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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7517

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PAPER

Stereoselective preparation of β,γ-methano-GABA derivatives†‡

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Received 6th July 2011, Accepted 5th August 2011
DOI: 10.1039/c1ob06095c

Published on 08 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB06095C
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The Kulinkovich–de Meijere reaction between an unsaturated Grignard reagent and a chiral amide takes place with a high *trans* stereoselectivity and provides a convenient access to non-racemic *trans* cyclopropylamines. These compounds are transformed in four steps into the corresponding *N*-protected β,γ-methano-GABA derivatives, which are obtained for the first time in enantiomerically pure form. The corresponding transformations of the *cis* cyclopropylamine adducts are also described.

Introduction

There is a growing interest in oligomeric materials which can adopt well-defined spatial conformations (foldamers), since these self-organized non-natural structures can provide new insights into the rules which govern macromolecular folding, and inspire the design of functional molecular structures fulfilling specific functions in biological systems or in materials science.[1] β-Peptides have emerged at the forefront of foldamer science in the last decade or so, largely due to the capacity of these materials to form intramolecular hydrogen bonds in analogy with Nature's α-peptides, thus inducing regular conformational preferences.[2] Among the most promising building blocks for such materials are cyclic β-amino acids: homo-oligomers and mixed peptides incorporating these compounds have been studied, and a number of regular folding preferences have been observed, including helices, sheets, and other well-defined conformational features.[3] Following the pioneering studies by Seebach[4] and Hanessian,[5] peptides containing γ-amino acids have now become a centre of focus for foldamer manifolds.[6–10] Significantly, γ-amino acids in which the backbone is rigidified by a cyclic feature appear to promote specific conformational preferences in oligopeptides.[9,10] In a particular case, Smith has shown that short peptide sequences based on a repeating cyclopropyl γ-amino acid sequence adopt parallel sheet structures in the solid state[10c] and in reverse turn mimetics[10a] which are stabilised by unique C–H···O hydrogen bonds.

γ-Amino acids have in fact been of interest to chemists for quite some time, partly due to the importance of GABA in the central nervous system; thus derivatives and structural analogues of GABA are of great interest for the treatment of diverse neurodegenerative disorders, including Parkinson's and Alzheimer's diseases.[11] A wide diversity of strategies have been developed for the stereoselective synthesis of γ-amino acids.[12] The inclusion of two of the GABA backbone carbon atoms into a cyclopropane ring provides conformationally restricted GABA analogues, and both the *cis* and *trans* isomers α,β-methano-GABA (CAMP, **1** and TAMP, **2**, respectively) have been the focus of some attention (Fig. 1). (+)-CAMP is a potent agonist of human ρ1 and ρ2 $GABA_C$ receptors, while (−)-CAMP exerts weak antagonist activity.[13] Racemic TAMP is a non-inhibiting substrate for GABA and pyruvate transaminases;[14] it also differentiates ρ3 from other $GABA_C$ receptors *in vitro*,[15] while each of its enantiomers show partial agonist activity at both $GABA_C$ and $GABA_A$ receptors.[13b] Synthetic efforts have progressed in parallel with the advances in pharmacology studies, and several preparations of racemic[16] and enantiopure[17] CAMP and racemic[14,16,18] and enantiopure[10c,17c,17e,19] TAMP have been described to date.

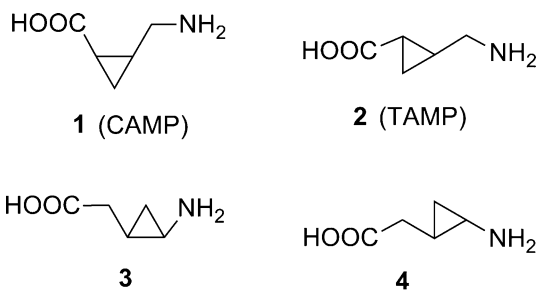

Fig. 1 The four methano-analogues of GABA, differentiated by the ring position and the relative ring stereochemistry (*cis* or *trans*); absolute stereochemistry is not shown.

In marked contrast with their α,β- congeners, the *cis* and *trans* isomers of β,γ-methano-GABA, **3** and **4**, have received very little attention (Fig. 1). Indeed, only racemic syntheses have been described: one of the *cis* compound **3**,[20,21] and three of the *trans* compound **4**.[14,20,22] In this paper, we present our work on the Kulinkovich–de Meijere reaction using a chiral non-racemic electrophilic partner, which provides for the first time an access to single enantiomeric forms of *trans*-β,γ-methano-GABA **4**, as well

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† This article is part of an *Organic & Biomolecular Chemistry* web theme issue on Foldamer Chemistry

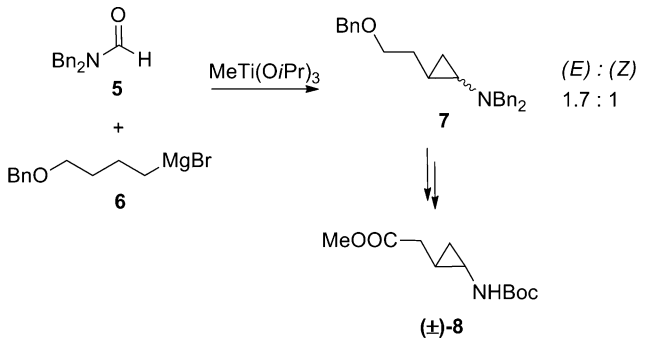
‡ Electronic supplementary information (ESI) available. CCDC reference number 809952. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06095c

as the *cis* isomer **3** in racemic form. With a view to using these materials in future peptide construction, the *N*-Boc derivatives were selected as the targets in the present work.

Results and Discussion

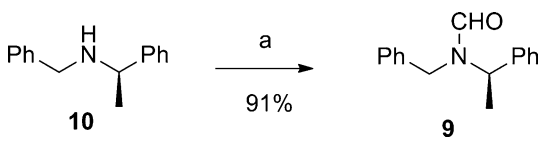
Synthetic strategy for cyclopropylamine formation

The titanium-mediated transformation of *N*,*N*-dialkylcarboxamides to cyclopropylamines using alkyl magnesium bromides was first described by de Meijere.[22] In one particular case, the reaction of *N*,*N*-dibenzylformamide **5** with 4-benzyloxybutyl magnesium bromide **6** gave a good yield of the cyclopropylamine **7** (Scheme 1). The reaction had a low diastereoselectivity (*E* : *Z* ratio of 1.7 : 1) but the isomers were separable, and the *E*-isomer was transformed in several steps into **8**, a protected derivative of racemic **4** (Scheme 1).



Scheme 1 de Meijere's approach to a derivative of racemic **4**.

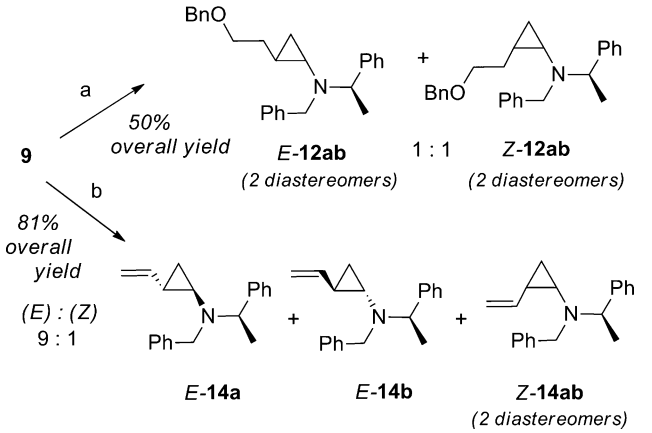
We felt that it should be possible to adapt this synthetic approach to incorporate a chiral non-racemic moiety as part of the formamide component, thus providing an entry to single enantiomers of **4**. We decided to investigate the reactivity profile of a chiral version of the formamide reagent, and for this purpose we selected (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)formamide **9**. Somewhat surprisingly, this compound has not been described previously in enantiomerically pure form.[23] We prepared it in 91% yield by treatment of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine **10** with mixed acetic formic anhydride (Scheme 2).



Scheme 2 Preparation of the chiral formamide **9**. *Reagents and conditions*: a) $HCOOH/Ac_2O$, CH_2Cl_2, 20 °C.

We began our investigations by treating the chiral formamide **9** with methyltitanium triisopropoxide and 4-benzyloxybutyl magnesium bromide **6**. The requisite cyclopropylamines **12** were obtained in 50% overall yield as a 1 : 1 mixture of *E* and *Z* geometrical isomers; each of these was a 1 : 1 mixture of diastereoisomers (Scheme 3). While the *E* and *Z* components could be separated fairly easily by chromatography, efforts to separate the diastereomeric forms proved fruitless.

We therefore decided to modify the Grignard component in the Kulinkovich–de Meijere reaction, and repeated the above-

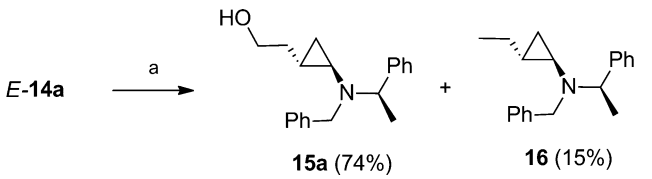


Scheme 3 Kulinkovich–de Meijere reactions using chiral formamide **9**. *Reagents and conditions*: a) **6** (1.5 eq.), $MeTi(OiPr)_3$ (1.2 eq.), Et_2O, THF, 0 °C. b) $CH_2{=}CHCH_2CH_2MgBr$ (**13**) (1.5 eq.), $MeTi(OiPr)_3$ (1.2 eq.), Et_2O, THF, 0 °C.

described procedure using 3-butenyl magnesium bromide **13**. This time, the cyclopropylamines **14** were formed in 81% overall yield with an *E* : *Z* ratio of 9 : 1; once again, each of these geometric isomers was present as a 1 : 1 mixture of diastereoisomers (Scheme 3). A key point was that the minor *Z* component mixture as well as each of the two major *E* stereoisomers were separable by column chromatography. Thus, each *trans*-vinylcyclopropylamine *E*-**14a** and *E*-**14b** was obtained in enantiomerically pure form and in exploitable yield. The absolute configurations of these compounds (indicated on Scheme 3) were not known at this stage, but were deduced from a subsequent X-ray crystallography study (*vide infra*).

Access to enantiomerically pure *trans*-β,γ-methano-GABA derivatives

With the enantiomerically pure *trans*-vinylcyclopropylamines in hand, we embarked on a functional group transformation sequence leading to the γ-amino acid moiety. The first step was the oxidation of the vinyl side chain to provide a primary alcohol. Our initial efforts, conducted on *E*-**14a** using borane–THF, were hampered by the formation of a by-product. Indeed, after work-up with hydrogen peroxide in basic medium, a 5 : 1 mixture of the required alcohol **15a** and the double bond reduction product **16** was obtained (Scheme 4).



Scheme 4 Reaction of borane with the vinylcyclopropylamine *E*-**14a**. *Reagents and conditions*: a) (i) $BH_3{\cdot}THF$ (0.7 eq.), 20 °C; (ii) 3 M NaOH, 35% H_2O_2, 20 °C.

This problem was resolved by replacing borane with 9-borabicyclo[3.3.1]nonane (9-BBN). Using this latter reagent, *E*-**14a** was transformed into **15a** as a single product and in excellent yield (Scheme 5).

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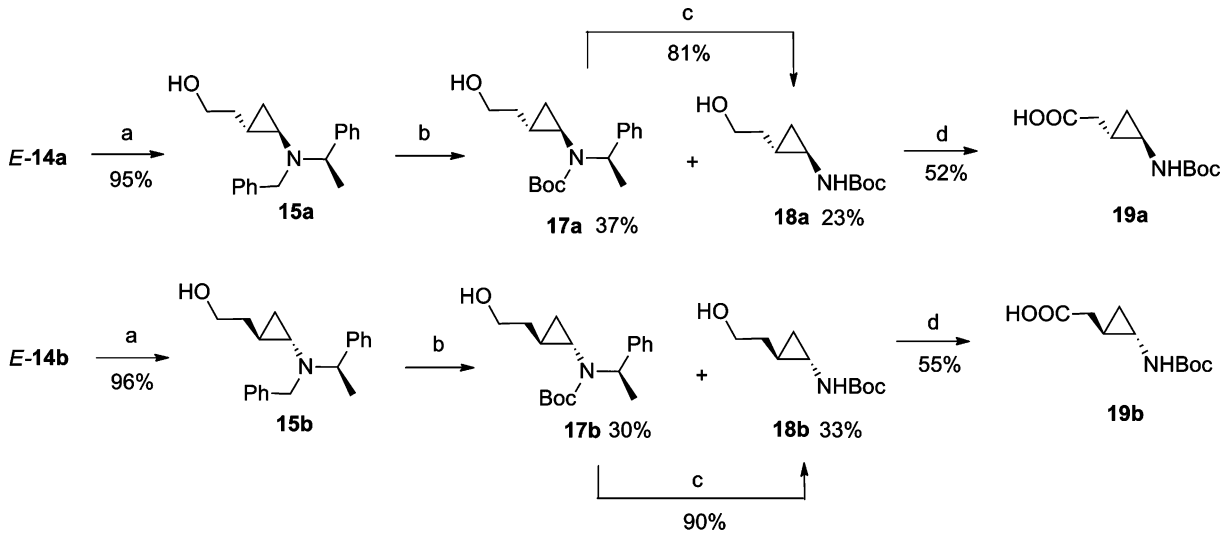

Scheme 5 Preparation of enantiomerically pure *trans*-β,γ-methano-GABA derivatives. *Reagents and conditions*: a) (i) 9-BBN (2.5 eq.), THF, 0 °C; (ii) 3 M NaOH, 35% H_2O_2, 20 °C. b) (i) HCOOH, 10% Pd–C, MeOH, reflux; (ii) Boc_2O (1.8 eq.), MeOH, NaOH to pH 11, 0 °C to 20 °C. c) H_2, 20% $Pd(OH)_2$-C, THF, 20 °C. d) $KMnO_4$, *t*-BuOH, 20 °C.

As indicated in the introduction, we aimed to prepare the target γ-amino acids as their *N*-Boc protected derivatives. The next step, therefore, was the removal of the benzylic groups from the amine of **15a** and protection of this latter as its *t*-butyl carbamate.

We attempted this operation without isolation of the intermediate primary amine. A solution of compound **15a** in methanol was treated with formic acid in the presence of Pd–C as a transfer hydrogenation catalyst. After filtration through Celite, the crude debenzylated product solution was treated with Boc_2O to afford a mixture of the desired *N*-Boc-cyclopropylamine derivative **18a** and the partially deprotected product **17a** (Scheme 5). Evidently, the removal of the second benzylic substituent (the α-methylbenzyl moiety) was sluggish, but studies of other hydrogenolysis conditions did not provide a remedy; for example, when a solution compound **15a** was treated for 3 days under hydrogen (4 atm) in the presence of 20% $Pd(OH)_2$–C, followed by the Boc_2O treatment, only **17a** was obtained. Fortunately, we had previously observed that *N*-benzyl-*N*-Boc-GABA derivatives may be debenzylated in dry THF solution using hydrogen and $Pd(OH)_2$–C as the catalyst.[19a] Gratifyingly, this operation allowed the smooth transformation of **17a** into **18a** thus improving the overall yield of **18a** from **15a**. Finally, $KMnO_4$ was used to convert **18a** into **19a**, the *N*-protected derivative of a single enantiomer of *trans*-β,γ-methano-GABA **4** (Scheme 5).

With the complete synthetic scheme thus established, we performed the same sequence of operations on the second *trans*-vinylcyclopropylamine, *E*-**14b** ostensibly with comparable reaction profiles and yields in each step, to provide **19b**, the opposite enantiomer of the *N*-protected *trans*-β,γ-methano-GABA **4** (Scheme 5). Optical rotation values for these two new compounds were of equal magnitude and opposite sign: $[\alpha]_D^{25}$ = +32.4 (*c* 1.18, $CHCl_3$) for **19a**; $[\alpha]_D^{21}$ −32.3 (*c* 1.17, $CHCl_3$) for **19b**. However, the absolute configuration of each still had to be determined. The salt formed from an equimolar mixture of **19a** and (1*S*,2*R*)-(−)-ephedrine provided crystals which were amenable to X-ray diffraction analysis. The crystal structure of the salt (shown in Fig. 2) revealed the 1*S*,2*R* configuration for **19a** (where the numbering system refers to the 2-amino-cyclopropane moiety).

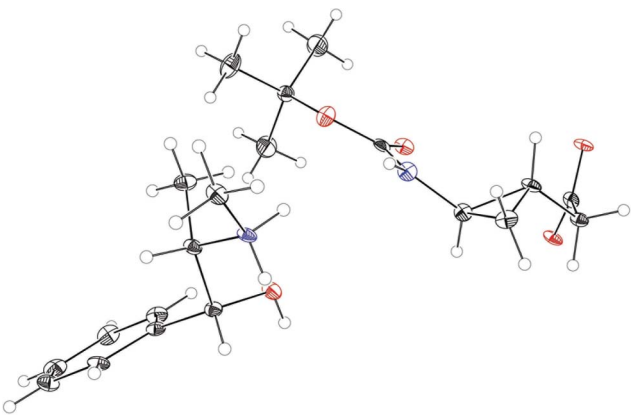

Fig. 2 ORTEP drawing of the salt from **19a** and (1*S*,2*R*)-ephedrine. Ellipsoids are drawn at the 30% probability level.

Access to a racemic *cis*-β,γ-methano-GABA derivative

The principle application of the Kulinkovich–de Meijere aminocyclopropanation reaction was the establishment of a route to enantiomerically pure derivatives of *trans*-β,γ-methano-GABA. While the *cis* structures *Z*-**14ab** were only obtained as minor (and inseparable) products in the reaction of chiral formamide **9** with 3-butenyl magnesium bromide **13** (Scheme 3), we confirmed the utility of the above sequence of transformations to prepare the *N*-Boc derivative of *cis*-β,γ-methano-GABA **3**. In the event, the *cis* vinylcyclopropylamine mixture *Z*-**14ab** was transformed using 9-BBN into the inseparable mixture of diastereomeric alcohols **20ab** in high yield (Scheme 6). The debenzylation/Boc protocol furnished a mixture of **21ab** and **22**, with the former being debenzylated to the latter in an analogous fashion to the *trans* series. Subsequent oxidation of **22** provided the target *N*-Boc-protected *cis*-cyclopropane GABA analogue **23** in racemic form (Scheme 6).

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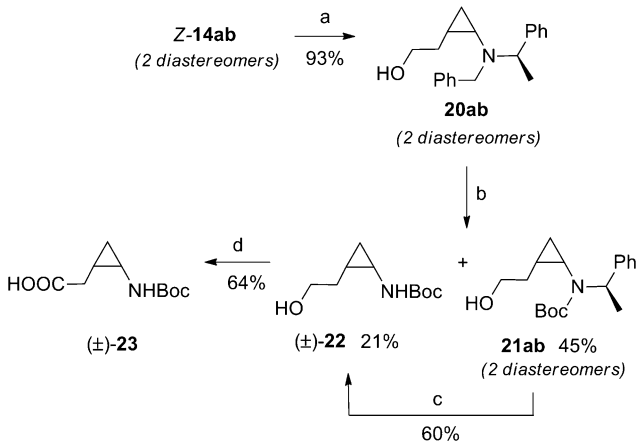

Scheme 6 Preparation of a racemic *cis*-β,γ-methano-GABA derivative. *Reagents and conditions*: a) (i) 9-BBN (2.5 eq.), THF, 0 °C; (ii) 3 M NaOH, 35% H_2O_2, 20 °C. b) (i) HCOOH, 10% Pd–C, MeOH, reflux, (ii) Boc_2O (1.8 eq.), MeOH, NaOH to pH 11, 0 °C to 20 °C. c) H_2, 20% $Pd(OH)_2$–C, THF, 20 °C. d) $KMnO_4$, *t*-BuOH, 20 °C.

Conclusions

In summary, the Kulinkovich–de Meijere protocol has been applied using a chiral *N*,*N*-dialkylcarboxamide, allowing easy access to vinylcyclopropylamines in a diastereoselective manner. While the minor *cis* diastereomers were not separable, the major *trans* diastereomers were isolated in enantiomerically pure form, and were transformed into the corresponding *N*-Boc-β-γ-methano GABA derivatives. This methodology permits a first synthetic entry to these conformationally restricted γ-amino acids, which expand the inventory of available building blocks for peptidomimetic foldamer construction.

Experimental

General

All reactions were carried out under argon using solvents which were purified using standard procedures. Reagent grade solvents were used without purification for all extractions and work-up procedures. Flash chromatography (FC) was performed on columns of silica gel 60 (0.040–0.063 mm); mobile phases are indicated in parentheses. R_f values were obtained by TLC on 0.25 mm silica gel plates (60-F254) using the same eluent as the FC procedure, unless otherwise stated. Optical rotations were measured on a Jasco P-1010 polarimeter, using a 10 cm quartz cell. Values for $[\alpha]$ were obtained with the D-line of sodium at the indicated temperature T, using solutions of concentration (c) in units of g·100 mL^{-1}. IR spectra were acquired on a Perkin Elmer Spectrum One spectrophotometer; only significant absorbances (ν_{max}) are reported. ^1H NMR spectra were recorded at 25 °C on a Bruker AM250 (250 MHz) or Bruker AC360 (360 MHz) or Bruker AC300 (300 MHz) spectrometer. Chemical shifts (δ) are recorded in parts per million from the residual protonated solvent resonance ($CHCl_3$ at 7.26 ppm). ^{13}C NMR spectra were recorded at 25 °C on a Bruker AM250 (63 MHz) or Bruker AC300 (75 MHz) or Bruker AC360 (90 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million from the solvent resonance ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95S instrument operation in electrospray ionisation mode (ESI).

***N*-Benzyl-*N*-[(1*R*)-1-phenylethyl]formamide 9.** At room temperature, acetic formic anhydride (8.60 g, 98 mmol, 2.5 equiv.) was added dropwise to a solution of (*R*)-*N*-benzyl-1-phenylethanamine (8.30 g, 39 mmol) in CH_2Cl_2 (50 mL). After stirring for 1 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 25 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure, then the residue was purified by FC (petroleum ether/EtOAc, 3 : 1) to give **9** as a colourless oil (8.60 g, 91%). The compound exists as a mixture of rotamers (7 : 3 ratio). R_f 0.15. $[\alpha]_D^{23}$ +50.0 (c 1.03, CH_2Cl_2). δ_H (360 MHz, $CDCl_3$) 8.57 (s, 1 H, *H*COmaj), 8.35 (s, 1 H, *H*COmin), 7.07–7.40 (m, 20 H, Ar*H*maj+min), 5.79 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*min), 4.65 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*maj), 4.51 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*Hmaj), 4.32 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, CH*H*maj), 4.30 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H, C*H*Hmin), 4.09 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H, CH*H*min), 1.55 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, C*H*$_3$maj), 1.39 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, C*H*$_3$min). δ_C (90 MHz, $CDCl_3$) 163.7 (H*C*Omin), 162.6 (H*C*Omaj), 140.5 (Ar*C*qmaj), 139.8 (Ar*C*qmin), 137.7 (Ar*C*qmin), 137.5 (Ar*C*qmaj), 128.9, 128.7, 128.6, 128.6, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 126.9 (Ar*C*Hmaj+min), 57.8 (*C*Hmaj), 50.8 (*C*Hmin), 48.5 (*C*H_2maj), 45.5 (*C*H_2min), 20.3 (*C*H_3maj), 17.1 (*C*H_3min). This compound has previously been described in racemic form.[23]

Preparation of Aminocyclopropanes 14

An oven-dried 250-mL three-necked round-bottomed flask was charged with a solution of 9.50 g (39.8 mmol) of formamide **9** in 15 mL of anhydrous THF. $MeTi(OiPr)_3$ (11.5 mL, 47.7 mmol, 1.2 equiv.) was added in one portion by syringe and then 3-butenyl magnesium bromide (1.38 M in THF, 43.2 mL, 59.6 mmol, 1.5 equiv.) was added dropwise over 30 min. The resulting black suspension was stirred further at ambient temperature for an 1 h, then quenched by slow addition of Et_2O (75 mL) followed by water (16 mL). The mixture was stirred vigorously for 1 h, filtered, and the colourless precipitate was washed with Et_2O (2 × 25 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a mixture of aminocyclopropanes ***E*-14a**, ***Z*-14b**, ***E*-14a** and ***Z*-14b** (9 : 1 ratio *E* : *Z*-isomers) as a deep yellow oil (9.6 g). This mixture was separated by FC (petroleum ether/Et_2O, 49 : 1) to yield the following three components, which represent a combined reaction yield of 81%.

(1*R*,2*S*)-{*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]}-2-vinylcyclopropanamine *E*-14a. Yellowish oil (3.99 g, 36%). R_f 0.45 (petroleum ether/Et_2O, 19 : 1). $[\alpha]_D^{25}$ +36.0 (c 1.35, $CHCl_3$). ν_{max} (film) 3000 (CH), 1650 (C=C), 1450 (CN) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.20–7.40 (m, 10 H, Ar*H*), 5.33 (ddd, $^3J_{H,H}$ = 18.0 Hz, $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_2C=C*H*), 4.83 (dd, $^3J_{H,H}$ = 18.0 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, *H*$_2$C=CH), 4.81 (dd, $^3J_{H,H}$ = 11.0 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, *H*$_2$C=CH), 3.91 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*CH$_3$), 3.69 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 3.50 (d, $^3J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 1.80 (ddd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 4.5 Hz, $J_{H,H}$ = 3.0 Hz, 1 H, *c*Pr-*H*), 1,42 (d, $J_{H,H}$ = 7.0 Hz, 3H, C*H*$_3$),1.25 (ddd, $J_{H,H}$ = 9.0 Hz,

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$J_{H,H}$ = 6.0 Hz, $J_{H,H}$ = 3.0 Hz, 1 H, *c*Pr-*H*), 0.78 (ddd, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 4.5 Hz, 1 H, *c*Pr-*H*), 0.64 (dd, $J_{H,H}$ = 12.0 Hz, $J_{H,H}$ = 5.5 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 143.5 (Ar*C*), 139.8 (CH_2=*C*H), 139.7 (Ar*C*), 129.3, 128.0, 127.9, 127.8, 126.7, 126.6, 126.5 (Ar*C*H), 112.3 (*C*H_2=CH), 60.5 (*C*H), 55.9 (*C*H_2Bn), 43.0 (*C*H), 26.2 (*C*H), 17.6 (*C*H_3), 15.6 (*C*H_2). HRMS (ESI): *m*/*z* for $C_{20}H_{24}N$ $[M+H]^+$ requires 278.1903; found 278.1902.

(1*S*,2*R*)-{*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]}-2-vinylcyclopropanamine *E*-14b. Yellowish oil (3.92 g, 36%). R_f 0.4 (petroleum ether/Et_2O, 19 : 1). $[\alpha]_D^{25}$ +15.0 (*c* 1.16, $CHCl_3$). ν_{max} (film) 3000 (CH), 1650 (C=C), 1450 (CN) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.20–7.40 (m, 10 H, Ar*H*), 5.36 (ddd, $^3J_{H,H}$ = 16.5 Hz, $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 9.5 Hz, 1 H, H_2C=C*H*), 4.88 (dd, $^3J_{H,H}$ = 16.5 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, *H*$_2$C=CH), 4.83 (dd, $^3J_{H,H}$ = 11.0 Hz, $^2J_{H,H}$ = 2.0 Hz, *H*$_2$C=CH), 3.91 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*CH$_3$), 3.79 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 3.42 (d, $^3J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 1.77 (ddd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 4.5 Hz, $J_{H,H}$ = 3.0 Hz, 1 H, *c*Pr-*H*), 1,47 (d, $J_{H,H}$ = 7.0 Hz, 3H, C*H*$_3$), 1.33–1.44 (m, 1 H, *c*Pr-*H*), 0.73 (ddd, $J_{H,H}$ = 9.5 Hz, $J_{H,H}$ = 9.5 Hz, $J_{H,H}$ = 4.5 Hz, 1 H, *c*Pr-*H*), 0.61 (dd, $J_{H,H}$ = 12.0 Hz, $J_{H,H}$ = 5.0 Hz,1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 142.1 (Ar*C*), 140.0 (Ar*C*), 139.8 (CH_2=*C*H), 129.1, 128.2, 127.9, 126.8, 126.6 (Ar*C*H), 112.3 (*C*H_2=CH), 60.4 (CH), 56.1 (*C*H_2Bn), 42.6 (*C*H), 25.7 (*C*H), 18.6 (*C*H_3), 16.0 (*C*H_2). HRMS (ESI): *m*/*z* for $C_{20}H_{24}N$ $[M+H]^+$ requires 278.1903; found 278.1906.

(Z)-{*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]}-2-vinylcyclopropanamine *Z*-14ab. Yellowish oil (1.00 g, 9%). R_f 0.65 (petroleum ether/Et_2O, 19 : 1). ν_{max} (film) 3000 (CH), 1636 (C=C), 1602, 1493 (C=CAr) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 7.25–7.35 (m, 20 H, Ar*H*), 5.87 (ddd, $^3J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 10.0 Hz, $^3J_{H,H}$ = 1.5 Hz, 1 H, H_2C=C*H*), 5.83 (ddd, $^3J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 10.0 Hz, $^3J_{H,H}$ = 1.5 Hz, 1 H, H_2C=C*H*), 5.16 (dd, $^3J_{H,H}$ = 17.5 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, C*H*$_2$=CH), 5.08 (dd, $^3J_{H,H}$ = 17.5 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, C*H*$_2$=CH), 4.97 (dd, $^3J_{H,H}$ = 10.0 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, C*H*$_2$=CH), 4.93 (dd, $^3J_{H,H}$ = 10.0 Hz, $^2J_{H,H}$ = 2.0 Hz, 1 H, C*H*$_2$=CH), 3.98 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*), 3.87 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*), 3.83 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 3.63 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, C*H*$_2$Bn), 3.59 (d, $^2J_{H,H}$ = 13.5 Hz, 1H, C*H*$_2$Bn), 3.32 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 2.20 (ddd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 1.99 (ddd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*),1.44 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, C*H*$_3$), 1.41 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, C*H*$_3$), 0.97 (dd, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.94 (dd, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.80 (dd, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.78 (dd, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.57 (dd, $J_{H,H}$ = 10.5 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.22 (dd, $J_{H,H}$ = 11.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*). δ_C (75 MHz, $CDCl_3$) 144.1 (Ar*C*), 141.9 (Ar*C*), 140.1 (ArC), 139.8 (Ar*C*), 139.2 (CH_2=*C*H), 139.1 (CH_2=*C*H), 129.5, 129.1, 128.4, 128.2, 128.1, 128.0, 127.9, 126.9, 126.8, 126.7 (Ar*C*H), 113.3 (*C*H_2=CH), 113.1 (*C*H_2=CH), 60.7 (*C*H), 58.6 (*C*H), 56.1 (*C*H_2Bn), 55.7 (*C*H_2Bn), 40.9 (*C*H), 39.7 (*C*H), 23.3 (*C*H), 22.2 (*C*H), 20.2 (*C*H_3), 16.5 (*C*H_2), 15.9 (*C*H_2), 14.1 (CH_3). HRMS (ESI): *m*/*z* for $C_{20}H_{24}N$ $[M+H]^+$ requires 278.1903; found 278.1900.

General procedure for hydroboration/oxidation using 9-BBN

To a stirred solution of the alkene (***E*-14a**, ***E*-14b** or ***Z*-14ab**) (0.98 mmol) in anhydrous THF (15 mL) at 0 °C was slowly added a THF solution of 9-BBN (0.5 M, 4.9 mL, 2.5 equiv.). The reaction was stirred at room temperature and progress was monitored by TLC (petroleum ether/Et_2O, 95 : 5). When no starting material remained (~3 h), the reaction mixture was treated with NaOH (3 M, 1.0 mL), followed by H_2O_2 (35% aqueous solution, 1.0 mL) and stirred for 2 h. Brine (15 mL) was then added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FC (petroleum ether/Et_2O, 3 : 1).

2-{(1*S*,2*R*)-2-(*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amino)cyclopropyl}ethanol 15a. Following the general procedure, this compound was obtained from ***E*-14a** as a colourless oil (95%). R_f 0.2. $[\alpha]_D^{21}$ −3.0 (*c* 0.96, $CHCl_3$). ν_{max} (film) 3400 (OH) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.21–7.39 (m, 10 H, Ar*H*), 3.98 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*CH$_3$), 3.66 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 3.59 (d, $^2J_{H,H}$ = 14.0 Hz, 1H, C*H*$_2$Bn), 3.46 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, C*H*$_2$OH), 1.68 (ddd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 3.5 Hz, $J_{H,H}$ = 3.5 Hz, 1 H, *c*Pr-*H*), 1.46 (d, $^3J_{H,H}$ = 7.0 Hz, 4 H, C*H*$_3$, CH$_2$O*H*), 1.15–1.25(m, 2 H, C*H*$_2$CH$_2$OH), 0.63 (dd, $J_{H,H}$ = 11.5 Hz, $J_{H,H}$ = 3.5 Hz, 1 H, *c*Pr-*H*), 0.59 (dd, $J_{H,H}$ = 9.5 Hz, $J_{H,H}$ = 4.0 Hz, 1H, *c*Pr-*H*), 0.33 (m, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 143.4 (ArCq), 140.4 (Ar*C*q), 128.9, 128.1, 128.0, 127.9, 126.7, 126.6 (Ar*C*H), 62.4 (*C*H_2), 59.9 (*C*H), 55.8 (*C*H_2Bn), 40.7 (*C*H), 35.7 (*C*H_2), 18.9 (*C*H), 15.7 (CH_3), 13.6 (*C*H_2). HRMS (ESI): *m*/*z* for $C_{20}H_{26}NO$ $[M+H]^+$ requires 296.2009; found 296.2000.

2-{(1*R*,2*S*)-2-(*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amino)cyclopropyl}ethanol 15b. Following the general procedure, this compound was obtained from ***E*-14b** as a colourless oil (96%). R_f 0.2. $[\alpha]_D^{23}$ = +54.7 (*c* 1.06, $CHCl_3$). ν_{max} (film) 3351 (OH) cm^{-1}. δ_H (360 MHz, $CDCl_3$, 25 °C) 7.24–7.37 (m, 10 H, Ar*H*), 3.97 (q, $^3J_{H,H}$ = 7.0 Hz, 1H, C*H*CH$_3$), 3.87 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Bn), 3.47 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, C*H*$_2$OH), 3.39 (d, $^2J_{H,H}$ = 14.0 Hz, 1H, C*H*$_2$Bn), 1.56 (ddd, $J_{H,H}$ = 10.0 Hz, $J_{H,H}$ = 3.5 Hz, $J_{H,H}$ = 3.5 Hz, 1 H, *c*Pr-*H*), 1.48 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, C*H*$_3$), 1.38 (dd, $J_{H,H}$ = 13.5 Hz, $J_{H,H}$ = 6.0 Hz, 1 H, *c*Pr-*H*), 1.10–1.25 (m, 2H, C*H*$_2$CH$_2$OH), 0.60–0.72 (m, 1H, *c*Pr-*H*), 0.49 (dat, $J_{H,H}$ = 8.5 Hz, $J_{H,H}$ = 4.0 Hz, $J_{H,H}$ = 4.0 Hz, 1 H, *c*Pr-*H*), 0.25 (dd, $J_{H,H}$ = 5.0 Hz, $J_{H,H}$ = 12.0 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 142.4 (ArCq), 140.7 (ArCq), 128.8, 128.1, 127.9, 126.8, 126.6 (ArCH), 62.4 (CH_2), 60.9 (CH), 55.8 (CH_2Bn), 41.4 (CH), 35.6 (CH_2), 18.5 (CH), 17.9 (CH_3), 13.9 (CH_2). HRMS (ESI): *m*/*z* for $C_{20}H_{26}NO$ $[M+H]^+$ requires 296.2009; found 296.2003.

2-{(*Z*)-2-(*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amino)cyclopropyl}ethanol *Z*-20ab. Following the general procedure, this compound was obtained from ***Z*-14ab** as a colourless oil (93%). R_f 0.5. ν_{max} (film) 3369 (OH) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.19–7.40 (m, 20 H, Ar*H*), 3.96 (q, $^3J_{H,H}$ = 9.0 Hz, 1 H, C*H*CH$_3$), 3.83 (d, $^2J_{H,H}$ = 16.5 Hz, 1H, C*H*CH$_3$), 3.66 (d, $^2J_{H,H}$ = 16.5 Hz, 2 H, C*H*$_2$Bn), 3.55 (d, $^2J_{H,H}$ = 16.5 Hz, 2 H, C*H*$_2$Bn), 3.37–3.47 (m, 4 H, C*H*$_2$OH), 1.50–1.60 (m, 4 H, *c*Pr-*H*), 1.47 (d, $^3J_{H,H}$ = 9.0 Hz, 3 H, CHC*H*$_3$), 1.45 (d, $^3J_{H,H}$ = 9.0 Hz, 3 H, CHC*H*$_3$), 1.35–1.45 (m, 4 H, C*H*$_2$CH$_2$OH), 1.10–1.23 (m, 2 H, CH$_2$O*H*), 0.57–0.70 (m, 1 H, *c*Pr-*H*), 0.46 (ddd, $J_{H,H}$ = 16.0 Hz, $J_{H,H}$ = 10.5 Hz, $J_{H,H}$ = 5.5 Hz, 1 H, *c*Pr-*H*), 0.32 (ddd, $J_{H,H}$ = 8.0 Hz, $J_{H,H}$ = 5.0 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.23 (dd, $J_{H,H}$ = 14.5 Hz, $J_{H,H}$ = 6.5 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 143.3 (ArC), 142.5 (ArC), 140.6 (ArC), 140.2

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Published on 08 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB06095C
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(ArC), 129.7, 129.3, 129.0, 129.0, 128.8, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 126.8, 126.7, 126.6, 126.6 (ArCH), 62.3 (CH_2), 62.2 (CH_2), 60.8 (CH), 59.9 (CH), 55.8 (CH_2), 5.8 (CH_2), 41.4 (CH), 40.6 (CH), 35.6 ($2CH_2$), 18.8 (CH), 18.5 (CH), 17.8 (CH_3), 16.0 (CH_3), 14.1 (CH_2), 13.7 (CH_2). HRMS (ESI): *m/z* for $C_{20}H_{26}NO$ $[M+H]^+$ requires 296.2009; found 296.2004.

Hydroboration/oxidation of compound *E*-14a using borane

To a solution of aminocyclopropane ***E*-14a** (0.50 g, 1.81 mmol) in THF (28 mL) at 0 °C was added a 1 M solution of borane–THF complex (1.26 mL, 0.7 equiv.). After stirring for 2 h at room temperature, the reaction mixture was treated with 3 M NaOH (0.7 mL) and H_2O_2 (35% solution in water, 0.7 mL) and stirred for a further 2 h. The mixture was then partitioned between brine (25 mL) and Et_2O (25 mL), the phases were separated, and the aqueous layer was re-extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FC (petroleum ether/Et_2O, 3 : 1) afforded, in addition to the alcohol ***E*-15a** (0.39 g, 74%), the following compound:

(1*R*,2*R*)-{*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]}-2-ethylcyclopropanamine 16. Colourless oil (0.08 g, 15%). R_f 0.9. δ_H (360 MHz, $CDCl_3$) 7.20–7.40 (m, 10 H, Ar*H*), 3.92 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*CH_3), 3.70 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, CH_2Bn), 3.53 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, CH_2Bn), 1.59 (ddd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 3.5 Hz, 1 H, *c*Pr-*H*), 1.45 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.25–1.36 (m, 2 H, C$H_2$$CH_3$), 0.96–1.04 (m, 1 H, *c*Pr-*H*), 0.81 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3–CH_2), 0.37–0.44 (m, 1 H, *c*Pr-*H*), 0.27 (dddd, $J_{H,H}$ = 8.0 Hz, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 4.5 Hz, $J_{H,H}$ = 4.0 Hz, 1 H, *c*Pr-*H*). HRMS (ESI): *m/z* for $C_{20}H_{26}N$ $[M+H]^+$ requires 280.2060; found 280.2059.

General procedure for *N*-debenzylation/Boc protection

The substrate (**15a**, **15b** or **20ab**) was suspended in a mixture of MeOH (7 mL $mmol^{-1}$) and formic acid (5 mL $mmol^{-1}$). Pd–C (10%, Pd; 0.2 equiv.) was added and the reaction mixture was refluxed. After the completion of the reaction (~4 h), as evaluated by TLC analysis (petroleum ether/Et_2O, 1 : 1), the mixture was cooled to room temperature and filtered through a sand/Celite® pad, which was washed through with MeOH. The combined filtrate and washings were concentrated under reduced pressure to remove methanol. The acidic residual solution was treated with MeOH (2.0 mL $mmol^{-1}$) and aqueous NaOH (1 M) was added until pH 11 was obtained. The stirred reaction mixture was cooled to 0 °C and Boc_2O (1.8 equiv.) was added; after 5 min the mixture was allowed to return to room temperature and left for 9 h. After this time, TLC analysis (petroleum ether/EtOAc, 3 : 1) indicated complete disappearance of the starting material. The mixture was concentrated under reduced pressure and the remaining aqueous phase was washed with EtOAc (50 mL $mmol^{-1}$ then 2 × 20 mL $mmol^{-1}$). Combined organic extracts were washed with brine (10 mL $mmol^{-1}$), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford mixtures of partly and fully deprotected products. FC (petroleum ether/EtOAc, 3 : 1) allowed separation of each pair of components. From **15a** : **17a** (37%) and **18a** (23%); from **15b** : **17b** (30%) and **18b** (33%); from **20ab** : **21ab** (45%) and **22** (21%).

***tert*-butyl [(1*R*,2*S*)-2-(2-hydroxyethyl)cyclopropyl][(1*R*)-1-phenylethyl] carbamate 17a.** Colourless oil. R_f 0.6 (petroleum ether/EtOAc, 1 : 1). $[\alpha]_D^{26}$ +53.1 (*c* 1.25, $CHCl_3$). ν_{max} (film) 3422 (OH), 1676 (C═O) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.15–7.32 (m, 5 H, Ar*H*), 4.81 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*CH_3), 3.71–3.80 (m, 2 H, CH_2OH), 2.33 (ddd, $^3J_{H,H}$ = 7.0 Hz, $^3J_{H,H}$ = 3.0 Hz, $^3J_{H,H}$ = 3.0 Hz, 1 H, *c*Pr-*H*), 1.94–2.04 (m, 1 H, O*H*), 1.63 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CHCH_3), 1.25 (s, 9 H), 0.96–1.21 (m, 3 H, C$H_2$$CH_2$OH, *c*Pr-*H*), 0.79 (ddd, $J_{H,H}$ = 9.5 Hz, $J_{H,H}$ = 5.5 Hz, $J_{H,H}$ = 4.0 Hz, 1 H, *c*Pr-*H*), 0.42 (dd, $J_{H,H}$ = 13.0 Hz, $J_{H,H}$ = 6.0 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 157.2 (C═O), 142.7 (ArC), 127.9 (2ArCH), 126.4 (ArCH), 126.1 (2ArCH), 80.4 (*C*$(CH_3)_3$), 62.1 (CH_2), 57.4 (CH), 35.9 (CH_2), 35.7 (CH), 28.1 (C(*C*$H_3)_3$), 20.2 (CH), 17.7 (CH), 13.1 (CH_2). HRMS (ESI): *m/z* for $C_{18}H_{27}NNaO_3$ $[M+Na]^+$ requires 328.1883; found 328.1893.

***tert*-butyl [(1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl][(1*R*)-1-phenylethyl] carbamate 17b.** Colorless oil. R_f 0.3 (petroleum ether/EtOAc, 3 : 1). $[\alpha]_D^{24}$ +17.8 (*c* 1.28, $CHCl_3$). ν_{max} (film) 3419 (OH), 1683 (C═O) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 7.15–7.35 (m, 5 H, Ar*H*), 4.97 (q, $^3J_{H,H}$ = 7.0 Hz, 1 H, C*H*CH_3), 3.73–3.86 (m, 2 H, CH_2OH), 2.45–2.53 (m, 1 H, *c*Pr-*H*), 1.64 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CHCH_3), 1.46–1.55 (m, 3 H, C$H_2$$CH_2$OH, CH_2O*H*), 1.31 (s, 9 H, C(C$H_3)_3$), 0.96–1.00 (m, 1 H, *c*Pr-*H*), 0.54 (ddd, $J_{H,H}$ = 9.5 Hz, $J_{H,H}$ = 5.5 Hz, $J_{H,H}$ = 4.0 Hz, 1 H, *c*Pr-*H*), 0.32 (dd, $J_{H,H}$ = 13.0 Hz, $J_{H,H}$ = 7.0 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 157.4 (C═O), 143.5 (ArC), 128.0 (2ArCH), 126.5 (ArCH), 126.0 (2ArCH), 80.5 (*C*$(CH_3)_3$), 72.0 (CH), 62.1 (CH_2), 35.8 (CH_2), 35.5 (CH), 28.1 (C(*C*$H_3)_3$), 20.1 (CH), 17.9 (CH_3), 11.5 (CH_2). HRMS (ESI): *m/z* for $C_{18}H_{27}NNaO_3$ $[M+Na]^+$ requires 328.1883; found 328.1888.

***tert*-butyl [(*Z*)-2-(2-hydroxyethyl)cyclopropyl][(1*R*)-1-phenylethyl] carbamate 21ab.** Mixture of diastereomers (1 : 1) as a colourless oil. R_f 0.6 (petroleum ether/EtOAc, 1 : 1). ν_{max} (film) 3419 (OH), 1673 (C═O) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 7.16–7.32 (m, 10 H, Ar*H*), 4.96 (q, $^3J_{H,H}$ = 8.5 Hz, 1 H, C*H*CH_3), 4.79 (q, $^3J_{H,H}$ = 8.5 Hz, 1 *H*, $CHCH_3$), 3.70–3.84 (m, 4 H, CH_2OH), 2.48 (ddd, $^3J_{H,H}$ = 5.5 Hz, $^3J_{H,H}$ = 3.0 Hz, $^3J_{H,H}$ = 3.0 Hz, 1 H, *c*Pr-*H*), 2.30 (dd, $^3J_{H,H}$ = 6.0 Hz, $^3J_{H,H}$ = 3.0 Hz, 1 H, *c*Pr-*H*), 1.77–1.86 (m, 2 H, CH_2O*H*), 1.63 (d, $^3J_{H,H}$ = 8.5 Hz, 3 H, CH_3), 1.61 (d, $^3J_{H,H}$ = 8.5 Hz, 3 H, CH_3), 1.40–1.60 (m, 4 H, C$H_2$$CH_2$OH), 1.30 (s, 9 H, C(C$H_3)_3$), 1.24 (s, 9 H, C(C$H_3)_3$), 0.90–1.05 (m, 2 H, *c*Pr-*H*), 0.78 (ddd, $J_{H,H}$ = 8.0 Hz, $J_{H,H}$ = 4.5 Hz, $J_{H,H}$ = 3.5 Hz, 1 H, *c*Pr-*H*), 0.51 (ddd, $J_{H,H}$ = 8.0 Hz, $J_{H,H}$ = 4.5 Hz, $J_{H,H}$ = 4.5 Hz, 1 H, *c*Pr-*H*), 0.40 (dd, $J_{H,H}$ = 10.5 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*), 0.30 (dd, $J_{H,H}$ = 10.5 Hz, $J_{H,H}$ = 5.0 Hz, 1 H, *c*Pr-*H*). δ_C (75 MHz, $CDCl_3$) 153.7 (C═O), 143.6 (ArC), 143.0 (ArC), 128.1, 128.0, 126.6, 126.5, 126.1 (ArCH), 80.7 (Cq), 80.5 (*C*$(CH_3)_3$), 62.3 (CH_2), 62.3 (CH_2), 57.5 (CH), 56.4 (CH), 36.0 (CH_2), 35.9 (CH_2), 35.7 (CH), 35.7 (CH), 28.2 (C(*C*$H_3)_3$), 28.2 (C(*C*$H_3)_3$), 20.4 (CH), 20.4 (CH), 18.0 (CH_3), 17.8 (CH_3), 13.1 (CH_2), 11.5 (CH_2). HRMS (ESI): *m/z* for $C_{18}H_{27}NNaO_3$ $[M+Na]^+$ requires 328.1883; found 328.1874.

General procedure for *N*-demethylbenzylation

The α-methylbenzyl carbamate (**17a**, **17b** or **21ab**) was suspended in anhydrous THF (70 mL $mmol^{-1}$) at room temperature. $Pd(OH)_2$–C (60% wet, 20%, Pd: 1.0 equiv.) was added, then hydrogen was bubbled through the solution for 3 min. The reaction mixture was stirred vigorously under hydrogen (1 atm)

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Published on 08 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB06095C
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for 2 h, by which time TLC analysis (petroleum ether/EtOAc, 1 : 1) showed the disappearance of starting material and the formation of a single new product. The mixture was carefully filtered through a sand/Celite® pad which was washed through with EtOAc. Combined filtrate and washings were concentrated under reduced pressure and the residue was subjected to FC (petroleum ether/EtOAc, 1 : 1).

***tert*-butyl [(1*R*,2*S*)-2-(2-hydroxyethyl)cyclopropyl]carbamate 18a.** Following the general procedure, this compound was obtained from **17a** as a colourless oil (81%). R_f 0.5. $[\alpha]_D^{26}$ +73.6 (*c* 0.80, $CHCl_3$). ν_{max} (film) 3343 (OH), 1686 (C═O), 1171 cm^{-1}. δ_H (360 MHz, $CDCl_3$) 5.08 (br s, 1 H, N*H*), 3.72–3.80 (m, 2 H, CH_2OH), 2.29 (dd, $^3J_{H,H}$ = 7.0 Hz, $^3J_{H,H}$ = 4.0 Hz, 1 H, *c*Pr-*H*), 1.95–2.05 (m, 1 H, O*H*), 1.40 (s, 9 H, C(CH_3)$_3$), 1.24 (m, 1 H, *c*Pr-*H*), 0.76–0.95 (m, 2 H, CH_2CH$_2$OH), 0.59 (ddd, $J_{H,H}$ = 13.0 Hz, $J_{H,H}$ = 9.5 Hz, $J_{H,H}$ = 5.5 Hz, 1 H, *c*Pr-*H*), 0.40 (dd, $J_{H,H}$ = 13.0 Hz, $J_{H,H}$ = 5.5 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 157.7 (C═O), 80.0 (*C*(CH$_3$)$_3$), 62.3 (CH$_2$), 35.0 (CH$_2$), 28.6 (CH), 28.2 (C(*C*H$_3$)$_3$), 19.3 (CH), 11.3 (CH$_2$). HRMS (ESI): *m*/*z* for $C_{10}H_{19}NNaO_3$ $[M+Na]^+$ requires 224.1257; found 224.1271.

***tert*-butyl [(1*S*,2*R*)-2-(2-hydroxyethyl)cyclopropyl]carbamate 18b.** Following the general procedure, this compound was obtained from **17b** as a colourless oil (90%). $[\alpha]_D^{25}$ −75.5 (*c* 0.85, $CHCl_3$). IR and NMR data identical to those for **18a** above. HRMS (ESI): *m*/*z* for $C_{10}H_{19}NNaO_3$ $[M+Na]^+$ requires 224.1257; found 224.1258.

***tert*-butyl [(*Z*)-(2-hydroxyethyl)cyclopropyl]carbamate 22.** Following the general procedure, this compound was obtained from **21ab** as colourless oil (60%). R_f 0.4. ν_{max} (film) 3342 (OH), 1686 (C═O) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 5.05 (br s, 1 H, N*H*), 3.69–3.78 (m, 2 H, CH_2OH), 2.29 (dd, $J_{H,H}$ = 7.0 Hz, $J_{H,H}$ = 3.5 Hz, 1 H, *c*Pr-*H*), 1.91–1.96 (m, 1 H, O*H*), 1.40 (s, 9 H, C(CH_3)$_3$), 1.10–1.35 (m, 1 H, *c*Pr-*H*), 0.78–0.94 (m, 2 H, CH_2CH$_2$OH), 0.50–0.65 (m, 1 H, *c*Pr-*H*), 0.43 (dd, $J_{H,H}$ = 12.5 Hz, $J_{H,H}$ = 6.5 Hz, 1 H, *c*Pr-*H*). δ_C (75 MHz, $CDCl_3$) 157.6 (C═O), 79.8 (*C*(CH$_3$)$_3$), 62.3 (CH$_2$), 34.5 (CH$_2$), 28.5 (CH), 28.1 (C(*C*H$_3$)$_3$), 19.1 (CH), 11.2 (CH$_2$). HRMS (ESI): *m*/*z* for $C_{10}H_{19}NNaO_3$ $[M+Na]^+$ requires 224.1257, found 224.1261.

General procedure for primary alcohol oxidation

A solution of the alcohol (**18a**, **18b** or **22**) in *t*-BuOH (10 mL $mmol^{-1}$) was treated with aqueous NaOH (0.5 M, 4.0 equiv.) followed by aqueous $KMnO_4$ (0.7 M, 4.0 equiv.) and the mixture was stirred in the dark for 16 h. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium thiosulphate (3 mL $mmol^{-1}$) and then washed with Et_2O (120 mL $mmol^{-1}$). The aqueous layer was then cooled to 0 °C and acidified to pH 1 by addition of HCl (1 M). The resulting mixture was extracted with EtOAc (3 × 90 mL $mmol^{-1}$). The combined EtOAc extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FC (EtOAc) to afford the target *N*-Boc cyclopropane γ-amino acid.

2-{(1*S*,2*R*)-[(*tert*-butoxycarbonyl)amino]cyclopropyl}acetic acid 19a. Following the general procedure, this compound was obtained from **18a** as a colourless oil (52%). R_f 0.5. $[\alpha]_D^{25}$ +32.4 (*c* 1.19, $CHCl_3$). ν_{max} (film) 3323 (OH), 1712 (C═O) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 9.00–10.00 (br s, 1 H,COO*H*), 5.09 (br s, 1 H, N*H*), 2.70–2.83 (m, 1 H, CH_2COOH), 2.33 (m, 1 H, *c*Pr-*H*), 2.03–2.17 (m, 1 H, CH_2COOH), 1.45 (s, 9 H, C(CH_3)), 1.10–1.22 (m, 1 H, *c*Pr-*H*), 0.80–0.90 (m, 1 H, *c*Pr-*H*), 0.66 (dd, $J_{H,H}$ = 12.5 Hz, $J_{H,H}$ = 5.5 Hz, 1 H, *c*Pr-*H*). δ_C (90 MHz, $CDCl_3$) 173.2 (CO_2H), 157.8 (C═O), 81.0 (*C*(CH$_3$)$_3$), 37.8 (CH$_2$), 29.3 (CH), 28.3 (C(*C*H$_3$)$_3$), 15.8 (CH), 13.3 (CH$_2$). HRMS (ESI): *m*/*z* for $C_{10}H_{17}NNaO_3$ $[M+Na]^+$ requires 238.1050; found 238.1052.

2-{(1*R*,2*S*)-[(*tert*-butoxycarbonyl)amino]cyclopropyl}acetic acid 19b. Following the general procedure, this compound was obtained from **18b** as a colourless oil (55%). R_f 0.5. $[\alpha]_D^{21}$ −32.3 (*c* 1.17, $CHCl_3$). IR and NMR data identical to those for **19a** above. HRMS (ESI): *m*/*z* for $C_{10}H_{17}NNaO_3$ $[M+Na]^+$ requires 238.1050; found 238.1050.

2-{(*Z*)-[(*tert*-butoxycarbonyl)amino]cyclopropyl}acetic acid 23. Following the general procedure, this compound was obtained from **22** as a pale yellow oil (64%). R_f 0.6. ν_{max} (film) 3329 (OH), 1710 (C═O) cm^{-1}. δ_H (360 MHz, $CDCl_3$) 10.60 (br s, 1H, COO*H*), 5.10 (br s, 1 H, N*H*), 2.64–2.44 (m, 1 H, CH_2COOH), 2.32 (m, 1 H, *c*Pr-*H*), 2.10–2.26 (m, 1 H, CH_2COOH), 1.42 (s, 9 H), 1.10–1.20 (m, 1 H, *c*Pr-*H*), 0.75–0.84 (m, 1 H, *c*Pr-*H*), 0.63 (dd, $J_{H,H}$ = 12.8 Hz, $J_{H,H}$ = 5.8 Hz, 1 H, *c*Pr-*H*). δ_C (75 MHz, $CDCl_3$) 181.0 (CO_2H), 169.4 (C═O), 80.6 (*C*(CH$_3$)$_3$), 37.6 (CH$_2$), 29.3 (CH), 28.3 (C(*C*H$_3$)$_3$), 24.2 (CH$_2$), 13.5 (CH$_2$). HRMS (ESI): *m*/*z* for $C_{10}H_{17}NNaO_4$ $[M+Na]^+$ requires 238.1050, found 238.1049.

X-Ray crystallographic study on compound 19a

N-Boc cyclopropane γ-amino acid **19a** (24 mg) was suspended in EtOAc (300 μL) and (1*S*,2*R*)-(−)-ephedrine (18.8 mg, 1.0 equiv.) was added. The mixture was heated at 60 °C for 15 min. Upon cooling a white precipitate appeared, and was recovered by filtration. This solid was recrystallised by being suspended in acetonitrile, then warmed up to 70 °C. EtOAc was then added dropwise until the solution became slightly turbid. Slow cooling of the mixture gave crystals which were suitable for analysis.

X-ray diffraction data were collected by using a Kappa X8 APPEX II Bruker diffractometer with graphite-monochromated MoK radiation (λ = 0.71073 Å). The temperature of the crystal was maintained at 100 K by means of a 700-Series Cryostream cooling device, with an accuracy of ±1 K. The data were corrected for Lorentz polarization and absorption effects. The structure was solved by direct methods using SHELXS-97[24] and refined against *F*2 by full-matrix least-squares techniques using SHELXL-97[25] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the software package WINGX.[26]

X-ray crystal data of $C_{20}H_{32}NO_5$, *M* = 380.48, orthorhombic, space group P $2_12_12_1$, *Z* = 4, *T* = 100 K, *a* = 8.1131(17) Å, *b* = 10.109(2) Å, *c* = 25.357(6) Å, *V* = 2079.6(8) Å^3, *d* = 1.215 g cm^{-3}, R_1 = 0.0532, wR_2 = 0.1137, 3359 independent reflections were collected (R_{int} = 0.0900). CCDC 809952† contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Acknowledgements

M. S. is grateful for financial support from the Regione Autonoma of Sardinia (Programma Master and Back – bando 2007–08).

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Published on 08 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB06095C
Downloaded by Universitaire d'Angers on 12 February 2012

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