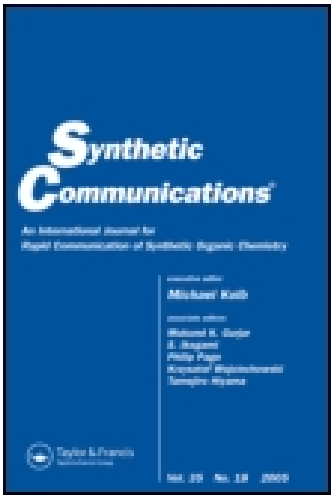

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SYNTHESIS OF D-ALBIZZIINE DERIVATIVES FROM L-SERINE

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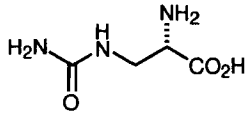
Abstract: A 5 step synthesis of *N*-Boc-D-albizziine from Garner's aldehyde, *via* a protected derivative of (*R*)-2,3-diaminopropanol, is reported. The overall yield is 30%.

L-Albizziine **1**, a non proteic amino acid, was isolated first from the seeds of *Albizzia julibrissiin* Durazz, a mimosa tree[1] and more recently from hyphae of *Coniophora putanea*, a wood-rotting basidiomycete.[2] It exhibits antiviral activity against Newcastle disease and herpes infection[3] as well as other biological activities.[4] Also the dipeptide γ-glutamylalbizziine has been isolated from *Acacia georginae* seeds.[5] Soon after its isolation two syntheses of **1** were reported.[6] In contrast D-albizziine **2** is much less known. To the best of our knowledge, this compound has been obtain so far only by a biotransformation procedure from the idantoin derivative of racemic albizziine.[7]



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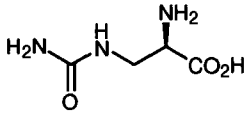

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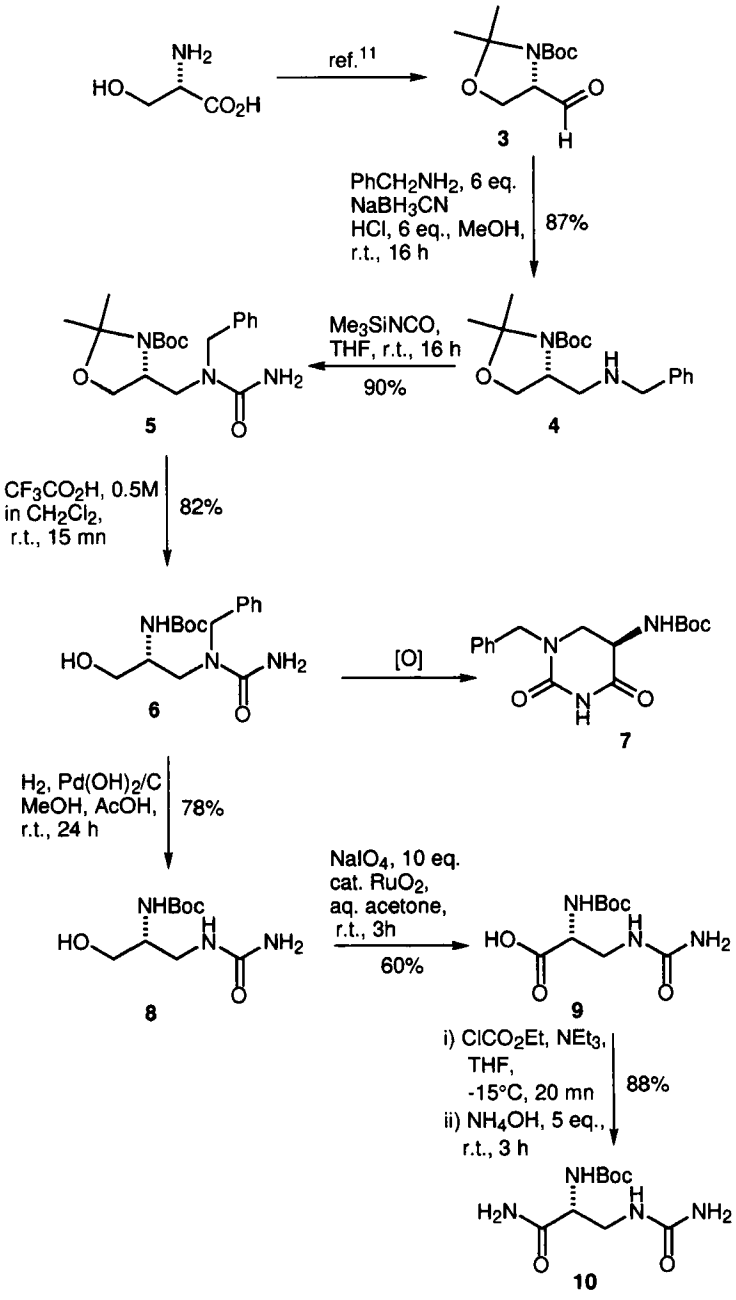
D-Amino acids are important starting materials for the synthesis of bio-active compounds, including peptides.[8,9] For instance, it has been reported that the antibiotics bagougeramines A and B contain a guanidino-D-alanine fragment, very close to D-albizziine.[10] For that reasons, we were interested in obtaining protected derivatives of compound **2**.

Our synthesis started with L-serine which was converted into Garner's aldehyde **3** in 4 steps by a known procedure.[11] In our hands **3** was isolated with 84% e.e.. Treatment of this aldehyde with an excess of benzylamine in the presence of $NaBH_3CN$[12] gave the amine **4**.[13] This amine is a convenient protected derivative of (*R*)-2,3-diaminopropanol which could be used in the synthesis of other amino-alcools. It was transformed into the urea **5**[13] by treatment with trimethylsilylisocyanate.[14] When treated with 0.5M trifluoroacetic acid in CH_2Cl_2, **5** gave the deprotected alcool **6**.[13] Various oxidizing reagents were tested to obtain the corresponding acid (PDC, Jones, $KMnO_4$, $NaIO_4/RuO_2$). However, in every case, the only isolated product was the dihydrouracil **7**.[13] The best yield (70%) was obtained by using Jones reagent in acetone for 2 h at room temperature. As this product may result from the cyclisation of the expected acid, *via* a nucleophilic attack of one of the urea nitrogen onto the C=O double bond of the acid function,[15] we assumed that a less nucleophilic urea should allow the isolation of the acyclic form. Thus compound **6** was first debenzylated with H_2 in the presence of $Pd(OH)_2$ and the resulting diaminoalcool **8**[13] was treated with $NaIO_4/RuO_2$.[16] In this way, acid **9**[13] was the only isolated product. **9** is a protected derivative of D-albizziine suitable for peptide synthesis. Finally, as the fragment present in Zwittermicine A[9] is not an acid but an amide, **9** was transformed into the amide **10**[13] by treatment with ethylchloroformate in the presence of triethylamine and then NH_4OH.[17]

For comparison commercially available L-albizziine was transformed in two non-epimerizing steps (N-protection with Boc_2O, amidation with $ClCO_2Et$ and NH_4OH)[17] into the enantiomer of **10**. $[\alpha]_D^{20}$ for this enantiomer was -14.8 (c 2, methanol). For **10**, the obtained $[\alpha]_D^{20}$ was +12 (c 2, methanol). This corresponds to 81% e.e.. Considering that the used Garner's aldehyde had 84% e.e., this synthesis can be regarded as largely non-epimerizing.



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13. Representative data for compounds **4-10**:

4 : $[\alpha]_D^{20}$ -37.33 (c 1.5, CH_3OH). ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 7.32-7.2 (m, 5H, C_6H_5), 4.06-3.88 (m, 2H, CH_2), 3.95 (br. s, 2H, CH_2), 3.8 (s, 2H, CH_2), 2.91-2.8 (m, 1H, NH), 2.72-2.62 (m, 1H, CHN), 1.53 (s, 3H, $(CH_3)_2C$), 1.48 (s, 9H, $(CH_3)_3C$), 1.42 (s, 3H, $(CH_3)_2C$). ^{13}C-NMR (50 MHz, $CDCl_3$, TMS) : δ 152.39, 151.75 (CO_2), 140.42, 128.28, 127.88, 126.83 (C_6H_5), 93.69, 93.38 ($C(CH_3)_2$), 80.01, 79.56 ($C(CH_3)_3$), 66.29 (CH_2), 57.31 (CHN), 53.84 (CH_2), 51.15 (CH_2), 28.35 ($(CH_3)_3C$), 27.45, 26.72 (CH_3), 24.37, 23.09 (CH_3). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found : C, 67.48; H, 8.83; N, 8.83.

5 : $[\alpha]_D^{20}$ -20.1 (c 1.5, CH_3OH). ^{13}C-NMR (50 MHz, $CDCl_3$, TMS) : δ 159.21 (NCON), 152.79 (CO_2), 138.51, 128.56, 127.4, 127.19 (C_6H_5), 93.12 ($C(CH_3)_2$), 81.16 ($C(CH_3)_3$), 66.61 (CH_2), 57.03 (CHN), 51.76 (CH_2), 49.71 (CH_2), 28.24 ($(CH_3)_3C$), 27.32, 23.71 (CH_3). Anal. Calcd for $C_{19}H_{29}N_3O_4$: C, 62.79; H, 8.04; N, 11.56. Found : C, 63.04; H, 8.17; N,11.47.

6 : $[\alpha]_D^{20}$ -5.9 (c 1.5, CH_3OH). ^{1}H-NMR (200 MHz, $CDCl_3$, TMS) : δ 7.38-7.22 (M, 5H, C_6H_5), 5.28 (d, 1H, J = 7.2, NHBoc), 4.76 (br. s, 2H, NH_2), 4.56 and 4.43 (AB, 2H, J = 17.83 , CH_2), 3.84-3.55 (m, 4H, CH_2O and CH_2N), 3.22 (d, 1H, J = 9.61, CHN), 1.42 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR (50 MHz, $CDCl_3$, TMS) : δ 161.1 (NCON), 156.93 (CO_2), 138.85, 129.5, 129.32, 128.14, 127.93 (C_6H_5), 79,53 ($C(CH_3)_3$), 61.78 (CH_2), 52.26 (CH_2), 51.57 (CHN), 47.52 (CH_2), 28.52 ($(CH_3)_3C$).

7 : $[\alpha]_D^{20}$ -13.4 (c 1.5, CH_3OH). ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 8.22 (br. s, 1H, NH), 7.39-7.27 (m, 5H, C_6H_5), 5.32 (d, 1H, J = 4.12, NHBoc), 4.93 (d, 1H, J = 16.45, CH_2Ph), 4.5-4.36 (m, 1H, CH_2), 4.33 (d, 1H, J = 16.46, CH_2Ph), 3.73 (m, 1H, CH_2), 3.16 (t, 1H, J = 12, CHN), 1.42 (s, 9H, $(CH_3)_3C$). Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found : C, 60.17; H, 6.71; N,12.96.

8 : ^{1}H-NMR (200 MHz, $(CD_3)_2CO$, TMS) : δ 6.07 (m, 1H, NH), 5.85 (d, 1H, J = 9.44, NHBoc), 5.4 (br. s, 2H, NH_2), 4.49 (t, 1H, J = 6.41, OH), 3.61-3.48 (m, 2H, CH_2), 3.42 (m, 1H, CHN), 3.25 (dd, 2H, J = 5.49 and 5.8, CH_2), 1.39 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR (50 MHz,

$(CD_3)_2CO$, TMS) : δ 160.99 (NCON), 156.38 (CO_2), 79,7 ($C(CH_3)_3$), 61.36 (CH_2), 52.49 (CHN), 40.4 (CH_2), 28.38 ($(CH_3)_3C$).

9 : $[\alpha]_D^{20}$ +10.5 (c 2.3, CH_3OH). ^{1}H-NMR (200 MHz, $(CD_3)_2CO$, TMS) : δ 6.49 (d, 1H, J = 6.4, NH), 6.12 (m, 1H, NH), 5.51 (br. s, 2H, NH_2), 4.17 (m, 1H, CHN), 3.64-3.34 (m, 2H, CH_2), 1.4 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR (50 MHz, $(CD_3)_2CO$, TMS) : δ 173.00 (NCON), 160.85 (CO_2H), 79.23 ($C(CH_3)_3$), 56.28 (CHN), 42.14 (CH_2), 28.47 (CH_3). Anal. Calcd for $C_9H_{17}N_3O_5$: C, 43.72; H, 6.93; N, 17.00. Found : C, 43.81; H, 7.10; N,16.85.

10 : $[\alpha]_D^{20}$ +12 (c 2, CH_3OH). ^{1}H-NMR (200 MHz, $(CD_3)_2CO$, TMS) : δ 7.15 (m, 1H, NH), 6.60 (m, 2H, NH_2), 6.17 (m, 1H, NH), 5.41 (br.s, 2H, NH_2), 4.14 (m, 1H, CH), 3.45 (m, 2H, CH_2), 1.40 (s, 9H, $(CH_3)_3C$). Anal. Calcd for $C_9H_{18}N_4O_4$: C, 43.90; H, 7.37; N, 22.75. Found : C, 44.05; H, 7.50; N,22.45.

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