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A short diastereoselective synthesis of 1-aminoindolo-[2,3-*a*]quinolizidines via an *N*-acyliminium ion cyclisation

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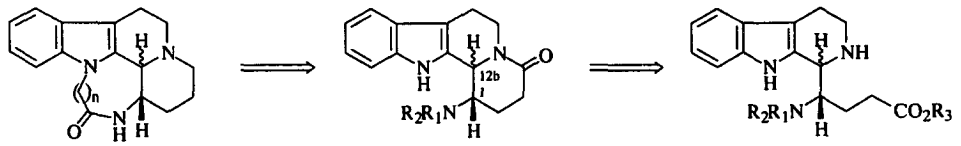
Abstract

trans 1-Aminoindolo[2,3-*a*]quinolizidines were synthesised using an intramolecular Pictet–Spengler-like reaction. Starting from commercially available *N*-Cbz-L-glutamic acid, indoloquinolizidines were obtained in only five steps with good yields. This improved synthesis is the result of both a highly regioselective imide reduction and a highly diastereoselective reaction using *N*-acyliminium ions. © 1999 Published by Elsevier Science Ltd. All rights reserved.

During the past few years, *E*-azaeburnane type compounds **1** have shown interesting activity as tyrosine hydroxylase (TH) gene inductors.[1] We, therefore, sought stereoselective synthetic pathways to compounds of type **3**, precursors of the pentacyclic derivatives **1**. Whereas the *cis* series is readily accessible with high diastereo- and enantioselectivity, this is not the case of the *trans* series.[2,3] Indeed, although *trans* β-carbolines **3a** have been obtained in good yields using pyrrole and phthalimide as amine precursors or protecting groups,[4] these were not useful in the subsequent synthetic steps since the *N*-phthaloyl-β-carboline **3a** (R_1R_2=phth) did not cyclise to form the corresponding lactam **2a**. Moreover, the 1-pyrrolo-lactam **2a** (R_1R_2N=pyrrole) could not be cleaved to release the corresponding 1-aminoindolo[2,3-*a*]quinolizidin-4-one. Other less bulky protecting groups, such as carbamates, mainly led to *cis* β-carbolines **3b** (Scheme 1).[4]



1a *trans* 12bαH
1b *cis* 12bβH

2a *trans*
2b *cis*

3a "*trans*"
3b "*cis*"

Scheme 1.

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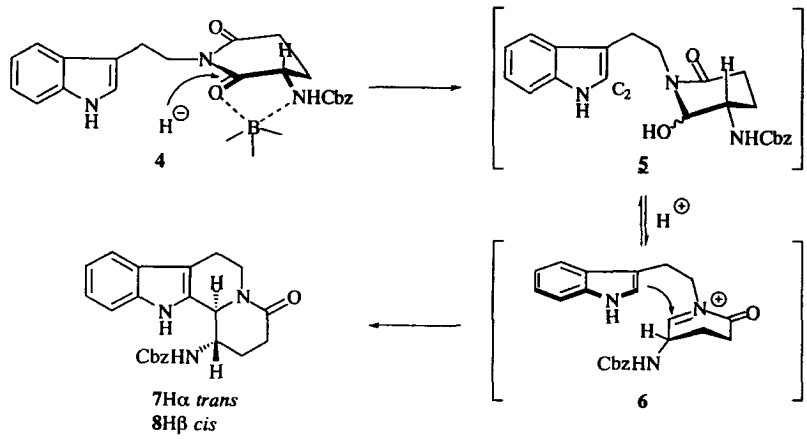
Therefore, a new pathway had to be developed to access the *trans* series with high diastereo- and enantioselectivity. It is well-known that the intramolecular Pictet–Spengler reaction leads mainly to the *trans* product,[5] especially when a bulky substituent is present close to the reactive centre (Scheme 2).[6] As our 1-aminoindoloquinolizidine bears such a substituent, we decided to investigate this approach.



Scheme 2.

We therefore report, in the present paper, an improved and highly diastereoselective synthesis of *trans* indoloquinolizidines of types **2a**, ex: **7**, **9** and **10**, using an intramolecular Pictet–Spengler-like reaction based on the cyclisation of an *N*-acyliminium intermediate.[7]

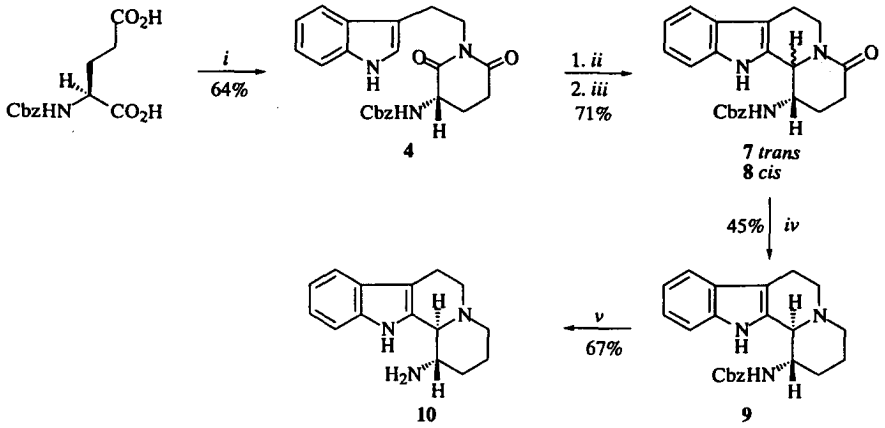
Our approach is based on a regioselective reduction of the imide derivative **4** using sodium borohydride. It was reasoned that the complexation of the reductive species with both the imide carbonyl and the carbamate nitrogen should induce the selective reduction of the imide carbonyl group as shown in Scheme 2.

Under acidic conditions, the acylcarbinolamine **5** would then be in equilibrium with the corresponding highly reactive *N*-acyliminium **6**. This should favour a fast Pictet–Spengler-like reaction, and thereby avoid any racemisation of the C_α centre. Furthermore, as the reaction is intramolecular, indole attack should occur on the upper less-hindered face thus leading to the *trans* diastereomer.

Compound **4** was thus prepared from L-glutamic acid by activating both carboxylic functions with dicyclohexylcarbodiimide, followed by condensation with tryptamine (Scheme 3).[8] Reduction of imide **4** with sodium borohydride in ethanol led to the acylcarbinolamine **5** which was immediately treated with trifluoroacetic acid in methylene chloride to give the *trans* indoloquinolizidinone **7** with 40% overall yield and good diastereoselectivity (de=80%).[9]

Whereas one might have expected both high enantio- and diastereoselectivity resulting from the increased reactivity of the *N*-acyliminium ion relative to the corresponding iminium ion, this was not the case. Indeed, formation of the *N*-acyliminium did not occur below 0°C. Furthermore, an increase to room temperature dramatically favoured the acyliminium–acylenamine equilibrium, resulting in partial racemisation (ee=24% for **7**). Altering the amount of trifluoroacetic acid added at low temperature did not drive the equilibrium toward *N*-acyliminium formation, as might have been expected.

After an easy separation of the diastereomeric lactams **7** and **8** by chromatography, the former was reduced with lithium aluminium hydride and the benzyloxycarbonyl group was removed by hydrogenolysis. The *trans* 1-aminoindoloquinolizidine **10** obtained was identical in all respects to the previously described compound.[1,3]



Scheme 3. (i) (1) DCC 1.1 equiv., TEA 2.2 equiv., DMAP cat., THF, 0°C, 1 h; (2) tryptamine, DCC 1.1 equiv., CH_2Cl_2, 0°C→rt 24 h, 67% yields not optimised; (ii) $NaBH_4$, EtOH, pH 8; (iii) TFA CH_2Cl_2 rt, 3 h; (iv) $LiAlH_4$ 1.2 equiv., THF, rt, 24 h; (v) H_2, Pd/C, MeOH, rt, 10 min

In conclusion, we have achieved an improved diastereoselective synthesis of *trans* 1-aminoindolo[2,3-*a*]quinolizidin-4-one and 1-aminoindolo[2,3-*a*]quinolizidine. Although partial racemisation occurred, the present strategy provides a more expedient route to the biologically interesting *trans* series in 40% overall yield.

Acknowledgements

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8. {1-[2-(1*H*-Indol-3-yl)-ethyl]-2,6-dioxopiperidin-3-yl}-carbamic acid benzyl ester **4**. To a solution of 1.06 g (3.78 mmol) of *N*-Cbz-L-glutamic acid, 860 mg (4.16 mmol) of dicyclohexylcarbodiimide, and 100 mg (10%) of dimethylaminopyridine in 30 ml of tetrahydrofuran, was added dropwise 1.15 ml (8.32 mmol) of triethylamine. After stirring for 1 h at room temperature, 663 mg (4.16 mmol) of tryptamine and 860 mg (4.16 mmol) of dicyclohexylcarbodiimide were added. After stirring for a further 15 h at the same temperature, the resultant white precipitate which had formed was filtered off, and the filtrate concentrated under reduced pressure, the residue was solubilised in ethyl acetate and washed with 1N hydrochloric acid and then brine. Finally, the combined organic layers were dried over sodium sulfate and concentrated under reduced

pressure. The residue was then purified by flash chromatography (ethyl acetate:heptane, 70:30) to give a white solid 1.02 g (64%). IR ($CHCl_3$): ν=3480, 3422, 3028, 1719 (C=O), 1680 (C=O), 1501, 1457; MS (CI+): *m/z*=406 ($[M+H]^+$, 100%), 328 (M-Ph), 253 (M-Cbz), 144, 130. Analysis: found: C, 67.54; H, 5.85; N, 9.92; calculated: C, 68.13; H, 5.72; N, 10.36. ^1H NMR ($CDCl_3$): 8.10 (1H, bs, NH Ind.), 7.85 (1H, d, H_8, J_{8-7}=6.5 Hz), 7.35 (5H, bs, arom. Cbz), 7.30 (1H, d, H_5, J_{5-6}=6.5 Hz), 7.25–7.05 (2H, m, H_6, H_7), 7.00 (1H, s, H_2), 5.65 (1H, bs, NH Cbz), 5.15 (2H, bs, CH_2Ph), 4.25 (1H, m, $H_{3'}$), 4.15–3.95 (2H, m, $H_{2''}$), 3.00 (2H, t, $H_{1''}$), 2.90–2.50 (2H, m, $H_{5'}$), 2.40 (1H, m, $H_{4'eq}$), 1.80–1.55 (1H, m, $H_{4'ax}$); ^{13}C NMR (CD_3OD): 171.5 (*C*O), 171.1 (*C*O), 156.2 (*C*O Cbz), 136.2 (C_9), 128.7 (C_o), 128.4 (C_p), 128.2 (C_m), 127.6 (C_4), 122.4 (C_2), 122.2 (C_7), 119.6 (C_6), 119.8 (C_8), 112.5 (C_3), 111.2 (C_5), 67.3 (*C*H_2Ph), 52.8 ($C_{3'}$), 41.4 ($C_{2''}$), 31.7 ($C_{5'}$), 24.6 ($C_{1''}$), 23.6 ($C_{4'}$).

9. {1(*S*)-12b(*S*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizin-1-yl)}-carbamic acid benzyl ester **7**. To a stirred solution of 60 mg (0.148 mmol) of imide **4** in 5 ml of ethanol at 0°C was added 5 mg of sodium borohydride. The pH of the reaction was maintained at 8 by dropwise addition of 1N hydrochloric acid in ethanol. After 3 h, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting acylcarbinolamine **5**, used without any further purification, was dissolved in 6 ml of methylene chloride, and 0.057 ml (0.741 mmol) of trifluoroacetic acid was added at room temperature. After stirring for 2 h at rt, the reaction mixture was washed sequentially with 5% sodium hydrogenocarbonate solution and then with brine. The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and purified using preparative thin layer chromatography (ethyl acetate:heptane, 70:30), to give 41 mg (71%) of a beige solid. IR ($CHCl_3$): ν=3422 (NH), 3070 (NH), 3007, 1687 (C=O), 1645 (C=N), 1513 (C=C), 1135 (C–O). MS (EI), *m/z*=389 ($M^{+\cdot}$, 100%), 298 (M–CH_2Ph), 171, 91. HRMS ($C_{23}H_{23}N_3O_3$): found: 389.1735; calculated: 389.1734. ^1H NMR ($CDCl_3$): 9.20 (1H, bs ex., NH Ind.), 7.40 (1H, d, H_8, J_{8-9}=8 Hz), 7.30 (5H, bs, arom Cbz), 7.25 (1H, d, H_{11}, J_{11-10}=8 Hz), 7.10 (1H, t, H_{10}), 7.05 (1H, t, H_9), 5.55 (1H, bs ex., NH Cbz), 5.15 (2H, s, CH_2Ph), 4.95 (1H, m, H_{6eq}), 4.65 (1H, d, H_{12b}, J_{12b-1}=5.9 Hz), 4.15 (1H, m, H_1), 2.95–2.20 (5H, m, H_3, H_{6ax}, H_7), 2.05–1.70 (2H, m, H_2); ^{13}C NMR (CD_3OD): 168.9 (C_4), 156.6 (*C*O Cbz), 136.2 (C_{11a}), 135.9 (C_Φ), 131.7 (C_{12a}), 128.9 (*C*H_o), 128.7 (*C*H_p), 128.4 (*C*H_m), 124.6 (C_{7b}), 122.4 (C_{10}), 119.8 (C_9), 118.4 (C_8), 111.5 (C_{11}), 110.3 (C_{7a}), 67.8 (*C*H_2Ph), 60.1 (C_{12b}), 51.6 (C_1), 41.9 (C_6), 30.1 (C_3), 26.3 (C_2), 20.9 (C_7).