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

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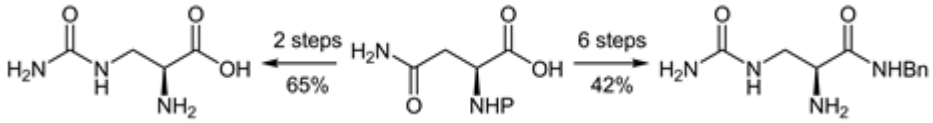
Graphical abstract:



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

Abstract

A two-step route for the synthesis of albizziine from *Nα*-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 julibrissiin* (**Figure 1**).[1] It has more recently been isolated from both the seeds of *Dialium ovoideum*,[2] and a wood-rotting bastidiomycete, *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 analyses[7] 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 *Nα*-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**.

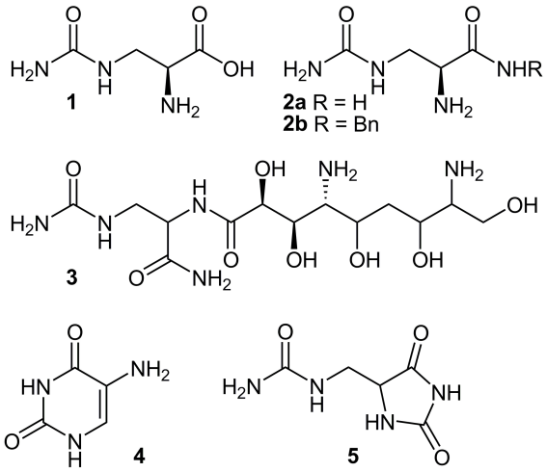
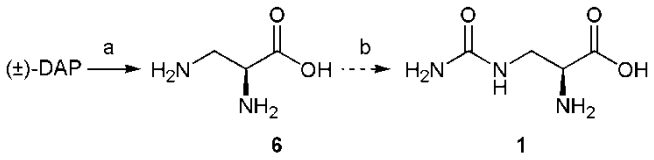


Figure 1. Albizziine and its derivatives.

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 *Nα*-protected D- or L-asparagine.

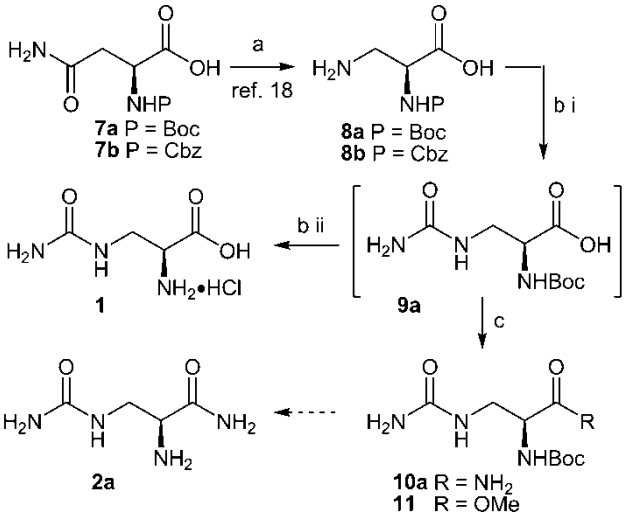
Results and Discussion

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 deracemisation[14] 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 (±)-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), H_2O, 37 °C, 24 h (98 %ee); (b) KOCN, H_2O, r.t., 4 h.

Of the reported approaches to the synthesis of L-albizziine, those based on a Hofmann rearrangement of *Nα*-tosylated asparagine were of most interest to us for development using more recent methodologies:[9c,d] firstly, due to the commercial availability of the *Nα*-carbamate-protected derivatives (*e.g.* Boc, Cbz, Fmoc) of both enantiomers of asparagine; and secondly, due to the widespread use of *Nα*-carbamate-protected amino acids in synthesis. We chose to develop our synthetic route to albizziine starting from *Nα*-Boc- and *Nα*-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.

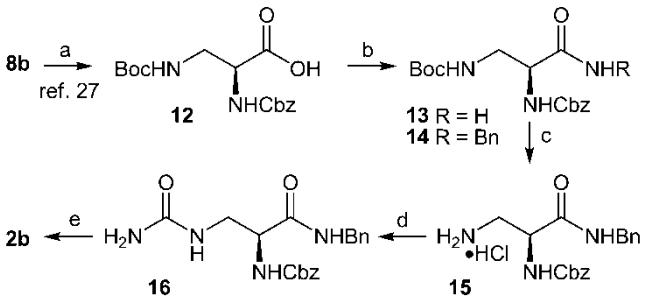


Scheme 2. Reagents and Conditions: (a) PIDA, EtOAc:MeCN:H_2O (2:2:1), r.t., 4 h, then -4 °C, 18 h (**8a** = 80%; **8b** = 93%); (b) i. KOCN, H_2O/H^+, pH 7.5, 50 °C, 5 h; ii. HCl, H_2O/EtOH, recryst. (81%); (c) i. NH_3, MeOH, r.t., 1 h; ii. DMT-MM, MeOH, r.t., 2 h (50% from **8a**).

A number of reagents may be used to effect the Hofmann rearrangement of *Nα*-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 ~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 *Nα*-carbamoylation of a range of α-amino acids.[19] Deprotection of *Nα*-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 *Nα*-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 *Nα*-Boc albizziine (**11**) as the sole product in 50% yield.



Scheme 3. Reagents and Conditions: (a) Boc_2O, Na_2CO_3 (aq.): 1,4-dioxane (1:1), r.t., 18 h (90%); (b) $BnNH_2$, EDCI, DMAP (cat.), r.t., 18 h (92%); (c) HCl (1 M, Et_2O), CH_2Cl_2, r.t., 20 h (96%); (d) KOCN, H_2O/H^+, pH 7.5, 50 °C, 1 h (77%); (e) Pd/C (cat.), AcOH, H_2 (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 *Nα*-Cbz diamine **8b** was preferred, since it would allow facile temporary protection of the *Nβ*-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 CH_2Cl_2 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 *Nα*-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 *Nα*-Cbz protected L-asparagine, benzyl amide formation, then urea formation and hydrogenolytic Cbz deprotection. Given the availability of either enantiomer of these *Nα*-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

(2*S*)-2-Amino-3-ureidopropanoic acid hydrochloride salt (1): To a warm (50 °C) stirred solution of (2*S*)-3-amino-2-*tert*-butoxycarbonylamino-propanoic acid **8a**[18] (0.550 g, 2.69 mmol) in water (25 cm^3) 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 acidifed 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 (H_2O/EtOH), lit.[9a] 216-217 (EtOH aq.), lit.[9e] 206-211 (EtOH aq.); ν_{max} (nujol)/cm^{-1} 1685, 1660, 1613, 1578; δ_H (250 MHz, D_2O) 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, D_2O) 170.8 (C), 161.9 (C), 54.3 (CH), 40.0 (CH_2); *m/z* (FAB, THIOG) 148 ($[M+H]^+$, 44%), 133 (22), 123 (19), 105 (24), 99 (17); HRMS (FAB, THIOG): *m/z* calcd for $C_4H_9N_3O_3$ $[M]^+$: requires 147.0644, found 147.0648.

Benzyl (2*S*)-2-benzyloxycarbonylamino-3-*tert*-butyl-oxycarbonylamino-propanamide (14): To a solution of acid **12**[27] (0.440 g, 1.32 mmol) in CH_2Cl_2 (10 cm^3) was added EDCI (0.300 g, 1.59 mmol), DMAP (cat.), then benzylamine (0.170 cm^3, 1.59 mmol). The resulting mixture was stirred at r.t. for 18 h. The solution was concentrated and redissolved in EtOAc (10 cm^3) and water (10 cm^3), and the aqueous layer was extracted with EtOAc (3 x 50 cm^3), washed with NH_4Cl (10 cm^3; sat.), brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel (CH_2Cl_2:Et_2O, 4:1) to give benzyl amide **14** (0.520 g, 92%) as a colourless solid. R_f[CH_2Cl_2 : Et_2O (4 : 1)] 0.35; $[\alpha]_D$ −14.3 (c 0.21, $CHCl_3$); mp 157-159 °C; ν_{max} (nujol)/cm^{-1} 1685, 1658, 1539; δ_H (250 MHz, $CDCl_3$) 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, $CDCl_3$) 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 (CH_2), 43.3 (CH_2), 42.5 (CH_2), 28.1 ($3CH_3$); *m/z* (FAB, THIOG) 427 ([M]$^+$, 25%), 371 (33), 327 (34), 194 (25), 120 (21), 106 (40), 91(76); HRMS (FAB, NOBA) $C_{23}H_{30}N_3O_5$ $[M+H]^+$ requires 428.2186, found 428.2189.

Benzyl (2*S*)-3-amino-2-benzyloxycarbonylamino-pro-panamide hydrochloride salt (15): To a solution of benzyl amide **14** (0.122 g, 1.17 mmol) in CH_2Cl_2 (20 cm^3) was added HCl (10.0 cm^3, 10.0 mmol; 1 M in Et_2O) 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. $[\alpha]_D$ −13.3 (c 0.3, MeOH); mp 176-178 °C; ν_{max} (nujol)/cm^{-1} 1704, 1687, 1659, 1535, 1462; δ_H (360 MHz, D_2O) 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, D_2O) 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 (CH_2), 53.3 (CH), 44.1 (CH_2), 40.9 (CH_2); *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) $C_{18}H_{22}N_3O_3$ $[M+H]^+$ requires 328.1661, found 328.1661.

Benzyl (2*S*)-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 cm^3 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 cm^3) and dried using a freeze drier overnight to give urea **16** (0.078 g, 77%) as a colourless solid. $[\alpha]_D$ v35.3 (c 0.085, MeOH); mp 182-184 °C; ν_{max} (nujol)/cm^{-1} 1673, 1645, 1540; δ_H (360 MHz, $(CD_3)_2SO$) 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, $(CD_3)_2SO$) 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 ($2CH_2$), 128.4 (2CH), 128.2 (CH), 67.1 (CH_2), 57.8 (CH), 43.5 (CH_2), 42.6 (CH_2); *m/z* (FAB, NOBA) 371 ($[M+H]^+$, 95%), 307 (46), 154 (95), 137 (79), 91 (100); HRMS (FAB, NOBA) $C_{19}H_{23}N_4O_4$ $[M+H]^+$ 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 cm^3) 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 cm^3) 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. $[\alpha]_D$ + 11.43 (c 0.35, MeOH); mp 131-133 °C (decomp.); ν_{max} (nujol)/cm^{-1} 1721, 1652; δ_H (250 MHz, CD_3OD) 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, CD_3OD) 170.8 (C), 162.8 (C), 140.2 (C), 130.5 (2CH), 129.6 ($2CH_2$), 129.3 (CH), 56.5 (CH), 45.0 (CH_2), 43.9 (CH_2); *m/z* (FAB, NOBA) 259 ($[M+Na]^+$, 11%), 237 ($[M+H]^+$, 62), 154 (100), 136 (85); HRMS (FAB, NOBA) $C_{11}H_{17}N_4O_2$ $[M+H]^+$ requires 237.1346, found 237.1344.

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