An Expedient Asymmetric Synthesis of N-Protected (*S*,*S*)-2-Aminomethyl-1-cyclopropanecarboxylic Acid

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Received 21 July 2010

Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

Abstract: An enantioselective synthesis of a *N*-Boc-protected *trans*-cyclopropane γ-amino acid is reported. The key chiral aldehyde intermediate is prepared in enantiomerically pure form using a three-step aldol–cyclopropanation–retro-aldol protocol.

Key words: aldol reaction, amino acids, asymmetric synthesis, carbocycle, chiral auxiliary, enantioselectivity

γ-Amino acids have been of interest to chemists for some time, since the parent compound, GABA, plays an important role in the central nervous system, and structural analogues are of significant therapeutic value.[1] General synthetic methods for this family of compounds have evolved as a consequence.[2] In the rapidly developing area of foldamer science,[3] oligomers containing γ-amino acids have been shown to adopt well-defined conformations.[4] In this regard, Smith recently identified the unique role played by a *trans*-cyclopropyl γ-amino acid **1** (Figure 1) in peptides which adopted parallel sheet structure in the solid state[5] and in reverse turn mimetics.[6] Smith's synthetic building block was the azide ester derivative **2** (Figure 1), which is obtained in four steps from the expensive (*S*)-benzyl glycidol.

Given the increasing interest in the γ-amino acid **1** and the established interest in cyclopropane-based amino acids in general,[7–9] we thought that access to the complementary *N*-Boc-derivative **3** would be a welcome addition (Figure 1). This compound has been described in enantiomerically enriched form only twice before, using a six-step synthesis which involved the enantioselective cyclopropanation of (*E*)-cinnamyl alcohol (89% ee),[10] or the diastereoselective cyclopropanation of a protected allylic alcohol derived from (*R*)-glyceraldehyde,[11] with both protocols proceeding through azide intermediates.

Previous work in the Bath group has focused around the use of β-hydroxy-β-vinyl-*N*-acyl-oxazolidin-2-one substrates as novel synthons for the asymmetric synthesis of chiral aldehydes.[12] This methodology often relies on the reversible generation of a novel 'temporary stereocentre' that is used to relay stereocontrol, which enables a chiral auxiliary fragment to be used to generate remote stereocentres in very high de. In this paper we report application of this methodology to the enantioselective synthesis of compound **3**. The strategy employed relies on the convenient and stereo-controlled access to the intermediate chiral cyclopropane aldehyde **9**, using a three-step aldol–cyclopropanation–retro-aldol protocol, which implicates intermediate structures **6**–**8** (Scheme 1).

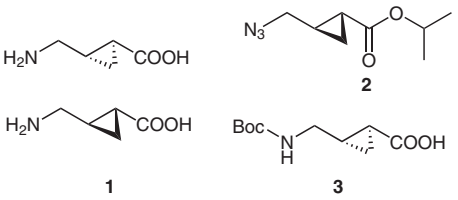

Figure 1 The two enantiomers of the parent γ-amino acid **1** and two synthetically useful derivatives **2** and **3**; the latter is the target structure in this work

The requisite starting aldehyde (*E*)-4-(benzyloxy)but-2-enal **5** was prepared in quantitative yield by chromium(VI)-mediated oxidation–isomerisation of (*Z*)-4-(benzyloxy)but-2-en-1-ol **4**, according to literature precedent,[13] and was used without purification.

In previous work on aldol reactions of *N*-acyl-oxazolidinone **6**, 9-BBNOTf/*i*-Pr_2NEt-mediated efficient condensation with simple α,β-unsaturated aldehydes gave the desired *syn*-aldol products in good yield.[12] However, reaction of **6** with aldehyde **5** under these conditions gave the desired *syn*-aldol **7** in only 5% yield. A modified set of conditions employing *n*-Bu_2BOTf/Et_3N for the aldol reactions of Evans *N*-acyl-oxazolidin-2-ones in good yield had been reported previously by Anderson and coworkers,[14] and we were pleased to observe that application of this procedure resulted in the formation of the desired allylic alcohol *syn*-aldol adduct **7** in 81% yield and >95% de.[15] Compound **7** was subjected to Furukawa-modified Simmons–Smith cyclopropanation[16] to provide cyclopropane-aldol **8** in 92% yield with complete diastereoselectively (>95% de).[17] The chiral auxiliary fragment was then cleaved by treating **8** with LiHMDS in toluene at 0 °C, which resulted in a clean retro-aldol reaction to afford the desired cyclopropane aldehyde **9** in 92% yield,[18] as well as **6** which could be recovered and recycled. It is

SYNLETT 2010, No. 18, pp 2729–2732
Advanced online publication: 08.10.2010
DOI: 10.1055/s-0030-1258814; Art ID: D19810ST
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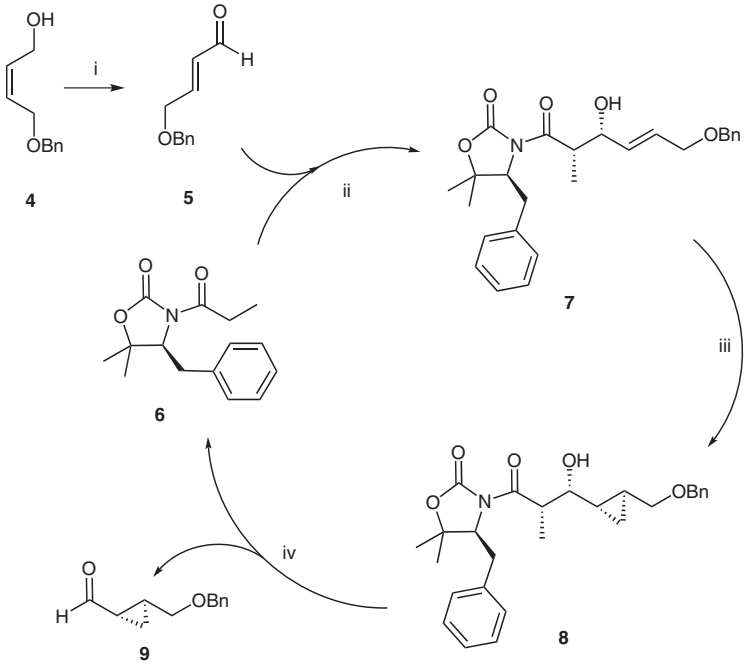
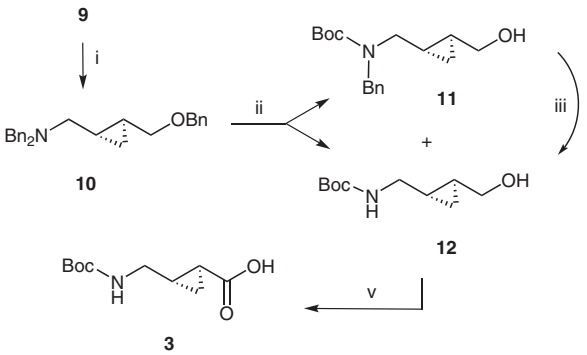


Scheme 1 *Reagents and conditions*: i) PCC (3.0 equiv), NaOAc (3.0 equiv), Celite, CH_2Cl_2, r.t., 3 h, ca. 100%; ii) *n*-Bu_2BOTf (1.2 equiv), *N*-acyl-oxazolidin-2-one **6** (1.0 equiv.), Et_3N (1.3 equiv), CH_2Cl_2, –10 °C to 0 °C, 30 min,; then aldehyde **5** (1.2 equiv), CH_2Cl_2, –78 °C, 45 min then 0 °C, 3 h, 81%; iii) Et_2Zn (10.0 equiv), CH_2I_2 (10.0 equiv), CH_2Cl_2, –10 °C, 5 min, then aldol **7** (1.0 equiv), 2 h, –10 °C to r.t., 92%; iv) LiHMDS (2.2 equiv), cyclopropane-aldol **8** (1.0 equiv), toluene, 0 °C, 3 h, 92%.

noteworthy that 2.2 equivalents of LiHMDS were necessary to drive the reaction to completion and ensure full reproducibility of this step.

This oxazolidinone-based 'temporary stereocentre' strategy therefore provided a convenient access to the key cyclopropane aldehyde intermediate **9**. There is only one literature precedent which provides characterisation data for this compound (as the enantiomer),[19] and in our hands it had a limited shelf life and required a cold environment for storage. With this intermediate in hand, we embarked on functional-group manipulation to afford the target *N*-Boc-γ-amino acid **3**, as summarised in Scheme 2.



Scheme 2 *Reagents and conditions*: i) $NaBH(OAc)_3$ (1.6 equiv), Bn_2NH (1.0 equiv), aldehyde **9** (1.0 equiv), DCE, 4 Å MS, 20 °C, 4 h, 62%; ii) Pd/C (10%), amine **10** (1.0 equiv), HCO_2H, MeOH, 16 h, 20 °C; then Boc_2O (1.0 equiv), NaOH, MeOH, 16 h, 20 °C: *N*-Boc-*N*-Bn-amine **11**, 50% + *N*-Boc-amine **12**, 50%; iii) $Pd(OH)_2/C$ (20%, 60% wet), THF, H_2, 20 °C, 2.5 h, ca. 100%; iv) Jones reagent, acetone, 0 °C, 2 h, then 20 °C, 2 h, 63%.

Reductive amination of aldehyde **9** with dibenzylamine in the presence of sodium triacetoxyborohydride[20] led to amine **10** in 62% yield,[21] thus establishing an entry to the target skeleton without the need for proceeding through azide-based intermediates. Attempts to remove the *N*-benzyl protecting groups of amine **10** under commonly used hydrogenolysis conditions (Pd/C, H_2, MeOH) were unsatisfactory. Transfer hydrogenolysis conditions proved to be more productive, and treatment of amine **7** with HCO_2H and Pd/C in methanol followed by *N*-Boc protection afforded the desired *N*-Boc-protected cyclopropane alcohol **12** in 50% yield,[22] along with the *N*-benzyl-*N*-Boc derivative **11** in 50% yield.[23] After some investigation, we found that the *N*-benzyl protecting group of **11** could be removed by treatment with $Pd(OH)_2/C$ (20%; 60% wet) in dry tetrahydrofuran under a H_2 atmosphere to afford cyclopropane alcohol **12** in quantitative yield.[24] When amine **10** was subjected to the above-mentioned hydrogenolysis conditions [$Pd(OH)_2/C$ (20%; 60% wet), H_2], followed by the *N*-Boc protection procedure, **12** was isolated as the sole product, but in only 23% yield.

Finally, treatment of **12** with Jones reagent gave the target *N*-Boc-protected *trans*-cyclopropane γ-amino acid derivative **3** in 63% yield.[25] Spectroscopic characterisation of this compound was in agreement with previously reported data.[10,11]

In conclusion, the three-step aldol–cyclopropanation–retro-aldol protocol allowed access to the key chiral aldehyde intermediate **9**, which was easily transformed via a straightforward, azide-free sequence into the *N*-Boc-protected *trans*-cyclopropane γ-amino acid derivative **3** in enantiomerically pure form. These procedures should fa-

cilitate future access to peptides and other materials which incorporate this rigid building block.

Acknowledgment

We acknowledge support from COST (Action CM 0803) for an STSM grant (to I. R. D).

References and Notes

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(15) **(*S*)-4-Benzyl-3-[(2*S*,3*R*,*E*)-6-(benzyloxy)-3-hydroxy-2-methylhex-4-enoyl]-5,5-dimethyloxazolidin-2-one (7)**
Colorless oil. $[\alpha]_D^{25}$ –4.7 (*c* 0.87, $CHCl_3$). IR (film): ν = 3461 (OH), 1774 (C=O) cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): δ = 7.45–7.21 (10 H, m, Ph), 5.93 (1 H, dtd, *J* = 15.5, 5.5, 1.0 Hz, C=C*H*CH_2), 5.78 (1 H, ddt, *J* = 15.5, 5.0, 1.0 Hz, C=C*H*CHOH), 4.62–4.41 (4 H, m, CHN, CH_2Ph, C*H*OH), 4.08 (2 H, br d, *J* = 5.5 Hz, CH_2OBn), 3.94 (1 H, qd, *J* = 7.0, 4.0 Hz, C*H*CH_3), 3.10 (1 H, dd, *J* = 14.5, 4.5 Hz, CH^AH^BPh), 2.94 (1 H, dd, *J* = 14.5, 9.0 Hz, CH^AH^BPh), 1.43 [3 H, s, (CH^A_3)C(CH^B_3)], 1.40 [3 H, s, (CH^A_3)C(CH^B_3)], 1.20 (3 H, d, *J* = 7.0 Hz, C$H_3$$CH_2$). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 176.6, 152.4, 138.3, 136.6, 131.8, 129.1, 128.9, 128.7, 128.4, 127.7, 127.6, 126.9, 82.4, 72.2, 70.0, 63.4, 42.7, 35.5, 28.4, 22.2, 11.5. ESI-HRMS: *m/z* calcd for $C_{26}H_{31}NNaO_5$: 460.2094 $[M + Na]^+$; found: 460.2086.

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(17) **(*S*)-4-Benzyl-3-{(2*S*,3*R*)-3-[(1*S*,2*S*)-2-(benzyloxymethyl)-cyclopropyl]-3-hydroxy-2-methyl propanoyl}-5,5-dimethyloxazolidin-2-one (8)**
Colorless oil. IR (film): ν = 3454 (OH), 1774 (C=O) cm^{-1}; $[\alpha]_D^{25}$ +5.6 (*c* 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.18 (10 H, m, Ph and CH_2*Ph*), 4.61–4.46 (3 H, m, CH_2Ph, CHN), 4.02 (1 H, qd, *J* = 7.0, 3.5 Hz, C*H*CH_3), 3.49–3.30 (3 H, m, CH_2OBn, C*H*OH), 3.11 (1 H, dd, *J* = 14.5, 4.0 Hz, CHCH^AH^BPh), 2.91 (1 H, dd, *J* = 14.5, 9.0 Hz, $CHCH^AH^B$Ph), 2.65 (1 H, br s, OH), 1.40 [3 H, s, (CH^A_3)C(CH^B_3)], 1.36 [3 H, s, (CH^A_3)C(CH^B_3)], 1.29 (3 H, d, *J* = 7.0 Hz, CHCH_3), 1.20–1.09 (1 H, m, C*H*-cyclopropyl), 1.01–0.90 (1 H, m, C*H*-cyclopropyl), 0.71 (1 H, dt, *J* = 5.0, 8.5 Hz, CH^AH^B-cyclopropyl), 0.56 (1 H, dt, *J* = 5.0, 8.5 Hz, CH^AH^B-cyclopropyl). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 176.8, 152.6, 138.6, 136.7, 129.1, 128.7, 128.3, 127.7, 127.6, 127.5, 126.9, 82.2, 74.7, 73.2, 72.5, 63.5, 43.1, 35.4, 28.4, 22.2, 20.3, 15.9, 11.5, 8.9. ESI-HRMS): *m/z* calcd for $C_{27}H_{33}NNaO_5$: 474.2251 $[M + Na]^+$; found: 474.2241.

(18) **(*S*,*S*)-2-(Benzyloxymethyl)cyclopropane Carboxaldehyde (9)**
Colorless oil. IR (film): ν = 2859, 2731 (CHO), 1708 (C=O) cm^{-1}. $[\alpha]_D^{25}$ +80 (*c* 0.45, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ = 9.17 (1 H, d, *J* = 5.0 Hz, CHO), 7.40–7.21 (5 H, m, Ph), 4.53 (2 H, s, CH_2Ph), 3.50 (1 H, dd, *J* = 10.5, 5.5 Hz, CH^AH^BOBn), 3.42 (1 H, dd, *J* = 10.5, 5.0 Hz, CH^AH^BOBn), 1.89–1.77 (2 H, m, C*H*-cyclopropyl), 1.33 (1 H, dt, *J* = 8.5, 5.0 Hz, CH^AH^B-cyclopropyl), 1.12–1.04 (1 H, m, CH^AH^B-cyclopropyl). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 200.2, 138.0, 128.4, 127.7, 127.6, 72.8, 70.9, 28.1, 12.4. ESI-HRMS: *m/z* calcd for $C_{12}H_{14}NaO_2$: 213.0886 $[M + Na]^+$; found: 213.0886.

(19) Our synthesis of aldehyde (*S*,*S*)-**9** provided material whose specific rotation of +80 (*c* 0.45, $CHCl_3$) did not match that described in the literature for the *R*,*R*-enantiomer [+43.37 (*c* 0.52, $CHCl_3$)]: Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511; we are grateful to Prof. Shuto and his group for cooperative

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(21) **[(1*S*,2*S*)-2-(Dibenzylaminomethyl)cyclopropyl]-methanol (10)**
Yellow oil which solidified to give an amorphous solid on standing. $[\alpha]_D^{15}$ +18 (*c* 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.30 (1 H, ddd, *J* = 5.0, 5.0, 10.5 Hz, CH^AH^B-cyclopropyl), 0.39 (1 H, ddd, *J* = 5.0, 5.0, 10.5 Hz, CH^AH^B-cyclopropyl), 0.80–0.86 (2 H, m, C*H*-cyclopropyl), 2.27 (1 H, dd, 7.0, 13.0 Hz, CH^AH^BOBn), 2.41 (1 H, dd, *J* = 6.0, 13.0 Hz, CH^AH^BOBn), 3.26–3.32 (2 H, m, CH_2NBn_2), 3.59 (2 H, d, *J* = 13.5 Hz, CH_2NBn), 3.65 (2 H, d, *J* = 13.5 Hz, CH_2NBn), 4.47 (2 H, s, CH_2Ph), 7.16–7.40 (15 H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0 (2 × Cq), 138.6 (Cq), 128.7 (4 × ArCH), 128.3 (2 × ArCH), 128.1 (4 × ArCH), 127.5 (2 × ArCH), 127.4 (ArCH), 126.7 (2 × ArCH), 73.9 (CH_2), 72.4 (CH_2), 58.1 (2 × CH_2), 57.2 (CH_2), 17.9 (CH), 14.8 (CH), 9.5 (CH_2). ESI-HRMS: *m/z* calcd for $C_{26}H_{30}NO$: 372.2322 $[M + H]^+$; found: 372.2349.

(22) ***N*-*tert*-Butoxycarbonyl [(1*S*,2*S*)-2-(Aminomethyl)-cyclopropyl]methanol (12)**
Colorless oil. IR (film): ν = 3344 (OH), 1691 (C=O) cm^{-1}. $[\alpha]_D^{20}$ +7.1 (*c* 0.50, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.42 (2 H, dd, *J* = 5.0, 5.0 Hz, CH^AH^B-cyclopropyl), 0.83–0.91 (1 H, m, C*H*-cyclopropyl), 0.93–1.10 (1 H, m, C*H*-cyclopropyl), 1.42 [9 H, s, $(CH_3)_3C$], 2.90 (1 H, dd, *J* = 5.0, 9.5 Hz), 3.09 (1 H, dd, *J* = 4.5, 9.5 Hz), 3.28 (1 H, dd, *J* = 5.0, 8.0 Hz), 3.57 (1 H, dd, *J* = 4.5, 8.0 Hz). ^{13}C NMR (60 MHz, $CDCl_3$): δ = 156.1 (C=O), 79.2 [$(CH_3)C$], 66.0 (CH_2), 44.5 (CH_2), 28.3 [$(CH_3)C$], 19.9 (CH), 17.1 (CH), 8.2 (CH_2). ESI-HRMS: *m/z* calcd for $C_{10}H_{19}NNaO_3$: 224.1257 $[M + Na]^+$; found: 224.1254.

(23) ***N*-Benzyl *N*-*tert*-Butoxycarbonyl [(1*S*,2*S*)-2-(Aminomethyl)cyclopropyl]methanol (11)**
Colorless oil. IR (film): ν = 3354 (OH), 1698 (C=O), 1172 cm^{-1}. $[\alpha]_D^{27}$ +16 (*c* 1.77, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.42–0.50 (2 H, m, CH^AH^B-cyclopropyl), 0.86–0.93 (1 H, m), 0.95–1.04 (1 H, m), 1.45 [9 H, s, $C(CH_3)_3$], 2.95–3.10 (2 H, m), 3.29 (1 H, dd, *J* = 6.5, 10.0 Hz), 3.37 (1 H, dd, *J* = 6.5, 10.0 Hz), 4.53 (2 H, s, CH_2Bn), 7.27–7.39 (5 H, m, ArCH). ^{13}C NMR (86 MHz, $CDCl_3$): δ = 156.0 (C=O), 138.6 (ArC), 128.5 (2 × ArCH), 127.7 (2 × ArCH), 127.6 (ArCH), 100.1 (CH_2Bn), 73.5 (CH_2), 72.6 (CH_2), 71.0 (Cq), 28.5 [$C(CH_3)_3$], 17.4 (CH), 17.2 (CH), 8.8 (CH_2). ESI-HRMS: *m/z* calcd for $C_{13}H_{17}NNaO_3$: 314.1732 $[M + Na]^+$; found: 314.1716.

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(25) **(1*S*,2*S*)-2-(*tert*-Butoxycarbonyl)aminomethyl Cyclopropanecarboxylic Acid (3)**
Colorless oil. $[\alpha]_D^{27}$ +51 (*c* 0.30, $CHCl_3$) {lit. for (*S*,*S*)-**3**: $[\alpha]_D$ +52.4 (*c* 2, $CHCl_3$);[10] lit. for (*R*,*R*)-**3**: $[\alpha]_D^{25}$ –53.3 (*c* 1.87, $CHCl_3$)[11]}. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.93 (1 H, dd, *J* = 7.0, 11.0 Hz), 1.23 (1 H, ddd, *J* = 13.0, 4.5, 4.5 Hz), 1.48 (9 H, s), 1.57 (1 H, ddd, *J* = 13.0, 4.5, 4.5 Hz), 1.60–1.74 (1 H, m), 2.95–3.15 (1 H, m), 3.16–3.30 (1 H, m), 4.72 (1 H, br s), 5.62 (1 H, br s). ESI-HRMS: *m/z* calcd for $C_{10}H_{17}NNaO_4$: 238.1050 $[M + Na]^+$; found: 238.1049.

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