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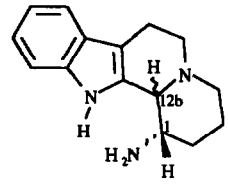
A New Diastereoselective Synthesis of (±) Cis 1-Aminoindoloquinolizidine

Patricia Melnyk, Pierre Ducrot, Luc Demuynck, Claude Thal*

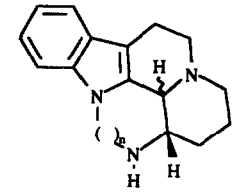
Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

Abstract: *An unexpected Bischler-Napieralski reaction between tryptamine and pyroglutamic acids led to a new diastereoselective access to 1-aminoindolo[2,3-a]quinolizidine* ***1****.*

In the course of a study of the pharmacologically interesting[1] pentacyclic azaeburnane **3**, we reinvestigated[2] stereospecific syntheses of aminoindoloquinolizidines **1** and **2**, precursors of compound **3**.



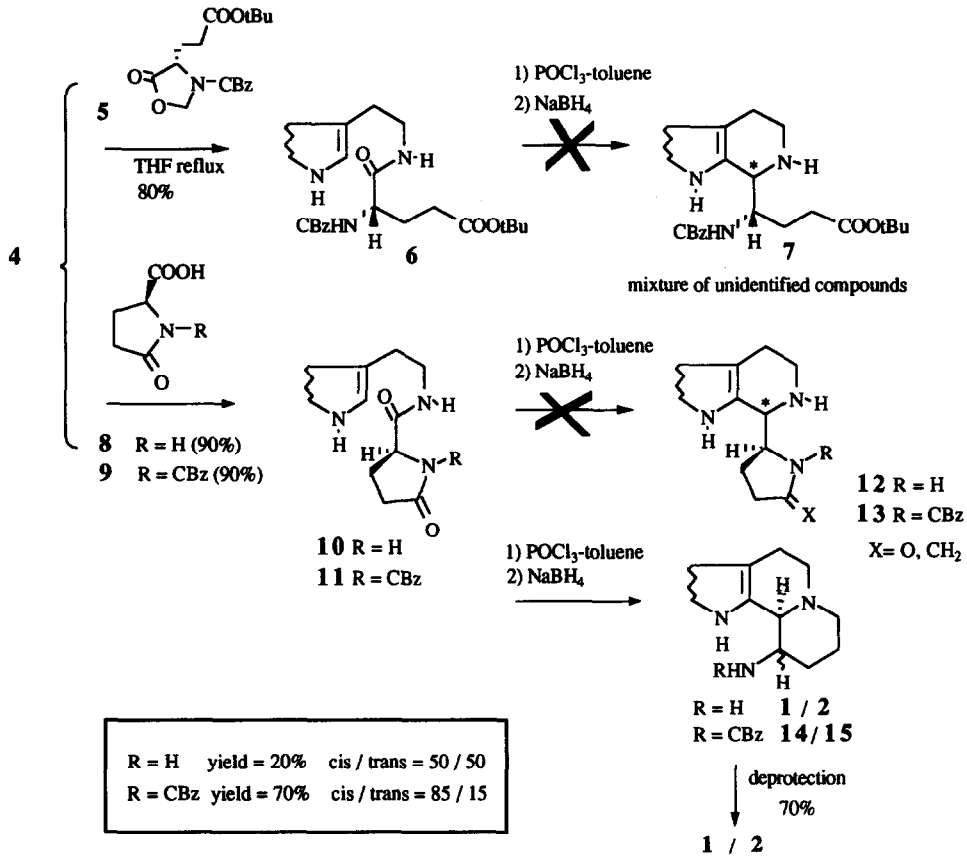
1 cis 12b β H
2 trans 12b α H



3 n = 1, 2

Thus, the Bischler-Napieralski cyclodehydration of amides **6**, **10** and **11**, resulting from condensation between tryptamine **4** and glutamic acid derivatives such as oxazolidine **5**[3], or pyroglutamic acids **8** or **9** was considered.

A mixture of unidentified compounds arose from the Bischler-Napieralski reaction of amide **6**[4] (Scheme 1). However, when starting from amides **10** and **11**[4], the same procedure yielded *directly* the 1-aminoindoloquinolizidines without isolation of compounds **12** or **13**. The *cis/trans* ratio obtained is governed by the substituent on the nitrogen of amide derivatives **10** (R=H) and **11** (R=CBz). Thus, a yield of 20% (**1** + **2**)[1] without any selectivity was obtained when starting from compound **10** while a yield of 70% (**14** + **15**)[4] with a 85/15 *cis/trans* ratio was obtained when starting from compound **11**. In all cases, the chiral center coming from pyroglutamic acid was racemized (chiral HPLC comparison with optically pure samples obtained by resolution of racemic amines **1** and **2**)[5].



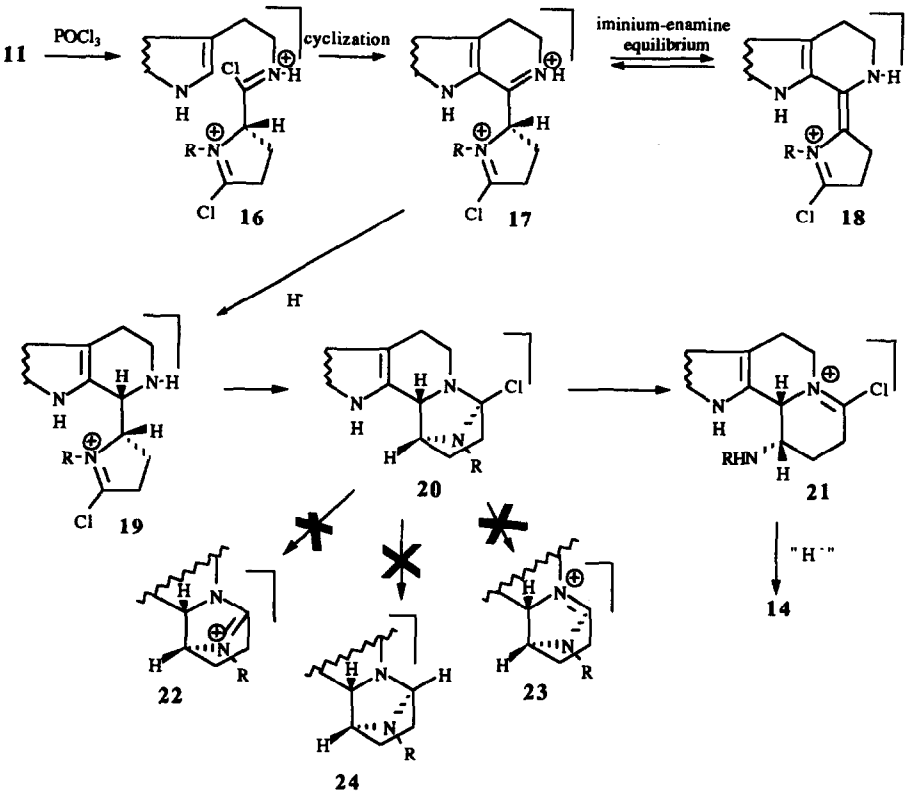
Scheme 1

Scheme 2 describes a mechanism explaining these results. Reaction of the diamide **11** with $POCl_3$ gives the dichloroiminium ion **16** which undergoes cyclization to give the iminium ion **17**. Equilibrium with the tautomeric compound **18** explains the racemization of the pyroglutamic chiral center observed in the course of this reaction.

The diastereoselectivity obtained when starting from compound **11** can be explained by a stereoselective reduction of compound **17** into compound **19**. If one applies the Cram-Felkin-Ahn rules to this type of reduction, the most reactive conformation of compound **17** would be the one where the bulkiest group near the iminium bond is anti to it. Molecular calculations[6] show it is the most stable in our case (Figure 1). This stability is due to stacking interactions between phenyl moities of the CBz group and the indole. Thus sodium borohydride predominantly approaches this conformation of compound **17** on its least hindered side. Of course, since such stabilisation cannot exist in the case of the unprotected intermediate **17** (R = H) and since the methylene group has about the same size as the amino group, no diastereoselectivity is expected. This is in accordance with the experimental results.

Computer calculation also indicates the same stacking effect in the case of compound **19** (Figure 2). Since, in this conformation, the distance between N_b and the iminium nucleophilic center is only 3.1 Å, this provides an explanation for the readiness of compound **19** cyclization into the intermediate **20**.

Then, since according to Bredt's rule, the chloroaminal **20** can only evolve to give the iminium ion **21** and none other, this final intermediate is reduced into the isolated amine **14**.



Scheme 2

In conclusion, this new sequence of reactions provides a quick access to racemic cis-1-aminoindoloquinolizidine. Since the diastereoselectivity observed depends on the amino protecting group, further work is in progress to increase the selectivity obtained so far.

Acknowledgments

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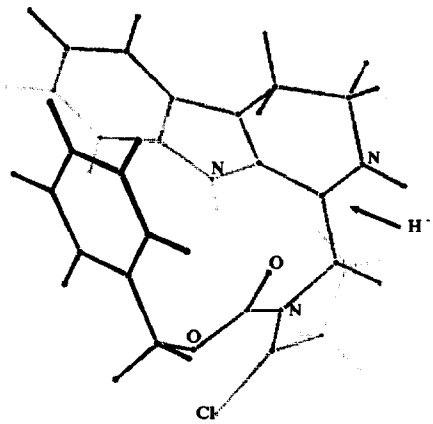

Figure 1

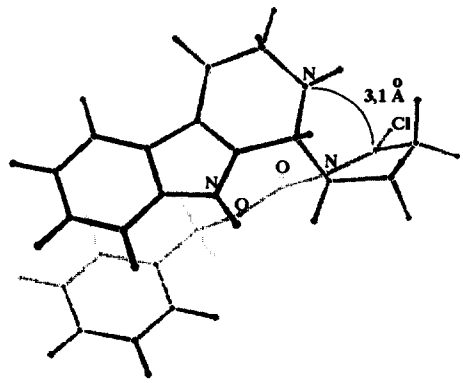

Figure 2

References and notes

1 Schmitt, P.; Melnyk, P.; Bourde, O.; Demuynck, L.; Pujol, J.-F.; Thal, C. *Med. Chem. Research* **1993**, in print.

2 Pilleboue - Melnyk, P. Doctorat de l'Université Paris VI (the 26th of january 1993).

3 Itoh, M. *Chem. Pharm. Bull.* **1969**, *17*, 1679.

4 All compounds are characterized by mass spectroscopy, IR, ^1H and ^{13}C NMR spectroscopy. Final products **1** and **2** are identical to those described[1]:
(**1**): Mp 137-139°C (iPrOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.50 (dd, 1H, H_8; J_{8-9} = 7 Hz; J_{8-10} = 2 Hz); 7.35 (dd, 1H, H_{11}; J_{11-10} = 7 Hz; J_{11-9} = 2 Hz); 7.20 (dt, 1H, H_{10}; J_{10-9} = J_{10-11} = 7 Hz; J_{10-8} = 2 Hz); 7.11 (dt, 1H, H_9; J_{9-10} =J_{9-8} = 7 Hz; J_{9-11} = 2 Hz); 3.32 (d, 1H, H_{12b}; J_{12b-1} = 3 Hz); 2.5-3.1 (m, 6H, H_{7a}, H_{7e}, H_1, H_{6a}, H_{6e}, H_{4e}); 2.37 (dt, 1H, H_{4a}; J_{4a-4e} = 11 Hz; J_{4a-3a} = 11 Hz; J_{4a-3e} = 2.5 Hz); 1.5-2.0 (m, 4H, H_{2a}, H_{2e}, H_{3a}, H_{3e}). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 136.3 (C_{11a}); 133.2 (C_{12a}); 127.4 (C_{7b}); 121.3 (C_{10}); 119.2 (C_9); 118.0 (C_8); 111.1 (C_{11}); 110.4 (C_{7a}); 63.6 (C_{12b}); 52.9-52.8 (C_4-C_6); 48.9 (C_1); 30.9 (C_2); 21.2 (C_7); 20.9 (C_3). EIMS: m/e 241 ($M^{+\cdot}$); 240; 225; 197; 170; 169; 168 (100); 140; 133; 117. FT-IR ($CHCl_3$) : 3420-3275; 1455.
(**2**): Mp 185-186°C (MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 10.45 (bs, H_{12}); 7.48 (dd, 1H, H_8; J_{8-9} = 7 Hz; J_{8-10} = 1.5 Hz); 7.35 (dd, 1H, H_{11}; J_{11-10} = 7 Hz; J_{11-9} = 1.5 Hz); 7.13 (dt, 1H, H_{10}; J_{10-9} = J_{10-11} = 7 Hz; J_{10-8} = 1.5 Hz); 7.08 (dt, 1H, H_9; J_{9-10} = J_{9-8} = 7 Hz; J_{9-11} = 1.5 Hz); 2.6-3.1 (m, 7H, H_1, H_{4e}, H_{6a}, H_{6e}, H_{7a}, H_{7e}, H_{12b}); 2.28 (dt, 1H, H_{4a}; J_{4a-4e} = 11 Hz; J_{4a-3a} = 11 Hz; J_{4a-3e} = 0.8 Hz); 1.1-1.9 (m, 4H, H_{2a}, H_{2e}, H_{3a}, H_{3e}); 1.50 (bs, NH_2). ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 135.6-135.5 (C_{11a} -C_{12a}); 126.9 (C_{7b}); 120.6 (C_{10}); 118.6 (C_3); 117.9 (C_8); 110.9 (C_{11}); 107.5 (C_{7a}); 65.6 (C_{12b}); 55.3-53.6 (C_4-C_6); 53.0 (C_1); 38.9 (C_2); 24.8 (C_7); 21.8 (C_3). EIMS: m/e 241 ($M^{+\cdot}$); 240; 225; 197; 170; 169; 140; 133; 117. FT-IR ($CHCl_3$) : 3450-3350; 1600.

5 Separation from racemic mixture of compounds **1** and **2**[1]:
i) monobenzylation: BrBn, NaH, THF, reflux 85%,
ii) R(+)-α-methylbenzylisocyanate, $CHCl_3$, r.t. 64%,
iii) diastereomer separation (silica gel, CH_2Cl_2 98,5 / MeOH 1,5),
iv) hydrolysis: Na, nBuOH, reflux 90%,
v) deprotection: Pd / C 10%, $HCOONH_4$, MeOH, reflux 80%.

6 Molecular mechanics calculations were performed on a Silicon Graphics Work Station (4D35) with Macromodel v3.1 as software using Allinger's basic MM2 force field and Monte Carlo method to generate conformers: Still, W.C.; Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; De Gunst, F. and Hasel, W.; MacroModel V 3.1, Dept of Chemistry, Columbia University, New York, N.Y. 10027.

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