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Chemoenzymatic and Chemical Routes to the Non-Proteinaceous Amino Acid Albizziine and its Amide Derivative**

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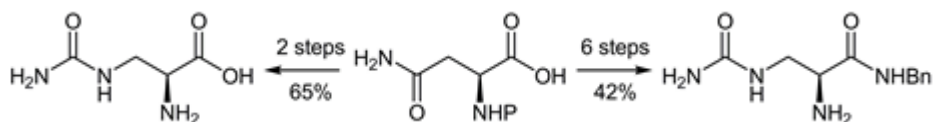
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Graphical abstract:



Keywords:

D-amino acid oxidase; Hoffmann rearrangement; amidation; urea formation

Abstract

A two-step route for the synthesis of albizziine from *N* α -Boc-asparagine which proceeds in 65% overall yield is disclosed. A high-yielding, six-step route for the synthesis of its protected amido derivative gives rapid access to a key component of the complex aminopolyol natural product, zwittermicin A.

Introduction

The non-proteinaceous amino acid L-albizziine (**1**) (2-amino-3-ureidopropanoic acid) was first isolated in 1959 from the seeds of the mimosa tree *Albizzia julibrissin* (**Figure 1**).¹ It has more recently been isolated from both the seeds of *Dialium ovoideum*,² and a wood-rotting basidiomycete, *Coniophora puteana*.³ It is incorporated as its amido derivative (**2a**), in the antifungal plant protection agent zwittermicin A (**3**), produced by *Bacillus cereus* UW85;⁴ and it is found as its oxalyl derivative in the seeds of *Acacia angustissima*.⁵ Biosynthetic studies indicate that albizziine is formed in the seedlings of *Albizzia julibrissin* by catabolism of 5-aminouracil (**4**).⁶ The exact biosynthetic origin of the amido analogue, as found in the mixed non-ribosomal peptide synthase – polyketide synthase (NRPS-PKS) derived natural product zwittermicin A,⁷ has not as yet been determined.

Recent chemical,⁸ and genetic analyses⁷ have led to a proposed absolute configuration for zwittermicin A (**3**). As part of a synthetic programme directed towards understanding the biosynthesis of this unusual natural product, we required a rapid route to the synthesis of albizziine (**1**) and its amido analogues (**2a/b**) which might allow ready access to either enantiomer to allow us to establish the validity of these proposals. Whilst a number of approaches to the synthesis of L-albizziine (**1**) have been reported,⁹ only two syntheses of D-albizziine [*ent*-(**1**)], have been achieved to date.^{10,11} In the most recent of these, a five-step synthetic sequence is used to convert the Garner aldehyde derived from L-serine,¹² into *N* α -Boc-D-albizziine (81 %ee).¹⁰ In the second, synthesis is accomplished through a dynamic kinetic resolution of the hydantoin derivative of racemic albizziine (**5**) with an *Agrobacterium radiobacter* bacterial culture at pH 8.4, to give *ent*-(**1**) (99 %ee).¹¹ Each of these approaches has drawbacks with regards to our principle aim, the establishment of a route that is equally applicable to the synthesis of either enantiomer of **1**.

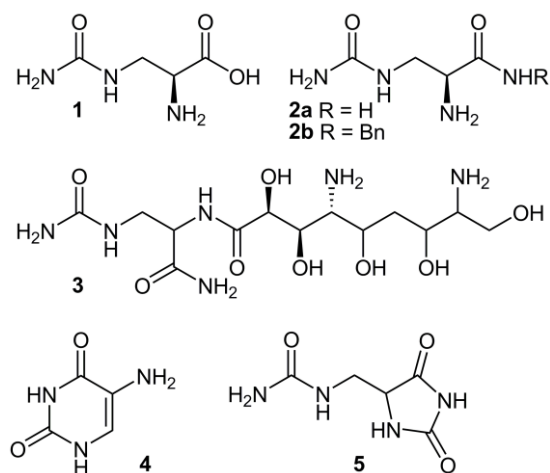
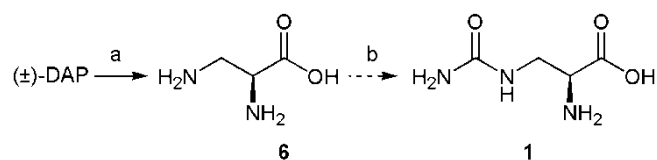


Figure 1. Albizziine and its derivatives.

We envisaged two possible approaches to the enantioselective synthesis of albizziine: the first was based upon selective functionalisation of either enantiomer of 2,3-diaminopropionic acid (DAP); and the second was based upon a Hofmann rearrangement of *N* α -protected D- or L-asparagine.

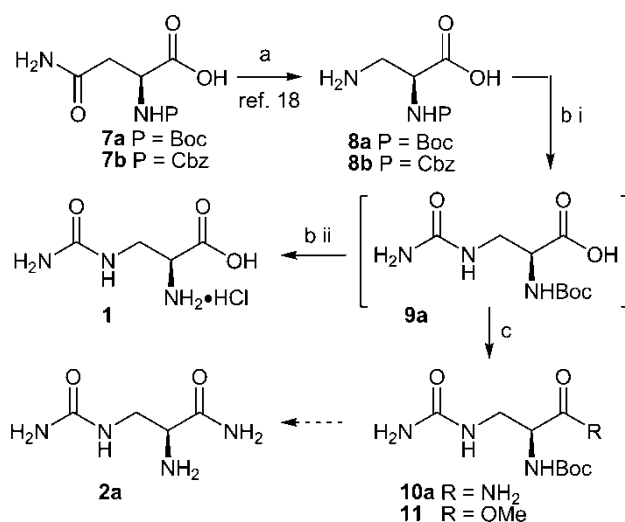
Results and Discussion

Inouye et al. have reported that L-albizziine can be synthesised from L-2,3-diaminopropionic acid (DAP) in 24% yield through reaction of the terminal amine with potassium cyanate (Scheme 1).^{9b} For the synthesis and stereochemical characterisation of zwittermicin A the production of L-albizziine was essential, but the high commercial cost of L-DAP (**6**) led us to consider alternative sources of this starting material. D-amino acid oxidases (DAAOs) are widespread in nature, and enzymatic resolution,¹³ and deracemisation¹⁴ of α -amino acids using immobilised DAAOs is operationally simple, and attractive in this instance as racemic diaminopropionic acid is more reasonably priced. However, only a few examples of the use of AAOs on diaminoacid substrates have been reported; significantly these include the resolution of 2,4-diaminobutyric acid,¹⁵ and 2,6-diamino-pimelic acid.¹⁶ Based on this literature precedent we set out to investigate the reaction of 2,3-diaminopropionic acid using resin-bound DAAO from *Trigonopsis variabilis* (Scheme 1). Gratifyingly, we observed that treatment of (\pm)-DAP with 10% w/v resin-bound enzyme at 37 °C for 24 h resulted in an excellent resolution of the racemic diamino acid to give L-DAP in 98 %ee, and the by-product glycine.¹⁷ However, in our hands selective functionalisation of the terminal amine as described by Inouye et al.^{9b} did not proceed cleanly, and thus we chose not pursue this route any further.



Scheme 1. Reagents and Conditions: (a) DAAO (10% w/v), H₂O, 37 °C, 24 h (98 %ee); (b) KOCN, H₂O, r.t., 4 h.

Of the reported approaches to the synthesis of L-albizziine, those based on a Hofmann rearrangement of *N*α-tosylated asparagine were of most interest to us for development using more recent methodologies:^{9c,d} firstly, due to the commercial availability of the *N*α-carbamate-protected derivatives (*e.g.* Boc, Cbz, Fmoc) of both enantiomers of asparagine; and secondly, due to the widespread use of *N*α-carbamate-protected amino acids in synthesis. We chose to develop our synthetic route to albizziine starting from *N*α-Boc- and *N*α-Cbz-protected L-asparagine (**7a/b**) to allow us to compare analytical data of the resultant synthetic L-albizziine with that of the natural product.

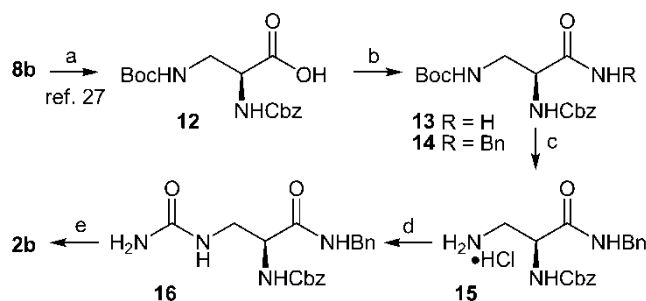


Scheme 2. Reagents and Conditions: (a) PIDA, EtOAc:MeCN:H₂O (2:2:1), r.t., 4 h, then -4 °C, 18 h (**8a** = 80%; **8b** = 93%); (b) i. KOCN, H₂O/H⁺, pH 7.5, 50 °C, 5 h; ii. HCl, H₂O/EtOH, recryst. (81%); (c) i. NH₃, MeOH, r.t., 1 h; ii. DMT-MM, MeOH, r.t., 2 h (50% from **8a**).

A number of reagents may be used to effect the Hofmann rearrangement of *N*α-carbamate protected asparagine, but we were attracted to the use of iodosobenzene diacetate (PIDA), as reported by Zhang *et al.*, due to the simplicity of the procedure and purity of the product which resulted.¹⁸ Indeed, in our

hands we obtained results which matched, or bettered, those which were previously reported (Scheme 2). Conversion of the β -amino functionality of 2,3-diaminopropionic acid derivative **8a** (P=Boc) to the requisite urea was achieved through reaction with aqueous potassium cyanate. We found that maintenance of the pH of this reaction mixture at \sim pH 7.5 was critical to the success of this reaction, which is in good agreement with results reported by Taillades *et al.* for the $N\alpha$ -carbamoylation of a range of α -amino acids.¹⁹ Deprotection of $N\alpha$ -Boc protected albizziine (**9a**) was achieved through treatment of the crude solution of urea **9a** with 1 N HCl (aq.), removal of the solvent and recrystallisation of the resultant solid from water/ethanol, to give the hydrochloride salt of L-albizziine (**1**) in excellent yield (2 steps, 65% from **7a**).

Conversion of the intermediate $N\alpha$ -Boc protected albizziine (**9a**) to its amido derivative (**10a**) was pursued using a number of methods,^{10,20-23} including the use of water-soluble carbodiimides such as EDCI, and the lesser known reagent DMT-MM.²⁴ However, none of these coupling reactions met with any significant success when combined with a range of ammonia sources. Indeed, in unexpected contrast both to literature precedent,²⁵ and our own recent experience,²⁶ DMT-MM mediated coupling of the ammonium salt of **9a** in neat methanol resulted in the formation of the methyl ester of $N\alpha$ -Boc albizziine (**11**) as the sole product in 50% yield.



Scheme 3. Reagents and Conditions: (a) Boc₂O, Na₂CO₃ (aq.): 1,4-dioxane (1:1), r.t., 18 h (90%); (b) BnNH₂, EDCI, DMAP (cat.), r.t., 18 h (92%); (c) HCl (1 M, Et₂O), CH₂Cl₂, r.t., 20 h (96%); (d) KOCN, H₂O/H⁺, pH 7.5, 50 °C, 1 h (77%); (e) Pd/C (cat.), AcOH, H₂ (10 bar), r.t., 36 h (92%).

Since the problems inherent to amide formation, appeared to be largely related to poor solubility of the intermediate urea **9a** we decided to switch the order of steps; thus forming the amide prior to formation of the urea. In pursuing this strategy use of the $N\alpha$ -Cbz diamine **8b** was preferred, since it would allow facile temporary protection of the $N\beta$ -amine as its Boc derivative. To this end the β -amino group of **8b** was protected using Boc anhydride (Scheme 3), to give the differentially protected diamine **12** in excellent yield (90%).²⁷ Although formation of the primary amide **13** was once again

unsuccessful under a range of coupling conditions, EDCI/DMAP mediated coupling to benzylamine in CH₂Cl₂ was now found to be facile, and allowed the isolation of amide **14** in an excellent yield following chromatography (92%). Selective Boc-deprotection using ethereal HCl gave amine hydrochloride **15**,²⁸ which was converted to the urea **16** through reaction with potassium cyanate under pH-controlled conditions. Selective hydrogenolytic cleavage of the Cbz group was readily achieved using Pearlman's catalyst in the presence of ethereal HCl (74%) or at medium pressure using Pd/C in acetic acid (92%),²⁹ to give the salt of the protected amide derivative of albizziine (**2b**).

Conclusions

We have developed a highly efficient two-step synthesis of L-albizziine (**1**) which proceeds in 62% overall yield from *N*α-Boc protected L-asparagine. In addition we have developed a six-step route to its protected amide derivative (**2b**), which proceeds via Hoffmann rearrangement of *N*α-Cbz protected L-asparagine, benzyl amide formation, then urea formation and hydrogenolytic Cbz deprotection. Given the availability of either enantiomer of these *N*α-protected derivatives of asparagine we anticipate that this synthetic route will allow us to fully investigate the synthesis of the unusual mixed PKS-NRPS natural product zwittermicin A (**3**). The successful resolution of 1,2-diaminopropionic acid using an immobilised DAAO from *Trigonopsis variabilis* suggests exciting possibilities for the future application of this methodology in the enantioselective synthesis of other 1,*n*-diaminoacids.

Experimental section

(2S)-2-Amino-3-ureidopropanoic acid hydrochloride salt (1): To a warm (50 °C) stirred solution of (2S)-3-amino-2-*tert*-butoxycarbonylamino-propanoic acid **8a**¹⁸ (0.550 g, 2.69 mmol) in water (25 cm³) was added potassium cyanate (0.330 g, 4.07 mmol). The pH was regulated at pH 7.5 by dropwise addition of HCl (2 M aq.). The reaction was followed by mass spectrometry. After completion (~ 5 h), the reaction mixture was cooled to room temperature and the crude solution of **9a** was acidified to pH 1 by dropwise addition of HCl (6 M aq.). The solvent was removed using a freeze dryer, and the resultant solid was recrystallised from water/ethanol to give the hydrochloride salt of L-albizziine **1** (0.320 g, 81%) as a colourless solid. $[\alpha]_D -16.9$ (c 0.71, MeOH); mp 210-212 °C (H₂O/EtOH), lit.^{9a} 216-217 (EtOH aq.), lit.^{9c} 206-211 (EtOH aq.); ν_{\max} (nujol)/cm⁻¹ 1685, 1660, 1613, 1578; δ_H (250 MHz, D₂O) 4.35 (1H, dd, *J* 5.8, 4.0), 3.92 (1H, dd, *J* 15.3, 4.0), 3.80 (1H, dd, *J* 15.3, 5.8); δ_C (62.9 MHz, D₂O) 170.8 (C), 161.9 (C), 54.3 (CH), 40.0 (CH₂); *m/z* (FAB, THIOG) 148 ([M+H]⁺, 44%), 133 (22), 123 (19), 105 (24), 99 (17); HRMS (FAB, THIOG): *m/z* calcd for C₄H₉N₃O₃ [M]⁺: requires 147.0644, found 147.0648.

Benzyl (2S)-2-benzyloxycarbonylamino-3-tert-butyl-oxycarbonylamino-propanamide (14): To a solution of acid **12**²⁷ (0.440 g, 1.32 mmol) in CH₂Cl₂ (10 cm³) was added EDCI (0.300 g, 1.59 mmol), DMAP (cat.), then benzylamine (0.170 cm³, 1.59 mmol). The resulting mixture was stirred at r.t. for 18 h. The solution was concentrated and redissolved in EtOAc (10 cm³) and water (10 cm³), and the aqueous layer was extracted with EtOAc (3 x 50 cm³), washed with NH₄Cl (10 cm³; sat.), brine (10 cm³), dried (MgSO₄) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel (CH₂Cl₂:Et₂O, 4:1) to give benzyl amide **14** (0.520 g, 92%) as a colourless solid. R_f[CH₂Cl₂ : Et₂O (4 : 1)] 0.35; [α]_D -14.3 (c 0.21, CHCl₃); mp 157-159 °C; ν_{max} (nujol)/cm⁻¹ 1685, 1658, 1539; δ_H (250 MHz, CDCl₃) 7.25-7.13 (10H, m), 6.91 (1H, br s), 6.28 (1H, br d, *J* 6.1), 5.13 (1H, br s), 5.02 (2H, s), 4.33 (1H, dd, *J* 14.9, 5.5), 4.31 (1H, m), 4.28-4.20 (1H, m), 3.51-3.35 (2H, m), 1.33 (9H, s); δ_C (62.9 MHz, CDCl₃) 169.9 (C), 156.7 (C), 156.6 (C), 137.6 (C), 135.9 (C), 128.5 (2CH), 128.4 (2CH), 128.1 (CH), 127.9 (2CH), 127.3 (3CH), 80.1 (C), 67.1 (CH), 67.0 (CH₂), 43.3 (CH₂), 42.5 (CH₂), 28.1 (3CH₃); *m/z* (FAB, THIOG) 427 ([M]⁺, 25%), 371 (33), 327 (34), 194 (25), 120 (21), 106 (40), 91(76); HRMS (FAB, NOBA) C₂₃H₃₀N₃O₅ [M+H]⁺ requires 428.2186, found 428.2189.

Benzyl (2S)-3-amino-2-benzyloxycarbonylamino-pro-panamide hydrochloride salt (15): To a solution of benzyl amide **14** (0.122 g, 1.17 mmol) in CH₂Cl₂ (20 cm³) was added HCl (10.0 cm³, 10.0 mmol; 1 M in Et₂O) and the resulting solution was stirred at r.t. for 20 h then transferred to a fridge at -4 °C for 18 h. The precipitate was removed by filtration and dried *in vacuo* to give amine hydrochloride **15** (0.100 g, 96 %) as a colourless solid. [α]_D -13.3 (c 0.3, MeOH); mp 176-178 °C; ν_{max} (nujol)/cm⁻¹ 1704, 1687, 1659, 1535, 1462; δ_H (360 MHz, D₂O) 7.40-7.23 (10H, m), 5.13 (2H, br s), 4.50-4.47 (1H, m), 4.40 (1H, d, *J* 15.5), 4.32 (1H, d, *J* 15.5), 3.49 (1H, dd, *J* 13.3, 4.8), 3.26 (1H, dd, *J* 13.3, 9.0); δ_C (90.6 MHz, D₂O) 171.5 (C), 158.5 (C), 138.6 (C), 137.0 (C), 129.9 (3CH), 129.6 (CH), 128.9 (2CH), 128.6 (2CH), 128.2 (2CH), 68.7 (CH₂), 53.3 (CH), 44.1 (CH₂), 40.9 (CH₂); *m/z* (FAB, THIOG) 655 ([2M+H]⁺, 46%), 328 ([M+H]⁺, 100), 284 (29), 238 (57), 215 (69), 199 (57), 181 (65); HRMS (FAB, NOBA) C₁₈H₂₂N₃O₃ [M+H]⁺ requires 328.1661, found 328.1661.

Benzyl (2S)-2-benzyloxycarbonylamino-3-ureido-pro-panamide (16): To a warm (50 °C) stirred solution of amine hydrochloride **15** (0.10 g, 0.27 mmol) in 20 cm³ of water was added potassium cyanate (0.055 g, 0.67 mmol). The pH was regulated at pH 7.5 by dropwise addition of HCl (2 M aq.). The resulting mixture was stirred for 1 h, allowed to cool to r.t. and the precipitate formed was removed by filtration; was washed with water (20 cm³) and dried using a freeze drier overnight to give urea **16** (0.078 g, 77%) as a colourless solid. [α]_D +35.3 (c 0.085, MeOH); mp 182-184 °C; ν_{max} (nujol)/cm⁻¹ 1673, 1645, 1540; δ_H (360 MHz, (CD₃)₂SO) 8.54 (1H, t, *J* 5.9), 7.48 (1H, d, *J* 7.4), 7.38-7.24 (10H, m), 6.17 (1H, t, *J* 5.9), 5.69 (2H, br s), 5.05 (2H, s), 4.31-4.29 (2H, m), 4.07 (1H, td, *J* 8.0, 4.6), 3.39 (1H, ddd, *J* 13.9, 6.1, 4.6), 3.18 (1H, ddd, *J* 13.9, 8.0, 6.1); δ_C (90.6 MHz, (CD₃)₂SO) 171.9

(C), 160.8 (C), 157.5 (C), 140.6 (C), 138.3 (C), 129.9 (2CH), 129.7 (2CH), 129.3 (CH), 129.2 (2CH₂), 128.4 (2CH), 128.2 (CH), 67.1 (CH₂), 57.8 (CH), 43.5 (CH₂), 42.6 (CH₂); *m/z* (FAB, NOBA) 371 ([M+H]⁺, 95%), 307 (46), 154 (95), 137 (79), 91 (100); HRMS (FAB, NOBA) C₁₉H₂₃N₄O₄ [M+H]⁺ requires 371.1719, found 371.1719.

Benzyl (2*S*)-2-amino-3-ureido-propanamide hydro-acetate salt (2b): Urea **16** (0.064 g, 0.17 mmol) was dissolved in acetic acid (15 cm³) and Pd/C (0.15 g, 100 wt%) was added. The mixture was stirred vigorously under hydrogen (10 bar) at r.t. for 36 h. The reaction mixture was filtered through celite which was washed with MeOH (3 x 15 cm³) and the combined organics were concentrated under reduced pressure to give the hydroacetate salt of benzyl amide **2b** (0.11 g, 92%) as a colourless solid. [α]_D + 11.43 (c 0.35, MeOH); mp 131-133 °C (decomp.); ν_{\max} (nujol)/cm⁻¹ 1721, 1652; δ_{H} (250 MHz, CD₃OD) 7.43-7.25 (5H, m), 4.51 (1H, d, *J* 14.9), 4.41 (1H, d, *J* 14.9), 4.18-4.08 (1H, m), 3.64 (1H, br d, *J* 13.6), 3.47 (1H, dd, *J* 13.6, 5.2); δ_{C} (62.9 MHz, CD₃OD) 170.8 (C), 162.8 (C), 140.2 (C), 130.5 (2CH), 129.6 (2CH₂), 129.3 (CH), 56.5 (CH), 45.0 (CH₂), 43.9 (CH₂); *m/z* (FAB, NOBA) 259 ([M+Na]⁺, 11%), 237 ([M+H]⁺, 62), 154 (100), 136 (85); HRMS (FAB, NOBA) C₁₁H₁₇N₄O₂ [M+H]⁺ requires 237.1346, found 237.1344.

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