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Concise synthesis of enantiomerically pure (1'S, 2'R)- and (1'R, 2'S) 2S-amino-3-(2'-aminomethyl-cyclopropyl)-propionic acid – two *E*-diastereoisomers of 4,5-methano-L-lysine

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1 **Abstract**

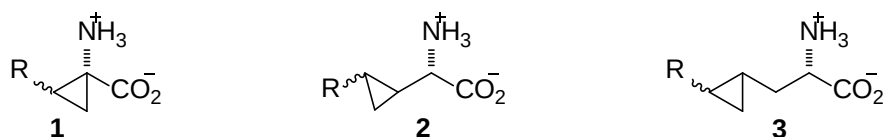
2 A concise synthesis of both *E*-isomers of 2*S*-amino-3-(2'-aminomethyl-cyclopropyl)-
3 propionic acid, new methano-L-lysines, is described. The synthetic route includes nine steps
4 from L-methionine, with a key step involving the cyclopropanation of an intermediate *E*-
5 allylic alcohol. The resultant hydroxymethylcyclopropanes were readily separated and
6 converted to the title α -amino acids. The stereochemistry around the cyclopropane rings was
7 deduced by conducting the cyclopropanation in the presence of *N,N,N',N'*-tetramethyl-D-
8 tartaric acid diamide butylboronate, a chiral controller which is known to favour the
9 production of *S*-hydroxymethyl cyclopropanes from allylic alcohols.

10 **Keywords**

11 synthesis of α -amino acids · cyclopropanated amino acids · cyclopropanation · 4,5-methano-
12 L-lysine · stereoselective synthesis

1 Introduction

2 α -Amino acids incorporating highly strained rings are of significant interest as mimics of
3 natural amino acids, for incorporation into conformationally constrained peptidomimetics and
4 as biologically active compounds or precursors to biologically active compounds.¹ Amongst
5 this class of compounds, cyclopropanated α -amino acids have been widely investigated^{2,3}
6 while cyclobutyl-^{4,5}, bicyclo[1.1.1]pentanyl-^{6,7,8,9,10,11} and cubanyl-^{12,13} α -amino acids have
7 received much less attention. Cyclopropanated versions of proteogenic amino acids are
8 termed methanoamino acids and are classified according to the position of the cyclopropane
9 ring on the amino acid side chain (Fig 1).² Examples of 2,3-methano-, 3,4-methano- and 4,5-
10 methanoamino acids are known. The 2,3- and 3,4-analogues have considerable
11 conformational constraint at, or near, the amino acid centre, which is presumably why they
12 have been much more extensively studied. Of the possible 4,5-methanoamino acids, 4,5-
13 methanoisoleucine¹⁴, a natural plant growth regulator¹⁵, 4,5-methanoproline¹⁶ and 4,5-
14 methanoornithine¹⁷ have been synthesized. The latter is the central component of belactosin
15 A and B, biologically active compounds isolated from *Streptomyces* sp. fermentation broth¹⁸.
16 The *N*-Boc protected form of 4,5-methanoleucine has also been prepared¹⁹, which leaves only
17 4,5-methanolysine and 4,5-methanoarginine as potential 4,5-cyclopropanated forms of
18 proteogenic amino acids that remain unreported.



19 2,3-methanoamino acids

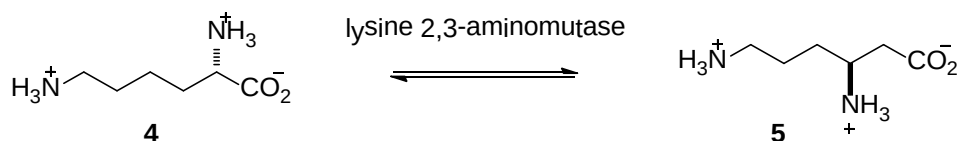
20 3,4-methanoamino acids

21 4,5-methanoamino acids

22 **Figure 1** General structures of methanoamino acids

23 Cyclopropanated compounds are of interest as potential mechanism-based
24 inhibitors of enzymes that employ free radical intermediates, as cyclopropylmethyl radicals
25 can undergo rapid and irreversible ring opening reactions²⁰. One fascinating class of free
26 radical enzyme employs *S*-adenosylmethione to generate a substrate free radical within the
27 enzyme active site^{21,22}. The most widely studied enzyme in this class is lysine-2,3-
28 aminomutase which catalyses the isomerisation of α -L-lysine **4** to β -L-lysine **5** (Scheme 1).
A potential mechanistic probe for this enzyme is 4,5-methano-L-lysine (**3**, R = -CH₂NH₃⁺),
as it would be expected to undergo ring opening when a free radical is generated at the 3-

position. Herein is described an expedient synthesis of the two *E*-diastereomers of 4,5-methano-L-lysine.

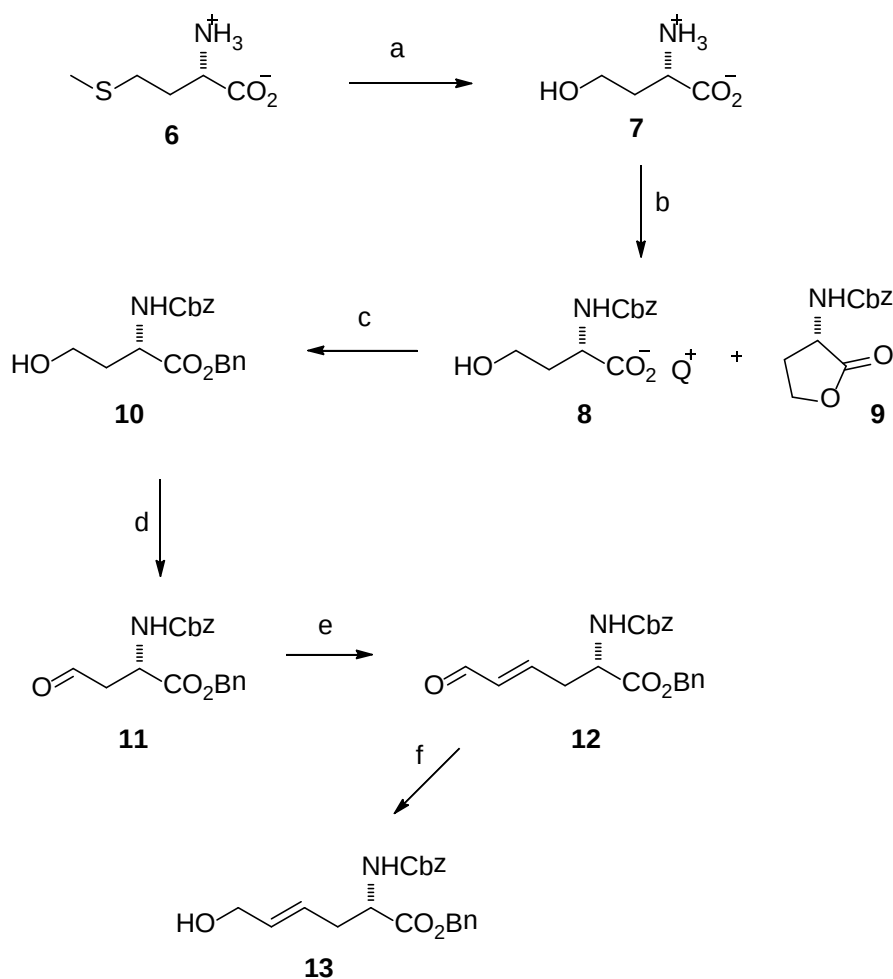


Scheme 1 Interconversion of α -L-lysine and β -L-lysine catalysed by the SAM dependent enzyme lysine 2,3-aminomutase

Results and Discussion

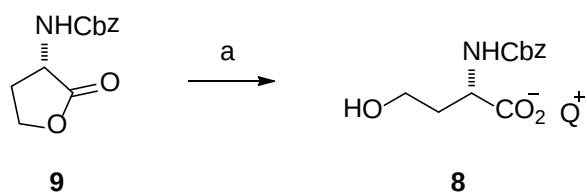
To ensure enantiomeric purity at the α -position in the final products, the initial starting material employed for the synthesis of the target 4,5-methano-L-lysines was a natural α -L-amino acid. L-Methionine **6** served this purpose and was easily converted to L-homoserine **7**^{*} via a two-step process involving S-methylation then hydrolysis, following the method of Baldwin and Flinn²³ (Scheme 2). The amine functionality of L-homoserine was then protected as the benzylcarbamate and precipitated from diethyl ether as the stable dicyclohexylammonium salt **8**,²⁴ which was obtained in 48% yield from L-methionine. A γ -lactone side product **9**, which resulted from cyclisation of the intermediate hydroxyl-acid, was also produced during the course of this experiment, and was isolated in 23% yield. This γ -lactone **9** could be converted to the ammonium salt **8** in 61% yield through a sequence of basic hydrolysis, acidification and precipitation, as shown in Scheme 3.

^{*} Note that L-homoserine is also commercially available but its two step preparation from L-methionine is convenient and economical.



1

2 **Scheme 2** Reagents and conditions: *a* (i) CH_3I , 45% aq. MeOH (ii) NaHCO_3 , reflux; *b* (i) $\text{PhCH}_2\text{OCOCl}$,
 3 NaHCO_3 , H_2O (ii) HCl (conc.), (iii) Et_2O , dicyclohexylamine, **8**, 48%, **9**, 23% from **6**; *c* PhCH_2Br , DMF; *d*
 4 PCC, NaOAc , 4Å sieves, CH_2Cl_2 , 73% from **8**; *e* $\text{Ph}_3\text{P}=\text{CHCHO}$, CH_2Cl_2 , 81%; *f* NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, THF,
 5 0 °C, 84%. Q^+ = dicyclohexylammonium.

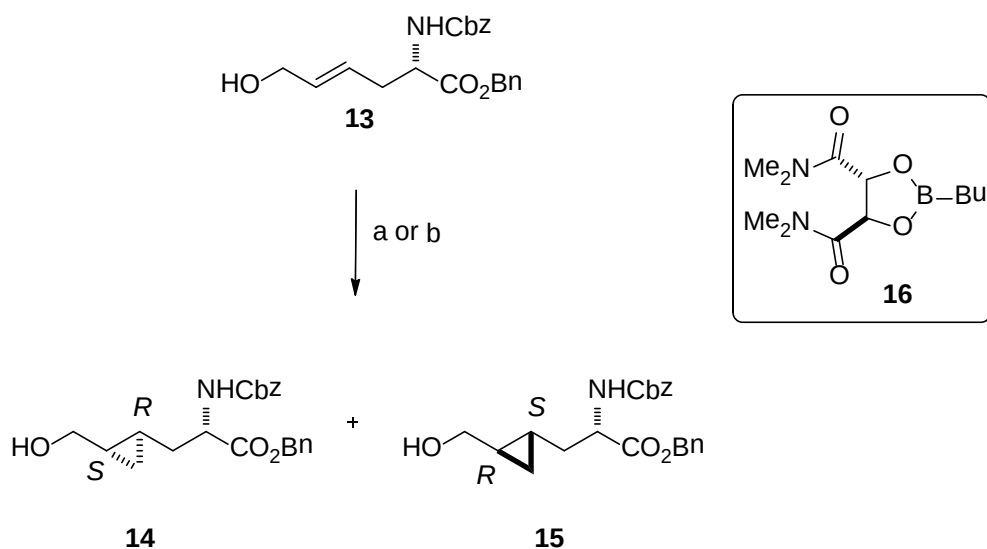


6

7 **Scheme 3** Reagents and conditions: *a* (i) 0.1 M KOH_{aq} , 60 °C, (ii) HCl , (iii) Et_2O , dicyclohexylamine, 61%. Q^+
 8 = dicyclohexylammonium.

9 Protection of the carboxylate functionality as the benzyl ester **10**, by treatment of the
 10 ammonium salt **8** with benzyl bromide in DMF, ensured that both amino and carboxylate
 11 groups could later be deprotected simultaneously under hydrogenolysis conditions. Chain
 12 extension was achieved by pyridinium chlorochromate oxidation of the alcohol to the
 13 aldehyde **11**,²⁴ followed by a Wittig reaction with triphenylphosphanylidene acetaldehyde to

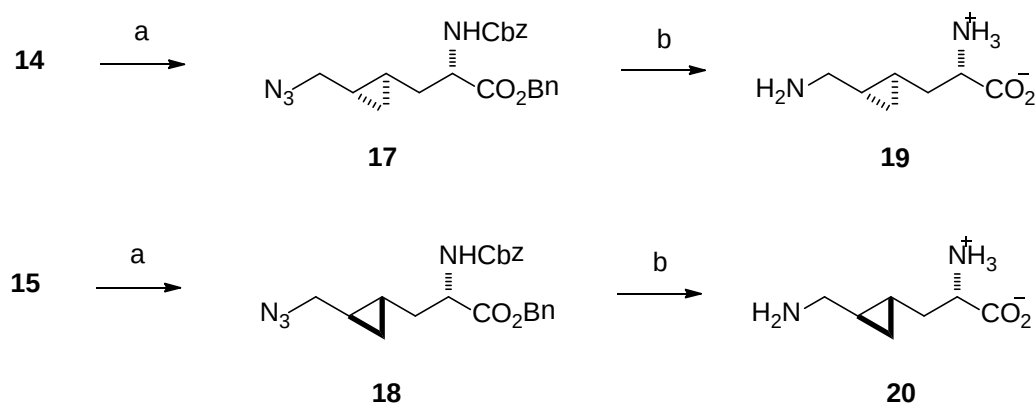
give the α,β -unsaturated aldehyde **12**. Some experimentation was required in order to find the optimum conditions for the reduction of the α,β -unsaturated aldehyde **12** to the allylic alcohol **13**. Treatment with sodium borohydride in THF at 0°C, in the presence of cerium chloride heptahydrate²⁵, gave the best result, furnishing the required allylic alcohol **13** in 84% yield.



Scheme 4 Reagents and conditions: *a* Et₂Zn, CH₂I₂, CH₂Cl₂, **14**, 34%, **15**, 35% (isolated); *b* Et₂Zn, CH₂I₂, CH₂Cl₂, *N,N,N',N'*-tetramethyl-D-tartaric acid diamide butylboronate (**16**); **14**, 94%, **15**, 6% (hplc).

Treatment of the *E*-allylic alcohol **13** with diethyl zinc and diiodomethane in dichloromethane gave an almost equimolar mixture of the two possible *E*-cyclopropanes **14** and **15**, which could be separated by careful column chromatography to give one isomer in 34% isolated yield and the other in 35% yield. The stereochemistry of these products was deduced by repeating the cyclopropanation reaction in the presence of the chiral dioxaborolane, *N,N,N',N'*-tetramethyl-D-tartaric acid diamide butylboronate (**16**), derived from D-tartaric acid. This latter experiment yielded the same *E*-cyclopropanes in a ratio of 94:6. It has been demonstrated by Charette's group that cyclopropanation of *E*-allylic alcohols in the presence of **16** consistently gives the cyclopropane with the *S*-configuration at the position bearing the hydroxymethyl substituent as the major product^{26,27}. The major product from the stereoselective cyclopropanation reaction performed on **13** was therefore assigned to have the 1'*R*, 2'*S* configuration (**14**), with the minor product assigned to have the 1'*S*, 2'*R* configuration (**15**), as indicated in Scheme 4.

The hydroxymethyl cyclopropanes **14** and **15**, were separately converted to the corresponding azides **17** and **18**, in a two-step process involving initial conversion to the corresponding bromides by treatment with carbontetrabromide and triphenylphosphine, then displacement of the bromides with azide. Reduction of the azides under hydrogenation conditions simultaneously cleaved the protecting groups on the amino acid centres to give the target 4,5-methano-L-lysines **19** and **20** in good yield and high purity.



Scheme 5 Reagents and conditions: *a* (i) CBr_4 , PPh_3 , CH_2Cl_2 (ii) NaN_3 , DMF, **17** 72%, **18**, 74%; *b* H_2 , 10%Pd-C, MeOH, **19** 78%, **20** 86%.

Conclusion

The non-natural amino acid, 4,5-methano-L-lysine, is one of the few possible cyclopropanated analogues of proteogenic α -amino acids that have yet to be reported. The four possible diastereomers of 4,5-methano-L-lysine are of interest as possible mechanism based inhibitors of lysine 2,3-aminomutase. Described here is a convenient synthesis of the two *E*-isomers of 4,5-methano-L-lysine starting from L-methionine. A key step in the sequence involved the cyclopropanation with diethyl zinc and diiodomethane of a homochiral *E*-allylic alcohol bearing a protected α -amino acid functionality. Surprisingly, the protected α -amino acid did not noticeably influence the stereochemical outcome of this cyclopropanation reaction, but the two resulting hydroxymethyl *E*-cyclopropanes could be readily separated and converted separately to the target α -amino acids. The inclusion of the chiral controller *N,N,N',N'*-tetramethyl-D-tartaric acid diamide butylboronate in the cyclopropanation reaction led to the two hydroxymethyl *E*-cyclopropanes in a diastereomeric ratio of 94:6. The known preference of this reagent to favour the production of cyclopropanes from *E*-allylic alcohols with the *S*-configuration at the position bearing the

hydroxymethyl substituent was used to deduce the stereochemistry of each of the cyclopropanated products.

Experimental

General Remarks

Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone, dichloromethane was dried by distillation from calcium hydride, methanol was dried by storage over freshly activated 3Å molecular sieves and dimethylformamide (DMF) was dried by storage over 4Å molecular sieves.

Thin layer chromatography was performed on silica coated aluminium-backed sheets (silica gel 60/F₂₅₄). Flash chromatography was performed with Merck silica gel 60 (0.040-0.063 mm), and gravity chromatography was performed with Merck silica gel 60 (0.063-0.200 mm). Optical rotations were recorded at room temperature on a Perkin Elmer 141 Polarimeter. The units for concentration (*c*) are g/100 mL. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 300 MHz spectrometer (¹H, 300 MHz; ¹³C, 75.5 MHz) unless otherwise stated. CDCl₃ solutions were referenced to internal TMS and D₂O solutions were referenced to internal *d*₆-acetone. Infrared spectra were recorded on a Perkin Elmer 1600 Series Fourier Transform Spectrophotometer of either thin films (neat) or nujol mulls between sodium chloride plates. Low resolution electrospray mass spectra were recorded on a Micromass Platform Spectrometer and high resolution mass spectra were recorded on a Bruker BioApex 47e Fourier Transform spectrometer, both using electrospray ionisation.

HPLC analysis of diastereomeric mixtures of **14** and **15** were carried out on an Agilent Technologies 1260 Infinity System, (1260 series pump, 1260 autosampler and a Diode Array detector 1260 series) using an reverse phase C18 column (Luna (2) 150 × 4.50 mm, 5µm, Phenomenex). The gradient used consisted of acetonitrile (AcN) / water with 0.1% trifluoroacetic acid (TFA) with the following program: *t* = 0-3 min. 50% AcN; *t* = 23 min. 100% AcN.

1 Synthesis

2 *Dicyclohexylammonium 2S-benzyloxycarbonylamino-4-hydroxy butyrate (8)* and 2S-
3 *[(Benzyloxycarbonylamino)-4-butyrolactone (9)]*

4 Iodomethane (21.1 mL, 0.34 mmol) was added dropwise to a stirred mixture of L-methionine
5 (25.1 g, 0.17 mol) in 45% aq. methanol (500 mL), and the resulting mixture was stirred at
6 room temperature for 20 h. Thereafter, the solution was placed under reduced pressure for
7 half an hour to remove excess iodomethane before being cooled to 0 °C. This reaction
8 mixture was then used in the next step without further purification. A small sample was
9 removed, concentrated *in vacuo* and then analysed to confirm formation of the sulphonium
10 salt.

11 ¹H NMR (D₂O) δ 3.90 (t, *J* = 6.3 Hz, 1H), 3.70-3.49 (m, 2H), 2.98 (s, 6H), 2.53-2.44 (m,
12 2H); ¹³C NMR (D₂O) δ 172.9, 53.4, 49.6, 40.2, 25.7; IR (Nujol) ν 3444, 1614 cm⁻¹; MS
13 *m/z* 328 (2M⁺), 164 (M⁺); HRMS *m/z* Calcd for C₆H₁₄NO₂S⁺ [M⁺] : 164.0745, found
14 164.0739.

15 Sodium hydrogen carbonate (16.93 g, 0.20 mol) was added to the mixture containing the
16 sulphonium salt, described above, and the resulting solution was stirred at reflux for 24 h.
17 Thereafter, the mixture was concentrated *in vacuo* to yield crude **7** as a pale yellow oil. This
18 crude oil was used in the next step without purification.

19 ¹H NMR (D₂O, 400 MHz) δ 3.71 (t, *J* = 8 Hz, 1H), 3.43 dd, *J* = 12, 8 Hz, 2H), 2.58 (t, *J* = 8
20 Hz, 2H); ¹³C NMR (D₂O) δ 177.2, 61.7, 56.4, 35.2; IR (Nujol) ν 3424, 1631, 1058 cm⁻¹;
21 MS *m/z* 261 ((2M+Na)⁺), 142 ((M+Na)⁺); HRMS *m/z* Calcd for [(C₄H₉O₃N)Na]⁺ :
22 142.0480, found 142.0473.

23 The crude oil containing **7**, described above, was dissolved in water (350 mL) with sodium
24 hydrogen carbonate (35.7 g, 0.43 mol). Benzyl chloroformate (31.5 mL, 0.22 mol) was
25 added dropwise, and the resulting solution stirred for 2.25 h. Thereafter, the reaction mixture
26 was washed with diethyl ether (3 x 60 mL) and the aqueous phase acidified with concentrated
27 HCl (to pH~3). The butyrolactone **9** (10.1 g, 23% from L-methionine) was isolated from the
28 ether wash as a white solid. The acidified aqueous phase was extracted with diethyl ether (5 x
29 80 mL), the organic layers combined, dried over sodium sulphate and filtered.

Dicyclohexylamine was added to the filtrate to afford **8** (25.0 g, 31% from L-methionine) as a white precipitate.

Characterisation for Dicyclohexylammonium 2S-benzyloxycarbonylamino-4-hydroxy butyrate (8):

Mp 139-141 °C; ¹H NMR (CDCl₃) δ 9.27 (br s, 2H), 7.36 (br s, 5H), 5.96 (br d, *J* = 6.1 Hz, 1H), 5.11 (s, 2H), 4.13 (m, 1H), 3.80-3.70 (m, 2H), 2.95-2.85 (m, 2H), 2.06 – 1.22 (m, 22H); ¹³C NMR (CDCl₃) δ 176.4, 156.4, 136.6, 128.5, 128.1 (2 carbons), 66.8, 60.2, 54.6, 52.8, 37.2, 29.6, 25.4, 24.9; IR (Nujol) ν 3358, 1712, 1628, 1552 cm⁻¹; MS *m/z* 435 (*M* + *H*)⁺; HRMS *m/z* Calcd for [(C₂₄H₃₈N₂O₅)H]⁺ : 435.2859, found 435.2851.

Characterisation for 2S-[(Benzyloxycarbonylamino)-4-butyrolactone (9):

Mp 126-127 °C (lit., 129-130 °C²⁸); ¹H NMR (CDCl₃) δ 7.36 (br s, 5H), 5.37 (br s, 1H), 5.13 (s, 2H), 4.43 (m, 2H), 4.25 (m, 1H), 2.20 (m, 2H); ¹³C NMR (CDCl₃) δ 175.0, 156.1, 135.9, 128.6, 128.3, 128.1, 67.4, 65.9, 50.6, 30.3; IR (Nujol) ν 3329, 1779, 1695, 1543, 742 cm⁻¹; MS *m/z* 258 ((*M*+Na)⁺), 236 ((*M*+H)⁺).

Dicyclohexylammonium 2S-benzyloxycarbonylamino-4-hydroxy butyrate (8) from 2S-[(Benzyloxycarbonylamino)-4-butyrolactone (9)

The lactone **9** (0.25 g, 1.1 mmol) was added to KOH aq. (0.1M, 10 mL) and the resulting solution was heated to 60 °C for 24 h. The mixture was allowed to cool to room temperature and then washed with diethyl ether (15 mL). The aqueous phase was acidified to pH~3 with conc. HCl and extracted with diethyl ether (3 x 15 mL). These latter extracts were combined, dried over sodium sulphate and filtered. Dicyclohexylamine was added to the filtrate to afford **8** (0.28 g, 61%) as a white powder. mp 138-141 °C.

2S-Benzyloxycarbonylamino-4-hydroxy butyric acid benzyl ester (10)

Benzyl bromide (1.7 mL, 14 mmol) was added to a suspension of **8** (5.13 g, 12 mmol) in dry DMF (20 mL) and left to stir for 21 h at room temperature under an atmosphere of nitrogen. Thereafter, the mixture was poured into water (150 mL) and subsequently extracted with diethyl ether (5 x 50 mL). The organic layers were combined, washed with water (50 mL), dried over sodium sulphate and filtered. The filtrate was concentrated *in vacuo* to yield

crude **10** (3.89 g, 95% crude yield) as a viscous, yellow oil. This crude product was used in the next reaction without further purification.

^1H NMR (CDCl_3) δ 7.31 (br s, 10H), 5.72 (br d, $J = 7.3$ Hz, 1H), 5.18 (s, 2H), 5.11 (s, 2H), 4.59 (m, 1H), 3.75-3.65 (m, 2H), 2.15 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (CDCl_3) δ 172.2, 156.6, 136.0, 135.1, 128.5 (4 carbons), 128.2, 128.1, 67.4, 67.3, 58.4, 51.6, 35.4; IR (neat) ν 3343, 1721, 1669, 1530, 1498, 1060, 738 cm^{-1} ; MS m/z 366 ($\text{M}+\text{Na}$) $^+$; HRMS m/z Calcd for $[(\text{C}_{19}\text{H}_{21}\text{NO}_5)\text{Na}]^+$: 366.1317, found 366.1307.

2S-Benzylloxycarbonylamino-4-oxo-butyrac acid benzyl ester (**11**)

Pyridinium chlorochromate (0.62 g, 2.9 mmol), anhydrous sodium acetate (0.25 g, 2.9 mmol) and powdered 4Å molecular sieves ($\sim$ 0.25 g) was added to a solution of **10** (0.83 g, 2.4 mmol) in dry dichloromethane (15 mL). The reaction mixture was left to stir at room temperature under nitrogen for 1.5 h. Thereafter, the reaction mixture was filtered through a plug of silica eluting first with dichloromethane (100 mL) followed by ethyl acetate (100 mL). The ethyl acetate fraction was concentrated *in vacuo* to yield the crude product as a yellow oil. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 7:3, R_f 0.16) to yield **11** (0.67 g, 73% from **8**) as a white solid.

Mp 74-75 $^\circ\text{C}$ (lit. 76-78 $^\circ\text{C}^{24}$); ^1H NMR (CDCl_3) δ 9.68 (s, 1H), 7.29 (br s, 10H), 5.71 (br d, $J = 8.1$ Hz, 1H), 5.17 (s, 2H), 5.10 (s, 2H), 4.64 (m, 1H), 3.25-2.95 (m, 2H), 3.11 (dd, $J = 19.1$, 35.1); ^{13}C NMR (CDCl_3) δ 199.0, 170.5, 155.9, 136.0, 135.7, 128.4 (4 carbons), 128.2, 128.1, 67.9, 67.3, 49.3, 46.0; IR (Nujol) ν 3316, 1746, 1716, 1681, 1538, 1053, 753 cm^{-1} ; MS m/z 705 ($(2\text{M}+\text{Na})^+$), 342 ($(\text{M}+\text{H})^+$).

2S-Benzylloxycarbonylamino-6-oxo-hex-4-enoic acid benzyl ester (**12**)

Triphenylphosphoranylidene acetaldehyde (2.15 g, 7.1 mmol) was added to a solution of **11** (0.81 g, 2.4 mmol) in dry dichloromethane (30 mL). The resulting mixture was stirred at room temperature under nitrogen for 20 h. Thereafter, the reaction mixture was concentrated *in vacuo* to yield the crude product as a sticky red solid. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 10:3, R_f 0.24) to yield **12** (0.71 g, 81%) as a yellow oil.

$[\alpha]_D +9.2$ (c 0.4, CHCl_3); ^1H NMR (CDCl_3) δ 9.42 (d, $J = 7.8$ Hz, 1H), 7.35 (br s, 10H), 6.64 (dt, $J = 7.2$, 15.6 Hz, 1H), 6.10 (dd, $J = 7.8$, 15.6 Hz, 1H), 5.40 (m, 1H), 5.23 (d, $J = 12.0$ Hz,

1H), 5.14 (d, $J = 12.0$ Hz, 1H), 5.11 (s, 2H), 4.66 (m, 1H), 3.00-2.63 (m, 2H); ^{13}C NMR (CDCl_3) δ 193.1, 170.6, 155.6, 150.8, 135.5, 134.7 (2 carbons), 128.8, 128.7, 128.6, 128.3, 128.1, 67.7, 67.2, 52.9, 35.7; IR (neat) ν 3331, 1724, 1642, 1526, 1052, 977, 739, 698 cm^{-1} . MS m/z 757 ($(2\text{M}+\text{Na})^+$), 390 ($(\text{M}+\text{Na})^+$). HRMS m/z Calcd for $[(\text{C}_{21}\text{H}_{21}\text{NO}_5)\text{Na}]^+$: 390.1317, found 390.1299.

2S-Benzylloxycarbonylamino-6-hydroxy-hex-4-enoic acid benzyl ester (13)

Sodium borohydride (0.01, 0.3 mmol) was added in small portions to a cooled solution of **12** (0.10 g, 0.3 mmol) and cerium trichloride heptahydrate (0.12 g, 0.3 mmol) in dry THF (5 mL). The resulting solution was allowed to warm to room temperature and stirred for 1 h under nitrogen. Thereafter, the reaction mixture was diluted with water (30 mL, dropwise at first) then extracted into chloroform (3 x 30 mL). The organic layers were combined, washed with water (10 mL), brine (10 mL), dried over sodium sulphate and filtered. The filtrate was concentrated *in vacuo* to yield the crude product as a yellow oil. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 4:1, R_f 0.14) to yield **13** (0.87 g, 84%) as a yellow oil.

$[\alpha]_D + 12.3$ (c 0.4, CHCl_3); ^1H NMR (CDCl_3) δ 7.40-7.25 (m, 10H), 5.64 (m, 1H), 5.49 (m, 1H), 5.20 (d, $J = 5.8$ Hz, 1H), 5.15 (d, $J = 5.8$ Hz, 1H), 5.10 (s, 2H), 4.49 (m, 1H), 3.99 (d, $J = 5.5$ Hz, 2H), 2.60-2.40 (m, 2H); ^{13}C NMR (CDCl_3) δ 172.1, 155.9, 136.3, 135.4, 134.2, 128.6 (2 carbons), 128.7, 128.6, 128.3, 128.1, 125.3, 67.6, 67.3, 63.0, 53.8, 35.6; IR (neat) ν 3343, 1783, 1715, 1609, 1588, 1530, 1053, 913, 739, 698 cm^{-1} ; MS m/z 761 ($(2\text{M}+\text{Na})^+$), 392 ($(\text{M}+\text{Na})^+$); HRMS m/z Calcd for $[(\text{C}_{21}\text{H}_{23}\text{NO}_5)\text{Na}]^+$: 392.1474, found 392.1472.

(1'R, 2'S)- and (1'S, 2'R) 2S-Benzylloxycarbonylamino-3-2(2'-hydroxymethyl cyclopropyl)-propionic acid benzyl ester (14 and 15)

Diiodomethane (2.4 mL, 30.0 mmol) was added dropwise to a solution of 1M diethyl zinc in *n*-hexane (15.1 mL, 15.0 mmol) in dry dichloromethane (10 mL), under nitrogen at 0 $^\circ\text{C}$. This mixture was stirred for 10 minutes while a white precipitate formed. A solution of **13** (1.77 g, 4.7 mmol) in dry dichloromethane (10 mL) was added to the mixture. The reaction mixture allowed to warm to room temperature and stirred for 4 h. Thereafter, the reaction mixture was cooled to 0 $^\circ\text{C}$ and quenched with saturated aq. ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried over magnesium sulphate and filtered. The filtrate was concentrated *in*

vacuo to give the crude product as a yellow oil. The crude product was purified by gravity column chromatography (*n*-hexane/ethyl acetate 7:3) allowing separation of the two diastereomers.

The lower R_f (0.19 in *n*-hexane/ethyl acetate 7:3) alcohol, **14** (0.62 g, 34%) was obtained as colourless oil. HPLC retention time: 6.9 min.

$[\alpha]_D +2.0$ (*c* 0.4, CHCl_3); ^1H NMR (CDCl_3) δ 7.40-7.25 (m, 10H), 5.54 (br d, $J = 8.0$ Hz, 1H), 5.20-5.05 (m, 4H), 4.48 (m, 1H), 3.55 (m, 1H), 3.06 (dd, $J = 9.7, 9.9$ Hz, 1H), 2.03 (m, 1H), 1.40 (m, 1H), 0.74 (m, 1H), 0.57 (m, 1H), 0.34 (m, 2H). ^{13}C NMR (CDCl_3) δ 172.4, 156.2, 136.2, 135.1, 128.8 (2 carbons), 128.7 (2 carbons), 128.4, 128.3, 67.3, 67.0, 66.4, 54.3, 36.0, 20.8, 14.2, 9.1; IR (neat) ν 3335, 2928, 1719, 1586, 1528, 1499, 1455, 1343, 1194, 1104, 1054, 918, 751, 698 cm^{-1} ; MS m/z 789 ((2M+ Na) $^+$), 406 ((M+ Na) $^+$); HRMS m/z Calcd for $[(\text{C}_{22}\text{H}_{25}\text{NO}_5)\text{Na}]^+$; 406.1630; found 406.1618.

The higher R_f (0.20 in *n*-hexane/ethyl acetate 7:3) alcohol, **15** (0.64 g, 35%) was obtained as a colourless oil. HPLC retention time: 7.4 min.

$[\alpha]_D -12.8$ (*c* 0.6, CHCl_3); ^1H NMR (CDCl_3) δ 7.40-7.25 (m, 10H), 5.59 (br d, $J = 9.0$ Hz, 1H), 5.20-5.05 (m, 4H), 4.58 (m, 1H), 3.83 (m, 1H), 2.98 (br d, $J = 5.3$ Hz, 1H), 2.86 (t, $J = 4.6$ Hz, 1H), 1.99 (m, 1H), 1.30 (m, 1H), 0.94 (m, 1H), 0.57 (m, 1H), 0.40-0.30 (m, 2H); ^{13}C NMR (CDCl_3) δ 172.1, 156.5, 136.2, 135.2, 128.8, 128.7 (2 carbons), 128.5, 128.4 (2 carbons), 67.3, 67.2, 66.7, 54.5, 37.6, 21.2, 14.6, 9.2; IR (neat) ν 3335, 2928, 1719, 1586, 1528, 1499, 1455, 1343, 1194, 1104, 1054, 918, 751, 698; MS m/z 789 ((2M+Na) $^+$), 406 ((M+Na) $^+$); HRMS m/z Calcd for $[(\text{C}_{22}\text{H}_{25}\text{NO}_5)\text{Na}]^+$; 406.1630, found 406.1622.

Stereoselective synthesis of (1'R, 2'S)-2S-Benzoyloxycarbonylamino-3-2(2'-hydroxymethyl cyclopropyl)-propionic acid benzyl ester (14)

To a solution of diethylzinc (0.675 mmol) in anhydrous dichloromethane (1.4 mL) at 0°C was added diiodomethane (110 μL , 1.35 mmol, 4.4 eq). The mixture was stirred at 0°C for 10 min while a white precipitate formed. A solution of *N,N,N',N'*-tetramethyl-D-tartaric acid diamide butylboronate **16** (93.7 mg, 0.344 mmol, 1.1 eq) and allylic alcohol **13** (112 mg, 0.30 mmol, 1 eq.) in dichloromethane (2.0 mL) was added rapidly *via* cannula. The resulting mixture was stirred at room temperature for 2 h and then cooled to 0°C. Saturated aq. ammonium chloride was added and the mixture was extracted with 3 portions of ethyl

acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The crude residue was analysed by NMR and HPLC showing >95% conversion and 94:6 d.r. The major diastereomer was found to have identical NMR and HPLC properties as the lower R_f compound mentioned above. Based on consistent stereochemical outcomes observed by Charette,^{26,27} the configuration of this major diastereomer was assigned to be 1'R, 2'S.

(1'S, 2'R) 3-(2'-Azidomethyl cyclopropyl)-2S-benzyloxycarbonylamino-propionic acid benzyl ester (18)

Triphenylphosphine (0.16 g, 0.6 mmol) and carbon tetrabromide (0.20 g, 0.6 mmol) was added to a solution of **15** (0.15 g, 0.4 mmol) in dichloromethane (5 mL). The resulting mixture was stirred under nitrogen at room temperature for 2 h. Thereafter, the reaction mixture was quenched with saturated aq. NaHCO₃ (5 mL). The organic layer was separated from the aqueous layer, washed with brine, dried over sodium sulphate and filtered. The filtrate was then concentrated *in vacuo* and redissolved in dry DMF (5 mL). Sodium azide (0.10 g 2.4 mmol) was then added and the reaction mixture was stirred under nitrogen for 4 h. Thereafter, the reaction mixture was treated with water and extracted into dichloromethane. The organic layer was separated from the aqueous layer, dried over sodium sulphate and filtered. The filtrate was concentrated *in vacuo* to yield the crude product as a yellow oil. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate 15:5) to yield **18** (0.12 g, 74%) as a colourless oil.

R_f (0.18 in *n*-hexane/ethyl acetate, 15:5); $[\alpha]_D$ -31.9 (c 0.3, MeOH); ¹H NMR (CDCl₃) δ 7.36 (br s, 10H), 5.64 (br d, J = 8.4 Hz, 1H), 5.19 (s, 2H), 5.12 (s, 2H), 4.53 (m, 1H), 3.07 (m, 2H), 1.77 (m, 2H), 0.86 (m, 1H), 0.58 (m, 1H), 0.42 (m, 2H); ¹³C NMR (CDCl₃) δ 171.2, 155.8, 136.3, 135.3, 129.3-127.9 (6 carbons), 68.3 (3 carbons), 53.4, 35.4, 23.8, 13.3, 11.1; IR (neat) ν 3340, 2128, 1786, 1726, 1587, 1520, 1055, 739, 698 cm⁻¹. MS m/z 409 ((M+H)⁺), 381 (((M-N₂)+H)⁺).

(1'S, 2'R) 3-(2'-Azidomethyl cyclopropyl)-2S-benzyloxycarbonylamino-propionic acid benzyl ester (17)

The alcohol **14** (0.13 g, 0.3 mmol) was converted to the azide **17** (0.10 g, 72%) following the same method as that used to prepare **18**.

R_f (0.15 in *n*-hexane/ethyl acetate, 15:5); $[\alpha]_D$ -5.4 (*c* 0.3, MeOH); ^1H NMR (CDCl_3) δ 7.34 (br s, 10H), 5.72 (br d, J = 8.4 Hz, 1H), 5.17 (s, 2H), 5.11 (s, 2H), 4.52 (m, 1H), 3.05 (m, 2H), 1.76 (m, 2H), 0.86 (m, 1H), 0.57 (m, 1H), 0.42 (m, 2H); ^{13}C NMR (CDCl_3) δ 172.0, 155.9, 136.4, 135.2, 128.7-128.1 (6 carbons), 67.3, 67.0, 55.3, 54.1, 36.1, 20.9, 13.3, 10.3; IR (neat) ν 3340, 2126, 1784, 1726, 1587, 1520, 1055, 739, 698 cm^{-1} ; MS m/z 409 (($\text{M}+\text{H}$) $^+$), 381 ((($\text{M}-\text{N}_2$) H) $^+$).

(1'S, 2'R) 2S-Amino-3-(2'-aminomethyl-cyclopropyl)-propionic acid (20)

Palladium on charcoal (10%, ~10 mg) was added to a solution of **18** (0.12g, 0.3 mmol) in dry methanol (5 mL). The resulting mixture was placed under an atmosphere of hydrogen and stirred vigorously for 5 h. Thereafter, the reaction mixture was filtered through Celite, concentrated *in vacuo* and the residue redissolved in a minimal amount of methanol. The solution was then triturated with diethyl ether and centrifuged. The supernatant was decanted and the precipitate redissolved in water prior to lyophilization to yield **20** (0.04g, 86%) as a cream coloured solid.

$[\alpha]_D$ -10.4 (*c* 0.5, H_2O); mp 188-189°C; ^1H NMR (D_2O) δ 3.70 (m, 1H), 2.90 (dd, J =7.2, 13.2 Hz, 1H), 2.80 (dd, J = 7.5, 12.9 Hz, 1H), 1.89 (m, 1H), 1.67 (m, 1H), 1.00-0.80 (m, 2H), 0.75-0.40 (m, 2H); ^{13}C NMR (D_2O) δ 178.1, 55.4, 39.6, 31.9, 17.6, 13.6, 11.4; IR (Nujol) ν 3123, 2094, 1626, 1600 cm^{-1} . MS m/z 159 ($\text{M}+\text{H}$) $^+$; HRMS m/z Calcd for $[(\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2)\text{H}]^+$; 159.1134, found 159.1136.

(1'R, 2'S) 2S-Amino-3-(2'-aminomethyl-cyclopropyl)-propionic acid (19)

The azide **17** (0.10 g, 0.2 mmol) was converted to the lysine analogue **19** (0.03 g, 78%) following the same procedure as that used to prepare **20**. The product was obtained as a cream coloured solid.

$[\alpha]_D$ -8.1 (*c* 0.3, H_2O); mp 162-163°C; ^1H NMR (D_2O) δ 3.68 (m, 1H), 2.90 (dd, J = 7.1, 13.2 Hz, 1H), 2.75 (dd, J = 8.0, 13.2 Hz, 1H), 1.80-1.60 (m, 2H), 0.95-0.75 (m, 2H), 0.65-0.30 (m, 2H); ^{13}C NMR (CDCl_3) δ 176.2, 55.2, 44.0, 34.5, 15.5, 13.7, 10.6; IR (Nujol) ν 3132, 2098, 1626, 1601 cm^{-1} ; MS m/z 159 ($\text{M}+\text{H}$) $^+$; HRMS m/z Calcd for $[(\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2)\text{H}]^+$; 159.1134, found 159.1138.

Supplementary Material

Characterisation data for compounds **12-15** and **19-20** as well as hplc traces and proton nmr spectra relevant to the stereoselective cyclopropanation reaction are available on the Journal's website.

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