Tetrahedron: *Asymmetry* 20 (2009) 1719–1721

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

A new and general route to 2-pyrrolylglycine, 2-pyrrolylalanine and homo-2-pyrrolylalanine derivatives

Kaushik Sarkar, Sovan K. Singha, Shital K. Chattopadhyay *

Department of Chemistry, University of Kalyani, Kalyani 741 235, West Bengal, India

ARTICLE INFO

Article history:
Received 4 June 2009
Accepted 26 June 2009
Available online 17 July 2009

ABSTRACT

A general route to α-, β- and γ-pyrrole-branched α-amino acid derivatives has been developed, which featured a one-pot ring-closing metathesis and aromatization reaction as the key step.

1. Introduction

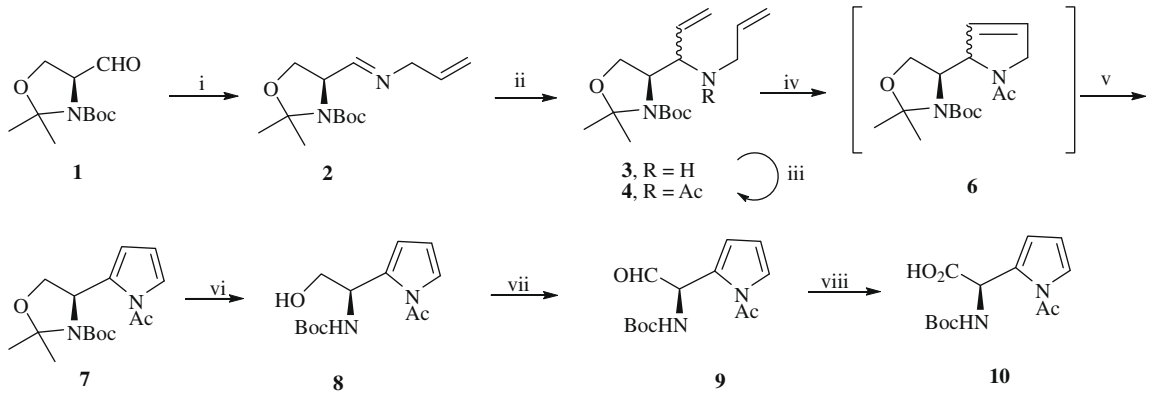
The synthesis and biological evaluation of non-proteinogenic α-amino acids are of continuing interest due to their widespread utility in the synthesis of designed peptides, proteins and other compounds of biological interest.[1] Moreover, their use as chemical building blocks is also well documented.[2] Of particular interest has been the synthesis of heterocycle-substituted α-amino acids, which may alter the physico-chemical properties of some proteinogenic amino acids and their peptides.[3] For example, the translational ability of thienylalanines,[4] DNA-binding ability of pyrrole amino acids,[5] histidine replacement ability of pyridylalanine in angiotensin,[6] and the metal-binding ability of bipyridylalanines[7] are only some examples of the important properties of this type of unusual amino acids. The most frequently used methods for the synthesis of enantiomerically pure heterocycle-substituted α-amino acids include: (a) construction[8] of the heterocyclic moiety involving transformations of readily available D- and L-amino acids/carbohydrates from the chiral pool, (b) asymmetric synthesis[9] of the chiral α-amino acid entity from a pre-formed heterocyclic structure using chiral nucleophilic or electrophilic glycine/alanine equivalents, (c) biocatalytic or chemical resolution of racemic precursors;[10] and (d) asymmetric hydrogenation of α-amino-α,β-didehydro acids and derivatives.[11] Most of these methods have found application in the synthesis of regioisomeric pyrrole-linked α-amino acids.[12] However, a general route to pyrrolylglycine, pyrrolylalanine and homo-pyrrolylalanine derivatives has to the best of our knowledge not been reported. Herein, we report the asymmetric synthesis of 2-pyrrolylglycine, 2-pyrrolylalanine and homo-2-pyrrolylalanine derivatives as potential analogues of phenylglycine, phenylalanine and homo-phenylalanine in a continuation of our interest[13] in the synthesis of heterocycle-substituted α-amino acid derivatives from naturally occurring amino acids.

2. Results and discussion

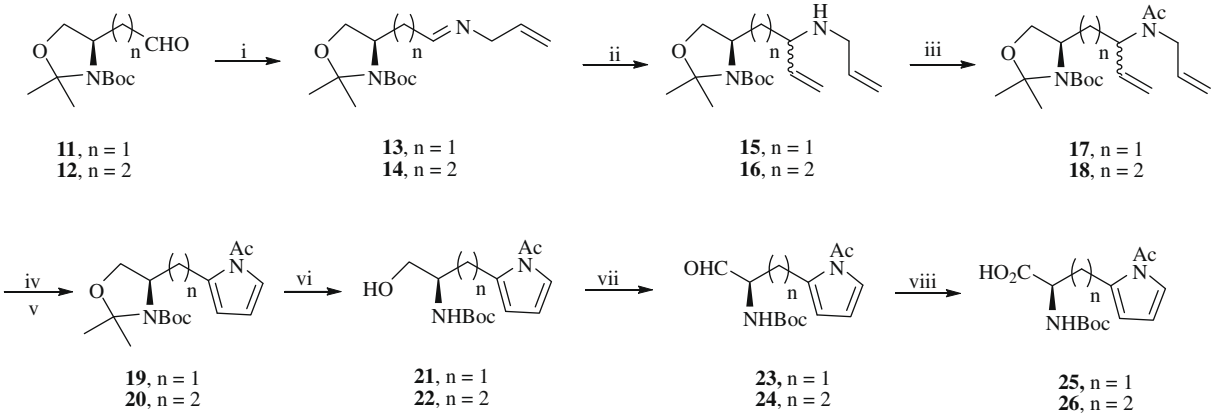
Our synthesis of the pyrrolylglycine derivative **7** (Scheme 1) started from the known Garner's aldehyde[14] **1** (Scheme 1), which on dehydrative condensation with allylamine led to the formation of the corresponding imine **2**. The latter was obtained in essentially pure form and was used as such in the next step. We anticipated that the pyrrolidinylglycine ring system could possibly be constructed by ring-closing metathesis of an appropriate N-tethered diene, obtainable from the addition of suitable vinyl metal species to the *N*-allylimine derivative **2**. Aromatization of the thus obtainable pyrrolidinyl derivative could then be effected either separately or in a one-pot way to give the desired pyrrole derivative based on the precedence of aromatic or heteroaromatic ring formation via a RCM-aromatization sequence.[15] Alkylation of imines has been extensively studied as a route to the preparation of amines and excellent protocols for catalyst-controlled, auxiliary-controlled and substrate-controlled addition reactions have been developed.[16] Thus, the addition of imine **2** to vinylmagnesium bromide in ether solution proceeded well at −30 °C and the corresponding amine **3** was obtained under optimized conditions in an acceptable yield, but as a mixture of diastereoisomers (83:17, HPLC), which could not be separated by chromatography. The stereochemical outcome of this reaction was thought to be less consequential for the present study as the stereocentre would be destroyed in a subsequent step. Thus, the mixture of amines **3** was N-acylated under conventional conditions to provide the corresponding N-tethered dienes **4** also as an inseparable mixture. Ring-closing metathesis of **4** with Grubbs' first generation catalyst,[17] benzylidene bis-tricyclohexyl-phosphinoruthenium(IV) dichloride **5,** proceeded well in dichloromethane at ambient temperature and the desired dihydropyrrole derivative **6** was obtained in a good yield. However, we took recourse to a one-pot RCM-aromatization sequence as developed by us and others.[18] Thus, the crude reaction mixture from the RCM reaction was treated with DDQ in refluxing benzene to obtain pyrrole derivative **7** in a combined yield of 54% over two steps. Acid-catalyzed deprotection of the oxazolidine unit present

* Corresponding author. Fax: +91 33 25828282.
E-mail address: skchatto@yahoo.com (S.K. Chattopadhyay).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.06.021



Scheme 1. Reagents and conditions: (i) allyl amine, MS (4 Å), CH_2Cl_2, 0 °C, 24 h, 95%: (ii) vinylmagnesium bromide, Et_2O, −30 °C, 12 h, 66%; (iii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, 12 h, 83%; (iv) Grubbs' catalyst **5** (5 mol %), CH_2Cl_2, rt, 8 h; (v) DDQ, benzene, reflux, 18 h, 54% over two steps; (vi) HCl (0.5 M), MeOH, rt, 5 h, 84%; (vii) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h; (viii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, ^{t}BuOH, H_2O, rt, 12 h, 51% over two steps.



Scheme 2. Reagents and conditions: (i) allylamine, MS (4 Å), CH_2Cl_2, 0 °C, 24 h, **13**, 94%; **14**, 92% (ii) vinylmagnesium bromide, Et_2O, −30 °C, 12 h, **15**, 69%; **16**, 72%; (iii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, 12 h, **17**, 78%; **18**, 81%; (iv) Grubbs' catalyst **5** (5 mol%), CH_2Cl_2, rt, 8 h; (v) DDQ, benzene, reflux, 18 h, **19**, 56%; **20**, 54%; (vi) HCl (0.5 M), MeOH, rt, 5 h, **21**,79%; **22**, 77%; (vii) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h; (viii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, ^{t}BuOH, H_2O, rt, 12 h, **25**, 52%; **26**, 49% over two steps.

in **7** using dilute hydrochloric acid in methanol then led to the formation of the primary alcohol **8** in a very good yield. This was then subjected to a two-step oxidation to the corresponding carboxylic acid involving initial formation of the corresponding aldehyde **9** using Dess–Martin periodinane[19] followed by Pinnick oxidation[20] of the latter to compound **10** in a combined yield of 61% over two steps. The synthesis of the pyrrolylglycine derivative **10** proceeded in an overall yield of 12% over eight steps from **1**.

The aspartic acid-derived chiral aldehyde **11** (Scheme 2), prepared following the literature,[21] was similarly converted to imine **13** and was then treated with vinylmagnesium bromide to furnish the mixture (∼1:1) of amines **15** in a good yield. This mixture was then N-acylated to the corresponding amides **17**, which when subjected to the developed one-pot RCM-aromatization sequence, provided the pyrrole derivative **19** in 56% yield over two steps. Acid-catalyzed deprotection of the latter to aminoalcohol **21** followed by its sequential oxidation then led to the pyrrolylalanine derivative **25** in an overall yield of 11.6% over eight steps from **11**.

Similarly, the glutamic acid-derived aldehyde **12**, prepared analogously, when subjected to the same sequence of events *viz.* conversion to the imine **14**, vinylation of the latter to the mixture (∼1:1) of amines **16**, one-pot RCM-aromatization of the *N*-acetyl derivatives **18** to the pyrrole derivative **20** followed by sequential deprotection (leading to **22**) and oxidation led to the homo-pyrrolylalanine derivative **26** in an overall yield of 11% over eight steps from **12**.[22]

3. Conclusion

In short, we have demonstrated that 2-pyrrolylglycine, 2-pyrrolylalanine and 2-pyrrolyl-homo-alanine derivatives can be conveniently prepared from enantiomerically pure aldehydes derived from serine, aspartic acid and glutamic acid using commonly available reagents and easy to conduct experiments. The compounds prepared may find uses as an analogue of phenylglycine, phenylalanine or homo-phenylalanine in the design and synthesis of modified peptides/proteins. The compounds may also serve as building blocks in organic synthesis and the developed methodology may complement those existing in the literature for the preparation of such type of compounds.

Acknowledgement

We are thankful to DST, New Delhi, for funds (Grant No. SR/S1/OC-51/2005).

References

1. Synthesis of peptides and peptidomimetics: *Houben-Weyl Methods in Organic Chemistry*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, 2001.
2. (a) Barret, G. C.. In *Amino Acids, Peptides and Proteins*; The Chemical Society: London, 2001; Vol. 32; (b) Williams, R. M. In *Synthesis of Optically Active a-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Organic Chemistry Series; Pergamon Press: Oxford, 1989; Vol. 7,.

3. For some elegant reports on heterocyclic amino acids, see: (a) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303; (b) Hanessian, S. *Heterocycles* **2000**, *52*, 1231; (c) Davies, S. G.; Bull, S. D.; Fox, D. J.; Kelley, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1858; (d) Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666; (e) Bunnage, M. E.; Davies, S. G.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2763; (f) Lygo, B.; Andrews, B. I.; Crossby, J.; Peterson, J. A. *Tetrahedron Lett.* **2005**, *46*, 6629.
4. Kothakota, K.; Mason, T. L.; Tirrell, D. A.; Fournier, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 536.
5. Chakraborty, T. K.; Mohan, B. K.; Gnanamani, M.; Maiti, S. *Tetrahedron Lett.* **2005**, *46*, 647.
6. Hsieh, K.; Jorgensen, E. C.; Lee, T. C. *J. Med. Chem.* **1979**, *22*, 1199.
7. Ghadiri, M. R.; Soares, C.; Choi, C. *J. Am. Chem. Soc.* **1992**, *114*, 4000.
8. For instance, see: (a) Wasserman, H. H.; Long, Y. O.; Parr, J. *Tetrahedron Lett.* **2003**, *44*, 361; (b) Dondoni, A.; Giovannini, P. P.; Massi, A. *Org. Lett.* **2004**, *6*, 2929; (c) Molina, L.; Moreno-Vargas, A. J.; Carmona, A. T.; Robina, I. *Synlett* **2006**, 1327; (d) Merino, P.; Padar, P.; Delso, I.; Thirumalaikumar, M.; Tejero, T.; Kovacs, L. *Tetrahedron Lett.* **2006**, *47*, 5013; (e) Barr, A.; Vankar, Y. D. *Tetrahedron Lett.* **2006**, *47*, 9035; (f) Greco, G.; Panzella, L.; Napolitano, A.; d'Ischia, M. *Tetrahedron Lett.* **2009**, *50*, 3095.
9. For instance, see: (a) Cremonesi, G.; Croce, P. D.; Fontana, F.; Forni, A.; Rosa, C. L. *Tetrahedron: Asymmetry* **2007**, *18*, 1667; (b) Shieh, W.-C.; Xue, S.; Reel, N.; Wu, R.; Fitt, J.; Repic, O. *Tetrahedron: Asymmetry* **2001**, *12*, 2421; (c) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Wishart, N.; Ellis, D.; Wythes, M. J. *Synlett* **1993**, 499.
10. For instance, see: (a) Podea, P. V.; Tosa, M. I.; Paizs, C.; Irimie, F. D. *Tetrahedron: Asymmetry* **2008**, *19*, 500; (b) Rolland-Fulerand, V.; Haroune, N.; Roumestant, M.-L.; Martinez, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4719; (c) Hoffman, K.; Bohn, H. *J. Am. Chem. Soc.* **1966**, *88*, 5914; (d) Bladon, C. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1151.
11. For instance, see: (a) Jones, S. W.; Palmer, C. F.; Paul, J. M.; Tiffin, P. D. *Tetrahedron Lett.* **1999**, *40*, 1211; (b) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Tetrahedron: Asymmetry* **2001**, *12*, 2381; (c) Dobler, C.; Kreuzfeld, H.-J.; Michalik, M.; Krause, H. W. *Tetrahedron: Asymmetry* **1996**, *7*, 117; (d) Walker, M. A.; Kaplita, K. P.; Chen, D.; King, H. D. *Synlett* **1997**, 169.
12. (a) Alongi, M.; Minetto, G.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 7069; (b) Wasserman, H. H.; Long, Y. O.; Zhang, R.; Parr, J. *Tetrahedron Lett.* **2002**, *43*, 3351; (c) Saaby, S.; Bayon, P.; Aburel, P. S.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352; (d) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **2000**, *11*, 3063; (e) Welch, M.; Philips, R. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 637; (f) Beecher, J. E.; Tirrell, D. A. *Tetrahedron Lett.* **1998**, *39*, 3927; (g) Bonauer, C.; Konig, B. *Synthesis* **2005**, 2367; (h) Yamano, K.; Shirahama, H. *Tetrahedron* **1992**, *48*, 1457; (i) Masquelin, T.; Broger, E.; Muller, K.; Schmid, K.; Obrecht, D. *Helv. Chim. Acta* **1994**, *77*, 1395.
13. (a) Thander, L.; Sarkar, K.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* **2009**, *20*, 1213; (b) Chattopadhyay, S. K.; Biswas, T.; Biswas, T. *Tetrahedron Lett.* **2008**, *49*, 376; (c) Bandyopadhyay, A.; Pal, B. K.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* **2008**, *19*, 1875; (d) Chattopadhyay, S. K.; Sarkar, K.; Thunder, L.; Roy, S. P. *Tetrahedron Lett.* **2007**, *48*, 6113.
14. (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979; (b) McKillop, A.; Taylor, R. J. K.; Watson, R.; Lewis, N. *Synthesis* **1994**, 31.
15. (a) Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. *Eur. J. Org. Chem.* **2005**, 1969; (b) Dieltiens, N.; Stevens, C. V.; DeVos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45*, 8995; (c) Grigg, R.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 4899; (d) van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311; (e) Chen, Y.; Diass, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2003**, *44*, 1379; (f) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732; (g) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803.
16. For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207; (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (c) Block, R. *Chem. Rev.* **1998**, *98*, 1407; (d) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895; (e) Thomas, E. J. *Chem. Commun.* **1997**, 411; (f) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125.
17. (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; For recent reviews, see: (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 2117; (c) Martin, S. F.; Dieters, A. *Chem. Rev.* **2004**, *104*, 2199; (d) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919.
18. (a) Chattopadhyay, S. K.; Pal, B. K.; Maity, S. *Chem. Lett.* **2003**, *32*, 1190; (b) Chattopadhyay, S. K.; Sarkar, K.; Karmakar, S. *Synlett* **2005**, 2083; (c) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 2585.
19. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
20. Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
21. Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.
22. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **10**: $[\alpha]_D = -106$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (1H, s), 6.41 (1H, s), 6.25 (1H, s), 5.93 (1H, d, *J* = 8.5), 5.75 (1H, d, *J* = 8.5), 3.65 (1H, br s), 2.57 (3H, s), 1.43 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 170.5, 154.7, 130.1, 121.8, 117.2, 112.5, 80.3, 52.1, 28.3, 23.5. Elemental Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.44; H, 6.58; N, 10.19. MS (TOF MS ES+): 305 (M+Na).*Compound* **25**: $[\alpha]_D = +16$ (*c* 1.0, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (1H, s), 6.16 (1H, s), 6.10 (1H, s), 5.23 (1H, br s), 4.55 (2H, br s), 3.56 (1H, d, *J* = 13.0), 3.15–3.13 (1H, m), 2.55 (3H, s), 1.36 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 167.8, 154.2, 132.1, 122.6, 118.6, 114.5, 86.2, 54.7, 28.4, 24.4, 21.5. MS (TOF MS ES+): 319 (M+Na).*Compound* **26**: $[\alpha]_D = -62$ (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (1H, s), 6.52 (1H, s), 6.40 (1H, d, *J* = 8.5), 5.80 (1H, br s), 5.302–5.26 (1H, m), 3.38–3.35 (2H, m), 2.56 (3H, s), 2.18–2.01 (2H, m), 1.45 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 169.1, 157.3, 133.4, 124.9, 119.6, 115.0, 87.6, 53.8, 28.9, 25.0, 22.8, 20.1. Elemental Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.18; H, 7.36; N, 9.29. MS (TOF MS ES+): 333 (M+Na).