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**PAPER**

# Asymmetric synthesis of *α,β*-diamino acid derivates *via* Mannich-type reactions of a chiral Ni(II) complex of glycine with *N*-tosyl imines†

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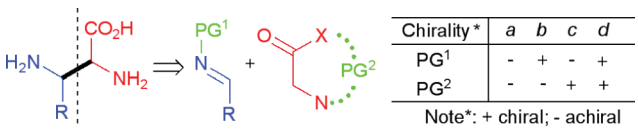
A practical procedure composed of an asymmetric Mannich-type reaction between *N*-tosyl imine and a Ni(II) complex of glycine with (*R*)-*o*-[*N*-(*N*-benzylprolyl)amino]bezaophenone (**BPB**) as a chiral auxiliary catalyzed by $Et_3N$ in DMF to (*R*,2*R*,3*S*)-complexes, and decomposition of products with HCl to offer *syn*-(2*R*,3*S*)-*α,β*-diamino acids, was developed. Stereochemical mechanism of the Mannich reaction was proposed and supported by determining the absolute configuration of the product of the Mannich reaction relying on X-ray analysis. This two-step approach to amino acids was a general method and adapted to large-scale preparation.

## Introduction

*α,β*-Diamino acids are important non-coded amino acids and have presented various biological significance.[1] These diamino acids have attracted a great deal of attention due mainly to the following features: 1) free *α,β*-diamino acids were detected as biologically active ingredients in natural products such as *β*-*N*-oxalyl-L-*α,β*-diaminopropionic acid[2] and L-*β*-methylaminoalanine[3] in plants leading to the Guam disease;[4] 2) *α,β*-diamino acids were found as key structural fragments in natural peptidic antibiotics from bacteria or marine organisms;[5] 3) *α,β*-diamino acids also were used to synthesize peptidomimetics[6] and other useful drugs;[7] 4) *α,β*-diamino acids were found in the Murchison meteorite fell in Australia in 1969 and considered to be essential materials for peptide nucleic acids as evolutionary substance before life.[8]

In the past decades, a number of synthetic routes toward *α,β*-diamino acids have been reported.[1] Generally speaking, the strategy by forming the basic carbon skeleton was an important one, in which the Mannich reaction was significant to the synthesis of *α,β*-diamino acids or their derivates. In the direct-type Mannich reaction of three-component including an aldehyde, an amine and an *α*-acidic carbonyl compound, *α*-amino acid ester was seldom used as carbonyl donor to prepare *α,β*-diamino acids due to the inadequate acidity of the *α*-proton.[9] Instead, the Mannich-type reactions focusing on utilizing preformed imines and enolate equivalents attracted our attention.[10] In Scheme 1, four strategies for the asymmetric synthesis of *α,β*-diamino acids through the Mannich-type reactions between chiral or achiral imines and chiral or achiral glycine ester derivatives were illustrated. Catalytic asymmetric Mannich-type reactions were widely investigated recently to prepare *α,β*-diamino acids (Scheme 1, strategy *a*).[11] Organocatalytic methods[12] and metal- catalyzed methods[13] with high diastereo- or enantiocontrol were applied but limited in large scale enantiomeric synthesis for the aim of medicine. Long reaction time and high loading of chiral catalyst were required unless more efficient catalysts were developed. Other methods to synthesize *α,β*-diamino acids through the Mannich-type reaction using chiral auxiliary were applied in some case. The imines with chiral directing group linking to nitrogen atom such as sulfinimines were employed to prepare *α,β*-diamino acids (Scheme 1, strategy *b*).[14] However, the limited categories of chiral imines hindered general methods from developing. On the other hand, glycine equivalents with chiral auxiliaries were plentiful and used successfully in the large scale preparation of enantiopure amino acids.[15] To our surprise, the potential strategy by using glycine equivalent with a chiral auxiliary in the Mannich-type reactions with imines (Scheme 1, strategy *c*), was not well developed to prepare *α,β*-diamino acids. Chiral Ni(II) complex of the Schiff base of glycine **1** displayed unique reactivity and stereoselectivity has been widely used to synthesize enantiopure tailor-made amino acids successfully.[15f,g] Another focus of the Mannich-type reaction is on searching for stable and activated imines due mainly to pool reactivity and unstability of ordinary imines. Soloshonok reported an asymmetric Mannich reaction of chiral Ni(II) complex of glycine with the imine activated by $CF_3$ group to synthesize




| Chirality* | *a* | *b* | *c* | *d* |
|---|---|---|---|---|
| $PG^1$ | - | + | - | + |
| $PG^2$ | - | - | + | + |

Note*: + chiral; - achiral

**Scheme 1** Four strategies for the synthesis of *α,β*-diamino acids through the Mannich-type reactions.

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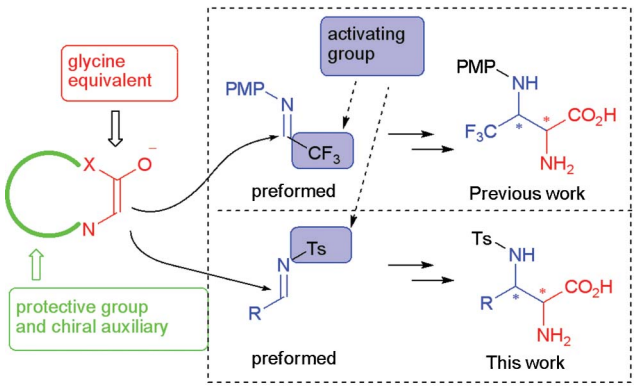
$\alpha,\beta$-diamino acids (Scheme 2).[16] Unfortunately, this fluorinated imine run short of alterable structures. Liu and co-workers used *N*-Boc-$\alpha$-amido sulfones to replace imines.[17] Strong base such as NaH, *t*-BuOK and DBU *et al.* and long reaction time were required due to the poor reactivity of these amido sulfones. Especially, the $\alpha$-amido sulfones derived from aliphatic aldehydes gave low yields in the reactions. Thus, we were eager to search for activated imines. As one of the few types of electron-deficient imines, *N*-sulfonylimines with strong electron withdrawing group at nitrogen atom were stable enough to be isolated but reactive enough to undergo reactions.[18]



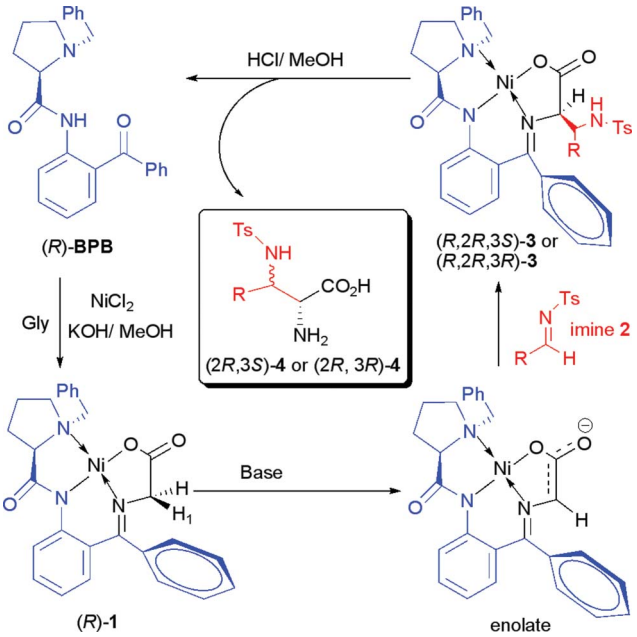

**Scheme 2** The strategies for the synthesis of $\alpha,\beta$-diamino acids with *N*-sulfonylimines in this work compared with previous work.

Herein, we reported a two-step approach to prepare $\alpha,\beta$-diamino acids *via* the Mannich-type reactions between *N*-sulfonylimines **2** and (*R*)-Ni(II) complex of glycine **1** with (*R*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (**BPB**) as a chiral auxiliary mediated by base (Scheme 3), which would be a general method with high stereoselectivity.

## Results and discussion

The Ni(II)-complex **1** was synthesized in three steps based on an improved method.[19] *N*-Tosyl imines were produced as described in the literature reported by us previously.[20] A notable merit of Ni(II) complex of glycine **1** was high acidity of the $\alpha$-protons of glycine part. The acidity of $\alpha$-$H_1$ (labeled in Scheme 3) of complex **1** (The p$K_a$ was about 17–19 in DMSO or 11–12 in water[21]) was equal to phenol (The p$K_a$ was about 18 in DMSO). Thus, it could use both inorganic base (even $Na_2CO_3$) and organic bases that can lead to a mild condition of reaction to convert complex **1** into an enolate form. Therefore, a wider range of bases can be selected to catalyze the asymmetric Mannich reaction between Ni(II) complex of glycine **1** and *N*-tosyl imines **2**. Another consideration about this reaction was about the solution which should be propitious to the stabilization of enolate depending on the intermolecular hydrogen bond. Also, complex **1** is a strong polar molecule and the solvent should be able to dissolve the complex well. Polar aprotic solvents would be good choices to this kind of reaction.

Initially, we selected chiral (*R*)-Ni(II) complex of glycine **1** and *N*-tosyl imine derived from benzaldehyde as model reaction for optimizing reaction conditions about bases and solvents




**Scheme 3** The system of preparing $\alpha,\beta$-diamino acids *via* the Mannich–type reactions of a chiral Ni(II) complex of glycine with *N*-tosyl imines.

**Table 1** The optimizing for the reaction conditions in the asymmetric Mannich reaction between Ni(II) complex of glycine and *N*-tosyl imine derived from benzaldehyde

| Entry | Base[a] | Solvent | *t*/h | *T*/°C | (*R*,2*R*,3*S*)-**3**/(*R*,2*R*,3*R*)-**3**[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $NEt_3$ | DMF | 0.3 | 30 | 90/10 | 81 |
| 2 | NaOH | DMF | 2 | 30 | 74/26 | 56 |
| 3 | NaH | DMF | 12 | 30 | — | Trace |
| 4 | KO$^t$Bu | DMF | 2 | 30 | 81/19 | 51 |
| 5 | $NEt_3$ | THF | 24 | 30 | — | Trace |
| 6 | $NEt_3$ | Acetone | 24 | 30 | — | — |
| 7 | $NEt_3$ | $CH_2Cl_2$ | 24 | 30 | — | — |
| 8 | $NEt_3$ | MeCN | 24 | 30 | — | Trace |
| 9 | $NEt_3$ | DMF | 0.5 | –60 | 89/11 | 83 |
| 10 | $NEt_3$ | DMF | 1 | 60 | — | — |

[a] The reactions were carried out at 30 °C under $N_2$. Ratio of complex (*R*)-**1**/imine **2**/base = 1/1.3–1.5/1–1.3; 10 mmol. [b] Determined by $^1$H NMR analysis of crude reaction mixtures. [c] Chemical yield of (*R*,2*R*,3*S*)-**3** determined after their separation from unreacted substrate by column chromatography.

(Table 1). First, we chose $NEt_3$ to catalyze the asymmetric Mannich-type reaction in DMF. The reaction proceeded smoothly and an excellent yield was got within 20 min. Ratio of diastereomers of (*R*,2*R*,3*S*)-**3** and (*R*,2*R*,3*R*)-**3** was about 90/10 which was determined by $^1$H NMR analysis of crude reaction mixtures. Then, NaOH, NaH and *t*-BuOK were used to catalyze the reactions (entry 2–4). Modest yield and lower diastereoselectivity were obtained in the reactions when NaOH and *t*-BuOK were used (entry 2 and 4). NaH was not a good choice for the reaction (entry 3). Further, we selected different solvents (entry 5–8) to investigate the reactivity of the reaction and there were almost no reaction products that were detected by TLC. At last, the temperature was changed. The yield and diastereoselectivity had no conspicuous changes at –60 °C (entry 9). At a higher temperature (60 °C),

a significant decomposition of the Ni(II)complex was observed (entry 10).

Encouraged by the good reactivity of this asymmetric Mannich-type reaction with $NEt_3$ in DMF, we investigated the stereoselectivity of the reaction further using the same model above. The temperature of the inter-conversion about *E*, *Z* of C,N double bound was about 50 °C (the$\Delta G^{\#}$ value was about 16 kcal $mol^{-1}$).[22] So *N*-tosyl imines existed mainly in the way of *E*-isomer at 30 °C. The enolate of chiral complex **1** was attacked at the position of $\alpha$-C of glycine by *E*-*N*-benzylidene-4-methylbenzene-sulfonimide which worked as electrophilic reagent. In the light of the chiroptical properties of complex **1**, $\alpha$-C of glycine generated to be the second chiral center which was determined to be (*R*)-configuration.[16,17,23] The configuration of $\beta$-C came from the carbon of C,N double bound was first deduced from the steric effect of complex **3** (Fig. 1). In the mixture of products, (*R*,2*R*,3*S*)-**3** was predominantly isomer. A serious nonbonded repulsion between the substituting group at $\beta$-C and the neighboring phenyl group was responsible for this preference. The steric repulsion in isomer (*R*,2*R*,3*R*)-**3** was much stronger than that in (*R*,2*R*,3*S*)-**3** (Fig. 2). The largest group kept away from the Ni(II)-complex plane and the neighboring phenyl group to avoid the most serious repulsion. In order to prove our inference, we got the absolute configuration

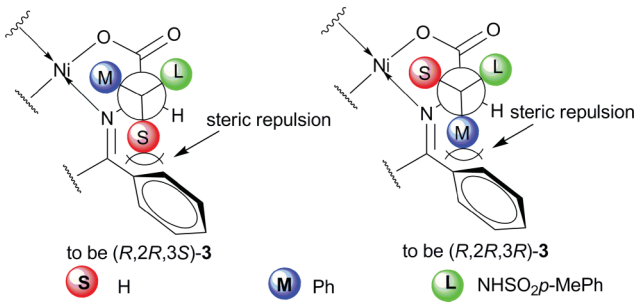



**Fig. 1** The probable products of the asymmetric Mannich-type reactions.

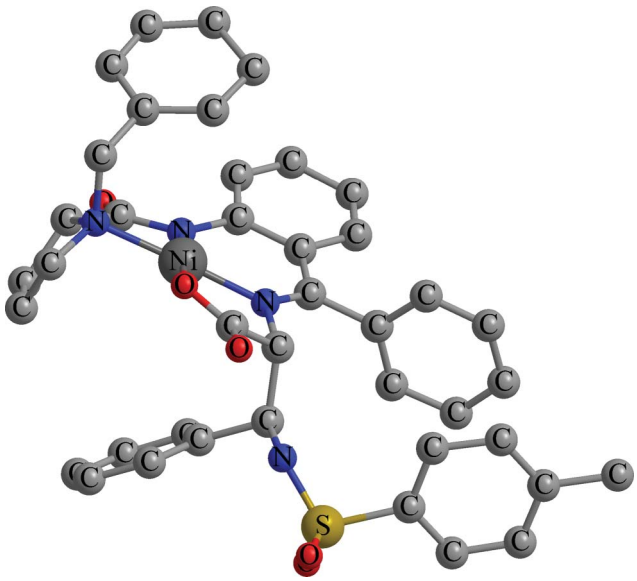
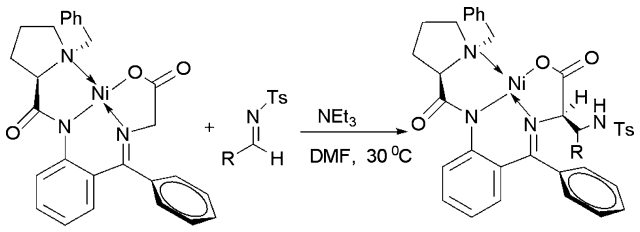


**Fig. 2** (*R*,2*R*,3*S*)-**3**: the absolute configuration of the main product of the Mannich reaction determined by X-ray analysis.

of the major product by single crystal X-ray diffraction (Figure 2). The major product was (*R*,2*R*,3*S*)-**3** as we presumed above.

Having determined the absolute configuration of (*R*,2*R*,3*S*)-**3**, the scope of the reaction was investigated. First, serial *N*-tosyl imines derived from adipic, aromatic and heterocyclic aldehydes were prepared. Then the asymmetric Mannich-type reactions of chiral Ni(II) complex of glycine **1** with *N*-sulfonyl imines were checked. As summarized in Table 2, we established that both aromatic (Table 2, entries 1–5) and heterocyclic (entry 6) *N*-tosyl imines had a good yield and diastereoselectivity. Excitingly, adipic imine (entry 7) also had a satisfactory yield and diastereoselectivity. The aromatic imines with electron-withdrawing groups in substituent (entries 4–5) had better reactivity than that with electron-donating groups (entries 2–3).

**Table 2** Asymmetric Mannich-type reactions of chiral Ni(II) complex of glycine with N-sulfonyl imines, using $NEt_3$ in DMF[a]

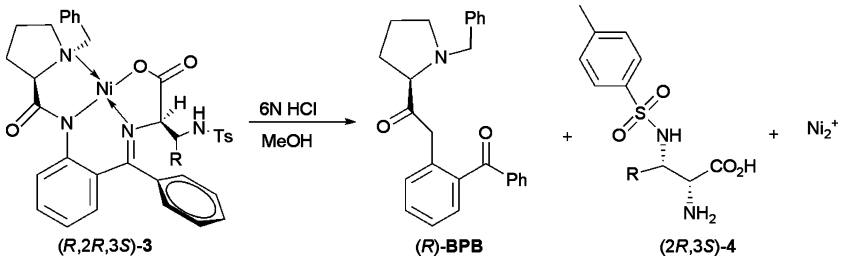



| Entry | *R* | **3** | *T*/min | Ratio of diastereomers (*R*,2*R*,3*S*)-**3**/(*R*,2*R*,3*R*)-**3**[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | Phenyl | **3a** | 20 | 90/10 | 81 |
| 2 | 4-Methoxyphenyl | **3b** | 38 | 91/9 | 76 |
| 3 | 4-Methyphenyl | **3c** | 35 | 89/11 | 79 |
| 4 | 3-Nitrophenyl | **3d** | 18 | 86/14 | 82 |
| 5 | 2-Chlorophenyl | **3e** | 15 | 89/11 | 85 |
| 6 | 2-Furyl | **3f** | 30 | 87/13 | 86 |
| 7 | Isobutyl | **3g** | 25 | 78/22 | 74 |

[a] The reactions were carried out at 30 °C under $N_2$. Ratio of complex (*R*)-**1**/imine **2**/base = 1/1.5/1–1.3; 10 mmol scale. [b] Determined by $^1$H NMR analysis of crude reaction mixtures. [c] Chemical yield of (*R*,2*R*,3*S*)-**3** determined after their separation from unreacted substrate by column chromatography.

**Table 3** The preparation of (2*R*,3*S*)-diamino acids derivates by hydrolyzing the main products (*R*,2*R*,3*S*)-**3** of the Mannich-type reactions[a]




(*R*,2*R*,3*S*)-**3** (*R*)-**BPB** (2*R*,3*S*)-**4**

| Entry | *R* | **4** | Yield (%)[b] | *Syn*-(2*R*,3*S*)-**4**:*Anti*-(2*R*,3*S*)-**4**[c] |
|---|---|---|---|---|
| 1 | Phenyl | **4a** | 84 | 95 : 5 |
| 2 | 4-Methoxyphenyl | **4b** | 80 | > 99 : 1 |
| 3 | 4-Methyphenyl | **4c** | 81 | > 99 : 1 |
| 4 | 3-Nitrophenyl | **4d** | 87 | 99 : 1 |
| 5 | 2-Chlorophenyl | **4e** | 84 | > 99 : 1 |
| 6 | 2-Furyl | **4f** | 86 | > 99 : 1 |
| 7 | Isobutyl | **4g** | 82 | > 99 : 1 |

[a] 20 mmol of the complex **3** was decomposed in 50 mL MeOH with 20 mL 6 N HCl at 70 °C. [b] Isolated yield of (2*R*,3*R*)-**4** determined after their from reaction mixture by column chromatography. [c] Determined by $^1$H NMR of amino acids **4** after recrystallization from alcohol.



*α*,*β*-Diamino acids were generated by hydrolyzing the Ni(II)-complex **3** at 70 °C with 6 *N* HCl in MeOH. The chiral auxiliary (*R*)-**BPB** was recovered in 90% yield which can be used in the regeneration of Ni(II)-complex of glycine **1**. The target amino acids were then obtained by separation from a $H^+$ form ion exchange resin column in aqueous phase. The result had showed in Table 3. The amino acids (2*R*,3*S*)-**4** were got with excellent yield and *syn*-selectivity, which can be prepared on multi-gram scales (over 20 g).

## Conclusion

In summary, we have successfully developed a general method to synthesize *α*,*β*-diamino acids *via* the asymmetric Mannich-type reactions between Ni(II) complex of glycine with *N*-tosyl imines including aryl-, heteroaryl- and alkyl-derived imines. All the reactions had good reactivity and stereoselectivity within one hour catalyzed by $Et_3N$ in DMF. The absolute configuration of the main products of Mannich reactions was determined to be (*R*,2*R*,3*S*)-configuration by X-ray analysis and *syn*-(2*R*,3*S*)-*α*,*β*-diamino acids were obtained in excellent yield. This asymmetric Mannich-type reaction was a general, mild and high performance method to prepare *α*,*β*-diamino acids on multi-gram scale.

## Experimental

All air or moisture-sensitive reactions were carried out under nitrogen or argon atmosphere and glassware was dried at high temperature and cooled under nitrogen before use. Solvents were purified and stored according to standard procedures. Thin layer chromatography was performed using silica gel plates coated with $GF_{254}$ silica. Plates were visualised using UV light (254 nm). Column chromatography was performed in glass columns with G60 silica (100–200 mesh). Melting points were recorded on a XRC-1 and were uncorrected. $^1$H NMR (300 or 500 MHz) and $^{13}$C NMR (125 MHz) were recorded on a Bruker DRX 300 or Varian 500 spectrometer. *J* values are reported in Hz and TMS as internal standard. Mass spectra were recorded on an ABI Mariner ESI-TOF instrument. X-ray diffraction data were collected in a D/Max-RA automatic diffractometer.

### General procedures for the synthesis of (*R*,2*R*,3*S*)-3

To a solution of complex **1** (5.0 g, 10 mmol) and DMF (20 mL) was added imine (15 mmol) and $NEt_3$ (1.4–1.8 mL, 10–13 mmol) in one portion with vigorous stirring under inert gas at 30 °C. The reaction was monitored by TLC ($EtOAc : CH_2Cl_2$ = 5 : 1). The reaction mixture was stirred for 0.5 h and then quenched with 5% aqueous acetic acid (500 mL). The crystals formed in refrigerator at 0–5 °C overnight. The crystals were filtered off, washed with $H_2O$ and dried in vacuum at 50 °C. Products **3** were obtained by the purification of crude products with silica gel (column 25 × 4 cm, $EtOAc : CH_2Cl_2$ = 3 : 1), and further purified by the recrystallization from EtOH.

**(*R*,2*R*,3*S*)-3a.** Yield red solid (6.1 g, 81%), mp 177–180 °C, $\delta_H$ (500 MHz; $CDCl_3$) 1.41–1.44 (1H, m, Pro-H), 1.73–1.76 (1H, m, Pro-H), 1.85–1.86 (1H, m, Pro-H), 1.91–2.09 (1H, m, Pro-H), 2.10–2.24 (1H, m, Pro-H), 2.30 (3H, s, -$CH_3$), 2.83–2.84 (1H, m, Pro-H), 3.16–3.20 (1H, m, Pro-H), 3.36 (1H, d, *J* 12.5 Hz, $CH_2$Ph), 4.11 (1H, d, *J* 12.5 Hz, $CH_2$Ph), 4.38 (1H, d, *J* 4.8 Hz, *α*-CH), 4.51–4.52 (1H, dd, *J* 4.8 Hz, *J* 9.2 Hz, *β*-CH), 6.66–6.70 (2H, m, ArH), 6.86 (1H, d, *J* 9.2 Hz, ArH), 6.95 (2H, d, *J* 8.0 Hz, ArH), 7.09 (2H, d, *J* 7.4 Hz, ArH), 7.12–7.21 (4H, m, ArH), 7.26–7.33 (5H, m, ArH), 7.37–7.40 (1H, t, ArH), 7.56–7.63 (3H, m, ArH), 7.95 (2H, d, *J* 7.3 Hz, ArH), 8.26 (1H, d, *J* 8.6 Hz, ArH); $\delta_C$ (125 MHz; $CDCl_3$; $Me_4Si$) 21.25, 22.78, 30.39, 57.06, 57.18, 63.61, 70.30, 72.57, 120.55, 123.13, 125.66, 126.32, 126.43, 127.63, 128.22, 128.43, 128.67, 128.74, 129.39, 129.56, 130.30, 131.32, 132.89, 133.18, 133.57, 133.86, 136.18, 138.35, 142.28, 143.24, 173.45, 177.38, 180.13; MS (ESI+) *m*/*z* 757.2 $[M+H]^+$.

**(*R*,2*R*,3*S*)-3b.** Yield red solid (6.0 g, 76%), mp 183–185 °C, $\delta_H$ (500 MHz; $CDCl_3$; $Me_4Si$) 1.46–1.48 (1H, m, Pro-H), 1.88–1.91 (H, m, Pro-H), 2.05–2.08 (1H, m, Pro-H), 2.16–2.18 (1H, m,

Pro-H), 2.32 (3H, s, -$CH_3$), 2.90–2.92 (1H, m, Pro-H), 3.19–3.21 (1H, m, Pro-H), 3.36 (1H, d, *J* 12.6 Hz, $CH_2$Ph), 3.80 (3H, s, -$OCH_3$), 4.13 (1H, d, *J* 12.6 Hz, $CH_2$Ph), 4.34 (1H, d, *J* 4.7 Hz, *α*-CH), 4.45–4.48 (1H, dd, *J* 4.7 Hz, *J* 9.1 Hz, *β*-CH), 6.67–6.68 (2H, m, ArH), 6.78 (1H, d, *J* 9.2 Hz, ArH), 6.84 (2H, d, *J* 8.7 Hz, ArH), 6.97 (2H, d, *J* 8.0 Hz, ArH), 7.00 (2H, d, *J* 8.6 Hz, ArH), 7.12–7.16 (3H, m, ArH), 7.21 (2H, d, *J* 8.6 Hz, ArH), 7.26–7.29 (3H, m, ArH), 7.57–7.58 (3H, m, ArH), 7.97 (2H, d, *J* 7.1 Hz, ArH), 8.25 (1H, d, *J* 8.6 Hz, ArH); $\delta_C$ (125 MHz; $CDCl_3$) 21.27, 22.70, 30.38, 55.26, 56.68, 57.34, 63.69, 70.35, 72.68, 76.75, 77.00, 77.26, 114.00, 120.55, 123.12, 125.68, 126.35, 126.50, 127.61, 128.10, 128.68, 129.36, 129.50, 129.53, 130.27, 131.33, 132.84, 133.22, 133.57, 133.83, 138.47, 142.20, 143.20, 159.86, 173.31, 177.48, 180.13; MS (ESI+) *m/z* 787.2 $[M+H]^+$.

**(*R*,2*R*,3*S*)-3c.** Yield red solid (6.1 g, 79%), mp 183–185 °C, $\delta_H$ (500 MHz; $CDCl_3$) 1.43–1.45 (1H, m, Pro-H), 1.76–1.78(1H, m, Pro-H), 1.85–1.89 (1H, m, Pro-H), 2.01–2.03 (1H, m, Pro-H), 2.15–2.20 (1H, m, Pro-H), 2.32 (3H, s, -$CH_3$), 2.37 (3H, s, -$CH_3$), 2.86–2.90 (1H, m, Pro-H), 3.17–3.21 (1H, m, Pro-H), 3.37 (1H, d, *J* 12.6 Hz, $CH_2$Ph), 4.13 (1H, d, *J* 12.6 Hz, $CH_2$Ph), 4.34 (1H, d, *J* 4.8 Hz, *α*-CH), 4.45–4.48 (1H, dd, *J* 4.8 Hz, *J* 9.1 Hz, *β*-CH), 6.67–6.68 (2H, m, ArH), 6.79 (1H, d, *J* 9.2 Hz, ArH), 6.95–6.98 (4H, m, ArH), 7.11–7.17 (5H, m, ArH), 7.20 (2H, d, *J* 8.3 Hz, ArH), 7.25–7.28 (3H, m, ArH), 7.55–7.61 (3H, m, ArH), 7.96 (2H, d, *J* 7.1 Hz, ArH), 8.26 (1H, d, *J* 8.6 Hz, ArH). $\delta_C$(125 MHz; $CDCl_3$) 21.08, 21.29, 22.55, 30.27, 56.90, 57.24, 63.66, 70.35, 72.56, 76.74, 76.99, 77.25, 120.55, 123.14, 125.69, 126.35, 126.51, 127.65, 128.35, 128.69, 128.76, 128.83, 129.30, 129.36, 129.54, 130.28, 131.34, 132.86, 133.16, 133.20, 133.59, 133.85, 138.06, 138.44, 142.23, 143.22, 173.33, 177.45, 180.07; MS (ESI+) *m/z* 771.2 $[M+H]^+$.

**(*R*,2*R*,3*S*)-3d.** Yield red solid (6.6 g, 82%), mp 194–196 °C, $\delta_H$ (500 MHz; $CDCl_3$; $Me_4Si$) 1.45–1.47 (1H, m, Pro-H), 1.63–1.67 (2H, m, Pro-H), 1.78–1.80 (1H, m, Pro-H), 1.89–1.91 (1H, m, Pro-H), 2.16 (3H, s, Pro-H), 2.27 (3H, s, -$CH_3$), 2.81–2.82 (1H, m, Pro-H), 3.17–3.21 (1H, m, Pro-H), 3.38 (1H, d, *J* 12.7 Hz, $CH_2$Ph), 4.12 (1H, d, *J* 12.7 Hz, $CH_2$Ph), 4.40 (1H, d, *J* 4.9 Hz, *α*-CH), 4.58–4.61 (1H, dd, *J* 4.9 Hz, *J* 8.8 Hz, *β*-CH), 6.69–6.75 (2H, m, ArH), 6.94–6.96 (3H, m, ArH), 7.12–7.15 (1H, m, ArH), 7.17–7.22 (4H, m, ArH), 7.26–7.29 (1H, m, ArH), 7.32–7.33 (1H, m, ArH), 7.39 (1H, d, *J* 7.6 Hz, ArH), 7.57–7.60 (1H, m, ArH), 7.62–7.67 (3H, m, ArH), 7.81 (1H, s, ArH), 7.92 (2H, d, *J* 7.3 Hz, ArH), 8.23 (1H, d, *J* 8.7 Hz, ArH), 8.30 (1H, d, *J* 8.7 Hz, ArH); $\delta_C$ (125 MHz; $CDCl_3$) 21.20, 22.61, 30.45, 56.67, 57.05, 63.67, 70.13, 71.86, 76.74, 77.00, 77.25, 120.81, 123.06, 123.13, 123.23, 125.36, 126.35, 127.53, 128.83, 129.18, 129.41, 129.72, 129.75, 130.65, 131.30, 133.10, 133.44, 134.06, 134.98, 138.12, 138.46, 142.95, 143.40, 148.81, 174.25, 176.82, 180.08; MS (ESI+) *m/z* 802.2 $[M+H]^+$.

**(*R*,2*R*,3*S*)-3e.** Yield red solid (6.7 g, 85%), mp 179–182 °C, $\delta_H$ (500 MHz; $CDCl_3$) 2.10–2.14 (1H, m, Pro-H), 2.16–2.19 (1H, m, Pro-H), 2.20 (3H, s, -$CH_3$), 2.57–2.62 (1H, m, Pro-H), 2.94–2.98 (1H, m, Pro-H), 3.45–3.49 (2H, m, Pro-H), 3.53 (1H, d, *J* 12.7 Hz, $CH_2$Ph), 3.66–3.69 (1H, m, Pro-H), 4.23 (1H, d, *J* 7.4 Hz, $CH_2$Ph), 4.36–4.38 (1H, d, *J* 12.7 Hz, *α*-CH), 5.67–5.68 (1H, m, -NH), 5.75 (1H, d, *J* 7.5 Hz, *β*-CH), 6.36–6.38 (1H, dd, *J* 1.6 Hz, J 8.3 Hz, ArH), 6.55–6.56 (1H, m, ArH), 6.57–6.58 (1H, m, ArH), 6.87–6.89 (1H, m, ArH), 6.91–6.97 (4H, m, ArH), 6.98–7.00 (1H, m, ArH), 7.05–7.09 (1H, m, ArH), 7.09–7.14 (3H, m, ArH), 7.25–7.29 (2H, m, ArH), 7.35–7.45 (2H, m, ArH), 7.54 (2H, d, *J* 7.1 Hz, ArH), 8.05 (2H, d, J 7.2 Hz, ArH), 8.30 (1H, d, *J* 8.6 Hz, ArH). $\delta_C$(125 MHz; $CDCl_3$) 21.25, 23.85, 30.77, 57.36, 63.46, 70.78, 72.08, 76.74, 77.00, 77.25, 120.32, 123.20, 125.84, 126.89, 127.24, 127.47, 128.52, 128.66, 128.79, 128.83, 128.91, 128.98, 129.26, 129.50, 130.11, 131.40, 132.76, 132.98, 133.18, 133.34, 133.64, 133.97, 136.49, 143.17, 143.21, 172.32, 179.92, 180.15; MS (ESI+) *m/z* 791.1 $[M+H]^+$.

**(*R*,2*R*,3*S*)-3f.** Yield red solid (6.3 g, 86%) mp 185–188 °C, $\delta_H$ (500 MHz; $CDCl_3$) 1.64–1.67 (1H, m, Pro-H), 1.87–1.93 (1H, m, Pro-H), 2.21–2.26 (1H, m, Pro-H), 2.28 (3H, s, -$CH_3$), 2.31–2.33 (1H, m, Pro-H), 2.43–2.46 (1H, m, Pro-H), 3,12–3.16 (1H, m, Pro-H), 3.19–3.23 (1H, m, Pro-H), 3.44 (1H, d, *J* 12.7 Hz, $CH_2$Ph), 4.16 (1H, d, *J* 12.6 Hz, $CH_2$Ph), 4.18 (1H, d, *J* 5.1 Hz, *α*-CH), 4.48–4.51 (1H, dd, *J* 5.5 Hz, *J* 9.1 Hz, *β*-CH), 6.21 (1H, d, *J* 3.2 Hz, Furan-H), 6.33–6.34 (1H, m, Furan-H), 6.54–6.60 (2H, m, ArH), 6.77 (1H, d, *J* 9.1 Hz, Furan-H), 7.00 (2H, d, *J* 8.2 Hz, ArH), 7.04 (1H, d, *J* 7.0 Hz, ArH), 7.06–7.09 (2H, m, ArH), 7.16 (1H, d, *J* 7.2 Hz, ArH), 7.20 (1H, d, *J* 5.2 Hz, ArH), 7.22–7.24 (3H, m, ArH), 7.33–7.34 (1H, m, ArH), 7.43–7.52(3H, m, ArH), 7.90 (2H, d, *J* 7.7 Hz, ArH), 8.18 (1H, d, *J* 8.7 Hz, ArH). $\delta_C$(125 MHz; $CDCl_3$) 21.34, 22.86, 30.43, 51,25, 57.00, 63.59, 70.40, 70.65, 76.75, 77.00, 77.25, 109.49, 110.89, 120.56, 123.15, 125.88, 126.15, 126.46,127.82, 128.73, 128.80, 129.07, 129.30, 129.52, 130.31, 131.39, 132.83, 133.09, 133.59, 133.81, 138.00, 142.46, 142.83, 142.84, 143.09, 150.38, 173.76, 177.47, 180.06; MS (ESI+) *m/z* 747.2 $[M+H]^+$.

**(*R*,2*R*,3*S*)-3g.** Yield red solid (6.1 g, 74%), mp 213–215 °C. $\delta_H$ (300 MHz; $CDCl_3$) 1.24–1.28 (1H, m, Pro-H), 1.40–1.44 (1H, m, Pro-H), 1.58 (6H, s, -$CH_3$), 1.67–1.87 (2H, m, Pro-H), 2.02–2.05 (1H, m, -CH), 2.14–2.19 (2H, m, -$CH_2$), 2.31 (3H, s, -Ph$CH_3$), 2.79–2.86 (1H, m, Pro-H), 3.15–3.21 (1H, m, Pro-H), 3.38 (1H, d, *J* 12.0 Hz, -$CH_2$Ph), 4.10 (1H, d, *J* 12.0 Hz, -$CH_2$Ph), 4.38 (1H, d, *J* 4.8 Hz, *α*-CH), 4.49–4.54 (1H, dd, *J* 4.9 Hz, *J* 4.8 Hz, *β*-CH), 6.69–6.70 (2H, m, ArH), 6.83(1H, d, *J* 6.3 Hz, ArH), 6.94–6.97 (2H, m, ArH), 7.08–7.10 (2H, m, ArH), 7.14–7.21 (4H, m, ArH), 7.28–7.31 (3H, m, ArH), 7.58–7.61 (2H, m, ArH), 7.95 (2H, d, *J* 8.4 Hz, ArH), 8.26 (1H, d, *J* 9.0 Hz, ArH). $\delta_C$ (125 MHz; $CDCl_3$) 21.41, 23.64, 30.70, 57.53, 61.25, 63.15, 69.92, 76.75, 77.00, 77.25, 120.80, 124.22, 125.14, 126.23, 126.35, 128.87, 129.07, 129.15, 129.30, 129.52, 129.56, 129.68, 132.69, 132.16, 133.13, 133.34, 134.61, 142.54, 171.62, 177.27, 181.37. MS (ESI+) *m/z* 737.23 $[M+H]^+$; HRMS (ESI+) *m/z*: Calc. for $C_{39}H_{42}N_4NiO_5S$: 737.2297 $[M+H]^+$. Found 737.2316.

### X-Ray crystal structure determination for 3a

The crystalline sample of **3a** recrystallised from ethanol. Data were collected using a D/Max-RA automatic diffractometer with Mo-K*α* graphite monochromated radiation using standard procedures at 293 K. The structure was solved and refined using SHELXS-97.

**X-Ray crystal structure data for 3a.** Empirical formula: $C_{41}H_{38}N_4NiO_5S\ C_2H_5OH$; formula weight: 803.09; crystal dimensions = 0.40 × 0.30 × 0.10 mm; crystal colour: red; crystal system: monoclinic; space group: $P2_1$; lattice parameters: *a* = 9.859(2), *b* = 17.767(2), *c* = 12.361(3) Å, *β* = 91.25(3), *V* = 2164.7(8) $Å^3$;

$Z = 2$; $\mu = 0.546$ mm$^{-1}$, $D_c = 1.415$ Mg m$^{-3}$; $R_1 = 0.1003$, $\omega R_2$ ($I > 2\sigma(I)$) = 0.1919, $R_2 = 0.0678$, $\omega R_2$ (all data) = 0.1661; CCDC number: 777524.

### General procedures for the synthesis of (2*R*,3*S*)-4

Complex **3** (15.0–16.0 g, 20 mmol) was decomposed by refluxing with methanolic solution of 6 *N* HCl (20 mL) until the solution was clean. Then the solution was evaporated to dryness. Water (50 mL) was added to the residue and the insoluble material was filtered, washed with water and dried to afford (*R*)-BPB·HCl. To the aqueous layer a solution of aq. $NH_3$ was added to pH 6 and the solution was extracted with $CHCl_3$ several times. Amino acid **4** was recovered from the solution by the ion-exchange technique ($H^+$ form).

**(2*R*,3*S*)-4a.** Yield white solid (5.6 g, 84%), mp 187–190 °C, $[\alpha]_D^{30}$ −12.9 (*c* 1, $H_2O$). $\delta_H$ (500 MHz; DMSO-$d_6$) 2.32 (3H, s, -$CH_3$), 3.21 (1H, d, *J* 5.3 Hz, $\alpha$-CH), 4.61–4.62 (1H, d, *J* 5.3 Hz, $\beta$-CH), 7.17–7.19 (5H, m, ArH), 7.22 (2H, d, *J* 8.1 Hz, ArH), 7.47–7.52 (2H, m, ArH). $\delta_C$ (125 MHz; DMSO) 20.74, 55.67, 56.85, 126.16, 127.32, 127.77, 127.84, 129.17, 136.96, 138.29, 142.22, 168.59; MS (ESI+) *m*/*z* 357.1 $[M+Na]^+$.

**(2*R*,3*S*)-4b.** Yield white solid (5.8 g, 80%), mp 186–188 °C, $[\alpha]_D^{30}$ −23.4 (*c* 1, $H_2O$). $\delta_H$ (500 MHz; DMSO-$d_6$) 2.33 (3H, S, -$CH_3$), 3.16–3.17 (1H, d, *J* 5.0 Hz, $\alpha$-CH), 3.69 (3H, s, -$OCH_3$), 4.55–4.56 (1H, d, *J* 5.0 Hz, $\beta$-CH), 6.70–6.72 (2H, m, ArH), 7.05–7.07 (2H, m, ArH), 7.22–7.24 (2H, m, ArH), 7.48–7.50 (2H, m, ArH). $\delta_C$ (125 MHz; DMSO) 20.85, 55.01, 55.22, 56.01, 113.44, 126.26, 128.61, 129.15, 129.29, 138.37, 142.27, 158.80, 168.27; MS (ESI+) *m*/*z* 365.1 $[M+H]^+$.

**(2*R*,3*S*)-4c.** Yield white solid (5.6 g, 81%), mp 183–185 °C, $[\alpha]_D^{30}$ −15.5 (*c* 1, $H_2O$). $\delta_H$ (500 MHz; $D_2O$ + HCl) 2.23 (s, 3H, -Ph$CH_3$), 2.33 (s, 3H, -$CH_3$), 3.14–3.15 (1H, d, *J* 5.0 Hz, $\alpha$-CH), 4.54–4.55 (1H, d, *J* 5.0 Hz, $\beta$-CH), 6.96–6.97 (2H, d, *J* 5.0 Hz, ArH), 7.02–7.04 (2H, d, *J* 10.0 Hz, ArH), 7.23–7.24 (2H, d, *J* 5.0 Hz, ArH), 7.49–7.51 (2H, d, *J* 10.0 Hz, ArH). $\delta_C$ (125 MHz; DMSO-$d_6$) 20.58, 20.85, 55.22, 56.31, 126.26, 127.86, 128.53, 129.30, 133.74, 136.71, 138.32, 142.35, 168.27. MS (ESI+) *m*/*z* 349.1 $[M+H]^+$.

**(2*R*,3*S*)-4d.** Yield white solid (6.6 g, 87%), mp 194–196 °C, $[\alpha]_D^{30}$ −38.0 (*c* 1, $H_2O$). $\delta_H$ (500 MHz; DMSO-$d_6$) 2.25 (3H, s, -$CH_3$), 3.38 (1H, d, *J* 5.3 Hz, $\alpha$-CH), 4.82 (1H, d, *J* 5.3 Hz, $\beta$-CH), 7.13 (2H, d, *J* 8.1 Hz, ArH), 7.41–7.46 (3H, m, ArH), 7.60 (1H, d, *J* 7.6 Hz, ArH), 7.90 (1H, s, ArH), 8.00 (1H, d, *J* 8.1 Hz, ArH). $\delta_C$ (125 MHz; DMSO-$d_6$) 20.70, 55.87, 56.50, 122.30, 122.88, 126.17, 129.20, 134.84, 137.99, 138.69, 142.40, 147.30, 168.17. MS (ESI+) *m*/*z* 380.1 $[M+H]^+$.

**(2*R*,3*S*)-4e.** Yield white solid (6.3 g, 84%), mp 179–182 °C, $[\alpha]_D^{30}$ −9.8 (*c* 1, $H_2O$). $\delta_H$ (500 MHz; DMSO-$d_6$) 2.25–2.27 (3H, d, *J* 10.0 Hz, -$CH_3$), 3.37–3.38 (2H, d, *J* 5 Hz, $\alpha$-CH), 4.77–4.78 (1H, d, *J* 5.0 Hz, $\beta$-CH), 7.12–7.14 (2H, d, *J* 10.0 Hz, ArH), 7.40–7.47 (3H, m, ArH), 7.57–7.59 (1H, d, *J* 5.0 Hz, ArH), 7.88 (1H, m, ArH), 8.00–8.02 (1H, m, ArH). $\delta_C$ (125 MHz; DMSO-$d_6$) 20.67, 56.00, 56.61, 122.25, 122.85, 126.16, 129.43, 134.78, 138.78, 138.01, 138.80, 142.37, 147.31, 168.32; MS (ESI+) *m*/*z* 369.1 $[M+H]^+$.

**(2*R*,3*S*)-4f.** Yield white solid (5.6 g, 86%), mp 185–188 °C, $[\alpha]_D^{30}$ −12.6 (*c* 1, $H_2O$). $\delta_H$ (500 MHz; DMSO-$d_6$) 2.35 (3H, s, -$CH_3$), 3.29 (1H, d, J 4.9 Hz, $\alpha$-CH), 4.81 (1H, d, *J* 4.9 Hz, $\beta$-CH), 6.12–6.14 (1H, m, Furan-H), 6.22 (1H, s, Furan-H), 7.29 (2H, d, *J* 8.0 Hz, ArH), 7.38 (1H, d, *J* 7.1 Hz, Furan-H), 7.58 (2H, d, *J* 8.1 Hz, ArH). $\delta_C$ (125 MHz; DMSO-$d_6$) 20.82, 51.29, 54.32, 108.25, 110.08, 126.23, 129.23, 129.28, 138.27, 142.37, 142.44, 150.28, 168.65. MS (ESI+) *m*/*z* 324.1 $[M+H]^+$.

**(2*R*,3*S*)-4g.** Yield white solid (5.2 g, 82%), mp 213–215 °C, $[\alpha]_D^{30}$ −19.8 (*c* 1, $H_2O$). $\delta_H$ (300 MHz; $D_2O$ + HCl) 0.11–0.13 (3H, d, *J* 10.0 Hz, -$CH_3$), 0.34–0.36 (3H, d, *J* 10.0 Hz, -$CH_3$), 0.83–0.87 (1H, m, -CH), 1.00–1.08 (2H, m, -$CH_2$), 2.08 (3H, s, -Ph$CH_3$), 3.46–3.48 (1H, m, $\beta$-CH), 3.82–3.83 (1H, d, *J* 5.0 Hz, $\alpha$-CH), 7.09–7.12 (2H, d, *J* 15.0 Hz, ArH), 7.45–7.47 (2H, d, *J* 10.0 Hz, ArH). $\delta_C$ (125 MHz; $D_2O$ + HCl) 23.23, 23.48, 24.37, 26.46, 43.00, 54.24, 59.20, 129.83, 132.86, 137.87, 148.22, 172.28; HRMS (ESI+) *m*/*z*: Calc. for $C_{14}H_{22}N_2O_4S$: 337.1198 $[M+Na]^+$. Found 337.1193.

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