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Convenient, asymmetric synthesis of enantiomerically pure 2′,6′-dimethyltyrosine (DMT) via alkylation of chiral equivalent of nucleophilic glycine

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Abstract

Asymmetric synthesis of (*S*)-2′,6′-dimethyltyrosine (DMT) via reactions of 4′-benzyloxy-2′,6′-dimethylbenzyl bromide with Ni(II)-complexes of the chiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]-benzophenone was developed. Inexpensive and readily available reagents and solvents involved, including recyclable chiral auxiliary, simplicity of the experimental procedures and high chemical yields, make this method synthetically attractive for preparing the target amino acids on a multi-gram scale. © 2000 Published by Elsevier Science Ltd.

1. Introduction

The concept of global and local constraints for de novo peptide design, introduced and developed by our group,[1] has proven to be one of the most fruitful and promising methodologies for the rational design of peptides and peptide mimics with a pre-supposed pattern of biological properties. In particular, introduction of the chi (χ)-constrained[1d,2] α-amino acids in strategic positions of peptides (local side-chain constraints) allows for a substantial reduction of the corresponding side-chain conformers and, thus, usually leads to the increased biological activity of the target peptide.[1,2] A successful example of this approach is the recent discovery of high affinity and ultraselective δ opioid dipeptide antagonist composed of (*S*)-2′6′-dimethyltyrosine **1** (DMT) and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.[3] The unique topographical profile of DMT could find numerous applications in the de novo peptide design providing, of course, ready availability and low cost of this (χ)-constrained amino acid.

Analysis of the relevant literature revealed, surprisingly, only one report on the asymmetric synthesis of DMT.[4,5] The method utilized an asymmetric hydrogenation protocol using methyl (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate **2** as a starting compound and

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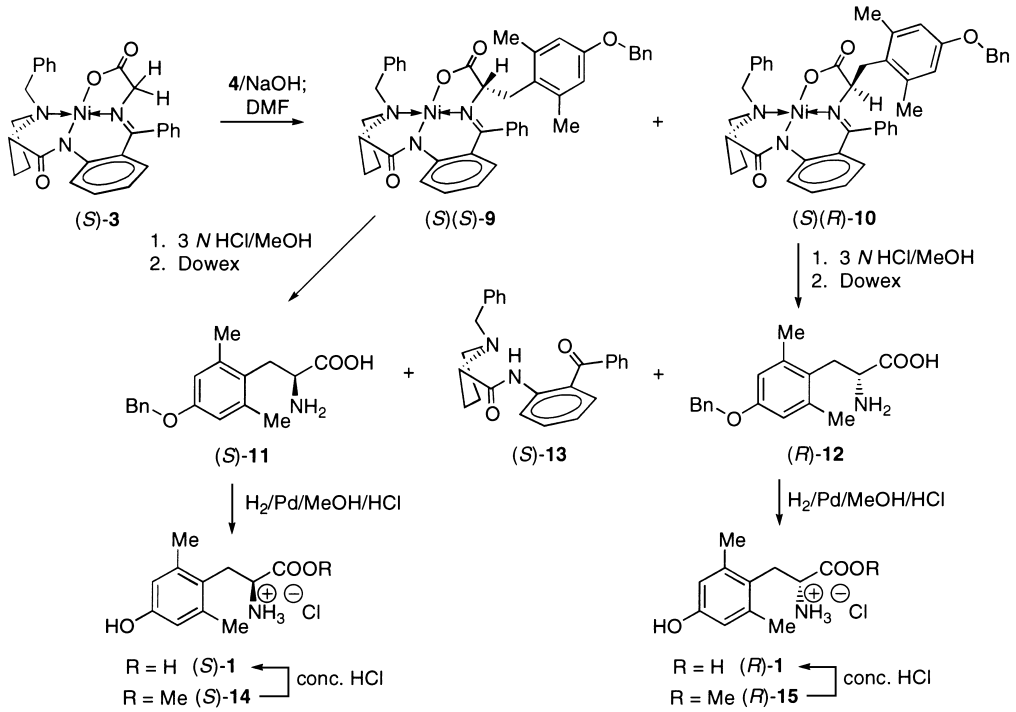
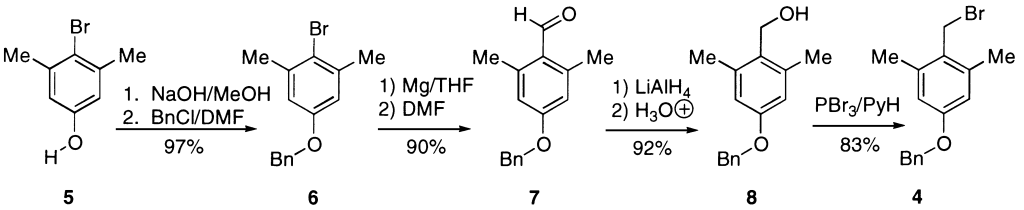
[Rh(1,5-COD)(*R*,*R*-DIPAMP)]BF_4 as a catalyst (1–5 mol%). Due to the sterically congested nature of the starting dehydroamino acid **2**, the hydrogenation step proceeds very slowly requiring 12–24 h for completion at 60°C under 60 psig of hydrogen to afford the (*S*)-4-acetoxy-*N*-acetyl-2,6-dimetyltyrosine methyl ester in 87% yield and of 92% ee. We believe that the development of an alternative method featuring simple experimental procedures and providing a fast and reliable protocol for preparing gram-quantities of DMT would be highly desirable. In this paper we describe such a method using, for the first time, a methodologically straightforward and general approach, an alkylation of the readily available chiral equivalent of a nucleophilic glycine **3** (Scheme 1) with the corresponding 4′-benzyloxy-2′,6′-dimethylbenzyl bromide **4** (Scheme 2).



Scheme 1.



Scheme 2.

2. Results and discussion

Asymmetric synthesis of enantiomerically pure DMT could be achieved via alkylation of an appropriate chiral equivalent of nucleophilic glycine with the corresponding 2′,6′-dimethylbenzyl halide. However, as we mentioned in the introductory section, this simple and most methodologically straightforward approach has not been reported so far. Most of the methods developed for the asymmetric homologation of glycine equivalents involve the kinetically controlled reaction between lithium-derived enolates of the latter and alkyl halides under very mild conditions at –78°C.[6] However, the highly sterically hindered nature of the corresponding 2′,6′-dimethylbenzyl halides could interfere with a successful chemical and/or stereochemical reaction outcome. Indirect support for this comes from the fact that all attempts to conduct a standard Erlenmeyer condensation between 2′,6′-dimethyl-4-*O*-protected benzaldehyde and *N*-acetylglycine were unsuccessful, which was attributed to the highly sterically hindered nature of the corresponding aldehyde.[4]

From our extended experience in the asymmetric synthesis of novel, tailor-made amino acids, an Ni(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone [(*S*)-BPB] (*S*)-**3**, introduced by Belokon' et al., possesses significant advantages over other chiral equivalents of a nucleophilic glycine in terms of its low cost and ready availability, even on a kilogram scale,[7] as well as the simplicity of experimental procedures and isolation of products. The synthetic value of complex (*S*)-**3** for preparing natural and unnatural amino acids via alkylation and aldol reactions of (*S*)-**3** has been well-documented.[8,9] The most important feature of complex (*S*)-**3**, distinguishing it from other commercially available chiral equivalents of nucleophilic glycine, is the fact that alkylation of (*S*)-**3** is usually conducted under thermodynamically controlled conditions at room temperature in the presence of regular KOH or NaOH.[8,9] These conditions provide an important synthetic advantage for involvement (as alkylating agents) of less reactive and sterically bulky alkyl halides. Therefore, we assumed that application of complex (*S*)-**3** for alkylation with the correspondingly substituted benzyl halide would give us a reasonable chance to implement our goal of developing a methodologically most straightforward, simple and reliable approach for preparing the target DMT **1**.

2.1. *Design and synthesis of* O-*benzyl-2′,6′-dimethylbenzyl bromide* **4**

The hitherto unknown title compound **4** was designed as the alkylating agent for the following reasons. First, the *O*-benzyl-protecting group is stable towards moderate nucleophilic and electrophilic reaction conditions but can be easily removed via conventional hydrogenation procedures. Second, benzyl bromides and chlorides are generally equally available, but the former are much more reactive and thus more suitable for our purpose. The synthesis of benzyl bromide **4** is outlined in Scheme 2. Transformation of the commercially available and cheap phenol **5** to the corresponding benzyl ether **6** was previously described in the literature[10] using benzyl chloride and K_2CO_3, as a base, to afford **6** in 72% yield. We found that generation of the corresponding phenolate of **5** with NaOH in methanol followed by the treatment with benzyl chloride in DME allowed us to increase substantially the yield of compound **6**. After crystallization of the crude product from methanol ether **6** was obtained in 97% yield. Conventional one-pot transformation of **6** to aldehyde **7**, through formation of the corresponding Grignard derivative and its reaction with DMF, was accomplished cleanly affording compound **7** in 90% chemical yield. Reduction of aldehyde **7** to alcohol **8** with lithium aluminum hydride also proceeded smoothly, giving rise to

the product **8** in 92% yield. Transformation of alcohol **8** to bromide **4** with phosphorus tribromide was found to be rather difficult. However, after optimization of the reaction conditions the target alkylating reagent **4** was obtained in 83% yield.

2.2. Synthesis of (S)-DMT via alkylation of Ni(II)-complex (S)-3 with benzyl bromide 4

The reaction between Ni(II)-complex (*S*)-**3** and benzyl bromide **4** was conducted at room temperature (22–25°C) in a commercial-grade DMF using powdered NaOH as a base (Scheme 2). The benzylation occurred with an unexpectedly high reaction rate (5 min), furnishing two products **9** and **10** in a ratio of 8:1[11] and in 95% chemical yield. Compounds **9** and **10** were isolated in a diastereomerically pure form by column chromatography and fully characterized. Based on the NMR spectra, complexes **9** and **10** were found to be the diastereomeric derivatives containing the 2′,6′-dimethyltyrosine moiety. Investigation of the chiroptical properties[12] of complexes **9** and **10** allowed us to assign absolute configuration of the corresponding α-stereogenic carbons of the 2′,6′-dimethyltyrosine residues in **9** and **10** as (*S*) and (*R*), respectively. These data suggest that the corresponding *bis*-benzylation process, the most problematic side-reaction in all previously studied benzylations of complex (*S*)-**1**,[8,9] does not take place in this case at all. This fact might be attributed to the highly sterically hindered nature of the benzyl bromide **4**.

Attempts to amend the stereochemical outcome by lowering the reaction temperature gave the opposite result. The reaction between Ni(II)-complex (*S*)-**3** and benzyl bromide **4** conducted at 0°C gave a mixture of diastereomers **9** and **10** in a ratio of 4:1. This outcome stands in contrast to the general observation that the lowering of the reaction temperature usually increases a reaction stereoselectivity. However, the observed result could be rationalized by considering the kinetic and thermodynamic diastereoselectivity of complex (*S*)-**3** homologation. Recently, we showed that cinnamylation of complex (*S*)-**3** with cinnamyl halides conducted under the kinetically controlled conditions (K_2CO_3 as a base) gave rise to a mixture of the corresponding α-(*S*)/(*R*)-diastereomers in a ratio of 4.5:1, while the same reaction run under the thermodynamically controlled conditions (KOH as a base) afforded the diastereomeric products in a ratio of 26.5:1.[9j] Thus, we can assume that the 4:1 ratio of the diastereomers **9** and **10**, obtained at 0°C, reflects the kinetic diastereoselectivity, while the 8:1 ratio observed room temperature reaction for is a result of thermodynamic equilibration of the diastereomeric products. Plausibility of this rationale is strongly supported by the results obtained by a resubmission of the diastereomerically pure α-(*R*)-configured complex **10** to the original reaction conditions. Treatment of a DMF solution of complex α-(*R*)-**10** with 5 mol excess of NaOH for 8 h resulted in a mixture of diastereomers **9** and **10** in a ratio of approximately 8:1, suggesting that α-(*R*)-**10** undergoes epimerization at the α-stereogenic carbon of the 2′,6′-dimethyltyrosine residue to give thermodynamically more stable α-(*S*)-configured diastereomer **9** with a ratio of 8:1 and is being thermodynamically controlled.

Separation of diastereomeric complexes α-(*S*)-**9** and α-(*R*)-**10** via column chromatography presents no problems due to the large difference in R_f values of the products. Diastereomerically pure α-(*S*)-**9** and α-(*R*)-**10** were decomposed following our standard procedure[9] to afford free amino acids (*S*)-**11** and (*R*)-**12**, along with quantitative recovery of the chiral ligand (*S*)-**13**, which was readily converted back to the starting glycine complex (*S*)-**3**.[9] It is important to note that amino acids (*S*)-**11** and (*R*)-**12** were found to be extremely hydrophobic, necessitating application of a mixture of NH_4OH/EtOH as an eluent to isolate (*S*)-**11** and (*R*)-**12** from cation-exchange column. Hydrogenation of benzyl ethers (*S*)-**11** and (*R*)-**12** in a solution of conc. HCl/MeOH was accompanied by partial esterification of the corresponding amino acids that necessitated

treatment of the mixtures resulting from the hydrogenation with conc. HCl to afford the target enantiomerically pure DMT (*S*)-**1** and (*R*)-**1** in quantitative chemical yield.

In conclusion, we have demonstrated, for the first time, that sterically constrained DMT could be efficiently prepared via a reaction of chiral equivalent of nucleophilic glycine, Ni(II)-complex (*S*)-**3**, with benzyl bromide **4** designed by us. The inexpensive and readily available reagents and solvents involved, including a recyclable chiral ligand (*S*)-**13**, and the simplicity of the experimental procedures and high stereochemical outcome render this method as a synthetically attractive, reliable and affordable alternative to the previously reported approach[4] for preparing enantiomerically pure DMT on a multi-gram scale.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR were performed on a Varian Unity-300 (299.94 MHz) and Gemini-200 (199.98 MHz) spectrometers using TMS and $CDCl_3$ as internal standards. High Resolution Mass Spectra (HRMS) were recorded on a JEOL HX110A instrument. Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points (mp) are uncorrected and were obtained in open capillaries. All reagents and solvents, unless otherwise stated, are commercially available and were used as received. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{13}C NMR spectrometry. All new compounds were characterized by ^{1}H, ^{13}C NMR and HRMS.

3.2. (4-Bromo-3,5-dimethyl)phenyl benzyl ether **6**[10]

To a solution of 10.0 g of 4-bromo-3,5-dimethylphenol (49.7 mmol, 1 equiv.) in a minimal amount of anhydrous methanol (ca. 13 mL), at 0°C, was added 2.0 g of NaOH (50 mmol, 1 equiv.) dissolved in minimal amount of methanol. After 2 h, the solvent was removed in vacuo and the residue was dried in vacuo to afford sodium (4-bromo-3,5-dimethyl)phenoxide. The former was dispersed in 80 mL of DME and treated with 5.7 mL of benzyl chloride dissolved in 20 mL of DME and heated at 35°C for 24 h, and was then quenched with 100 mL of water. The reaction mixture was extracted with diethyl ether 3 times (200 mL each). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo to afford the product that was further dried in vacuo. The resultant product was recrystallized from methanol to give compound **6** in 97% yield; mp 52–54°C; ^{1}H NMR ($CDCl_3$) δ 7.42–7.25 (m, 5H), 1.16 (s, 2H), 4.77 (s, 2H), 2.26 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 152.4, 137.2, 133.4, 131.4, 128.6, 128.1, 127.8, 116.5, 74.1, 16.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{15}H_{15}BrO$ 290.0306, found 290.0304.

3.3. 4-Benzyloxy-2,6-dimethylbenzaldehyde 7

To a solution of 10.7 g (36.5 mmol, 1 equiv.) of (4-bromo-3,5-dimethyl)phenyl benzyl ether **6** in 100 mL of freshly distilled THF, 0.2 g of I_2 and 3.5 g of Mg (146 mmol, 4 equiv.) were added. The reaction mixture was refluxed in an Ar atmosphere for 4 h. To the obtained Grignard reagent, 11.4 mL (146 mmol, 4 equiv.) of anhydrous DMF was slowly added at 0°C. The reaction mixture was stirred for 2 h at 0°C and overnight at room temperature. The reaction was quenched with

saturated ammonium chloride and the organic layer was separated from the aqueous layer. The aqueous layer was washed twice with diethyl ether (100 mL each). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo to afford the crude product which was purified by column chromatography (hexanes:ethyl acetate, 7:3). Yield: 90%; mp 54–56°C; ^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1H), 7.42–7.30 (m, 5H), 6.68 (s, 2H), 5.09 (s, 2H), 2.59 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 191.5, 161.8, 144.4, 136.1, 128.6, 128.2, 127.4, 126.1, 115.6, 69.8, 21.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{16}H_{16}O_2$ 241.1229, found 241.1226.

3.4. 4-Benzyloxyl-2,6-dimethylbenzyl alcohol **8**

To a solution of 6.2 g (21.4 mmol, 1 equiv.) of **7** in 100 mL freshly distilled THF 1.47 g (25.8 mmol, 1.2 equiv.) of lithium aluminum hydride was added at –78°C. The reaction mixture was stirred at –78°C for 2 h, warmed to room temperature and refluxed for 4 h. The reaction was quenched with 1N HCl and the THF layer was separated from the aqueous phase. The aqueous layer was washed twice with ethyl ether (100 mL each). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo to afford the product **8**, which did not need further purification. Yield: 92%; mp 77–79°C; ^{1}H NMR ($CDCl_3$) δ 7.45–7.30 (m, 5H), 6.66 (s, 2H), 5.02 (s, 2H), 4.66 (d, 2H, $J=3$ Hz), 2.39 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 158.1, 139.0, 137.1, 129.6, 128.6, 127.9, 127.4, 114.5, 69.8, 59.0, 19.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{16}H_{18}O_2$ 242.1307, found 243.1305.

3.5. 4-Benzyloxyl-2,6-dimethylbenzyl bromide **4**

To a solution of 4.84 g (20 mmol, 1 equiv.) of **8** in 100 mL of anhydrous ethyl ether and in an Ar atmosphere, 2.1 mL (44 mmol, 2.2 equiv.) of anhydrous pyridine was added via a syringe at –78°C. After 5 min, 2.1 mL (22 mmol, 1.1 equiv.) of phosphorus tribromide was slowly dropped into the solution over a period of 1 h. A formation of white slurry was observed. The mixture was stirred for 2 h at –78°C and overnight at room temperature. Completion of the reaction was monitored by TLC. The reaction was quenched by adding slowly an ice–water mixture with stirring at 0°C, and the resuling mixture was stirred for 30 min at 0°C. The ether layer was separated from the aqueous layer and the aqueous phase was washed twice with diethyl ether (150 mL each). The combined ethyl ether solution was washed with ice-cold 85% phosphorus acid (50 mL), saturated sodium bicarbonate (2×100 mL) and water (2×100 mL). The ether solution was dried over anhydrous magnesium sulfate and evaporated in vacuo to yield a white solid residue. No further purification of compound **4** was necessary. Yield: 83%; mp 99–101°C; ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5H), 6.67 (s, 2H), 5.03 (s, 2H), 4.58 (s, 2H), 2.39 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 158.7, 139.3, 136.9, 128.5, 127.9, 127.4, 126.6, 114.7, 69.8, 30.1, 19.6. HRMS (FAB) $[M+H]^+$ calcd. for $C_{16}H_{17}BrO$ 305.0538, found 305.0541.

3.6. Reaction of Ni(II)-complex (S)-**3** with bromide **4**. Preparation of diastereomers (S),(S)-**9** and (S),(R)-**10**

A 100 mL round-bottom flask with 4.982 g (10 mmol, 1 equiv.) of (*S*)-**3** and 4.0 g (100 mmol, 10 equiv.) of NaOH was purged with Ar and 20 mL of anhydrous DMF was added to dissolve the complex and the base. Upon formation of a greenish enolate solution, 3.666 g (11 mmol, 1.1 equiv.) of bromide **4**, dissolved in 20 mL of anhydrous DMF, was dropped into the solution via a

syringe. The reaction mixture was stirred under an Ar atmosphere and the reaction progress was monitored by TLC. Upon completion, the reaction was quenched by addition of 500 mL of icy water and the precipitated material was filtered off and dried in vacuo. The diastereomerically pure products (*S*),(*S*)-**9** (R_f = 0.43) and (*S*),(*R*)-**10** (R_f = 0.62) were isolated by column chromatography on silica-gel using acetone:chloroform, 1:10, as an eluent; the (*S*),(*R*)-**10** diastereomer emerged first.

3.7. *Ni(II)-Complex of Schiff base of* (S)-**13** *with* (S)-*4′*-O-*benzyl-2′,6′-dimethyltyrosine* **9**

Yield: 84%; mp 112–114°C; $[\alpha]_D^{25}$ = +1472 (*c* 0.0196, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.22 (d, 1H, *J* = 8.4 Hz), 8.06 (d, 2H, *J* = 6.8 Hz), 7.41–7.25 (m, 10H), 7.14–7.02 (m, 3H), 6.90–6.78 (m, 1H), 6.62–6.54 (m, 1H), 6.57 (s, 2H), 6.42 (d, 1H, *J* = 8.3 Hz), 5.66 (d, 1H, *J* = 7.4 Hz), 4.96 (s, 2H), 4.30 (d, 1H, *J* = 12.6 Hz), 4.25 (dd, 1H, J_1 = 9.9 Hz, J_2 = 4.3 Hz), 4.04–3.91 (m, 2H), 3.56–3.43 (m, 4H), 2.72–2.59 (m, 2H), 2.40–2.28 (m, 1H), 2.08 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 179.7, 178.5, 170.5, 156.9, 142.0, 138.8, 136.8, 133.4, 133.2, 132.9, 131.9, 131.0, 128.7, 128.5, 128.4, 128.2, 128.0, 127.7, 127.5, 127.1, 127.0, 125.7, 124.6, 122.9, 120.2, 114.4, 77.2, 70.1, 69.2, 62.7, 56.9, 36.7, 30.3, 23.9, 19.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_{43}H_{42}O_4N_3Ni$ 722.2529, found 722.2524

3.8. *Ni(II)-Complex of Schiff base of* (S)-**13** *with* (R)-*4′*-O-*benzyl-2′,6′-dimethyltyrosine* **10**

Yield: 10%; mp 130–132°C; $[\alpha]_D^{25}$ = –1094 (*c* 0.0138, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.61 (d, 1H, *J* = 8.25 Hz), 7.89 (d, 2H, *J* = 6.1 Hz), 7.55–7.23 (m, 12H), 7.11–7.06 (m, 1H), 6.87–6.83 (m, 1H), 6.68–6.63 (m, 1H), 6.57–6.46 (m, 1H), 6.47 (s, 2H), 5.55 (s, 1H), 4.98 (s, 2H), 4.35 (d, 2H, *J* = 13.3 Hz), 4.23 (d, 1H, *J* = 7.8 Hz), 3.91–3.89 (m, 2H), 3.45 (d, 1H, *J* = 12.9 Hz), 3.27 (d, 1H, *J* = 13.6 Hz), 2.92–2.82 (m, 1H), 2.32–2.18 (m, 2H), 2.17–2.06 (m, 1H), 1.94 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 181.2, 179.1, 171.3, 157.2, 142.8, 139.7, 137.0, 134.1, 133.4, 132.6, 131.9, 129.2, 129.1, 128.9, 128.6, 128.5, 128.1,127.8, 127.3, 127.1, 125.7, 125.1, 123.1, 120.6, 114.7, 70.7, 69.5, 68.5, 60.0, 58.5, 36.2, 29.7, 22.7, 20.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{43}H_{42}O_4N_3Ni$ 722.2529, found 722.2524.

3.9. *Decomposition of Ni(II)-complexes* (S),(S)-**9** *and* (S),(R)-**10**. *Isolation of* O-*benzyl DMT* (S)-**11** *and* (R)-**12**.

A solution of **9** or **10** (15 mmol, 1 equiv.) in 20 mL of MeOH was slowly dropped into the mixture of 40 mL of 3N HCl and MeOH (1:1) at 70°C. When the red color disappeared, the solution was evaporated to dryness and the solid residue was dissolved in water (3×50 mL) and evaporated again to remove HCl. The solid residue was treated with 100 mL of concentrated ammonium hydroxide and 100 mL of water and evaporated to dryness. The resultant material was dissolved in 100 mL of water and extracted with 100 mL of $CHCl_3$. (Sometimes, part of the product stayed in the interface between the aqueous phase and organic phase due to the limited solubility of the product in water. The undissolved product was filtered and washed with water and $CHCl_3$. Then this part of the product was combined with the rest of the product obtained later. Also, the washings were combined with the filtrate.) The $CHCl_3$ layer were separated from the aqueous layer and the aqueous layer was washed with $CHCl_3$ (2×50 mL). The chloroform layers were dried over anhydrous $MgSO_4$ and evaporated to recover chiral ligand (*S*)-**13**. The aqueous layer was evaporated in vacuo, the resultant material was dissolved in minimal amount

of ethanol:water, 1v:1v, and the solution was applied to Dowex 50X2 100 ion-exchange column. First, the column was washed with water until the eluent showed a neutral pH. Then, the column was washed with 1:4 water:concentrated ammonium hydroxide to yield a solution of **11** or **12**, which was evaporated to give the solid amino acids. If necessary, a mixture of 2:3:5 concentrated ammonium hydroxide: ethanol:water could be used as eluent.

3.10. *Hydrogenation of* O-*benzyl DMT* (S)-***11*** *and* (R)-***12***. *Isolation of DMT* (S)-***1*** *and* (R)-***1***

O-Benzyl DMT (*S*)-**11** or (*R*)-**12** (10 mmol) was dissolved in 20 mL of concentrated HCl and 20 mL of MeOH in a hydrogenation vessel, Ar was bubbled through the solution for 5 min, 0.5 g of 10% Pd/C was added into the solution and Ar was bubbled for 30 min more. The vessel was connected to a hydrogenator and shaken for 24 h under H_2 of 40 Psi. Twenty-four hours later the catalyst was filtered off and washed with a small amount of methanol and water. The filtrate was evaporated and lyophilized to yield the crude product, containing the target amino acid and its methyl ester. The crude product was dissolved in 20 mL of concentrated HCl and refluxed for 6 h. The resultant mixture was evaporated in vacuo and the residue was triturated with water (3×50 mL) followed by lyophilization to afford quantitatively the target amino acids as white powder.

3.11. (R)-2′,6′-Dimethyltyrosine (DMT)

Yield: 99%, mp 248–250°C. $[\alpha]_D^{25} = -40.29$ (*c* 0.984, MeOH). $[\alpha]_D^{25} = -60.10$ (*c* 0.81, AcOH). ^{1}H NMR (CD_3OD) δ 5.51 (s, 2H), 4.00 (t, 1H, $J = 8.0$ Hz), 3.29 (dd, 1H, $J_{BX} = 8.0$ Hz, $J_{AB} = 14.5$ Hz), 3.08 (dd, 1H, $J_{AX} = 8.0$ Hz, $J_{AB} = 14.5$ Hz), 2.28 (s, 6H). ^{13}C NMR (CD_3OD) δ 171.9, 157.3, 139.7, 123.6, 116.4, 54.0, 31.4, 20.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{11}H_{16}O_3N$ 210.1130, found 210.1134.

3.12. (S)-2′,6′-Dimethyltyrosine (DMT)

Yield: 99%, mp 247–249°C. $[\alpha]_D^{25} = +39.41$ (*c* 1.017, MeOH). $[\alpha]_D^{25} = +60.56$ (*c* 0.85, AcOH). ^{1}H NMR (CD_3OD) δ 6.51 (s, 2H), 4.00 (t, 1H, $J = 8.0$ Hz). 3.29 (dd, 1H, $J_{BX} = 8$ Hz, $J_{AB} = 14.5$ Hz), 3.08(dd, $J_{AX} = 8$ Hz, $J_{AB} = 14.5$Hz), 2.28 (s, 6H). ^{13}C NMR (CD_3OD) δ 171.8, 157.3, 139.7, 123.6, 116.4, 53.9, 31.4, 20.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{11}H_{16}O_3N$ 210.1130, found 210.1134.

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11. Determined by ^{1}H NMR (500 MHz) on the crude reaction mixture.
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