Convenient Synthesis and Conversion of a (*Z*)-α,β-Didehydroornithine Derivative to α,β-Didehydrokyotorphin

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Abstract: Hydrogenolysis of the azido group of methyl (*Z*)-2-(*N*-Cbz)amino-5-azidopent-2-enoate, derived by selective reduction and azidation of the side chain carboxyl group of *N*-protected (*Z*)-ΔGlu-OMe, gave (*Z*)-α,β-didehydroornithine derivative (**7**). The formed **7** was further converted to the basic (*Z*)-α,β-didehydroarginine and the acid containing (*Z*)-α,β-didehydrokyotorphin.

Key words: amines, azides, peptides, condensations, coupling, reductions, didehydroamino acids, didehydroornithine

In previous papers,[1–3] we have reported the convenient synthesis of *N*-benzyloxycarbonyl-(*Z*)-α,β-didehydroglutamic acids [Cbz-ΔGlu(OR)-OR (**1**); **a**: R = H; **b**; R = Me] by the direct condensation of α-oxoglutaric acids with benzyl carbamate (Cbz-NH_2). Meanwhile, the synthesis of Cbz-ΔGlu-OMe (**1c**) was reported by Baldwin et al.[4] and we have also reported briefly a useful synthetic method for **1c** by the selective enzymatic hydrolysis of the γ-ethyl ester of **1b** using esterase α-chymotrypsin.[5] The structurally unique α,β-didehydroglutamate **1c** is thought to be most applicable to various syntheses of other useful (*Z*)-α,β-didehydroamino acids (ΔAA) and heterocycles.[1]

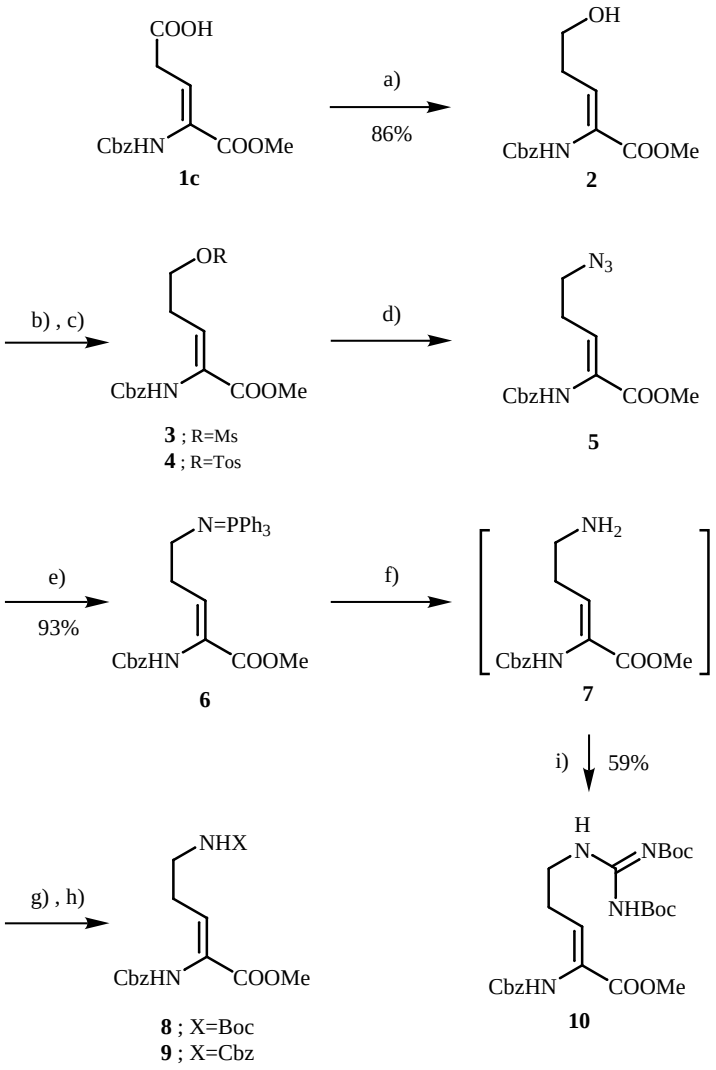
In this paper, we wish to report the convenient synthesis of 2-amino-5-hydroxypent-2-enoate derivative **2** from **1c** and the facile conversion of **2** to two kinds of basic ΔAA, such as (*Z*)-α,β-didehydroornithine (ΔOrn) and (*Z*)-α,β-didehydroarginine (ΔArg). Furthermore, in connection with the study on the structure-bioactivity relationship of analgesic dipeptide kyotorphin,[6] the synthesis of various convertible (*Z*)-α,β-didehydrokyotorphins (Tyr-ΔArg) from Tyr-ΔOrn derivative was first achieved.

Selective reduction of the side chain carboxyl group of **1c** with $NaBH_4$ in the presence of BF_3•OEt_2 in THF proceeded smoothly to give the expected methyl (*Z*)-2-(*N*-Cbz)amino-5-hydroxypent-2-enoate (**2**) in 86% yield (Scheme 1). In order to examine the azidation of the hydroxy group, mesylation or tosylation of **2** with methanesulfonyl chloride (MsCl) or toluenesulfonyl chloride (TosCl) in the presence of pyridine was attempted to give the corresponding 5-mesyloxy **3** and 5-tosyloxy **4** derivatives, respectively. Subsequent azidation of **3** with NaN_3 in DMF in the presence of catalytic 15-crown-5 was performed to give the corresponding 5-azidopent-2-enoate derivative **5**. Unfortunately, the yield was found to be markedly low (44%). On the other hand, the azidation of **4** with NaN_3 proceeded smoothly to give **5** almost quantitatively (Scheme 1).

Attempts to reduce only the azide group of **5** directly by using reducing agents, such as $LiAlH_4$ and $NaBH_4$, were unsuccessful, because of further hydrogenation of the C=C bond and the methyl ester. Therefore, after conversion of the 5-azido group to a 5-triphenylphosphinimino group, subsequent syntheses of two basic ΔAA were effected successfully. Reaction of **5** with Ph_3P proceeded readily to give methyl 5-triphenylphosphiminopent-2-enoate (**6**), which was then treated with water in THF[7] to give the expected Cbz-(*Z*)-ΔOrn-OMe (**7**). Since the formed **7** was slightly unstable, one-pot reaction with Boc_2O was carried out, without complete isolation, to give Cbz-(*Z*)-ΔOrn(Boc)-OMe (**8**)[8,9] in 58% yield in two steps. On the other hand, the reaction of **7** with CbzCl in the presence of Et_3N gave Cbz-(*Z*)-ΔOrn(Cbz)-OMe (**9**) in 60% yield. Furthermore, guanidylation of **7** with $(Boc\text{-}NH)_2CS$ in the presence of $HgCl_2$, according to the reported method,[10] gave first the expected Cbz-(*Z*)-ΔArg(Boc_2)-OMe (**10**) in 59% yield, as shown in Scheme 1.

Hydrolysis of the methyl ester of **9** with 1 M LiOH, followed by cyclization of the resulting Cbz-(*Z*)-ΔOrn(Cbz)-OH (**11**) with $SOCl_2$ in diethyl ether gave *N*-carboxy-α,β-didehydroornithine anhydride [Cbz-(*Z*)-ΔOrnNCA] (**12**) in 93% yield, according to the method reported previously.[8] Subsequently, facile coupling of **12** with Boc-l-Tyr(MOM)-OH using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 gave the protected Boc-l-Tyr(MOM)-ΔOrn(Cbz)-OMe (**13**) in 62% yield. Then, selective deprotection of the Cbz group of **13** with triethylsilane and $PdCl_2$ in the presence of Et_3N,[11] followed by guanidylation of the formed intermediate as for **10**, gave the desired protected Boc-l-Tyr(MOM)-(*Z*)-ΔArg(Boc_2)-OMe (**14**) in 62% yield. Finally, deprotection of all the protecting groups of **14** with 1 M LiOH in MeOH and then trifluoroacetic acid (TFA) in CH_2Cl_2 were effected successfully to give the expected H-l-Tyr-(*Z*)-ΔArg-OH **(15)** in 65% yield (Scheme 2).

In conclusion, a convenient synthetic method for basic ΔAA and the acid containing didehydrokyotorphin has been developed. Further investigation on the various reactions of ΔOrn and ΔArg derivatives is currently under way in our laboratory.



Reagents and conditions: a) $NaBH_4/BF_3.OEt_2$, −10°C, 3 min, 86%; b) **3**/MsCl/pyridine/CH_2Cl_2, r.t., 5 h, 74%; c) **4**/TosCl/pyridine/CH_2Cl_2, 6 h, 93%; d) NaN_3/15-crown-5/DMF, r.t., 2 h, 44% from **3**, 94% from **4**; e) Ph_3P/THF, r.t. 3 h; f) H_2O/THF, r. t., 6 h; g) **8**/Boc_2O/THF, r.t.. 51%; h) **9**/CbzCl/TEA/THF, r.t., 3 h, 60%; i) $(BocNH)_2CS/HgCl_2$/TEA/DMF, r.t. 3 h

Scheme 1

Melting points were determined with Yamato Mp-21 micro melting points apparatus, and are uncorrected. The IR spectra in KBr were recorded on a Hitachi 270-30 spectrometer. The ^1H NMR spectra were measured with a JEOL FX 200 spectrometer in $CDCl_3$ solution with TMS as the internal standard.

Methyl (*Z*)-2-(*N*-Cbz)Amino-5-hydroxypent-2-enoate (2)

To a stirred solution of $NaBH_4$ (2.10 g, 55.5 mmol) in THF (100 mL) was added **1c** (10.00 g, 34.0 mmol) at −10°C. After stirring for 2 min, BF_3•OEt_2 (9.0 mL, 71.0 mmol) was added slowly over 2 h and then the mixture was poured into a chilled, satd aq $NaHCO_3$ (150 mL). After removal of THF in vacuo, the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were successively washed with satd aq NH_4Cl (3 × 100 mL), satd aq $NaHCO_3$ (3 × 100 mL), brine (3 × 100 mL), and then dried (Na_2SO_4). Concentration in vacuo gave crude crystals, which were recrystallized from a mixture of Et_2O and pentane to give **2** as colorless needles; yield: 8.21 g (86%); mp 63−64°C.

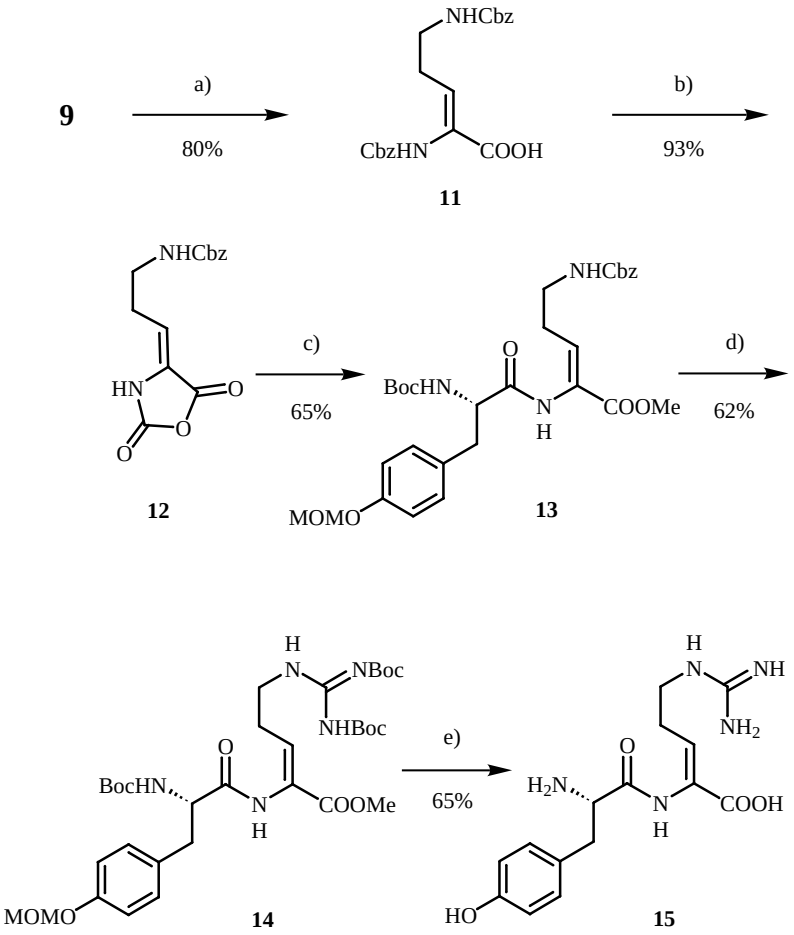
IR: ν = 3508, 3290, 3004, 2995, 1720, 1689, 1510 cm^{-1}.

^1H NMR: δ = 2.45 (dt, 2 H, *J* = 5.9, 7.8 Hz, 4-H), 2.96 (br s, 1 H, OH), 3.75 (s, 3 H, CO_2CH_3), 3.78 (t, 2 H, *J* = 5.9 Hz, 5-H), 5.13 (s, 2 H, CH_2Ph), 6.65 (t, 1 H, *J* = 7.8 Hz, 3-H), 6.81 (br s, 1 H, NH), 7.35 (s, 5 H, C_6H_5).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 59.69; H, 6.18; N, 5.30.

Methyl (*Z*)-2-(*N*-Cbz)Amino-5-mesyloxypent-2-enoate (3)

To a stirred solution of **2** (1.50 g, 5.4 mmol) in CH_2Cl_2 (30 mL) was added pyridine (0.9 mL, 10.7 mmol) and MsCl (0.60 mL, 7.8 mmol) at 0°C. After stirring at r.t. for 6 h, the mixture was poured into H_2O (30 mL) and then the resulting solution was extracted with $CHCl_3$ (3 × 10 mL). The organic layer was washed with 1 M HCl (3 × 10



Reagents and conditions: a) 1 M LiOH/dioxane, r. t., 3 h; b) $SOCl_2/Et_2O$, r. t., 1.5 h; c) (i) BocTyr(MOM)-OH/DCC/DMPA/CH_2Cl_2, −5°C to r. t., 1.5 h; (ii) MeOH/TEA, r. t., 2 h; d) (i) $Et_3SiH/PdCl_2$/TEA/CH_2Cl_2, r.t., 2 h; (ii) TBAF/$(Boc)_2CS/HgCl_2$/TEA/DMF, r.t. 3 h; e) (i) 1 M LiOH/MeOH, r.t., 2 h, (ii) TFA/CH_2Cl_2, r. t. 1 h

Scheme 2

mL), satd aq $NaHCO_3$ (3 × 10 mL), brine (3 × 10 mL), and then dried (Na_2SO_4). Concentration in vacuo gave crude crystals, which were recrystallized from a mixture of EtOAc and hexane to give **3** as colorless needles; yield: 1.41 g (74%); mp 66−67°C.

IR: ν = 3454, 3316, 1758, 1725, 1695, 1515 cm^{-1}.

^1H NMR: δ = 2.68 (dt, 2 H, *J* = 6.4, 7.3 Hz, 4-H), 3.01 (s, 3 H, SO_3CH_3), 3.79 (s, 3 H, CO_2CH_3), 4.36 (t, 2 H, *J* = 6.4 Hz, 5-H), 5.14 (s, 2 H, C*H*$_2$Ph), 6.45 (br s, 1 H, NH), 6.60 (t, 1 H, *J* = 7.3 Hz, 3-H), 7.37 (s, 5 H, C_6H_5).

Anal. Calcd for $C_{15}H_{19}NO_7S$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.32; H, 5.40; N, 4.12.

Methyl (*Z*)-2-(*N*-Cbz)Amino-5-tosyloxypent-2-enoate (4)
Reaction of **2** (1.51 g, 5.4 mmol) with TosCl (1.30 g, 6.8 mmol) was carried out analogous to the mesylation of **3** as above and worked up to give **4** as a colorless syrup; yield: 2.20 g (93%).

IR: ν = 3634, 3496, 3354, 3064, 3028, 2950, 2926, 2854, 2254, 1725, 1665, 1599, 1503 cm^{-1}.

^1H NMR: δ = 2.44 (s, 3 H, ArC*H*$_3$), 2.57 (dt, 2 H, *J* = 6.4, 7.3 Hz, 4-H), 3.77 (s, 3 H, CO_2CH_3), 4.15 (t, 2 H, *J* = 6.4 Hz, 5-H), 5.11 (s, 2 H, C*H*$_2$Ph), 6.39 (br s, 1 H, NH), 6.49 (t, 1 H, *J* = 7.3 Hz, 3-H), 7.33 (d, 2 H_{arom}, *J* = 8.3 Hz), 7.36 (s, 5 H, C_6H_5), 7.78 (d, 2 H_{arom}, *J* = 8.3 Hz)

Anal. Calcd for $C_{21}H_{23}NO_7S$: C, 58.19; H, 5.35; N, 3.23. Found: C, 58.53; H, 5.38; N, 3.31.

Methyl (*Z*)-2-(*N*-Cbz)Amino-5-azidopent-2-enoate (5)
From **3**: To a solution of **3** (1.00 g, 2.8 mmol) in DMF (15 mL) was added NaN_3 (220 mg, 3.4 mmol) and catalytic 15-crown-5 (0.15 mL) at 50°C. After stirring for 2 h, the mixture was poured into H_2O (50 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with 10% citric acid (2 × 10 mL), satd aq $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL), and then dried (Na_2SO_4). Concentration in vacuo gave a residual syrup, which was chromatographed on a silica-gel column using a mixture of EtOAc and hexane (2 : 1 v/v) to give **5** as a colorless syrup; yield: 370 mg (44%).

IR: ν = 3552, 3360, 2960, 2104, 1838, 1716, 1516 cm^{-1}.

^1H NMR: δ = 2.49 (dt, 2 H, *J* = 6.8, 7.3 Hz, 4-H), 3.44 (t, 2 H, *J* = 6.8 Hz, 5-H), 3.78 (s, 3 H, CO_2CH_3), 5.15 (s, 2 H, C*H*$_2$Ph), 6.40 (br s, 1 H, NH), 6.58 (t, 1 H, *J* = 7.3 Hz, 3-H), 7.28−7.38 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.31; N, 18.41. Found: C, 55.60; H, 5.22; N, 18.62.

From **4**: A suspension of **4** (1.40 g, 3.20 mmol) and NaN_3 (230 mg, 3.54 mmol) in DMF (20 mL) in the presence of catalytic 15-crown-5 (0.15 mL) was stirred at r.t. for 4 h. The mixture was diluted with H_2O (60 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with 10% aq citric acid (3 × 10 mL), satd aq $NaHCO_3$ solution (3 × 10 mL), brine (3 × 10 mL), and then dried (Na_2SO_4). Concentration in vacuo gave a residual syrup, which was purified on a silica gel column using a mixture of EtOAc and hexane (1:10 v/v) to give **5** as a colorless syrup; yield: 915 mg (94%).

Methyl (*Z*)-2-(*N*-Cbz)Amino-5-triphenylphosphiminopent-2-enoate (6)

A solution of **5** (500 mg, 1.60 mmol) and Ph_3P (431 mg, 1.64 mmol) in benzene (10 mL) was stirred at r.t. for 4 h. Concentration of the mixture in vacuo gave a residual syrup, which was crystallized from hexane. The crude crystals were recrystallized from a mixture of EtOAc and hexane (1:50 v/v) to give **6** as colorless prisms; yield: 800 mg (93 %); mp 69−70°C.

IR: ν = 3052, 2944, 2842, 2818, 2464, 2296, 2248, 2134, 2014, 1965, 1941, 1908, 1887, 1866, 1827, 1719, 1650, 1614, 1590, 1488 cm^{-1}.

^1H NMR: δ = 2.40−2.56 (m, 2 H, 4-H), 3.16−3.34 (m, 2 H, 5-H), 3.73 (s, 3 H, CO_2CH_3), 5.08 (s, 2 H, C*H*$_2$Ph), 6.36 (t, 1 H, *J* = 7.8 Hz, 3-H), 7.28−7.90 (m, 20 H, 4 × C_6H_5), 10.00 (br s, 1 H, NH).

Anal. Calcd for $C_{32}H_{31}N_2O_4P$: C, 71.35; H, 5.81; N, 5.20. Found: C, 71.16; H, 5.78; N, 5.26.

Cbz-(*Z*)-ΔOrn(Boc)-OMe (8)

A solution of **6** (500 mg, 0.93 mmol) in THF (10 mL) and H_2O (1 mL) was stirred at r.t. for 6 h. To the mixture was added Boc_2O (203 mg, 0.93 mmol) and then the resulting solution was continuously stirred for 6 h. Concentration in vacuo gave a residual syrup, which was purified on a silica gel column using a mixture of EtOAc and hexane (1 : 5 v/v) as eluent to give **8** as a colorless syrup; yield: 180 mg (51%).

IR: ν = 3323, 2928, 1773, 1653, 1508 cm^{-1}.

^1H NMR: δ = 1.44 (s, 9 H, *t*-C_4H_9), 2.42 (dt, 2H, *J* = 6.4, 7.8 Hz, 4-H), 3.27 (dt, 2 H, *J* = 6.4, 7.8 Hz, 5-H), 3.76 (s, 3 H, CO_2CH_3), 4.90 (br s, 1 H, NH), 5.14 (s, 2 H, C*H*$_2$Ph), 5.38 (br s, 1 H, NH), 6.63 (t, 1 H, *J* = 7.8 Hz, 3-H), 7.36 (s, 5 H, C_6H_5).

Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.38; H, 7.15; N, 7.35.

Cbz-(*Z*)-ΔOrn(Cbz)-OMe (9)

A solution of **6** (1.08 g, 2.00 mmol) in THF (20 mL) and H_2O (2 mL) was stirred at r. t. for 6 h. To the mixture was added CbzCl (375 mg, 2.20 mmol), Et_3N (202 mg, 2.00 mmol) and then the resulting solution was continuously stirred for 3 h. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of EtOAc and hexane (1 : 5 v/v) as eluent to give a colorless syrup. The obtained syrup was crystallized from hexane. The crystals were recrystallized from cyclohexane to give **9** as colorless needles; yield: 495 mg (60%); mp 80−82°C.

IR: ν = 3319, 3303, 1735, 1689, 1553, 1505 cm^{-1}.

^1H NMR: δ = 2.45 (dt, 2 H, *J* = 6.5, 7.5 Hz, 4-H), 3.36 (m, 2 H, 5-H), 3.76 (s, 3 H, CO_2CH_3), 5.10 (s, 2 H, C*H*$_2$Ph), 5.13 (s, 2 H, C*H*$_2$Ph), 5.24 (br s, 1 H, CH_2NH), 6.37 (br s, 1 H, NH), 6.58 (t, 1 H, *J* = 7.5 Hz, 3-H), 7.33−7.36 (m, 10 H, 2 × C_6H_5).

Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.06; H, 5.87; N, 6.79. Found: C, 64.18; H, 5.75; N, 6.55.

Cbz-(*Z*)-ΔArg(Boc$_2$)-OMe (10)

A solution of **6** (500 mg, 0.90 mmol) in THF (10 mL) and H_2O (1 mL) was stirred at r.t. for 6 h. The mixture was concentrated in vacuo to give a residual syrup, which was dissolved in DMF (10 mL). To the resulting solution was added Et_3N (0.43 mL, 3.10 mmol), $(BocNH)_2CS$ (257 mg, 0.90 mmol), and $HgCl_2$ (277 mg, 1.00 mmol) at 0°C and the mixture was continuously stirred at r.t. for 3 h. After removal of insoluble material, the filtrate was diluted with H_2O (30 mL). The aqueous solution was extracted with EtOAc (3 × 5 mL) and the combined extracts were washed with 10% aq citric acid (3 × 5 mL), satd aq $NaHCO_3$ (3 × 5 mL), brine (3 × 5 mL), and then dried (Na_2SO_4). Concentration in vacuo gave residual crystals, which were recrystallized from a mixture of EtOAc and hexane to give **10** as colorless needles; yield: 279 mg (59%); mp 128−129°C.

IR: ν = 3370, 2974, 1722, 1668, 1596, 1572, 1518 cm^{-1}.

^1H NMR: δ = 1.45 (s, 18 H, 2 × *t*-C_4H_9), 2.51 (dt, 2 H, *J* = 7.3, 7.8 Hz, 4-H), 3.25-3.76 (m, 2 H, 5-H), 3.70 (s, 3 H, CO_2CH_3), 5.06 (AB q, 2 H, *J* = 12.2, 20.0 Hz, C*H*$_2$Ph), 6.41 (br s, 1 H, NH), 6.47 (t, 1H, *J* = 7.8 Hz, 3-H), 6.95 (br s, 1 H, NH), 7.22-7.44 (m, 5 H, C_6H_5). 9.45 (br s, 1 H, NH).

Anal. Calcd for $C_{25}H_{36}N_4O_8$: C, 57.68; H, 6.97; N, 10.76. Found: C, 57.95; H, 6.92; N, 11.15.

Cbz-(*Z*)-ΔOrn(Cbz)-OH (11)

A solution of **9** (1.00 g, 2.40 mmol) in dioxane (5 mL) and 1 M LiOH (3 mL) was stirred at 20°C for 3 h. To the mixture was added satd aq $NaHCO_3$ solution (30 ml). After removal of dioxane in vacuo, the residual aqueous layer was washed with Et_2O (3 × 5 mL) and acidified with 10% aq citric acid to pH 3-4. The aqueous solution was extracted with EtOAc (3 × 7 mL) and the combined organic extracts were washed with 10% aq citric acid (3 × 5 mL), brine (3 × 5 mL), and then dried (Na_2SO_4). Concentration in vacuo gave residual crystals, which were recrystallized from a mixture of $CHCl_3$ to give **11** as colorless needles; yield: 765 mg (80%), mp 121−123°C.

IR: ν = 3424, 1698, 1515, 1404 cm^{-1}.

^1H NMR δ = 1.46 (s, 9 H), 1.49 (d, 3 H, *J* = 6.4 Hz), 1.65 (s, 6 H), 1.88 (d, 3 H, *J* = 7.0 Hz, =CHC*H*$_3$), 4.05 (d, 1 H, *J* = 7.5 Hz), 4.38 (dq, 1 H, *J* = 6.4, 7.5 Hz), 6.57 (q, 1 H, *J* = 7.5 Hz, =C*H*CH_3), 8.00 (br s, 1 H, NH), 8.11 (s, 1 H, NH at C-5), 8.54 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: 63.45; H, 5.72; N, 7.25.

(*Z*)-ΔOrn(Cbz)NCA (12)

To a stirred suspension of **11** (1.00 g, 2.50 mmol) in Et_2O (10 mL) was added $SOCl_2$ (10 mL) at 0°C. After stirring at r. t. for 1 h, the mixture was thoroughly concentrated in vacuo to give a residual syrup, which was crystallized from benzene. The crude crystals were recrystallized from benzene to afford **12** as colorless prisms; yield: 675 mg (93%); mp 87−89°C.

IR: ν = 3342, 1852, 1806, 1694, 1534, 1315 cm^{-1}.

^1H NMR: δ = 2.48 (q, 2 H, *J* = 7.0 Hz, 4-H), 3.29 (dt, 2 H, *J* = 6.0, 7.0 Hz), 5.12 (s, 2 H, C*H*$_2$Ph), 5.19 (br s, 1 H, CH_2NH), 5.94 (t, 1 H, 3-H), 7.31-7.40 (m, 5 H, C_6H_5), 9.43 (br s, 1H, NH).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.95; H, 4.92; N, 9.35.

Boc-l-Tyr(MOM)-(*Z*)-ΔOrn(Cbz)-OMe (13)

To a stirred solution of Boc-Tyr(MOM)-OH (2.57 g, 7.89 mmol) and DCC (1.78 g, 8.64 mmol) in CH_2Cl_2 (40 mL) was added over 30 min at −10°C. After stirring for 30 min, **12** (2.18 g, 1.72 mmol) and DMAP (3.00 g, 1.50 mmol) were added over 1.5 h at r. t. Finally, after treating further with MeOH (10 mL) and stirring for 2 h, TEA (1.26 mL, 9.01 mmol) was added to the mixture. After remov-

al of CH_2Cl_2 and MeOH in vacuo, the residue was dissolved in EtOAc (10 mL) and the *N,N'*-dicyclohexylurea separated out was filtered. The filtrate was diluted in EtOAc (10 mL) and the resultant solution was washed successively with 10% aq citric acid (2 x 5 mL), satd aq $NaHCO_3$ (2 x 5 mL), H_2O (5 mL) and then dried (Na_2SO_4). Concentration in vacuo gave a residual syrup, which was purified on a silica gel column using a mixture of $CHCl_3$ and acetone (25:1 v/v) to give colorless crystals, which were recrystallized from a mixture of EtOAc and hexane to give **13** as colorless needles; yield: 2.85 g (65%); mp 98−99°C; $[\alpha]_D^{25}$ +1.1 (*c* = 0.97, MeOH).

IR: ν = 3330, 3295, 2951, 1733, 1695, 1684, 1670, 1585, 1525, 1512 cm^{-1}.

^1H NMR: δ =1.41 (s, 9 H, *t*-C_4H_9), 2.27 (dt, 2 H, *J* = 6.5, 7.5 Hz, ΔOrn's 4-H), 3.00 (dd, 1 H, *J* = 7.0, 14.0 Hz, Tyr's 3-H), 3.10 (dd, *J* = 6.5, 14.0 Hz, Tyr's 3-H), 3.32 (dt, 2 H, *J* = 6.0, 6.5 Hz, ΔOrn's 5-H), 3.46 (s, 3 H, OCH_3), 3.74 (s, 3 H, CO_2CH_3), 4.42 (m, 1 H, Tyr's 2-H), 5.01 (br s, 1 H, NH), 5.10 (s, 2 H, C*H*$_2$Ph), 5.14 (s, 2 H, OCH_2O), 5.47 (t, 1 H, *J* = 6.0 Hz, CH_2NH), 6.63 (t, 1 H, ΔOrn's 3-H), 6.96 (d, 2 H, *J* = 8.5 Hz, Tyr's H_{arom}), 7.13 (d, 2 H, *J* = 8.5 Hz. Tyr's H_{arom}), 7.36 (m, 5 H, C_6H_5), 7.55 (br s, 1 H, NH).

Anal. Calcd for $C_{30}H_{39}N_3O_9$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.75; H, 6.87; N, 7.25.

Boc-l-Tyr(MOM)-(*Z*)-DArg(Boc$_2$)-OMe (14)

To a solution of **13** (378 mg, 0.64 mmol) in CH_2Cl_2 (20 mL) was added Et_3SiH (0.4 mL, 3.44 mmol), Et_3N (0.17 mL. 0.77 mmol), and $PdCl_2$ (10 mg, 0.06 mmol). The resultant solution was heated under reflux for 20 min. The mixture was concentrated in vacuo to give a residual syrup, to which a solution of Bu_4NF (TBAF, 1 M solution in THF, 0.7 mL) in DMF (15 mL) was added with stirring over 5 min at r. t. To the resulting solution was added Et_3N (0.43 mL, 3.1 mmol), $(BocNH)_2CS$ (257 mg, 0.90 mmol), and $HgCl_2$ (277 mg, 1.0 mmol) at 0°C and then the mixture was continuously stirred at r. t. for 3 h. After removal of insoluble material, the filtrate was diluted with H_2O (30 mL). The aqueous solution was extracted with EtOAc (3 × 15 mL) and the combined extracts were washed with 10% aq citric acid (3 × 5 mL), satd aq $NaHCO_3$ (3 × 5 mL), brine (3 × 5 mL), and then dried (Na_2SO_4). Concentration in vacuo gave a residual amorphous, which was recrystallized from a mixture of EtOAc and hexane to give **14** as a colorless amorphous material; yield: 279 mg (62%); mp 68−69°C; $[\alpha]_D^{25}$ −3.4 (*c* = 0.93, MeOH).

IR: ν = 3438, 2979, 2934, 1721, 1680, 1640, 1617, 1511, 1368 cm^{-1}.

^1H NMR: δ = 1.42 (s, 9 H, *t*-C_4H_9), 1.49 (s, 18 H, 2 *t*-C_4H_9), 2.35 (m, 2 H, ΔArg's 4-H), 3.04 (dd, 1 H, *J* = 6.0, 14.0 Hz, Tyr's 3-H), 3.11 (dd, 1 H, *J* = 7.0, 14.0 Hz, Tyr's 3-H), 3.46 (s, 3 H, OCH_3), 3.51 (dt, 2 H, *J* = 7.0, 5.5 Hz, ΔArg's 5-H), 3.75 (s, 3 H, CO_2CH_3), 4.43 (m, 1 H, Tyr's 2-H), 5.02 (br s, 1H, NH), 5.14 (s, 2H, OCH_2O), 6.65 (t, 1H, *J*=7.0 Hz, ΔArg's 3-H), 6.97 (d, 2 H, *J* = 9.0 Hz, Tyr's H_{arom}), 7.15 (d, 2 H, *J* = 9.0 Hz, Tyr's H_{arom}), 7.56 (br s, 1 H, NH), 8.31 (t, 1 H, *J* = 7.0 Hz, CH_2NH), 11.5 (br s, 1 H, guanidino group's NH).

Anal. Calcd for $C_{33}H_{51}N_5O_{11}$: C, 57.13; H, 7.41; N, 10.09. Found: C, 57.26; H, 7.60; N, 10.21.

H-l-Tyr-(*Z*)-ΔArg-OH (15)

A solution of **14** (105 mg, 0.15 mmol) in dioxane (1 mL) was stirred with 1 M LiOH (0.20 mL) at r.t. over 3 h. The mixture was washed with H_2O/Et_2O (15 mL; 2:1 v/v) and the aqueous layer was acidified to pH 3 with 3 M HCl and then extracted with EtOAc (3 × 7 mL). The combined organic layers were concentrated in vacuo. The obtained residue was dissolved in $CHCl_3/Et_3N$ (1.4 mL; 1:1 v/v) and the resulting solution was stirred at r.t. for 3 h. After concentration in vacuo, the crude residue was purified by DOWEX 50W-X18-OH using EtOH as eluent to give a solid, which was recrystallized from $EtOH/Et_2O$ to give **15** as colorless amorphous material; yield: 33 mg (65%); mp 190−195°C; $[\alpha]_D^{25}$ −5.4 (*c* = 0.93, MeOH).

IR: ν = 3438, 2979, 2934, 1721, 1680, 1640, 1617, 1511, 1368 cm^{-1}.

^1H NMR: δ = 2.05 (m, 2 H, ΔArg's 4-H), 3.04 (dd, 1 H, *J* = 6.5, 14.0 Hz, Tyr's 3-H), 3.13 (dd, 1 H, *J* = 7.0, 14.0 Hz, Tyr's 3-H), 3.23 (t, 2 H, *J* = 6.5 Hz, ΔArg's 5-H), 4.12 (m, 1 H, Tyr's 2-H), 6.47 (t, 1 H, *J* = 7.0 Hz, ΔArg's 3-H), 6.77 (d, 2 H, *J* = 8.0 Hz, Tyr's H_{arom}), 7.35 (d, 2 H, *J* = 8.0 Hz, Tyr's H_{arom}).

Anal. Calcd for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.89. Found: C, 53.45; H, 6.05; N, 21.22.

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