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Radical reaction of Williams' glycinate auxiliaries with α-amidoacrylates: synthesis of orthogonally functionalized (2*R*,4*R*)- and (2*R*,4*S*)-diaminoglutamic acids

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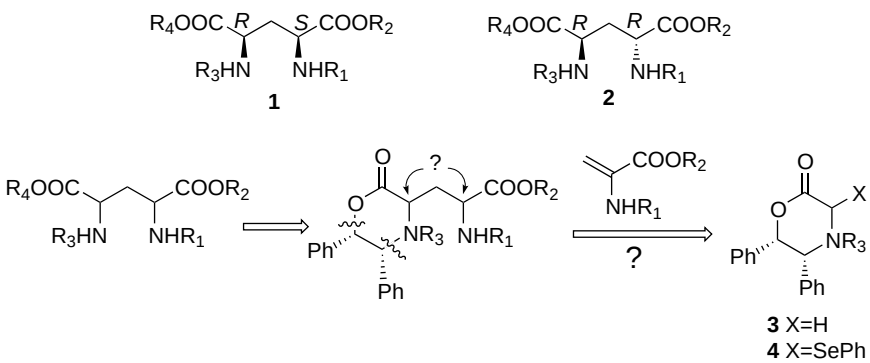
Abstract—Orthogonally functionalized (2*R*,4*S*)- and (2*R*,4*R*)-diaminoglutamic acids **10**, **11**, and **12**, **13** were obtained in three steps starting from (2*S*,3*R*)-(+)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate **5**, employing a radical reaction of selenide **6** with methyl 2-acetamidoacrylate **7** as a key step.

Glutamic acid is an important chemical messenger which is released in most of the excitatory synapses of mammalian central nervous systems.[1] However, excessive or disregulated release has been linked to neuronal degeneration in such devastating brain disorders as Huntington's chorea, Alzheimer's disease, schizophrenia and others.[2] The interest in identifying and mapping the role of different glutamic acid receptors has stimulated the synthesis of a number of 4-substituted analogs.[3]

Disclosed herein is the synthesis of differentially functionalized (2*R*,4*S*)- and (2*R*,4*R*)-diaminoglutamic acids **1** and **2** (Scheme 1) by adaptation of an approach which has previously found utility in peptidomimetic research for peptides having hemoregulatory activity.[4]

It has been demonstrated by R. M. Williams[5] and others[6] that enantiomerically pure morpholinecarboxylates **3** are useful templates for the stereoselective preparation of a number of proteino- and non-proteinogenic amino acids. Although these auxiliaries have been applied for amino acid synthesis under various nucleophilic and electrophilic conditions, to the best to our knowledge, a homolytic process has not been explored. It was anticipated that the title aminoglutamic acid derivatives should be accessible via a radical reaction of morpholinecarboxylates **3** and α-amidoacrylates. Based on precedents in ionic reactions[5a] we expected the



Scheme 1.

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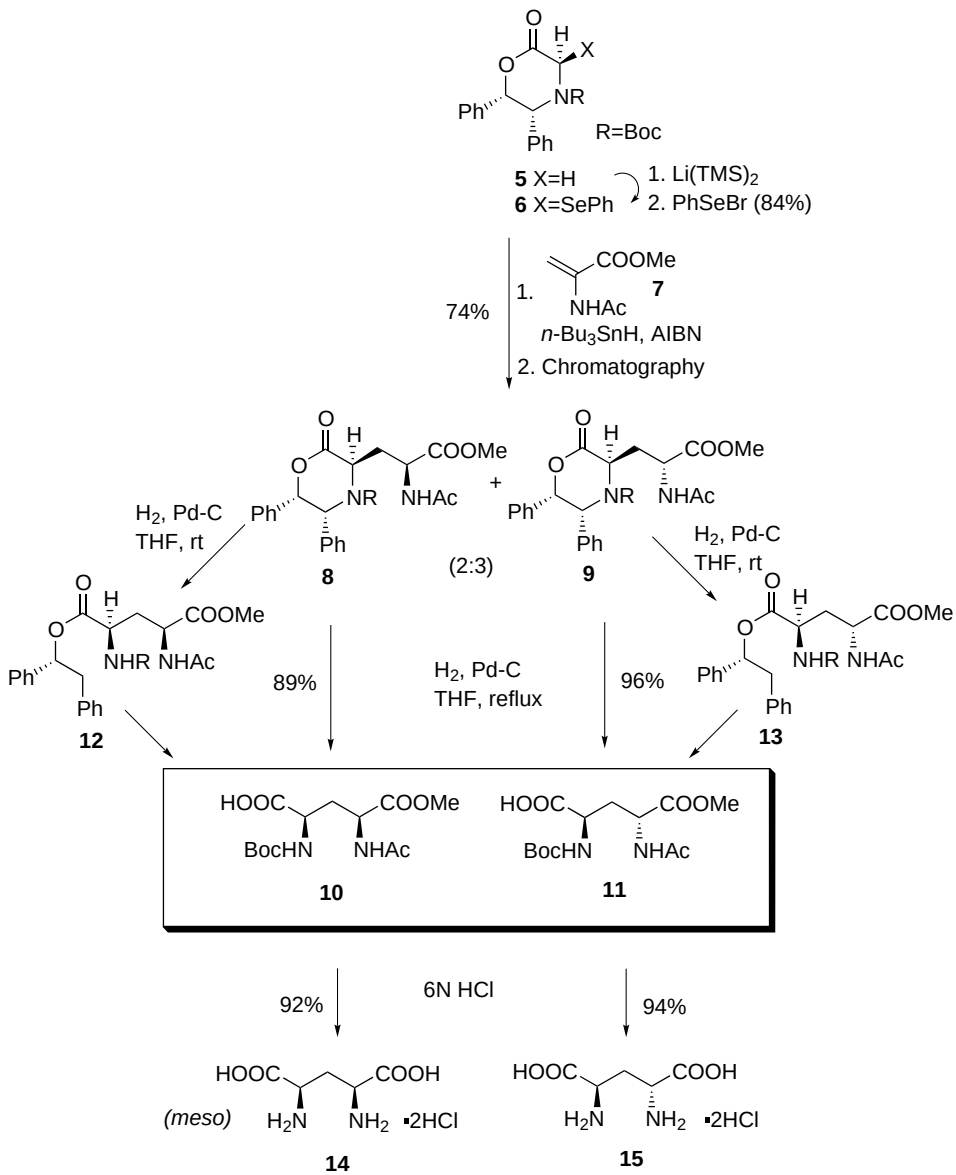
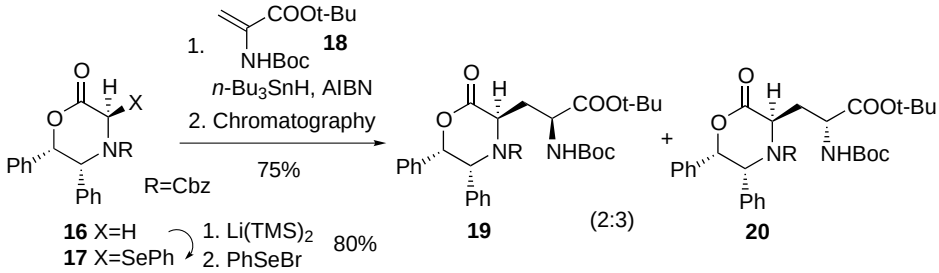
respective Williams' radicals to react stereoselectively with the amidoacrylate acceptors. The stereochemical outcome of such designed radical reactions at newly created centers which could result in formation of four possible diastereomers was of interest.

Treatment of commercially available (2*S*,3*R*)-(+)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate **5** with lithium bis(trimethylsilyl)amide (THF, −78°C) followed by PhSeBr produced selenide **6** in 84% yield (Scheme 2). ^{1}H NMR analysis of the crude product revealed that alkylation with PhSeBr occurred exclusively *anti* to the phenyl groups with 98% ds [^{1}H NMR, δ: benzyl methine protons at 5.16 (d, *J* 3Hz) and 6.17 (d, *J* 3 Hz), PhSeC<u>H</u> at 6.26 (s)].[7] A single recrystallization of crude **6** from MeOH afforded diastereomerically pure selenide **6**.

The reaction of selenide **6** with *n*-Bu_3SnH/AIBN and methyl 2-acetamidoacrylate **7**, carried out in toluene solution at 80°C for 2 h, produced a 2:3 mixture of only two, out of the four possible, diastereomers. The diastereomers were separated by chromatography and analyzed by ^{1}H NMR. The stereochemical assignment was based on the chemical shifts and coupling constants of the methine benzylic proton signals. In less polar diastereomer **8**, these methine protons appeared at δ 5.11 ppm (1H, d, *J* 3Hz) and 6.18 ppm (1H, d, *J* 3 Hz) and in the more polar diastereomer **9**, at δ 5.13 ppm (1H, d, *J* 3Hz) and 6.20 ppm (1H, d, *J* 3 Hz). Correlation with reported data showed that the substituent was introduced *anti* to the phenyl groups and therefore, the absolute configuration at this center is *R* in both diastereomers.[7] However, at this stage the configuration could not be established at the second



Scheme 2.



Scheme 3.

newly created asymmetric center and therefore correlation to known substances was necessary.

Compounds **8** and **9** were subjected separately to hydrogenolysis in a refluxing mixture of THF/EtOH (10% Pd/C, 3 h) producing the desired orthogonally functionalized amino acids **10** and **11**, respectively. Interestingly, we observed that when the hydrogenolysis reaction of compounds **8** and **9** was carried out at room temperature a selective cleavage of the carbon–nitrogen bond occurred, thus providing compounds **12** and **13**. Assignment of the second stereogenic center was solved by the removal of all protecting groups from **10** and **11** and correlation to the known *meso*-2,4-diaminoglutamic acid[8] and (2*R*,4*R*)-2,4-diaminoglutamic acids.[9] Thus, hydrolysis of **10** in boiling 6N HCl afforded diaminoglutamic acid hydrochloride with optical rotation $\{[\alpha]_D^{25}=0$ (c 1.0, H_2O)$\}$ and ^{1}H NMR spectra [δ: 2.38 and 2.54 (2H, triplet of ABquartet, J_{AB} 15.1 Hz, J 6.2 Hz), 4.20 (2H, t, J 6.2 Hz)] corresponding with the *meso* structure **14**.[9b] Similarly, acidic hydrolysis of compound **11** produced (2*R*,4*R*)-diaminoglutamic acid hydrochloride **15**; $\{[\alpha]_D^{25}=-20$ (c 1.0, H_2O)$\}$; ^{1}H NMR, δ: 2.36 (2H, t, J 6.8 Hz), 3.97 (2H, t, J 6.8 Hz).[9a]

In a similar radical reaction, both components, the CBz-protected selenide **17** and *N*-Boc-*t*-butylaminoacrylate **18**, were selected as being more conveniently protected for suitable manipulation of its orthogonal functional groups in the expected products. When the reaction of **17** with **18** was carried out under the above described conditions (as for **6** with **7**), a mixture of two diastereomers **19** and **20** (Scheme 3) in a 2:3 ratio was obtained which differed only by the configuration at the remote center.

In summary, a three-step procedure for the synthesis of orthogonally functionalized (2*R*,4*R*)-diaminoglutamic acid and (2*R*,4*S*)-diaminoglutamic acid was developed using morpholinecarboxylate **5** and amidoacrylate **7**, as starting materials, by applying a radical addition–trapping sequence to create both stereogenic centers. The formation of a carbon–carbon bond between morpholine auxiliaries and acrylates, under radical addition to amidoacrylates, is fully stereoselective and *anti* to the phenyl groups on the morpholine ring; however, hydrogen trapping reactions proceed with modest selectivity at the remote centers.

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References

1. (a) Chamberlin, R.; Bridges, R. In *Drug Design for Neuroscience*; Kozikowski, A. P., Ed.; Raven Press: New York, 1993; p. 261; (b) Brown, P. *New Scientist* **1992**, *136*, 1.
2. (a) Krogsgaard-Larsen, P.; Ebert, B.; Lund, T. M.; Brauner-Osborne, H.; Slok, F. A.; Johansen, T. N.; Brehm, L.; Madsen, U. *Eur. J. Med. Chem.* **1996**, *31*, 515; (b) Lees, G. *CNS Drugs* **1996**, Jan 5 (1).
3. (a) Hanessian, S.; Margarita, R. *Tetrahedron Lett.* **1998**, *39*, 5887; (b) Dugave, C.; Cluzeau, J.; Menez, A.; Gaudry, M.; Marquet, A. *Tetrahedron Lett.* **1998**, *39*, 5775; (c) Dugave, C.; Menez, A. *J. Org. Chem.* **1996**, *61*, 6067; (d) Gu, Z-Q.; Hesson, D. P.; Pelletier, J. C.; Maccecchini, M-L.; Zhou, L-M.; Skolnick, P. *J. Med. Chem.* **1995**, *38*, 2518; (e) Gu, Z-Q.; Hesson, D. P. *Tetrahedron: Asymmetry* **1995**, *6*, 2101; (f) Johnstone, A. N. C.; Lopatriello, S.; North, M. *Tetrahedron Lett.* **1994**, *35*, 6335; (g) Echalier, F.; Constant, O.; Bolte, J. *J. Org. Chem.* **1993**, *58*, 2747; (h) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401; (i) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.
4. (a) Bhatnagar, P. K.; Agner, E. K.; Albers, D.; Arbo, B. E.; Callahan, J. F.; Cuthbertson, A. S.; Engelsen, A. J.; Fjerdingstad, H.; Hartmann, M.; Heerding, D.; Hiebl, J.; Huffman, W. F.; Hysben, M.; King, A. G.; Kremminger, P.; Kwon, C.; LoCastro, S.; Lovhaug, D.; Pelus, L. M.; Petteway, S.; Takata, J. S. *J. Med. Chem.* **1996**, *39*, 3814; (b) Undheim, K.; Kremminger, P. Patent Application WO 93-GB1171 930602.
5. For a review of asymmetric syntheses of α-aminoacids, see: (a) Williams, R. M. *Synthesis of Optically Active α-Aminoacids*; Pergamon Press: Oxford, 1989; Vol. 7; (b) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11.
6. (a) Baker, S. R.; Parsons, A. F.; Pons, J-F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 7197; (b) Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 2815; (c) Kessler, H.; Wittmann, V.; Koeck, M.; Kottenhahn, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 902; (d) Goodall, K.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3257.
7. See Ref. 5a, p. 111.

8. (a) Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.* **1998**, *46*, 674; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555; (c) Arakawa, Y.; Goto, T.; Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.* **1995**, *43*, 535; (d) Krasov, V. P.; Zhdanova, E. A.; Korolyova, M. A.; Burina, I. M.; Kodess, M. I.; Kravtsov, V. Kh.; Biyushin, V. N. *Russ. Chem. Bull.* **1997**, *46*, 319.
9. (a) Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1998**, *9*, 71; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 863; (c) Belokon, Yu. N.; Chernoglazova, N. I.; Batsanov, A. S.; Garbalinskaya, N. S.; Bakhmutov, V. I.; Struchkov, Yu. T.; Belikov, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, 852.