Stereoselective Synthesis of β-Methoxytyrosine Derivatives for Identification of the Absolute Configuration of Callipeltin E

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Abstract: Asymmetric syntheses of all diastereoisomers of β-methoxytyrosine, an unusual amino acid contained in callipeltin A, were accomplished starting from a cinnamyl ester derivative. The stereochemistry of β-methoxytyrosine in callipeltin E was estimated to be 2R,3R by 1H and 13C NMR analyses of four diastereoisomeric tripeptides, each containing a β-methoxytyrosine isomer. These results obtained from the synthetic peptide derivatives were identical to D’Auria’s results obtained by a degradative procedure.

Key words: callipeltin, cyclodepsipeptide, β-methoxytyrosine, marine sponge, unusual amino acid, anti-HIV activity

Callipeltin A (1) (Figure 1) is a novel cyclodepsipeptide isolated from the shallow water sponge Callipelta, collected in New Caledonia. Callipeltin A (1) is the first natural peptide found to act against HIV. Additionally, it displays antifungal activity and potent cytotoxicity against a broad range of human carcinoma cell lines. It was also found that callipeltin A (1) was a selective and powerful inhibitor of the Na+/Ca2+ exchanger and a positive ionotropic agent in guinea pig left atria. These interesting biological activities as well as its unique structure have aroused interest.

Callipeltin A (1) is composed of a 22-membered macrocycle containing three unusual amino acids: β-methoxytyrosine (β-MeOTyr) (2), (2R,3R,4S)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE), and (3S,4R)-3,4-dimethyl-L-glutamine (diMeGln). The configuration of β-MeOTyr (2) in callipeltin A (1) could not be determined due to its lability to acid. The total synthesis of callipeltin A (1) has not yet been achieved although several groups reported the synthesis of unusual amino acids contained in callipeltin A (1). Since the stereostructure of β-MeOTyr (2) in callipeltin A (1) had not been identified in initial studies, preparations of all four stereoisomers of β-MeOTyr derivatives have been reported independently by three research groups: those of Hamada, Joullié, and D’Auria. The strategies used by the Hamada and Joullié research groups were based on the stereoselective addition of arylimetal reagents to serine aldehyde equivalents followed by methylation. For the preparation of the four stereoisomers of β-MeOTyr (2), a rather long sequence starting from L- and D-serine, respectively, was necessary. In contrast, D’Auria’s group employed photo-assisted bromination of D- and L-tyrosine derivatives for the synthesis of intermediates as diastereomixtures. The stereochemistry of β-MeOTyr (2) in callipeltin A (1) was estimated to be 2R,3R by a comparison of oxidative degradation products obtained from callipeltin A (1) and four separately synthesized β-MeOTyr derivatives. Based on this assignment, Lipton et al. recently reported the solid phase syntheses of callipeltin E (3) (Figure 1) and a cyclized peptide, callipeltin B. The stereostructure of β-MeOTyr (2) in these natural products was confirmed to be identical with that in callipeltin A (1).

In the course of studying callipeltin A (1), we have estimated the absolute configuration of β-MeOTyr (2) in callipeltin A (1) by a synthetic procedure instead of a degradative procedure. We herein report the simple asymmetric synthesis of all four diastereoisomers of protected β-MeOTyr 6 starting from a single cinnamyl ester derivative 5. Sharpless asymmetric dihydroxylation or aminohydroxylation was used for each stereoselective synthesis. Identification of the absolute configuration of β-MeOTyr (2) was successfully achieved by a comparison of 1H and 13C NMR data of all four diastereoisomeric tripeptides, H-Gln-β-MeOTyr-N-Me-Ala-OMe (4), with natural products (Scheme 1).

Four diastereoisomers of protected β-MeOTyr 6 were prepared according to the route shown in Scheme 2. The synthesis begins with the conversion of 4-hydroxybenzaldehyde into 4-methoxyethylmethoxycinnamyl ethyl ester (5) via protection with MEMCl and Horner–Emmons olefination in 95% overall yield. Ost(VIII)/(DHQD)2AQN-catalyzed asymmetric aminohydroxylation gave the desired syn-β-hydroxy-a-Boc-tyrosine derivatives as a major product with the use of tert-buty carbamate as the nitrogen source. The reaction provided a mixture of two regioisomers with 7:1 regioselectivity in 85% chemical yield. The enantiomeric excess of the major product was determined to be 89% ee. The mixture of regioisomers was then treated with MeI and NaOH in DMSO–THF to give the methyl ether (2S,3R)-6a in 77% yield. After O-methylation, (2S,3R)-6a was separated from the undesired regioisomer by silica gel column chromatography. Application of this route to (DHQD)2AQN, in-
stead of (DHQD)$_2$AQN, afforded the desired (2$R$,3$S$)-6b with similar regio- (8:1) and stereoselection (90% ee) and chemical yield.

Next, 5 was subjected to Sharpless asymmetric dihydroxylation in the presence of (DHQ)$_2$PHAL (AD-mix $\alpha$) and methanesulfonamide. The reaction proceeded smoothly to give (2$R$,3$S$)-diol in high yield with excellent optical purity (99% ee). The $\alpha$-hydroxy group of diol was converted in azide (2$S$,3$S$)-9 via 4-nitrobenzenesulfonylate 13 as a leaving group in 82% yield. Direct conversion of the hydroxy group of 9 into the methoxy group, however, was difficult to achieve since the retro-aldol reaction was dominant and the substrate decomposed to give the corresponding benzaldehyde and glycine derivatives. Thus, 9 was converted into aziridine 10 by treatment with Ph$_3$P in refluxing MeCN. Treatment of 10 with methanol in CH$_2$Cl$_2$ in the presence of BF$_3$·Et$_2$O and following Boc-protection of the amino group resulted in N-Boc-protected $\beta$-methoxytyrosine (2$S$,3$S$)-6c in 67% yield. This ring-opening process occurred through a stereospecific S$_N$2 manner at the C-3 position. By switching the Sharpless chiral catalytic ligand to (DHQD)$_2$PHAL (AD-mix $\beta$), the anti isomer (2$R$,3$R$)-6d was prepared with similar stereoselectivity (99% ee) and chemical yield.

![Figure 1](image-url) Callipeltin A (1), $\beta$-MeOTyr (2), and callipeltin E (3)

![Scheme 1](image-url) Plan for synthesizing four diastereoisomeric tripeptides

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Each β-MeOTyr derivative 6a–d thus obtained was then used for the preparation of the tripeptide esters 4a–d. After hydrolysis of 6a with LiOH, the product was condensed with N-Me-Ala-OMe using O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)\textsuperscript{15}/1-hydroxy-7-azabenzotriazole (HOAt)\textsuperscript{16}/i-Pr\textsubscript{2}NEt to give Boc-(2S,3R)-β-MeOTyr(MEM)-N-Me-Ala-OMe. After removal of the Boc group under acidic conditions (TFA–CH\textsubscript{2}Cl\textsubscript{2} (1:1), 30 min), the resulting deprotected dipeptide was condensed with Fmoc-Gln(Trt)-OH using HATU/HOAt/Et\textsubscript{3}N to give the tripeptide. TFA-mediated deprotection of the trityl and MEM groups and subsequently Fmoc deprotection under standard conditions (20% piperidine in MeCN) proceeded cleanly to provide the desired tripeptide H-Gln-(2S,3R)-β-MeOTyr-N-Me-Ala-OMe (4a) after purification by preparative HPLC in moderate yield (Scheme 3). The remaining three diastereomeric tripeptides 4b, 4c, and 4d were similarly synthesized starting from 6b, 6c, and 6d, respectively.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectral data of the four synthetic tripeptides 4a–d and natural callipeltin E (3) were then compared with those of callipeltin A (1) and E (3), a natural linear hexapeptide containing the Gln-β-MeOTyr-N-Me-Ala sequence. The chemical shifts of compound 4d agreed very closely with those of the natural products, especially with linear callipeltin E (3). In particular, the \(\alpha\)-CH chemical shifts of N-Me-Ala and β-MeOTyr of 4d in the \textsuperscript{1}H NMR spectra exhibited only 0.13 and 0.03 ppm differences from those reported for callipeltin E (3), whereas those for 4a–c were 0.54–0.67 and
Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm). Amino acids and coupling reagents were purchased from Novabiochem. All manipulations were conducted under an inert atmosphere (N₂). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH₂Cl₂ was distilled from CaH₂. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F-254, Plates 0.25 mm).
EtOAc to give (2R,3S)-diol (20.0 g, 89%); yellow oil; [α]D26 +4.9 (c 1.1, CHCl3).

IR (film): 3428, 2970, 2929, 1732, 1610, 1539, 1447, 1392, 1366, 1225, 1210, 1005, 837 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.27 (t, J = 7.1 Hz, 3 H), 3.39 (s, 3 H), 3.54 (m, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.97 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H).

13C NMR (100 MHz, CDCl3): δ = 13.10, 33.35, 57.25, 67.6, 71.6.


Intermediate (2S,3R)-Diol

[α]D26 -5.0 (c 1.1, CHCl3).

Step 2: Intermediate α-Nosyl Product: To a solution of (2R,3S)-diol (1.30 g, 4.20 mmol) in DMF (14 mL) were added Et3N (1.20 mL, 8.30 mmol) and 4-nitrobenzenesulfonyl chloride (1.40 g, 6.30 mmol). The solution was stirred at –10 °C for 56 h, and then H2O (20 mL) and EtOAc (100 mL) were added. The organic layer was washed with brine (50 mL), dried (MgSO4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (4:1 hexane–EtOAc) to give (2R,3S)-9 (67%); yellow oil; [α]D26 -14.2, 28.2, 57.2, 58.4, 61.4, 67.6, 71.6.

[α]D23 +156.4 (c 1.2, CHCl3).

Ethyl (2S,3R)-2-tert-Butyloxycarbonylalino-3-(4'-methoxyethoxyphenyl)-3- methoxypenoanproante ([2S,3R]-6c)

To a solution of (2S,3R)-10 (526 mg, 1.68 mmol) in MeOH–CH2Cl2 (1.2, 1.8 mL) was added BF3·OEt2 (0.212 mL, 1.68 mmol) and conc. HCl (1 mL). The mixture was stirred for 1 h, H2O (5 mL), and EtOAc (10 mL) were added. The organic layer was washed with brine (50 mL), dried (MgSO4), filtered, and concentrated in vacuo. To a solution of the residue in EtOAc (2.5 mL) were added aq NH4Cl (2 mL). To the mixture was added EtOAc (10 mL) and the organic layer was washed with brine (50 mL), dried (MgSO4), filtered, and concentrated in vacuo to give the crude amino alcohol. To a solution of the crude amino alcohol in THF (2.5 mL) were added Et3N (0.620 ml, 4.47 mmol) and (Boc)2O (650 mg, 2.98 mmol). After stirring for 20 h at r.t., H2O (5 mL) and EtOAc (10 mL) were added. The organic layer was dried (MgSO4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane–EtOAc) to give (2S,3R)-6c (498 mg, 67%); colorless oil; [α]D26 -3.1 (c 1.0, CHCl3).


(2R,3S)-9

[α]D26 -3.1 (c 1.0, CHCl3); 99% ee.

Ethyl (2S,3R)-2-trans-Aziridine-3-(4'-methoxyethoxyphenyl)-2-propionate ([2S,3R]-10)

To a stirred solution of (2S,3R)-9 (87.5 mg, 0.230 mmol) in MeCN (1.5 mL) was added Ph3P (120 mg, 0.459 mmol). The mixture was heated at 40 °C for 22 h and then concentrated in vacuo. H2O (5 mL) and EtOAc (20 mL) were added to the residue. The organic layer was dried (MgSO4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (4:1 hexane–EtOAc) to give (2S,3R)-10 (72 mg, 93%); yellow oil; [α]D26 -142.6 (c 1.0, CHCl3).

IR (film): 3363, 2979, 2933, 1747, 1716, 1610, 1507, 1377, 1214, 1167, 1102, 1003, 814 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.31 (t, J = 7.1 Hz, 3 H), 2.54 (m, 1 H), 3.21 (d, J = 4.6 Hz, 1 H), 3.37 (s, 3 H), 3.55 (m, 2 H), 3.81 (m, 1 H), 4.31–4.29 (m, 2 H), 5.25 (d, 1 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.19 (d, J = 8.5 Hz, 2 H).

13C NMR (100 MHz, CDCl3): δ = 14.4, 39.5, 40.1, 59.1, 61.9, 67.7, 71.7, 93.5, 116.3, 127.3, 131.2, 156.9, 171.7.


Ethyl (2S,3R)-2-tert-Butyloxycarbonylalino-3-(4'-methoxyethoxyphenyl)-3- methoxypenoanproante ([2S,3R]-6c)

To a solution of (2S,3R)-10 (526 mg, 1.68 mmol) in MeOH–CH2Cl2 (1.2, 1.8 mL) was added BF3·OEt2 (0.212 mL, 1.68 mmol) at –78 °C. After stirring at –78 °C for 26 h, the mixture was added to sat. aq NH4Cl (2 mL). To the mixture was added EtOAc (10 mL) and the organic layer was washed with brine (50 mL), dried (MgSO4), filtered, and concentrated in vacuo to give the crude amino alcohol. To a solution of the crude amino alcohol in THF (2.5 mL) were added Et3N (0.620 ml, 4.47 mmol) and (Boc)2O (650 mg, 2.98 mmol). After stirring for 20 h at r.t., H2O (5 mL) and EtOAc (10 mL) were added. The organic layer was dried (MgSO4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane–EtOAc) to give (2S,3R)-6c (498 mg, 67%); colorless oil; [α]D26 -3.5 (c 1.0, CHCl3).

IR (film): 3363, 2979, 2933, 1747, 1716, 1610, 1507, 1377, 1214, 1167, 1102, 1005, 867 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.28 (t, J = 7.1 Hz, 3 H), 3.39 (s, 3 H), 3.56 (m, 2 H), 3.73 (m, 2 H), 4.09 (d, J = 7.1 Hz, 1 H), 4.25 (m, 2 H), 4.97 (d, J = 7.1 Hz, 1 H), 5.24 (s, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.26 (d, J = 8.5 Hz, 2 H).

13C NMR (100 MHz, CDCl3): δ = 14.2, 59.1, 62.2, 66.9, 67.7, 71.6, 73.7, 93.4, 116.3, 127.9, 132.3, 157.5, 168.9.


The enantiomeric excess was determined to be 99% ee by the Mosher method.17

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Me-Ala-OMe (108 mg, 0.705 mmol), i-
Pr2NEt (0.131 mL, 0.940 mmol), HATU (268 mg, 0.705 mmol), and HOAt (96 mg, 0.705 mmol) and the mixture was stirred for 30 min at r.t. The solvent was removed in vacuo. EtOAc (5 mL) and H2O (2 mL) were added to the residue, and the organic layer was washed with brine (5 mL), dried (MgSO4), and evaporated in vacuo. To a solution of the crude product in CH2Cl2 (1 mL) was added TFA (1 mL). The mixture was stirred for 30 min at r.t. and the solvent was removed in vacuo. To a solution of the residue in DMF (2 mL) were added Fmoc-N-Me-Gln(Tri)-OH (431 mg, 0.705 mmol), i-
Pr2NEt (0.131 mL, 0.940 mmol), HATU (268 mg, 0.705 mmol), and HOAt (96 mg, 0.705 mmol). The mixture was stirred for 30 min at r.t. and the product was similarly isolated as above. The resulting product was dissolved in CH2Cl2 (1 mL) and TFA (1 mL) was added. The mixture was stirred for 30 min at r.t. and the solvent was removed in vacuo. To a solution of the crude tripeptide in MeCN (2 mL) was added piperidine (0.50 mL). The mixture was stirred for 30 min at r.t. and the solvent was removed in vacuo. The residue was purified by preparative HPLC (MeCN-H2O, 90:10) to give H-Gln-[β-MeOTyr]-N-
Me-Ala-OMe ([2S,3R]-4a: 408 mg, 35%; white powder; [α]25
D
8.8 Hz, 1 H), 6.82 (d, J = 7.3 Hz, 3 H), 2.11 (m, 2 H), 2.43 (m, 2 H), 2.86 (s, 3 H), 3.21 (s, 3 H), 3.59 (s, 3 H), 4.04 (t, J = 6.6 Hz, 1 H), 4.37 (d, J = 8.8 Hz, 1 H), 4.46 (q, J = 7.1 Hz, 1 H), 4.95 (d, J = 8.8 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.5 Hz, 2 H).

1H NMR (300 MHz, CDCl3): δ = 1.15 (d, J = 7.1 Hz, 3 H), 2.11 (m, 2 H), 2.43 (m, 2 H), 2.86 (s, 3 H), 3.21 (s, 3 H), 3.59 (s, 3 H), 4.04 (t, J = 6.6 Hz, 1 H), 4.37 (d, J = 8.8 Hz, 1 H), 4.46 (q, J = 7.1 Hz, 1 H), 4.95 (d, J = 8.8 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.5 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 12.6, 26.9, 30.1, 33.1, 51.2, 52.1, 55.4, 55.5, 82.3, 115.2, 126.9, 128.8, 157.9, 168.2, 169.8, 171.4, 175.8.


The following compounds 4b-d were prepared in a manner similar to 4a.

(2R,3S)-4b
From 6d; yield: 17%; [α]25
D
+3.8 (c 0.2, MeOH).

IR (film): 3315, 2964, 2929, 1739, 1670, 1641, 1612, 1501, 1203, 1137, 845, 800 cm−1.

1H NMR (400 MHz, CDCl3): δ = 1.43 (d, J = 7.3 Hz, 3 H), 1.72 (m, 2 H), 1.80 (m, 2 H), 2.88 (br s, 3 H), 3.15 (s, 3 H), 3.72 (s, 3 H), 4.00 (m, 1 H), 4.35 (d, J = 9.5 Hz, 1 H), 5.02 (q, J = 7.6 Hz, 1 H), 5.24 (dd, J = 9.5, 2.9 Hz, 1 H), 6.80 (d, J = 8.5 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 14.1, 26.7, 31.5, 33.9, 52.6, 55.8, 56.9, 57.8, 83.7, 116.4, 116.5, 129.9, 130.1, 169.7, 171.4, 172.9, 181.6.


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