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A Short Diastereoselective Synthesis of Orthogonally Protected Diaminosuccinic Acid Derivatives

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Abstract: Homogeneous, Rh-catalyzed hydrogenation of heteromeric olefinic glycine dimers presents an efficient route to diastereomerically pure, orthogonally protected diaminosuccinic acid derivatives depending on the double bond geometry of the starting material. The products were obtained as racemates.

α,β-Diamino acids constitute a structural element in several antibiotics, such as capreomycins, antrimycin, and lavendomycin.[1] A variety of different routes have been reported for the synthesis[2] of α,β-diamino propanoic and α,β-diamino butanoic acids, highlighting the great interest in these vicinal diamine components.[3] In addition, natural and synthetic diamino dicarboxylic acids play an important role as cross-linking elements and may be used for stabilization of peptide secondary structures and the introduction of conformational constraints. To date, most synthetic efforts have concentrated on diaminopimelic acid, an essential component of bacterial peptidoglycan cell walls,[4] and diaminosuberic acid, a dicarba analogue of cystine.[5] However, it has also been shown that shorter connections can be advantageous for biological activity.[6] Major approaches to diaminosuccinic acid derivatives[7] include oxidative dimerization with the possible use of chiral esters for asymmetric induction,[8] Pd-catalyzed α-alkylation,[9] and chiral pool derived electrophilic amination of aspartic acid enolates.[10] However, these methods often need special protecting groups or, as in the latter case, require different syntheses for each diastereomer. Herein, we report an efficient method for the preparation of racemic diastereomerically pure, orthogonally protected diaminosuccinic acids starting from easily accessible olefinic glycine dimers.[11]

We envisaged a *cis*-selective hydrogenation of olefinic glycine dimers to provide either the *syn*- or *anti*-isomers of the diamino dicarboxylic acids, depending on the double bond geometry. Catalytic hydrogenation of dehydroamino acids is one of the most efficient methods for the enantioselective preparation of α-[12] and β-amino[13] acids. In our case, however, the strong deactivation[14] of the tetrasubstituted double bond[15] had to be overcome, and additionally, the hydrogenation should be stereoselective[16] and compatible with *N*-carbamate protecting groups[17] to facilitate later deprotection of the products.

To study and optimize the reaction conditions, we chose the symmetrical *N*-Boc-glycinate dimer **1** as an example. The *Z*- and *E*-isomers of **1** are easily accessible,[11] and the

(1) For comprehensive overviews of biologically active α,β-diamino acids, see: (a) Luo, Y.; Blaskovich, M. A.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106−6111. (b) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017−5025 and references therein.

(2) Most methodologies rely on stepwise preparations, often starting from chiral pool precursors. Recently, some new catalytic approaches such as olefinic diamination[2a−c] or Mannich reaction of imines with glycine derivatives[2d] have been developed: (a) Muñiz, K.; Nieger, B. *Synlett* **2003**, 211−214. (b) Pei, W.; Timmons, C.; Xu, X.; Wei, H.-X.; Li, G. *Org. Biomol. Chem.* **2003**, *1*, 2919−2921. (c) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem.* **2003**, *67*, 4777−4781. (d) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583−2591. A summary of different synthetic methods and related literature can be found in ref 1a and (e) Ambroise, L.; Dumez, E.; Szeki, A.; Jackson, R. F. W. *Synthesis* **2002**, 2296−2308. (f) Viso, A.; de la Pradilla, R. F.; López-Rodríguez, M. L.; García, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542−1547.

(3) (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (b) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755−1792 and references therein.

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(5) (a) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130−2132. (b) Nutt, R. F.; Strachan, R. G.; Veber, D. F.; Holly, F. W. *J. Org. Chem.* **1980**, *45*, 3078−3080. (c) Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M.; Taylor, R. J. K. *J. Org. Chem.* **2002**, *67*, 1802−1815 and references therein.

(6) Bhatnagar, P. K.; Agner, E. K.; Alberts, D.; Arbo, B. E.; Callahan, J. F.; Cuthbertson, A. S.; Engelsen, S. J.; Fjerdingstad, H.; Hartmann, M.; Heerding, D.; Hiebl, J.; Huffman, W. F.; Hysben, M.; King, A. G.; Kremminger, P.; Kwon, C.; LoCastro, S.; Løvhaug, D.; Pelus, L. M.; Petteway, S.; Takata, J. S. *J. Med. Chem.* **1996**, *39*, 3814−3819.

(7) Diaminosuccinic acid (3-aminoaspartic acid)[7a,c,d] has been isolated from *Streptomyces rimosus* ((+)-(*S,S*)-diastereomer).[7b] Several studies support its possible use as ligand for aspartate-dependent enzymes that might be of interest for tumor therapy:[7e] (a) Ozaki, Y.; Iwasaki, T.; Miyoshi, M.; Matsumoto, K. *J. Org. Chem.* **1979**, *44*, 1714−1716. (b) Hochstein, F. A. *J. Org. Chem.* **1959**, *24*, 679−680. (c) McKennis, H.; Yard, A. S. *J. Org. Chem.* **1958**, *23*, 980−982. (d) Biernat, J. F. *Rocz. Chem.* **1971**, *45*, 2081−2087. (e) Chang, P. K.; Sciarini, L. J.; Handschumacher, R. E. *J. Med. Chem.* **1973**, *16*, 1277−1280.

(8) Alvarez-Ibarra, C.; Csáky, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478−2482.

(9) Chen, Y.; Yudin, A. K. *Tetrahedron Lett.* **2003**, *44*, 4865−4868.

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(11) Schumann, S.; Zeitler, K.; Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron* **2000**, *56*, 4187−4195.

(12) (a) Ager, D. J. *Curr. Opin. Drug Discov. Devel.* **2002**, *5*, 892−905. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151. (c) Burk, M. J.; Bienewald, F. In *Transition Metals in Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, pp 13−24 and references therein.

(13) As a consequence of the increasing interest in β-amino acids,[13a] several examples have been described; for a recent review, see ref 13b and references therein: (a) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905−925. (b) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355−361.

(14) Only few examples for the hydrogenation of diamino dehydroamino acid derivatives are known: (a) McGarrity, J.; Spindler, F.; Fuchs, R.; Eyer, M. European Patent EP-A 624 587A2, 1995; *Chem. Abstr.* **1995**, *122*, P81369q. (b) Kuwano, R.; Okuda, S.; Ito, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2773−2775. (c) Robinson, A. R.; Lim, C. Y.; He, L.; Ma, P.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4141−4147. (d) Robinson, A. J.; Stanislawski, P.; Mulholland, D.; He, L.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4148−4152.

(15) Hydrogenation of tetrasubstituted double bonds remains challenging; for some selected examples, see: (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375−9376. (b) Burk, M. J.; Gross, M. F.; Harper, G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem* **1996**, *68*, 37−44.

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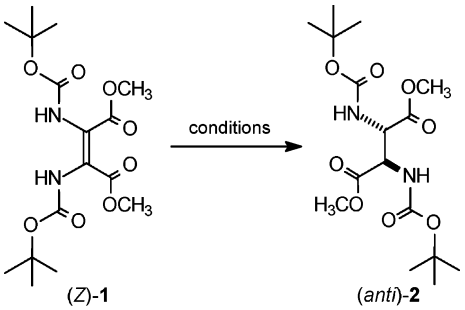
TABLE 1. Conditions for Hydrogenation of Dimer 1



entry	catalyst[a]/reagent	solvent	*T* [°C]	*p* [bar]	result[b]
1[c]	PtO_2	MeOH	rt	5	27% conv; **2** *anti*/*syn*; isomerized **1**
2	Pd/C	MeOH	85	85	36% conv; **2** *anti*/*syn* = 2:1
3	N_2H_2	CH_2Cl_2	rt		
4	Mg/ultrasound	MeOH	rt		
5	$Pd(PPh_3)4/Bu_3SnH$	THF	rt		
6[c]	Et_3SiH/TFA	TFA	rt		
7[c]	$Rh(PPh_3)_3Cl$	MeOH	60	1	
8	$[Rh(COD)Cl]_2$; dppe	MeOH	rt	5	29% conv; **2** *anti*/*syn* = 5:1
9	$[Rh(COD)Cl]_2$; dppf	toluene	50	70	55% (*anti*)-**2**
10	$[Rh(COD)Cl]_2$; dppf	toluene	80	90	92% (*anti*)-**2**
11[d]	$[Rh(COD)Cl]_2$; dppf	toluene	80	90	90% (*syn*)-**2**

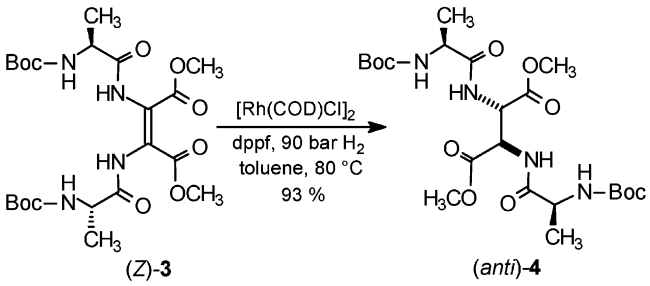
[a] 10 mol % catalyst was used; entries 3−6 represent non-catalytic reaction conditions. [b] Ratio of *anti*/*syn*-isomers determined by integration of baseline separated methyl ester singlets in the ^{1}H NMR spectra. [c] Instead of Boc-protected dimer (*Z*)-**1**, the corresponding benzoyl derivative was used. [d] (*E*)-**1** was used as substrate.

spectroscopic data of both diastereomers of the resulting diamino dicarboxylic acid derivative **2** are known from the literature.[10a,18] Disappointingly, all of our attempts (see Table 1; entries 1−8) to achieve the hydrogenation with different heterogeneous and homogeneous catalyst systems either failed or provided diastereomeric mixtures with only low conversions.

Hydrogenation of (*Z*)-**1** with H_2/PtO_2 under mild conditions yielded just 27% of a diastereomeric mixture (entry 1). On raising temperature and H_2 pressure and using Pd/C as a catalyst (entry 2), a 2:1 mixture of *anti*- and *syn*-isomers was obtained.[19] First attempts with Rh-catalyzed homogeneous hydrogenations (entry 8) showed similar problems. However, on introducing the more stable 1,1′-bis(diphenylphosphino)ferrocene (dppf) catalyst system, the expected diastereomer (*anti*)-**2** could be obtained exclusively (entry 9); further optimization by increasing the temperature and H_2 pressure led to full conversion and afforded (*anti*)-**2** in 92% (entry 10) and (*syn*)-**2** in 90% yield (entry 11).

To study the influence of adjacent chiral centers on the stereochemical outcome of the reaction, the terminal

SCHEME 1. Stereospecific Hydrogenation of the *cis* Dipeptide Dimer (*Z*)-3



dipeptide dimer (*Z*)-**3** (see Scheme 1) was used. It yielded a single diastereomer, (*anti*)-**4**, thus proving the stereospecifity of the hydrogenation.[20]

Further studies addressed the selection of suitable orthogonal protecting groups,[21] which had to be compatible with the reagents used for dimer synthesis (SO_2Cl_2) as well as the hydrogenation conditions. Moreover, they should allow a simple separation of the *E*- and *Z*-olefinic dimers to facilitate the access to the *E*-substrate. All of these prerequisites are met with the heteromeric diaminosuccinic acid derivative **5** shown in Figure 1, whichshould permit the selective removal of all four protecting groups.[22]

(16) In many cases the *E*- and *Z*-isomers show differences in respect to selectivity and conversion: (a) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 913−916. For cases in which only one enantiomer was obtained from an *E*/*Z* mixture, see: (b) Lee, S.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429−2431. (c) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159−4161 and references therein.

(17) Most procedures have been developed for *N*-acyl protecting groups. Recently, successful approaches for *N*-carbamate-protected dehydroamino acids have been reported: (a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534−3543. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372. (c) Kuwano, R.; Ito, Y. *J. Org. Chem.* **1999**, *64*, 1232−1237. (d) See ref 12c. (e) Almena Perea, J. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 375−384.

(18) Both *syn*- and *anti*-(*meso*) diastereomers **2** show slight but distinct differences in their ^{1}H and ^{13}C NMR spectra. Their stereochemical assignment was established by Sardina et al. by the analysis of NOE effects and coupling constants of their cyclic urea derivatives.[10a]

(19) The low stereoselectivity might be due to isomerization processes on the catalyst's surface promoted by the long reaction times: King, A. O.; Larsen, R. D. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-VCH: Weinheim, 1998; Vol. 2, chapter VII.2, pp 13−24. This assumption is supported by the isolation of isomerized starting material (entry 1).

(20) Because of the symmetry of starting material (*Z*)-**3** *syn* addition of dihydrogen (as known from the model systems) at both sides of the double bond furnishes the same nonracemic diastereomer (*anti*)-**4**.

(21) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999. (b) Clarke, P. A.; Martin, W. H. C. *Annu. Rep. Prog. Chem., Sect. B* **2003**, *99*, 84−103.

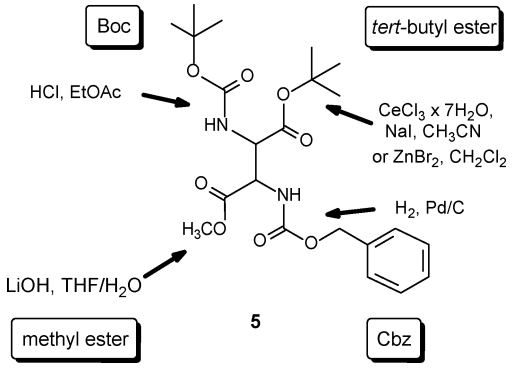
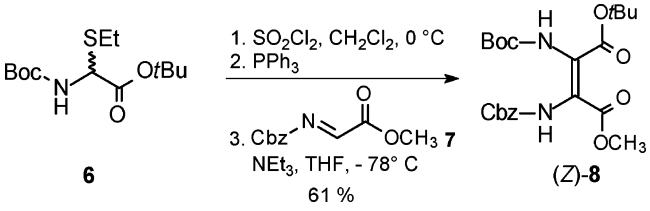


FIGURE 1. Orthogonally protected diaminosuccinic acid derivative **5** with possible conditions for deprotection.

SCHEME 2. Synthesis of Orthogonally Protected *cis* Dipeptide Dimer (*Z*)-8

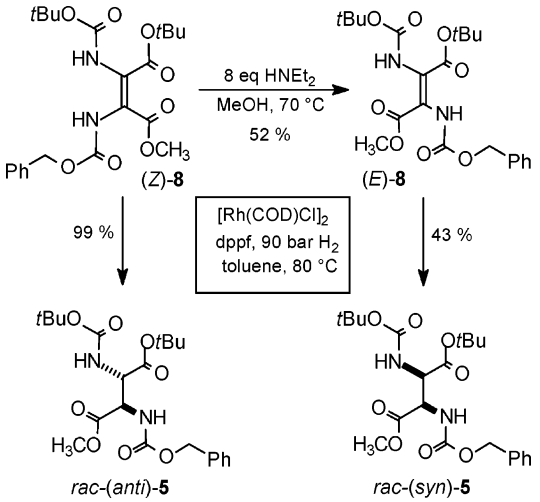


The diastereoselective synthesis of **5** started from two different α-(ethylthio)glycine precursors,[23] **6** and **7**, that were cross-coupled to (*Z*)-**8** in 61% yield (Scheme 2).

Isomerization of the central double bond under basic conditions afforded the *trans*-isomer (*E*)-**8**[24] (Scheme 3). Hydrogenation of each isomer produced the racemic diaminosuccinic acid derivatives (*anti*)-**5** and (*syn*)-**5**, respectively, in good yield.

In conclusion, hydrogenation of olefinic glycine dimers and their corresponding peptide derivatives provides a short and flexible route to diastereopure diaminosuccinic acid derivatives in racemic form. An extension of this reaction to the synthesis of optically pure compounds should be possible by using asymmetric hydrogenation conditions or chiral ester groups.

SCHEME 3. Stereospecific Hydrogenation of Orthogonally Protected Dimers (*Z*)-8 and (*E*)-8



Experimental Section

General Procedure for Homogeneous Hydrogenation of Glycinate Dimers. For the hydrogenation of 0.15 mmol of a glycinate dimer, a solution of 10 mol % of the respective Rh-complex in 5 mL of absolute and degassed toluene was prepared. After addition of 2 equiv of a suitable phosphine ligand (dppf, etc.) (based on Rh-complex), the mixture was stirred for 30 min at room temperature and then transferred via cannula to the hydrogenation flask containing the glycinate dimer (c = 0.4 mmol/mL) under an argon atmosphere. After three cycles of evacuation and H_2 refilling, the hydrogenation was conducted at the H_2 pressure and temperature given in Table 1. Upon complete conversion (TLC) the reaction mixture was concentrated in vacuo. To remove catalyst remains, the residue was purified by column chromatography on silica gel.

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Supporting Information Available: Experimental details and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Several methods are known for deprotection of *tert*-butyl esters in the presence of Boc groups[22a,b] and vice versa.[22c] Selective cleavage of Cbz-protection is achievable via Pd-catalyzed hydrogenation; however, homogeneous hydrogenation leaves the Cbz group untouched.[22d] (a) Marcantoni, E.; Massaccesi, M.; Torregiani, E.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2001**, *66*, 4430−4432. (b) Wu, Y.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett.* **2000**, *41*, 2847−2849. (c) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216−3218. (d) Kreuzfeld, H.-J.; Döbler, C.; Krause, H. W.; Facklam, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2047−2051.

(23) For a general procedure for peptide dimerization see Supporting Information and ref 11.

(24) After reaching an approximately 1:1 ratio of *Z*- and *E*-isomers, the reaction is terminated; non-converted *Z*-starting material can be recovered and reused.