Tetrahedron: *Asymmetry* 20 (2009) 2629–2634

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Michael addition reactions between various nucleophilic glycine equivalents and (*S*,*E*)-1-enoyl-5-oxo-*N*-phenylpyrrolidine-2-carboxamide, an optimal type of chiral Michael acceptor in the asymmetric synthesis of β-phenyl pyroglutamic acid and related compounds

Trevor K. Ellis *, Hisanori Ueki, Rohit Tiwari, Vadim A. Soloshonok *

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, USA

ARTICLE INFO

Article history:
Received 9 September 2009
Accepted 7 October 2009
Available online 10 November 2009

ABSTRACT

(*S*)-5-Oxo-*N*-phenyl-1-[(*E*)-3-phenylacryloyl]pyrrolidine-2-carboxamide, easily prepared from inexpensive and readily available, in both enantiomeric forms, glutamic/pyroglutamic acid was designed as an optimal type of chiral Michael acceptor for reactions with a series of nucleophilic glycine equivalents. A study of the corresponding Michael addition reactions revealed that the new generation of modular glycine derivatives, as a counterpart to the Michael acceptor, provides for operationally convenient preparation of β-phenyl pyroglutamic acids and related compounds with virtually complete chemical and stereochemical outcomes.

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1. Introduction

In the post-genomic era, the synthetic availability of tailor-made α-amino acids[1] of desired structural and functional complexity has become of critical importance in the development of a new paradigm of peptide-based approaches to the treatment of dysfunction in human health.[2] Of particular biological importance are α-amino acids containing substituents at the β-position.[3] Such derivatives substantially restrict the number of possible conformations in the χ-(chi)-space,[4] thus providing a powerful tool for the preparation of peptides and peptidomimetics with a pre-supposed 3-D structure. However, the preparation of β-substituted-α-amino acids, containing at least two stereogenic centers, presents a significant synthetic challenge in terms of control of the absolute as well as relative stereochemistry.

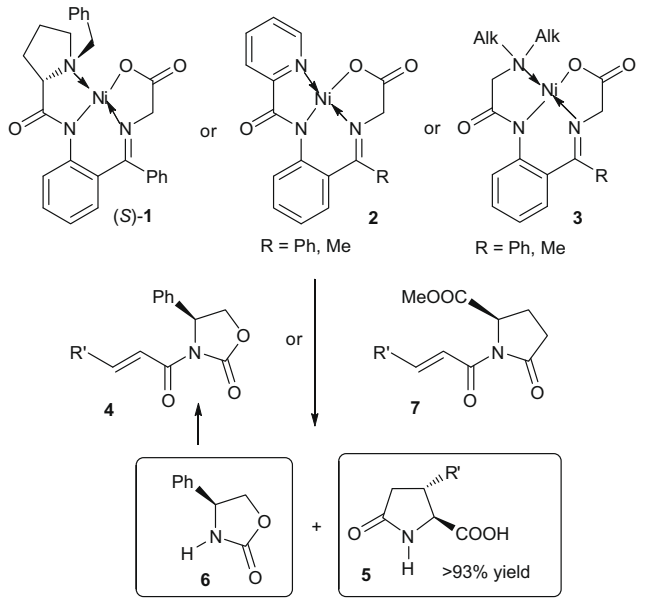
Recently, in response to the growing demand for β-substituted-α-amino acids, Kobayashi et al.,[5] Kazmaier et al.,[6] Szabó et al.,[7] Ohfune et al.,[8] Ooi and Maruoka et al.[9] have developed synthetically useful and methodologically elegant approaches to various structural types of amino acids, which belong to this family of tailor-made α-amino acids. The interest of our group in this area is the development of operationally convenient[10] methods for the preparation of enantiomerically pure sterically constrained α-amino acids in general,[11] and β-substituted glutamic/pyroglutamic acids in particular. Our choice for this type of compounds as synthetic targets is based on the proven feasibility of their transformation to a generalized family of the corresponding χ-(chi)-constrained five-carbon-atom amino acids including glutamines, prolines, ornithines, and arginines.[12] Therefore, one may envision that the development of practical, simple, and stereochemically reliable access to β-substituted glutamic/pyroglutamic acids will also allow the preparation of various types of other β-substituted amino acids and related biologically important compounds.[12]

2. Results and discussion

Recently, we have developed a new concept of organic base-catalyzed, room-temperature Michael addition reactions between nucleophilic glycine equivalents and α,β-unsaturated carboxylic acid derivatives as an operationally convenient and generalized method for preparing β-substituted glutamic/pyroglutamic acids.[13] In particular, we demonstrated that *N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones[14] **4** (Scheme 1) can be successfully used as Michael acceptors in these organic base-catalyzed reactions, regardless of the fact that the usual application of derivatives **4** as chiral electrophiles necessitates the presence of metals as chelating agents.[15] The most important feature in the concept of organic base-catalyzed Michael addition reactions is the *topographical* nature of the observed stereochemical outcome.[16] A beneficial consequence of this extremely rare mode of stereo-control in asymmetric synthesis, is that the stereochemical outcome of these Michael addition reactions does not depend on the structure of the starting nucleophilic glycine equivalent or Michael acceptor.[16] Thus, glycine derivatives **1**,[17,18], **2a**,**b**[19,20], and **3a**,**b**[21] (Scheme 1) can be used as nucleophilic glycine equivalents in the addition reactions

* Corresponding authors. Tel.: +1 405 325 3820; fax: +1 405 325 6111 (T.K.E.).
E-mail address: tellis@ou.edu (T.K. Ellis).

0957-4166/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2009.10.006



Scheme 1.

with oxazolidin-2-ones **4**. Similarly, the structure of the chiral auxiliary in **4** can also be modified without any significant effect on the stereochemical outcome of the corresponding Michael addition reactions. In particular, Michael acceptors **7**, derived from very inexpensive esters of naturally occurring pyroglutamic acid, can be efficiently used in the addition reactions with different types of glycine derivatives **1**, **2a**,**b** and **3a**,**b**.[22,23] Taking into account that natural (*S*)-pyroglutamic acid, as well its (*R*)-enantiomer, are considerably less expensive when compared with Evans-type oxazolidin-2-one auxiliary **6**,[24] the recovery of (*S*)- or (*R*)-pyroglutamic acids is not an issue, thereby simplifying the procedure for isolation of the target β-substituted amino acids **5**.

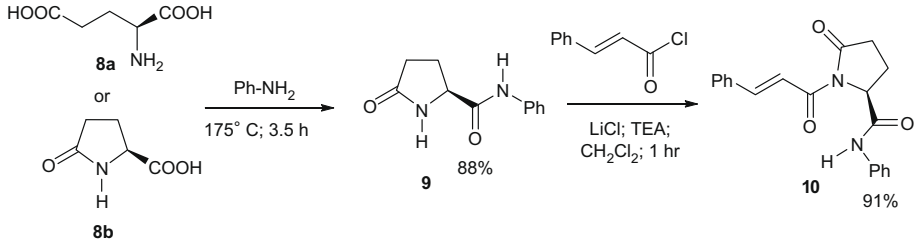
However, despite these advantageous characteristics of ester-type Michael acceptors **7**, we found that the physical properties of derivatives **7** present some operational inconvenience. Most of the esters of pyroglutamic acid are liquids (at ambient temperatures) while the Michael acceptors **7** derived from them have very low crystallinity. These factors make the derivatives **7** relatively unstable upon storage under regular laboratory conditions and inconvenient to manipulate. Therefore, we decided to find other derivatives of pyroglutamic acid to overcome these shortcomings. After consideration of several possibilities, our choice eventually fell on anilide-type derivatives **10** (Scheme 2), which possess excellent physical properties. Moreover, compounds of type **10** are even less expensive than esters **7**, as they can be prepared simply by heating glutamic **8a** or pyroglutamic acid **8b** with aniline to form the corresponding amide **9** in high (88%) chemical yield.[25] Further transformation of anilide **9** to the target Michael acceptor **10** can also be performed under the standard conditions previously reported by us.[14]

According to X-ray analysis (Fig. 1), Michael acceptor **10** exists exclusively in the *s-cis* conformation due to the strong electrostatic repulsive interactions between the 2-enoyl and 5-oxo-pyrrolidine carbonyl groups. Furthermore, the planes of the 2-enoyl and 5-oxo-pyrrolidine moieties are nearly coplanar, while the *N*-(phenyl)carboxamide residue is pointed at about an angle of 90° relative to the 2-enoyl functionality. As one can reasonably assume, in this position, being pointed away from the 2-enoyl residue, the *N*-(phenyl)carboxamide group cannot exercise any effective stereo-control over the face selectivity of Michael acceptor **10**. However, due to the topographical nature[16] of the stereochemical outcome in these Michael addition reactions, the virtually perpendicular position of the *N*-(phenyl)carboxamide group to the 2-enoyl residue, is efficient to completely prevent one side of Michael acceptor **10** (as well as of types **4** and **7**) from mutual approach with enolates, derived from planar Ni(II) complexes **1**–**3**, to a sufficient close proximity for the addition reaction to take place. Therefore, the observed geometry of compound **10** met our expectations for an efficient Michael acceptor.

First, we studied the addition reaction between this new Michael acceptor with picolinic acid derived Ni(II) complexes **11** and **12** (nucleophilic glycine equivalents of type **2**, Scheme 1). As shown in Scheme 3, the reactions were conducted at room temperature in commercial-grade DMF, and in the presence of catalytic (15 mol %) amounts of DBU. The reaction of benzophenone-derived complex **11** with **10** proceeded very sluggishly, with it being less than 50% complete after 24 h. The corresponding product **13** was isolated in 30% yield, only for the purpose of structural and stereochemical characterization. By contrast, the acetophenone-derived complex **12**, containing the less sterically shielded glycine moiety, reacted with Michael acceptor **10** substantially faster allowing the reaction to be completed in 4.5 h and furnishing the product **14** in high (93%) yield. However, the isolation of product **14** should be accomplished in an expeditious manner as compound **14** was found to be partially soluble in DMF/water mixture.

Overall, the Michael acceptor **10** was found to be less reactive, when compared to derivatives **4** and **7** (Scheme 1) in the additions with **11** and **12**, and therefore, these reactions can be considered less synthetically attractive.

Next, we investigated the reaction of the Michael acceptor **10** with a series of a new generation of achiral nucleophilic glycine equivalents (type **3**, Scheme 1) **15** and **16**. The addition reactions (Scheme 4) were conducted under standard conditions at ambient temperatures in the presence of 15 mol % of DBU. Dimethyl/ and diethylamine/benzophenone-derived complexes **15a** and **15b**, respectively, showed substantially improved reaction rates, when compared with the reactions of **11** and **12**, allowing a complete conversion of the starting materials in less than 1 h (Table 1, entries 1 and 2). However, the isolation of the corresponding products **17a**,**b** was complicated by their physical properties. Thus, compounds **17a**,**b** were precipitated as very small, fine particles significantly hindering their isolation via filtration. Due to this property, the isolated yields of products **17a**,**b** were only 70% and 75%, respectively.



Scheme 2.

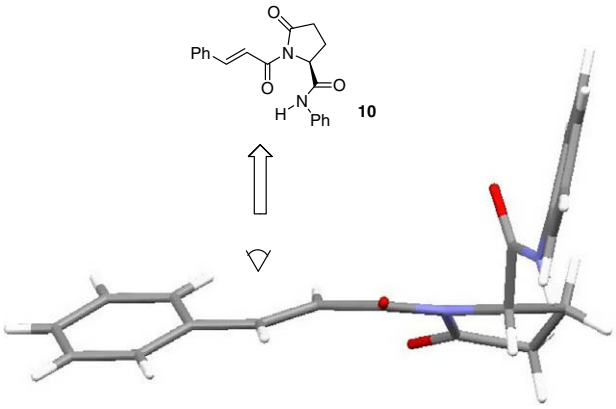
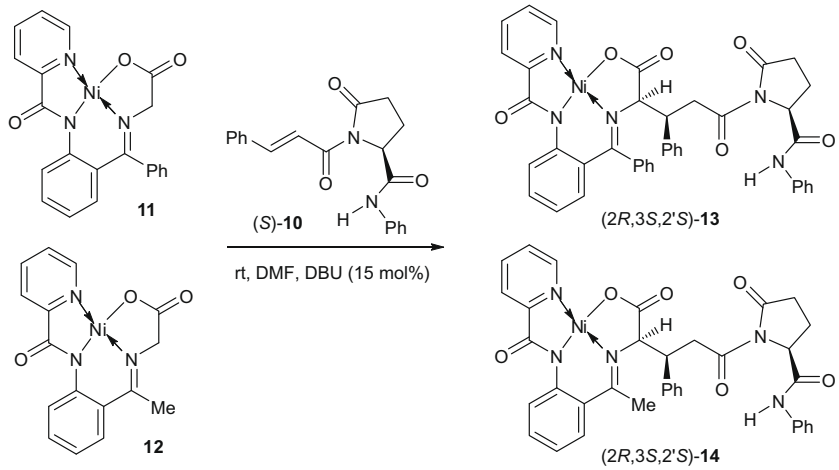


Figure 1. X-ray structure of Michael acceptor **10**.

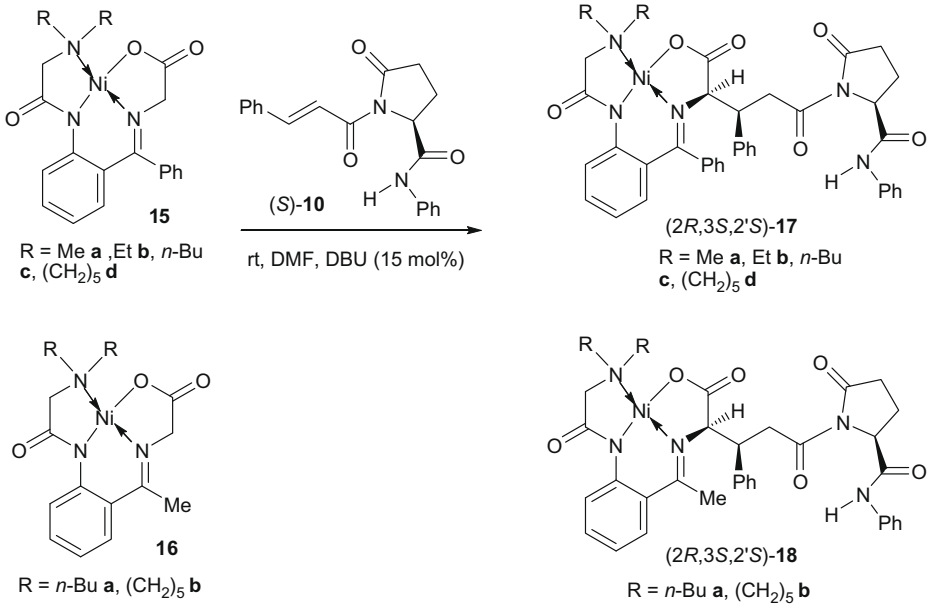
Table 1

Entry	Complex	Time (min)	Conversion (%)	Yield (%)
1	**15a**	60	>98	70
2	**15b**	60	>98	75
3	**15c**	20	>98	>95
4	**15d**	20	>98	>95
5	**16a**	25	>98	>95
6	**16b**	25	>98	>95

On the other hand, the di-*n*-butylamine/ and piperidine/benzophenone-derived complexes **15c** and **15d**, respectively, demonstrated even higher reactivity toward Michael acceptor **10**, allowing the formation of the corresponding addition products **17c**,**d** in less than 20 min. Compounds **17c**,**d** were found to be completely insoluble in the DMF/water mixture and precipitated as a



Scheme 3.



Scheme 4.

well-formed crystals leading to their isolation in quantitative chemical yields.

With these successful results in hand, we studied the reactions of Michael acceptor **10** with di-*n*-butylamine/ and piperidine/acetophenone-derived complexes **16a**,**b**, respectively. The corresponding additions occurred at rates slightly slower, when compared with **15c**,**d**, without compromising the virtually complete chemical and stereochemical outcome furnishing products **18a**,**b** in quantitative yield.

The absolute (2*R*,3*S*,2′*S*)-configuration of the β-phenyl-substituted glutamic acid residue in **17c** was determined by the isolation of the corresponding pyroglutamic acid (2*R*,3*S*)-**20** (see Scheme 5). Consequently the (2*R*,3*S*,2′*S*) stereochemistry of products **13** and **14** and **17a**,**b**,**d** and **18a**,**b** was assigned based on similarity of their spectral as well as chiroptical data to complex **17c**. It should be noted that in contrast to **4** and similarly to **7** (Scheme 1), the Michael acceptor (*S*)-**10** induced the α-(*R*) absolute configuration in the addition products **13**,**14**, **17a**–**d,** and **18a**,**b**. This difference in the stereochemical outcome is simply due to the Cahn–Ingold–Prelog priority rules[26] as compounds **4**, **7,** and **10** have the same relative stereochemistry in terms of the position of the substituent above or beneath the oxazolidin-2-one or pyrrolidin-2-one ring, respectively.

The isolation of the β-phenyl pyroglutamic acid **20** (Scheme 5) from the addition products was demonstrated by disassembling complex **17c** under the standard conditions: heating of **17c** in methanol/3 M HCl, followed by neutralization of the reaction mixture with 8 M ammonia and isolation of acid **20** using Dowex ion-exchange resin.[21] Pyroglutamic acid **20** was obtained in 93% yield, along with quantitative recovery of ligand **21**, which can be recycled and converted back to the corresponding Ni(II) complexes **15c**.[21d] Recovery of the corresponding chiral auxiliary, (*S*)-5-oxo-*N*-phenylpyrrolidine-2-carboxamide, was not studied. The (2*R*,3*S*)-absolute configuration of acid **20** was confirmed by comparison of its spectroscopic and chiroptical data with the literature data.[16b,18e,21d]

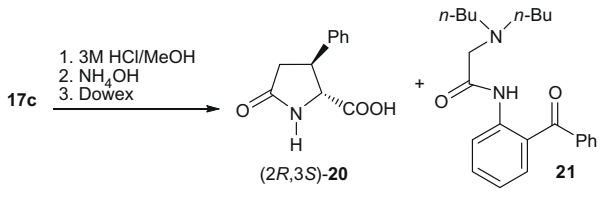
3. Conclusion

In conclusion, we have demonstrated that inexpensive, and readily available in both enantiomeric forms Michael acceptor **10** can be efficiently used in the corresponding addition reactions with the new generation of achiral nucleophilic glycine equivalents **15c**,**d**, **16a**,**b** and chiral glycine derivative (*S*)-**1**. High chemical and stereochemical yields as well as operationally convenient conditions[10] for each synthetic step render these Michael addition reactions as a practical and scalable generalized approach for the preparation of enantiomerically pure β-phenyl glutamic/pyroglutamic acid and related compounds.

4. Experimental

4.1. General methods

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification.



Scheme 5.

All of the reactions were carried out under atmospheric conditions without any special caution to exclude air. Unless indicated ^{1}H and ^{13}C NMR spectra, were taken in $CDCl_3$ solutions at 299.95 and 75.42 MHz, respectively. Chemical shifts refer to TMS as the internal standard.

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, and ^{13}C NMR, high-resolution mass spectrometry (HRMS-ESI), melting point, and optical rotation, when applicable.

4.1.1. (*S*)-5-Oxo-*N*-phenyl-1-((*E*)-3-phenylacryloyl)pyrrolidine-2-carboxamide 10

Compound **10** was prepared according to the general procedure previously described in Ref. 14. Yield (from glutamic or pyroglutamic acid) 87%. Mp 148.8 °C. ^{1}H NMR δ 2.25 (1H, m), 2.40 (1H, t, J = 9.3 Hz), 2.58 (1H, dq, J = 9.2, 2.4 Hz), 2.99 (1H, m), 4.99 (1H, dd, J = 8.4, 2.1 Hz), 7.05 (1H, t, J = 8.7 Hz), 7.24 (1H, t, J = 6.9 Hz), 7.37–7.41 (3H, m), 7.50 (2H, dd, J = 8.7, 1.2 Hz), 7.58–7.61 (2H, m), 7.92 (2H, q, J = 15.9 Hz), 8.81 (1H, s). ^{13}C NMR δ 21.5, 32.9, 60.1, 118.2, 118.3, 119.9, 120.1, 124.7, 128.7, 128.9, 129.1, 134.6, 137.5, 167.3, 168.1, 175.5. HRMS [M+Na] found m/s 357.1269, calcd for $C_{20}H_{18}N_2NaO_3$ is 357.1209. $[\alpha]_D^{25} = -42.5$ (c 0.0008, $CHCl_3$).

4.2. The Michael addition reactions between the pyroglutamic acid derived amide of cinnamic acid 10 and nucleophilic glycine equivalents 1, 11, 12, 15, 16

4.2.1. General procedure

To a flask containing **1**, **11**, **12**, **15** or **16** (1.00 equiv), (*S*)-5-oxo-*N*-phenyl-1-((*E*)-3-phenylacryloyl)pyrrolidine-2-carboxamide (1.05 equiv)and 2.0 mL (per 1 g of the corresponding Ni(II) complex) of DMF, DBU (15 mol %) was added to the reaction mixture, which was stirred at room temperature and monitored by TLC. After the disappearance of starting glycine equivalent (monitoring by TLC), the reaction mixture was poured into a beaker containing 100 mL ice water. After the ice had melted, the corresponding product was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high (see text) chemical yields.

4.2.1.1. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenylpyrrolidine-2′-carboxamide] glutamic acid Schiff base with 2-(picolinoylamino)-benzophenone 13. Mp 163.2 °C. ^{1}H NMR δ 1.42 (1H, d, J = 6.6 Hz), 1.97–2.27 (3H, m), 2.42 (1H, m), 2.77 (1H, m), 3.48 (1H, t, J = 5.4 Hz), 4.57 (1H, dd, J = 8.4, 1.8 Hz), 4.66 (1H, d, J = 4.8 Hz), 6.72–6.80 (2H, m), 7.02–7.13 (3H, m), 7.16–7.60 (13H, m), 7.69 (1H, d, J = 7.2 Hz), 7.85 (2H, m), 8.59 (1H, s), 8.62 (2H, d, J = 6.3 Hz). ^{13}C NMR δ 21.3, 32.3, 37.7, 44.6, 59.7, 74.3, 121.3, 123.5, 124.4, 126.4, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.6, 128.8, 128.9, 129.2, 129.3, 129.7, 129.8, 130.0, 130.2, 130.3, 133.2, 133.5, 134.6, 137.9, 139.0, 139.9, 143.0, 146.5, 153.1, 168.6, 168.9, 171.6, 172.3, 175.0, 177.2. HRMS [M+Na] found m/s 772.1743, calcd for $C_{41}H_{33}N_5NaNiO_6$ is 772.1676. $[\alpha]_D^{25} = -413.2$ (c 0.006, $CHCl_3$).

4.2.1.2. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenylpyrrolidine-2′-carboxamide] glutamic acid Schiff base with 2-(picolinoylamino)-acetophenone 14. Mp 193.6 °C. ^{1}H NMR δ 2.18 (1H, m), 2.26 (2H, m), 2.49 (1H, d, J = 8.6 Hz), 2.81 (3H, s), 3.55 (1H, d, J = 5.6 Hz), 3.77 (1H, m), 4.40 (1H, dd, J = 8.6, 1.4 Hz), 4.86 (2H, m), 6.74 (1H, t, J = 6.3 Hz), 6.92 (1H, m), 7.70 (3H, m), 7.29 (4H, m), 7.44 (3H, m), 7.64 (2H, d, J = 6.2 Hz), 7.69 (1H, d, J = 8.2 Hz), 7.86 (1H, t, J = 9.4 Hz), 8.49 (1H, m), 9.12 (1H, s). ^{13}C NMR δ 18.7, 22.2, 29.3, 32.1, 38.0, 44.8, 59.7, 74.3, 119.9, 121.8, 123.5, 124.0, 124.3, 126.3, 127.3, 127.8, 128.2, 129.0, 130.2, 130.5, 132.6, 138.2, 139.0, 139.8, 141.9, 146.5, 153.3, 168.6, 169.4, 173.3, 175.3, 177.8. HRMS

[M+Na] found *m/s* 710.1449, calcd for $C_{36}H_{31}N_5NaNiO_6$ is 710.1520. $[\alpha]_D^{25} = -582.6$ (*c* 0.0007, $CHCl_3$).

4.2.1.3. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenyl-pyrrolidine-2′-carboxamide] glutamic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-dimethylamino-acetamide 17a. Mp 177 °C. ^{1}H NMR δ 1.62 (3H, s), 1.88–2.18 (2H, m), 2.26–2.45 (1H, m), 2.37 (3H, m), 2.45–2.80 (2H, m), 2.56 (1H, d, *J* = 15.8 Hz), 3.20 (1H, d, *J* = 15.5 Hz), 3.28–3.60 (2H, m), 4.43 (1H, d, *J* = 4.98 Hz), 4.49 (1H, dd, *J* = 8.70, 2.35 Hz), 6.64–6.72 (2H, m), 6.96–7.06 (2H, m), 7.08–7.48 (14H, m), 8.40 (1H, d, *J* = 8.50 Hz), 8.74 (1H, br s). ^{13}C NMR δ 21.3, 32.1, 37.7, 44.1, 47.4, 49.5, 59.4, 66.9, 73.0, 119.7, 121.0, 123.1, 124.1, 126.7, 127.0, 127.8, 128.0, 128.7, 128.8, 129.0, 129.1, 129.8, 130.2, 132.7, 133.4, 134.0, 137.9, 139.3, 142.5, 168.5, 171.2, 171.8, 174.6, 174.9, 177.2. HRMS [M+Na] found *m/s* 752.2152, calcd for $C_{39}H_{37}N_5NaNiO_6$ is 752.1990. $[\alpha]_D^{25} = -1088$ (*c* 0.05, $CHCl_3$).

4.2.1.4. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenyl-pyrrolidine-2′-carboxamide] glutamic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-diethylamino-acetamide 17b. Mp 183 °C. ^{1}H NMR δ 0.74 (3H, t, *J* = 7.03 Hz), 1.65 (3H, t, *J* = 7.03 Hz), 1.80–2.40 (6H, m), 2.50–2.80 (2H, m), 2.68 (1H, d, *J* = 15.5 Hz), 3.29 (1H, d, *J* = 15.8 Hz), 3.33–3.68 (3H, m), 4.41 (1H, d, *J* = 4.10 Hz), 4.44 (1H, m), 6.64–6.72 (2H, m), 6.96–7.08 (2H, m), 7.10–7.55 (14H, m), 8.30 (1H, d, *J* = 8.50 Hz), 8.77 (1H, br s). ^{13}C NMR δ 5.78, 12.7, 21.3, 32.1, 37.9, 44.3, 47.9, 50.7, 59.4, 62.8, 72.9, 119.6, 121.0, 123.3, 124.0, 126.8, 127.1, 127.8, 128.0, 128.7, 128.8, 129.0, 129.1, 129.9, 130.0, 132.6, 133.4, 133.9, 138.0, 139.4, 142.3, 168.6, 171.2, 171.8, 175.0, 175.3, 177.1. HRMS [M+Na] found *m/s* 780.2086, calcd for $C_{41}H_{41}N_5NaNiO_6$ is 780.2305. $[\alpha]_D^{25} = -416$ (*c* 0.05, $CHCl_3$).

4.2.1.5. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenyl-pyrrolidine-2′-carboxamide] glutamic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 17c. Mp 142.3 °C. ^{1}H NMR δ 0.93 (3H, t, *J* = 7.2 Hz), 0.97 (3H, t, *J* = 6.9 Hz), 1.13–1.31 (4H, m), 1.35–1.53 (2H, m), 1.60–1.89 (2H, m), 1.92–2.23 (4H, m), 2.30–2.47 (3H, m), 2.68–2.91 (3H, m), 3.42–3.56 (4H, m), 3.64 (1H, m), 3.35 (1H, d, *J* = 5.1 Hz), 4.51 (1H, d, *J* = 6.6 Hz), 6.73–6.79 (3H, m), 7.10–7.15 (2H, m), 7.26–7.54 (13H, m), 8.22 (1H, s), 8.38 (1H, d, *J* = 9.0 Hz). ^{13}C NMR δ 13.9, 14.1, 20.4, 20.8, 21.2, 23.1, 29.3, 29.7, 32.4, 38.3, 44.7, 54.5, 57.4, 59.6, 63.8, 118.8, 119.8, 121.1, 123.5, 124.5, 127.0, 127.6, 128.0, 128.4, 128.9, 129.0, 129.2, 129.3, 129.9, 130.1, 132.8, 134.0, 137.6, 139.6, 142.6, 168.0, 171.0, 172.9, 174.9, 175.7, 176.7. HRMS [M+Na] found *m/s* 836.2889, calcd for $C_{45}H_{44}N_5NaNiO_6$ is 836.2929. $[\alpha]_D^{25} = -2270.0$ (*c* 0.0011, $CHCl_3$).

4.2.1.6. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenyl-pyrrolidine-2′-carboxamide] glutamic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 17d. Mp 186.1 °C. ^{1}H NMR δ 1.46 (7H, m), 2.02 (1H, q, *J* = 6.6 Hz), 2.19 (2H, m), 2.40 (2H, m), 2.77 (1H, m), 2.92 (1H, d, *J* = 6.8 Hz), 3.21 (3H, m), 3.52 (2H, m), 3.65 (2H, t, *J* = 12.6 Hz), 4.44 (1H, d, *J* = 3.9 Hz), 4.51 (1H, d, *J* = 7.8 Hz), 6.73 (2H, m), 7.07 (2H, dt, *J* = 17.1, 6.3 Hz), 7.39 (13H, m), 8.39 (1H, d, *J* = 8.4 Hz), 8.49 (1H, m), 9.15 (1H, s). ^{13}C NMR δ 19.9, 21.3, 22.8, 32.3, 38.0, 44.4, 53.5, 54.6, 55.6, 56.1, 59.6, 73.1, 119.8, 123.4, 124.4, 125.9, 127.4, 128.2, 128.9, 129.0, 129.2, 129.3, 129.6, 129.9, 130.3, 132.7, 133.7, 134.0, 137.9, 139.5, 168.4, 171.2, 172.4, 175.0, 175.4, 177.1. HRMS [M+Na] found *m/s* 792.2393, calcd for $C_{42}H_{41}N_5NaNiO_6$ is 792.2308. $[\alpha]_D^{25} = -405.2$ (*c* 0.0007, $CHCl_3$).

4.2.1.7. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenyl-pyrrolidine-2′-carboxamide] glutamic acid Schiff base with *N*-(2-acetyl-phenyl)-2-dibutylamino-acetamide 18a. Mp 167 °C. ^{1}H NMR δ 0.87–1.00 (6H, m), 1.00–1.20 (1H, m), 1.30–1.50 (3H, m), 1.70–2.50 (9H, m), 2.60–2.95 (4H, m), 2.70 (3H, s), 3.19 (1H, d, *J* = 14.7 Hz), 3.49 (1H, dd, *J* = 19.3, 2.48 Hz), 3.61 (1H, m), 4.38 (1H, dd, *J* = 19.3, 11.3 Hz), 4.56 (1H, d, *J* = 4.67 Hz), 4.78 (1H, dd, *J* = 7.70, 2.75 Hz), 6.90–7.06 (2H, m), 7.14–7.32 (3H, m), 7.36–7.45 (2H, m), 7.45–7.60 (5H, m), 7.63 (1H, d, *J* = 8.26 Hz), 8.22 (1H, d, *J* = 8.52 Hz), 8.83 (1H, br s). ^{13}C NMR δ 13.8, 14.0, 18.7, 20.4, 20.7, 22.2, 22.8, 29.3, 32.1, 38.4, 44.4, 54.1, 56.8, 59.6, 63.8, 72.8, 119.5, 121.5, 123.8, 124.2, 126.7, 128.2, 128.8, 129.0, 129.6, 130.7, 132.2, 138.1, 139.6, 141.5, 168.7, 168.7, 173.4, 175.0, 175.3, 177.7. HRMS [M+Na] found *m/s* 774.2629, calcd for $C_{40}H_{47}N_5NaNiO_6$ is 774.2772. $[\alpha]_D^{25} = -974$ (*c* 0.08, $CHCl_3$).

4.2.1.8. Ni(II) complex of (2*R*,3*S*,2′*S*)-3-phenyl-5-[5′oxo-*N*-phenyl-pyrrolidine-2′-carboxamide] glutamic acid Schiff base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 18b. Mp 218.6 °C. ^{1}H NMR δ 1.31 (2H, m), 1.47 (2H, m), 1.60 (1H, dt, *J* = 6.9, 3.6 Hz), 2.02 (1H, m), 2.27 (4H, m), 2.72 (3H, s), 2.86 (3H, m), 3.01 (1H, m), 3.15 (2H, t, *J* = 8.2 Hz), 3.52 (1H, dd, *J* = 8.6, 2.4 Hz), 3.63 (1H, m), 4.44 (1H, dd, *J* = 9.4, 1.4 Hz), 4.66 (1H, d, *J* = 4.5 Hz), 4.88 (1H, t, *J* = 5.4 Hz), 6.97 (1H, dt, *J* = 6.9, 1.2 Hz), 7.04 (1H, m), 7.26 (3H, m), 7.44 (2H, m), 7.60 (5H, m), 7.65 (1H, dd, *J* = 8.4, 1.5 Hz), 8.28 (1H, dd, *J* = 8.4, 1.2 Hz), 9.31 (1H, s). ^{13}C NMR δ 18.6, 19.6, 19.8, 22.0, 22.9, 32.1, 38.3, 44.2, 54.8, 55.6, 59.5, 60.5, 72.7, 119.6, 121.6, 123.8, 124.1, 126.6, 128.3, 128.8, 128.9, 129.0, 129.7, 130.7, 132.2, 138.2, 139.5, 141.5, 168.8, 169.1, 173.2, 174.8, 175.4, 178.1. HRMS [M+Na] found *m/s* 730.2189, calcd for $C_{37}H_{39}N_5NaNiO_6$ is 730.2146. $[\alpha]_D^{25} = -432.8$ (*c* 0.002, $CHCl_3$).

4.2.2. X-ray data for compound 10

The data were collected at 120(2) K on a Bruker Apex diffractometer[27] using MoKα (λ = 0.71073 A) radiation. Intensity data, which approximately covered the full sphere of the reciprocal space, were measured as a series of ω oscillation frames each 0.3° for 35 s/frame. The detector was operated in 512 × 512 mode and was positioned 6.12 cm from the crystal. Coverage of unique data was 97.6% complete to 55.0°(2θ). Cell parameters were determined from a non-linear least squares fit of 6283 reflections in the range of $2.6 < \theta < 27.5°$. A total of 8276 reflections were measured. The structure was solved by the direct method using SHELXTL system,[28] and refined by full-matrix least squares on F^2 using all reflections. All the non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were included with idealized parameters. Final $R1 = 0.058$ is based on 3190 'observed reflections' [$I > 2\sigma(I)$], and $wR^2 = 0.140$ is based on all reflections (3629 reflections).

Empirical formula: $C_{20}H_{18}N_2O_3$; formula weight: 334.36; wavelength: 0.71073 Å; crystal system: monoclinic; space group: *Pc*; unit cell dimensions: $a = 15.114(3)$ Å, $\alpha = 90°$; $b = 6.3646(14)$ Å, $\beta = 93.565(3)°$; $c = 8.6912(19)$ Å, $\gamma = 90°$; volume: 834.4(3) Å^3; *Z*: 2; density (calculated): 1.331 Mg/m^3; absorption coefficient: 0.091 mm^{-1}; *F*(0 0 0): 352; crystal size: 0.40 × 0.08 × 0.04 mm^3; θ range for data collection: 2.70–27.49°; index ranges: $-19 \leqslant h \leqslant 19$, $-8 \leqslant k \leqslant 8$, $-11 \leqslant l \leqslant 11$; reflections collected: 8276; independent reflections: 3629 [R(int) = 0.0396]; completeness to $\theta = 27.49°$ 97.6%; absorption correction: semi-empirical from equivalents, max. and min. transmission: 0.9964 and 0.9647; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 3629/2/226; goodness-of-fit on F^2: 1.133; final R indices [$I > 2\sigma(I)$]: $R1 = 0.0578$, $wR2 = 0.1357$; R indices (all data) $R1 = 0.0662$, $wR2 = 0.1402$; absolute structure parameter: 0.4(13); largest diff. peak and hole: 0.387 and −0.285 e Å^{-3}.

Acknowledgements

This work was supported by the Department of Chemistry and Biochemistry, University of Oklahoma. The authors gratefully acknowledge generous financial support from Central Glass Company (Tokyo, Japan) and Ajinomoto Company (Tokyo, Japan).

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