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Large-scale asymmetric synthesis of novel sterically constrained 2′,6′-dimethyl- and α,2′,6′-trimethyltyrosine and -phenylalanine derivatives via alkylation of chiral equivalents of nucleophilic glycine and alanine

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Abstract—Asymmetric synthesis of (*S*)-2′,6′-dimethyltyrosine (DMT), (*S*)-2′,6′-dimethylphenylalanine (DMP), (*S*)-α,2′,6′-trimethyltyrosine (α-TMT) and (*S*)-α,2′,6′-trimethylphenylalanine (α-TMP) via reactions of 4′-benzyloxy-2′,6′-dimethylbenzyl bromide or 2′,6′-dimethylbenzylbromide with Ni(II)-complexes of the chiral Schiff base of glycine or alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone were developed. Inexpensive and readily available reagents and solvents, a 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.

1. Introduction

Peptides and proteins are some of the most important chemical messengers along with their receptors–targets, because they critically influence all vital processes of human and animal biology. The Human Genome Project will reveal thousands of new polypeptide ligands and their receptors, thus providing an unprecedented opportunity to obtain an in-depth understanding of all physiological and social aspects of human health. A central objective in modern peptide chemistry, as well as medicinal and organic chemistry, directed towards the ultimate goal of development of highly selective and potent peptide-based drugs, is an understanding of peptide three-dimensional (3D) structure and its relationship to biological activity.[1] Peptide 3D structure is a function of three major constituents: peptide sequence (primary structure), conformation (secondary structure), and topographical position of side-chain functional groups. While peptide sequence and conformation have been widely recognized as critical issues in the phenomenon of peptide biological activity, the third factor, the position of side-chains on the peptide backbone has received little attention until recently.[1] The importance of the torsional angles ϕ (phi), ψ (psi) and ω (omega) in determining the 3D structure of the peptide backbone,[2] as well as the χ (chi) torsional angles in defining the position of side-chain functional groups (Fig. 1) for elucidating peptide biological activity, has been demonstrated.[1,c,d,3] While ϕ-, ψ- and ω-angles are, in most cases, controlled by the nature of amino acid residues and peptide secondary structure (e.g. cyclization), control over χ-angles is much more difficult. For instance, a single residue of glutamic acid in a peptide could give rise to up to 27 possible biologically active side-chain conformations (Fig. 1) as a result of three χ-angles determining the amino acid 3D structure.

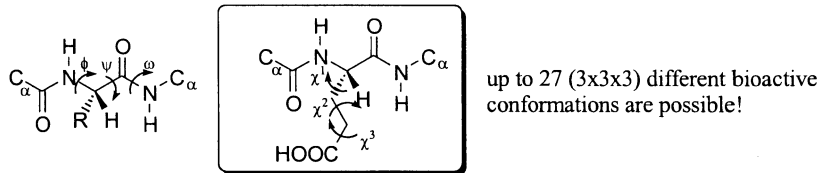

Figure 1. Depiction of ϕ-, ψ-, ω- and *c*-dihedral angles for amino acid residues in peptides.

Keywords: asymmetric synthesis; alkylation reactions; amino acids; nickel(II) complexes.

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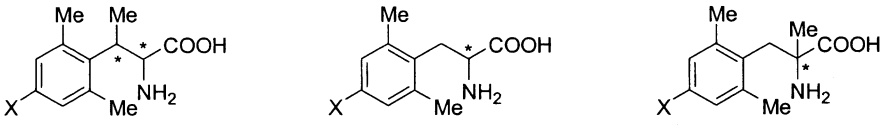


Figure 2.

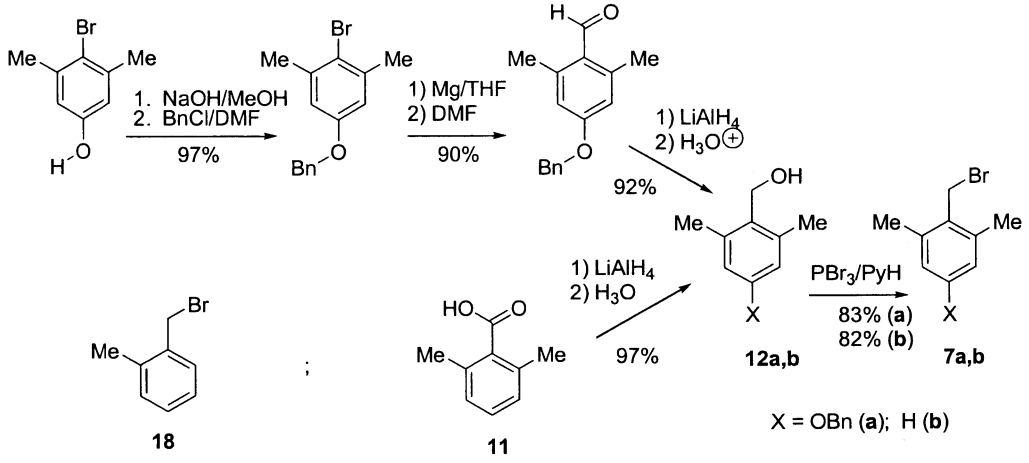
Thus, the necessity to control χ-space led our group to develop the concept of local side-chain constraints for de novo peptide design. This has proven to be a fruitful and promising methodology for the rational design of peptides and peptide mimics with a pre-supposed pattern of biological properties.[1c–f] In particular, the design and synthesis of χ-constrained α-amino acids such as β,2′6′-trimethylphenylalanine (β-TMP) (**1**) (Fig. 2), -tyrosine (β-TMT) (**2**), 2′6′-dimethylphenylalanine (DMP) (**3**) and -tyrosine (DMT) (**4**), and their incorporation in strategic positions of peptides (local side-chain constraints), has allowed for a substantial reduction of the corresponding side-chain conformers and this has led to increased selectivity and/or potency of several target peptides.[1e,f,4] A successful example of this approach is the recent discovery of a high affinity and ultraselective δ opioid dipeptide antagonist composed of (*S*)-**4** DMT and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic),[5] and a series of dipeptides composed of **2** TMT and Tic[6] in which the dipeptide containing (2*S*,3*R*)-**2** was found to be a potent inverse agonist.[6] Surprisingly, the analogues of β-TMP **1** and β-TMT **2** containing a methyl in the α-position, α-TMP **5** and α-TMT **6** (Fig. 2), which would allow for simultaneous modification of ϕ-, ψ- and χ^1-angles, have not been reported. In this paper, we describe the large-scale asymmetric synthesis of the novel amino acids **5** and **6**, as well as improved (chemical yields and diastereoselectivities) procedures for preparing DMP-**3** and DMT-**4**.

2. Results and discussion

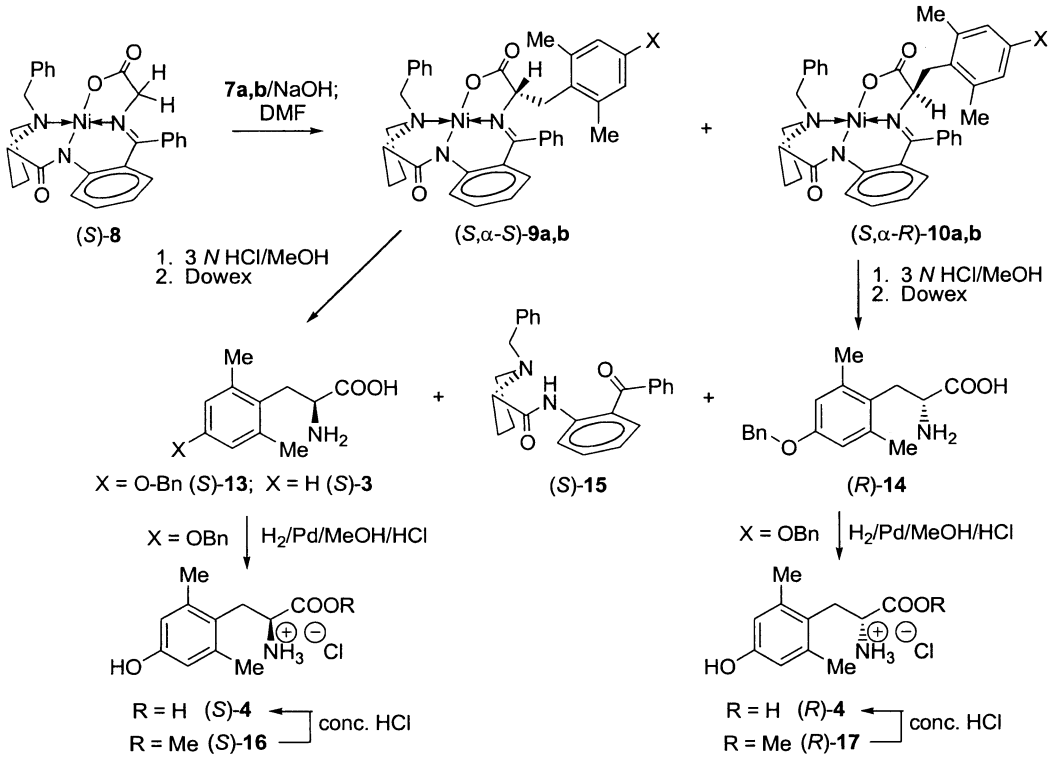
For the asymmetric synthesis of enantiomerically pure 2′6′-dimethyl derivatives of phenylalanine and tyrosine, as well as their α-methylated analogues, the alkylation of an appropriate chiral equivalent of nucleophilic glycine or alanine with the corresponding 2′,6′-dimethylbenzyl halide, represents simple and straightforward approach.[7] However, most of the methods developed for the asymmetric homologation of glycine and alanine equivalents involve kinetically controlled reaction between lithium-derived enolates and alkyl halides under very mild conditions at −78°C.[7] Because of the highly sterically hindered nature of the corresponding 2′,6′-dimethylbenzyl halides, it is quite possible that the steric bulk of the alkylating agent could interfere with a successful chemical and/or stereochemical reaction outcome.[8] However, as outlined below, we have found efficient asymmetric methods for these syntheses.

2.1. Benzylation of Ni(II)-complexes (*S*)- and (*R*)-8 with 2′6′-dimethylphenyl bromides 7a and 7b

Recently we reported the design and synthesis of *O*-benzyl-2′6′-dimethylbenzyl bromide (**7a**) (Scheme 1) and its use as an alkylating agent for reaction with the chiral glycine Ni(II)-complex (*S*)-**8** (Scheme 2).[9] The reaction of the Ni(II)-complex (*S*)-**8**[10,11] with benzyl bromide **7a** was found to occur at room temperature at a high rate to yield two diastereomeric products (*S*,α-*S*)-**9a** and (*S*,α-*R*)-**10a** in a ratio of 8:1, respectively. The obtained stereochemical outcome (8:1 ratio; roughly 78% de) was noticeably lower when compared with the usually observed over 90% de in the reactions of (*S*)-**8** with substituted benzyl bromides.[12] It is assumed that the highly sterically hindered nature of the 2′6′-dimethylphenyl moiety lowered the thermodynamically controlled diastereoselectivity. However, repeating this alkylation reaction several times and on various scales it was observed that the stereochemical outcome of the reaction was time-dependent. Thus, as reported,[9] quenching of



Scheme 1.



Scheme 2.

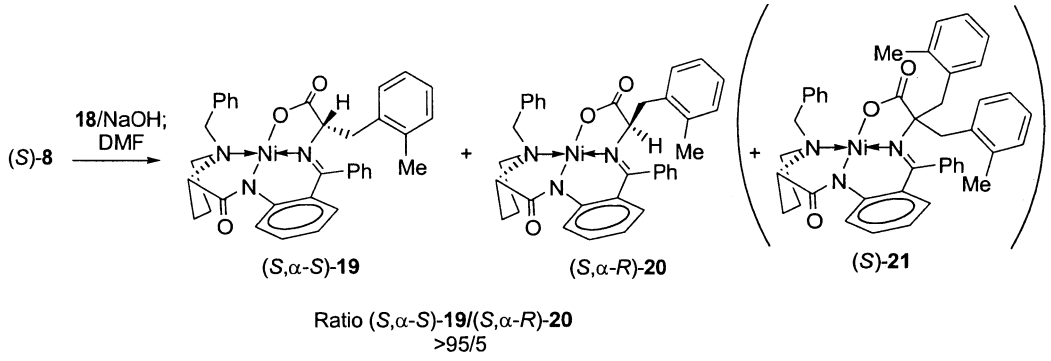
the reaction soon after complete conversion of the starting complex (*S*)-**8** gave the diastereomeric products (*S*,α-*S*)-**9a** and (*S*,α-*R*)-**10a** in a ratio of 8:1, while work-up, after the reaction was allowed to stand at room temperature for 4 h following disappearance of starting material, afforded a mixture (*S*,α-*S*)-**9a** and (*S*,α-*R*)-**10a** with up to 94% de (30:1 ratio) of the (*S*,α-*S*)-**9a** diastereomer. The same dramatic increase in diastereoselectivity was achieved by heating the reaction mixture of (*S*,α-*S*)-**9a** and (*S*,α-*R*)-**10a** (8:1 ratio) at 50°C for a few minutes. These results suggest that the stereochemical requirements of the 2′6′-dimethylphenyl moiety in (*S*,α-*S*)-**9a** and (*S*,α-*R*)-**10a** does not interfere with the thermodynamically controlled excess of (*S*,α-*S*)-**9a** over (*S*,α-*R*)-**10a**, but does dramatically influence the rate of equilibration. Accordingly, the asymmetric synthesis of (*S*)-DMT **4** by direct alkylation of the glycine complex (*S*)-**8** with benzyl bromide **7a**, through intermediates **13** and **16** (Scheme 2) as described previously,[9] becomes a much more practical and highly diastereoselective approach for the preparation of the target amino acid in high chemical yield. Application of the enantiomerically pure glycine complex derived from (*R*)-Pro, in place of (*S*)-**8**, mirrored the results obtained for alkylation of (*S*)-**8**, affording α-(*R*)-configured DMT **4** by the corresponding derivatives **14**, **17** (Scheme 2). This approach makes both (*S*)- and (*R*)-DMT **4** readily available in multigram quantities.

Taking advantage of these results, 2′6′-dimethylbenzyl bromide **7b** was synthesized by reduction of the commercially available carboxylic acid **11** followed by bromination of the intermediate benzyl alcohol **12b** (Scheme 1). The alkylation reactions of **7b** with glycine complex (*S*)-**8b** were then studied under different conditions (Table 1). The alkylations conducted at −10°C (entry 1) and 0°C (entry 2) gave similar stereochemical outcomes suggesting that the observed diastereoselectivity is kinetically controlled and is relatively low compared with the stereochemical outcome of the reactions conducted at 25°C (entry 3) and 50°C (entry 4). The best diastereoselectivity (>93% de) (entry 4) is in the range of the normally observed thermodynamically controlled benzylation of (*S*)-**8**.[11] On the other hand, these results, combined with the data discussed above on the alkylation of (*S*)-**8** and (*R*)-**8** with **7a**, demonstrate the generality of the decelerating effect of the 2′,6′-dimethylphenyl residue on the rate of the thermodynamic equilibration of the diastereomeric products of (*S*,α-*S*)-**9a**,**b** and (*S*,α-*R*)-**10a**,**b**. To study the stereochemical requirements of this effect further, the reactions of complex (*S*)-**8** with commercially available 2′-methylbenzyl bromide (**18**) (Scheme 3) were studied under different conditions. It was found that, regardless of the reaction conditions applied, the diastereoselectivities of the reactions (Scheme 3) were uniformly above 90% de, affording complex (*S*,α-*S*)-**19** as the major reaction product and (*S*,α-*R*)-**20** as the minor one. These data demonstrate that, in contrast to the effect of

Table 1. The reactions of Ni(II)-complex (*S*)-**8** with benzyl halide **7b**

Entry	*T* (°C)	Time (min)	Ratio[a] (*S*,α-*S*)-**9b**/(*S*,α-*R*)-**10b**	Yield[b] (%)
1	−10	15	6.3/1	99
2	0	5	6.2/1	99
3	25	<5	8.2/1	98
4	50	<2	29.5/1	93

All reactions were conducted in DMF in a nitrogen atmosphere.
[a] Ratios of diastereomers were determined by ^{1}H NMR (500 or 600 MHz) analysis of the crude reaction mixtures.
[b] Combined yield of all listed products.

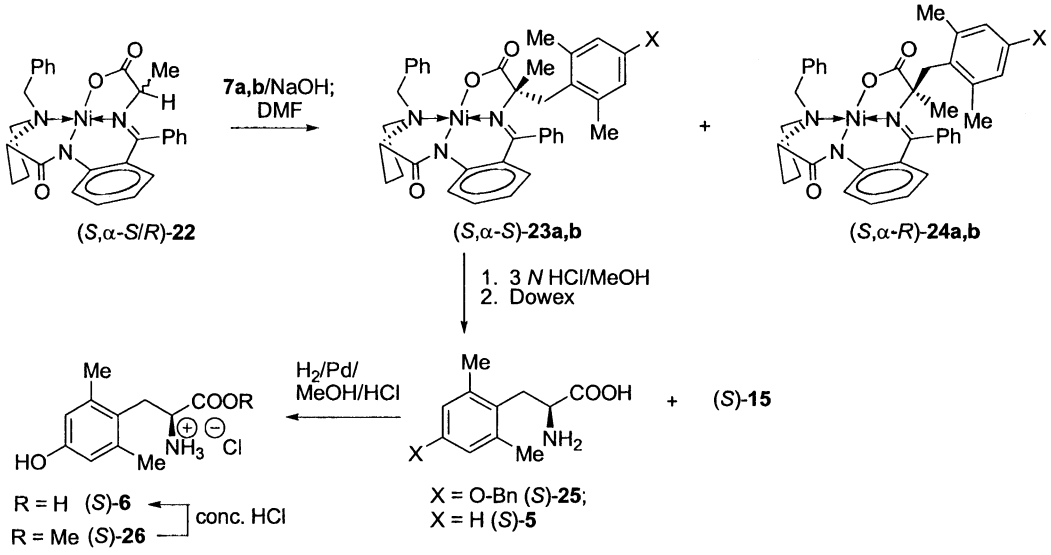


Scheme 3.

the 2′,6′-dimethylphenyl in (*S*,α-*S*)-**9a**,**b** and (*S*,α-*R*)-**10a**,**b**, the presence of one *ortho*-methyl substituent on the phenyl ring in (*S*,α-*S*)-**19** and (*S*,α-*R*)-**20** does not influence the rate of the thermodynamic equilibration of these complexes. Moreover, in the reactions of bromide **18** with complex (*S*)-**8**, the bis-benzylated product (*S*)-**21** (Scheme 3) was obtained in yield ranging from 2 to 15% depending on the ratio of the starting **18** and (*S*)-**8**, as is regularly observed in the reactions of (*S*)-**8** with benzyl halides.[12] In contrast, in the reaction of 2′,6′-dimethylbenzyl bromides **7a**,**b** no bis-benzylation products were observed, even when an excess of the bromide was used.

2.2. Benzylation of Ni(II)-complex (*S*,α-*S*/*R*)-22 with 2′6′-dimethylphenyl bromides 7a and 7b

The reactions between alanine Ni(II)-complex (*S*,α-*S*/*R*)-**22** and benzyl bromides **7a**,**b** were conducted at various temperatures in commercial-grade DMF using powdered NaOH as base (Scheme 4). The results are summarized in Table 2. The benzylations occurred at lower reaction rates compared with the rates of the glycine complex (*S*)-**8** reactions (Table 1). In these reactions the observed stereochemical outcome is kinetically controlled since there is no possibility for equilibration of the resultant products



Scheme 4.

Table 2. The reactions of Ni(II)-complex (*S*,α-*S*/*R*)-**22** with benzyl halides **7a**,**b**

Entry	**7a**,**b**	*T* (°C)	Time (min)	Ratio[a] (*S*,α-*S*)-**23**/(*S*,α-*R*)-**24**	Yield[b] (%)
1	**a**	−10	210	5.7/1	93
2	**a**	0	60	5.5/1	95
3	**a**	25	20	6.3/1	96
4	**b**	−10	210	5.5/1	92
4	**b**	0	80	5.9/1	94
4	**b**	25	20	6.6/1	93

All reactions were conducted in DMF in a nitrogen atmosphere.
[a] Ratios of diastereomers were determined by ^{1}H NMR (500 or 600 MHz) analysis of the crude reaction mixtures.
[b] Combined yield of all listed products.

(*S*,α-*S*)-**23a**,**b** and (*S*,α-*R*)-**24a**,**b**. The reaction temperature had a small effect on the diastereoselectivity of the benzylations, which was in the range 5.5:1–6.6:1 (70–74% de). This is in a good agreement with the kinetically controlled stereochemical outcome of the reactions of glycine complex (*S*)-**8** with bromides **7a**,**b** (Table 1). Products (*S*,α-*S*)-**23a**,**b** and (*S*,α-*R*)-**24a**,**b** were easily separated by column chromatography and isolated in diastereomerically pure form. Decomposition of the tyrosine-containing complex products (*S*,α-*S*)-**23a** gave the intermediate *O*-benzyl protected amino acid (*S*)-**25**, which was hydrogenated under standard conditions to afford a mixture of the target (*S*)-α-TMT **6** and its methyl ester (*S*)-**26**. The mixture was treated with concentrated hydrochloric acid at 70°C to afford, after evaporation, enantiomerically pure (*S*)-α-TMT **6**.

Decomposition of the diastereomerically pure complex (*S*,α-*S*)-**23b** gave the target (*S*)-α-TMP **5**, which was isolated in high chemical yield by cation-exchange chromatography. As previously documented,[9–13] the chiral ligand (*S*)-**15** (Schemes 2 and 4) was readily recovered upon decomposition of complexes (*S*,α-*S*)-**23a**,**b** and was reused for preparing starting glycine or alanine complexes (*S*)-**8** and (*S*,α-*S*/*R*)-**22**.

In conclusion, we have demonstrated that sterically constrained 2′,6′-dimethyl (DMP, DMT) as well as α,2′,6′-trimethyl derivatives of phenylalanine and tyrosine (α-TMP, α-TMT) can be efficiently prepared by reaction of the chiral nucleophilic glycine equivalent, Ni(II)-complex (*S*)-**8**, or alanine complex (*S*,α-*S*/*R*)-**22**, with benzyl bromides **7a** and **7b**. The inexpensive and readily available reagents and solvents involved, including the recyclable chiral ligand (*S*)-**15**, and the simplicity of the experimental procedures, make this method 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 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 obtained using 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.

Complex (*S*)-**8** is available from ACROS Chemical Company or it can be readily prepared by literature procedures, as can complexes (*R*)-**8** and (*S*,α-*S*/*R*)-**22**.[13] The stereochemical outcome of the reactions was determined by integration (^{1}H NMR, 500 MHz) of characteristic peaks in the 7.5–9.0 ppm region. Absolute configurations of products were determined using spectral and chiroptical data as describe previously by us and others.[9–12] Benzyl bromide **7a** was prepared as described previously.[9]

3.1.1. 2′,6′-Dimethylbenzyl alcohol (12b). To a solution of 20.0 g of 2,6-dimethylbenzoic acid (0.133 mol, 1 equiv.) in 150 mL of freshly distilled THF at −78°C, 10.1 g of $LiAlH_4$ (0.266 mol, 2 equiv.) was slowly added. The solution was stirred for 2 h at −78°C, warmed to room temperature and then refluxed for 10 h. The reaction was quenched with 200 mL of 3N HCl. The aqueous layer was separated from the organic layer and washed with diethyl ether (2×200 mL). The combined ether layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo to provide product. Yield: 97%. Mp 82–84°C. R_f=0.56 (EtOAc/hexanes, 3:7). ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H), 4.72 (s, 2H), δ 7.02–7.11 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 19.4, 59.3, 128.0, 128.4, 136.5, 137.3. HRMS (FAB) $[M+H]^+$ calcd for $C_9H_{12}O$ 137.0966, found 137.0963.

3.1.2. 2′,6′-Dimethylbenzyl bromide (7b). To a solution of 5.45 g of 2,6-dimethylbenzyl alcohol (40 mmol, 1 equiv.) and 7.13 mL of anhydrous pyridine (88 mmol, 2.2 equiv.) in 150 mL of anhydrous diethyl ether at −78°C, 4.14 mL of PBr_3 (44 mmol, 1.1 equiv.) was added dropwise over a period of 1 h by a syringe. The resulting white slurry was stirred under Ar for 2 h at −78°C and then overnight at room temperature. The reaction progress was monitored with TLC. Upon complete disappearance of the starting material, the reaction was quenched by slowly adding an ice-water mixture. The resulting reaction mixture was stirred at 0°C for 30 min. After the ether layer was separated from the aqueous layer, the aqueous phase was washed with ether (3×100 mL). Then the combined ether solutions were washed with ice-cold 1N HCl (2×100 mL), saturated sodium bicarbonate (2×100 mL) and distilled water (2×100 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo to afford the product. Yield: 82%. Mp 36–38°C. R_f=0.82 (EtOAc/hexanes, 1:9). ^{1}H NMR ($CDCl_3$) δ 2.37(s, 6H), 4.51 (s, 2H), 6.97–7.08 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 19.1, 29.2, 128.4, 128.5, 134.0, 137.4. HRMS (FAB) $[M+H]^+$ calcd for $C_9H_{11}Br$ 199.0122, found 199.0115.

3.1.3. Reaction of Ni(II)-complex (*S*)-8 with bromides 7b and 18. A 100 mL round-bottom flask with 4.982 g (10 mmol, 1 equiv.) of (*S*)-8 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, 11 mmol (1.1 equiv.) of bromide **7b** or **18**, dissolved in 20 mL of anhydrous DMF, was added dropwise to the solution by syringe. The reaction mixture was stirred under Ar and the reaction progress was monitored by TLC. Upon completion, the reaction was quenched by addition of 500 mL of ice-water and the precipitated material was filtered and then dried in vacuo. The diastereomerically pure products (*S*,α-*S*) and (*S*,α-*R*) were isolated by column chromatography on silica-gel; the (*S*,α-*R*) diastereomer emerged first.

3.1.4. Ni(II)-complex of the Schiff base of (*S*)-15 with (*S*)-2′,6′-dimethylphenylalanine (*S*,α-*S*)-9b. Mp 122–124°C. R_f=0.35 (acetone/hexanes, 1:1). $[\alpha]_D^{25}$=+2437 (*c* 0.02002, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.08–2.12 (m, 1H), 2.14 (s, 6H), 2.27–2.33 (m, 1H), 2.57–2.66 (m, 1H), 2.76–2.80 (m, 1H), 3.51–3.57 (m, 2H), 3.53 (d, 1H, *J*=12.9 Hz), 3.91–3.97 (m, 1H), 4.11 (dd, 1H, *J*=10.5, 14.0 Hz), 4.30 (dd, 1H, *J*=4.0, 10.5 Hz), 4.46 (d, 1H, *J*=12.5 Hz), 5.55 (d, 1H, *J*=7.4 Hz), 6.41–6.43 (m, 2H), 6.56–6.60 (m, 1H), 6.82 (d, 2H, *J*=7.6 Hz), 6.93–7.00 (m, 2H), 7.06–7.16 (m, 3H), 7.28–7.38 (m, 4H), 8.07 (d, 2H, *J*=7.1 Hz), 8.22 (d, 1H, *J*=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 20.0, 24.2, 30.6, 37.5, 57.1, 63.0, 70.3, 70.4, 120.6, 123.2, 126.0, 126.9, 127.4, 128.1, 128.3, 128.6, 128.8, 128.9, 129.0, 131.4, 132.3, 132.4, 133.1, 133.3, 133.8, 137.8, 142.3, 171.0, 178.8, 180.0. HRMS (FAB) $[M+H]^+$ calcd for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2100.

3.1.5. Ni(II)-complex of the Schiff base of (*S*)-15 with (*R*)-2′,6′-dimethylphenylalanine (*S*,α-*R*)-10b. Mp 295–297°C. R_f=0.47 (acetone/hexanes, 1:1). $[\alpha]_D^{25}$=−1481(*c* 0.0280, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.85–1.94 (m, 1H), 1.98 (s, 6H), 2.22–2.30 (m, 1H), 2.87–2.92 (m, 1H), 3.34 (dd, 1H, J_1=3.0 Hz, J_2=14.0 Hz), 3.43 (d, 1H, *J*=13.0 Hz), 3.94 (d, part of AB, 1H, J_{AB}=9.0 Hz), 4.02 (t, 1H, *J*=13.6 Hz), 4.29 (dd, 1H, *J*=3.5, 10.5 Hz), 4.29 (dd, 1H, *J*=3.5, 10.5 Hz), 4.34 (d, 1H, *J*=12.0 Hz), 5.41 (d, 1H, *J*=6.5 Hz), 6.54–6.56 (d, 1H, *J*=8.5 Hz), 6.62–6.65 (m, 1H), 6.81 (d, 2H, *J*=7.5 Hz), 6.92–6.95 (m, 1H), 6.98–7.01 (m, 1H), 7.11–7.12 (m, 1H), 7.22–7.23 (m, 1H), 7.31–7.33 (m, 2H), 7.46–7.49 (m, 1H), 7.52–7.55 (m, 2H), 7.92 (d, 1H, *J*=7.5 Hz), 8.61 (d, 1H, *J*=9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 19.7, 22.7, 29.6, 36.7, 58.6, 60.0, 68.5, 70.4, 120.6, 123.1, 125.7, 126.8, 127.1, 128.1, 128.5, 128.6, 128.9, 129.1, 129.2, 131.9, 132.5, 132.6, 133.2, 133.4, 134.1, 138.3, 142.7, 171.5, 179.0, 181.1. HRMS (FAB) $[M+H]^+$ calcd for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2105.

3.1.6. Reaction of the Ni(II)-complex (*S*,α-*S*/*R*)-22 with bromides 7a and 7b. A 100 mL round-bottom flask with 5.121 g (10 mmol, 1 equiv.) of **22** 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, 11 mmol (1.1 equiv.) of either bromides **7a** or **7b**, dissolved in 20 mL of anhydrous DMF, was added to the solution by syringe. The reaction mixture was stirred under Ar and the reaction progress was monitored by TLC. Upon completion, the reaction was quenched by addition of 500 mL of ice-water and the precipitated material was filtered and then dried in vacuo. The diastereomerically pure products (*S*,α-*S*) and (*S*,α-*R*) were isolated by column chromatography on silica-gel.

3.1.7. Ni(II)-complex of the Schiff base of (*S*)-15 with (*S*)-*O*-benzyl-α,2′,6′-trimethyltyrosine (*S*,α-*S*)-23a. Mp 108–110°C, $[\alpha]_D^{25}$=+1666.7 (*c* 0.0099, $CHCl_3$), ^1H NMR ($CDCl_3$, DRX500) δ 0.92 (s, 3H), 1.92–1.97 (m, 1H), 2.06–2.12 (m, 1H), 2.34 (s, 6H), 2.43–2.49 (m, 1H), 2.53–2.61 (m, 1H), 3.08–3.13 (m, 1H), 3.41–3.47 (m, 2H), 3.52 (d, 1H, *J*=12.5 Hz),3.64 (d, H, *J*=14.5 Hz), 3.84 (d, 1H, *J*=14.5 Hz), 4.47 (d, 1H, *J*=14.5 Hz), 5.02 (s, 2H), 6.39 (d, 1H, *J*=7.0 Hz), 6.53–6.59 (m, 2H), 6.69 (s, 2H), 7.05–7.08 (m, 1H), 7.11–7.17 (m, 2H), 7.20–7.22 (m, 1H), 7.30–7.33 (m, 3H), 7.24–7.43 (m, 6H), 8.08–8.11(m, 3H). ^{13}C NMR ($CDCl_3$, DRX500) δ 21.9, 23.8, 27.8, 30.5, 42.0, 57.8, 63.6, 69.6, 70.1, 80.4, 115.0, 120.3, 123.2, 125.8, 126.7, 127.2, 127.4, 127.8, 127.9, 128.1, 128.5, 128.8, 128.9, 130.3, 131.5, 131.9, 133.4, 134.0, 136.9, 137.1, 140.6, 141.9, 157.3, 171.6, 180.1, 180.4. HRMS (FAB) $[M+H]^+$ calcd for $C_{44}H_{43}N_3O_4Ni$ 736.2685, found 736.2695.

3.1.8. Ni(II)-complex of the Schiff base of (*S*)-15 with (*R*)-*O*-benzyl-α,2′,6′-trimethyltyrosine (*S*,α-*R*)-24a. Mp 243–245°C. $[\alpha]_D^{25}$=−372.8 (*c* 0.01725, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.61–1.69 (m, 2H), 2.13–2.17 (m, 1H), 2.28 (s, 6H), 2.40–2.45 (m, 1H), 2.48–2.53 (m, 1H), 3.20 (d, 1H, *J*=14.5 Hz), 3.32 (d, 1H, *J*=14.5 Hz), 3.46–3.52 (m, 1H), 3.57 (d, 1H, *J*=13.5 Hz), 3.96 (d, 1H, *J*=13.5 Hz), 4.01–4.05 (m, 1H), 4.93 (d, 1H, *J*=11.5 Hz). 5.00 (d, 1H, *J*=11.5 Hz), 6.63–6.69 (m, 2H), 6.81 (s, 2H), 6.78–6.81 (m, 1H), 7.17–7.22 (m, 2H), 7.33–7.47 (m, 11H, 7.62–7.63 (m, 2H), 8.21 (d, 1H, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 21.8, 23.5, 28.5, 30.9, 42.5, 56.8, 61.2, 69.4, 69.5, 80.2, 114.9, 120.6, 123.7, 126.8, 127.2, 127.3, 127.4, 127.6, 127.8, 127.9, 128.5, 128.6, 128.7, 128.8, 129.1, 129.8, 131.8, 131.9, 133.0, 133.9, 137.0, 137.4, 141.0, 142.1, 157.4, 172.1, 180.4, 180.9. HRMS (FAB) $[M+H]^+$ calcd for $C_{44}H_{43}N_3O_4Ni$ 736.2685, found 736.2695.

3.1.9. Ni(II)-complex of the Schiff base of (*S*)-15 with (*S*)-α,2′,6′-trimethylphenylalanine (*S*,α-*S*)-23b. Mp 224–225°C. R_f=0.46 (acetone/hexanes, 1:1). $[\alpha]_D^{25}$=+2253 (*c*, 0.01988, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.95–2.00 (m, 1H), 2.06–2.11 (m, 1H), 2.38 (s, 6H), 2.44–2.51 (m, 1H), 2.55–2.58 (m, 1H), 3.10–3.15 (m, 1H), 3.37–3.41 (m, 1H), 3.44–3.49 (m, 1H), 3.53 (d, 1H, *J*=12.5 Hz), 3.68 (d, 1H, *J*=14.0 Hz), 3.96 (d, 1H, *J*=14.5 Hz), 4.47 (d, 1H, *J*=12.5 Hz), 6.29 (d, 1H, *J*=8.0 Hz), 6.58–6.52 (m, 2H), 7.02–7.18 (m, 6H), 7.21–7.22 (m, 1H), 7.30–7.33 (m, 2H), 7.36–7.39 (m, 2H), 8.08 (d, 2H, *J*=7.5 Hz), δ 8.11 (d, 1H, *J*=9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 21.6, 23.8, 27.8, 30.5, 42.5, 57.3, 63.5, 70.1, 80.4, 120.4, 123.2, 126.7, 127.1, 127.2, 127.8, 128.1, 128.8, 128.9, 130.3, 131.6, 131.9, 133.2, 133.4, 134.0, 136.8, 139.2, 141.9, 171.7, 180.1, 180.4. HRMS (FAB) $[M+H]^+$ calcd for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2262.

3.1.10. Ni(II)-complex of the Schiff base of (*S*)-15 with (*R*)-α,2′,6′-trimethylphenylalanine (*S*,α-*R*)-24b. R_f=0.36 (acetone/hexanes, 1:1). Mp 230–232°C. $[\alpha]_D^{25}$=−228.0 (*c* 0.06058, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.71–1.69 (m, 1H), 1.79–1.72 (m, 1H), 2.22–2.18 (m, 1H), 2.28 (s, 6H), 2.53–2.45 (m, 2H), 3.26 (d, 1H, *J*=14.4 Hz), 3.41 (d, 1H, *J*=14.3 Hz), 3.50 (dd, 1H, *J*=3.8, 9.6 Hz), 3.54 (d, 1H, *J*=13.4 Hz), 3.97 (d, 1H, *J*=13.3 Hz), 4.00–4.02 (m, 1H), 6.63–6.66 (m, 1H), 6.68 (d, 2H, *J*=7.4 Hz), 7.08 (d, 2H, *J*=7.5 Hz), 7.14–7.21 (m, 3H), 7.30–7.45 (m, 5H), 7.70 (d, 2H, *J*=7.3 Hz), 8.20 (d, 1H, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 21.4, 23.3, 28.2, 30.7, 42.6, 56.8, 61.1, 69.2, 79.8, 120.4, 123.6, 127.0, 127.2, 127.6, 127.7, 128.5, 128.7, 129.0, 129.5, 131.6, 131.8, 132.9, 133.6, 134.1, 137.1, 139.2, 141.9, 172.2, 180.2, 180.7. HRMS (FAB)

$[M+H]^+$ calcd for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2287.

3.1.11. Decomposition of the Ni(II)-complexes. Isolation of (*S*)-3, (*S*)-5 and (*S*)-25. A solution of **9b**, **23a** or **23b** (15 mmol, 1 equiv.) in 20 mL of MeOH was slowly dropped into a mixture of 40 mL of 3N HCl and MeOH (1:1) at 70°C. After the red color has 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 then evaporated to dryness. The resulting material was dissolved in 100 mL of water and extracted with 100 mL of $CHCl_3$. (Sometimes, part of the product stayed at the interface between the aqueous and organic phases due to its limited solubility in water. The undissolved product was then filtered and washed with water and $CHCl_3$. Then this part the product was combined with the rest of product obtained later. Also the washings were combined with the filtrate.) The $CHCl_3$ layer was separated from the aqueous layer and the aqueous layer was washed with $CHCl_3$ (2×50 mL). The chloroform layers were dried over anhydrous $MgSO_4$, filtered, and then evaporated to recover the chiral ligand (*S*)-**15**. The aqueous layer was evaporated in vacuo, the resulting material was dissolved in a minimal amount of ethanol/water (1:1, v/v) and the solution was applied to a 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 a 1:4 water/concentrated ammonium hydroxide solution to yield a solution of either (*S*)-**3**, (*S*)-**5** or (*S*)-**25**, which was evaporated to give the solid amino acid. If necessary, a mixture of 2:3:5 concentrated ammonium hydroxide/ethanol/water could be used as eluent.

3.1.12. α-(*S*)-2′,6′-Dimethylphenylalanine ((*S*)-3). Yield: 85%. Mp 259–261°C. $[\alpha]_D^{25}=+31.12$ (*c* 0.8444, MeOH). ^1H NMR (d_6-DMSO/DCl) δ 2.77 (dd, another part of AB, $J_{BX}=6.5$ Hz, $J_{AB}=14.5$ Hz), 2.86 (dd, part of AB, 1H, $J_{AX}=11.0$ Hz, $J_{AB}=14.0$ Hz), 3.62 (dd, ABX, 1H, $J_{AX}=10.0$ Hz, $J_{BX}=6.5$ Hz), 6.62–6.56 (m, 3H). ^{13}C NMR (d_6-DMSO/DCl) δ 23.1, 33.7, 55.2, 131.1, 132.0, 134.6, 140.9, 173.8. HRMS (FAB) $[M+H]^+$ calcd for $C_{11}H_{15}NO_2$ 194.1181, found 194.1182.

3.1.13. α-(*S*)-α,2′,6′-Trimethylphenylalanine ((*S*)-5). Yield: 87%. Mp 243–245°C. $[\alpha]_D^{25}=+10.25$ (*c* 1.026, MeOH). ^1H NMR (d_6-DMSO/DCl) δ 1.13 (s, 3H), 1.86 (s, 6H), 2.95 (d, 1H, *J*=5.5 Hz), 2.99 (d, 1H, *J*=5.5 Hz), 6.95–7.00 (m, 3H). ^{13}C NMR (d_6-DMSO/DCl) δ 21.3, 22.0, 36.5, 40.9, 126.6, 128.4, 133.7, 138.6, 172.2. HRMS (FAB) $[M+H]^+$ calcd for $C_{12}H_{17}NO_2$ 208.1338, found 208.1344.

3.1.14. α-(*S*)-*O*-Benzyl-α,2′,6′-trimethyltyrosine ((*S*)-25). Yield: 85%. Mp 210–212°C. $[\alpha]_D^{25}=+19.08°$ (*c* 0.5781, MeOH). ^1H NMR (d_6-DMSO/DCl): 1.89 (s, 3H), 2.06 (s, 6H), 3.35 (d, 1H, *J*=6.5 Hz), 3.41 (d, 1H, *J*=6.2 Hz), 4.67 (s, 2H), 6.40(s, 2H), 7.06–7.15 (m, 5H). ^{13}C NMR (d_6-DMSO/DCl) δ 170.3, 157.3, 138.7, 138.2, 130.0, 128.9, 127.9, 113.2, 69.0, 51.3, 31.5, 21.5, 18.2. HRMS (FAB) $[M+H]^+$ calcd for $C_{19}H_{19}NO_3$ 314.1756, found 314.1764.

3.1.15. Hydrogenation of *O*-benzyl DMT (*S*)-11 and (*R*)-12. *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 at 40 psi. After 24 h the catalyst was filtered and washed with a small amount of methanol and water. The filtrate was evaporated and lyophilized to yield the crude product, which contained 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 the target amino acids in quantitative chemical yield as white powders.

3.1.16. (*S*)-α,2′,6′-Trimethyltyrosine ((*S*)-α-TMT) (6). Yield: 99%. Mp 224–226°C. $[\alpha]_D^{25}=+20.15$ (*c* 0.9124, MeOH). ^1H NMR (d_6-DMSO/DCl) δ 1.52 (s, 3H), 2.01 (s, 6H), 2.64 (d, *J*=6.2 Hz), 2.70 (d, 1H, *J*=6.3 Hz), 6.42 (s, 2H). ^{13}C NMR (d_6-DMSO/DCl) 17.9, 19.4, 30.4, 53.0, 112.4, 123.6, 137.7, 155.3, 170.8,. HRMS (FAB) $[M+H]^+$ calcd for $C_{12}H_{17}NO_3$ 224.1287, found 224.1276.

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