Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9159–9162
Tetrahedron Letters

Asymmetric synthesis of enantiomerically pure 4-aminoglutamic acids via methylenedimerization of chiral glycine equivalents with dichloromethane under operationally convenient conditions

Stephen M. Taylor, Takeshi Yamada, Hisanori Ueki and Vadim A. Soloshonok*

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

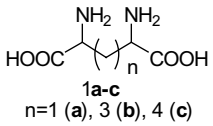
Received 23 September 2004; revised 19 October 2004; accepted 20 October 2004

This article is dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—We found that simple stirring of a biphasic mixture of the Ni(II) complex of glycine Schiff base **2** solution in dichloromethane with 30% aqueous NaOH in the presence of PT catalyst $^{n}Bu_4N^{+}Br^{-}$ at room temperature for 24 h results in the formation of diastereo- and enantiomerically pure Ni(II) complex **3**, containing (2*S*,4*S*) 4-aminoglutamic acid, in high chemical yield. The procedure described in this communication represents a synthetically efficient method for the asymmetric synthesis of 4-aminoglutamic acid on large scale.
© 2004 Elsevier Ltd. All rights reserved.

Bis-α-amino acids (bis-AAs) are naturally occurring compounds found in various microorganisms and higher plants[1] (Fig. 1).

The interest of our group in bis-AAs is also concerned with the synthesis of conformationally constrained amino acids and peptides.[2–4] In particular, we needed a reliable and operationally convenient method to access (2*S*,4*S*)- and (2*S*,4*R*)-2,4-diaminoglutaric acid (4-aminoglutamic acid) (**1a**). Moreover, the development of a convenient synthetic approach to enantiomerically pure 4-aminoglutamic acid **1a** may allow for an extended and systematic study of its intriguing multi-fold biological activity.[5] Analysis of the relevant literature[6] revealed that most of the literature methods for the asymmetric synthesis of bis-AA **1a** are based on a multi-step (seven steps or more) elaboration of enantiomerically pure naturally occurring amino acids, such as γ-hydroxy proline[6a] or serine,[6b,c] and they are unappealing from a preparative standpoint. Other, more straightforward approaches include Michael addition reactions between chiral equivalents of nucleophilic glycine and corresponding derivatives of α-aminoacrylic acids.[7] However, the major drawback of these Michael additions is a low stereoselectivity, close to a 1:1 mixture of diastereomers, therefore requiring tedious chromatographic separations.



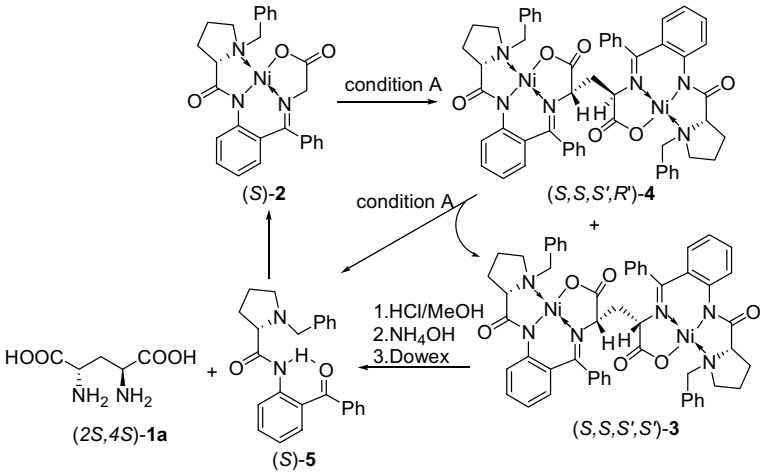
1a-c
n=1 (**a**), 3 (**b**), 4 (**c**)

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

The most concise and direct method for preparation of enantiomerically pure bis-AA **1a** is the methylenedimerization[8] of a glycine equivalent with CH_2Br_2. The asymmetric version of this reaction was reported by Belokon et al.[9] According to that protocol, the treatment of chiral 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**, containing (2*S*,4*S*)-**1a**, as a major product. Regardless of the need for dry solvents and inert atmospheres, as well as the

Keywords: Asymmetric synthesis; Methylenedimerization; Bis-amino acids; 4-Aminoglutamic acids.
* Corresponding author. Tel.: +1 4053258279; fax: +1 4053256111; e-mail: vadim@ou.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.111



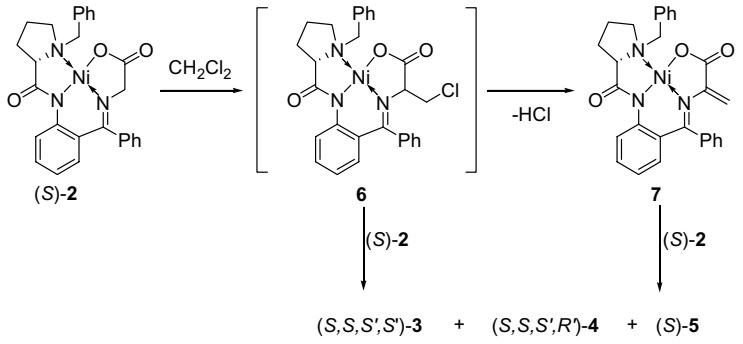
Scheme 1.

necessity of 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** 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 on these reaction conditions by varying the ratios of the starting compounds, reaction temperature, and nature of the base gave us little improvement, allowing for the preparation of the target product (*S*,*S*,*S*′,*S*′)-**3** in about 50% yield after painstaking column purification.[10] On the other hand, our experience with the synthesis of compounds **3** and **4** brought an unexpected synthetic bonus. An unrelated research project in our laboratory involves the alkylation of complex (*S*)-**2** under phase transfer conditions (PTC). Alkylation of complex (*S*)-**2** under PTC in CH_2Cl_2 with sterically constrained alkyl halides usually requires prolonged reaction times. By checking a content of the reaction mixtures through TLC we noticed the formation of some byproducts with the R_f similar to those of compounds **3** and **4**. The eventual isolation and characterization of these byproducts obtained under PTC allowed us to conclude that they are indeed the complexes (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4**. This finding was truly remarkable, because to the best of our knowledge CH_2Cl_2 has been alleged as a 'safe' solvent for homologation of glycine equivalents under PTC, until now.

Our next goal was to optimize the syntheses of these two complexes with the unprecedented application of CH_2Cl_2 as a solvent and an alkylating reagent. Using our standard PTC, 25 mol% of tetrabutylammonium bromide (TBAB), 30% aqueous NaOH, and 0.2 M solution of complex (*S*)-**2** in CH_2Cl_2 (condition A) we found that within the first two hours of the reaction, complete consumption of the starting Ni(II) complex (*S*)-**2** was observed by TLC, leading to a approximate 1:1 ratio of products (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4**. However, when the reactions were allowed to continue further, surprisingly, the ratio of the two complexes gradually changed. The formation of (*S*,*S*,*S*′,*S*′)-**3** increased and (*S*,*S*,*S*′,*R*′)-**4** decreased gradually. When the reactions were ran for 24 h, the complex (*S*,*S*,*S*′,*S*′)-**3** was observed as the sole product.

With isolated and diastereomerically pure (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4** in hand, we subjected each to the original reaction conditions separately. Surprisingly, complex (*S*,*S*,*S*′,*S*′)-**3** showed no chemical or stereochemical change, but complex (*S*,*S*,*S*′,*R*′)-**4** underwent partial decomposition giving rise to complex (*S*,*S*,*S*′,*S*′)-**3** and the ligand (*S*)-**5**. Complete transformation of complex (*S*,*S*,*S*′,*R*′)-**4** to the product (*S*,*S*,*S*′,*S*′)-**3** was detected after about 24 h of the reaction. This revealed that complex (*S*,*S*,*S*′,*R*′)-**4** is not thermodynamically stable. Therefore, the observed epimerization of (*S*,*S*,*S*′,*R*′)-**4** to (*S*,*S*,*S*′,*S*′)-**3** might proceed via enolization of a glycine moiety, followed by the highly diastereoselective protonation. Realization of this epimerization was totally unexpected, as it should lead to the products of bis-alkylation of (*S*)-**2** with various alkyl halides, which were never observed under PTC.

From a mechanistic standpoint, the reaction obviously proceeds through the intermediate formation of *mono*-alkylated complex **6** (Scheme 2). Further transformation of **6** to the dimerization products can proceed via two possible pathways. In the first scenario, the intermediate **6** can be engaged in the direct alkylation of the starting complex **2**, giving rise to the products **3** and **4**. Alternatively, complex **6** can undergo dehydrochlorination, leading to formation of unsaturated derivative **7**. Complex **7**, a Michael acceptor can react with (*S*)-**2** furnishing the observed reaction products (*S*,*S*,*S*′,*S*′)-**3** and (*S*,*S*,*S*′,*R*′)-**4**. Unfortunately, neither *mono*-alkylated complex **6** nor Michael acceptor **7** were ever observed at any point of the reactions conducted under our standard phase transfer conditions (condition A). To gain



Scheme 2.

some insight on a possible mechanism of this reaction, we conducted a large series of experiments varying all possible parameters, including solvent, base, catalyst, and reaction temperature. Gratifyingly, we isolated 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 a reaction with starting (*S*)-**2** under condition A. To our satisfaction, the Michael addition between complexes **7** and (*S*)-**2** 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 reaction of (*S*)-**2** in CH_2Cl_2 when the starting Ni complex (*S*)-**2** was completely consumed. These results suggested that the *mono*-alkylation of (*S*)-**2** with CH_2Cl_2, resulting in the formation of intermediate complex **6**, is the rate limiting step, followed by relatively fast dehydrochlorination of **6** and Michael addition between **7** and (*S*)-**2**. From a synthetic standpoint methylenedimerization reported here is highly operationally convenient, leading to clean formation of diasteromerically pure (*S*,*S*,*S*′,*S*′)-**3** and the ligand (*S*)-**5**. Since the ligand (*S*)-**5** is one of the products of the disassembling of (*S*,*S*,*S*′,*S*′)-**3**, the crude reaction product does not require any purification, significantly simplifying the synthetic procedure. Thus, the mixture of (*S*,*S*,*S*′,*S*′)-**3** and ligand (*S*)-**5** was disassembled using our standard conditions (MeOH/3 N HCl, 30 min, 60 °C) to give the target bis-AA **1a** and ligand (*S*)-**5**, which was regenerated and used again to prepare the starting (*S*)-**2**.

In summary, we found that the chiral Ni(II) complex (*S*)-**2** reacts with CH_2Cl_2, used as a solvent, under PTC, leading to the formation of two diastereomeric products. One of the diastereomers was found to be thermodynamically unstable, undergoing epimerization to the more stable stereoisomer, along with partial decomposition. The overall procedure allows for the preparation of target (*S*,*S*,*S*′,*S*′)-**3** and consequently bis-AA **1** with virtually complete enantio- and diastereoselectivity under the operationally convenient reaction conditions. The nature of unprecedented decomposition and epimerization of (*S*,*S*,*S*′,*R*′)-**4** as well as asymmetric catalytic version of this reaction using achiral Ni(II) complexes and chiral ammonium quants is under active investigation in our laboratory, and the result will be published in due course.

Acknowledgements

The work was supported by the start-up fund provided by the Department of Chemistry and Biochemistry, University of Oklahoma. We also pleased to acknowledge Mr. Collin H. Martin (undergraduate student, University of Oklahoma) and Mr. Anatolii V. Soloshonok (high school student, Norman High) for help in conducting numerous experiments.

References and notes

1. (a) Cox, R. J. *Nat. Prod. Rep.* **1998**, *15*, 279; (b) Ward, J. B. *Pharmac. Ther.* **1984**, *25*, 327, and references cited therein.
2. Soloshonok, V. A. *Current Org. Chem.* **2002**, *6*, 341.
3. (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 135; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688.
4. (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2172; (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 9645; (d) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339; (e) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984.
5. (a) Folbergrova, J.; Haugvicova, R.; Mares, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1919; (b) Jullian, N.; Brabet, I.; Pin, J.; Acher, F. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1721; (c) Kostantino, G.; Macchiarulo, A.; Pellicciari, R. *J. Med. Chem.* **1999**, *42*, 1546; (d) Panfil, I.; Urbanczyk-Lipkowska, Z.; Suwinska, K.; Solecka, J.; Chmielewski, M. *J. Med. Chem.* **1999**, *42*, 2816; (e) Conti, P.; De Amici, M.; De Sarro, G.; Stensbol, T. B.; Braeuner-Osborne, H.; Madsen, U.; De Micheli, C. *J. Med. Chem.* **1999**, *42*, 2816.
6. (a) Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1998**, *9*, 71; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555; (c) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 863; (d) Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.* **1995**, *43*, 535; (e) Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.* **1998**, *46*, 674; (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.
7. Kabat, M. M. *Tetrahedron Lett.* **2001**, *42*, 7521.
8. Eberson, L. *Acta Chem. Scand.* **1958**, *12*, 314.

9. Belokon, Y. N.; Chernoglazova, N. I.; Batsanov, A. S.; Garbalinskaya, N. S.; Bakhmutov, V. I.; Struchkov, Y. T.; Belikov, V. M. *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya* **1987**, *4*, 852.

10. Complete details of our experiments aimed to improve preparation of product **3** under acetonitrile/NaOH (Belokon's) conditions will be reported in the full publication on this project.