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A stereodivergent route to two epimeric 2-pyrrolidinylglycine derivatives

Ayan Bandyopadhyay, Amit K. Pahari, Shital K. Chattopadhyay *

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

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ABSTRACT

A new route to two epimeric 2-pyrrolidinylglycine derivatives is developed, which features Mitsunobu amination of a chiral allyl alcohol and ring-closing metathesis as key steps.

α,β-Diamino acids belong to an important class of compounds of chemical and biological significance.[1] Therefore, there is growing interest in their synthesis.[1,2] In particular, diamino acids with a heterocyclic ring are important as conformationally constrained amino acids, chiral auxiliaries/building blocks and are present in several natural products, compounds **1–4** (Fig. 1).[3] Moreover, the synthesis and biological evaluation of heterocycle substituted non-proteinogenic α-amino acids are of current interest.[4]

We have recently reported the asymmetric synthesis of α,β-diamino acids such as piperidinylglycine[5] (**5**) and azetidinylglycine (**6**) derivatives.[6] Pyrrolidinylglycine (**4**) derivatives have also been synthesised and used as synthetic intermediates/scaffolds.[7] Herein, we report a stereodivergent route to two epimeric 2-pyrrolidinylglycine derivatives in continuation of our interest in the synthesis of heterocyclic amino acids utilising coded amino acids as chiral pool.[8]

Over the years, Garner's aldehyde[9] (**7** and its enantiomer, Fig. 2) has emerged as a valuable amino acid-derived building block for the asymmetric synthesis of diverse class of α-amino acids and related compounds.[10] We anticipated that the dihydropyrrolidinylglycine ring system **10** could possibly be constructed by ring-closing metathesis of an appropriate N-tethered diene **9** obtainable from Mitsunobu-type amination of the known chiral allyl alcohol **8a.** The epimeric allyl alcohol **8b** could then possibly be used to prepare another stereo-isomer of **10** in an analogous manner.

We thus focused on the preparation of the allyl alcohols **8a–b** (Scheme 1) from the common intermediate **7**. Direct vinylation of Garner's aldehyde with vinylmagnesium bromide/chloride has been reported[11] by many workers, including us,[8a] with varying degrees of selectivities for isomers **8a–b**, depending on the conditions used. However, this has invariably involved tedious separation of the undesired isomer which is usually formed in significant amount. We decided to use the three-step procedure

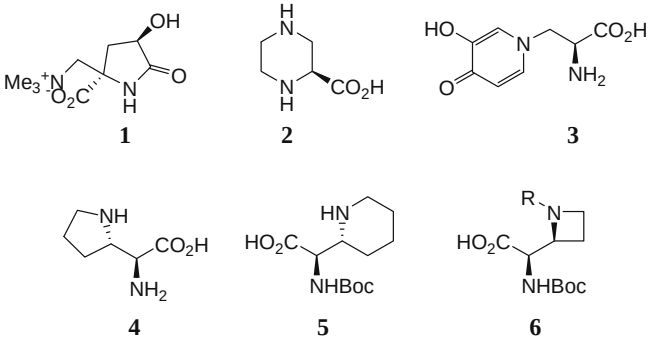

Figure 1. Some α,β-diamino acids of importance.

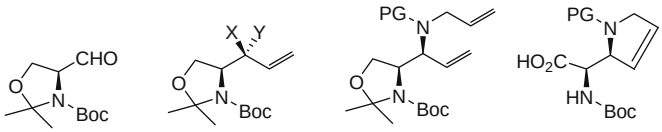

Figure 2. Synthetic plan for compound **10**.

* Corresponding author. Tel.: +91 33 25828750; fax: +91 33 25828282.
E-mail address: skchatto@yahoo.com (S.K. Chattopadhyay).

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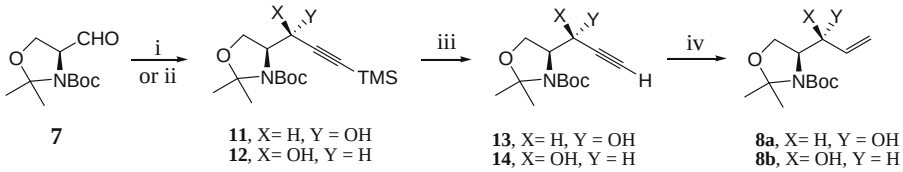
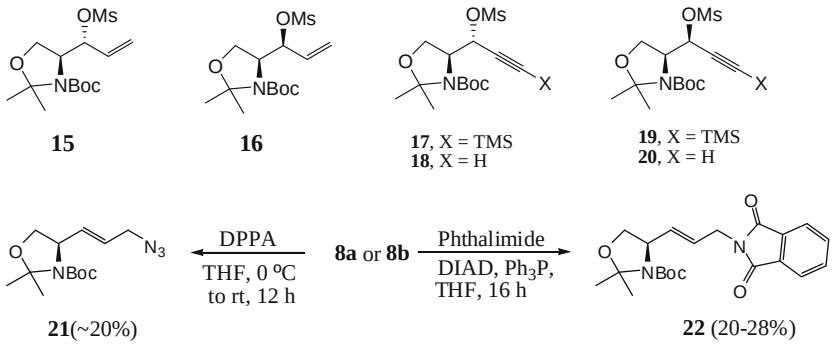


Scheme 1. Reagents and conditions: (i) ethynyltrimethylsilane (1.5 equiv), *n*-BuLi(1.5 equiv), HMPA (2 equiv), THF, −78 °C, 3 h, **11**, 90%; (ii) ethynyltrimethylsilane (1.5 equiv), *n*-BuLi (1.5 equiv), $ZnBr_2$ (1.5 equiv), Et_2O, −78 °C to rt, 18 h, **12**, 81%; (iii) NH_4F, *n*-$Bu_4N^+HSO_4^-$, CH_2Cl_2, rt, 1 h, **13**, 86%; **14**, 81%; (iv) Lindlar's catalyst (10 mol %), H_2, MeOH, 0.5–2 h, **8a**, 96%; **8b**, 99%.



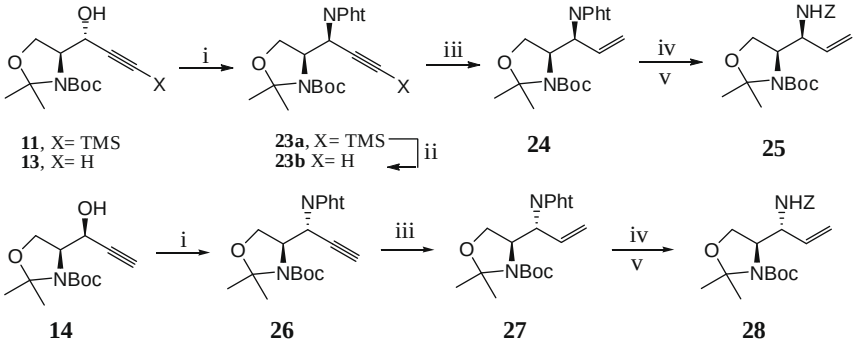
Scheme 2. Attempted substitutions of compounds **15**–**20** and **8a**–**b**.

developed by Herold[12] for its simplicity and higher level of selectivity in favour of **8a** or **8b**. Thus, the addition of lithium trimethylsilylacetelyde to **7**, prepared following an improved method,[13] proceeded well under the reported conditions to provide a separable mixture of the *anti*-propargyl alcohol **11** together with the corresponding *syn*-isomer (*anti*/*syn* = 19:1). Deprotection of the trimethylsilyl group from **11** then led to the acetylene derivative **13** which on partial hydrogenation with Lindlar's catalyst smoothly provided the desired allyl alcohol **8a** in good overall yield. Similarly, the isomeric alcohol **8b** was prepared through compounds **12** and **14**.

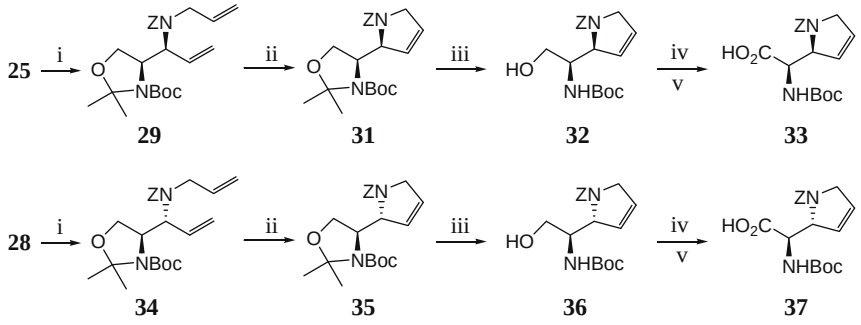
We then focused on the amination of alcohols **8a–b**. To this end, the corresponding mesylates **15** and **16** (Scheme 2) were prepared under conventional conditions. However, direct displacement of the –OMs group in either of **15** or **16** with sodium azide proved to be difficult under a range of conditions. Similarly, attempted reaction of each of the mesylates **17–20** separately with azide ion did not meet our needs and resulted mainly in the formation of intractable products. Our attempts on direct azidation of the alcohols **8a–b** using diphenylphosphoryl azide (DPPA)[14] also proved to be frustrating. A S_N2' displacement leading to **21** in poor yield was observed. While the S_N2- versus S_N2'-dichotomy of nucleophilic displacement of allylic alcohols under Mitsunobu conditions is reported,[15] success on analogous substrates[16] prompted us to study the direct amination of alcohols **8a** and **8b** with phthalimide/DEAD (or DIAD)/Ph_3P combination. However, again only the transposed product **22** was formed in poor yield in various attempts. Pleasingly, the propargylic alcohol **11** (Scheme 3) under the same conditions provided the desired product **23a** in 43% yield. The TMS-deprotected acetylenic alcohol **13** reacted slightly better to provide the corresponding phthalimide **23b**. The latter on partial hydrogenation in the presence of Lindlar's catalyst provided the olefin **24** in near quantitative yield. Careful monitoring of the reaction was crucial to avoid further reduction of the alkene during prolonged reaction times.

Removal of the phthalimido group from the latter using hydrazine hydrate proceeded without events and the resulting amine was protected with Cbz group to provide **25** in an overall yield of 83% over two steps. Similarly, the *syn*-propargylic alcohol **14** was converted into the inverted amine derivative **28**.

Having access to stereoisomerically pure *syn*- and *anti*-allylic amines **25** and **28**, we focused on their conversion to the corre-



Scheme 3. Reagents and conditions: (i) phthalimide (3 equiv), Ph_3P (3 equiv), DIAD (3 equiv), toluene, 0 °C to rt, 16 h, **23a**, 40%; **23b**, 46%; **26**, 47%; (ii) NH_4F, *n*-$Bu_4N^+HSO_4^-$ CH_2Cl_2, rt, 1 h, 88%; (iii) Lindlar's catalyst (10 mol %), H_2, MeOH, 0.5–2 h, **24**, 99%; **27**, 99%; (iv) $NH_2NH_2{\cdot}H_2O$, EtOH, rt, 7–12 h; (v) Cbz-Cl, Na_2CO_3, Et_2O–H_2O, rt, 3–4 h **25**, 91%; **28**, 83% over two steps.



Scheme 4. Reagents and conditions: (i) allyl bromide, NaH, *N*,*N*-DMF, 0 °C to rt, 4 h, **29**, 95%; **34**, 81%; (ii) Grubbs' catalyst **30** (5 mol %), CH_2Cl_2, rt, 6–10 h, **31**, 87%; **35**, 77%; (iii) *p*-TsOH, MeOH, rt, 2–4 h, **32**, 94%; **36**, 91%; (iv) Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, rt, 1 h; (v) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, ^{t}BuOH–H_2O, rt, 12 h **33**, 90%; **37**, 78% over two steps.

sponding pyrrolidine derivatives by the projected ring-closing metathesis reaction. Thus, the *N*-allyl derivatives **29** and **34** were prepared under conventional conditions (Scheme 4). Ring-closing metathesis of each of these dienes separately with Grubbs' catalyst, benzylidene bistricyclohexyl-phosphinoruthenium(IV) dichloride[17] **30**, proceeded well under optimised conditions to provide the pyrrolidine derivatives **31** and **35** in good yields. Acid-catalysed deprotection of the oxazolidine unit in **31** resulted in the smooth formation of the amino alcohol **32** which was converted to the corresponding carboxylic acid **33** involving sequential oxidation with Dess–Martin periodinane[18] to the corresponding aldehyde followed by its Pinnick oxidation[19] to the acid in a combined yield of 90%. Repetition of the same sequence of events on compound **35** led to the isomeric unsaturated pyrrolidinylglycine derivative **37** in good overall yield.[20]

In summary, we have developed a brief synthesis of two epimeric 2-pyrrolidinylglycine derivatives in which one of the stereogenic centres of the system comes from the starting material and the second one is created in a stereodivergent fashion. A Mitsunobu-type amination protocol was developed as the key synthetic step to install the required *syn*- and *anti*-diamine relationships. The methodology developed may prove to be useful for the preparation of other related 1,2-diamino compounds. The compounds prepared may find application as a α-amino acid, β-amino acid and/or α,β-diamino acid in the design and synthesis of modified peptides. Work will be continued in this laboratory along some of these directions.

Acknowledgements

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20. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **24**: $[\alpha]_D$ +28.3 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): 1717, 1695, 1392, 1366,1220 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92–7.88 (2H, m, ArH), 7.85–7.78 (2H, m, ArH), 6.61–6.52 (1H, m, C*H*=CH_2), 5.47 (1H, d, *J* = 17.0, CH=CH_{trans}), 5.40 (1H, d, *J* = 11.0, CH=CH_{cis}), 4.87 (1H, t, *J* = 9.5, C*H*NPht), 4.73 (1H, dd, *J* = 4.0, 8.5, C*H*NBoc), 3.99 (2H, dd, *J* = 9.6, 14.0, OCH_2), 1.73 (3H, s, CMe), 1.29 (3H, s, CMe), 1.14 (9H, s, CMe_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1 (*C*O–N–*C*O), 152.7 (*C*ONBoc), 133.9 (ArC), 133.4 (ArCH), 132.8(ArCH), 122.9 (*C*H=CH_2), 121.5 (CH=CH_2), 94.3 (O–*C*–N), 80.1 ($OCMe_3$), 64.7 (OCH_2), 57.0 (*C*HN), 56.8 (*C*HN), 27.7 (*CMe*), 27.0 (*CMe*), 24.3 (CMe_3). Mass (TOF MS ES+): *m*/*z* 409 (M+Na). Elemental Anal.: C, 65.45; H, 6.94; N, 7.59; $C_{21}H_{26}N_2O_5$ requires C, 65.27; H, 6.78; N, 7.25.
Compound **32**: IR ($CHCl_3$): 3435, 3346, 2977, 1691, 1499, 1393, 1318 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.35 (5H, m, ArH), 5.81–5.77 (2H, m, C*H*=C*H*), 5.18 (2H, s, OCH_2Ph), 4.95 (1H, s, NC*H*), 4.63 (1H, d, *J* = 8.6, N*H*), 4.36 (1H, dd, *J* = 1.3, 15.5, NCH_aCH_b), 4.18 (1H, t, *J* = 6.8, NC*H*)), 4.05(1H, d, *J* = 15.3, NCH_aCH_b), 3.87 (1H, br s, O*H*), 3.78–3.72 (1H, m, OC$H_a$$H_b$), 3.46–3.39 (1H, m, OC$H_a$$H_b$), 1.42 (9H, s, CMe_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2 (NCO), 155.8 (NCO), 136.0 (ArC), 128.5 (ArCH), 128.3(ArCH), 128.0 (CH=CH), 125.7 (CH=CH), 79.3 ($OCMe_3$), 67.7 (OCH_2), 65.9 (NCH), 62.7 (NCH), 54.8 (NCH_2), 28.2 (CMe_3).

Mass (TOF MS ES+): *m/z* 385 (M+Na).

Compound **33**: $[\alpha]_D$ −119 (*c* 1.4, $CHCl_3$). IR ($CHCl_3$): 3327, 2924, 1705, 1499, 1416, 1366 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.34 (5H, m, ArH), 5.91–5.82 (2H, m, C*H*═C*H*), 5.61 (1H, br s, NH), 5.29 (1H, dd, *J* = 7.1, 10.8, NC*H*), 5.12 (2H, s, OCH_2Ph), 4.55–4.46 (1H, m, NC*H*), 4.27 (1H, d, *J* = 14.3, NCH_aCH_b), 4.10 (1H, d, *J* = 13.6, NCH_aCH_b), 1.42 (9H, s, CMe_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (CO_2H), 155.8 (NC═O), 155.0 (NC═O), 136.1 (ArC), 128.4 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.5 (*C*H═CH), 127.0 (CH═*C*H), 80.0 (O*C*Me_3), 67.4 (OCH_2Ph), 67.2 (NCH), 66.9 (NCH), 54.3 (NCH_2), 28.2 (CMe_3). Mass (TOF MS ES+): *m/z* 399 (M+ Na).

Compound **36**: $[\alpha]_D$ +52 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): 3422, 1700, 1417, 1366 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.28 (5H, m, ArH), 5.79–5.77 (2H, m, C*H*═C*H*), 5.60 (1H, d, *J* = 6.0, NH), 5.11 (2H, s, OCH_2Ph), 4.58 (1H, t, *J* = 6.4, NCH), 4.28 (1H, d, *J* = 15.6, NCH_aCH_b), 4.01 (1H, dd, *J* = 4.8, 15.6, NCH_aCH_b), 3.63 (1H, dd, *J* = 3.2, 12.0, OCH_aH_b), 3.56 (br s, 1H, NCH), 3.47 (1H, d, *J* = 11.6, OCH_aH_b),1.60 (1H, br s, OH), 1.42 (9H, s, CMe_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5 (NC═O), 156.0 (NC═O), 136.2 (ArC), 128.5 (ArCH), 128.1 (ArCH), 127.8 (*C*H═CH), 126.3 (CH═*C*H), 79.5 (O*C*Me_3), 67.4 (OCH_2Ph), 65.8 (HOCH_2), 62.6 (NCH), 55.9 (NCH), 54.1 (NCH_2), 28.3 (CMe_3). Elemental Anal.: C, 63.14; H, 7.41; N, 7.99; $C_{19}H_{26}N_2O_5$ requires C, 62.97; H, 7.23; N, 7.73. Mass (TOF MS ES+): *m/z* 385 (M+Na).