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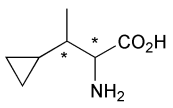
The unknown stereostructure of 2-amino-3-cyclopropylbutanoic acid 1, a novel plant growth regulator isolated from the mushroom *Amanita castanopsidis* Hongo, was determined to be (2*S*,3*S*)-2 through its racemic and enantioselective syntheses employing the chelate–enolate Claisen rearrangement as a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

2-Amino-3-cyclopropylbutanoic acid **1** was isolated as a novel α-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.[1] 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 α-amino acids closely related to **1**, such as coronatine,[2] cyclopropylalanine,[3] methylenecyclopropylglycine and hypoglycin A[4] 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 α-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**.



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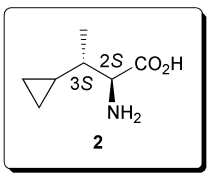

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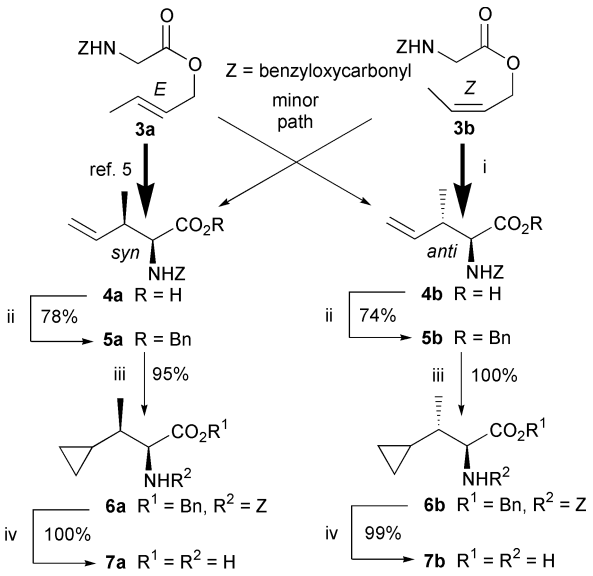
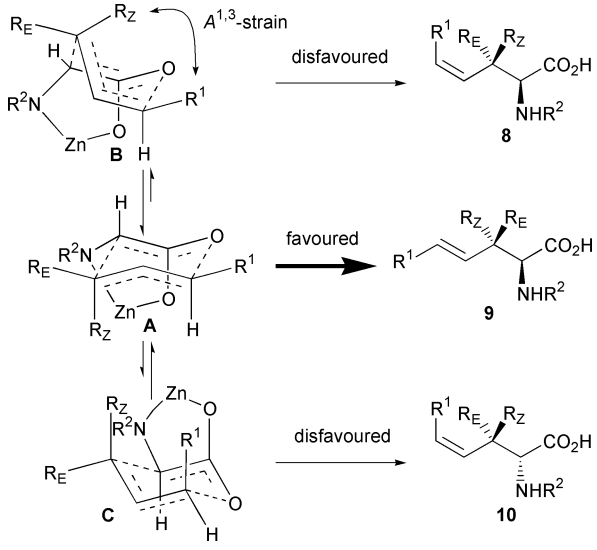
First, we decided to synthesize two possible diastereomers, *syn* **7a** and *anti* **7b**, to elucidate the unknown relative configuration. In 1994, it has been reported by Kazmaier that *syn* amino acid **4a** can diastereoselectively be obtained in a ratio of *syn*:*anti* = 95:5 from (*E*)-ester **3a** *via* the [3,3]-sigmatropic rearrangement of a chelate-bridged zinc enolate (Scheme 1).[5] 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).[6] 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**[7] 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, $ZnCl_2$, THF, −78 °C to RT, 30 min, 47%; ii, DCC, DMAP, BnOH, Et_2O, RT, 20 h; iii, CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C, 1 h; iv, H_2, 10% Pd–C, MeOH, RT, 15 min.



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

† Deceased on June 18, 1998.

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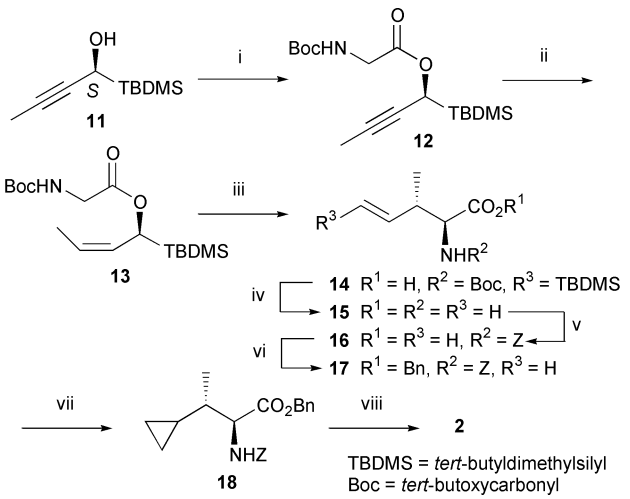
energy difference between **A** and the boatlike transition state **B** leading to the *syn* **4a** becomes smaller than that in (*E*)-**3a**, the lowering of the diastereoselectivity might be observed. Anyway, both the diastereomers **4a** and **4b** were converted into the desired *syn* and *anti* 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) $Pd(OAc)_2$-catalyzed cyclopropanation of the terminal double bond with diazomethane;[8] and (iii) hydrogenolysis of the benzylic protective groups. Comparing the ^1H and ^{13}C NMR of synthetic **7a** and **7b** with those of the natural product **1**,[1] 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*.[1] 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 α-amino acids in a complete chirality-transferring manner.[9] 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 esterfication of the readily available chiral (*S*)-alcohol **11**,[10] $[\alpha]_D^{23}$ −90.2 (*c* 1.01, $CHCl_3$); 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^1 = TBDMS, R^2 = Boc, R_Z = Me, R_E = H) leading to *syn* **8** and **C** leading to **10** enantiomeric to **9** except for the alkene geometry, sterically encumbered $A^{1,3}$-strain and 1,3-diaxial-like interaction, respectively, occur between the bulky R^1 and R_Z. 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-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), DMAP, CH_2Cl_2, RT, 2 h, 94%; ii, H_2, 5% Pd–$CaCO_3$, Py, EtOAc, RT, 1 h, 81%; iii, LDA, $ZnCl_2$, THF, −78 °C to RT, 2 h, 97%; iv, 42% aq. HBF_4, 1,4-dioxane, 65 °C, 14 h, 100%; v, ZCl, K_2CO_3, 1,4-dioxane–H_2O (1 : 1), 0 °C to RT, 12 h, 73%; vi, BnOH, EDCI, DMAP, CH_2Cl_2, 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_4[11] furnished free amino acid **15**, *N*-Z protection of which yielded **16** consistent with (±)-**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**, $[\alpha]_D^{31}$ −9.08 (*c* 0.5, H_2O), was identical with that reexamined for the natural amino acid **1** generously gifted by Professor Wakabayashi (Osaka City University), $[\alpha]_D^{26}$ −9.46 (*c* 0.035, H_2O). 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_2O, RT, 22 h, 97%) and subsequent Lindlar reduction of the resulting alkyne (H_2, 5% Pd–$CaCO_3$, Py, EtOAc, RT, 40 min, 89%). All new compounds were satisfactorily characterized using ^1H and ^{13}C NMR, IR, MS and HRMS spectra and also by elemental analyses whenever possible. *Selected data* for **7a**: mp 262–264 °C; δ_H (400 MHz, D_2O) 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); δ_C (100 MHz, D_2O) 174.6, 60.1, 39.8, 14.12, 14.10, 4.3, 4.0; ν_{max} (KBr)/cm^{-1} 3600–2200, 3410, 1672; *m*/*z* (FAB-MS) 144 [(M + H)$^+$, 100%] (FAB-HRMS: calc. for $C_7H_{14}O_2N$ [(M + H)$^+$], 144.1025; found, 144.1032) (Calc. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.54; H, 9.30; N, 9.64%). **2**: mp 265–268 °C; δ_H (400 MHz, D_2O) 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); δ_C (100 MHz, D_2O) 174.3, 60.2, 39.6, 16.1, 12.9, 4.0, 2.7; ν_{max} (KBr)/cm^{-1} 3600–2200, 3342, 1628; *m*/*z* (FAB-MS) 144 [(M + H)$^+$, 100%] (FAB-HRMS: calc. for $C_7H_{14}O_2N$ [(M + H)$^+$], 144.1025; found, 144.1010) (Calc. for $C_7H_{13}O_2N$: 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**, $[\alpha]_D^{24}$ +9.94 (*c* 1.00, $CHCl_3$), has been confirmed by leading the enantiomer of **14**, $[\alpha]_D^{19}$ –8.6 (*c* 1.05, $CHCl_3$), 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^1 = R^2 = R^3 = H) to **15′** [R^1 = Me, R^2 = (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl, R^3 = H] and integration of the signals in the^1 H NMR spectrum.

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