4-chloro-2-(benzylidenamino)-3-alkylbutyronitriles. With this synthetic strategy in mind, we investigated the possibility of performing the cyclisation of compounds **8** and **9** under different basic conditions.

It can be seen from the results in Table 1 that **8** and **9** were successfully cyclised either by using 1.2 equiv. of KOH in DMF or 1.2 equiv. of ^{t}BuOK in THF. After workup a mixture of 2-benzyloxy-1-(*N*-methoxycarbonyl-*N*-benzylamino)cyclopropanecarbonitriles (**10a**+**10b**) was obtained in high yields. The use of weak bases, such as triethylamine or K_2CO_3 in THF, was completely ineffective. Interestingly, the type of halogen atom, chloro or bromo, present in the starting aminonitrile was found to have a significant influence on the stereochemical course of the ring-closing process. Whereas (2*R*,3*S*)-3-benzyloxy-4-bromo-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitrile **9** gave the desired cyclopropylaminonitrile as a mixture of diastereoisomers **10a** and **10b**, which could be cleanly separated by column chromatography, (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-chlorobutyronitrile **8** underwent cyclisation with total stereoselectivity to give the diastereomerically pure compound **10a** (Scheme 3). The stereochemistry at the stereogenic C1 atom in the major or unique diastereoisomer **10a**, which is directly involved in the anionic intermediate, was unambiguously assigned as 1*S* by single crystal X-ray analysis.

Table 1
Base-induced cyclisation of the 4-haloaminonitriles **8** and **9**

Entry	Compound	Base	Solvent	Yield (%)	10a/10b
1	**8**	KOH	DMF	82	> 98/2
2	**8**	^{t}BuOK	THF	80	> 98/2
3	**8**	Et_3N	THF	-	-
4	**8**	K_2CO_3	THF	-	-
5	**9**	KOH	DMF	94	79/21
6	**9**	^{t}BuOK	THF	94	75/25
7	**9**	Et_3N	THF	-	-
8	**9**	K_2CO_3	THF	-	-



Scheme 3.

This assignment shows that base-induced cyclisation occurs with inversion of configuration at this stereogenic centre. From this finding it can be postulated that the (1*S*,2*R*)-diastereoisomer **10a**, with a relative configuration *E*, is likely to arise from the aminonitrile carbanion intermediate in the conformation depicted in Fig. 3, where the benzyloxy and nitrile groups would have a *syn* relationship to minimise steric interactions.

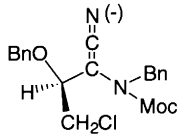


Fig. 3.

At this point it is worth noting that the same stereochemical result was observed when an 85:15 diastereomeric mixture was used as the starting material instead of the diastereomerically pure compound **8** (i.e. the diastereoisomer **10a** was obtained exclusively). This means that it is not necessary to remove the minor diastereoisomer **4b** obtained in the Strecker-type process and, in this way, the global yield of our synthetic methodology could be considerably improved. This observation has a simple explanation given that the absolute configuration at the tetrahedral β-carbon in the aminonitrile **4a** is completely modified when the intermediate carbanion is formed. A carbanion stabilised by resonance is essentially planar,[20] although, in certain cases, unsymmetrical solvatation ion-pairing effects may cause the structure to deviate somewhat from true planarity.

The last step in our synthesis involved the hydrolysis of the cyano group. Although under acidic conditions total decomposition of compound **10a** was observed, when this compound was treated with hydrogen peroxide under basic conditions, the cyano group was readily converted into the amide group to afford the fully protected cyclopropylamino acid derivative **11** with the serine skeleton.

3. Conclusion

In summary, we have designed new, inexpensive and easily available chiral building blocks for the synthesis of β-hydroxy-α-amino acids in enantiomerically pure form. (2*R*,3*S*)-4-Halo-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitriles **8** and **9** were prepared in high overall yields and fully characterised. The key step in the stereoselective synthesis is the nucleophilic addition of a cyanide group to the *N*-benzylimine derived from 2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-D-glyceraldehyde **2**. As an illustration of the synthetic potential of these compounds, we developed a simple procedure for the preparation of the fully protected cyclopropylserine analogue **11**. With the wide array of nucleophiles available, it is believed that compounds **8** and **9** would be very useful in combinatorial organic chemistry, and their application to the synthesis of different β-hydroxy-α-amino acids is currently underway in our laboratory.

4. Experimental

4.1. Methods and materials

Melting points were determined using a Büchi capillary melting point apparatus and are not corrected. Infrared spectra were recorded on a Perkin–Elmer 1600FT spectrophotometer as neat liquids or as Nujol

dispersions, and prominent peaks are expressed in cm^{-1}. NMR spectra were recorded on Varian Unity-300 or Bruker ARX-300 instruments operating at 300 MHz for ^1H NMR and at 75 MHz for ^{13}C NMR. The chemical shifts (δ) are reported in parts per million and the coupling constants (J) in hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal; bd, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets. The ^1H NMR and ^{13}C NMR spectra of *N*-Moc protected compounds were not conclusive at room temperature due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen–carbon bond of the urethane group. In order to overcome this problem NMR spectra of these compounds were acquired at 333 K. Optical rotations were measured on a Perkin–Elmer 241-C polarimeter at 25°C with concentrations given in g/100 ml. Elemental analyses were performed using a Perkin–Elmer 200 C,H,N,S elemental analyser. Electron impact mass spectra were obtained on a high resolution VG-autospec spectrometer.

4.2. Chemicals

All reactions were carried out in dry solvents. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Diethyl ether was distilled from $LiAlH_4$. Chloroform and methylene chloride were distilled from P_2O_5. Dimethylformamide was dried for 2 days with 3 Å molecular sieves. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and anisaldehyde:sulphuric acid:ethanol (2:1:100). Column chromatography was performed using silica gel (Kiesegel 60). Chemicals for reactions were used as purchased from Aldrich Chemical Co. 2-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-D-glyceraldehyde **2** was obtained according to the literature procedure.[15]

*4.3. (*S*)-2-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)propylidene(benzyl)azane **3***

To a stirred solution of (*R*)-2-*O*-benzyl-3-*O*-(*tert*-butyldimethylsilyl)-D-glyceraldehyde **2** (3 g, 0.01 mmol) in dry ether (30 ml) were added anhydrous magnesium sulphate (2 g) and a solution of benzylamine (1.092 g, 0.01 mol) in dry ether (10 ml). After 3 h the reaction mixture was filtered and evaporated in vacuo to afford the crude imine **3**, which was used in the next step without further purification.

*4.4. (2*R,*3*S*)-2-Benzylamino-3-benzyloxy-4-(*tert*-butyldimethylsilyloxy)butyronitrile **4a***

A mixture of crude (*S*)-2-benzyloxy-3-(*tert*-butyldimethylsilyloxy)propylidene(benzyl)azane **3** (3.9 g, 0.01 mol) and trimethylsilyl cyanide (1.6 ml, 0.012 mol) in dry methylene chloride (80 ml) was stirred under argon at room temperature for 12 h. The reaction mixture was poured into aqueous saturated ammonium chloride solution (10 ml) and the organic phase extracted with ether. The combined organic phases were washed successively with sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulphate. Removal of the solvent in vacuo yielded 2-benzylamino-3-benzyloxy-4-(*tert*-butyldimethylsilyloxy)butyronitrile as a mixture of diastereoisomers **4a**+**4b** (d.r. 85:15). Purification of the residue by flash chromatography on a silica gel column using ether:hexane (1:1) as eluent afforded 2.67 g (64% yield) of diastereoisomerically pure (2*R*,3*S*)-2-benzylamino-3-benzyloxy-4-(*tert*-butyldimethylsilyloxy)butyronitrile **4a** as an orangish oil. $[\alpha]_D^{25}=-61.1$ (*c* 1, $CHCl_3$); IR (neat) 3334, 2227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.80 (s, 9H), 1.98 (brs, 1H), 3.64–3.71 (m, 1H), 3.73–3.87 (m, 3H), 3.77 (d, 1H, *J*=12.9 Hz), 4.08 (d, 1H, *J*=12.9 Hz), 4.67 (d,

1H, *J*=11.5 Hz), 4.73 (d, 1H, *J*=11.5 Hz), 7.15–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.6, 18.1, 25.7, 50.4, 51.5, 61.1, 73.5, 79.2, 119.4, 127.4, 127.9, 128.0, 128.4, 128.5, 137.4, 138.3; HRMS(FAB) calcd for $C_{24}H_{35}N_2O_2Si$ (MH^+): 411.2468. Found: 411.2460.

4.5. *(2*S*,3*S*)-2-Benzylamino-3,4-dihydroxybutyric acid **5***

Hydrogen chloride gas was added to a stirred suspension of pure (2*R*,3*S*)-2-benzylamino-3-benzyloxy-4-(*tert*-butyldimethylsilyloxy)butyronitrile **4a** (0.8 g, 2 mmol) in concentrated hydrochloric acid (30 ml) at room temperature until all the compound had dissolved. The solution was stirred at room temperature for 24 h. After completion of the reaction, the hydrochloric acid was evaporated to dryness under reduced pressure. The residue was dissolved in water (15 ml), washed with ether, applied to a Dowex 50 W×8 column (H^+ form, 50 ml) and eluted with 5% aqueous ammonia. The fractions containing the *N*-benzylamino acid were combined and evaporated under reduced pressure to give a pale yellow solid. Further purification was performed by silica gel column chromatography using acetonitrile:water (2:1) as eluent to afford *(2S,3S)*-2-benzylamino-3,4-dihydroxybutyric acid **5** as a colourless solid whose physical and spectroscopic data were identical to those described previously for the same compound in Ref. 14b.

4.6. *(2*R*,3*S*)-3-Benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-(*tert*-butyldimethylsilyloxy) butyronitrile **6***

A solution of (2*R*,3*S*)-2-benzylamino-3-benzyloxy-4-(*tert*-butyldimethylsilyloxy)butyronitrile **4a** (2 g, 4.88 mmol), methyl chloroformate (0.92 g, 9.75 mmol) and K_2CO_3 (4.04 g, 29.28 mmol) in dry THF (40 ml) was stirred at room temperature for 5 h. The reaction mixture was then filtered and concentrated in vacuo to afford a crude product, which was purified by silica gel flash chromatography using ether:hexane (1:3) as eluent to provide 2.24 g (98% yield) of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-(*tert*-butyldimethylsilyloxy) butyronitrile **6** as a colourless oil. $[\alpha]_D^{25}$=−59.6 (*c* 1, $CHCl_3$); IR (neat) 2248, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, 333 K) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 3.72 (s, 3H), 3.75 (dd, 1H, *J*=11.7 Hz, *J*=3.6 Hz), 3.86 (dd, 1H, *J*=11.7 Hz, *J*=3 Hz), 3.92–4.03 (m, 1H), 4.27 (d, 1H, *J*=15.6 Hz), 4.40 (d, 1H, *J*=11.5 Hz), 4.59 (d, 1H, *J*=11.5 Hz), 4.81 (d, 1H, *J*=8.1 Hz), 4.86 (d, 1H, *J*=15.6 Hz), 7.20–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ −5.6, −5.5, 18.2, 25.8, 49.6, 52.1, 53.1, 61.5, 72.7, 78.5, 116.1, 127.7, 127.8, 127.9, 127.9, 128.4, 128.7, 136.8, 137.7, 156.3; HRMS(FAB) calcd for $C_{26}H_{36}N_2O_4Si$ (M^+): 468.2444. Found: 468.2452.

4.7. *(2*R*,3*S*)-3-Benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-hydroxybutyronitrile **7***

Water (6 ml) was added to a stirred solution of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-(*tert*-butyldimethylsilyloxy)butyronitrile **6** (2.2 g, 4.7 mmol) in acetic acid (15 ml) at room temperature. After being stirred at room temperature for 4 days the mixture was diluted with dichloromethane (50 ml). The organic solution was washed with saturated aqueous K_2CO_3, dried over magnesium sulphate and concentrated in vacuo. Purification of the residue by flash chromatography [ether:hexane (2:1) as eluent] afforded 1.65 g (99% yield) of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-hydroxybutyronitrile **7** as a colourless oil. $[\alpha]_D^{25}$=−45.7 (*c* 1, $CHCl_3$); IR (neat) 3478, 2247, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, 333 K) δ 2.04 (brs, 1H), 3.69 (dd, 1H, *J*=12.3 Hz, *J*=3.9 Hz), 3.73 (s, 3H), 3.77 (dd, 1H, *J*=12.3 Hz, *J*=4.5 Hz), 4.00 (ddd, 1H, *J*=7.2 Hz, *J*=3.9 Hz, *J*=4.5 Hz), 4.36 (d, 1H, *J*=15.9 Hz), 4.49 (d, 1H, *J*=11.5 Hz), 4.57 (d, 1H, *J*=11.5 Hz), 4.83 (d, 1H, *J*=15.9 Hz), 4.93 (d, 1H, *J*=7.2 Hz), 7.15–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333

K) δ 49.7, 51.9, 53.3, 60.3, 73.1, 78.7, 115.9, 127.6, 127.7, 127.9, 128.1, 128.5, 128.6, 136.6, 137.2, 156.6; HRMS(FAB) calcd for $C_{20}H_{23}N_2O_4$ (MH^+): 355.1657. Found: 355.1651.

*4.8. (2*R*,3*S*)-3-Benzyloxy-2-(*N*-methoxycarbonyl-N-benzylamino)-4-chlorobutyronitrile **8***

Triphenylphosphine (1.78 g, 6.78 mmol) was added to a stirred solution of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-hydroxybutyronitrile **7** (1.6 g, 4.52 mmol) in carbon tetrachloride (50 ml). After being refluxed for 3 days the reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography [ether:hexane (1:1) as eluent] afforded 1.68 g (nearly quantitative yield) of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-chlorobutyronitrile **8** as a slightly yellowish oil. $[\alpha]_D^{25}=-72.1$ (*c* 1, $CHCl_3$); IR (neat) 2246, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 3.66 (dd, 1H, *J*=12.6 Hz, *J*=3.9 Hz), 3.74 (s, 3H), 3.75 (dd, 1H, *J*=12.6 Hz, *J*=3.6 Hz), 4.17–4.28 (m, 1H), 4.26 (d, 1H, *J*=15.9 Hz), 4.44 (d, 1H, *J*=11.7 Hz), 4.64 (d, 1H, *J*=11.7 Hz), 4.77 (d, 1H, *J*=7.8 Hz), 4.88 (d, 1H, *J*=15.9 Hz), 7.20–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 43.0, 50.9, 52.4, 53.4, 73.2, 76.9, 115.3, 127.8, 127.9, 128.1, 128.3, 128.6, 128.8, 136.4, 136.8, 156.1; HRMS(FAB) calcd for $C_{20}H_{21}N_2O_3Cl$ (M^+): 372.1240. Found: 372.1245.

*4.9. (2R,3S)-3-Benzyloxy-4-bromo-2-(N-methoxycarbonyl-N-benzylamino)butyronitrile **9***

Small portions of triphenylphosphine (1.83 g, 6.99 mmol) were added over a period of 30 min to a stirred solution of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-hydroxybutyronitrile **7** (1.65 g, 4.66 mmol) and carbon tetrabromide (1.85 g, 5.59 mmol) at 0°C. The cooling bath was then removed and the reaction was stirred for a further 1 h. After evaporation of the solvent, the crude product was purified by flash chromatography [EtOAc:hexane (1:3) as eluent] to give 1.79 g (92% yield) of (2*R*,3*S*)-3-benzyloxy-4-bromo-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitrile **9** as a slightly yellowish oil. $[\alpha]_D^{25}=-63.8$ (*c* 0.95, $CHCl_3$); IR (neat) 2251, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 3.53 (dd, 1H, *J*=11.7 Hz, *J*=3.9 Hz), 3.60 (dd, 1H, *J*=11.7 Hz, *J*=3.9 Hz), 3.74 (s, 3H), 4.12–4.21 (m, 1H), 4.26 (d, 1H, *J*=15.9 Hz), 4.41 (d, 1H, *J*=11.4 Hz), 4.64 (d, 1H, *J*=11.4 Hz), 4.75 (d, 1H, *J*=7.8 Hz), 4.88 (d, 1H, *J*=15.9 Hz), 7.22–7.48 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 31.3, 52.0, 52.4, 53.4, 73.1, 76.3, 115.3, 127.8, 128.0, 128.1, 128.3, 128.6, 128.8, 136.4, 136.8, 156.1; HRMS(FAB) calcd for $C_{20}H_{21}N_2O_3Br$ (M^+): 416.0735. Found: 416.0741.

*4.10. General procedure for base-induced cyclisation of 4-haloaminonitriles **8** and **9***

To a stirred solution of (2*R*,3*S*)-3-benzyloxy-2-(*N*-methoxycarbonyl-*N*-benzylamino)-4-chlorobutyronitrile **8** or (2*R*,3*S*)-3-benzyloxy-4-bromo-2-(*N*-methoxycarbonyl-*N*-benzylamino)butyronitrile **9** (3 mmol) in the selected dry solvent (35 ml) was added the desired base (3.6 mmol) and the mixture was stirred until the halocompound was consumed (monitored by TLC). The reaction mixture was purified by flash chromatography [EtOAc:hexane (1:2) as eluent].

*4.11. (1S,2R)-2-Benzyloxy-1-(N-methoxycarbonyl-N-benzylamino)cyclopropanecarbonitrile **10a***

M.p.=88°C; $[\alpha]_D^{25}=+40.6$ (*c* 0.85, $CHCl_3$); IR (Nujol) 2234, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 1.43 (dd, 1H, *J*=7.5 Hz, *J*=7.2 Hz), 1.67 (dd, 1H, *J*=7.5 Hz, *J*=5.1 Hz), 3.68 (dd, 1H, *J*=7.2 Hz, *J*=5.1 Hz), 3.83 (s, 3H), 4.41 (d, 1H, *J*=15.6 Hz), 4.58 (d, 1H, *J*=15.6 Hz), 4.68 (d, 1H, *J*=11.4 Hz), 4.95 (d, 1H, *J*=11.4 Hz), 7.10–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 23.8, 34.7, 51.5, 53.3,

64.1, 73.0, 117.5, 127.5, 127.9, 128.0, 128.1, 128.4, 128.7, 136.6, 156.5. Anal. calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.43; H, 6.02; N, 8.30.

4.12. (1R,2R)-2-Benzyloxy-1-(N-methoxycarbonyl-N-benzylamino)cyclopropanecarboxamide **11**

An aqueous solution of NaOH (1 M, 25 ml) was added to a stirred solution of (*1S*,2*R*)-2-benzyloxy-1-(*N*-methoxycarbonyl-*N*-benzylamino)cyclopropanecarbonitrile **10a** (1 g, 3 mmol) in ethanol (50 ml). An aqueous solution of H_2O_2 (30%) (25 ml) was then added dropwise. After being stirred for 30 min at room temperature the reaction mixture was concentrated in vacuo. Water (20 ml) was added and the solution was extracted with dichloromethene (3×30 ml). The combined organic layers were dried over magnesium sulphate and concentrated in vacuo. Purification of the residue by flash chromatography [EtOAc:hexane (3:1)] afforded 917 mg (87% yield) of (*1R*,2*R*)-2-benzyloxy-1-(*N*-methoxycarbonyl-*N*-benzylamino)cyclopropanecarboxamide **11** as a colourless oil. $[\alpha]_D^{25}=-8.5$ (*c* 0.97, $CHCl_3$); IR (neat) 3442, 3347, 2246, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 333 K) δ 1.31–1.42 (m, 1H), 1.56–1.64 (m, 1H), 3.76 (s, 3H), 3.80 (dd, 1H, *J*=6 Hz, *J*=6 Hz), 4.21–4.49 (m, 1H), 4.59–4.96 (m, 3H), 5.23 (brs, 1H), 6.19 (brs, 1H), 7.15–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333 K) δ 21.8, 47.6, 52.6, 53.0, 66.2, 73.4, 127.0, 127.2, 128.1, 128.1, 128.5, 128.6, 136.9, 139.1, 159.2, 172.0; HRMS(FAB) calcd. for $C_{20}H_{23}N_2O_4$ (MH^+): 355.1657. Found: 355.1665.

4.13. Single crystal X-ray diffraction analysis of **10a**

Crystallographic measurements were carried out at ambient temperature on a 4-circle Siemens P4 diffractometer using graphite monochromated molybdenum *K*α X-radiation (λ=0.71069 Å). One equivalent set of data was collected in the range $4°<2\theta<50°$ using $\omega/2\theta$ scans. No significant variation was observed in the intensity of the three standard reflections. Lorentz and polarisation corrections were applied to the data set. The structure was solved by direct methods using SIR92[21] and was refined by full-matrix least squares (based on F^2) using SHELXL-93,[22] which used all data for refinement. The weighting scheme was $\omega=[\sigma^2(F_o^2)+(0.0402P)^2+0.0327P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions.

$C_{20}H_{20}N_2O_3$, 0.56×0.24×0.16 mm, M_t=336.38, monoclinic, space group $P2_1$, *a*=9.739(5), *b*=9.588(5), *c*=10.482(5) Å, β=112.120(5), *V*=906.7(8) $Å^3$, *Z*=2, ρ_{calc}=1.232 g cm^{-3}, *F*(000)=356.0, μ=0.84 cm^{-1}. 1902 independent reflections measured at 293 K. Final *R*=0.0604, ωR=0.0821 for all data, *R*=0.0374, ωR=0.0729 for 1402 observed reflections with $F_o>2\sigma F_o$.

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