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Communication

Concise Synthesis of Enantiomerically Pure (1′*S*,2′*R*)- and (1′*R*,2′*S*)-2*S*-Amino-3-(2′-aminomethyl-cyclopropyl)propionic Acid: Two *E*-Diastereoisomers of 4,5-Methano-L-lysine

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

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Introduction

α-Amino acids incorporating highly strained rings are of significant interest as mimics of natural amino acids, for incorporation into conformationally constrained peptidomimetics, and as biologically active compounds or precursors to biologically active compounds.[1] Amongst this class of compounds, cyclopropanated α-amino acids have been widely investigated[2,3] while cyclobutyl-,[4,5] bicyclo[1.1.1]pentanyl-,[6–11] and cubanyl-[12,13] α-amino acids have received much less attention. Cyclopropanated versions of proteogenic amino acids are termed methanoamino acids and are classified according to the position of the cyclopropane ring on the amino acid side chain (Fig. 1).[2] Examples of 2,3-methano-, 3,4-methano-, and 4,5-methanoamino acids are known. The 2,3- and 3,4-analogues have considerable conformational constraint at, or near, the amino acid centre, which is presumably why they have been much more extensively studied. Of the possible 4,5-methanoamino acids, 4,5-methanoisoleucine,[14] a natural plant growth regulator,[15] 4,5-methanoproline,[16] and 4,5-methanoornithine[17] have been synthesised. The latter is the central component of belactosin A and B, biologically active compounds isolated from *Streptomyces* sp. fermentation broth.[18] The *N*-Boc protected form of 4,5-methanoleucine has also been prepared,[19] which leaves only 4,5-methanolysine and 4,5-methanoarginine as potential 4,5-cyclopropanated forms of proteogenic amino acids that remain unreported.

Cyclopropanated compounds are of interest as potential mechanism-based inhibitors of enzymes that employ free radical intermediates, as cyclopropylmethyl radicals can undergo rapid and irreversible ring opening reactions.[20] One fascinating class of free radical enzyme employs *S*-adenosylmethione to generate a substrate free radical within the enzyme active site.[21,22] The most widely studied enzyme in this class is lysine-2,3-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 = $-CH_2NH_3^+$), 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.

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 into L-homoserine **7**[†] by a two-step process involving

[†]Note that L-homoserine is also commercially available but its two step preparation from L-methionine is convenient and economical.

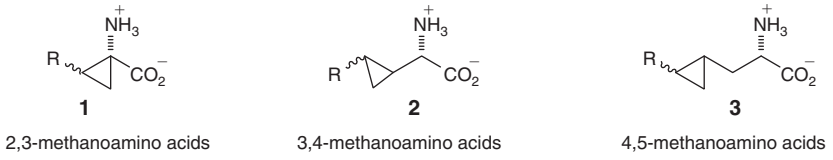
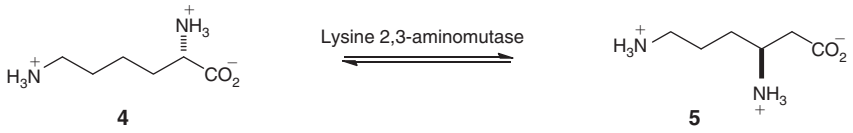
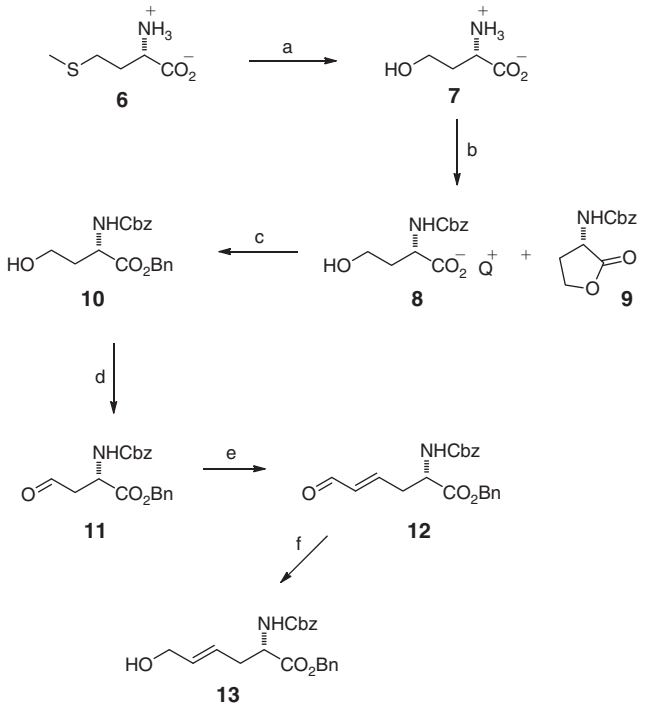


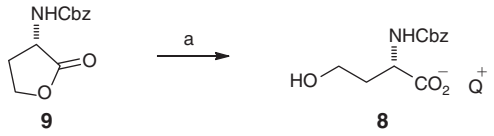
Fig. 1. General structures of methanoamino acids.



Scheme 1. Interconversion of α-L-lysine and β-L-lysine catalysed by the *S*-adenosyl methionine (SAM) dependent enzyme lysine 2,3-aminomutase.



Scheme 2. Reagents and conditions: a: (i) CH_3I, 45 % aq. MeOH, (ii) $NaHCO_3$, reflux; b: (i) $PhCH_2OCOCl$, $NaHCO_3$, H_2O, (ii) HCl (conc.), (iii) Et_2O, dicyclohexylamine, **8**, 48 %, **9**, 23 % from **6**; c: $PhCH_2Br$, DMF; d: pyridinium chlorochromate (PCC), NaOAc, 4 Å sieves, CH_2Cl_2, 73 % from **8**; e: $Ph_3P{=}CHCHO$, CH_2Cl_2, 81 %; f: $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, 0°C, 84 %. Q^+ = dicyclohexylammonium.



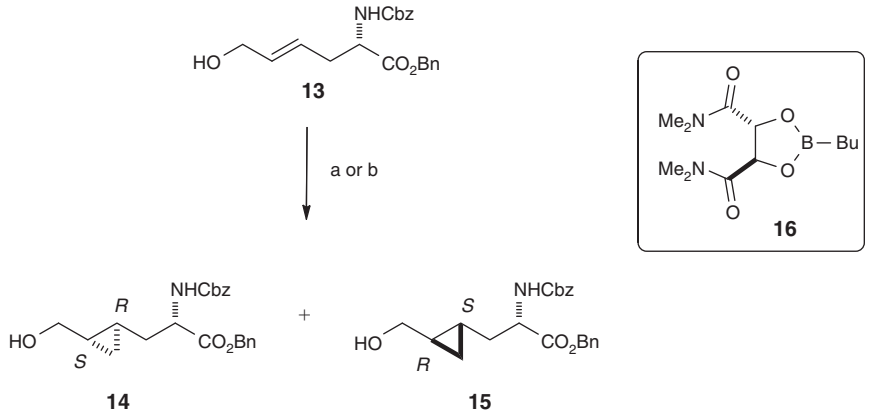
Scheme 3. Reagents and conditions: a: (i) 0.1 M $KOH_{aq.}$ 60°C, (ii) HCl, (iii) Et_2O, dicyclohexylamine, 61 %. Q^+ = dicyclohexylammonium.

S-methylation and hydrolysis, following the method of Baldwin and Flinn[23] (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 hydroxy acid, was also produced during the course of this experiment, and was isolated in 23 % yield. This γ-lactone **9** could be converted into the ammonium salt **8** in 61 % yield through a sequence of basic hydrolysis, acidification, and precipitation, as shown in Scheme 3.

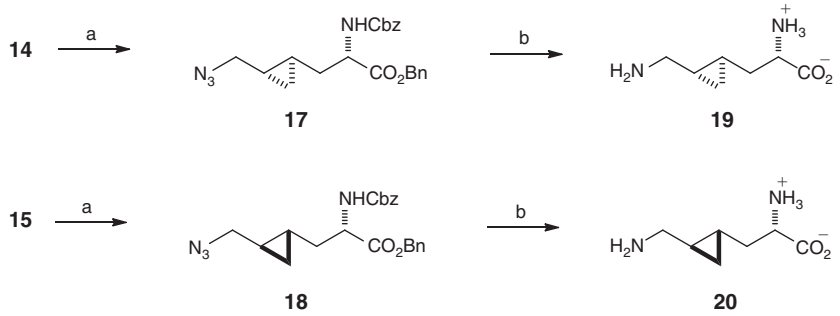
Protection of the carboxylate functionality as the benzyl ester **10**, by treatment of the ammonium salt **8** with benzyl bromide in DMF, ensured that both amino and carboxylate groups could later be deprotected simultaneously under hydrogenolysis conditions. Chain extension was achieved by pyridinium chlorochromate oxidation of the alcohol to the 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 heptahydrate,[25] gave the best result, furnishing the required allylic alcohol **13** in 84 % yield.

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 into the corresponding azides **17** and **18** in a two-step process involving initial conversion into the corresponding bromides by treatment with carbontetrabromide and triphenylphosphine, followed by displacement of the bromides with azide (Scheme 5). Reduction of the azides under hydrogenation



Scheme 4. Reagents and conditions: a: Et_2Zn, CH_2I_2, CH_2Cl_2, **14**, 34 %, **15**, 35 % (isolated); b: Et_2Zn, CH_2I_2, CH_2Cl_2, *N*,*N*,*N*′,*N*′-tetramethyl-D-tartaric acid diamide butylboronate (**16**); **14**, 94 %, **15**, 6 % (HPLC).



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 %.

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.

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 into 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

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

Thin-layer chromatography was performed on silica-coated aluminium-backed sheets (silica gel 60/F_{254}). 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 per 100 mL. NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz) unless otherwise stated. $CDCl_3$ solutions were referenced to internal tetramethylsilane (TMS) and D_2O 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.

High performance liquid chromatography (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 a reverse phase C18 column (Luna (2) 150 × 4.50 mm, 5 µm, 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.

Synthesis

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

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

δ_H (D_2O) 3.90 (t, *J* 6.3, 1H), 3.70–3.49 (m, 2H), 2.98 (s, 6H), 2.53–2.44 (m, 2H); δ_C (D_2O) 172.9, 53.4, 49.6, 40.2, 25.7; ν_{max} (Nujol)/cm^{-1} 3444, 1614; *m/z* 328 ($2M^+$), 164 (M^+); *m/z* (HRMS) Calc. for $C_6H_{14}NO_2S^+$ [M^+]: 164.0745, found 164.0739.

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

δ_H (D_2O, 400 MHz) 3.71 (t, *J* 8, 1H), 3.43 dd, *J* 12, 8, 2H), 2.58 (t, *J* 8, 2H); δ_C (D_2O) 177.2, 61.7, 56.4, 35.2; ν_{max} (Nujol)/cm^{-1} 3424, 1631, 1058; *m/z* 261 ([2M + Na]$^+$), 142 ([M + Na]$^+$); *m/z* (HRMS) Calc. for [($C_4H_9O_3N$)Na]$^+$: 142.0480, found 142.0473.

The crude oil containing **7**, described above, was dissolved in water (350 mL) with sodium hydrogen carbonate (35.7 g, 0.43 mol). Benzyl chloroformate (31.5 mL, 0.22 mol) was added dropwise, and the resulting solution stirred for 2.25 h. Thereafter, the reaction mixture was washed with diethyl ether (3 × 60 mL) and the aqueous phase acidified with concentrated HCl (to pH ~3). The butyrolactone **9** (10.1 g, 23 % from L-methionine) was isolated from the ether wash as a white solid. The acidified aqueous phase was extracted with diethyl ether (5 × 80 mL), the organic layers were combined, dried over sodium sulfate, and filtered. Dicyclohexylamine was added to the filtrate to afford **8** (25.0 g, 31 % from L-methionine) as a white precipitate.

Characterisation of Dicyclohexylammonium 2S-Benzyloxycarbonylamino-4-hydroxy Butyrate (**8**)

Mp 139–141°C; δ_H ($CDCl_3$) 9.27 (br s, 2H), 7.36 (br s, 5H), 5.96 (br d, *J* 6.1, 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); δ_C ($CDCl_3$) 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; ν_{max} (Nujol)/cm^{-1} 3358, 1712, 1628, 1552; *m/z* 435 ([M + H]$^+$); *m/z* (HRMS) Calc. for [($C_{24}H_{38}N_2O_5$)H]$^+$: 435.2859, found 435.2851.

Characterisation of 2S-[(Benzyloxycarbonylamino]-4-butyrolactone (**9**)

Mp 126–127°C (lit., 129–130°C[28]); δ_H ($CDCl_3$) 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); δ_C ($CDCl_3$) 175.0, 156.1, 135.9, 128.6, 128.3 128.1, 67.4, 65.9, 50.6, 30.3; ν_{max} (Nujol)/cm^{-1} 3329, 1779, 1695, 1543, 742; *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 aq. KOH (0.1 M, 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 × 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 × 50 mL). The organic layers were combined, washed with water (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum 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.

δ_H ($CDCl_3$) 7.31 (br s, 10H), 5.72 (br d, *J* 7.3, 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); δ_C ($CDCl_3$) 172.2, 156.6, 136.0, 135.l, 128.5 (4 carbons), 128.2, 128.1, 67.4, 67.3, 58.4, 51.6, 35.4; ν_{max} (neat)/cm^{-1} 3343, 1721, 1669, 1530, 1498, 1060, 738; *m/z* 366 ([M + Na]$^+$); *m/z* (HRMS) Calc. for [($C_{19}H_{21}NO_5$)Na]$^+$: 366.1317, found 366.1307.

2S-Benzyloxycarbonylamino-4-oxo-butyric Acid Benzyl Ester (**11**)

Pyridinium chlorochromate (0.62 g, 2.9 mmol), anhydrous sodium acetate (0.25 g, 2.9 mmol), and powdered 4 Å molecular sieves (~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 under vacuum 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°C (lit. 76–78°C[24]); δ_H ($CDCl_3$) 9.68 (s, 1H), 7.29 (br s, 10H), 5.71 (br d, *J* 8.1, 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); δ_C ($CDCl_3$) 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; ν_{max} (Nujol)/cm^{-1} 3316, 1746, 1716, 1681, 1538, 1053, 753; *m/z* 705 ([2M + Na]$^+$), 342 ([M + H]$^+$).

2S-Benzyloxycarbonylamino-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 under vacuum 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, $CHCl_3$); δ_H ($CDCl_3$) 9.42 (d, *J* 7.8, 1H), 7.35 (br s, 10H), 6.64 (dt, *J* 7.2, 15.6, 1H), 6.10 (dd, *J* 7.8, 15.6, 1H), 5.40 (m, 1H), 5.23 (d, *J* 12.0, 1H), 5.14 (d, *J* 12.0, 1H), 5.11 (s, 2H), 4.66 (m, 1H), 3.00–2.63 (m, 2H); δ_C ($CDCl_3$) 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; ν_{max} (neat)/cm^{-1} 3331, 1724, 1642, 1526, 1052, 977, 739, 698; *m/z* 757 ($[2M + Na]^+$), 390 ($[M + Na]^+$). *m/z* (HRMS) Calc. for $[(C_{21}H_{21}NO_5)Na]^+$: 390.1317, found 390.1299.

*2S-Benzyloxycarbonylamino-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) and then extracted into chloroform (3 × 30 mL). The organic layers were combined, washed with water (10 mL), brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum 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, $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.25 (m, 10H), 5.64 (m, 1H), 5.49 (m, 1H), 5.20 (d, *J* 5.8, 1H), 5.15 (d, *J* 5.8, 1H), 5.10 (s, 2H), 4.49 (m, 1H), 3.99 (d, *J* 5.5, 2H), 2.60–2.40 (m, 2H); δ_C ($CDCl_3$) 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; ν_{max} (neat)/cm^{-1} 3343, 1783, 1715, 1609, 1588, 1530, 1053, 913, 739, 698; *m/z* 761 ($[2M + Na]^+$), 392 ($[M + Na]^+$); *m/z* (HRMS) Calc. for $[(C_{21}H_{23}NO_5)Na]^+$: 392.1474, found 392.1472.

*(1′R,2′S)- and (1′S,2′R) 2S-Benzyloxycarbonylamino-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 1 M diethyl zinc in *n*-hexane (15.1 mL, 15.0 mmol) in dry dichloromethane (10 mL), under nitrogen at 0°C. This mixture was stirred for 10 min 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 was allowed to warm to room temperature and stirred for 4 h. Thereafter, the reaction mixture was cooled to 0°C and quenched with saturated aq. ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated under vacuum 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 a colourless oil. HPLC retention time: 6.9 min.

$[\alpha]_D$ +2.0 (*c* 0.4, $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.25 (m, 10H), 5.54 (br d, *J* 8.0, 1H), 5.20–5.05 (m, 4H), 4.48 (m, 1H), 3.55 (m, 1H), 3.06 (dd, *J* 9.7, 9.9, 1H), 2.03 (m, 1H), 1.40 (m, 1H), 0.74 (m, 1H), 0.57 (m, 1H), 0.34 (m, 2H). δ_C ($CDCl_3$) 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; ν_{max} (neat)/cm^{-1} 3335, 2928, 1719, 1586, 1528, 1499, 1455, 1343, 1194, 1104, 1054, 918, 751, 698; *m/z* 789 ($[2M + Na]^+$), 406 ($[M + Na]^+$); *m/z* (HRMS) Calc. for $[(C_{22}H_{25}NO_5)Na]^+$; 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, $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.25 (m, 10H), 5.59 (br d, *J* 9.0, 1H), 5.20–5.05 (m, 4H), 4.58 (m, 1H), 3.83 (m, 1H), 2.98 (br d, *J* 5.3, 1H), 2.86 (t, *J* 4.6, 1H), 1.99 (m, 1H), 1.30 (m, 1H), 0.94 (m, 1H), 0.57 (m, 1H), 0.40–0.30 (m, 2H); δ_C ($CDCl_3$) 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; ν_{max} (neat)/cm^{-1} 3335, 2928, 1719, 1586, 1528, 1499, 1455, 1343, 1194, 1104, 1054, 918, 751, 698; *m/z* 789 ($[2M + Na]^+$), 406 ($[M + Na]^+$); *m/z* (HRMS) Calc. for $[(C_{22}H_{25}NO_5)Na^+]$; 406.1630, found 406.1622.

*Stereoselective Synthesis of (1′R,2′S)-2S-Benzyloxycarbonylamino-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 equiv.). 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 equiv.) and allylic alcohol **13** (112 mg, 0.30 mmol, 1 equiv.) in dichloromethane (2.0 mL) was added rapidly by a 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 three 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 a 94 : 6 diastereomeric ratio (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 and co-workers,[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. $NaHCO_3$ (5 mL). The organic layer was separated from the aqueous layer, washed with brine, dried over sodium sulfate, and filtered. The filtrate was then concentrated under vacuum 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 sulfate, and filtered. The filtrate was concentrated under vacuum 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); δ_H ($CDCl_3$) 7.36 (br s, 10H), 5.64 (br d, *J* 8.4, 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); δ_C ($CDCl_3$) 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; ν_{max} (neat)/cm^{-1} 3340, 2128, 1786, 1726, 1587, 1520, 1055, 739, 698; *m/z* 409 ($[M+H]^+$), 381 ($[(M-N_2)+H]^+$).

*(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 into 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); δ_H ($CDCl_3$) 7.34 (br s, 10H), 5.72 (br d, *J* 8.4, 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); δ_C ($CDCl_3$) 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; ν_{max} (neat)/cm^{-1} 3340, 2126, 1784, 1726, 1587, 1520, 1055, 739, 698; *m/z* 409 ($[M+H]^+$), 381 ($[(M-N_2)+H]^+$).

*(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** (0.12 g, 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 under vacuum 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 before lyophilization to yield **20** (0.04 g, 86 %) as a cream coloured solid.

$[\alpha]_D$ −10.4 (*c* 0.5, H_2O); mp 188–189°C; δ_H (D_2O) 3.70 (m, 1H), 2.90 (dd, *J* 7.2, 13.2, 1H), 2.80 (dd, *J* 7.5, 12.9, 1H), 1.89 (m, 1H), 1.67 (m, 1H), 1.00–0.80 (m, 2H), 0.75–0.40 (m, 2H); δ_C (D_2O) 178.1, 55.4, 39.6, 31.9, 17.6, 13.6, 11.4; ν_{max} (Nujol)/cm^{-1} 3123, 2094, 1626, 1600; *m/z* 159 ($[M+H]^+$); *m/z* (HRMS) Calc. for $[(C_7H_{14}N_2O_2)H^+]$; 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 into 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; δ_H (D_2O) 3.68 (m, 1H), 2.90 (dd, *J* 7.1, 13.2, 1H), 2.75 (dd, *J* 8.0, 13.2, 1H), 1.80–1.60 (m, 2H), 0.95–0.75 (m, 2H), 0.65–0.30 (m, 2H); δ_C ($CDCl_3$) 176.2, 55.2, 44.0, 34.5, 15.5, 13.7, 10.6; ν_{max} (Nujol)/cm^{-1} 3132, 2098, 1626, 1601; *m/z* 159 ($[M+H]^+$); *m/z* (HRMS) Calc. for $[(C_7H_{14}N_2O_2)H^+]$; 159.1134, found 159.1138.

Supplementary Material

Characterisation data for compounds **12**–**15**, **19**, and **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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