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Stereoselective synthesis of (1*R*,2*R*)-1-amino-2-hydroxycyclobutanecarboxylic acid—serine derivative—, from racemic or optically active 2-benzyloxycyclobutanone☆

Damien Hazelard, Antoine Fadel* and Christian Girard

Laboratoire de Synthèse Organique et Méthodologie, UMR 8182, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bât. 420, Université Paris-Sud, 91405 Orsay, France

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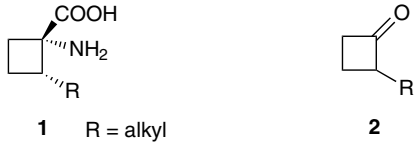
Abstract—An easy and efficient one-pot reaction from readily available 2-benzyloxycyclobutanone gave, by means of an asymmetric Strecker synthesis, a kinetic or thermodynamic nitrile with good selectivity. After separation, the major *trans*-amino nitrile underwent basic hydrolysis and hydrogenolysis, followed by acidic hydrolysis, to give optically active (1*R*,2*R*)-1-amino-2-hydroxycyclobutanecarboxylic acid, serine derivative. The absolute configuration has been established by X-ray analysis of the corresponding *cis*-amino nitrile.

1. Introduction

The incorporation of small-ring systems, in particular cyclobutane derivatives, in molecular building-blocks has recently gained much interest.[1] However, amino acids from cyclobutane series have been investigated very little.[2] Although, among these amino acids, very few have been detected in natural sources.[3] The biological activities of 1-aminocyclobutanecarboxylic acid derivatives have been well documented as *N*-methyl-D-aspartate (NMDA) receptor agonists or antagonists.[4] Despite the development of peptidomimetic and pseudopeptides with substituted 1-aminocycloalkanecarboxylic acids, which have been the focus of much research, the synthesis of substituted 1-aminocyclobutanecarboxylic acids has not received the same amount of attention.[5] Moreover, a few methods for the synthesis of 2-substituted 1-aminocyclobutanecarboxylic acids have been described in recent years.[6] Serine analogues that incorporate the cyclobutane skeleton (c_4Ser) have very recently been synthesised by a selective Michael-aldol reaction, but in racemic form. However, only a straightforward approach to the optically active form has been reported, without the preparation of desired enantiopure amino acid.[7]

Over the course of our work on the asymmetric synthesis of cyclic analogues of naturally occurring α-amino acids,[8] we have previously published the α-amino-2-alkylcyclobutanecarboxylic acids **1**[6b] prepared from readily available racemic α-substituted cyclobutanones **2**,[6b,9] by means of asymmetric Strecker reactions (Scheme 1).[10]



1 R = alkyl **2**

Scheme 1.

As part of our ongoing programme in this area, we herein report on the preparation of enantiopure 1-amino-2-hydroxycyclobutanecarboxylic acid **3** (serine analogue, c_4Ser)—in four steps—starting from the racemic or optically active cyclobutanones **4** and chiral benzylic amine as a chiral auxiliary, proceeding via amino nitriles **5** by an asymmetric Strecker reaction (Scheme 2).

2. Results and discussion

The optically active 2-benzyloxycyclobutanone (*S*)-**4** was prepared in 82% overall yield following our previously reported work, by protection of hydroxy acetal (*S*)-**6**

☆ Part of this study was previously reported at the Organic Chemistry Symposia at Villers-sur-Mer (GECO 44, September 2003) and at Palaiseau (SFC, September 2004), France.

* Corresponding author. Tel.: +33 1 6915 7252; fax: +33 1 6915 6278; e-mail: antfadel@icmo.u-psud.fr

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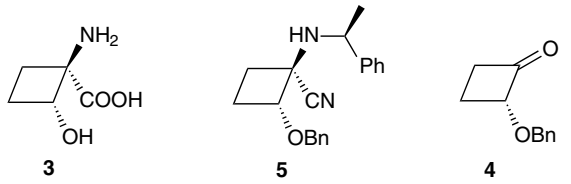


Scheme 2.

obtained with 99% ee by enzymatic transesterification and subsequent deacetalisation of benzyloxy acetal (*S*)-**7** under mild acidic conditions (Scheme 3).[11] Likewise, (*R*)-**4** was also obtained with 99% ee.

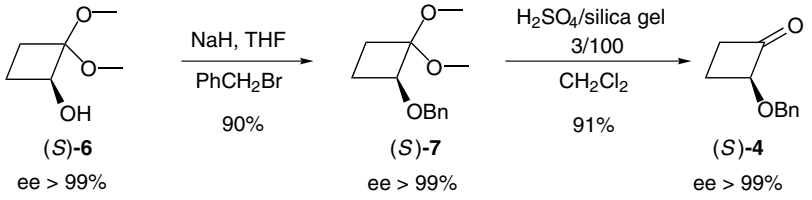
On the other hand, racemic cyclobutanone *rac*-**4** was obtained following the same sequence from readily available *rac*-**6**, in 82% overall yield. However, ketone *rac*-**4**, prepared directly from bis-(trimethylsiloxy)cyclobutene according to Frahm (BnOH, HCl gas), was only obtained in 38% yield.[12]

For the synthesis of α-amino nitriles **5A**–**D**, the racemic cyclobutanone *rac*-**4** was subjected to a one-pot procedure previously developed in our group[8,13] (Scheme 4). We anticipated that under acidic conditions, the ketone condensation with the chiral auxiliary (*S*)-1-phenylethylamine **8** would give the corresponding iminium mixtures **9** and **10**, which by in situ addition of sodium cyanide to the C=N bond would predominantly afford one diastereoisomer of the four possible α-amino nitrile isomers **5A**–**D**. By starting from optically active ketone (*R*)- or (*S*)-**4**, and changing the reaction conditions, we could make some interesting observations. The results of these investigations are summarised in Table 1.

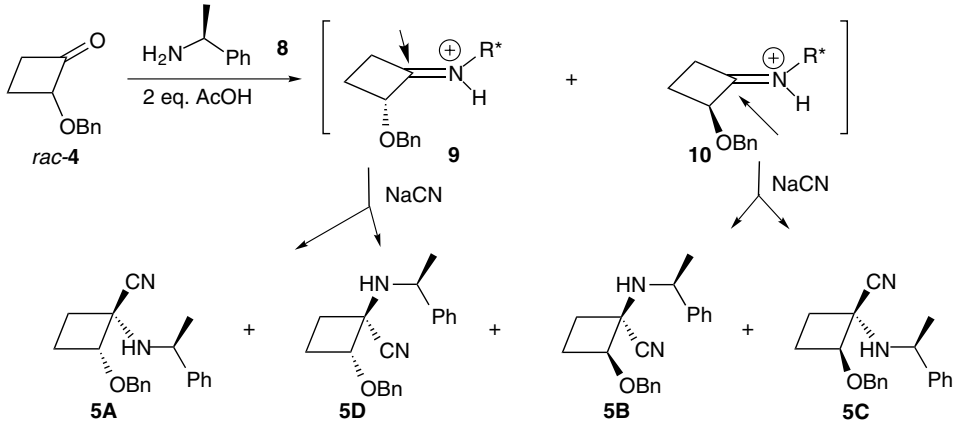
It can been seen from Table 1 that, from racemic **4** under kinetic or thermodynamic control, only two major isomers were isolated in each case with the same ratio (entries 1 and 2). However, from enantiopure (*R*)-**4** under kinetic control, a major isomer **5A** was obtained, and under thermodynamic conditions the **5D** was the major isomer (Table 1, entries 3 and 4). It is interesting to note that the major isomer **5A** or **5D** was accompanied with two minor isomers (in 6:6 or 2:10 ratio) derived from the other iminium intermediate **10**.

This minor formation was probably due to the partial racemisation, already known,[11] of starting benzyloxycyclobutanone (*R*)-**4** under Strecker conditions, and did not come from the supposed equilibrium between the two iminiums **9** and **10**, even though, this type of iminium equilibrium has previously been reported in similar cyclopentane or cyclohexane systems.[14] Likewise, from cyclobutanone (*S*)-**4**, under kinetic conditions (entry 5), the major amino nitrile **5B** was formed, accompanied by the thermodynamic product **5C** in a 73:19 ratio, respectively. In addition, these amino nitriles **5B** and **5C** were also accompanied with two minor isomers **5A** and **5D** derived from the partial racemisation of starting material (*S*)-**4**.

Thus, by changing the Strecker reaction control, each amino nitrile **5A**, **5B**, **5C** or **5D** can be separately obtained as a major product and isolated on silica gel as a pure compound.



Scheme 3.



Scheme 4. Synthesis of α-amino nitriles **5A**–**D**.

Table 1. Asymmetric Strecker reaction from either *rac*- or enantiopure 2-benzyloxycyclobutanone **4**

Entry	Ketone	Conditions[a]		Amino nitriles **5**				
		Time	Temperature (°C)	Yield (%)	**A**	**D**	**B**	**C**
1	*rac*-**4**	4 h	20	52	35	15	35	15
2	*rac*-**4**	4 days	50	54	10	40	10	40
3	(+)-(*R*)-**4**	4 h	20	55	**75**	13	6	6
4	(+)-(*R*)-**4**	4 days	50	54	28	**60**	2	10
5	(−)-(*S*)-**4**	5 h	20	55	5.8	2.5	**72.5**	19.2

[a] One-pot Strecker reactions of ketones **4** were conducted with 2 equiv of (*S*)-α-phenylethylamine, 2 equiv of NaCN in the presence of 2 equiv of AcOH in DMSO.

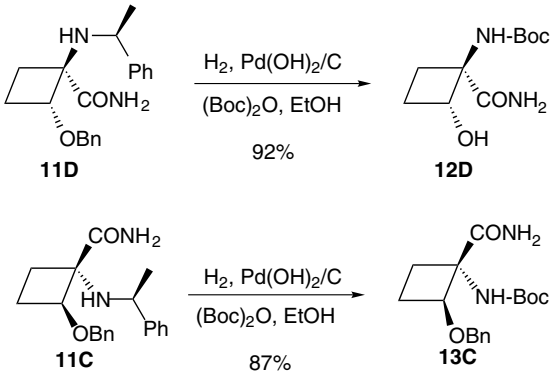
2.1. Basic hydrolysis

Subsequently, the α-amino nitrile mixtures **5A**–**D**, or each one, were subjected to hydrolysis in ethanolic potassium hydroxide solution in the presence of hydrogen peroxide (35 wt % in H_2O) at 0 °C, and then at rt for 2 days,[15] to afford the amides (1*S*,2*R*)-**11A**, (1*R*,2*R*)-**11D**, (1*R*,2*S*)-**11B** and (1*S*,2*S*)-**11C** in 60–75% yields, after easy chromatographic separation (Scheme 5).

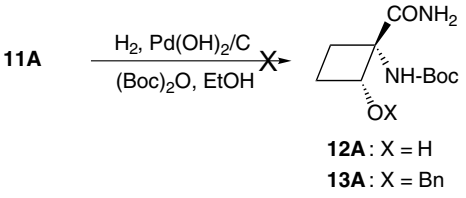
Treatment of nitrile **5A** with basic hydrogen peroxide (H_2O_2, aq NaOH) in the presence of transfer-phase catalyst Bu_4NHSO_4 in CH_2Cl_2,[16] gave only the amide **11A** in 43% yield. However, acidic hydrolysis with concentrated H_2SO_4 in CH_2Cl_2 at 0 °C or rt,[8a] led to a degradation of starting nitrile **5A**.

Hydrogenolysis of pure α-aminocarboxamide **11D** in the presence of a catalytic amount of 20% $Pd(OH)_2$ on activated carbon (w/w, 30%) in EtOH or AcOH under hydrogen (1 atm, 10 h) did not give the expected free amine, but a degradation product. Nevertheless, the treatment of amide **11D** under the same conditions and in the presence of di-*tert*-butylcarbonate [$(Boc)_2O$],[17] furnished simultaneously, by a double benzylic cleavage and by in situ protection of free amine, the desired amine **12D** in excellent yield. Moreover, amide **11C** provided under the same conditions in the presence of Boc_2O, amine **13C** without deprotection of benzyl group, on oxygen atom, in 87% yield (Scheme 6).

Conversely, hydrogenolysis of *cis*-**11A** or *cis*-**11B** under the same conditions as noted above, showed in the ^1H NMR spectra of the crude products, significant signals similar to those of amide **12D**. Unfortunately, purification of the crude residues on silica gel did not furnish the desired **12A** or **13A**, but gave a complete degradation of the products (Scheme 7).



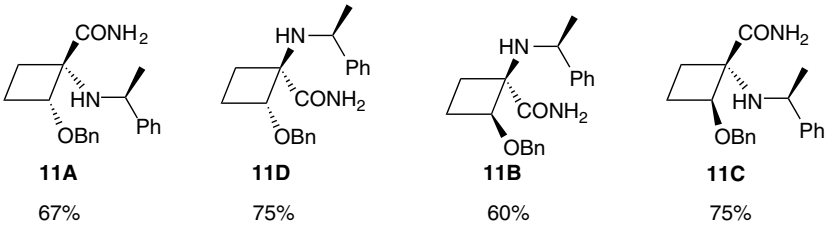
Scheme 6. Catalytic hydrogenolysis of benzyl groups.



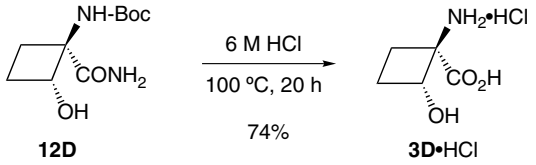
Scheme 7.

Amino amide *trans*-**12D** was finally hydrolysed with 6 M HCl at reflux to furnish the target α-amino-2-hydroxycyclobutanecarboxylic acid, HCl salt **3D**·HCl in 74% yield, and with specific rotation given for the first time $[\alpha]_D = -8.8$ (*c* 0.30, H_2O) (Scheme 8). Its spectral data were identical with those reported in the literature,[7a] while the specific rotation for the optically active amino acid had not been previously reported.[7b]

In contrast, the hydrolysis of amino amide **13C** under the same conditions did not give the expected amino acid, but led to degradation products.



Scheme 5. Synthesis of amides **11** from corresponding nitriles **5**, with H_2O_2, KOH in EtOH/H_2O at rt, for 2 days.



Scheme 8.

2.2. Absolute configuration: X-ray crystallography

To determine the absolute configuration of all these molecules, we found that the kinetic amino nitrile **5A** gave suitable crystals. The X-ray crystallographic analysis showed,[18] as depicted in Figure 1, a (1*R*,2*R*,1′*S*)-absolute configuration of **5A**. The (*R*)-configuration at the C_2 centre was also in accordance with the previously reported X-ray crystallographic analysis of the starting 2-benzyloxycyclobutanone (*R*)-(+)-**14**.[11] Consequently, nucleophilic attack of the cyanide anion, under kinetic conditions, occurred *anti* to the benzyloxy group with a like approach to iminium **9**. While, under thermodynamic control the *syn* attack with an unlike approach occurred to give the amino nitrile (1*S*,2*R*,1′*S*)-**5D**.

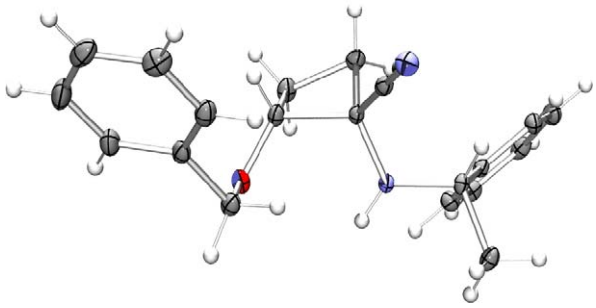
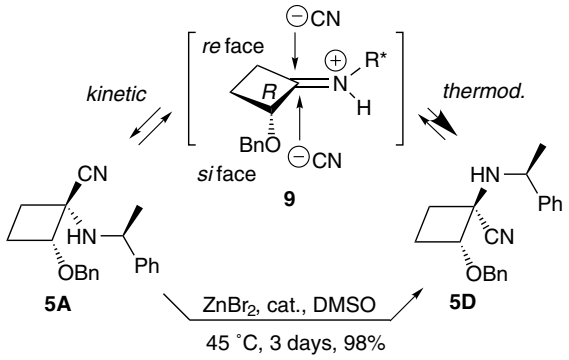


Figure 1. ORTEP plot of X-ray crystal structure of (1*R*,2*R*,1′*S*)-**5A**.

Moreover, it was observed in the X-ray structure of **5A** that the benzyloxy group at C_2 occupies an equatorial position, in accordance with the very recently reported conformational study.[19] The *syn* **5A** adopts only one ring-puckering conformation characterised by a positive pucker angle $\theta = +32.4°$. The cyclobutane-ring pucker angle θ, defined as the acute angle between the planes C_1–C_2–C_4 and C_2–C_3–C_4. The *syn* compound are stabilised by an intramolecular hydrogen bond between the NH of amine and oxygen of the ether group (NH···O = 2.52 Å).

On the other hand, the equilibrium between the kinetic and thermodynamic compound was confirmed by treating the pure kinetic **5A** with a catalytic amount of $ZnBr_2$ in DMSO at 45 °C, which exclusively gave **5D** within 3 days. The same equilibrium could occur between amino nitrile **5B** and **5C** (Scheme 9).

By analogy, the absolute configuration of the kinetic amino nitrile **5B**, derived from benzyloxycyclobutanone (*S*)-(−)-**4**, should be (1*S*,2*S*,1′*S*)-**5B**, and for the thermodynamic compound must be (1*R*,2*S*,1′*S*)-**5C**. Consequently, taking into account the priority order, the absolute configuration of amides were (1*S*,2*R*,1′*S*) for **11A**, (1*R*,2*S*,1′*S*) for **11B**, (1*S*,2*S*,1′*S*) for **11C** and (1*R*,2*R*,1′*S*) for **11D**. Furthermore, it should be (1*R*,2*R*) for **12D**, (1*S*,2*S*) for **13C** and (1*R*,2*R*) for **3D**.



Scheme 9. Kinetic–thermodynamic equilibrium.

Moreover, it is interesting to note that a meticulous study of the NMR spectra of proton H^2 located at C_2 centre, in amino nitriles **5A**–**D** furnished us with this conclusion: the H^2 proton is shielded when it is *trans* to the nitrile group, with $\delta = 3.76$ ppm for thermodynamic amino nitriles **5C** and **5D**. The H^2 proton is deshielded when the nitrile group is *cis*, with $\delta = 4.20$–4.25 ppm for kinetic nitriles **5A** and **5B**. This characteristic behaviour was also valid for the amides **11A**–**D**. Thus, H^2 protons *cis* to the amide groups are deshielded for **11A** and **11B** ($\delta = 4.20$–4.25 ppm) compared to the shielded H^2 protons for **11C** and **11D** ($\delta = 3.77$–3.85 ppm (Scheme 10).

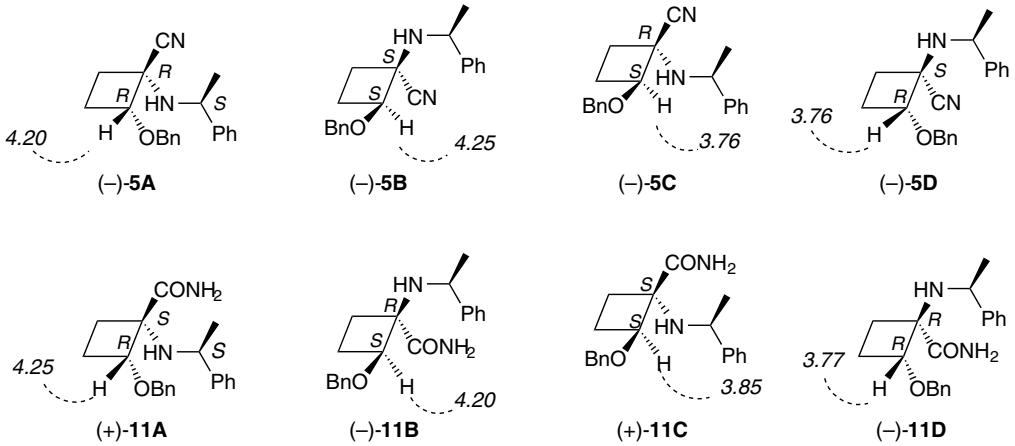
3. Conclusion

We have developed an easy and efficient four step synthesis of enantiopure (1*R*,2*R*)-(−)-1-amino-2-hydroxycyclobutanecarboxylic acid **3D**, starting from readily available racemic or optically active 2-benzyloxycyclobutanone.[11] We have demonstrated that these ketones undergo an asymmetric Strecker reaction to selectively give one major kinetic or thermodynamic amino nitrile **5A**, **5B** or **5C**, **5D**. Subsequent basic hydrolysis of each nitrile furnished the corresponding amide **11A**–**D**, in good yields. The hydrogenolysis of **11D** required treatment in the presence of Boc_2O to give the *N*-Boc derivative **12D**. Finally, acidic hydrolysis provided, for the first time, the optically active amino acid **3D** (c_4Ser derivative) in good yield.

4. Experimental

4.1. General

The general experimental procedures and the analytical instruments employed have been described in detail in a previous paper.[8b] Enantiomeric excesses were also performed on a GC (Fisons A130) chiral column Cydex B (SGE) (25 m, 180 °C, 1 bar).



Scheme 10. δ (*in italic*): chemical shifts in parts per million of H^2 protons in *cis* or *trans* to nitrile or amide functions.

4.1.1. (*R*)- and (*S*)-2-Benzyloxycyclobutanone 4. (*R*)- and (*S*)-2-Benzyloxycyclobutanone **4** were prepared according to our reported method.[11]

4.1.2. *rac*-2-Benzyloxycyclobutanone 4. *rac*-2-Benzyloxycyclobutanone **4** was prepared from the readily available *rac*-**6**[11] by protection (91% yield) with benzyl bromide to form *rac*-**7** and deacetalisation (91% yield) following the same sequence applied to prepare optically active benzyloxycyclobutanone.[11]

4.2. General procedure A

Preparation of the amino nitriles was carried out according to our reported methods.[6b,8a]

To a solution of *rac*-benzyloxycyclobutanone **4** (1.500 g, 8.52 mmol) in 20 mL of DMSO, were added successively AcOH (1.0 mL, 2 equiv), (*S*)-α-methylbenzylamine **8** (2.20 mL, 17 mmol) and 640 mg (13.07 mmol) of NaCN. The mixture was stirred at room temperature for 4–5 h (kinetic conditions) [or stirred and heated at 50 °C for 4–5 days (thermodynamic conditions)]. It was then concentrated under vacuum, diluted with EtOAc (30 mL), H_2O (5 mL) and basified to pH 9 with a saturated solution of $NaHCO_3$. The mixture was extracted with EtOAc (3×150 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated under vacuum to give 3.20 g of the crude amino nitriles as a mixture of four diastereoisomers. Purification by flash chromatography (twice, FC) on silica gel (eluent: EtOAc/petrol ether: 10/90), afforded (under thermodynamic conditions): 130 mg (5% yield) of **5A**, 130 mg (5%) of **5B**, 520 mg (20%) of **5C** and 520 mg (20%) of **5D** and 210 mg (8%) as a mixture.

4.2.1. (1*R*,2*R*,1′*S*)-2-Benzyloxy-1-[(1′-phenylethyl)amino]-cyclobutanecarbonitrile, 5A. Compound **5A** can also be prepared under kinetic conditions, from optically active cyclobutanone (*R*)-**4**, as major product (41% yield, see Table 1). Crystallisation from ether/pentane furnished colourless crystals. The X-ray analysis of these crystals showed a (1*R*,2*R*,1′*S*) configuration.[18] $[\alpha]_D = -65.8$ (*c* 1, $CHCl_3$); mp 66.7 °C (from ether/pentane); $R_f = 0.46$ (Et_2O/pentane: 25/75); IR (neat) *v*: 3340, 3063, 2218 (CN), 1453, 1132, 1099; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.20–1.60 (m, 2H, $2H_{cycle}$), 1.63 (br s, NH), 1.38 (d, $J = 6.7$ Hz, CH_3), 1.97–2.16 (m, 1H–C_4), 2.17–2.38 (m, 1H–C_4), 4.02 (q, $J = 6.7$ Hz, 1H–$C_{1'}$), 4.21 (dd, $J = 8.5$, 8.2 Hz, 1H–C_2), 4.63 (like AB system, $J = 12.2$ Hz, $\Delta\nu_{AB} = 29.3$ Hz, $2H_{benzyl}$), 7.10–7.65 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 24.8 (C_3), 25.2 (CH_3), 27.3 (C_4), 55.2 ($C_{1'}$), 56.9 (C_1), 72.5 ($C_{2\,benzyl}$), 76.4 (C_2), 120.8 (CN), [12 arom. C: 126.9 (2C), 127.2 (1C), 128.2 (2C), 128.3 (3C), 128.7 (2C), 137.0 (s), 145.6 (s)]; ES^+ MS *m*/*z*: calcd mass for $C_{20}H_{22}N_2O$, $[M+Na]^+$: 329.2. Found: 329.2. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.24; H, 7.45; N, 9.13.

4.2.1.1. X-ray structure analysis of (–)-5A.[18] Crystal data for (–)-(1*R*,2*R*,1′*S*)-**5A**: Colourless crystal of $0.30 \times 0.12 \times 0.12$ mm. $C_{20}H_{22}N_2O$, $M = 306.41$: orthorhombic system, space group $p2_1$, 2_1, 2_1 (No. 19), $Z = 4$, with $a = 5.4044$ (2), $b = 9.1016$ (4), $c = 33.7361$ (14) Å, $\alpha = \beta = \gamma = 90°$, $V = 1659.43$ (12) $Å^3$, $d = 1.226$ g cm^{-3}, $F(0\,0\,0) = 656$, $\lambda = 0.71073$ Å (Mo-Kα), $\mu = 0.076$ mm^{-1}; 4605 reflections measured ($-7 \leqslant h \leqslant 7$, $-10 \leqslant k \leqslant 12$, $-41 \leqslant l \leqslant 46$) on a Bruker X8 diffractometer. The structure was solved and refined with SHELXL-97.[20] Hydrogen atom riding, refinement converged to $R(gt) = 0.0359$ for the 4460 reflections having $I = 2\sigma(I)$, and $wR(gt) = 0.0969$, Goodness of Fit $S = 1.065$, residual electron density: −0.373 and 0.477 e $Å^3$.

4.2.2. (1*S*,2*S*,1′*S*)-Benzyloxy-1-[(1′-phenylethyl)amino]cyclobutanecarbonitrile, 5B. Compound **5B** can also be prepared under kinetic conditions, from optically active cyclobutanone (*S*)-**4**, as a colourless oil, major product (40% yield, see Table 1). $[\alpha]_D = -78.5$ (*c* 1, $CHCl_3$); $R_f = 0.42$ (Et_2O/pentane: 25/75); IR (neat) *v*: 3326, 3062, 2218 (CN), 1494, 1454; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.38 (d, $J = 6.7$ Hz, CH_3), 1.92–2.18 (m, 2H, 1HN and 1H–C_3), 2.10–2.50 (m, $3H_{cycle}$), 4.06 (q, $J = 6.7$ Hz, 1H–$C_{1'}$), 4.27 (dd, $J = 8.3$, 8.0 Hz, 1H–C_2), 4.56 (m, sharp, $2H_{benzyl}$), 7.20–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 24.6 (CH_3), 27.2 (C_3 and C_4), 55.2 ($C_{1'}$), 55.6 (s, C_1), 72.3 ($CH_{2\,benzyl}$), 76.6 (d, C_2), 120.4 (C≡N), [12 arom. C: 126.7 (2C), 127.4 (1C), 128.1 (2C), 128.2

(1C), 128.4 (2C), 128.6 (2C), 136.8 (s), 144.9 (s)]; ES^+ MS *m/z*: calcd mass for $C_{20}H_{22}N_2O$ + (Na–HCN): 302.2. Found: 302.1. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.51; H, 7.02; N, 9.13.

4.2.3. (1*R*,2*S*,1′*S*)-2-Benzyloxy-1-[(1′-phenylethyl)amino]-cyclobutanecarbonitrile, 5C. $[\alpha]_D = -101$ (*c* 1, $CHCl_3$); $R_f = 0.6$ (EtOAc/petrol ether: 3/7); IR (neat) *ν*: 3315, 3062, 2217 (CN), 1494, 1454, 1122; ^1H NMR ($CDCl_3$, 250 MHz) *δ*: 1.01 (ddd, $J = 9.7$, 9.1, 11.5 Hz, 1H–C_3), 1.20 (d, $J = 6.7$ Hz, CH_3), 1.30–1.52 (m, 2H, $1H_{cycle}$ and NH), 1.80–2.10 (m, $2H_{cycle}$), 3.77 (dd, $J = 8.0$, 8.7 Hz, 1H–C_2), 3.90 (q, $J = 6.7$ Hz, 1H–$C_{1'}$), 4.45 (d, AB syst., $J = 12.0$ Hz, $1H_{benzyl}$), 4.70 (d, AB syst., $J = 12.0$ Hz, $1H_{benzyl}$), 7.10–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) *δ*: 24.1 (CH_3), 24.7 (C_3), 26.4 (C_4), 55.6 ($C_{1'}$), 63.2 (C_1), 72.1 ($CH_{2\,benzyl}$), 78.8 (C_2), 119.7 (C≡N), [12 arom.: C 127.2 (2C), 127.4 (1C), 128.2 (3C), 128.4 (2C), 128.6 (2C), 137.6 (s), 144.2 (s)]; MS^+ ES *m/z*: 329.2 $[M+Na]^+$; HR ES^+ MS *m/z*: calcd mass for $C_{20}H_{22}N_2O$-Na, $[M+Na]^+$: 329.1630. Found: 329.1622.

4.2.4. (1*S*,2*R*,1′*S*)-Benzyloxy-1-[(1′-phenylethyl)amino]cyclobutanecarbonitrile, 5D. Compound **5D** can also be prepared under thermodynamic conditions, from optically active cyclobutanone (*R*)-**4**, as a colourless oil, major product (30% yield, see Table 1). $[\alpha]_D = -63.1$ (*c* 0.77, $CHCl_3$); $R_f = 0.55$ (EtOAc/petrol ether: 30/70); IR (neat) *ν*: 3320, 3063, 2223 (CN), 1495, 1454, 1127; ^1H NMR ($CDCl_3$, 250 MHz) *δ*: 1.32 (d, $J = 6.7$ Hz, 3H, CH_3), 1.50 (br s, NH), 1.67–1.84 (m, 1H–C_3), 1.92–2.25 (m, $2H_{cycle}$), 2.36 (ddd, $J = 2.2$, 10.0, 11.0 Hz, 1H–C_4), 3.69 (dd, $J = 8.0$, 8.3 Hz, 1H–C_2), 4.00 (q, $J = 6.7$ Hz, 1H–$C_{1'}$), 4.24 (m, sharp, AB syst., $2H_{benzyl}$), 7.10–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) *δ*: 24.2 (CH_3), 24.6 (C_3), 27.4 (C_4), 55.7 ($C_{1'}$), 62.4 (C_1), 71.6 ($CH_{2\,benzyl}$), 78.5 (C_2), 119.7 (C≡N), [12 arom. C: 126.8 (2C), 127.3 (1C), 127.9 (1C), 128.0 (2C), 128.35 (2C), 128.4 (2C), 137.5 (s), 144.8 (s)]; HR ES^+ MS *m/z*: calcd mass for $C_{20}H_{22}N_2ONa$, $[M+Na]^+$: 329.1630. Found: 329.1631.

4.3. Amide formation from nitrile: general procedure B

To a solution of amino nitrile **5A**–**D** (612 mg, 2 mmol) in EtOH (20 mL), were added (under argon) at 0 °C successively KOH (1.57 g, 28 mmol) and an excess amount of H_2O_2 (150 mmol, 35 wt % in water). The mixture was stirred at 0 °C for 8 h, then at room temperature for 1–2 days. The complete elimination of excess of peroxide was performed by the addition of an aqueous saturated solution of $Na_2S_2O_3$ (KI test). The resulting mixture was concentrated, diluted with 5 mL of H_2O, then extracted with EtOAc (3 × 80 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum, to give after FC (silica gel, 20 g, eluent: MeOH/CH_2Cl_2: 1/99 to 4/96), the desired amide **11A**–**D**.

4.3.1. (1*S*,2*R*,1′*S*)-2-Benzyloxy-1-[(1′-phenylethyl)amino]-cyclobutanecarboxamide, 11A. According to procedure B: From 460 mg (1.5 mmol) of nitrile **5A**, 1.12 g (20 mmol) of KOH and 10.6 mL of H_2O_2 (35 wt % in H_2O) and 20 mL of EtOH. After stirring at rt for 3 days and FC, we isolated 325 mg (67%) of pure amide **11A**, as a colourless oil. $[\alpha]_D = +62$ (*c* 1, $CHCl_3$); $R_f = 0.49$ (MeOH/CH_2Cl_2: 10/90); IR (neat) *ν*: 3436, 3325, 3062, 1676 (CON), 1453, 1126; ^1H NMR ($CDCl_3$, 250 MHz) *δ*: 1.29 (d, $J = 6.7$ Hz, 3H, CH_3), 1.80–2.00 (m, 2H–C_3), 2.05–2.28 (m, 1H–C_4), 2.28–2.50 (m, 1H–C_4), 3.90 (br s, NH), 4.00 (q, $J = 6.7$ Hz, 1H–C_1), 4.22 (dd, $J = 7.2$, 7.0 Hz, 1H–C_2), 4.45 (d, AB syst. $J = 11.6$ Hz, $1H_{benzyl}$), 4.55 (d, AB syst. $J = 11.6$ Hz, $1H_{benzyl}$), 6.90 (br d, $J = 5.3$ Hz, $1H_{amide}$), 7.20–7.53 (m, 10H), 7.64 (br d, $J = 5.3$ Hz, $1H_{amide}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) *δ*: 15.8 (C_3), 24.1 (CH_3), 25.1 (C_4), 53.8 ($C_{1'}$), 65.9 (C_1), 71.8 (OCH_2), 77.00 (C_2), [12 arom. C: 126.0 (2C), 127.0 (1C), 127.7 (3C), 128.2 (2C), 128.4 (2C), 137.1 (s), 146.0 (s)], 179.7 (CON); HRMS (EI) *m/z*: calcd mass for $C_{20}H_{24}N_2O_2$: 324.1838. Found: 324.1832.

4.3.2. (1*R*,2*S*,1′*S*)-2-Benzyloxy-1-[(1′-phenylethyl)amino]-cyclobutanecarboxamide, 11B. According to procedure B: From 90 mg (0.3 mmol) of nitrile **5B**, 230 mg of KOH (4.1 mmol), 2.2 mL (25 mmol) of H_2O_2 (35 wt % in water) and 4 mL of EtOH. After stirring for 22 h and FC, we isolated 60 mg (61%) of pure amide **11B** as a colourless oil. $[\alpha]_D = -67$ (*c* 1, $CHCl_3$); $R_f = 0.37$ (MeOH/CH_2Cl_2: 5/95); IR (neat) *ν*: 3442, 3329, 3063, 1676 (CON), 1454, 1125; ^1H NMR ($CDCl_3$, 250 MHz) *δ*: 1.47 (d, $J = 6.6$ Hz, 3H), 1.93–2.18 (m, $2H_{cycle}$), 2.18–2.50 (m, 3H, $2H_{cycle}$ and NH), 3.89 (q, $J = 6.6$ Hz, 1H–$C_{1'}$), 4.21 (dd, $J = 6.6$, 6.7 Hz, 1H–C_2), 4.43 (d, AB syst. $J = 11.5$ Hz, $1H_{benzyl}$), 4.54 (d, AB syst. $J = 11.5$ Hz, $1H_{benzyl}$), 5.30 (br d, $J = 4.0$ Hz, $1H_{amide}$), 6.80 (br d, $J = 4.0$ Hz, $1H_{amide}$), 7.15–7.46 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) *δ*: 18.3 (C_3), 25.5 (C_4), 26.0 (CH_3), 53.3 ($C_{1'}$), 67.1 (C_1), 72.1 (OCH_2), 77.1 (C_2), [12 arom. C: 126.4 (2C), 126.9 (1C), 127.9 (3C), 128.5 (2C), 128.6 (2C), 137.4 (s), 146.3 (s)], 178.3 (CON); HR ES^+ MS *m/z*: calcd mass for $C_{20}H_{24}N_2O_2Na$, $[M+Na]^+$: 347.1735. Found: 347.1736.

4.3.3. (1*S*,2*S*,1′*S*)-2-Benzyloxy-1-[(1′-phenylethyl)amino]-cyclobutanecarboxamide, 11C. According to procedure B: From 786 mg (2.57 mmol) of nitrile **5C**, 1.0 g (17 mmol) of KOH, 9 mL (102 mmol) of H_2O_2 (35 wt % in water) and 25 mL of EtOH. After stirring for 2 days and FC, we isolated 625 mg (75%) of pure amide **11C**. $[\alpha]_D = +13.9$ (*c* 1.1, $CHCl_3$); mp 38.4 °C; $t_R = 206.59$ min (Cydex B, 180 °C, 1 bar); $R_f = 0.36$ (EtOAc/petrol ether: 1/1); IR (neat) *ν*: 3454, 3318, 3062, 1682 (CON), 1454, 1122; ^1H NMR ($CDCl_3$, 250 MHz) *δ*: 1.15–1.40 (m, 1H–C_3), 1.33 (d, $J = 6.7$ Hz, 3H), 1.85–2.10 (m, $2H_{cycle}$), 2.20 (ddd, $J = 3.5$, 8.3, 8.6 Hz, 1H–C_3), 2.40 (br s, NH); 3.83 (dd, $J = 8.5$, 8.3 Hz, 1H–C_2), 3.86 (q, $J = 6.7$ Hz, 1H–C_1), 4.47 (like AB syst. $J_{AB} = 12.0$ Hz, $2H_{benzyl}$), 5.86 (br s, $1H_{amide}$), 7.15–7.48 (m, 11H, $10H_{arom}$ and $1H_{amide}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) *δ*: 22.4 (C_3), 24.0 (CH_3), 24.1 (C_4), 54.8 ($C_{1'}$), 70.2 (C_1), 71.3 (OCH_2), 80.5 (C_2), [12 arom. C: 126.5 (2C), 127.2 (1C), 127.6 (3C), 128.3 (2C), 128.5 (2C), 137.7 (s), 146.1 (s)], 175.6 (CON); HRMS (EI) *m/z*: calcd mass for $C_{20}H_{24}N_2O_2$: 324.1838. Found: 324.1829.

4.3.4. (1*R*,2*R*,1′*S*)-2-Benzyloxy-1-[(1′-phenylethyl)amino]-cyclobutanecarboxamide, 11D. According to procedure

B: From 786 mg (2.57 mmol) of nitrile **5D**, 1.0 g (17 mmol) of KOH, 9 mL (102 mmol) of H_2O_2 (35 wt % in H_2O) and 25 mL of EtOH. After stirring for 2 days and FC, we isolated 625 mg (75%) of amide **11D**. $[\alpha]_D = -26.6$ (*c* 0.9, $CHCl_3$); mp 70.1 °C; $R_f = 0.28$ (EtOAc/petrol ether: 1/1); IR (neat) *v*: 3387, 3317, 3062, 1674 (CON), 1454, 1122; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.35 (d, $J = 6.7$ Hz, 3H), 1.48–1.67 (m, $1H_{cycle}$), 1.75–2.40 (m, $2H_{cycle}$), 2.38 (ddd, $J = 9.4$, 10.2, 1.0 Hz, 1H–C_4), 2.84 (br s, 1H–N), 3.76 (q, $J = 6.7$ Hz, 1H–$C_{1'}$), 3.79 (m, 1H–C_2), 4.13 (like AB syst. $J = 11.8$ Hz, $2H_{benzyl}$), 5.37 (br s, $1H_{amide}$), 7.11–7.45 (m, 11H, $10H_{arom}$ and $1H_{amide}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 24.1 (C_3), 24.9 (C_4), 25.6 (CH_3), 54.8 ($C_{1'}$), 69.4 (C_1), 70.9 (OCH_2), 79.2 (C_2), [12 arom. C: 126.7 (3C), 127.5 (3C), 128.1 (4C), 137.4 (s), 145.8 (s)], 176.3 (CON); HRMS (EI) *m*/*z*: calcd mass for $C_{20}H_{24}N_2O_2$: 324.1838. Found: 324.1840. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.99; H, 7.45; N, 8.78.

4.4. Hydrogenolysis procedure

4.4.1. (1*R*,2*R*)-1-(*N*-*tert*-Butyloxycarbonyl)amino-2-hydroxycyclobutanecarboxamide, 12D. To a solution of amino amide **11D** (324 mg, 9 mmol) in 15 mL of EtOH, were added Boc_2O (872 mg, 4 mmol) and 20% $Pd(OH)_2/C$ (Pearlman's catalyst, 200 mg; 60% w/w). The flask was connected to a hydrogenation apparatus equipped with a graduated burette containing water that allowed the uptake of hydrogen to be monitored. TLC control showed that under 1 atm for 27 h, the reaction was complete, then degassed under a stream of argon, filtered through paper and the collected solid washed with EtOH (2×10 mL). The combined filtrate and washings were concentrated and purified by FC on silica gel (20 g), eluent (MeOH/CH_2Cl_2: 5/95) to give 215 mg (92%) of hydroxyamide **12D** as a solid. $[\alpha]_D = -35.8$ (*c* 0.5, MeOH); mp 108.2 °C; $R_f = 0.22$ (MeOH/CH_2Cl_2: 10/90); IR (KBr) *v*: 3474, 3427, 3327, 1715 (NCOO), 1685 (CON), 1634, 1384; ^1H NMR (CD_3OD, 250 MHz) δ: 1.37 (s, 9H), 1.30–1.60 (m, 1H–C_3), 1.75–2.00 (m, 1H–C_3), 2.00–2.20 (m, 1H–C_4), 2.38–2.55 (ddd, $J = 10.2$, 11.2, 1.5 Hz, 1H–C_4), 4.17 (dd, $J = 8.2$, 8.5 Hz, 1H–C_2); ^{13}C NMR (CD_3OD, 62.9 MHz) δ: 25.1 (C_3), 27.3 (C_4), 28.7 ($3CH_3$), 66.7 ($C_{1'}$), 73.6 (C_2), 80.7 (O-$C(CH_3)_3$), 157.0 (COO), 177.1 (CON); HR ES^+ MS *m*/*z*: calcd mass for $C_{10}H_{18}N_2O_4Na$, $[M+Na]^+$: 253.1164. Found: 253.1163.

4.4.2. (1*S*,2*S*)-1-(*N*-*tert*-Butyloxycarbonyl)amino-2-benzyloxy-cyclobutanecarboxamide, 13C. According to the general procedure of hydrogenolysis used for **12D**: From 208 mg (0.64 mmol) of amide **11C**, 430 mg (1.97 mmol) of $(Boc)_2O$, 90 mg of 20% Pd(OH)/C and 15 mL of EtOH. After stirring under H_2 (1 atm) for 51 h and FC, we isolated 155 mg (92%) of amide **13C** as a solid. $[\alpha]_D = +11.6$ (*c* 0.74, $CHCl_3$); mp 100.2 °C; $R_f = 0.64$ (MeOH/CH_2Cl_2: 10/90); IR (neat) *v*: 3481, 3301 (NH), 2978, 1699 (NCOO and CON), 1367, 1168; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.43 (s, 9H), 1.83–2.49 (m, $4H_{cycle}$), 4.50–4.67 (m, $2H_{benzyl}$ and 1H–C_2), 5.60 (br s, $1H_{carbamate}$), 6.08 (br s, $1H_{amide}$), 7.25–7.41 (m, 6H $5H_{Ph}$ and $1H_{amide}$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 24.2 (C_3), 24.8 (C_4), 28.2 ($3CH_3$), 64.4 (C_1), 71.3 ($CH_{2\,benzyl}$), 78.0 (C_2), 79.8 ($C(CH_3)_3$), [6 arom. C: 127.6, 127.7 (2C), 128.2 (2C), 137.5], 154.7 (COO), 174.1 ($CONH_2$); HRMS (EI) *m*/*z*: calcd mass for $C_{17}H_{24}N_2O_4$: 320.1736. Found: 320.1730.

4.5. (1*R*,2*R*)-1-Amino-2-hydroxycyclobutanecarboxylic acid·hydrochloride, 3D·HCl

A solution of 6 M HCl (2 mL) and 23 mg (0.100 mmol) of amide **12D** was heated at reflux for 18 h. After cooling to room temperature, 5 mL of H_2O was added and the resulting solution washed with ether (4 mL). The aqueous solution was concentrated to dryness, then the residue was washed with EtOAc (1 mL) and with ether (1 mL), to furnish 17 mg (100%) of the (1*R*,2*R*)-amino acid **3D**·HCl as a light yellow solid.

$[\alpha]_D = -8.8$ (*c* 0.30, H_2O); mp 188.5 °C decomp.; ^1H NMR (D_2O, 250 MHz) δ: 1.74–2.63 (m, $4H_{cycle}$), 3.99–4.21 (m, 1H–C_2); ^{13}C NMR (D_2O, 62.9 MHz) δ: 26.1 (t, C_4), 28.1 (t, C_3), 57.9 (s, C_1), 60.3 (d, C_2), 171.9 (COOH). The spectral data are identical with those reported for the racemic product.[7]

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