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Tetrahedron 62 (2006) 6412–6419
Tetrahedron

Operationally convenient, efficient asymmetric synthesis of enantiomerically pure 4-aminoglutamic acids via methylene dimerization of chiral glycine equivalents with dichloromethane

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Received 7 February 2006; revised 31 March 2006; accepted 6 April 2006
Available online 11 May 2006

Abstract—This paper presents a practical and efficient asymmetric synthesis of enantiomerically pure 4-aminoglutamic acids using a quite unusual methylene dimerization of chiral nucleophilic glycine equivalents with dichloromethane under phase-transfer catalysis (PTC) conditions. From a synthetic standpoint, the reported procedure is highly operationally convenient and scalable as it does not require any chromatographic purification of the intermediate products.

1. Introduction

Bis-α-amino acids (α,α′-diamino-dicarboxylic acids) (bis-AA) are naturally occurring compounds found in various microorganisms and higher plants.[1] For instance, 2,6-diaminopimelic acid (DAP) (**1b**) (Fig. 1) is a metabolic precursor of (*S*)-lysine in Gram-positive bacteria,[2] and serves as the key cross-linking unit in the peptidoglycan layers of the cell wall in most pathogenic bacteria.[3] In general the cross-linking property of **1b** and bis-AA was shown to be of enormous potential for an application in the design and synthesis of conformationally constrained cyclic peptides[4] and peptidomimetics, as aliphatic linkage providers between two C^{α} sites.[5] Thus, the ability of natural and tailor-made[6,7] bis-AA to support peptide secondary structures (turns, sheets, and helices) and to serve as dicarba cystine isosteres [2,7-diaminosuberic acid (**1c**)] has generated a great deal of interest in the development of stereoselective methods for preparing these amino acids.[8,9]

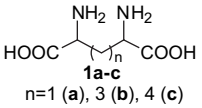

Figure 1. (a) Bis-AA: 4-aminoglutamic acid, (b) 2,6-diaminopimelic acid, (c) 2,7-diaminosuberic acid.

The interest of our group in bis-AA is concerned with syntheses of conformationally constrained amino acids and peptides.[10] In particular, for a systematic analysis of a series of cyclic bis-AA-based peptides, currently under study in our laboratories, we needed a reliable and operationally convenient and a simple access to (2*S*,4*S*)- and (2*R*,4*R*)-2,4-diaminoglutaric acid (4-aminoglutamic acid) (**1a**). Our interest in 4-aminoglutamic acid **1a**, as an example of substituted glutamic acid family, was also stimulated by our recent success in the design[11] and development[12] of the first truly practical methodology for stereocontrolled synthesis of sterically/configurationally constrained glutamic/pyroglutamic acids.[10–12] Moreover, an additional bonus for the development of an optimized synthetic approach to enantiomerically pure 4-aminoglutamic acid **1a** might be extended further and assist in a systematic study of its intriguing multifold biological activity.[13]

According to the relevant literature,[14] most of the methods for the asymmetric synthesis of bis-AA **1a** are based on an elaborate multistep (seven steps or more) transformation of enantiomerically pure naturally occurring amino acids, such as γ-hydroxyproline[14a] or serine,[14b,c] and all of these methods are unappealing from a preparative standpoint. More straightforward approaches include Michael addition reactions between chiral nucleophilic glycine equivalents

Keywords: Asymmetric synthesis; Bis-amino acid; Chiral glycine equivalents; Methylene dimerization.
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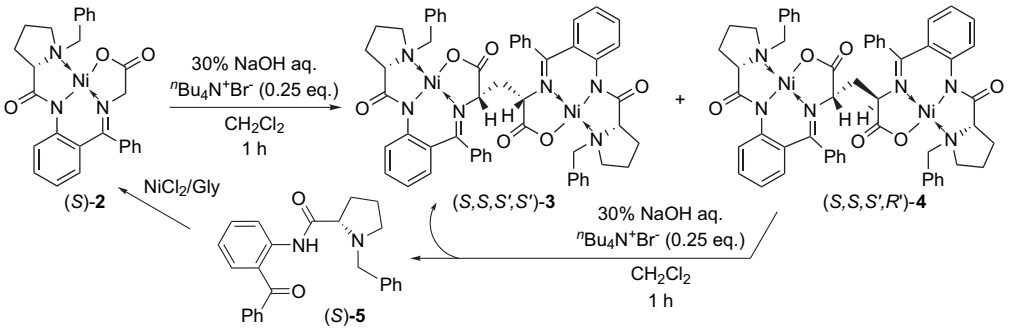
doi:10.1016/j.tet.2006.04.023



Scheme 1.

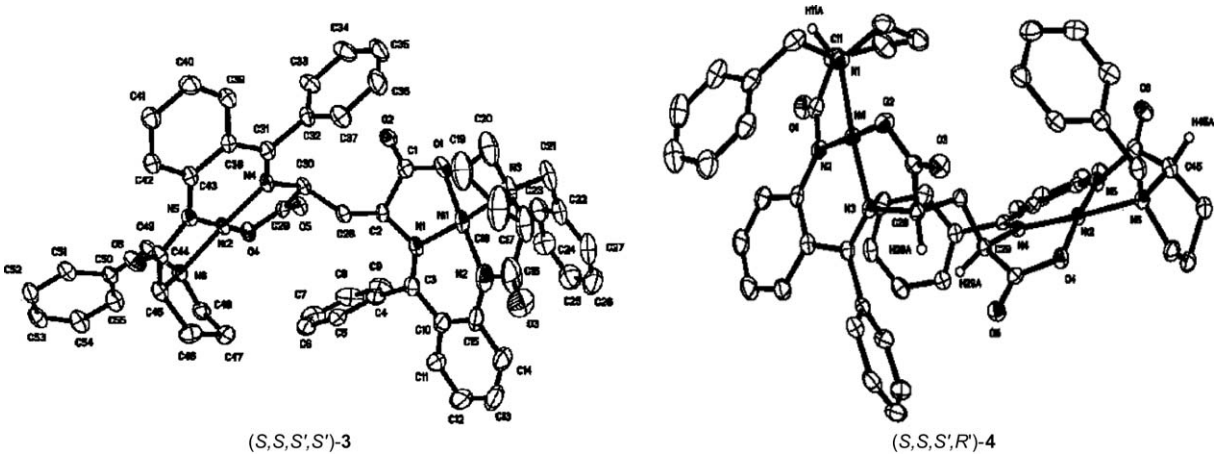


Figure 2. X-ray structures of both Ni(II) Complexes (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4**.

and corresponding derivatives of α-aminoacrylic acids.[15] However, the major drawback of these Michael additions is a low stereoselectivity, close to a 1:1 mixture of diastereomers, requiring tedious chromatographic separations.

The most concise and direct method for preparation of enantiomerically pure bis-AA **1a** is the methylene dimerization[16] of glycine equivalents with CH_2Br_2. The asymmetric version of this reaction was reported by Belokon et al.[17] According to the corresponding protocol, the treatment of a chiral glycine equivalent, Ni(II)-complex (*S*)-**2** (Scheme 1) in dry acetonitrile with 0.5 equiv of CH_2Br_2 and powdered NaOH resulted in the formation of Ni-complex **3** as a major product, which was easily converted into (2*S*,4*S*)-**1a**. Regardless of the need for a dry solvent and inert atmosphere, as well as the necessity for purification of complex **3** by column chromatography, the simplicity of this method seemed very attractive. Unfortunately, our attempts to reproduce this protocol failed. First, we found that 0.5 equiv of CH_2Br_2 is not quite enough for complete consumption of the starting complex (*S*)-**2**. Second, we also observed the formation of the diastereomeric product (*S*,*S*,*S*′,*R*′)-**4**[18] in a variable ratio to (*S*,*S*,*S*′,*S*′)-**3**, depending on the reaction time. Furthermore, we found that the major problem of these reaction conditions is the formation of a substantial amount of decomposition products. Our numerous attempts to improve these reaction conditions by varying the ratios of the starting compounds, reaction temperature, solvent, and nature of a base gave us little improvement; the target product (*S*,*S*,*S*′,*S*′)-**3** was obtained in about 50% yield after painstaking column purification.

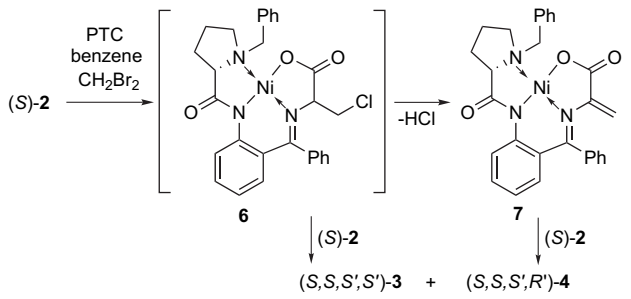
Fortunately, an unrelated research project in our laboratory gave us an unexpected solution to the synthesis of the product **3** and target amino acid **1a**. The alkylation of complex (*S*)-**2** under PTC in CH_2Cl_2 with sterically constrained alkyl halides usually requires prolonged reaction times. By checking the content of the reaction mixtures through TLC we noticed the formation of some byproducts, which were concluded to be (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** after isolation and characterization. The absolute configuration of each complex was determined by X-ray analysis (Fig. 2).

This unexpected finding showed us the possibility of preparing compounds (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** under PTC using dichloromethane as a solvent and a reagent at the same time. Our next goal was to optimize the reaction conditions of the methylene dimerization of complex (*S*)-**2** by screening various bases, solvents, phase-transfer catalysts, and concentration of the reagents.[19]

2. Results and discussions

After an extensive series of experiments we finally found the following most efficient reaction conditions: 25 mol % of tetrabutylammonium bromide (TBAB), 30% aqueous NaOH, and 0.2 M solution of complex (*S*)-**2** in CH_2Cl_2. Under these conditions the reaction was completed within 1 h and resulted in a mixture of products (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** (Scheme 1) in a ratio of 1:1 (95% in combined yield).

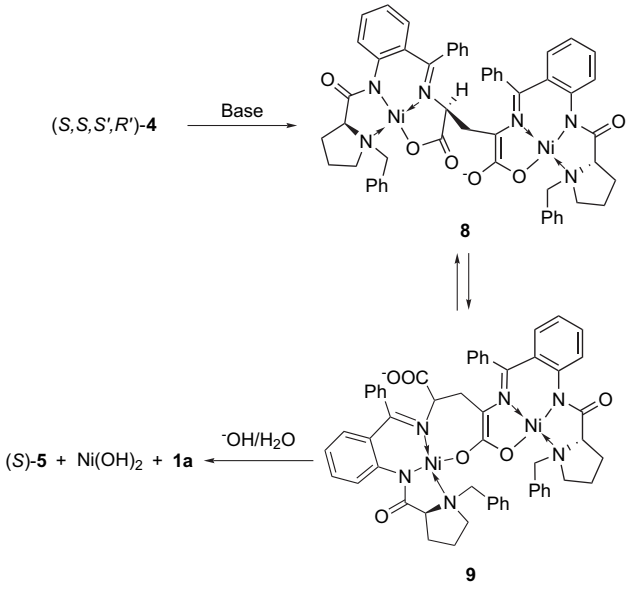
From a mechanistic standpoint, the reaction obviously proceeds through the formation of an intermediate mono-alkylated complex **6** (Scheme 2), which transformed into the products of dimerization via two possible pathways. In the first scenario, the intermediate **6** can be engaged in the direct alkylation of the starting complex **2**, resulting in the products **3** and **4**. Alternatively, the complex **6** can undergo dehydrochlorination, leading to the formation of an unsaturated derivative **7**. The complex **7**, which can act as a Michael acceptor, might react with the starting glycine complex (*S*)-**2** furnishing the reaction products **3** and **4**. Although, neither the mono-alkylated complex **6** nor the Michael acceptor **7** were observed at any point of the reactions that were conducted under our standard phase-transfer conditions, we were able to detect and isolate the intermediate Michael acceptor **7** (13% yield) in a reaction conducted in benzene with the application of CH_2Br_2 as an alkylating reagent. With the intermediate **7** in hand, we studied the reaction with (*S*)-**2** under the standard PTC conditions. The Michael addition between complexes **7** and (*S*)-**2** successfully gave rise to a mixture of products (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** in a ratio similar to that observed in the direct methylene dimerization of (*S*)-**2** in CH_2Cl_2.



Scheme 2.

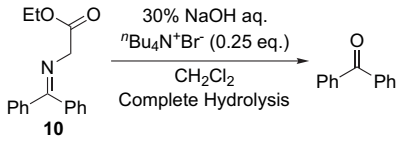
A very important and unexpected observation was made when the methylene dimerization under PTC condition was allowed to continue further. After complete consumption of the starting complex (*S*)-**2**, the initial 1:1 ratio of the two products gradually changed; a preference for the formation of (*S*,*S*,*S*′,*S*′)-**3** was observed while the amount of (*S*,*S*,*S*′,*R*′)-**4** was gradually decreasing (Scheme 1), besides a gradually increasing formation of ligand **5**. Complete disappearance of the complex (*S*,*S*,*S*′,*R*′)-**4** was observed after 24 h leaving complex (*S*,*S*,*S*′,*S*′)-**3** as a sole diastereomer in a mixture with the corresponding ligand (*S*)-**5**.

With isolated and diastereomerically pure (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** in hand, we subjected each complex to the original reaction conditions of the methylene dimerization separately. Surprisingly, the diastereomers (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** showed completely different reactivity. While the product (*S*,*S*,*S*′,*S*′)-**3** was found to be chemically and stereochemically intact, the diastereomer (*S*,*S*,*S*′,*R*′)-**4** underwent partial epimerization giving rise to the complex (*S*,*S*,*S*′,*S*′)-**3** and decomposition furnishing the ligand (*S*)-**5**. Complete consumption of the complex (*S*,*S*,*S*′,*R*′)-**4** was observed after about 24 h. Further experiments demonstrated that the diastereomer (*S*,*S*,*S*′,*R*′)-**4** can be obtained as the major product when the methylene dimerization of (*S*)-**2** was conducted at 0 °C. These results suggested that (*S*,*S*,*S*′,*S*′)-**3** is the thermodynamically controlled product and (*S*,*S*,*S*′,*R*′)-**4** is the kinetically controlled product. While the epimerization of (*S*,*S*,*S*′,*R*′)-**4** to the thermodynamic product (*S*,*S*,*S*′,*S*′)-**3** under basic conditions can be easily explained, the total difference in chemical reactivity between the diastereomers (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** was quite puzzling. Since the only difference between (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** is their absolute configuration, we based our rational on the different arrangement of the Ni(II)-coordinated planes in space. According to the crystallographic data, the carboxylic acid moieties in (*S*,*S*,*S*′,*R*′)-**4** are in close proximity to each other. Therefore, one may suggest that the mono-enolate **8**, generated under basic conditions, can substitute the carboxylic acid moiety in the second Ni(II)-coordination plane giving rise to complex **9** (Scheme 3). The uncoordinated carboxylic group in the complex **9** might render the complex **9** as polar and relatively soluble in the aqueous phase were it can undergo complete hydrolysis producing $Ni(OH)_2$, amino acid **1a**, and chiral ligand (*S*)-**5**.



Scheme 3.

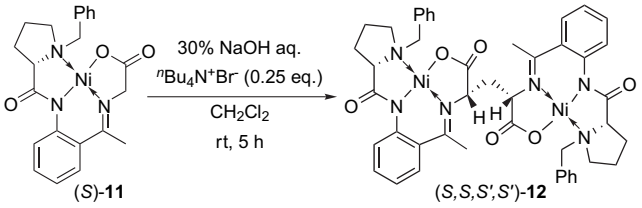
With these results in hand, we thought it would be interesting to explore the generality of this methylene dimerization using other nucleophilic glycine equivalents. First, we tried the commercially available O'Donnell's-type[20] nucleophilic glycine equivalent **10** under various reaction conditions, which include our standard PTC conditions. Under any conditions, we observed only complete hydrolysis of the compound **10** resulting in the formation of benzophenone (Scheme 4) and the corresponding methylene dimerization product was never detected in the reaction mixtures.



Scheme 4.

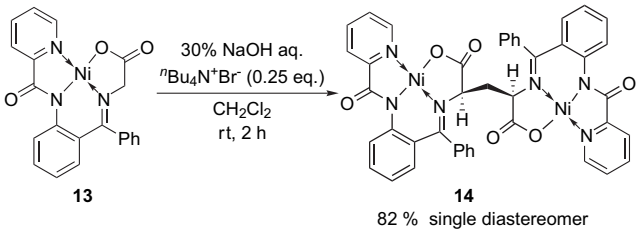
Next, with a goal to improve the stereochemical outcome of the reactions, we studied the methylene dimerization of

the acetophenone-derived chiral Ni(II)-complex (*S*)-**11** (Scheme 5).[21] Surprisingly, (*S*)-**11** showed very different reactivity compared with that of (*S*)-**2**. Thus, the application of our standard reaction conditions using 25 mol % of TBAB resulted in very fast consumption of the starting complex (*S*)-**11** and formation of a complex mixture of various unidentified byproducts. We found that an application of 5 mol % of the catalyst TBAB allowed to slow down the reaction rate and isolate a single reaction product (*S*,*S*,*S*′,*S*′)-**12** in 37% yield. The ^{1}H NMR spectrum of the product (*S*,*S*,*S*′,*S*′)-**12** showed a simple pattern of peaks, similar to those of (*S*,*S*,*S*′,*S*′)-**3**; in particular, only one singlet (at 2.46 ppm) of the acetophenone moiety was observed in the ^{1}H NMR spectrum, suggesting that the compound possesses a C_2-symmetry and therefore (*S*,*S*,*S*′,*S*′) absolute configuration. The observed remarkable difference in the reactivity between glycine equivalents (*S*)-**2** and (*S*)-**11** can be explained by considerably high C–H acidity of the acetophenone methyl group in the starting complex (*S*)-**11** as well as in the product of its methylene dimerization (*S*,*S*,*S*′,*S*′)-**12**.[22] Despite the formation of a single diastereomer in the methylene dimerization of (*S*)-**11**, the low chemical yield (37%) rendered this reaction unpractical for preparation of the target amino acid **1a**.



Scheme 5.

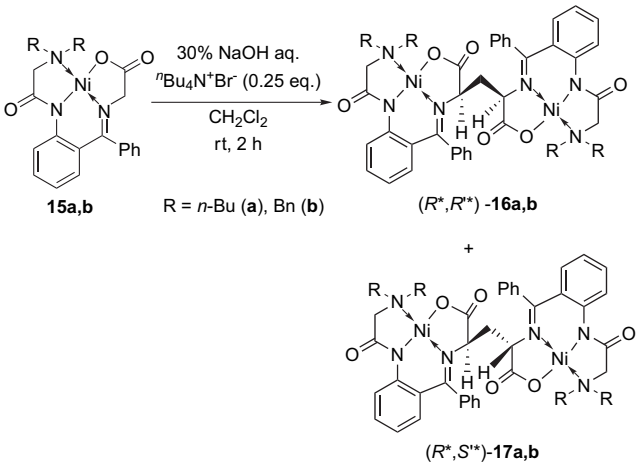
To further investigate the generality of this unusual methylene dimerization of glycine derivatives with dichloromethane under PTC conditions, we studied the reactions using a series of achiral Ni(II) complexes. First, we investigated the methylene dimerization of the picolinic acid derived Ni(II)-complex of glycine **13**[23] (Scheme 6). Surprisingly, the stereochemical outcome of this reaction was different from that of both chiral complexes (*S*)-**2** and (*S*)-**11**. This reaction was completed within 2 h giving rise to a single diastereomeric product **14**, isolated in 82% yield. As discussed above, the relative configuration of the product **14** was assigned (*R**,*R*′*) based on the symmetrical pattern of its ^{1}H NMR spectrum. The product (*R**,*R*′*)-**14** was found to be stable under the PTC conditions, as no decompositions of **14** were observed in the reaction even after 24 h. To rationalize the obtained high diastereoselectivity[24] in this reaction, we can suggest that the difference in geometry between



Scheme 6.

the flat picolinic acid moiety in **13** and the nonflat chiral (*N*-benzyl)prolyl moieties in (*S*)-**2** and (*S*)-**11**, may play an important role in determining the stereochemical outcome in these reactions.

Finally, we investigated the methylene dimerization of a new generation of modular nucleophilic glycine equivalents **15a**,**b** (Scheme 7), recently introduced by our group.[25]



Scheme 7.

Under the standard conditions, the starting complexes **15a**,**b** were completely consumed after 5 h of the reaction giving rise to a mixture of two diastereomers **16a**,**b** and **17a**,**b** in a ratio close to 1:1. The relative configuration of the symmetric complex **16b** was determined by X-ray analysis (Fig. 3). Considering the stereochemical outcome in these reactions, one may assume that it is similar to that observed in the reactions of complexes (*S*)-**2** and (*S*)-**11**. However, in sharp contrast to the diastereomers **3**, **4**, **12**, and **14**, both products **16a**,**b** and **17a**,**b** were found to be highly unstable under the

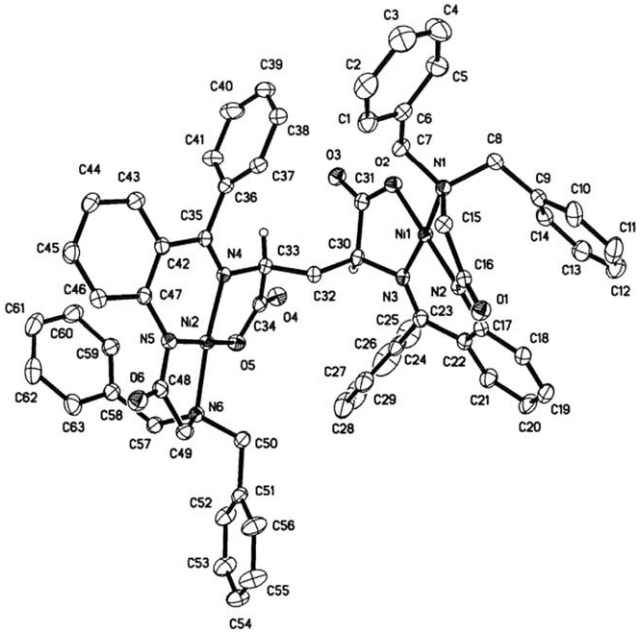
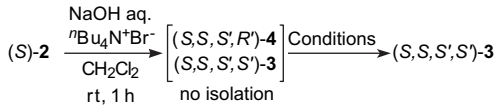


Figure 3. X-ray structure of Ni(II)-complex **16b**.

PTC conditions, undergoing complete decomposition within 24 h. Again, structural features of complexes **16a**,**b** and **17a**,**b**, such as nonflat and a more flexible arrangement of the chelating rings, maybe a reason for their instability.

With these results in hand, we decided to focus next on the development of an optimized and synthetically useful procedure for the preparation of enantiomerically pure 4-aminoglutamic acids. Considering the data obtained, it is clear that the methylene dimerization of complex (*S*)-**2** gave the most promising results furnishing a mixture of diastereomeric products **3** and **4** (Scheme 1) in high chemical yield. To make this reaction synthetically useful, we needed to find a way for selective epimerization of the unwanted isomer **4** to the symmetrical dimer **3**. To this end we conducted a series of experiments investigating the effect of various bases and solvents on the epimerization of diastereomer **4** to the target product **3** (Table 1).

Table 1. Synthesis of (*S*,*S*,*S*′,*S*′)-**3** from chiral Ni(II)-complex (*S*)-**2**[a]

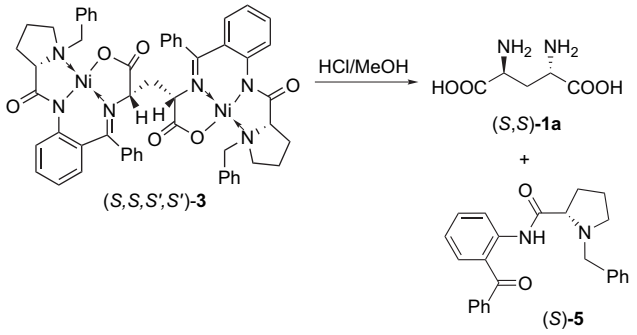


Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	NaOMe	MeOH	0.5	57
2	NaOH	DMF	0.33	[c]
3	Cs_2CO_3, TBTA	CH_2Cl_2	24	0
4	TEA	CH_2Cl_2	24	0
5	DBU	CH_2Cl_2	6	80
6	Guanidine[d]	CH_2Cl_2	1	80

[a] All reactions were conducted at rt in the indicated solvent.
[b] Isolated yield of the pure product **3**.
[c] No products were isolated.
[d] 2,3,4,6,7,8-Hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine.

The treatment of a 1:1 mixture of **3** and **4** with NaOMe in MeOH solution resulted in a relatively fast epimerization of diastereomer **4** to target product **3** (entry 1). However, substantial decomposition of both diastereomers allowed isolation of **3** only in 57% yield. Under more basic conditions, NaOH in DMF, resulted in almost complete decomposition of both **3** and **4** (entry 2). Cesium carbonate, under PTC conditions (entry 3), and NEt_3 in dichloromethane (entry 4), were found to be inefficient for the target transformation. However, we found that treatment of a 1:1 mixture of **3** and **4** with DBU in dichloromethane resulted in a clean and relatively fast epimerization of **4** to product **3**, which was isolated in 80% yield (entry 5). This conditions were applied to the isolated diastereomerically pure (*S*,*S*,*S*′,*R*′)-**4**, and the desired quantitative epimerization to product **3** was found without decomposition of **4** to ligand **5**. Encouraged by these results, we conducted reaction using guanidine (entry 6), which is a stronger base than DBU. Guanidine-catalyzed reaction occurred at a higher reaction rate (1 h) producing compound **3** as a sole product in 80% isolated yield. These reaction conditions were found to be scalable to 10 g scale.

Thus, prepared product **3** without any chromatographic purification was disassembled under the standard conditions (MeOH/3 N HCl, 30 min, and 60 °C) to give bis-AA **1a** and ligand (*S*)-**5**. The recovered ligand (*S*)-**5** was used for the preparation of starting complex (*S*)-**2** (Scheme 8).



Scheme 8.

In summary, we have developed a practical and efficient asymmetric synthesis of enantiomerically pure 4-aminoglutamic acid **1a** using quite unusual methylene dimerization reaction under PTC conditions. From a synthetic standpoint the reported procedure is highly operationally convenient and scalable as it does not require any chromatographic purification of the intermediate products.

3. Experimental

3.1. General

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. Unless indicated, ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ solutions at 300 and 75 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS and $CDCl_3$ as the internal standards.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H NMR spectrometry. All new compounds were characterized by ^{1}H and ^{13}C NMR.

3.2. General procedure for methylene dimerization of Ni-complex

NaOH (1 mL, 30%) and ^{n}Bu$_4$N$^+$Br$^-$ (16.2 mg, 0.05 mmol) were added to a solution of Ni-complex (0.20 mmol) in CH_2Cl_2 (1 mL) under N_2 atmosphere. The reaction mixture was stirred at room temperature, quenched with H_2O, and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to get a red solid. Silica gel chromatography ($CHCl_3$/acetone=10:1 then 5:1) of the crude product gave the corresponding Ni-complex dimer.

3.2.1. (*S*,*S*,*S*′,*S*′)-3. Mp 225.3–226.9 °C; R_f 0.41 ($CHCl_3$/acetone=4:1); $[\alpha]_D^{23}$ +991.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–8.02 (m, 6H), 7.59–7.26 (m, 4H), 7.39–7.32 (m, 2H), 7.32–7.22 (m, 6H), 7.14–7.00 (m, 6H), 6.65–6.59 (m, 2H), 6.53–6.50 (m, 2H), 4.40 (d, *J*=12.6 Hz, 2H), 4.26 (dd, *J*=8.4, 5.4 Hz, 2H), 3.90–3.68 (m, 2H), 3.56–3.40 (m, 4H), 3.39 (d, *J*=12.6 Hz, 2H), 2.73–2.42 (m, 6H), 2.39–2.23 (m, 2H), 2.19–2.02 (m,

2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.5, 177.0, 171.3, 142.2, 133.7, 133.5, 133.2, 132.2, 131.4, 131.2, 130.1, 129.9, 128.9, 128.6, 128.1, 126.4, 126.1, 123.5, 120.7, 70.0, 66.1, 63.2, 57.4, 42.7, 30.7, 25.0 ppm; HRMS (TOF) $[M+Na]^+$, calcd for $[C_{55}H_{50}N_6Ni_2O_6+Na]^+$: 1029.2397, found: 1029.2396.

3.2.2. (*S*,*S*,*S*′,*R*′)-4. Mp 132.9–134.1 °C; R_f 0.17 ($CHCl_3$/acetone=4:1); $[\alpha]_D^{23}$ +4.9 (*c* 3.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61–8.57 (m, 1H), 8.32–8.29 (m, 1H), 8.03 (d, *J*=7.2 Hz, 2H), 7.82 (d, *J*=7.5 Hz, 2H), 7.57–7.02 (m, 18H), 6.72–6.56 (m, 3H), 6.47 (dd, *J*=8.1, 1.2 Hz, 1H), 4.37 (d, *J*=12.6 Hz, 1H), 4.35 (d, *J*=12.9 Hz, 1H), 4.22–4.11 (m, 1H), 3.92 (br s, 1H), 3.83–3.76 (m, 1H), 3.75–3.59 (m, 1H), 3.53–3.33 (m, 5H), 3.22 (m, 1H), 2.84–1.98 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 180.3, 177.6, 177.3, 171.4, 170.8, 143.2, 142.6, 134.1, 133.6, 133.5, 133.4, 133.2, 132.7, 132.4, 132.0, 131.4, 130.9, 129.8, 129.4, 129.2, 128.9, 128.8, 128.8, 127.6, 127.3, 127.1, 126.0, 125.6, 123.3, 123.2, 120.5, 70.3, 68.9, 66.6, 66.5, 62.9, 60.9, 58.9, 57.3, 44.5, 31.0, 30.4, 24.3, 23.0 ppm; HRMS (TOF) $[M+Na]^+$, calcd for $[C_{55}H_{50}N_6Ni_2O_6+Na]^+$: 1029.2397, found: 1029.2396.

3.2.3. Synthesis of key intermediate 7.[17] To a solution of Ni-complex (*S*)-**2** (500 mg, 1.0 mmol) in benzene (50 mL), KOH (489 mg, 8.7 mmol), ^{n}Bu$_4$N$^+$Br$^-$ (81 mg, 0.25 mmol), and CH_2Br_2 (70 mg, 0.4 mmol) were added in N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h, quenched with H_2O, and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated to get a red solid. Silica gel chromatography ($CHCl_3$/acetone=10:1 then 5:1) of the crude product gave pure product **7** (71 mg, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (m, 3H), 7.52–7.13 (m, 9H), 6.86–6.83 (m, 1H), 6.72–6.67 (m, 1H), 5.63 (s, 1H), 4.36 (d, *J*=12.3 Hz, 1H), 4.15 (s, 1H), 3.70–3.45 (m, 3H), 3.45 (d, *J*=12.6 Hz, 1H), 2.77–2.62 (m, 1H), 2.61–2.41 (m, 1H), 2.26–1.90 (m, 1H) ppm.

3.2.4. (*S*,*S*,*S*′,*S*′)-12. Yield 37%; mp 342.7 °C (decomp.); $[\alpha]_D^{23}$ +1872 (*c* 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (m, 4H), 7.91 (dd, *J*=8.6, 1.2 Hz, 2H), 7.56 (dd, *J*=8.3, 1.6 Hz, 2H), 7.30–7.35 (m, 4H), 7.14–7.21 (m, 4H), 6.93 (ddd, *J*=8.3, 7.0, 1.2 Hz, 2H), 4.75 (dd, *J*=8.7, 5.8 Hz, 2H), 4.28 (d, *J*=12.5 Hz, 2H), 3.58–3.30 (m, 6H), 3.48 (d, *J*=12.6 Hz, 2H), 2.96 (dd, *J*=8.7, 5.8 Hz, 2H), 2.69 (m, 2H), 2.59–2.40 (m, 2H), 2.46 (s, 6H), 2.00–2.09 (m, 2H), 2.08–1.97 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 178.7, 168.7, 141.1, 133.4, 131.7, 131.3, 129.0, 128.9, 126.5, 124.3, 121.3, 70.5, 65.9, 63.5, 57.3, 42.6, 30.5, 24.2, 17.9 ppm; HRMS (TOF) $[M+Na]^+$, calcd for $[C_{45}H_{46}N_6Ni_2O_6+Na]^+$: 905.2083, found: 905.2145.

3.2.5. (*R,*R*′*)-14.** Yield 82%; mp 301.5 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (d, *J*=8.6 Hz, 2H), 8.20 (d, *J*=5.2 Hz, 2H), 7.80 (m, 4H), 7.47–7.22 (m, 14H), 7.05 (d, *J*=8.1 Hz, 2H), 6.86 (m, 2H), 4.15 (m, 2H), 2.02 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 177.4, 170.0, 152.4, 147.4, 142.6, 139.9, 135.4, 134.4, 133.7, 130.1, 129.6, 128.8, 128.3, 126.9, 126.8, 125.9, 123.7, 123.2, 122.0, 68.2, 35.1 ppm; HRMS (TOF) $[M+H]^+$, calcd for $[C_{43}H_{30}N_6Ni_2O_6+H]^+$: 843.1, found: 843.2.

3.2.6. 16a and 17a. Yield 72%; **16a/17a**=35:65. *Compound* **17a**: mp 301.3 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J*=8.6 Hz, 2H), 7.47–7.22 (m, 10H), 7.17 (d, *J*=7.4 Hz, 2H), 6.73 (m, 2H), 6.64 (dd, *J*=8.0, 1.3 Hz, 2H), 4.08–3.91 (m, 2H), 4.02 (d, *J*=16.2 Hz, 2H), 3.28 (quint, *J*=7.0 Hz, 1H), 3.02 (d, *J*=16.2 Hz, 2H), 2.96–2.83 (m, 3H), 2.60–2.32 (m, 10H), 2.22 (m, 2H), 1.98–1.82 (m, 2H), 1.54–1.30 (m, 8H), 1.00 (t, *J*=7.7 Hz, 6H), 0.98 (t, *J*=7.7 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 170.8, 142.7, 133.9, 133.2, 132.7, 130.0, 129.1, 129.0, 127.5, 127.2, 126.4, 123.3, 120.8, 66.6, 62.5, 60.0, 56.7, 53.7, 43.3, 29.0, 26.8, 20.7, 20.6, 13.8 ppm. *Compound* **16a**: mp 275.6 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (dd, *J*=8.7, 1.2 Hz, 2H), 7.52–7.18 (m, 10H), 7.02 (d, *J*=7.2 Hz, 2H), 6.76 (m, 2H), 6.69 (dd, *J*=8.0, 1.7 Hz, 2H), 4.07 (dd, *J*=8.3, 6.1 Hz, 2H), 3.96 (d, *J*=16.3 Hz, 2H), 3.14 (d, *J*=16.3 Hz, 2H), 3.03 (m, 2H), 2.72 (m, 2H), 2.68–2.20 (m, 10H), 2.02–1.90 (m, 2H), 1.74–1.60 (m, 2H), 1.58–1.36 (m, 8H), 1.03 (t, *J*=7.3 Hz, 6H), 0.99 (t, *J*=7.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 176.7, 171.4, 142.5, 133.9, 133.2, 132.8, 130.1, 129.7, 128.7, 127.5, 126.6, 126.3, 123.4, 121.0, 66.4, 63.8, 58.5, 56.9, 53.7, 43.2, 29.4, 24.7, 20.9, 20.8, 13.9 ppm. HRMS (TOF) $[M+Na]^+$, calcd for $[C_{51}H_{62}N_6Ni_2O_6+Na]^+$: 993.3335, found: 993.3293.

3.2.7. 16b and 17b. Yield 72%; **16b/17b**=44:56. *Compound* **17b**: mp 313.5 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J*=8.6 Hz, 2H), 8.13 (d, *J*=7.7 Hz, 4H), 7.66 (d, *J*=7.7 Hz, 2H), 7.52–7.02 (m, 26H), 6.60 (m, 2H), 6.43 (d, *J*=8.2 Hz, 2H), 4.56 (d, *J*=12.3 Hz, 2H), 4.30 (d, *J*=12.7 Hz, 2H), 4.14 (d, *J*=16.4 Hz, 2H), 3.81 (s, 2H), 3.61 (d, *J*=12.3 Hz, 2H), 3.40 (m, 1H), 3.26 (d, *J*=16.3 Hz, 2H), 3.08 (d, *J*=16.6 Hz, 2H), 2.98 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 170.9, 142.4, 133.6, 133.1, 132.8, 132.6, 132.3, 132.0, 131.9, 129.8, 129.5, 129.2, 129.0, 128.9, 128.9, 128.8, 128.3, 128.1, 127.4, 127.1, 126.9, 125.5, 123.2, 120.4, 66.5, 64.6, 61.6, 59.6, 53.0, 44.0, 29.6 ppm. *Compound* **16b**: mp 342.2 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88–8.22 (m, 4H), 7.94 (d, *J*=8.31 Hz, 2H), 7.89–7.82 (m, 4H), 7.58–7.21 (m, 16H), 7.13–6.98 (m, 6H), 6.84 (br d, *J*=7.6 Hz, 2H), 6.56 (m, 2H), 6.44 (dd, *J*=8.2, 1.5 Hz, 2H), 4.58 (d, *J*=13.9 Hz, 2H), 4.35 (dd, *J*=8.7, 6.2 Hz, 2H), 4.19 (d, *J*=12.2 Hz, 2H), 4.07 (d, *J*=16.9 Hz, 2H), 3.90 (d, *J*=13.7 Hz, 2H), 3.20 (d, *J*=12.0 Hz, 2H), 2.97 (d, *J*=16.9 Hz, 2H), 2.87 (dd, *J*=8.7, 6.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 176.4, 170.9, 141.7, 133.7, 133.0, 132.7, 131.8, 131.2, 131.0, 130.7, 129.6, 129.4, 129.1, 128.8, 128.6, 128.2, 127.6, 126.3, 126.0, 123.2, 120.3, 65.9, 64.3, 63.6, 61.7, 41.5 ppm. HRMS (TOF) $[M+H]^+$, calcd for $[C_{63}H_{55}N_6Ni_2O_6+H]^+$: 1107.2890, found: 1107.2972.

3.3. Synthesis of 4-aminoglutamic acid (*S*,*S*)-1a[17]

Compound (*S*,*S*,*S*′,*S*′)-**3** was decomposed following the procedure by Belokon and his co-workers, see Ref. 17. Yield 61%; $[\alpha]_D^{25}$ +20.1 (*c* 1.35, as HCl salt in D_2O).

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).

Supplementary data

X-ray crystallographic files for the complexes (*S*,*S*,*S*′,*S*′)-**3**, (*S*,*S*,*S*′,*R*′)-**4**, and **16b** in cif format. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.023.

References and notes

1. Ward, J. B. *Pharmacol. Ther.* **1984**, *25*, 327–369 and references cited therein.
2. (a) Cox, R. J. *Nat. Prod. Rep.* **1996**, *13*, 29–43; (b) Galili, G. *Plant Cell* **1995**, *7*, 899–906; (c) Bugg, T. D. H.; Walsh, C. T. *Nat. Prod. Rep.* **1992**, *9*, 199–215.
3. Patte, J.-C. *Amino Acids: Biosynthesis and Genetic Regulation*; Hermann, K. M., Sommerville, R. L., Eds.; Adison-Wesley: Reading, MA, 1983; pp 213–218.
4. For the importance of conformationally constrained peptides in the design of low-molecular weight therapeutic agents and for elucidation of structure–activity relationships, see: (a) Hruby, V. J. *Life Sci.* **1982**, *31*, 189–199; (b) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. M. *Biochem. J.* **1990**, *268*, 249–262; (c) Hruby, V. J. *Biopolymers* **1993**, *33*, 1073–1082; (d) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. D. *Biopolymers* **1997**, *43*, 219–266; (e) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389–397; (f) Hruby, V. J. *Nat. Rev. Drug Discov.* **2002**, *1*, 847–858.
5. For recent papers on the application of bis-AA cyclization motive in peptide design, see: (a) Di Costanzo, L.; Geremia, S.; Randaccio, L.; Ichino, T.; Yanagihara, R.; Yamada, T.; Marasco, D.; Lombardi, A.; Pavone, V. *J. Chem. Soc., Dalton Trans.* **2003**, *5*, 787–792; (b) McNamara, L. M. A.; Andrews, M. J. I.; Mitzel, F.; Siligardi, G.; Tabor, A. B. *J. Org. Chem.* **2001**, *66*, 4585–4594; (c) Maricic, S.; Ritzen, A.; Berg, U.; Frejd, T. *Tetrahedron* **2001**, *57*, 6523–6529; (d) Reichwein, J. F.; Versluis, C.; Liskamp, R. M. J. *J. Org. Chem.* **2000**, *65*, 6187–6195; (e) Reichwein, J. F.; Wels, B.; Kruijtzer, J. A. W.; Versluis, C.; Liskamp, R. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3684–3687; (f) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189–8198; (g) Blackwell, H. E.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3281–3284; (h) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614; (i) Fairlie, D. P.; Abbenante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654–686.
6. The rapidly growing list of amino acids isolated from various natural sources makes the terms *unnatural*, *unusual*, *noncoded* or *nonproteinogenic amino acids*, which are most frequently used in the literature, dependent on the success of the specific scientific achievements. For instance, amino acids containing the most xenobiotic element fluorine have been shown to be synthesized by microorganisms (see Ref. 7). Therefore, the time independent term *tailor-made*, meaning rationally designed/synthesized amino acids with presupposed physical, chemical, 3D-structural, and biological features, in the absence of a better definition, seems to be a more appropriate use for such amino acids.
7. Fluorine-Containing Amino Acids. In *Synthesis and Properties*; Kukhar', V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1994 and references cited therein.
8. For recent leading publications on the preparation of various types of bis-AA, see: (a) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **2003**, *44*, 2137–2139; (b) Mazaleyrat, J.-P.; Wright, K.; Azzini, M.-V.; Gaucher, A.; Wakselman, M. *Tetrahedron Lett.* **2003**, *44*, 1741–1745; (c) Ferioli, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1181–1187; (d) Paradisi, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2002**, *13*, 497–502; (e) Ami, E.; Rajesh, S.; Wang, J.; Kimura, T.; Hayashi, Y.; Kiso, Y.; Ishida, T. *Tetrahedron Lett.* **2002**, *43*, 2931–2934; (f) Roberts, J. L.; Chan, C. *Tetrahedron Lett.* **2002**, *43*, 7679–7682; (g) Sutherland, A.; Vederas, J. C. *Chem. Commun.* **2002**, 224–225; (h) Efskind, J.; Romming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703; (i) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 578–589; (j) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447–6453; (k) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389–1392; (l) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385–1388; (m) Lange, M.; Undheim, K. *Tetrahedron* **1998**, *54*, 5337–5344.
9. For recent leading publications on 2,7-diaminosuberic acid and its derivatives, used as dicarba cystine isosteres in the peptide design, see: (a) Hoven, G. B.; Efskind, J.; Romming, C.; Undheim, K. *J. Org. Chem.* **2002**, *67*, 2459–2463; (b) Hernandez, N.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 4934–4938; (c) Aguilera, B.; Wolf, B. L.; Nieczypor, P.; Rutjes, F. P. J. T.; Overkleeft, H. S.; van Hest, J. C. M.; Schoemaker, H. E.; Wang, B.; Mol, J. C.; Fuerstner, A.; Overhand, M.; van der Marel, G. A.; van Boom, J. H. *J. Org. Chem.* **2001**, *66*, 3584–3589; (d) Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *J. Org. Chem.* **1999**, *64*, 1947–1952.
10. Soloshonok, V. A. *Curr. Org. Chem.* **2002**, *6*, 341–364.
11. (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **1999**, *41*, 135–139; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688–6696.
12. For the protocol recently developed by our group for highly diastereoselective, organic base-catalyzed, room temperature Michael addition reactions see: (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747–750; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2172–2175; (c) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339–1350; (d) Soloshonok, V. A.; Ueki, H.; Ellis, T. K.; Yamada, T.; Ohfune, Y. *Tetrahedron Lett.* **2005**, *46*, 1107–1110; (e) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296–15303.
13. (a) Jullian, N.; Brabet, I.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **1999**, *42*, 1546–1555; (b) Costantino, G.; Macchiarulo, A.; Pellicciari, R. *J. Med. Chem.* **1999**, *42*, 2816–2827; (c) Conti, P.; De Amici, M.; De Sarro, G.; Rizzo, M.; Stensbol, T. B.; Braeuner-Osborne, H.; Madsen, U.; Toma, L.; De Micheli, C. *J. Med. Chem.* **1999**, *42*, 4099; (d) Olverman, H. J.; Jones, A. W.; MeWett, K. N.; Watkins, J. C. *Neuroscience* **1988**, *26*, 17–31; (e) Zygmunt, W. A.; Evans, R. L.; Stavely, H. E. *Can. J. Microbiol.* **1962**, *8*, 869–873.
14. (a) Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1998**, *9*, 71–77; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555–

1558; (c) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 863–871; (d) Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.* **1995**, *43*, 535–536; (e) Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.* **1998**, *46*, 674–680; (f) Krasnov, V. P.; Zhdanova, E. A.; Korolyova, M. A.; Bukrina, I. M.; Kodess, M. I.; Kravtsov, V. K.; Biyushkin, V. N. *Russ. Chem. Bull.* **1997**, *46*, 319–323.

15. Kabat, M. M. *Tetrahedron Lett.* **2001**, *42*, 7521–7524.
16. Eberson, L. *Acta Chem. Scand.* **1958**, *12*, 314–323.
17. Belokon, Y. N.; Chernoglazova, N. I.; Batsanov, A. S.; Garbalinskaya, N. S.; Bakhmutov, V. I.; Struchkov, Y. T.; Belikov, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, *4*, 852–857.
18. The primed configurations apply to 4-aminoglutamic acid and unprimed to the proline moieties.
19. For a preliminary communication see; Taylor, S. M.; Yamada, T.; Ueki, H.; Soloshonok, V. A. *Tetrahedron Lett.* **2004**, *45*, 9159–9162.
20. O'Donnell, M. J.; Plot, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666.
21. For practical, large-scale syntheses of chiral complexes (*S*)-**2** and (*S*)-**11**, see: Ueki, H.; Ellis, T. K.; Martin, C. H.; Bolene, S. B.; Boettiger, T. U.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7104–7107.
22. Ellis, T. K.; Martin, C. H.; Tsai, G. M.; Ueki, H.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 6208–6214.
23. For practical, large-scale syntheses of achiral complex **13**, see: Ueki, H.; Ellis, T. K.; Martin, C. H.; Soloshonok, V. A. *Eur. J. Org. Chem.* **2003**, 1954–1957.
24. Considering the significant high diastereoselectivity obtained in these reactions, it was of interest to study the asymmetric version of this methylene dimerization using achiral complex **15** and chiral phase-transfer catalyst. Investigation of this catalytic asymmetric methylene dimerization is currently under study and the results obtained will be reported in due course.
25. Soloshonok, V. A.; Ueki, H.; Ellis, T. K. *Tetrahedron Lett.* **2005**, *46*, 941–944.