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# Highly stereoselective and efficient synthesis of the dopa analogue in pepticinnamin E via enantioselective hydrogenation of dehydroamino acids

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An efficient and new method was developed to prepare the dopa analogue **11** in natural pepticinnamin via catalytic hydrogenation of dehydroamino acids (DDAA) with a good yield and *ee*. Product **11** is a key intermediate towards the total synthesis of pepticinnamin E and its analogues.

**Key Words:** Synthesis; dopa analogue; enantioselective hydrogenation; dehydroamino acid.

## Introduction

Pepticinnamin E[1] (Figure) is a major product of the pepticinnamins, which are isolated from the culture of *Streptomyces* sp. OH-4652. It was identified as a depsipeptide having an $O-Z$-pentenylcinnamin acid and a novel dopa analogue, whose configuration has been determined as $S$ by the Waldmann group using the Schöllkopf method.[2] Pepticinnamin E shows rather potent inhibitory activity against farnesyl protein transferase (FPTase) with an $IC_{50}$ of 0.3 $\mu$M and is the first competitive inhibitor derived from a natural product. Our interest in the exploitation of a new methodology to synthesise naturally bioactive peptides containing non-ribosomal amino acids led us to initiate the synthesis of pepticinnamin E (**1**). Emphasis was placed on preparing both dopa analogue **2** and $O-Z$-pentenylcinnamin acid.[3] This study reports the enantioselective synthesis of the precursor of the dopa analogue **2**, which would be suitable for the total synthesis of pepticinnamin E and its analogues.

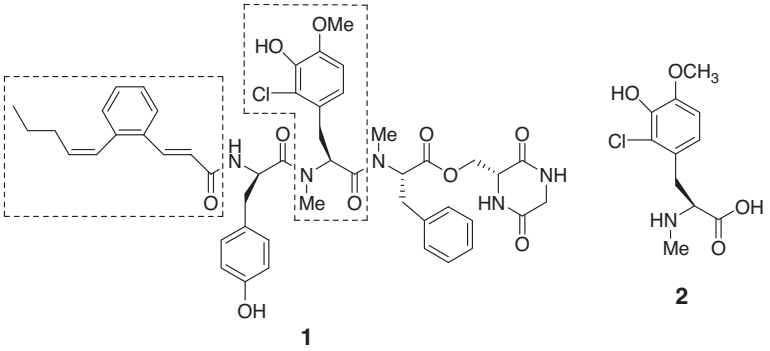



**Figure.** Structures of pepticinnamin E (**1**) and the dopa analogue **2**.

# Experimental section

*General.* Melting points were determined with an Electrothermol digital melting point apparatus, and were uncorrected. Optical rotation was recorded on a Perkin-Elmer Model 341 polarimeter, at the sodium D line. Elemental analysis was undertaken on a Carlo-1106 model automatic instrument. Infrared spectra (IR) were run on a Nicolet MX-1 and Nicolet-560 MAGNA. $^{1}$H-NMR and spectra were run either on a Bruker-200 and Bruker-300 or on a Varian-400. $^{13}$C-NMR was given by a Bruker-200. MS-EI mass spectra were obtained on a VG 7070E.

**2-Chloro-3-hydroxy-4-methoxybenzaldehyde (6)**: A solution of compound **5** (9.35 g, 61.0 mmol) in freshly distilled $CH_2Cl_2$ (260 mL) was bubbled into gas $Cl_2$ until the yellow colour disappeared. After stirring at RT for 1 h, the white solid was collected by filtration and washed with warm $CH_2Cl_2$ to give compound **6**, 8.0 g, yield 71%, mp 207∼208 °C. FT-IR (KBr): 3209, 3199, 1662, 1590, 1490, 1286, 1248, 1213, 1030, 810, 670 cm$^{-1}$. $^{1}$H-NMR (200 MHz, DMSO-$d_6$)$\delta$ = 10.3 (s, 1H, CHO), 7.57 (d, $J$ = 8.0 Hz, 1H, Ar-H), 6.90 (d, $J$ = 8 Hz, 1H, Ar-H), 3.98 (s, 3H, $OCH_3$); MS-EI (m/z): 187 ($M^+$), peak of isotope for Cl: 185/187 = 3:1, 187/189 = 3:1. Anal. Calcul. for $C_8H_7ClO_3$: C 51.49, H 3.78, Found: C 51.41, H 3.83.

**2-Chloro-3-acetyloxy-4-methoxybenzaldehyde (7)**: To a solution of compound **6** (1.94 g, 10.4 mmol) in dry pyridine (25 mL) was added dropwise the acetyl chloride (0.75 mL, 10.5 mmol) at 0 °C. After stirring at RT for another 2 h, the reaction solution was diluted with ethyl acetate, and then washed with cold 1N $H_2SO_4$ and water (until pH 7). The organic layer was dried over anhydrous $MgSO_4$, and concentrated to give a crude product, which was purified by flash column chromatography on silica gel (with petr./ethyl acetate 6:1, 4:1 as eluent) to obtain white solid **7**, 2.12 g, yield 89.1%, mp 64∼65 °C. FT-IR (KBr): 3082, 3012, 2883, 1778, 1685, 1594, 1496, 1435, 1370, 1298, 1256, 1190, 1167, 1037, 891, 818 cm$^{-1}$. $^{1}$H-NMR (200 MHz, $CDCl_3$)$\delta$ = 10.32 (s, 1H, CHO), 7.88 (d, $J$ = 8.8 Hz, 1H, Ar-H), 7.0 (d, $J$ = 8.8 Hz, 1H, Ar-H), 3.93 (s, 3H, $OCH_3$), 2.41 (s, 3H, $COCH_3$). Anal. Calcul. for $C_{10}H_9ClO_4$: C 52.53, H 3.97, Found: C 52.47, H 4.02

***(Z)*-Methyl3-(3-acetyloxy-2-chloro-4-methoxyphenyl-2-(*tert*-butyloxycarbonyl) acrylate (8):** To a solution of methyl *N*-protected-2-(diethoxycarbonyl)phosphinyl)-glycinate (2.2 mmol) in dry $CH_2Cl_2$ (6 mL) was added DBU (0.3 mL, 2.2 mmol) at 0 °C; after 1 min, the solution of compound **7** (2.0 mmol) in dry $CH_2Cl_2$ (6 mL) was added. After stirring at 0 °C for another 2 h, the reaction solution was diluted with 40

mL of ethyl acetate and then washed with cold 1 N $H_2SO_4$ (5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, and concentrated to give a crude product, which was purified by column chromatography on silica gel (with petr./ethyl acetate as eluent) to obtain white solid **8,** 0.78 g, yield 98%, mp 126-127 °C. FT-IR (KBr): 3526, 3349, 2980, 2949, 1782, 1720, 1642, 1601, 1494, 1440, 1371, 1337, 1302, 1247, 1174, 1034, 880, 772 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$)$\delta$ = 7.56 (d, $J$ = 8.91 Hz, Ar-H), 7.35 (s, 1H, = CH), 6.88 (d, $J$ = 8.91 Hz, Ar-H), 6.17 (bs, 1H, NH), 3.87 (s, 3H, $ArOCH_3$), 3.86 (s, 3H, COOMe), 2.38 (s, 3H, COMe), 1.41 (s, 9H, Boc). MS-EI (m/z): 399 ($M^+$); Anal. Calcul. for $C_{18}H_{22}ClNO_7$: C 54.52, H 5.57, N 3.46. Found: C 54.34, H 5.51, N 3.51.

***(S)-N-tert*-butyloxycarbonyl-(3-acetyloxy-2-chloro-4-methoxy)-phenylalanine methyl ester (9):** To a solution of DIPAMP (2.7 mg, 0.0059 mmol) in 1.5 mL of absolute acetone (deoxygenation before use) was added [Rh(COD)$BF_4$ (2.4 mg, 0.0059 mmol) under $Ar_2$. After stirring at RT for 1 h, this catalyst with a concentration of 0.0004 mmol/0.1 mL was prepared and used in subsequent procedure right away. To a solution of compound **8** (0.70 g, 1.75 mmol) in absolute acetone (26 mL) (deoxygenation before use) was added the catalyst prepared in the above procedure. The reaction solution was hydrogenated under 1 atm for 42 h at RT. Active carbon was then added by stirring. After 30 min, the solid was filtered off through a Celite pad and the filtrate was concentrated to give a crude product, 0.70 g, with a 90.6% *ee* value and *S* configuration (determined by chiralpak OD, Hexane:iPrOH/90:10, rate: 1 mL/min). The crude product was twice recrystallised from ethyl acetate and hexane to give a white needle solid **9**, 0.62 g with >99% *ee* value and 89.1% yield, mp 108∼109 °C. $[\alpha]_D^{28}$ +18 ($c$ 0.35, $CH_2Cl_2$). FT-IR (KBr): 3368, 2980, 2942, 1774, 1753, 1686, 1606, 1514, 1441, 1370, 1286, 1207, 1171, 1042 $cm^{-1}$. $^1$H-NMR (400 MHz, $CDCl_3$)$\delta$ = 7.06 (d, $J$= 8.4 Hz, 1H, Ar-H), 6.82 (d, $J$= 8.4 Hz, 1H, Ar-H), 5.06 (bs, 1H, NH), 4.56 (m, 1H, CH), 3.82 (s, 3H, $OCH_3$), 3.68 (s, 3H, $COOCH_3$), 3.25-3.11 (m, 2H, $\beta$-$CH_2$), 2.37 (s, 3H, $COCH_3$), 1.37 (s, 9H, Boc). MS-EI (m/z): 401 ($M^+$); Anal. Calcul. for $C_{18}H_{24}ClNO_7$: C 53.80, H 6.03, N 3.49. Found: C 53.88, H 5.96, N 3.45.

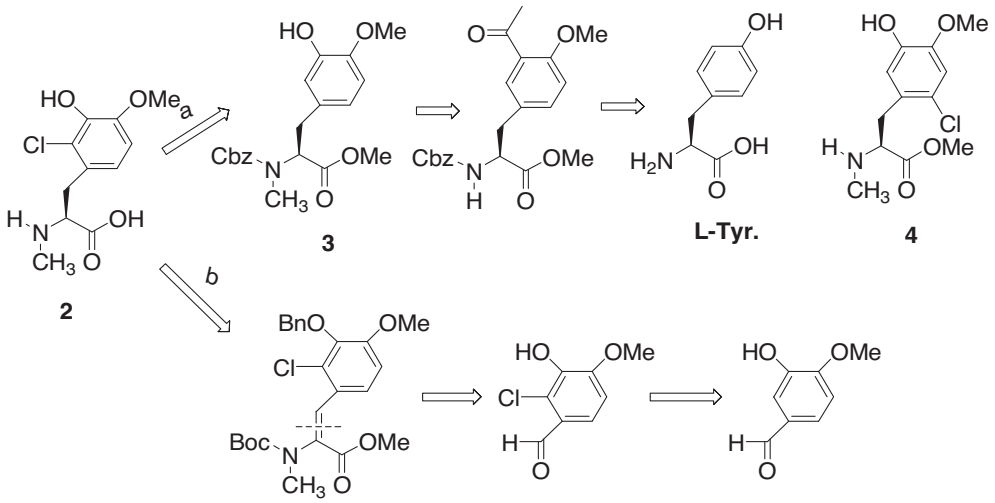
***(S)-N-tert*-butyloxycarbonyl-(3-benzyloxy-2-chloro-4-methoxy)-phenylalanine methyl ester (10):** To a solution of compound **9** (0.10 g, 0.25 mmol) in $CH_3OH$ (6 mL) and distilled water (2 mL) was added dropwise saturated $NaHCO_3$ (2 mL). The reaction solution was stirred at RT for 3 h and acidified to pH 3∼4 at 0 °C, and then extracted with ethyl acetate 4 times. The combined ethyl acetate layer was washed with brine and dried over anhydrous $MgSO_4$, and then concentrated to give a slight yellow slurry, which was dissolved in freshly distilled DMF (5 mL) at once. The powdered anhydrous $K_2CO_3$ (86 mg, 0.63 mmol) was added, followed by addition of BnBr (36.0 $\mu$L, 0.30 mmol) at 0 °C. After stirring at RT for 3 h under $N_2$, cold water was added and extracted with ethyl acetate 4 times. The combined organic layer was then washed in cold 1 N $KHSO_4$ and brine and dried over anhydrous $MgSO_4$, and concentrated to give a slight slurry, which was purified by column chromatography on silica gel (with hexane/ethyl acetate as an eluent) to obtain compound **10**[2a] as a slight yellow slurry, 63 mg, (23 mg of compound **9** was recovered), yield 73.7% for 2 steps (based on transformed starting material). $[\alpha]_D^{28}$+17.2 ($c$ 0.25, $CH_2Cl_2$). $^1$H-NMR (400 MHz, $CDCl_3$)$\delta$ (main rotamer) = 7.45 (m, 2H, Ar-H), 7.29 (m, 3H, Ar-H), 6.84 (d, $J$ = 8.0 Hz, 1H, Ar-H), 6.71 (d, $J$= 8.0 Hz, 1H, Ar-H), 4.95 (s, 2H, $OCH_2Ph$), 4.52 (m, 1H, $\alpha$-CH), 3.77 (s, 3H, $OCH_3$), 3.63 (s, 3H, $COOCH_3$), 3.16 (dd, $^2J$= 13.6 Hz, $^3J$= 6 Hz, 1H, $\beta$-$CH_2$), 3.01 (dd, $^2J$ = 13.6 Hz, $^3J$ = 6 Hz, 1H, $\beta$-$CH_2$), 1.33 (s, 9H, Boc). MS-EI ($m/z$): 449 ($M^+$). Anal. Calcul. for $C_{23}H_{28}ClNO_6$: C 61.40, H 6.27, N 3.11. Found: C 61.37, H 3.18, N 3.20.

***(S)-N-tert*-butyloxycarbonyl-*N*-methyl-(3-benzyloxy-2-chloro-4-methoxy)-phenylalanine methyl ester (11):** To a solution of compound **10** (0.10 g, 0.22 mmol) in THF (2.5 mL) was added a solution

of $LiOH.H_2O$ (25.0 mg) in water (0.5 mL) at 0 °C. After stirring at RT for 3 h, cold water was added and acidified to pH 3∼4 with 0.1 N HCl, and then extracted with ethyl acetate 4 times. The combined organic layer was washed with brine and dried over anhydrous $Na_2SO_4$, and concentrated to give a slight slurry, which was purified by column chromatography (petr./ethyl acetate: 3:1, 1:1, 1:2 as an eluent) to obtain the acid 81 mg (0.186 mmol), which was used for next *N*-methylation directly. The acid was dissolved in 4.5 mL of dry THF. To this solution was added NaH (22.4 mg, 0.56 mmol), followed by MeI (46 $\mu$L, 0.75 mmol) at 0 °C The reaction suspension was then stirred at 27 °C for 16 h. Cold water was added and acidified to pH 3∼4 with 0.1 N HCl, and then extracted with ethyl acetate 4 times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, and concentrated to give a crude product, which was purified by column chromatography on a silica gel (with petr./ethyl acetate: 3:1, 1:1, 1:2 as an eluent) to obtain a colourless oil **11**[2a] 50 mg, yield 50%. $[\alpha]_D^{20}$ -85.9 (*c* 0.11, $CH_2Cl_2$). FT-IR (Neat): 3010, 2984, 2936, 2851, 1739, 1705, 1487, 1444, 1374, 1245, 1947, 758 $cm^{-1}$. $^1$H-NMR (200 MHz, $CDCl_3$)$\delta$ (main rotamer) = 7.54 (m, 2H, Ar-H), 7.34 (m, 3H, Ar-H), 6.88 (d, 1H, $J$ = 8.6 Hz, Ar-H), 6.77 (d, $J$= 8.6 Hz, 1H, Ar-H), 5.05 (s, 2H, $OCH_2Ph$), 4.63 (m, 2H, $\alpha$-CH, COOH), 3.86 (s, 3H, $OCH_3$), 3.51-3.07 (m, 2H, $\beta$-$CH_2$), 2.70 (s, 3H, $NCH_3$), 1.43 (s, 9H, Boc). MS-EI ($m/z$): 449 ($M^+$). Anal. Calcul. for $C_{23}H_{28}ClNO_6$: C 61.40, H 6.27, N 3.11. Found: C 61.31, H 6.35, N 3.17.

## Results and discussion

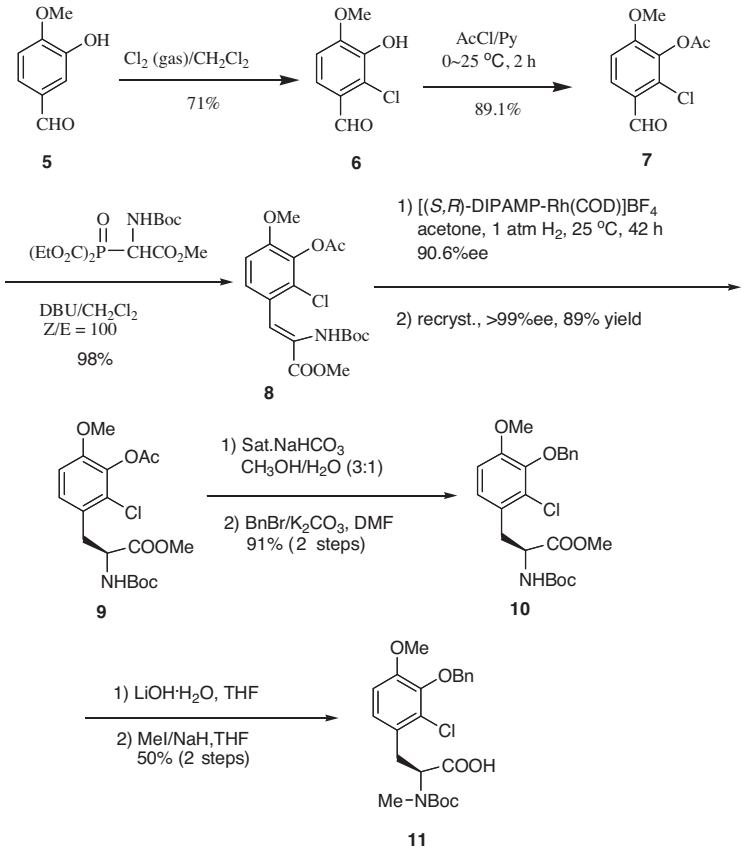
Many methods have been published for the preparation of enantiomerically pure dopa analogues, such as the improved synthesis of selectively protected *L*-dopa derivatives from *L*-tyrosine,[4] the traditional Schöllkopf method for chiral amino acids, and enantioselective catalysis with chiral auxiliaries.[5] We also wanted to obtain the dopa analogue **2** from *L*-tyrosine. As shown in the retro-synthetic route a (Scheme 1), compound **3** was obtained conveniently from *L*-tyrosine through acetylation, hydroxylation, and methylation under the Coggins condition.[6] Unfortunately, the final chlorination of compound **3** was unsuccessful, maybe because of the steric hindrance effect. Even when Cbz was firstly removed before chlorination, and the undesired compound **4** was obtained.




**Scheme 1.** Retro-synthesis of the dopa analogue.

Another method (according to retro-synthetic route b; Scheme 1) was then developed with the aim of obtaining the target compound via enantioselective catalytic hydrogenation of the chlorinated dehydroamino acid by employing a chiral catalyst such as DIPAMP.[7]

Chlorination of isovanillin gave compound **6**, and protection of the OH group by acetylation afforded aldehyde **7**, which was coupled with *N*-protected-2-(diethoxycarbonyl)phosphinyl)glycine ester[8,9] by using DBU as a base under the Horner–Emmons condensation condition[8] to afford DDAA **8.** Subsequently, **8** has been hydrogenated using the chiral catalyst DIPAMP to give **9** with 100% conversion and 90.6% *ee*. In particular, this step can be conducted on a large scale with good *ee*. After recrystallisation, compound **9** was obtained in enantiopure form (>99% *ee*, Scheme 2).




**Scheme 2.** Asymmetric synthesis of the dopa analogue **11**.

Since the acetyl group was unstable under strong basic conditions (such as LiOH and NaH), it was selectively removed by treatment of **9** with a saturated solution of $NaHCO_3$ in $MeOH/H_2O$ (Scheme 2) without removing the Me group;[10] then the OH group was protected by benzylation to give the closely related known compound **10.**[2a] Subsequently, under the Bnoiton condition,[6] **10** has been transformed into the known compound **11**.[2a]

## Conclusion

A new synthetic route was developed to prepare the dopa analogue by employing the methodology of asymmetric catalytic hydrogenation of dehydroamino acids. Such a method is of practical use for the total synthesis of pepticinnamin E and its analogues.

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