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TETRAHEDRON: *ASYMMETRY*

A straightforward synthesis of both enantiomers of *allo*-norcoronamic acids and *allo*-coronamic acids, by asymmetric Strecker reaction from alkylcyclopropanone acetals †

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Abstract

Methylcyclopropanone hemiacetal (2*S*)-**3a** underwent the asymmetric Strecker reaction induced by a chiral amine to provide a useful synthesis of enantiomerically pure (1*R*,2*S*)-(+)-*allo*-norcoronamic acid **1** in good yield and high enantiomeric excess. From racemic alkyl hemiacetal (±)-**3**, the same methodology also constituted a useful way to prepare both (+)-**1** and (−)-**1** and (+)-*allo*-coronamic acid **2** and its antipode (−)-**2** with good yield and high enantiomeric excess.

The preparation of derivatives of 1-aminocyclopropanecarboxylic acid (ACC) has been the subject of numerous synthetic efforts in recent years. This interest stems from their diverse documented biological activities,[1] and potential use in conformationally restricted peptides.[2] The *allo*-norcoronamic acid **1** is a substrate and the strongest known competitive inhibitor of the ethylene-forming enzyme (EFE) in mung bean hypocotyls.[3a] Another cyclopropylamino acid '*allo*-coronamic acid **2**' is converted into 1-butene by plant tissues and promises the control of enzymatic processes for plant growth and fruit ripening.[3] Most of the reported pure enantiomers of cyclopropaneamino acids especially for *allo*-norcoronamic acids **1**[4] and *allo*-coronamic acids **2**[5] have been produced by resolution of racemic mixtures, or by asymmetric synthesis. Many of the starting materials used in these processes are not readily available or are quite expensive. Furthermore, several of these syntheses suffer from low yield, unresolved mixture, and moderate enantiomeric excess.

We have recently reported a simple and convenient synthesis of 1-aminocyclopropanecarboxylic acid (ACC) from 1-methoxycyclopropanol **3** (R=H), which underwent a one-pot Strecker reaction in good overall yield.[6] The same methodology was also adopted to prepare (*S*) and (*R*)-1-amino-2,2-

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† Dedicated to Professor Dr. Dieter Seebach in honour of the occasion of his 60th birthday.

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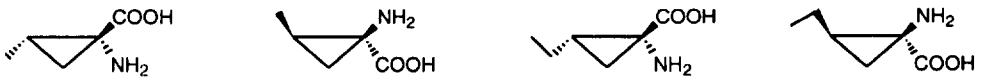
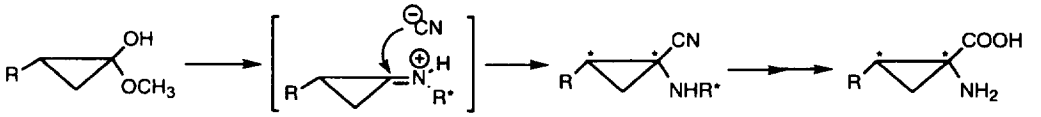
dimethylcyclopropanecarboxylic acids (methanovalines), using an asymmetric Strecker[7] reaction from dimethylcyclopropanone hemiacetal.[8]



(1*R*,2*S*)-(+)-**1** (1*S*,2*R*)-(-)-**1** (1*R*,2*S*)-(+)-**2** (1*S*,2*R*)-(-)-**2**

allo-norcoronamic acids *allo*-coronamic acids

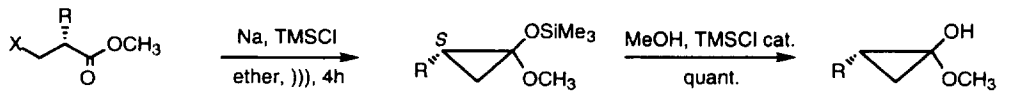
This strategy appeared to be a promising approach for asymmetric synthesis of *allo*-norcoronamic acids **1** and *allo*-coronamic acids **2**. These are provided from a chiral or racemic alkylcyclopropanone hemiacetal **3a,b** by a Strecker reaction induced by a chiral amine leading to the nitrile **5** via iminium **4**.



3a : R = Me **4a** : R = Me **5** **1** : R = Me
3b : R = Et **4b** : R = Et **2** : R = Et

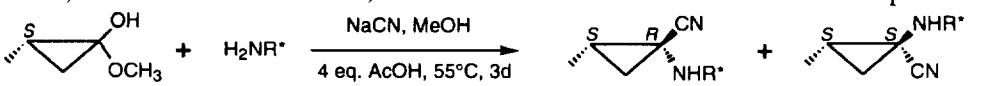
1. Synthesis of (1*R*,2*S*)-*allo*-norcoronamic acid 1 from chiral hemiacetal 3a

Acetal **3a** was obtained in three steps from commercially available (*S*)-methyl 3-hydroxy-2-methylpropionate **6a**. The corresponding bromide (+)-**6b**, obtained by reaction with Ph_3P/CBr_4,[9] underwent a sodium induced cyclisation, in the presence of Me_3SiCl and sonication at room temperature, to lead to the desired acetal **7a**. Simple methanolysis of the latter afforded the hemiacetal **3a** with 85% yield.[10]



6a : X = OH, R = Me **7a** : R = Me (2*S*)-**3a** : R = Me
6a' : X = Br, R = Me

The mixture of cyclopropanone hemiacetal (2*S*)-**3a**, NaCN and a chiral amine underwent a Strecker reaction to form, under various conditions, the aminonitriles **8** and **9**. Our results are reported in Table 1.

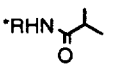
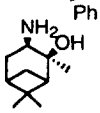


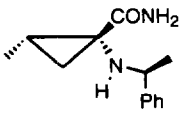
(2*S*)-**3a** **8** **9**

At 55°C in MeOH in the presence of (*S*)-phenylethylamine **10** or (*R*)-**11**,[11a] the hemiacetal (*S*)-**3a** gave the aminonitrile in 82% yield as a mixture of diastereoisomers **8a**:**9a** in 88:12 and 90:10 ratios, respectively (entries 1 and 3). On the other hand, reaction with amine (*R*)-**10** did not modify the selectivity (entry 2). In the presence of the non-aryl amine **12**,[11b] the major product (54%) was the amide **12d**, formed by ring opening of the hydroxy amine intermediate (entry 4). Other conditions such as utilisation of the chlorohydrate of the amine **10** in the presence of silica gel[8] or under sonication conditions did not improve the yield nor the diastereoselectivity.

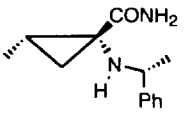
After separation, the α-aminocyanocyclopropanes **8a,b** were hydrolysed in the presence of concentrated H_2SO_4 in CH_2Cl_2 at 0°C to rt for 10 h, to afford the amides (1*R*,2*S*)-**13a,b** in 81–84% yield. Hydrolysis of the cyanocyclopropane **8c** under the same conditions, gave a mixture of the desired amide **13c** (68%), and the azalactone **14** (24% yield).

Table 1
Asymmetric Strecker reaction from chiral hemiacetal (2*S*)-**3**

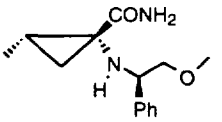
entry	H_2NR^*		yield of nitrile	product	ds ratio	
1		(*S*)-**10**	82%	**8a : 9a**	88 : 12	
2		(*R*)-**10**	77%	**8b : 9b**	87 : 13	
3		(*R*)-**11**	79%	**8c: 9c**	90 : 10	
4		**12**	9%	**8d : 9d**	---	**12d**



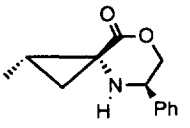
13a



13b



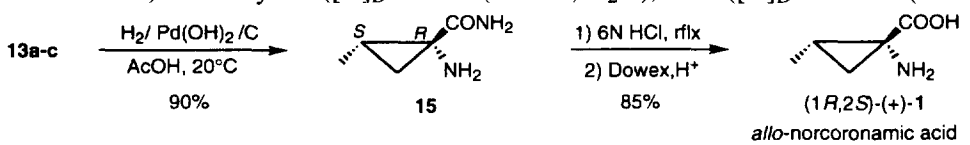
13c



14

Subsequent hydrogenolysis of the amides **13a–c** in the presence of a catalytic amount of 20% $Pd(OH)_2$ on activated carbon (w/w, 20%) in AcOH under hydrogen (1 atm, 10 h) gave after chromatography the amino amide **15** in 90% yield ($[\alpha]_D^{20}$=+95 (c=0.6, $CHCl_3$)). The enantiomeric excesses of **15** from **13a–c**, determined from chiral GC (cydex B, 105°C, 1 bar), were over 97%.

The usual hydrolysis of amide **15** with 6 N HCl at reflux (3 h) led, after treatment with ion-exchange resin (activated Dowex 50 WX.8.100), to (1*R*,2*S*)-1-amino-2-methylcyclopropanecarboxylic acid **1** ((+)-*allo*-norcoronamic acid) in 85% yield ($[\alpha]_D^{20}$=+76 (c=0.97, H_2O), lit.[3a] ($[\alpha]_D^{20}$=+75.5 (c=0.24, H_2O)).



On the other hand, the hydrogenolysis (H_2, $Pd(OH)_2$/C) of lactone **14** followed by hydrolysis (6 N HCl) then treatment on Dowex H^+, gave the same amino acid **1** in 77% yield.

The specific rotation of (+)-**1** was in agreement with the values previously reported,[3a] and confirmed the structure (1*R*,2*S*) of (+)-**1**. Its enantiomeric excess, determined by ^{19}F NMR analysis of the corresponding Mosher amide,[12] was found to be >97% ee in agreement with the value given above (GC, Cydex B, 105°C, 1 bar) of the corresponding amide **15**.

This stereochemistry showed that the nucleophilic attack of the cyanide anion on the iminium intermediate **4a**, took place from the less hindered face (*si*-face) opposite the methyl group on the cyclopropane with a relative like approach,[13] to give **8a** as the major product. Modification of the configuration of the amine did not affect this induction as shown in Table 1 (entries 1 and 2).

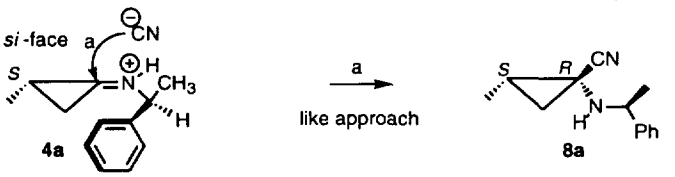
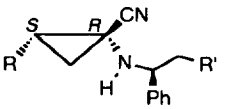
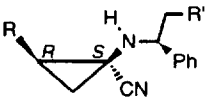


Table 2
Asymmetric Strecker reaction from racemic hemiacetal (±)-**3**



(1*R*,2*S*)-**18**

R = Me, Et
R' = H, OMe



(1*S*,2*R*)-**19**

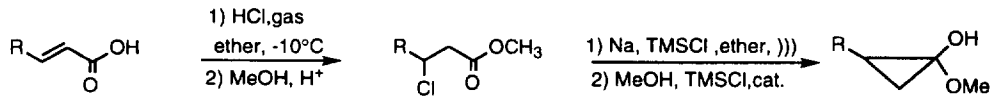
entry	R	H_2NR^*	R'	Yield %	**18***(1*R*,2*S*) : (1*S*,2*S*)		**19***(1*S*,2*R*) : (1*R*,2*R*)	
1	Me	(*S*)-**10**	H	78	**18a**	(47.5 : 5.5)	**19a**	(40.5 : 6.5)
2	Me	(*R*)-**11**	OMe	80	**18b**	(47.5 : 6.5)	**19b**	(38 : 8)
3	Et	(*R*)-**11**	OMe	82	**18c**	(47 : 4.5)	**19c**	(42.5 : 7)

* The mixture ratio were determined from the crude product by gas chromatography (Cydex B 135°C, 1 bar)

2. Synthesis of amino acid 1 and 2 from racemic hemiacetal 3

The successful synthesis of *allo*-norcoronamic acid (+)-**1** from the hemiacetal (2*S*)-**3a** described above, prompts us to adopt the same methodology, starting from the inexpensive and readily available racemic hemiacetal (±)-**3**.

Effectively, the β-chloroesters **16a,b**, readily available from the corresponding α,β-unsaturated acids **17a,b**,[14] gave, by sodium induced cyclisation in the presence of Me_3SiCl under sonication[10] followed by methanolysis, the corresponding racemic hemiacetals (±)-**3** in 86% yield.



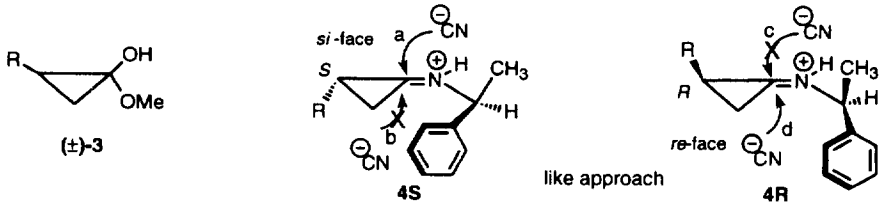
16a : R = Me
16b : R = Et

17a,b

(±)-**3**

The mixture of cyclopropanone acetal (±)-**3**, NaCN and a chiral amine underwent a Strecker reaction to form, via the iminium intermediates, the aminocyanocyclopropanes **18** and **19** as a mixture of diastereoisomers in 78–82% yield (see Table 2).

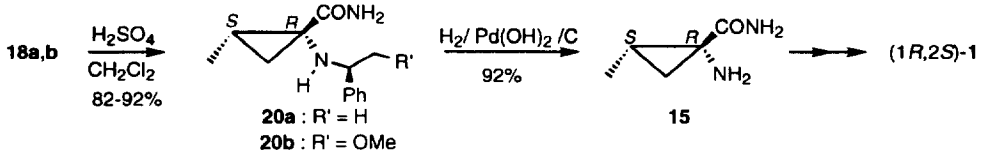
The major products (1*R*,2*S*)-**18** and (1*S*,2*R*)-**19** were obtained in 47% and 38–42% ratios respectively. From the nucleophilic attack of cyanide on the iminium intermediates **4S** and **4R** (obtained from (±)-**3**), we could expect one main diastereoisomer (path a or d in Scheme 1) on the four possible isomers.[15] However, the results obtained in Table 2 show that there is no large difference of cyanide attack on the iminium intermediates **4S** and **4R** (see paths a and d). Moreover, the diastereoselectivities of each intermediate are roughly the same (compare **18** or **19** in Table 2, entries 1–3).



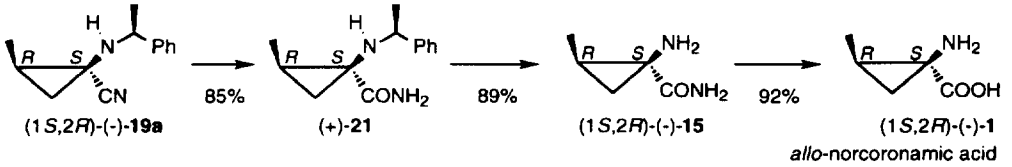
Scheme 1.

The major aminonitriles **18a–c** and **19a–c** were easily isolated by flash chromatography in enantiomerically and diastereoisomerically pure forms.

The major nitriles (1*R*,2*S*)-**18a,b** (R=Me), as the precedent nitriles **8a,c**, were transformed into amides **20**, by reaction with H_2SO_4. After hydrogenolysis into **15**, then hydrolysis, we obtained the *allo*-norcoronamic acid (1*R*,2*S*)-**1** with ee >97% as measured by chiral GC.

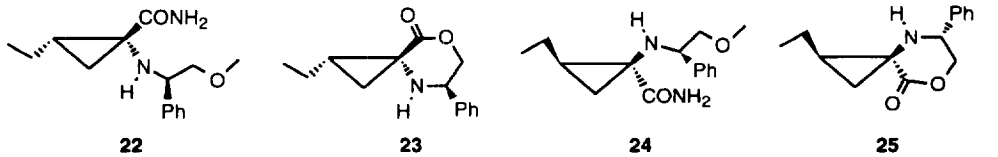


Similarly, the aminonitrile (−)-**19a** was transformed via the corresponding amides (+)-**21** then (−)-**15** (ee >96%, from GC Cydex B), into *allo*-norcoronamic acid (1*S*,2*R*)-(−)-**1** (70% overall yield), $([\alpha]_D^{20}=-72$ (c=0.7, $H_2O)$, lit.[4f] $([\alpha]_D^{20}=-74$ (c=0.3, $H_2O))$. Its enantiomeric excess, confirmed by ^{19}F NMR analysis of the corresponding Mosher amide,[12] was found to be 96% in agreement with the value given above by gas chromatography.

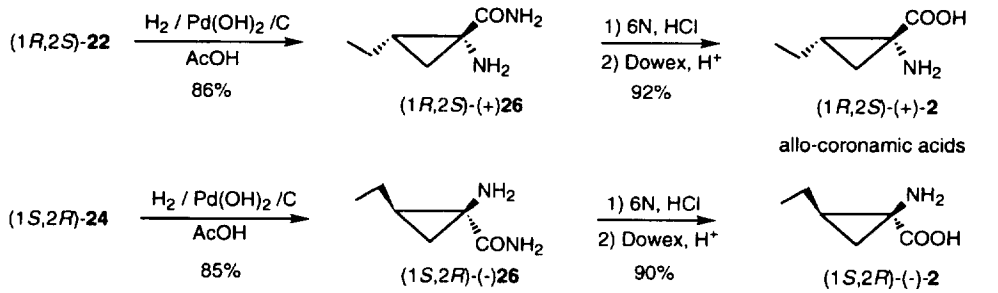


2.1. *Syntheses of (+)- and (−)-*allo-*coronamic acid 2*

The major nitrile **18c**, separated and hydrolysed (H_2SO_4, CH_2Cl_2), gave the corresponding amide **22** (70%), as a mixture with the lactone **23** (20%). Similarly, the major nitrile **19c** reacted with sulphuric acid to give a mixture of the amide **24** (68%), with the lactone **25** (20%).



Subsequent hydrogenolysis of (1*R*,2*S*)-**22** and (1*S*,2*R*)-**24** gave the free amines (1*R*,2*S*)-**26** and (1*S*,2*R*)-**26** respectively in 85% yield. Their enantiomeric excesses, determined by chiral GC (Cydex B, 110°C, 0.8 bar) were >97% and 96% respectively.



Finally, acidic hydrolysis and treatment over Dowex, H^+, of (+)-**26** and (−)-**26** separately, furnished the (1*R*,2*S*)-(+)-*allo*-coronamic acid **2** and its antipode (1*S*,2*R*)-**2**[16] in 92% and 90% yields, respectively, $([\alpha]_D^{20}=+67.2$ (c=0.6, $H_2O)$ for the (1*R*,2*S*)-**2**, lit.[4a] $[\alpha]_D^{20}=+65$ (c=1.3, $H_2O)$ lit.[5g] $[\alpha]_D^{20}=+67.3$ (c=1.52, $H_2O)$. Their enantiomeric excesses, determined by ^{19}F NMR analysis of the corresponding Mosher amides,[12] were found to be >97% for (+)-**2** and 96% for (−)-**2**. Moreover, the hydrolysis of **23**

and **25** followed by hydrogenolysis and treatment on Dowex, H^+, gave separately the amino acid (+)-**2** and (−)-**2** respectively.

In conclusion, methylcyclopropanone hemiacetal (2*S*)-**3a**[10] underwent the asymmetric Strecker reaction induced by a chiral amine and provided a useful synthesis of enantiomerically pure (1*R*,2*S*)-(+)-*allo*-norcoronamic acid **1** in good yield and high enantiomeric excess. Furthermore, from racemic alkyl hemiacetal (±)-**3** the same methodology[17] also constituted a useful way to prepare both (+)-**1** and (−)-**1** (R=CH_3) and (+)-*allo*-coronamic acid **2** and its antipode (−)-**2** (R=Et) with good yield and high enantiomeric excess. The synthesis of other cyclic amino acids, e.g., optically active substituted derivatives of ACC, and the improvement of the diastereoselective Strecker reaction, are currently under investigation.

3. Experimental section

All reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm). Proton and carbon-13 NMR spectra were recorded on a Bruker AM250 spectrometer in deuteriochloroform or deuterium oxide using the solvent signal as an internal standard, 7.27 and 4.80 ppm respectively. Chemical shifts (δ) are expressed in parts per million and the coupling constants (J) are given in hertz. IR spectra we recorded on a Perkin–Elmer 682 spectrophotometer. Melting points were determined on a Mettler FP51 capillary melting point apparatus and are uncorrected. Specific rotations were obtained at 20°C using a Perkin–Elmer 341 polarimeter. Enantiomeric excesses were performed on a GC (Fisons 9130) chiral column Cydex B (SGE) (25 m, 110°C, 0.8 bar).

3.1. (2S)-1-Methoxy-2-methyl-1-trimethylsiloxycyclopropane **7a**

This procedure has been described previously.[10] To 2.87 g of Na (125 mmol), cut into small cubic pieces (5 mm) in 45 mL of ether was added successively at 0°C, 17.75 mL (15.19 g, 140 mmol) of $ClSiMe_3$ and (dropwise) a solution of 9.05 g (50 mmol) of β-bromoester **6b**[9] in 10 mL of ether. The reaction flask kept under argon was immersed in an ultrasonic cleaning bath.[18] The reaction was complete within 4 h as shown by GC. The mixture was filtered on Celite, and washed with ether (20 mL). The solvent was removed by distillation (T<67°C) and the residue distilled at 50–55°C (20 mmHg) to yield 7.3 g of chiral acetal **7a** (84%) in a 6:4 diastereoisomeric mixture (*cis*:*trans*). ^1H NMR ($CDCl_3$) δ: (6:4 mixture of *cis*:*trans*): 3.35/3.40 (s, 3H), 1.20–0.84 (m, 2H), 1.06 (m, 3H), 0.50–0.30 (m, 1H), 0.21/0.19 (s, 9H).

3.2. (1R,2S,1′S)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropanecarbonitrile **8a**

To a solution of 870 mg (5 mmol) of chiral acetal **7a** in 4 mL of MeOH was added one drop of TMSCl. After 5 min of stirring (formation of (2*S*)-**3a**), were added successively, 1.1 g (10 mmol) of (*S*)-methylbenzylamine **10**, 1.2 mL (4 equiv.) of AcOH, 10 mL of MeOH and 500 mg (10 mmol) of NaCN. The reaction mixture was stirred and heated at 55°C for 3.5 days. The reaction evolution was followed by thin layer chromatography (TLC). The reaction mixture was concentrated, then eluted with ether (100 mL) and stirred in the presence of 300 mg of K_2CO_3 for 10 min. After filtration over Celite and concentration, 1.4 g of crude nitriles **8a** and **9a** were obtained as two diastereoisomers in 88:12 ratio.

Purification by flash chromatography (35 g of SiO_2, elution with ether:petroleum ether=10:90) afforded 720 mg (72% yield, 98% ee) of nitrile (1*R*,2*S*)-**8a** and 100 mg (10% yield) of isomer (1*S*,2*S*)-**9a**.

*Data for (1*R,2S*)-**8a**:* R_f=0.7 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}=-60$ (c=1.1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3334, 2240 (ν_{CN}); ^1H NMR ($CDCl_3$) δ: 7.42–7.20 (m, 5H), 4.20 (q, J=6.7 Hz, 1H), 1.84 (s, NH), 1.45 (d, J=6.7 Hz, 3H), 1.50–1.20 (m, 2H), 0.96 (d, J=6.3 Hz, 3H), 0.75 (dd, J=4.2 and 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 144.4 (s), 128.4 (2d), 127.5 (d), 127.1 (2d)], 122.2 (s, CN), 56.8 (d), 30.1 (s, C_1), 23.2 (d, C_2), 22.7 (q), 22.1 (t, C_3), 11.7 (q); MS (EI) (rel. int.): 200 (M^+, 2.2), 106 (12), *105* (100), 79 (10), 77 (15). Anal. calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.72; H, 8.22; N, 14.09.

Data for (1S,2S,1′S)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropanecarbonitrile ***9a****:* R_f=0.63 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}=-99$ (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.40–7.20 (m, 5H), 4.20 (q, J=6.7 Hz, 1H), 2.25 (br, s, NH), 1.38 (d, J=6.7 Hz, 3H), 1.50–1.20 (m, $1H_{cycle}$ and 3H), 0.90 (dd, J=5.2 and 8.4 Hz, 1H), 0.69 (dd, J=6.3 and 5.2 Hz, 1H).

3.3. (1R,2S,1′S)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropanecarbonitrile *8b*

Following the procedure given above: 870 mg (5 mmol) of chiral acetal **7a**, 1.1 g (10 mmol) of (*R*)-methylbenzylamine **10**, 1.2 mL (4 equiv.) of AcOH, 10 mL of MeOH and 500 mg (10 mmol) of NaCN, gave after heating at 50–55°C for 3 days and the usual work-up 1.1 g of crude nitriles as a mixture of **8b** and **9b** in an 87:13 ratio. Purification by flash chromatography afforded 710 mg (71%) of (1*R*,2*S*)-**8b** as the major nitrile and 90 mg (9%) of (1*S*,2*S*)-**9b**.

*Data for (1*R,2S*)-**8b** major:* R_f=0.7 (EtOAc:petroleum ether=1:3); $[\alpha]_D^{20}=+168$ (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3330, 2225; ^1H NMR ($CDCl_3$) δ: 7.40–7.20 (m, 5H), 4.19 (q, J=6.7 Hz, 1H), 1.90 (br, s, NH), 1.39 (d, J=6.7 Hz, 3H), 1.45–1.25 (m, $1H_{cycle}$), 1.21 (d, J=6.8 Hz, 3H), 1.05 (dd, J=5.3 and 9.4 Hz, $1H_{cycle}$), 0.29 (dd, J=5.3 and 6.8 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 144.4 (s), 128.1 (2d), 127.1 (d), 126.9 (2d)], 122.0 (s, CN), 56.4 (d), 30.1 (s, C_1), 23.5 (d, C_2), 21.7 (q), 21.5 (t, C_3), 11.7 (q); MS (EI) (rel. int.): 201 (M^++1, 1.3), 200 (M^+, 6.5), 171 (5), 106 (10), *105* (100), 79 (18), 77 (21); HRMS calcd for $C_{13}H_{16}N_2$: 200.1313. Found: 200.1308.

*Data for (1*R,2S*)-**9b** minor:* R_f=0.63 (EtOAc:petroleum ether=1:3); IR (neat) ν (cm^{-1}): 3600, 3330, 2225; ^1H NMR ($CDCl_3$) δ: 7.45–7.20 (m, 5H), 4.20 (q, J=6.7 Hz, 1H), 2.30 (br, s, NH), 1.40 (d, J=6.7 Hz, 3H), 1.27 (dd, J=8.4 and 6.3 Hz, $1H_{cycle}$), 1.15 (dd, J=5.1 and 8.4 Hz, $1H_{cycle}$), 1.00–0.63 (m, $1H_{cycle}$), 0.84 (d, J=6.3 Hz, 3H).

3.4. (1R,2S,1′R)-1-[(1′-Methoxymethylbenzyl)amino]-2-methylcyclopropanecarbonitrile *8c*

Following the procedure given above: 870 mg (5 mmol) of chiral acetal **7a**, 980 mg (6.5 mmol, 1.3 equiv.) of (*R*)-methoxymethylbenzylamine **11**, 1.2 mL (4 equiv.) of AcOH, 10 mL of MeOH and 500 mg (10 mmol) of NaCN gave, after heating at 50–55°C for 36 h and the usual workup, 1.2 g of crude nitriles as a mixture of **8c** and **9c** in a 90:10 ratio. Purification by flash chromatography as above afforded 815 mg (71%) of (1*R*,2*S*)-**8c** as the major nitrile and 80 mg (7%) of (1*S*,2*S*)-**9c**.

*Data for (1*R,2S*)-**8c** major:* R_f=0.56 (EtOAc:petroleum ether=1:3); $[\alpha]_D^{20}=-106.5$ (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3330, 2225; ^1H NMR ($CDCl_3$) δ: 7.45–7.20 (m, 5H), 4.23 (dd, J=8.6 and 4.5 Hz, 1H), 3.72–3.45 (m, 2H), 3.41 (s, 3H), 2.64 (br, s, NH), 1.38 (dd, J=9.5 and 4.7 Hz, $1H_{cycle}$), 1.34–1.10 (m, $2H_{cycle}$), 0.66 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 139.3 (s), 128.4 (2d), 128.2 (2d), 127.9 (d)], 122.1 (s, CN), 75.6 (q), 60.5 (d), 58.6 (t), 30.9 (s, C_1), 23.4 (d, C_2), 21.5 (t, C_3), 11.9 (q); MS

(EI) (rel. int.): 230 (M^+, 0.7), 185 (53), 135 (17), 105 (22), 104 (27), 103 (72), 92 (10), *91* (100), 78 (11), 77 (30). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.84; H, 7.88; N, 12.01.

*Data for (1R,2S)-**9c** minor:* R_f=0.51 (EtOAc:petroleum ether=1:3); IR (neat) ν (cm^{-1}): 3600, 3330, 2225; ^1H NMR ($CDCl_3$) δ: 7.45–7.20 (m, 5H), 4.33 (dd, J=8.7 and 4.4 Hz, 1H), 3.60–3.40 (m, 2H), 3.42 (s, 3H), 2.89 (br, s, NH), 1.40–1.05 (m, $1H_{cycle}$), 1.22 (d, J=6.3 Hz, 3H), 0.73 (dd, J=8.2 and 5.5 Hz, $1H_{cycle}$), 0.52 (dd, J=5.5 and 6.8 Hz, $1H_{cycle}$); MS (EI) (rel. int.): 231 (M^++1, 0.5), 230 (M^+, 1), 186 (19), *185* (100), 135 (11), 105 (10), 104 (14), 103 (35), 91 (62), 77 (26).

3.5. (1R,2S,2′R,3′S)-1-[(2′-Hydroxybornan-3′-yl)amino-2-methylcyclopropanecarbonitrile **8d**

Following the procedure given above: 175 mg (1 mmol) of chiral acetal **7a**, 225 mg (1.3 mmol) of amine **12**, 0.25 mL of AcOH, 3 mL of MeOH and 100 mg (2 mmol) of NaCN, gave after heating at 50–55°C for 48 h and the usual workup, 300 mg of crude residue. Purification by flash chromatography afforded 22 mg (9%) of (1*R*,2*S*)-**8d** and 130 mg (54%) of opening ring amide **12d** as a major product.

*Data for aminonitrile **8d**:* R_f=0.67 (EtOAc:petroleum ether=3:7); IR (neat) ν (cm^{-1}): 3600, 3440, 3340, 2230; ^1H NMR ($CDCl_3$) δ: 3.60 (m, 1H), 3.00 (m, 1H), 2.07 (br, s, NH), 1.95 (m, 1H), 1.37–1.15 (m, 1H), 1.58–1.33 (m, 3H), 1.25 (m, $1H_{cycle}$), 1.17 (d, J=6.3 Hz, 3H), 1.18–1.00 (m, $1H_{cycle}$), 1.05–0.80 (m, OH), 1.04 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H), 0.80 (m, $1H_{cycle}$).

*Data for amine **12d**:* R_f=0.4 (EtOAc:petroleum ether=3:7); IR (neat) ν (cm^{-1}): 3600, 3320, 1670; ^1H NMR ($CDCl_3$) δ: 6.50 (m, H_{amide}), 4.20 (d, J=8.5 Hz, 1H), 3.93 (d, J=8.5 Hz, 1H), 2.44 (sept., J=6.8 Hz, 1H), 2.04 (m, 1H), 1.80–1.57 (m, 2H), 1.57–1.35 (m, 1H), 1.35–1.15 (m, 1H), 1.30–1.00 (m, OH), 1.15 (d, J=6.8 Hz, 6H), 1.03 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 172.8 (s), 91.2 (d), 75.6 (d), 48.4 (d), 48.3 (s), 46.8 (s), 32.1 (d), 28.3 (t), 25.9 (t), 23.4 (q), 19.0 (q), 18.95 (q), 18.7 (q), 11.2 (q).

3.6. (1R,2S,1′S)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropanecarboxamide **13a**

A solution of nitrile (1*R*,2*S*)-**8a** (600 mg, 3 mmol) in CH_2Cl_2 (12 mL) was cooled to 0°C and concentrated sulphuric acid (5 mL) was added very slowly with efficient stirring. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The aqueous layer was separated, washed with CH_2Cl_2 (2 mL), then poured onto crushed ice (10 g), and was slowly basified with conc. NH_4OH. The mixture extracted with EtOAc (4×50 mL), dried over $MgSO_4$ and concentrated to give, after flash chromatography (SiO_2, 30 g, eluent EtOAc:petroleum ether=4:6 to 100%), the title amide (1*R*,2*S*)-**13a** (535 mg, 82%).

*Data for (1R,2S)-**13a**:* R_f=0.45 (EtOAc); $[\alpha]_D^{20}$=−63.7 (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3470, 3330, 1675 (ν_{amide}); ^1H NMR ($CDCl_3$) δ: 7.42–7.20 (m, 5H), 7.14 (br, s, $1H_{amide}$), 5.12 (br, s, $1H_{amide}$), 3.75 (q, J=6.7 Hz, 1H), 1.69–1.48 (m, 2H), 1.38 (d, J=6.7 Hz, 3H), 1.15 (d, J=6.3 Hz, 3H), 0.77 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 178.6 (s), [6 arom. C: 144.95 (s), 128.5 (2d), 127.1 (d), 126.7 (2d)], 56.8 (d), 43.5 (s, C_1), 24.0 (q), 23.2 (d, C_2), 20.6 (t, C_3), 13.0 (q); MS (EI) (rel. int.): 218 (M^+, 0.4), 113 (71), 106 (11), *105* (100), 104 (12), 103 (18), 96 (22), 91 (11), 79 (23), 77 (27), 68 (15); HRMS calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1415.

3.7. (1R,2S,1′R)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropanecarboxamide **13b**

Following the procedure given above: nitrile (1*R*,2*S*,1′*R*)-**8b** (600 mg, 3 mmol), 12 mL of CH_2Cl_2 and 5 mL of conc. H_2SO_4, gave after chromatography 530 mg (81%) of amide (1*R*,2*S*)-**13b**.

Data for ***13b****:* R_f=0.51 (EtOAc); $[\alpha]_D^{20}$=−5 (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3460, 3330, 1675; ^1H NMR ($CDCl_3$) δ: 7.75 (br, s, H_{amide}), 7.46–7.20 (m, 5H), 3.67 (q, J=6.7 Hz, 1H), 1.78–1.49 (m, $2H_{cycle}$), 1.35 (d, J=6.7 Hz, 3H), 1.04 (d, J=6.3 Hz, 3H), 0.69 (dd, J=5.3 and 4.1 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 179.7 (s), [6 arom. C: 145.2 (s), 128.4 (2d), 127.2 (d), 126.5 (2d)], 56.6 (s, C_1), 23.4 (d, C_2), 22.4 (t, C_3), 18.6 (q), 12.9 (q); MS (EI) (rel. int.): 219 (M^++1, 0.5), 218 (M^+, 0.7), 173 (11), 113 (64), 106 (10), *105* (100), 104 (11), 103 (17), 96 (19), 91 (10), 79 (22), 77 (27), 68 (16); HRMS calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1416.

3.8. (1R,2S,1′R)-1-[(1′-Methoxymethylbenzyl)amino]-2-methylcyclopropanecarboxamide ***13c***

Following the procedure given above: 690 mg (3 mmol) of nitrile (1*S*,2*R*)-**8c**, 12 mL of CH_2Cl_2 and 5 mL of conc. H_2SO_4, gave after chromatography 520 mg (70%) of amide **13c**, and 140 mg (22%) of lactone **14**.

*Data for amide (1R,2S)-****13c*** *major:* R_f=0.34 (EtOAc); $[\alpha]_D^{20}$=−100 (c=0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.45–7.10 (m, 5H), 5.35 (br, s, H_{amide}), 3.82 (dd, J=9 and 4.5 Hz, 1H), 3.60–3.37 (m, 2H), 3.38 (s, 3H), 2.63 (br, s, 1H), 1.65–1.43 (m, $2H_{cycle}$), 1.14 (d, J=6 Hz, 3H), 0.75 (dd, J=4.5 and 6 Hz, $1H_{cycle}$); HRMS calcd for $C_{14}H_{20}N_2O_2$: 248.1524. Found: 248.1529.

*Data for lactone (1R,2S)-****14*** *minor:* R_f=0.76 (EtOAc); $[\alpha]_D^{20}$=−23.7 (c=0.6, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3330, 1730; ^1H NMR ($CDCl_3$) δ: 7.50–7.15 (m, 5H), 4.74 (dd, J=11.3 and 4 Hz, 1H), 4.49 (dd, J=11.3 and 11.3 Hz, 1H), 4.21 (dd, J=11.3 and 4.0 Hz, 1H), 2.00 (br, s, NH), 1.80 (dd, J=9.6 and 4.6 Hz, $1H_{cycle}$), 1.74–1.47 (m, $1H_{cycle}$), 1.24 (d, J=6.0 Hz, 3H), 0.71 (dd, J=7.2 and 4.6 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 172.4 (s), [6 arom. C: 137.4 (s), 128.8 (2d), 128.3 (d), 126.3 (2d)], 75.1 (t), 55.5 (d), 41.0 (s, C_1), 26.5 (d, C_2), 23.6 (t, C_3), 11.5 (q); MS (EI) (rel. int.): 218 (M^++1, 2), 217 (M^+, 8), 105 (11), *104* (100), 103 (12), 91 (11), 78 (15), 77 (14); HRMS calcd for $C_{13}H_{15}NO_2$: 217.1102. Found: 217.1099.

3.9. (1R,2S)-1-Amino-2-methylcyclopropanecarboxamide ***15***

A solution of amide (1*R*,2*S*)-**13a** (525 mg, 2 mmol) in glacial acetic acid (8 mL) was hydrogenated in the presence of 20% palladium hydroxide on activated charcoal as catalyst (100 mg, w/w: 20%) at room temperature under hydrogen (1 atm) for 16 h (as shown by TLC). After purging with argon, the resulting mixture was filtered over Celite and washed with MeOH (15 mL). The combined washings were concentrated and the crude product was dissolved in $CHCl_3$ (20 mL), basified with aqueous $NaHCO_3$ solution to pH=9 and extracted with $CHCl_3$ (3×20 mL). The organic layer was dried, concentrated, and the residue purified by chromatography (MeOH:CH_2Cl_2=1:4) to afford the title free amine (1*R*,2*S*)-**15** (210 mg, 91% yield).

N.B. The amide **13b** under the same conditions gave the same amine **15** in the same yield.

*Data for (1R,2S)-****15****:* R_f=0.54 (MeOH:CH_2Cl_2=1:4); R_T (1*R*,2*S*)=19.19 min (chiral Cydex B, 105°C, 1 bar); $[\alpha]_D^{20}$=+95 (c=0.6, $CHCl_3$); IR (neat) ν (cm^{-1}): 3460, 3340, 1670 (ν_{amide}); ^1H NMR ($CDCl_3$) δ: 7.63 (br, s, $1H_{amide}$), 6.13 (br, s, $1H_{amide}$), 2.88 (br, s, $2H_{amide}$), 1.80–1.55 (m, 2H), 1.18 (d, J=6.3 Hz, 3H), 0.41 (dd, J=5.8 and 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 179.2 (s), 38.5 (s), 26.3 (d), 21.4 (t), 12.9 (q); MS (EI) (rel. int.): 115 (M^++1, 1), 114 (M^+, 8.7), 99 (10), 97 (22), 82 (20), 70 (27), *69* (100), 68 (26), 54 (40), 44 (25), 43 (24), 42 (30), 41 (29); HRMS calcd for $C_5H_{10}N_2O$: 114.0793. Found: 114.0796.

3.10. (1R,2S)-1-Amino-2-methylcyclopropanecarboxamide **15** from **13c**

Following the same procedure developed above: from 248 mg (1 mmol) of amide (1*R*,2*S*)-**13c**, AcOH (5 mL), 20% $Pd(OH)_2/C$ 50 mg, we obtained after flash chromatography 105 mg (92%) of free amine (1*R*,2*S*)-**15**. $[\alpha]_D^{20}$=+92 (c=0.8, $CHCl_3$).

The spectral data are identical with those reported above for the (1*R*,2*S*)-**15** and the enantiomeric excess was >97% ee as shown by chiral GC (R_T (1*R*,2*S*)=19.19 min and 17.51 min for antipode; Cydex B, 25 m, 105°C, 1 bar).

3.11. (1R,2S)-1-Amino-2-methylcyclopropanecarboxylic acid **1** (allo-norcoronamic acid **1**)

A mixture of (1*R*,2*S*)-amide **15** (114 mg, 1 mmol) and 6 N HCl (6 mL) was gently heated to reflux. The reaction was complete within 10 h as shown by TLC. The solution reaction was cooled to room temperature, and extracted with ether (5 mL) to remove coloured ether-soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure to give 150 mg of **1**·HCl as a white solid. Recrystallisation from MeOH–Et_2O furnished pure crystalline (1*R*,2*S*)-*allo*-norcoronamic acid hydrochloride **1**·HCl (140 mg, 92%).

Data for ***1***·*HCl:* m.p. 215°C decomposition; $[\alpha]_D^{20}$=+53 (c=1, H_2O); ^{1}H NMR (D_2O; HOD, 4.80 ppm) δ: 1.95–1.72 (m, 1H), 1.65 (dd, J=9.6 and 6.1 Hz, 1H), 1.20 (d, J=6.3 Hz, 3H), 1.07 (dd, J=7.2 and 6.1 Hz, 1H); ^{13}C NMR (D_2O)[19] δ: 173.3 (s), 38.1 (s), 20.6 (d), 20.3 (t), 11.3 (q); [lit.[4f] for (1*S*,2*R*) ^{13}C NMR (75.5 MHz, D_2O) δ: 175.8, 40.6, 23.1, 22.8, 13.7].

The amino acid hydrochloride (1*R*,2*S*)-**1**·HCl (140 mg) was diluted with distilled water (10 mL) and applied to a Dowex 50WX.8.100 ion-exchange (10 g) column in the activated form (NH_4^+). The column was washed with distilled water until neutral, and then the free amino acid was eluted with 1.3 N aq. NH_3 (120 mL). The eluant was concentrated under vacuum. Complete removal of NH_3 was accomplished by redissolving the substance in H_2O and concentrating in a rotary evaporator. Finally, drying for 2 h (20°C, 0.02 mmHg) provided pure crystalline (1*R*,2*S*)-*allo*-norcoronamic acid **1** (105 mg, quantitative yield).

Data for ***1****:* m.p. 212°C (dec) [lit.[4d] m.p. 215°C (dec) for its antipode]; $[\alpha]_D^{20}$=+76 (c=1, H_2O), lit.[3a] $[\alpha]_D^{20}$=+75.5 (c=0.24, H_2O); ^{1}H NMR (D_2O; HOD, 4.80 ppm) δ: 1.74–1.60 (m, 1H), 1.46 (dd, J=9.4 and 6.3 Hz, 1H), 1.22 (d, J=6.4 Hz, 3H), 0.91 (dd, J=6.5 and 6.3 Hz, 1H); [lit.[4a] ^{1}H NMR (D_2O; HOD, 4.63 ppm) δ: 1.52–1.40 (m, 1H), 1.24 (dd, J=9.5 and 6.0 Hz, 1H), 0.99 (d, J=6.5 Hz, 3H), 0.68 (dd, J=6.0 and 7.5 Hz, 1H)]; ^{13}C NMR (D_2O)[19] δ: 178.7 (s), 42.4 (s), 21.6 (d), 20.9 (t), 14.2 (q); [lit.[4f] for (1*S*,2*R*) ^{13}C NMR (75.5 MHz, D_2O) δ: 178.7, 42.3, 21.6, 20.9, 14.2].

3.12. General procedure for the Mosher amide preparation of amino acids **1** and **2**

To a stirred suspension of **1** (4 mg, 0.0348 mmol) in THF (1 mL) was added (*S*)-(+)-Mosher's acid chloride (8 μl, 0.035 mmol), 1 equiv.) and propylene oxide (10 μl, 0.14 mmol, 4 equiv.). The resulting mixture was heated to reflux for 1 h, cooled to room temperature, and thoroughly evaporated to provide a crude oil (12 mg, 100%). Racemic amino acid **1** was transformed in a similar manner (1 h at reflux) to provide the diastereoisomeric reference signals of the CF_3 groups. The enantiomeric excess was determined by ^{19}F NMR analysis of the MTPA amide (δ CF_3CH_2OH as a reference, −80 ppm): −69.97 (98.5%) for (1*R*,2*S*)-(+)-*allo*-norcoronamic acid **1**, −70.05 (1.5%) for (1*S*,2*R*)-antipode. Moreover the ^{1}H NMR spectra of the MTPA amide of racemic **1** showed two distinguished doublets at 1.16 ppm for the (1*S*,2*R*)-**1** and at 1.04 ppm for its antipode (1*R*,2*S*)-**1**.

3.13. (±)-1-Methoxy-2-methyl-1-trimethylsiloxycyclopropane 3a

Following the same procedure described above: from 2.87 g of Na (125 mmol), 17.75 mL of $ClSiMe_3$ (140 mmol) and 6.825 g (50 mmol) of (±)-β-chloroester **17a** under sonication for 4 h to afford after distillation 7.4 g (85%) of acetal (±)-**7a** into a 3:7 (*cis:trans*) diastereoisomeric mixture. The spectral data are identical with those of chiral **7a**.

To the acetal (±)-**7a** dissolved in MeOH (10 mL) was added one drop (20 μl) of TMSCl. After stirring for 5 min, the residue was distilled at 60–65°C/18 mmHg to give 4.3 g (quantitative) of hemiacetal (±)-**3a**.

Data for (±)-3a: ^{1}H NMR ($CDCl_3$) δ: (6:4 *cis:trans* mixture) 3.48/3.42 (s, 3H), 2.82/2.69 (br, s, OH), 1.34–1.19 (m, 1H), 1.11/1.15 (d, J=6.3 Hz, 3H), 1.13–0.90 (m, 1H), 0.45 (m, 1H).

3.14. (±)-2-Ethyl-1-hydroxy-1-methoxycyclopropane (±)-7b

Following the same procedure described above for chiral **7a**: from 2.87 g of Na (125 mmol), 17.75 mL of $ClSiMe_3$ (140 mmol) and 7.53 g (50 mmol) of (±)-methyl 3-chloropentanoate **17b**[14] under sonication for 3 h were afforded after distillation (65°C/15 mmHg) 8.18 g (87%) of 2-ethyl-1-methoxy-1-trimethylsiloxycyclopropane (±)-**7b** in a 3:7 (*cis:trans*) diastereoisomeric mixture.

Data for (±)-7b: IR (neat) ν (cm^{-1}): 3100, 1285, 1260, 1165, 875, 850; ^{1}H NMR ($CDCl_3$) δ (3:7 *cis/trans* mixture): 3.38/3.32 (s, 3H), 1.73–1.50/1.50–1.35 (m, 1H), 1.35–1.06 (m, 2H), 0.99/0.98 (t, J=7.2 Hz, 3H), 0.87 (dd, J=10 and 5.2 Hz, 1H), 0.53–0.34 (m, 1H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ (3:7 *cis/trans* mixture): 90.1/89.8 (s, C_1), 53.1/53.6 (q), 25.6/28.6 (d, C_2), 21.7/21.5 (t, C_3), 19.6 (t), 13.6 (q), 0.6 (3q).

3.15. (1S,2R,1′S)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropanecarbonitrile 19a and isomer 18a

To a solution of 870 mg (5 mmol) of acetal (±)-**7a** in 4 mL of methanol was added one drop of TMSCl. After 5 min of stirring, were added successively, 1.1 g (10 mmol) of (*S*)-methylbenzylamine **10**, 1.2 mL (4 equiv.) of AcOH, 10 mL of MeOH and 500 mg (10 mmol) of NaCN. The reaction mixture was stirred and heated at 50°C for 48 h. The reaction was complete as shown by TLC.

The usual workup as reported above gave 1.3 g of crude nitriles as a mixture of four diastereoisomers in 47.5:40.5:5.5:6.5 ratio (determined by chiral GC). Purification by flash chromatography (Et_2O:petroleum ether=10:90) gave 370 mg (37%) of nitrile (1*R*,2*S*)-**18a** and 315 mg (31.5%) of nitrile (1*S*,2*R*)-**19a** as major products and 30 mg (3%) of (1*S*,2*S*)-**18a** and 45 mg (4.5%) of nitrile (1*R*,2*R*)-**19a** as minor products (76% overall). Data for (1*R*,2*S*)-**18a** are identical with those reported above for the nitrile (1*R*,2*S*)-**8a**.

Data for (1S,2R)-19a: R_f=0.65 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}$=−155 (c=1.1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3335, 2240 (ν_{CN}); ^{1}H NMR ($CDCl_3$) δ: 7.40–7.20 (m, 5H), 4.20 (q, J=6.7 Hz, 1H), 2.25 (br, s, NH), 1.38 (d, J=6.7 Hz, 3H), 1.40–1.20 (m, 1H), 1.25 (d, m, J=6.2 Hz, 3H), 0.90 (dd, J=5.2 and 8.4 Hz, 1H), 0.69 (dd, J=5.7 and 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 144.6 (s), 128.3 (2d), 127.3 (d), 127.1 (2d)], 122.3 (s, CN), 56.6 (d), 30.3 (s, C_1), 23.7 (t, C_2), 21.9 (d), 21.7 (q, C_3), 11.9 (q); HRMS calcd for $C_{13}H_{16}N_2$: 200.1313. Found: 200.1309.

Data for (1*S*,2*S*)-**18a** are identical with those reported above for the nitrile (1*S*,2*S*)-**9a**.

Data for (1R,2R)-19a minor: R_f=0.58 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}$=−164 (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.40–7.20 (m, 5H), 4.00 (q, J=6.7 Hz, 1H), 2.27 (br, s, NH), 1.41 (d, J=6.7 Hz, 3H), 1.33 (dd, J=8.4 and 6.3 Hz, $1H_{cycle}$), 1.14 (dd, J=8.4 and 5.2 Hz, $1H_{cycle}$), 0.90–0.68 (m, $1H_{cycle}$), 0.85

(d, J=6.3 Hz, 3H); MS (EI) (rel. int.): 201 (M^++1, 0.4), 200 (M^+, 2), 171 (2), 106 (10), *105* (100), 103 (8), 79 (10), 77 (14).

3.16. (1S,2R,1'S)-2-Methyl-[(1'-methylbenzyl)amino]cyclopropanecarboxamide 21

Following the procedure given above: 600 mg (3 mmol) of nitrile (1*S*,2*R*)-**19a**, 12 mL of CH_2Cl_2 and 5 mL of conc. H_2SO_4, gave after chromatography 560 mg (85%) of amide (1*S*,2*R*)-**21**.

Data for 21: R_f=0.46 (EtOAc); $[\alpha]_D^{20}$=+4.1 (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3440, 3320, 1675 (ν_{amide}); ^1H NMR ($CDCl_3$) δ: 7.75 (br, s, H_{amide}), 7.40–7.30 (m, 5H), 5.62 (br, s, H_{amide}), 3.68 (q, J=6.6 Hz, 1H), 1.75–1.45 (m, 2H), 1.38 (d, J=6.6 Hz, 3H), 1.05 (d, J=6.3 Hz, 3H), 0.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 179.8 (s), [6 arom. C: 145.2 (s), 128.5 (2d), 127.3 (d), 126.5 (2d)], 56.7 (d), 42.4 (s, C_1), 23.5 (q), 22.4 (d, C_2), 18.6 (t, C_3), 13.0 (q); MS (EI) (rel. int.): 219 (M^++1, 0.4), 218 (M^+, 0.6), 113 (58), *105* (100), 104 (12), 103 (19), 96 (22), 91 (13), 79 (28), 78 (11), 77 (32), 68 (18); HRMS calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1420.

3.17. (1S,2R)-1-Amino-2-methylcyclopropanecarboxamide 15

Following the same procedure developed above: from 536 mg of amide (1*S*,2*R*)-**21** (2 mmol), AcOH (8 mL), 20% $Pd(OH)_2/C$ (100 mg), we obtained after flash chromatography 205 mg of free amine (1*S*,2*R*)-**15** (89%). R_f=0.54 ($MeOH:CH_2Cl_2$=1:4); $[\alpha]_D^{20}$=−91 (c=0.7, $CHCl_3$); R_T (1*S*,2*R*)=17.51 min (chiral Cydex B, 105°C, 1 bar).

The spectral data are identical with those reported above for the antipode (1*R*,2*S*)-**15**.

3.18. (1S,2R)-1-Amino-2-methylcyclopropanecarboxylic acid 1 ((1S,2R)-allo-norcoronamic acid)

Following the same procedure developed above: 114 mg of amide (1*S*,2*R*)-**15** and 5 mL of 6 N HCl, gave after treatment over Dowex (50WX8.100) 106 mg (92%) of pure crystalline (1*S*,2*R*)-*allo*-norcoronamic acid **1**. $[\alpha]_D^{20}$=−72 (c=0.5, H_2O); [lit.[4f] $[\alpha]_D^{20}$=−74 (c=0.3, H_2O)]. The spectral data are identical with those reported above for its antipode (1*R*,2*S*)-**1**.

The enantiomeric excess determined from ^{19}F NMR analysis of the MTPA amide (δ CF_3CH_2OH as reference, −80 ppm): −69.97 (2%) for (1*R*,2*S*)-**1**, and −70.05 (98%) for (1*S*,2*R*)-**1**, ee=96%.

3.19. (1S,2R,1'R)-2-Methyl-1-[(1'-methoxymethylbenzyl)amino]cyclopropanecarbonitrile 19b and isomer 18b

Following the same procedure noted above: 870 mg (5 mmol) of acetal (±)-**7a**, 980 mg (6.5 mmol, 1.3 equiv.) of (*R*)-methoxymethylbenzylamine **11**,[11] 1.2 mL (4 equiv.) of AcOH, 10 mL of MeOH and 500 mg (10 mmol) of NaCN, gave after heating at 55°C for 48 h and the usual workup, 1.3 g of crude nitriles as a mixture of 4 diastereoisomers in a 47:42.5:4.5:7 ratio determined by chiral GC. Purification by flash chromatography (Et_2O:petroleum ether=10:90) furnished 415 mg (36%) of nitrile (1*R*,2*S*)-**18b** and 370 mg (32%) of nitrile (1*S*,2*R*)-**19b** as major products and 35 mg (3%) of (1*S*,2*S*)-**18b** and 45 mg (4%) of nitrile (1*R*,2*R*)-**19b** as minor products (75% overall).

Data for (1*R*,2*S*)-**18b** are identical with those reported above for the nitrile (1*R*,2*S*)-**8c**.

Data for (1S,2R)-19b: R_f=0.65 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}$=−187 (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3330, 2222, 1612; ^1H NMR ($CDCl_3$) δ: 7.60–7.44 (m, 5H), 4.58 (dd, J=9.6 and 4.2 Hz, 1H), 3.80–3.58 (m, 2H), 3.64 (s, 3H), 2.86 (br, s, NH), 1.65–1.45 (m, $1H_{cycle}$), 1.44 (d, J=6.3 Hz, 3H),

1.12 (dd, J=9.5 and 5.2 Hz, $1H_{cycle}$), 0.41 (dd, J=7.9 and 5.2 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 139.8 (s), 128.2 (2d), 128.1 (2d), 127.8 (d)], 122.2 (s, CN), 76.3 (q), 60.3 (d), 58.4 (t), 30.2 (s, C_1), 22.4 (d, C_2), 20.6 (t, C_3), 11.8 (q); MS (EI) (rel. int.): 231 (M^++1, 0.4), 230 (M^+, 1), 186 (14), *185* (100), 135 (13), 104 (12), 103 (30), 91 (60), 77 (27); HRMS calcd for $C_{14}H_{18}N_2O$: 230.1419. Found: 230.1412.

Data for (1*S*,2*S*)-**18b** minor are identical with those reported above for the nitrile (1*S*,2*S*)-**9c**.

*Data for (1R,2R)-**19b** minor:* IR (neat) ν (cm^{-1}): 3600, 3335, 2222; ^1H NMR ($CDCl_3$) δ: 7.50–7.15 (m, 5H), 4.17 (dd, J=8.8 and 5.5 Hz, 1H), 3.78–3.54 (m, 2H), 3.43 (s, 3H), 2.65 (br, s, NH), 1.50–1.18 (m, $1H_{cycle}$), 1.28 (d, J=6.3 Hz, 3H), 1.19–1.05 (m, $1H_{cycle}$), 1.05–0.84 (m, $1H_{cycle}$); MS (EI) (rel. int.): 230 (M^+, 1.6), 186 (15), *185* (100), 135 (13), 104 (10), 103 (25), 91 (41), 77 (19).

*3.20. (1R,2S,1′R)-2-Ethyl-1-[(1′-methoxymethylbenzyl)amino]cyclopropanecarbonitrile **18c** and isomer (1S,2R,1R)-**19c***

To a solution of 665 mg (5 mmol) of acetal (±)-**7b** in 4 mL of methanol was added one drop of TMSCl. After 5 min of stirring, were added successively 1.37 g (6.5 mmol, 1.3 equiv.) of (*R*)-(methoxymethyl)benzylamine **11**,[11] 1.2 mL (4 equiv.) of AcOH, 10 mL of MeOH and 500 mg (40 mmol) of NaCN. The reaction mixture was stirred and heated at 55°C for 4 days. The reaction was complete as shown by TLC. Usual workup as reported above gave 1.4 g of crude nitriles as a mixture of four diastereoisomers in a 47:42.5:4.5:7 ratio as determined by chiral GC. Purification by flash chromatography (35 g of SiO_2, elution with Et_2O:petroleum ether=10:90) gave 440 mg (36%) of nitrile (1*R*,2*S*)-**18c** and 380 mg (31%) of nitrile (1*S*,2*R*)-**19c** as major products and 35 mg (3%) of (1*S*,2*S*)-**18c** and 60 mg (5%) of (1*R*,2*R*)-**19c** as minor products (77% overall).

*Data for (1R,2S)-**18c**:* R_f=0.60 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}$=−66.2 (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3335, 2225; ^1H NMR ($CDCl_3$) δ: 7.45–7.25 (m, 5H), 4.17 (dd, J=8.1 and 5 Hz, 1H), 3.45 (m, ABC system, 2H), 3.39 (s, 3H), 2.49 (br, s, NH), 1.35 dd, J=9.4 and 5 Hz, $1H_{cycle}$), 1.30–0.88 (m, 2H and $1H_{cycle}$), 0.78 (t, J=7.2 Hz, 3H), 0.70 (dd, J=7.5 and 5 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 139.5 (s), 128.1 (2d), 128.05 (2d), 127.7 (d)], 121.9 (s, CN), 75.5 (t), 60.5 (q), 58.5 (d), 30.9 (s, C_1), 30.5 (t), 20.3 (d, C_2), 19.8 (t, C_3), 13.0 (q); MS (EI) (rel. int.): 244 (M^+, 1.9), 200 (15), *199* (100), 135 (17), 105 (8), 104 (10), 103 (18), 91 (31); HRMS calcd for $C_{15}H_{20}N_2O$: 244.1575. Found: 244.1573.

*Data for (1S,2R)-**19c**:* R_f=0.67 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}$=−185 (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3330, 2220 (ν_{CN}); ^1H NMR ($CDCl_3$) δ: 7.40–7.24 (m, 5H), 4.45 (dd, J=9.2 and 4.5 Hz, 1H), 3.06 (like AB system, $\Delta\nu_{AB}$=18,7 Hz, J_{AB}=10 Hz, 2H), 3.43 (s, 3H), 2.68 (br, s, NH), 1.80–1.37 (m, 2H), 1.40–1.12 (m, $1H_{cycle}$), 1.02 (t, J=8.5 Hz, 3H), 0.88 (dd, J=9.5 and 5.5 Hz, $1H_{cycle}$), 0.22 (dd, J=7.5 and 5.5 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: [6 arom. C: 139.7 (s), 128.1 (2d), 128.0 (2d), 127.7 (d)], 122.1 (s), 76.2 (t), 60.3 (q), 58.2 (d), 30.3 (s, C_1), 27.7 (t), 21.1(d, C_2), 20.3 (t, C_3), 13.4 (q); MS (EI) (rel. int.): 245 (M^++1, 0.4), 244 (M^+, 1.3), 200 (15), *199* (100), 135 (32), 105 (13), 104 (14), 103 (26), 91 (54), 77 (22), 65 (14); HRMS calcd for $C_{15}H_{20}N_2O$: 244.1575. Found: 244.1577.

*Data for (1S,2S)-**18c** (minor 3%):* R_f=0.55 (EtOAc:petroleum ether=3:7); ^1H NMR ($CDCl_3$) δ: 7.50–7.15 (m, 5H), 4.31 (dd, J=8.6 and 4.6 Hz, 1H), 3.56–3.27 (m, 2H), 3.42 (s, 3H), 2.83 (br, s, NH), 1.45 (q, J=7.4 Hz, 2H), 1.35–1.12 (m, $1H_{cycle}$), 1.05 (t, J=7.4 Hz, 3H), 0.70 (dd, J=5 and 9.1 Hz, $1H_{cycle}$), 0.54 (dd, J=5 and 7.3 Hz, $1H_{cycle}$).

*Data for (1R,2R)-**19c** (minor 5%):* R_f=0.52 (EtOAc:petroleum ether=3:7); ^1H NMR ($CDCl_3$) δ: 7.45–7.20 (m, 5H), 4.33 (dd, J=4.8 and 7.9 Hz, 1H), 3.55–3.75 (m, 2H), 3.41 (s, 3H), 2.91 (br, s, NH), 1.60–0.65 (m, 5H), 0.45 (t, J=7.2 Hz, 3H).

3.21. (1R,2S,1'R)-2-Ethyl-1-[(1'-methoxymethylbenzyl)amino]cyclopropanecarboxamide 22

Following the procedure described above: 490 mg (2 mmol) of nitrile (1*R*,2*S*)-**18c**, 10 mL of CH_2Cl_2 and 4 mL of conc. H_2SO_4 gave after flash chromatography 370 mg (70%) of amide (1*R*,2*S*)-**22** and 140 mg (20%) of lactone (1*R*,2*S*)-**23**.

Data for amide (1R,2S)-22: R_f=0.15 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}=-48.5$ (c=1, $CHCl_3$); IR (neat) ν (cm^{-1}): 3460, 3360, 1675; ^1H NMR ($CDCl_3$) δ: 7.40 (m, 5H and $1H_{amide}$), 5.44 (br, s, H_{amide}), 3.79 (dd, J=9.8 and 3.7 Hz, 1H), 3.52 (dd, J=9.8 and 9.8 Hz, 1H), 3.43 (dd, J=9.8 and 3.7 Hz, 1H), 3.37 (s, 3H), 2.74 (br, s, NH), 1.60–1.30 (m, 2H and $2H_{cycle}$), 1.04 (t, J=7 Hz, 3H), 0.79 (d, J=1.5 Hz $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 178.65 (s), [6 arom. C: 140.2 (s), 128.2 (2d), 127.7 (2d), 127.6 (d)], 76.7 (t), 61.3 (q), 58.7 (d), 43.4 (s, C_1), 31.6 (t), 21.2 (d, C_2), 19.3 (t, C_3), 13.5 (q); HRMS calcd for $C_{15}H_{22}N_2O_2$: 262.1681. Found: 262.1674.

Data for lactone (1R,2S)-23: R_f=0.47 (EtOAc:petroleum ether=1:3); $[\alpha]_D^{20}=-20.8$ (c=0.9, $CHCl_3$); IR (neat) ν (cm^{-1}): 3690, 3300, 1730, 1608; ^1H NMR ($CDCl_3$) δ: 7.60–7.20 (m, 5H), 4.75 (dd, J=3.5 and 9.8 Hz, 1H), 4.49 (dd, J=9.8 and 9.8 Hz, 1H), 4.25 (dd, J=3.5 and 9.8 Hz, 1H), 1.77 (dd, J=3.7 and 8.7 Hz, $1H_{cycle}$), 1.68–1.40 (m, 2H and $1H_{cycle}$), 1.05 (t, J=7 Hz, 3H), 0.75 (dd, J=3.7 and 6 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 172.4 (s), [6 arom. C: 137.4 (s), 128.9 (2d), 128.3 (d), 126.3 (2d)], 75.1 (t), 55.6 (d), 41.2 (s, C_1), 34.1 (t), 22.7 (d, C_2), 20.0 (t, C_3), 13.8 (q); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1250.

3.22. (1S,2R,1'R)-2-Ethyl-1-[(1'-methoxymethylbenzyl)amino]cyclopropanecarboxamide 24

Following the procedure described above: 365 mg (1.5 mmol) of nitrile (1*S*,2*R*)-**19c**, 10 mL of CH_2Cl_2 and 3 mL of conc. H_2SO_4 gave, after flash chromatography, 270 mg (69%) of amide (1*S*,2*R*)-**24** and 70 mg (20%) of lactone (1*S*,2*R*)-**25**.

Data for amide (1S,2R)-24: R_f=0.47 (EtOAc:petroleum ether=3:7); $[\alpha]_D^{20}=-68$ (c=0.72, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3360, 1680; ^1H NMR ($CDCl_3$) δ: 8.06 (br, s, $1H_{amide}$), 7.57–7.15 (m, 5H), 5.78 (br, s $1H_{amide}$), 4.07 (dd, J=4.1 and 9.9 Hz, 1H), 3.55–3.25 (m, 2H), 3.44 (s, 3H), 1.78 (br, s, NH), 1.56–1.00 (m, 2H and $2H_{cycle}$), 0.96 (t, J=7.2 Hz, 3H), 0.28 (dd, J=4 and 6.3 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 179.6 (s), [6 arom. C: 142.0 (s), 128.4 (2d), 127.5 (d), 127.2 (2d)], 77.2 (t), 61.8 (q), 59.0 (d), 44.6 (s, C_1), 30.6 (t), 21.7 (d, C_2), 19.9 (t, C_3), 13.7 (q); HRMS calcd for $C_{15}H_{22}N_2O_2$: 262.1681. Found: 262.1676.

Data for lactone (1S,2R)-25: R_f=0.64 (EtOAc:petroleum ether=1:3); $[\alpha]_D^{20}=-39$ (c=0.3, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3350, 1730. ^1H NMR ($CDCl_3$) δ: 7.55–7.25 (m, 5H), 4.65 (dd, J=1 and 8.2 Hz, 1H), 4.52–4.30 (m, like, AB system, 2H), 2.30 (br, s, NH), 1.90–1.45 (m, 2H and $2H_{cycle}$), 1.08 (t, J=7.3 Hz, 3H), 0.70 (dd, J=4 and 7 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 172.5 (s), [6 arom. C: 137.8 (s), 128.8 (2d), 128.3 (d), 126.5 (2d)], 74.6 (t), 55.6 (d), 41.2 (s, C_1), 31.1 (t), 25.9 (d, C_2), 20.8 (t, C_3), 13.8 (q); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1258.

3.23. (1R,2S)-1-Amino-2-ethylcyclopropanecarboxamide 26

Following the same procedure developed above: from 265 mg of amide (1*R*,2*S*)-**22** (1 mmol), AcOH (5 mL), 20% $Pd(OH)_2/C$ (50 mg), we obtained after chromatography ($MeOH:CH_2Cl_2$=1:19), 110 mg of free amine (1*R*,2*S*)-**26** (86%).

Data for (1R,2S)-26: R_f=0.18 ($MeOH:CH_2Cl_2$=1:9); R_T=27.65 min (chiral Cydex B, 110°C, 0.8 bar); $[\alpha]_D^{20}$=+80 (c=0.65, $CHCl_3$); IR (neat) ν (cm^{-1}): 3600, 3350, 3060, 1675; ^1H NMR ($CDCl_3$) δ: 7.60

(br, s, H_{amide}), 6.00 (br, s, H_{amide}), 1.87 (s, $2H_{amine}$), 1.69–1.55 (m, 2H), 1.55–1.30 (m, 2H), 1.05 (t, J=7.7 Hz, 3H), 0.42 (dd, J=4.5 and 2.5 Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$) δ: 179.3 (s), 38.8 (s, C_1), 29.1 (d, C_2), 25.3 (t, C_3), 21.7 (t), 13.7 (q); HRMS calcd for $C_6H_{12}N_2O$: 128.0949. Found: 128.0947.

3.24. (1S,2R)-1-Amino-2-ethylcyclopropanecarboxamide 26

Following the same procedure as above: from 265 mg of amide (1*S*,2*R*)-**24** (1 mmol), AcOH (5 mL), 20% $Pd(OH)_2/C$ (50 mg), we obtained after chromatography (MeOH:CH_2Cl_2=1:19), 107 mg of free amine (1*S*,2*R*)-**26** (84%).

Data for (1S,2R)-26: R_f=0.18 (MeOH:CH_2Cl_2=1:9); R_T=26.04 min (chiral Cydex B, 110°C, 0.8 bar); $[\alpha]_D^{20}$=−78 (c=0.6, $CHCl_3$); HRMS calcd for $C_6H_{12}N_2O$: 128.0949. Found: 128.0948. The spectral data are identical with those reported above for the antipode (1*R*,2*S*)-**26**.

3.25. (1R,2S)-1-Amino-2-ethylcyclopropanecarboxylic acid 2 ((+)-allo-coronamic acid)

Following the same procedure described above, from 103 mg (0.8 mmol) of amide (1*R*,2*S*)-**26**, 3 mL of 6 N HCl, we obtained 132 mg of (1*R*,2*S*)-*allo*-coronamic acid hydrochloride **2**·HCl as a white solid. Recrystallisation from ethanol–ether gave pure **2**·HCl (127 mg, 96%).

Data for (1R,2S)-2·HCl: m.p.: 196°C decomp. $[\alpha]_D^{20}$=+40.7 (c=O.85, H_2O); ^1H NMR (D_2O) δ (HOD, 4.8 ppm): 1.80 (ddd, J=9.5, 7.6 and 6.3 Hz, 1H-C_2), 1.63 (dd, J=9.5 and 6 Hz, 1H-C_3), 1.70–1.46 (m, 1H), 1.50–1.20 (m, 1H), 1.10 (dd, J=7.6 and 6.0 Hz, 1H-C_3), 1.03 (t, J=7.3 Hz, 3H); ^{13}C NMR (D_2O) ($CDCl_3$ int. ref.) δ: 173.4 (s), 38.3 (s, C_1), 27.7 (d, C_2), 20.4 (t, C_3), 19.2 (t), 12.7 (q).

The amino acid hydrochloride (1*R*,2*S*)-**2**·HCl, treated on Dowex 50WX8.100 ion exchange resin provided pure crystalline (1*R*,2*S*)-*allo*-coronamic acid **2** (98 mg, 96% yield).

Data for (1R,2S)-2: m.p.: 185°C; $[\alpha]_D^{20}$=+67.2 (c=0.6, H_2O), lit.[4a] $[\alpha]_D^{20}$=+65.0 (c=1.3, H_2O); lit.[5g] $[\alpha]_D^{20}$=+67.3(c=1.52, H_2O); ^1H NMR (D_2O) δ (HOD, 4.8 ppm): 1.58 (ddd, J=6.0, 7.6 and 9.7 Hz, $1H_{cycle}$), 1.58–1.41 (m, 1H), 1.40 (dd, J=6.0 and 9.7 Hz, $1H_{cycle}$), 1.42–1.20 (m, 1H), 1.01 (t, J=7.3 Hz, 3H), 0.87 (dd, J=6.0 and 7.6 Hz, $1H_{cycle}$); [lit.[4a] ^1H NMR (D_2O) δ (HOD, 4.63 ppm): 1.45–1.07 (m, 4H, H-C_2, H-C_3,CH_2CH_3), 0.84 (t, J=7.0 Hz, CH_2CH_3), 0.70 (*ca* t, J=6.5 Hz, H-C_3)]; ^{13}C NMR (D_2O) ($CDCl_3$ int. ref.) δ: 176.0 (s), 39.9 (s, C_1), 25.8 (d, C_2), 20.7 (t, C_3), 17.9 (t), 13.0 (q). Anal. calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.45; H, 8.28; N, 10.52.

The enantiomeric excess was determined by ^{19}F NMR analysis of the MTPA amide (δ CF_3CH_2OH as a reference, −80 ppm): −70.00 (98.6%) for (1*R*,2*S*)-(+)-*allo*-coronamic acid **2**, and −70.14 (1.4%) for (1*S*,2*R*)-antipode (>97% ee).

3.26. (1S,2R)-1-Amino-2-ethylcyclopropanecarboxylic acid 2 ((−)-allo-coronamic acid)

Following the same procedure noted above, from 103 mg (0.8 mmol) of amide (1*S*,2*R*)-**26**, 3 mL of 6 N HCl, we obtained 130 mg of (1*S*,2*R*)-**2**·HCl as a white solid. Recrystallisation from ethanol–ether furnished pure (−)-**2**·HCl (125 mg, 95%). M.p.: 192°C dec.; $[\alpha]_D^{20}$=−38 (c=0.5, H_2O). After teatment over Dowex, pure crystalline (1*R*,2*S*)-(+)-**2** was obtained (95 mg, 95%). M.p.: 184°C dec; $[\alpha]_D^{20}$=−65 (c=0.5, H_2O).

Data for (1*S*,2*R*)-**2**·HCl are identical to those reported above for (1*R*,2*S*)-**2**·HCl. The enantiomeric excess determined as above by ^{19}F NMR analysis of the MTPA amide was 96% (ppm: −70.00 (2%) for (1*R*,2*S*)-(+)-**2**, −70.14 (98%) for (1*S*,2*R*)-(−)-**2**.

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17. It is interesting to note that the Strecker reaction can also occur directly from the acetal **7a** or (±)-**7b**.
18. Sonications were carried out in a Sonoclean TK 52 (Bransonic) cleaning bath at 60 KHz and 80–160 Wl^{-1}.
19. NMR spectra were recorded at 62.86 MHz in D_2O solution using internal $CDCl_3$=77.00 ppm as a reference.