

# Total synthesis and determination of the stereochemistry of 2-amino-3-cyclopropylbutanoic acid, a novel plant growth regulator isolated from the mushroom *Amanita castanopsidis* Hongo

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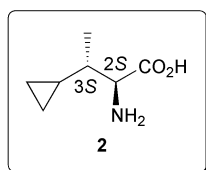
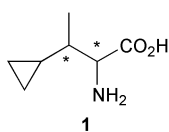
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The unknown stereostructure of 2-amino-3-cyclopropylbutanoic acid **1**, a novel plant growth regulator isolated from the mushroom *Amanita castanopsidis* Hongo, was determined to be (2*S*,3*S*)-**2** through its racemic and enantioselective syntheses employing the chelate–enolate Claisen rearrangement as a key step.

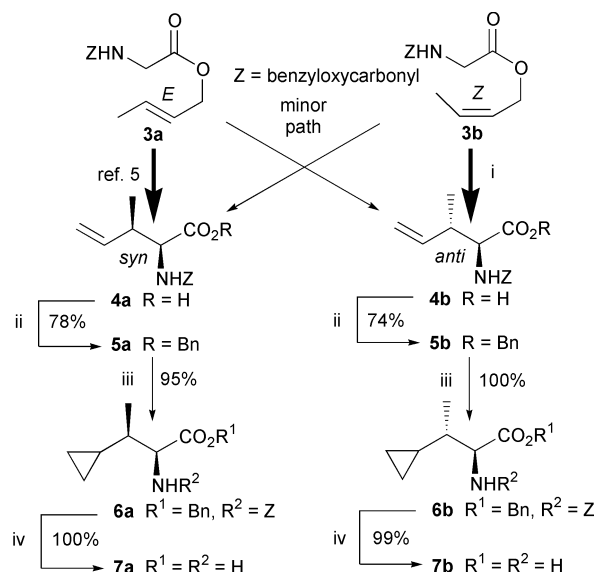
2-Amino-3-cyclopropylbutanoic acid **1** was isolated as a novel  $\alpha$ -amino acid from the mushroom *Amanita castanopsidis* Hongo (Koshiroonitake in Japanese) by Yoshimura *et al.* in 1999, and the plane structure was elucidated by spectroscopic analyses.<sup>1</sup> The relative and absolute configurations at the two chiral centres C2 and C3 have not, however, been determined. It is reported that **1** substantially inhibits root elongation in lettuce seedlings, and the biological activity is like indole-3-acetic acid known as an important plant growth regulator. There have also been many cyclopropane ring-containing  $\alpha$ -amino acids closely related to **1**, such as coronatine,<sup>2</sup> cyclopropylalanine,<sup>3</sup> methylenecyclopropylglycine and hypoglycin A<sup>4</sup> and so forth, possessing a broad spectrum of biological activities. Thus, it appeared desirable to clarify the stereostructure of **1** for exploring structure–activity relationships between the cyclopropane ring-containing  $\alpha$ -amino acids mentioned above and **1**. In this paper, we report that the stereochemistry of **1** is 2*S*,3*S* through the stereoselective syntheses of two possible *syn* and *anti* diastereomers **7a** and **7b**, respectively, in racemic form and the optically active *anti* **2**.



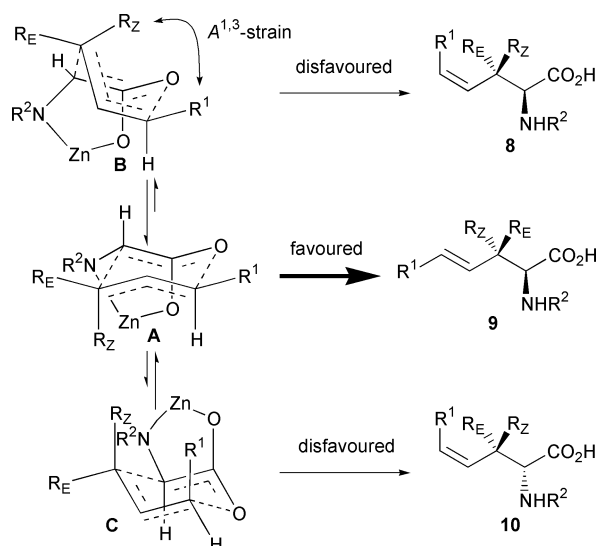
First, we decided to synthesize two possible diastereomers, *syn* **7a** and *anti* **7b**, to elucidate the unknown relative configuration. In 1994, it has been reported by Kazmaier that *syn* amino acid **4a** can diastereoselectively be obtained in a ratio of *syn*:*anti* = 95:5 from (*E*)-ester **3a** via the [3,3]-sigmatropic rearrangement of a chelate-bridged zinc enolate (Scheme 1).<sup>5</sup> The high diastereoselectivity was explained in terms of a chairlike transition state A ( $R^1 = R_Z = H$ ,  $R^2 = Z$ ,  $R_E = Me$ ) like that generally postulated for [3,3]-sigmatropic rearrangements of acyclic systems (Scheme 2).<sup>6</sup> Therefore, another *anti* amino acid **4b** could be constructed by applying Kazmaier's method to (*Z*)-ester **3b**.

In practice, the [3,3]-sigmatropic rearrangement of (*Z*)-ester **3b** under Kazmaier's conditions predominantly afforded the *anti* amino acid **4b**<sup>7</sup> in a modest yield (*anti*:*syn* = ca. 80:20). The somewhat lowered diastereoselectivity in the rearrangement of (*Z*)-**3b** may be due to the following reason. In the case

of (*Z*)-**3b**, a steric repulsion between the axial substituent  $R_Z$  and the rigid chelate-bridged zinc enolate moiety in the transition state A ( $R^1 = R_E = H$ ,  $R^2 = Z$ ,  $R_Z = Me$ ) leading to the *anti* **4b** is more serious than in that of (*E*)-**3a**. Therefore, since the



**Scheme 1** Reagents and conditions: i, LDA, ZnCl<sub>2</sub>, THF, -78 °C to RT, 30 min, 47%; ii, DCC, DMAP, BnOH, Et<sub>2</sub>O, RT, 20 h; iii, CH<sub>2</sub>N<sub>2</sub>, Pd(OAc)<sub>2</sub>, Et<sub>2</sub>O, 0 °C, 1 h; iv, H<sub>2</sub>, 10% Pd-C, MeOH, RT, 15 min.



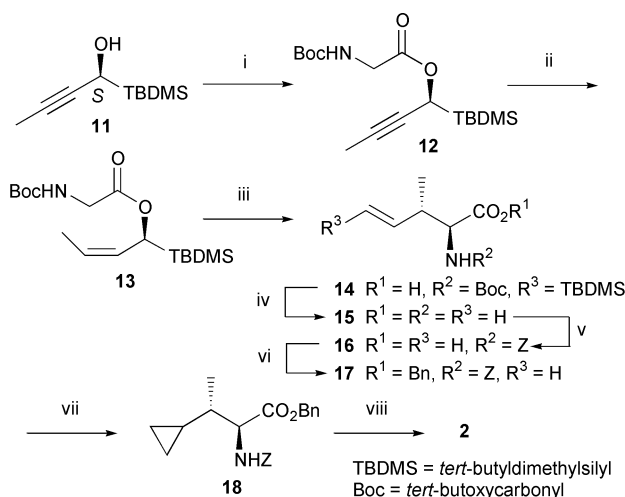
**Scheme 2** Plausible transition states for the [3,3]-sigmatropic rearrangement of chelate-bridged zinc enolates.

<sup>†</sup> Deceased on June 18, 1998.

energy difference between **A** and the boatlike transition state **B** leading to the *syn* **4a** becomes smaller than that in (*E*)-**3a**, the lowering of the diastereoselectivity might be observed. Anyway, both the diastereomers **4a** and **4b** were converted into the desired *syn* and *anti* 2-amino-3-cyclopropylbutanoic acids **7a** and **7b**, respectively, by a sequence of reactions: (i) protection of the carboxyl group as a benzyl ester; (ii) Pd(OAc)<sub>2</sub>-catalyzed cyclopropanation of the terminal double bond with diazomethane;<sup>8</sup> and (iii) hydrogenolysis of the benzylic protective groups. Comparing the <sup>1</sup>H and <sup>13</sup>C NMR of synthetic **7a** and **7b** with those of the natural product **1**,<sup>1</sup> it has been found that **1** is identical to **7b** possessing the *anti* relative stereochemistry.

Next, we embarked on the enantioselective synthesis of optically active *anti* **2** bearing 2*S* stereochemistry, because Yoshimura *et al.* have deduced that the absolute configuration at the C2 position of **1** is *S*.<sup>1</sup> Recently, Sakaguchi *et al.*, one of the authors in this paper, have developed silyl-assisted [3,3]-sigmatropic rearrangements of (1-acyloxy-2-alkenyl)trialkylsilanes to provide optically active vinylsilane-containing  $\alpha$ -amino acids in a complete chirality-transferring manner.<sup>9</sup> In conjunction with the key step for the syntheses of racemates **7a** and **7b**, we adopted the method to synthesize the optically active **2**.

The preparation of the rearrangement precursor (*Z*)-**13** (*J* = 11.0 Hz between the olefinic protons) was carried out by esterification of the readily available chiral (*S*)-alcohol **11**,<sup>10</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> -90.2 (*c* 1.01, CHCl<sub>3</sub>); 98% ee, with commercially available Boc-glycine followed by partial reduction of the resulting alkyne **12** with Lindlar catalyst (Scheme 3). The [3,3]-sigmatropic rearrangement of **13** diastereo- and enantioselectively proceeded under Kazmaier's conditions to give only the (*E*)-*anti* product **14** (*J* = 18.5 Hz between the olefinic protons) in 97% yield with complete chirality transfer. § In spite of the same (*Z*)-geometry as **3b**, the high diastereo- and enantioselectivity observed in this rearrangement could be attributed to the bulky *tert*-butyldimethylsilyl group. In the transition state **B** (R<sup>1</sup> = TBDMS, R<sup>2</sup> = Boc, R<sub>Z</sub> = Me, R<sub>E</sub> = H) leading to *syn* **8** and **C** leading to **10** enantiomeric to **9** except for the alkene geometry, sterically encumbered A<sup>1,3</sup>-strain and 1,3-diaxial-like interaction, respectively, occur between the bulky R<sup>1</sup> and R<sub>Z</sub>. Therefore, because the transition state **A** without such a repulsive interaction becomes relatively more stable than **B** and **C**, **14** might exclusively be formed.



**Scheme 3** Reagents and conditions: i, Boc-glycine, 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDCI), DMAP, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h, 94%; ii, H<sub>2</sub>, 5% Pd-CaCO<sub>3</sub>, Py, EtOAc, RT, 1 h, 81%; iii, LDA, ZnCl<sub>2</sub>, THF, -78 °C to RT, 2 h, 97%; iv, 42% aq. HBF<sub>4</sub>, 1,4-dioxane, 65 °C, 14 h, 100%; v, ZCl, K<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane-H<sub>2</sub>O (1:1), 0 °C to RT, 12 h, 73%; vi, BnOH, EDCI, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, RT, 4 h, 94%; vii, iii in Scheme 1, 100%; viii, iv in Scheme 1, 100%.

Concurrent removal of the TBDMS and Boc groups in the rearrangement product **14** with 42% HBF<sub>4</sub><sup>11</sup> furnished free amino acid **15**, *N*-Z protection of which yielded **16** consistent with ( $\pm$ )-**4b**. Finally, according to the racemic route, the carboxylic acid **16** was converted into the amino acid (2*S*,3*S*)-**2** in almost quantitative yield. The optical rotation of synthetic **2**, [ $\alpha$ ]<sub>D</sub><sup>31</sup> -9.08 (*c* 0.5, H<sub>2</sub>O), was identical with that reexamined for the natural amino acid **1** generously gifted by Professor Wakabayashi (Osaka City University), [ $\alpha$ ]<sub>D</sub><sup>26</sup> -9.46 (*c* 0.035, H<sub>2</sub>O). Thus, it has been found that the hitherto unknown absolute configuration of **1** is assigned to 2*S*,3*S*.

In conclusion, we have accomplished the stereoselective syntheses of two possible *syn* and *anti* diastereomers **7a** and **7b**, respectively, in racemic form and the optically active *anti* **2** using the chelate-enolate Claisen rearrangement as a key step, and determined the relative and absolute configurations of 2-amino-3-cyclopropylbutanoic acid **1**, a novel plant growth regulator. The elucidation of the stereochemistry of **1** will be useful for structure-activity relationships and conformational analysis.

We thank Professor K. Wakabayashi (Osaka City University) for generously supplying natural amino acid **1**, and are also grateful to Ms H. Yoshimura and Mr H. Suzuki (Osaka City University) for helpful discussions.

## Notes and references

‡ The (*Z*)-ester **3b** (*J* = 10.8 Hz between the olefinic protons) was prepared by condensation of commercially available *Z*-glycine with but-2-yn-1-ol (DCC, DMAP, Et<sub>2</sub>O, RT, 22 h, 97%) and subsequent Lindlar reduction of the resulting alkyne (H<sub>2</sub>, 5% Pd-CaCO<sub>3</sub>, Py, EtOAc, RT, 40 min, 89%). All new compounds were satisfactorily characterized using <sup>1</sup>H and <sup>13</sup>C NMR, IR, MS and HRMS spectra and also by elemental analyses whenever possible. Selected data for **7a**: mp 262–264 °C;  $\delta$ <sub>H</sub> (400 MHz, D<sub>2</sub>O) 3.74 (1H, d, *J* = 4.1 Hz), 1.34 (1H, ddq, *J* = 9.8, 4.1, 7.0 Hz), 0.98 (3H, d, *J* = 7.1 Hz), 0.68–0.44 (3H, m), 0.25–0.14 (2H, m);  $\delta$ <sub>C</sub> (100 MHz, D<sub>2</sub>O) 174.6, 60.1, 39.8, 14.12, 14.10, 4.3, 4.0;  $\nu$ <sub>max</sub> (KBr)/cm<sup>-1</sup> 3600–2200, 3410, 1672; *m/z* (FAB-MS) 144 [(M + H)<sup>+</sup>, 100%] (FAB-HRMS: calc. for C<sub>7</sub>H<sub>13</sub>O<sub>2</sub>N [(M + H)<sup>+</sup>, 144.1025; found, 144.1032] (Calc. for C<sub>7</sub>H<sub>13</sub>O<sub>2</sub>N: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.54; H, 9.30; N, 9.64%). **2**: mp 265–268 °C;  $\delta$ <sub>H</sub> (400 MHz, D<sub>2</sub>O) 3.64 (1H, d, *J* = 4.6 Hz), 1.30 (1H, ddq, *J* = 9.8, 4.6, 7.1 Hz), 1.06 (3H, d, *J* = 7.1 Hz), 0.65 (1H, m), 0.47 (2H, m), 0.22 (1H, m), 0.09 (1H, m);  $\delta$ <sub>C</sub> (100 MHz, D<sub>2</sub>O) 174.3, 60.2, 39.6, 16.1, 12.9, 4.0, 2.7;  $\nu$ <sub>max</sub> (KBr)/cm<sup>-1</sup> 3600–2200, 3342, 1628; *m/z* (FAB-MS) 144 [(M + H)<sup>+</sup>, 100%] (FAB-HRMS: calc. for C<sub>7</sub>H<sub>14</sub>O<sub>2</sub>N [(M + H)<sup>+</sup>, 144.1025; found, 144.1010] (Calc. for C<sub>7</sub>H<sub>13</sub>O<sub>2</sub>N: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.25; H, 9.13; N, 9.55%).

§ The absolute configuration of (2*S*,3*S*)-**14**, [ $\alpha$ ]<sub>D</sub><sup>24</sup> +9.94 (*c* 1.00, CHCl<sub>3</sub>), has been confirmed by leading the enantiomer of **14**, [ $\alpha$ ]<sub>D</sub><sup>19</sup> -8.6 (*c* 1.05, CHCl<sub>3</sub>), to (2*R*,3*R*)-*D*-isoleucine (ref. 9). The optical purity of **14** was determined to be >99% ee by derivatization of **15** (R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H) to **15'** [R<sup>1</sup> = Me, R<sup>2</sup> = (*R*)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl, R<sup>3</sup> = H] and integration of the signals in the <sup>1</sup>H NMR spectrum.

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