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SYNTHETIC STUDIES ON α,α-DISUBSTITUTED AMINO ACIDS EMPLOYING (2*S*,4*R*)-4-HYDROXYPROLINE AS THE CHIRAL POOL: PREPARATION OF METHYL *O*-BENZYL-2-(α-CYANOMETHYL)-D-TYROSINATE AND DIMETHYL 2-(4-HYDROXYBENZYL)-L-ASPARTATE

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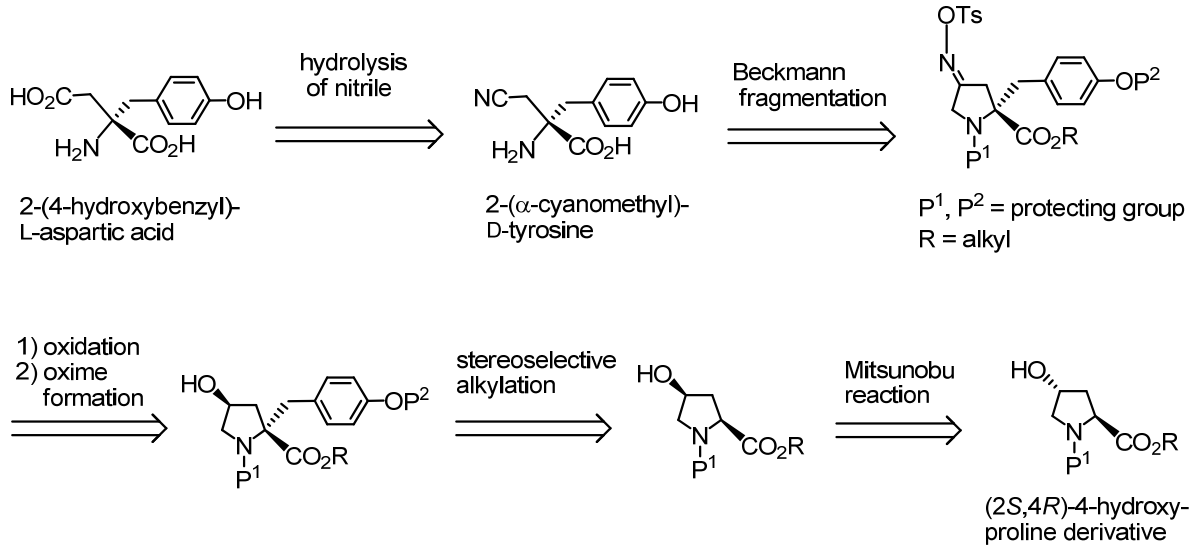
Abstract – Methyl *O*-benzyl-2-(α-cyanomethyl)-D-tyrosinate and dimethyl 2-(4-hydroxybenzyl)-L-aspartate were synthesized starting from (2*S*,4*R*)-4-hydroxyproline via Beckmann fragmentation of the corresponding oxime tosylate.

Recently we have developed a novel method for synthesis of a coccinellid alkaloid, (-)-adalinine,[1] in which (2*S*,4*R*)-4-hydroxyproline was recognized to be an important chiral template for constructing the quaternary carbon center having an amino group at its α-position, stereoselectively.

These results prompted us to utilize (2*S*,4*R*)-4-hydroxyproline as the chiral pool for preparation of α,α–disubstituted amino acids, where a newly developed regioselective bond cleavage reaction between the 4 and 5 positions of a proline ring was involved as a key step.

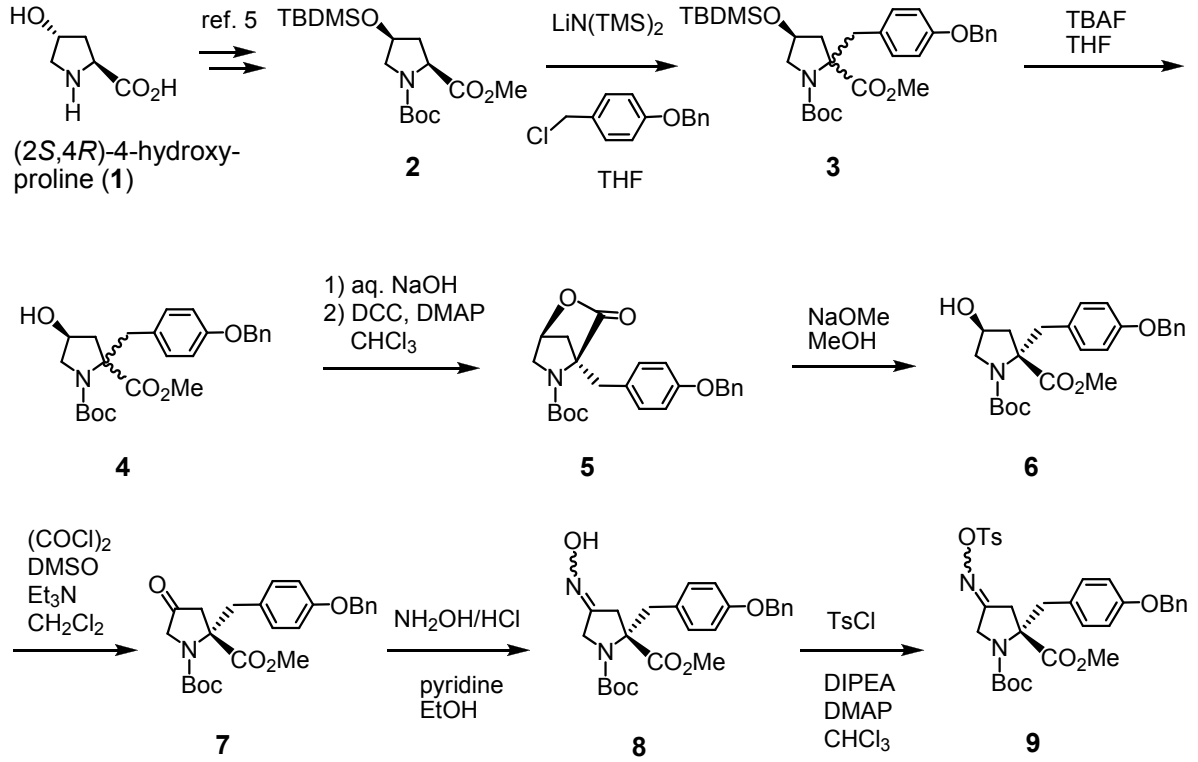
Thus, we decided to prepare 2-(α-cyanomethyl)-D-tyrosine and 2-(4-hydroxybenzyl)-L-aspartic acid as valuable chiral building blocks in the synthesis of biologically active compounds including natural products.

We envisioned that an α-substituted aspartic acid derivative could be obtained by hydrolysis of the corresponding nitrile, *O*-benzyl-2-(α-cyanomethyl)-D-tyrosine derivative. The desired nitrile would be derived from the oxime tosylate of the 2,2-disubstituted 4-ketoproline derivative by application of Beckmann fragmentation,[2,3] in which a regioselective bond cleavage between the 4 and 5 positions would be involved as depicted in Scheme 1. The desired 2,2-disubstituted 4-ketoproline might be prepared from the 4-hydroxyproline derivative by a stereoselective alkylation.[4,5]



Scheme 1. Retrosynthetic analysis of 2-(4-hydroxybenzy)-L-aspartic acid and 2-(α-cyanomethyl)-D-tyrosine

Thus, (2*S*,4*R*)-4-hydroxyproline (**1**) was converted to methyl (2*S*,4*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-pyrrolidine-2-carboxylate (**2**) according to the literature procedures.[6]



Scheme 2. Synthesis of oxime tosylates (**9**)

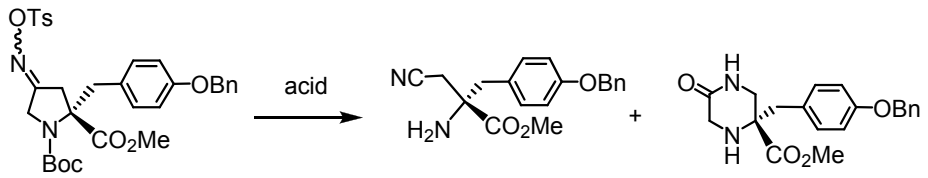
A stereoselective alkylation of **2** with 4-benzyloxybenzyl chloride[7] was carried out by adopting Nagumo's protocol[4] to provide a mixture of diastereomers (**3**) at the 2-position in 93% yield and in a ratio of *ca*. 2:1.

In this alkylation, the selectivity was found to be somewhat compromised, and the isomers could not be separated by column chromatography. In order to separate the diastereoisomeric mixture, the silyl group of **3** was removed upon treatment with tetrabutylammonium fluoride (TBAF) to give a hydroxyl-ester (**4**) in 97% yield. Alkaline hydrolysis of **4** afforded the corresponding acid, which, without further purification, was reacted with *N,N'*-dicyclohexylcarbodiimide (DCC) in $CHCl_3$ in the presence of *N,N*-dimethylaminopyridine (DMAP) by following Nagumo's procedure[4] to furnish the lactone (**5**) in 50% yield from **4**. Methanolysis of **5** provided pure hydroxyl-ester (**6**) in 98% yield.

Swern oxidation of **6** in the usual manner afforded the ketone (**7**), which was treated with hydroxylamine hydrochloride in EtOH in the presence of pyridine to give the oxime (**8**) as a mixture of *E* and *Z*-isomers in 88% yield and in a ratio of *ca*. 1:1. Since difficulties were encountered in separating *E* and *Z*-isomers as pure forms, we decided to use a mixture of the oximes in the following fragmentation. Tosylation of **8** with tosyl chloride in the presence of DMAP and diisopropylethylamine (DIPEA) gave oxime tosylates (**9**) as *E* and *Z*-isomers. (Scheme 2)

With the desired compound **9** in hand, a study was carried out to determine the best conditions for Beckmann fragmentation reaction, and the results obtained are summarized in Table 1.

Table 1. Beckmann fragmentation of oxime tosylates (**9**)



9 **10** **11**

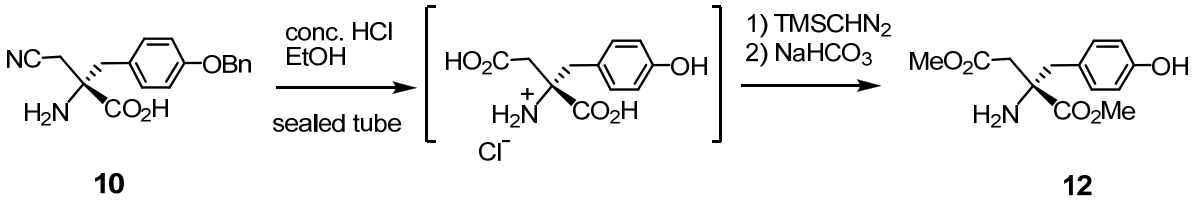
Entry	acid[a]	temp. (°C)	time (h)	**10** (%)[b]	**11** (%)[b]
1	TFA	- 20	72	18[c]	—
2	TFA	0	36	70	—
3	TFA	rt	12	27	36
4	$ZnBr_2$	0	36	5[c]	—
5	$ZnBr_2$	rt	24	12	52

[a]15 equimolar amounts of TFA and 6 equimolar amounts of $ZnBr_2$ were employed.
[b] Isolated yield. [c]Most of the starting material was recovered.

Based on consideration of the previously established heteroatom-assisted Beckmann fragmentation,[3] the desired bond cleavage reaction would be concomitant with removal of the Boc group on the nitrogen atom. Thus, the tosylate (**9**) was exposed to trifluoroacetic acid (TFA) at -20 °C for 72 h; however, the desired product (**10**) was isolated only in 18% yield together with the recovered starting material (entry 1).

When the reaction was carried out at 0 °C for 36 h, the yield was increased to 70% (entry 2). Interestingly, a higher temperature for the reaction brought about Beckmann rearrangement prior to Beckmann fragmentation, probably due to facile isomerization between *E* and *Z*-isomers under these reaction conditions (entry 3). When removal of the Boc group was attempted with the use of Lewis acid, the rearrangement product (**11**) was always generated preferentially (entries 4 and 5). The reason for the formation of the rearrangement product as the major product by the use of zinc bromide was not clear; however, zinc metal might participate both with pyrrolidine nitrogen and oxime oxygen (or oxime nitrogen) to accelerate isomerization of the *E*-isomer to the *Z*-isomer, leading to the observed rearrangement.

Although alkaline hydrolysis of the nitrile (**10**) with aqueous KOH solution was first attempted,[8-11] the desired di-acid or amide-acid could not be isolated under these reaction conditions. Similar hydrolysis with hydrochloric acid gave the di-acid, which, without purification, was subjected to an esterification with trimethylsilyldiazomethane,[12] to give its dimethyl ester (**12**).



10 **12**

Scheme 3. Synthesis of dimethyl 2-(4-hydroxybenzyl)-L-aspartate (**12**)

In summary, we established a novel synthesis of an optically pure methyl *O*-benzyl-2-(α-cyanomethyl)-D-tyrosinate and dimethyl 2-(4-hydroxybenzyl)-L-aspartate employing (2*S*,4*R*)-4-hydroxyproline as the starting chiral pool. This methodology will provide an alternative route for the synthesis of α,α-disubstituted α-amino acid, and its further application is now under investigation in our laboratory.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-4100 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on BRUKER AV400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-600W spectrometer. Elemental analyses were performed on a Yanaco-MT5.

1-*tert*-Butyl 2-methyl (4*S*)-2-[4-(benzyloxy)benzyl-4-{[*tert*-butyl(dimethyl)silyl]oxy}-pyrrolidine-1,2-

dicarboxylate (**3**). To a stirred solution of **2** (1.0 g, 2.8 mmol) in THF (18 mL) was added LiHMDS (1.6 M THF solution, 3.5 mL, 1.6 M, 5.6 mmol) at 0 °C under argon, and the resulting mixture was stirred for further 1 h at the same temperature. To this solution was added a solution of (4-benzyloxy)benzyl chloride (1.6 g, 7.0 mmol) in THF (10 mL), and the whole was stirred for 5 h at 0 °C. The mixture was treated with saturated aqueous NH_4Cl solution, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (7:1, v/v) afforded the benzylated compound (**3**) (1.44 g, 93%) as a mixture of diastereomers at the 2-position and Boc rotamers. IR ν max: 1744 1611 cm^{-1}; ^{1}H-NMR δ: 7.46-7.28 (m, 5H), 7.13-7.01 (m, 2H), 6.95-6.88 (m, 2H), 5.06-5.01 (m, 2H), 4.41-4.29 (m, 0.3H), 3.88-3.80 (m, 0.2H), 3.77-3.73 (m, 3H), 3.71-3.61 (m, 0.5H), 3.50-3.35 (m, 1H), 3.31-3.21 (m, 0.2H), 3.15-2.91 (m, 2.4H), 2.48 (dd, *J* = 7.8, 10.5 Hz, 0.2H), 2.40 (dd, *J* = 7.8, 10.5 Hz, 0.1H), 2.20-2.14 (m, 2.1H), 1.51 (s, 2.3H), 1.49 (s, 4.7H), 1.45 (s, 2H), 0.82 (s, 1H), 0.81 (s, 2H), 0.76 (s, 2.3H), 0.74 (s, 3.7H), 0.01 - -0.03 (m, 2H), -0.16 - -0.19 (m, 4H).; ^{13}C-NMR δ: 174.7, 174.6, 174.4, 158.0, 157.8, 157.6, 153.9, 153.2, 137.0, 137.0, 136.9, 132.1, 132.0, 131.4, 131.3, 129.6, 129.1, 128.6, 128.5, 128.5, 127.9, 127.9, 127.8, 127.4, 127.4, 127.3, 114.8, 114.6, 114.3, 80.49, 79.80, 69.98, 69.90, 68.23, 67.97, 67.73, 67.51, 67.25, 67.08, 67.00, 54.36, 54.14, 53.84, 52.23, 44.83, 43.90, 43.22, 42.23, 39.13, 38.57, 38.04, 28.30, 25.69, 17.95, 17.89, 17.84, -4.89, -4.95, -5.08, -5.18, -5.24, -5.27.; MS (EI): 555 (M^+); HRMS (EI): Calcd for : $C_{31}H_{45}NO_6Si$: 555.3016, Found: 555.3029.

1-*tert*-Butyl 2-methyl (4*S*)-2-[4-(benzyloxy)benzyl-4-hydroxypyrrolidine-1,2-dicarboxylate (**4**). To a stirred solution of **3** (3.36 g, 6.0 mmol) in THF (12 mL) was added TBAF (1.0 M THF solution, 7.3 mL, 7.3 mmol) at 0 °C, and the resulting mixture was stirred for further 3 h at the same temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with hexane:AcOEt (1:1, v/v) afforded the desilylated compound (**4**) (2.58 g, 97%) as a mixture of diastereomers at the 2-position and Boc rotamers. IR ν max: 3458, 1742, 1695 cm^{-1}; ^{1}H-NMR δ: 7.45-7.29 (m, 5H), 7.15-6.98 (m, 2H), 6.97-6.86 (m, 2H), 5.05-5.01 (m, 2H), 3.92-3.71 (m, 4.3H), 3.70-3.42 (m, 1.7H), 3.03 (d, *J* = 14.2 Hz, 0.2H), 3.02 (d, *J* = 14.2 Hz, 0.1H), 2.88 (d, *J* = 14.2 Hz, 0.4H), 2.84 (d, *J* = 14.2 Hz, 0.3H), 2.93-2.84 (m, 0.3H), 2.76 (dd, *J* = 4.4, 11.6 Hz, 0.4H), 2.61 (dd, *J* = 4.4, 11.6 Hz, 0.3H), 2.36-2.21 (m, 1H), 2.10-2.01 (m, 1H), 1.51 (s, 3H), 1.50 (s, 4H), 1.48 (s, 2H).; ^{13}C-NMR δ: 176.5, 176.0, 174.7, 157.9, 157.8, 157.7, 154.0, 153.2, 136.9, 136.8, 132.2, 132.1, 131.8, 131.7, 128.5, 128.2, 127.9, 127.9, 127.4, 114.9, 114.8, 114.8, 114.5, 80.87, 80.26, 69.92, 69.65, 68.88, 68.35, 67.89, 67.63, 67.35, 67.28, 57.00, 56.45, 56.11, 55.58, 53.08, 52.84, 52.33, 43.46, 43.19, 42.69, 42.04, 38.59, 38.15, 37.46, 36.73, 28.38, 28.33.; MS (EI): 441 (M^+); HRMS (EI): Calcd for : $C_{25}H_{31}NO_6$: 441.2151, Found: 441.2124.

***tert*-Butyl (1*S*,4*S*)-4-[4-(benzyloxy)benzyl]-3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate** (**5**). A solution of **4** (6.5 g, 14.7 mmol) in MeOH (75 mL) and 2.0 M NaOH solution (75 mL, 147 mmol) was heated at reflux for 4 h. The solution was acidified with 10% HCl solution and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude acid, which, without further purification, was used in the next step. To a stirred solution of the crude acid (6.3 g) in $CHCl_3$ (1.5 L) were added DMAP (180 mg, 1.5 mmol) and DCC (6.1 g, 29.5 mmol) at 0 °C, and the whole was stirred for 10 h at the same temperature. The mixture was treated with 1N HCl and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (5:1, v/v) afforded the lactone (**5**) (3.0 g, 50%) as colorless solid; mp 130-131 °C; $[\alpha]_D$ +154.3 (*c* 0.99, $CHCl_3$); IR ν max: 1790, 1703 cm^{-1}; ^{1}H-NMR δ: 7.45-7.30 (m, 5H), 7.21-7.16 (m, 2H), 6.92-6.87 (m, 2H), 5.03 (s, 2H), 4.83 (d, *J* = 1.7 Hz, 1H), 3.62-3.52 (m, 4H), 1.88 (d, *J* = 10.8 Hz, 1H), 1.50 (s, 9H).; ^{13}C-NMR δ: 171.8, 157.7, 155.2, 136.9, 131.4, 128.8, 128.1, 128.0, 127.9, 127.5, 115.1, 114.8, 81.60, 74.88, 69.99, 69.93, 68.47, 53.71, 43.42, 32.55, 28.28.; MS (EI): 409 (M^+); HRMS (EI): Calcd for $C_{24}H_{27}NO_5$: 409.1889. Found: 409.1881, *Anal.* Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42, Found: C, 70.12; H, 6.68; N, 3.41.

1-*tert*-Butyl 2-methyl (2*S*,4*S*)-[4-(benzyloxy)benzyl]-4-hydroxypyrrolidine-1,2-dicarboxylate (**6**). To a solution of **5** (7.1 g, 17.3 mmol) in MeOH (170 mL) was added NaOMe (28% MeOH solution, 5.3 mL, 26.0 mmol) at rt and the mixture was stirred for 1 h at the same temperature. The mixture was treated with saturated aqueous NH_4Cl solution and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (2:1, v/v) afforded the hydroxyl-ester (**6**) (7.5 g, 98%) as colorless solid; mp 103-104 °C; $[\alpha]_D$ +235.1 (*c* 1.00, $CHCl_3$); IR ν max: 3449, 1742, 1695 cm^{-1}; ^{1}H-NMR δ: 7.45-7.29 (m, 5H), 7.05-6.98 (m, 2H), 6.93-6.87 (m, 2H), 5.03 (d, *J* = 2.8 Hz, 2H), 3.84 (s, 1.5H), 3.83 (s, 1.5H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.66-3.44 (m, 2H), 2.88 (d, *J* = 14.3 Hz, 0.5H), 2.84 (d, *J* = 14.3 Hz, 0.5H), 2.76 (dd, *J* = 11.6 Hz, 0.5H), 2.61 (dd, *J* = 11.6 Hz, 0.5H), 2.32-2.22 (m, 1H), 2.10-2.00 (m, 1H), 1.51 (s, 4.5H), 1.50 (s, 4.5H). One proton (OH) was not observed.; ^{13}C-NMR δ: 176.5, 176.0, 158.0, 157.7, 154.0, 153.1, 136.9, 136.8, 131.8, 131.7, 128.5, 128.2, 127.9, 127.9, 127.4, 114.8, 114.5, 80.86, 80.25, 69.91, 69.64, 68.88, 67.34, 67.27, 57.00, 56.45, 53.08, 52.84, 43.19, 42.04, 38.15, 36.73, 28.38.; MS (CI): 441 (M^+); HRMS (CI): Calcd for $C_{25}H_{31}NO_6$: 441.2151, Found: 441.2159, *Anal.* Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17, Found: C, 68.04; H, 7.21; N, 3.22.

1-*tert*-Butyl 2-methyl (2*S*)-2-[4-(benzyloxy)benzyl]-4-oxopyrrolidine-1,2-dicarboxylate (**7**). To a stirred solution of oxalyl chloride (1.5 mL, 17.0 mmol) in CH_2Cl_2 (10 mL) was added a solution of

DMSO (1.9 mL, 27.2 mmol) in CH_2Cl_2 (10 mL) at -78 °C, and the resulting mixture was stirred for 15 min at the same temperature. To this solution was added a solution of **6** (3.0 g, 6.8 mmol) in CH_2Cl_2 (14 mL) and the whole was stirred for 30 min. Et_3N (7.5 mL, 54.4 mmol) was then added to the mixture and the whole mixture was stirred for further 30 min at the same temperature. The mixture was treated with water and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (7:1, v/v) afforded the ketone (**7**) (2.6 g, 86%) as a colorless oil. $[\alpha]_D$ +119.1 (*c* 0.99, $CHCl_3$); IR ν max: 1767, 1747, 1701 cm^{-1}; ^{1}H-NMR δ: 7.44-7.29 (m, 5H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.02 (s, 2H), 3.88-3.56 (m, 2H), 3.80 (s, 3H), 3.13 (d, *J* = 19.2 Hz, 0.5H), 3.05-2.95 (m, 1.5H), 2.84-2.69 (m, 2H), 1.52 (s, 4.5H), 1.51 (s, 4.5H).; ^{13}C-NMR δ: 207.0, 206.0, 173.4, 158.1, 152.9, 136.7, 131.7, 128.5, 127.9, 127.5, 127.3, 126.7, 115.2, 115.0, 81.75, 81.01, 69.93, 66.23, 54.39, 54.27, 52.69, 47.05, 46.59, 39.29, 38.05, 28.28.; MS (EI): 439 (M^+); HRMS (EI): Calcd for $C_{25}H_{29}NO_6$: 439.1995, Found: 439.1989.

1-*tert*-Butyl 2-methyl (2*S*,4E/Z)-2-[4-(benzyloxy)benzyl]-4-(hydroxyimino)pyrrolidine-1,2-dicarboxylate (**8**). To a stirred solution of **7** (2.6 g, 5.9 mmol) in pyridine (24 mL) and EtOH (8 mL) was added hydroxylamine hydrochloride (2.0 g, 29.4 mmol) and the resulting solution was heated at 60 °C for 1 h. The mixture was treated with water and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (2:1, v/v) afforded the oxime (**8**) (2.4 g, 88%) as a mixture of *E*/*Z*-isomers (*ca*. 1:1). This mixture was separated by careful column chromatography on silica gel to give *E* and *Z*-isomer, respectively. However, the stereochemistry of the isomer was not able to determine at this stage.

***E* or *Z*-isomer**; mp 51-53 °C; $[\alpha]_D$ +9.1 (*c* 1.00, $CHCl_3$); IR ν max: 3380, 1745, 1698 cm^{-1}; ^{1}H-NMR δ: 7.45-7.29 (m, 5H), 7.03 (t, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.02 (s, 2H), 4.13 (d, *J* = 15.8 Hz, 0.6H), 4.04 (d, *J* = 15.8 Hz, 0.4H), 3.78 (s, 3H), 3.80-3.71 (m, 0.4H), 3.54 (d, *J* = 14.2 Hz, 0.6H), 3.48 (d, *J* = 16.0 Hz, 0.6H), 3.39 (d, *J* = 16.0 Hz, 0.4H), 3.07 (d, *J* = 13.2 Hz, 0.4H), 3.02 (d, *J* = 13.2 Hz, 0.6H), 2.98 (d, *J* = 14.2 Hz, 1H), 2.88 (d, J = 18.4 Hz, 1H), 1.50 (s, 9H). One proton (OH) was not observed.; ^{13}C-NMR δ: 173.8, 157.9, 157.8, 156.8, 155.7, 153.7, 136.9, 131.5, 128.5, 127.9, 127.8, 127.5, 127.2, 114.9, 114.7, 81.43, 80.66, 69.86, 67.85, 67.71, 52.62, 52.53, 49.69, 39.24, 37.98, 36.31, 35.55, 28.29; MS (EI): 454 (M^+); HRMS (EI): Calcd for $C_{25}H_{30}N_2O_6$: 454.2104, Found: 454.2111.

***E* or *Z*-isomer**; mp 49-51 °C; $[\alpha]_D$ +129.8 (*c* 0.99, $CHCl_3$); IR ν max: 3381, 1745, 1699 cm^{-1}; ^{1}H-NMR δ: 7.74 (s, 0.5H), 7.65 (s, 0.5H), 7.44-7.28 (m, 5H), 7.03 (t, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.02 (s, 2H), 4.20 (d, *J* = 17.8 Hz, 0.5H), 4.12 (d, *J* = 17.8 Hz, 0.5H), 3.80-3.73 (m, 0.5H), 3.77 (s, 3H), 3.66 (d,

J = 17.8 Hz, 0.5H), 3.55 (d, *J* = 16.0 Hz, 1H), 3.00 (d, *J* = 14.2 Hz, 1H), 2.92-2.80 (m, 2H), 1.51 (s, 4.5H), 1.50 (s, 4.5H). One proton (OH) was not observed.; ^{13}C-NMR δ: 173.7, 157.8, 157.7, 157.0, 156.0, 154.0, 153.2, 136.8, 131.6, 131.6, 128.4, 127.8, 127.7, 127.3, 127.2, 114.9, 114.6, 81.32, 80.59, 69.78, 67.22, 66.98, 52.59, 52.48, 47.80, 38.99, 38.79, 37.91, 37.73, 28.21.; MS (EI): 454 (M^+); HRMS (EI): Calcd for $C_{25}H_{30}N_2O_6$: 454.2104, Found: 454.2111.

1-*tert*-Butyl 2-methyl (2*S*,4E/*Z*)-2-[4-(benzyloxy)benzyl]-4-(tosyloxyimino)pyrrolidine-1,2-dicarboxylate (**9**). To a stirred solution of **8** (3.0 g, 6.6 mmol) in $CHCl_3$ (70 mL) were successively added DIPEA (2.3 mL, 13.2 mmol), TsCl (2.5 g, 13.2 mmol), and DMAP (80 mg, 0.7 mmol) at 0 °C, and the resulting mixture was stirred for further 6 h at the same temperature. The mixture was treated with water and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (9:1, v/v) afforded the oxime tosylate (**9**) (3.9g, 96%) as a mixture of *E*/*Z*-isomers (*ca*. 1:1). This mixture was separated by careful column chromatography on silica gel.

***E* or *Z*-isomer**; $[\alpha]_D$ -23.7 (*c* 0.99, $CHCl_3$); IR ν max: 1747, 1701 cm^{-1}; ^{1}H-NMR δ: 7.76 (d, *J* = 8.0 Hz, 2H), 7.45-7.28 (m, 7H), 7.00-6.95 (m, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.99 (s, 2H), 4.14 (d, *J* = 17.2 Hz, 0.5H), 4.06 (d, *J* = 17.2 Hz, 0.5H), 3.75 (s, 3H), 3.78-3.68 (m, 0.5H), 3.51 (d, *J* = 14.4 Hz, 0.5H), 3.43 (d, *J* = 17.2 Hz, 0.5H), 3.35 (d, *J* = 17.2 Hz, 0.5H), 3.13 (dd, *J* = 6.8, 18.8 Hz, 1H), 3.03-2.95 (m, 1H), 2.94 (d, *J* = 14.2 Hz, 1H), 2.36 (s, 3H), 1.47 (s, 9H).; ^{13}C-NMR δ: 172.7, 166.0, 165.1, 158.0, 157.9, 153.2, 152.5, 145.2, 136.7, 132.1, 131.3, 129.6, 128.6, 128.4, 127.9, 127.5, 127.1, 126.5, 115.1, 114.9, 81.72, 81.00, 69.84, 67.79, 67.60, 52.71, 52.63, 49.59, 39.04, 38.04, 37.80, 37.27, 28.15, 21.50.; HRMS (ESI): Calcd for $C_{32}H_{36}N_2O_8S$: 631.2090, Found: 631.2061.

***E* or *Z*-isomer**; $[\alpha]_D$ +53.4 (*c* 0.99, $CHCl_3$); IR ν max: 1747, 1701 cm^{-1}; ^{1}H-NMR δ: 7.08-7.71 (m, 2H), 7.47-7.24 (m, 7H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.83-6.75 (m, 2H), 5.02 (s, 2H), 4.24 (d, *J* = 18.8 Hz, 0.4H), 4.15 (d, *J* = 18.8 Hz, 0.6H), 3.79-3.69 (m, 0.6H), 3.73 (s, 3H), 3.68-3.46 (m, 0.6H), 3.02-2.90 (m, 3H), 2.40 (s, 3H), 1.50 (s, 9H).; ^{13}C-NMR δ: 173.0, 166.5, 165.6, 158.1, 153.6, 152.9, 145.3, 136.9, 132.3, 131.7, 129.8, 128.7, 128.6, 128.0, 127.6, 127.1, 126.6, 115.1, 114.9, 81.87, 81.35, 70.05, 67.86, 67.66, 67.43, 52.87, 49.11, 39.27, 39.08, 38.50, 37.88, 28.35, 21.71.; HRMS (ESI): Calcd for $C_{32}H_{36}N_2O_8S$: 631.2090, Found: 631.2083.

Methyl *O*-benzyl-2-(α-cyanomethyl)-D-tyrosinate (**10**). To a stirred solution of **9** (3.5 g, 5.8 mmol) in CH_2Cl_2 (60 mL) was added TFA (6.4 mL, 86.3 mmol) at 0 °C, and the resulting mixture was stirred for further 24 h at the same temperature. The mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with

hexane:AcOEt (1:1, v/v) afforded the cyanide (**10**) (1.3 g, 70%) as a pale yellowish oil. $[\alpha]_D$ -24.1 (*c* 1.00, $CHCl_3$); IR ν max: 3379, 2249, 1738 cm^{-1}; ^{1}H-NMR δ: 7.44-7.29 (m, 5H), 7.07-7.02 (m, 2H), 6.94-6.88 (m, 2H), 5.03 (s, 2H), 3.73 (s, 3H), 3.05 (d, *J* = 13.6 Hz, 1H), 2.91 (d, *J* = 13.6 Hz, 1H), 2.77 (d, *J* = 16.5 Hz, 1H), 2.63 (d, *J* = 16.5 Hz, 1H). Two protons (NH) were not observed.; ^{13}C-NMR δ: 173.8, 158.2, 136.7, 130.7, 128.5, 127.9, 127.4, 126.5, 116.9, 114.9, 69.86, 60.27, 52.70, 44.24, 27.80.; MS (CI): 325 (M+H); HRMS (EI): Calcd for $C_{19}H_{21}N_2O_3$: 325.1552, Found: 325.1565.

Methyl (2S)-2-[4-(benzyloxy)benzyl]-5-oxo-piperadine-2-carboxylate (**11**). To a stirred solution of **9** (120 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added $ZnBr_2$ (260 mg, 1.2 mmol) at rt and the resulting mixture was stirred for further 24 h at the same temperature. The mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (1:1, v/v) afforded the amide (**11**) (36 mg, 52%) as a pale yellowish oil. $[\alpha]_D$ +27.8 (*c* 1.01, $CHCl_3$); IR ν max: 3351, 1756, 1732 cm^{-1}; ^{1}H-NMR δ: 7.45-7.30 (m, 5H), 7.10-7.05 (m, 2H), 6.94-6.88 (m, 2H), 5.04 (s, 2H), 3.70 (s, 3H), 3.37 (s, 2H), 3.18 (d, *J* = 13.5 Hz, 1H), 2.96 (d, *J* = 13.5 Hz, 1H), 2.78 (d, *J* = 18.2 Hz, 1H), 2.42 (d, *J* = 18.2 Hz, 1H). Two protons (NH) were not observed; ^{13}C-NMR δ: 213.4, 175.0, 158.0, 136.9, 130.8, 128.6, 129.0, 128.0, 127.5, 114.8, 69.96, 68.26, 53.74, 52.48, 45.79, 43.91.; MS (CI): 354 (M^+); HRMS (EI): Calcd for $C_{20}H_{22}N_2O_4$: 354.1580, Found: 354.1556. Further elution with the same solvent system furnished the fragmentation product (**10**) (0.22 g, 12%).

Dimethyl 2-(4-hydroxybenzyl)-L-aspartate (**12**). A solution of **10** (200 mg, 0.62 mmol) in EtOH (1 mL) and conc. HCl (10 mL) was heated at 100 °C using a sealed tube for 48 h. After removal of EtOH and water, the residue was dissolved into MeOH (6 mL). To this solution was added $TMSCHN_2$ (2M ether solution, 1.6 mL, 3.1 mmol) at 0 °C and the resulting mixture was stirred for further 6 h at the same temperature. The mixture was treated with AcOH (2 mL) and then saturated aqueous $NaHCO_3$ solution, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (4:1, v/v) afforded the diester (**12**) (90 mg, 55%) as a pale yellowish oil. $[\alpha]_D$ +16.3 (*c* 0.80, $CHCl_3$); IR ν max: 3355, 3297, 1732 cm^{-1}; ^{1}H-NMR δ: 6.84 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.19 (br s, 2H), 3.61 (s, 3H), 3.58 (s, 3H), 3.02 (d, *J* = 17.0 Hz, 1H), 2.89 (d, *J* = 13.5 Hz, 1H), 2.71 (d, *J* = 13.5 Hz, 1H), 2.57 (d, *J* = 17.0 Hz, 1H). One proton (OH) was not observed.; ^{13}C-NMR δ: 175.8, 171.9, 155.2, 131.0, 125.5, 115.6, 60.06, 52.40, 51.85, 44.80, 42.83.; MS (EI): 267 (M^+); HRMS (EI): Calcd for $C_{13}H_{17}NO_5$: 267.1107, Found: 267.1113.

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