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Stereospecific Pictet-Spengler Reaction: Synthesis of cis (+)-(1S, 12bR)-1-Aminoindoloquinolizidine from a Pure α-(S)-Aminoaldehyde Derivative

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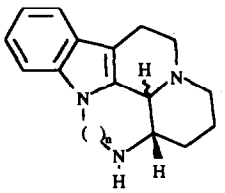
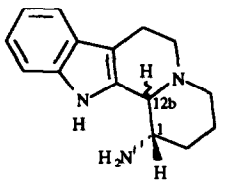
Abstract: *Pictet-Spengler reaction provides cis (+)-1-(S)-aminoindolo[2,3-a]quinolizidine in an enantio- and diastereoselective manner, using an α-aminoaldehyde derived from L-glutamic acid.*

Introduction

In the course of our study of the pharmacologically interesting pentacyclic azaeburnane **1**, we recently[1] established the importance of *cis-trans* relative-stereochemistry on biological activity. In the present work[2], we report the stereospecific synthesis of aminoindoloquinolizidine **2**, a key precursor to the pentacyclic compound **1**.

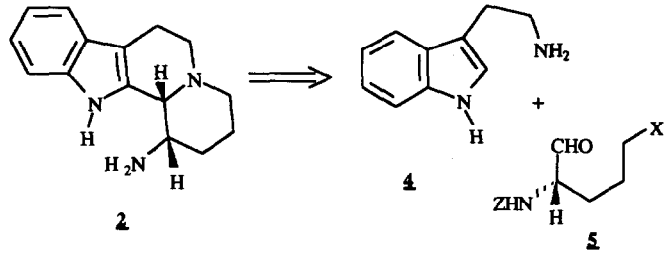


1 n = 1, 2



2 *cis* 12bβ H
3 *trans* 12bα H

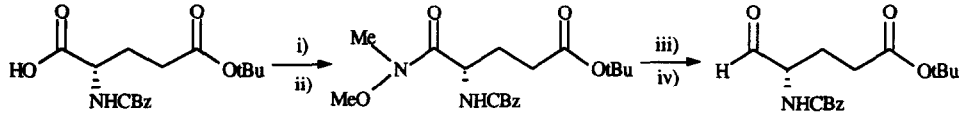
As shown in the retrosynthetic scheme (Scheme 1), compound **2** can, in principle, be synthetized by Pictet-Spengler cyclocondensation of tryptamine **4** with the optically active α-amino aldehyde derivative **5**[3], which should be easily prepared from L-glutamic acid.



Scheme 1

Synthesis

α-Amino aldehydes are known to be relatively sensitive and prone to racemization. This phenomenon has even been the subject of a controversy[4]. Recently, Fehrenz and Castro reported[5] an efficient strategy which avoids racemization and overreduction. We thus chose this method to prepare the previously unreported α-amino aldehyde **8** from the bisprotected L-glutamic acid derivative **6** according to the route of Scheme 2.



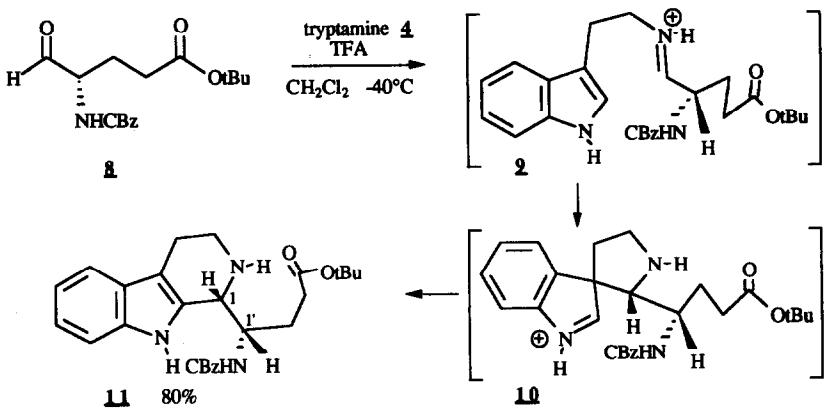
i) ClCOOiBu, N-Me morpholine, CH_2Cl_2 -15°C ii) HMeN-OMe (98%)

iii) $LiAlH_4$, Et_2O -20°C iv) NH_4Cl aq (90%)

Scheme 2

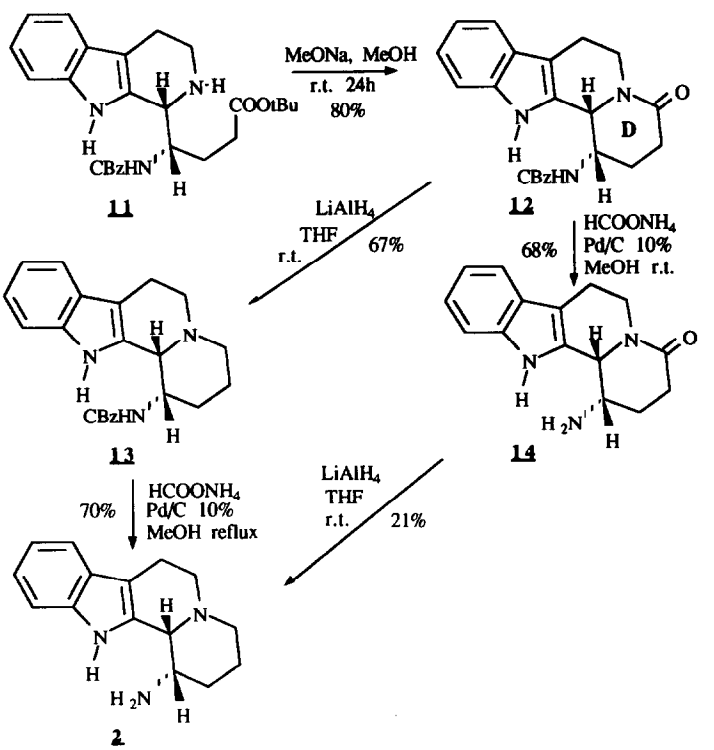
Fortunately, the α-aminoaldehyde **8** turned out to be reasonably stable. No $[\alpha]_D$ alteration was observed upon storing this compound at low temperature (-30 °C) for as long as 3 weeks. Since this is the first characterization of α-aminoaldehyde **8**, its enantiomeric purity was assessed at the end of the synthesis by comparison to an enantiomerically pure sample obtained by resolution of racemic **2**[6].

Reaction of α-amino aldehyde **8** with tryptamine **4** and trifluoroacetic acid at -40 °C gave carboline **11** in an optimized yield of 80 % (Scheme 3). Only one diastereoisomer was obtained; however, we could not definitively assign C-1 stereochemistry on the basis of H-1 and H-1' coupling constant (J = 7 Hz) due to free rotation.



Scheme 3

The synthesis of compound **2** from carboline **11** required three steps (Scheme 4): (1) formation of ring D, (2) reduction of lactam **12** and (3) deprotection of the primary amine. Even if the order of the last two steps could be theoretically reversed, experimentation showed that reduction of lactam **12** prior to the deprotection step gave better yields (47 % instead of 14 %).



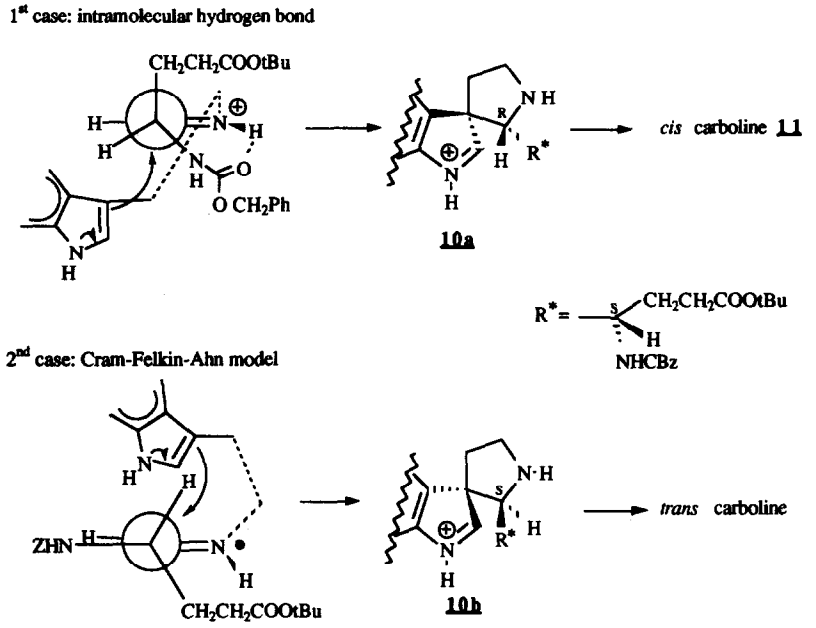
Scheme 4

Thus amine **2** was obtained in a 32% overall yield (after 6 steps) from the glutamic acid derivative **6**. Its ^1H NMR spectrum indicates that it possesses the H-1, H-12b *cis* stereochemistry ($^3J_{H1\text{-}H12b}$ = 3 Hz). HPLC (silica gel) revealed only one diastereoisomer. HPLC on cellulose carbamate column demonstrated that compound **2** was formed in 98 % enantiomeric excess. $[\alpha]_D$ Measurement proved that amine **2** was identical with the cis (+) amine previously[6] obtained from the resolution of a racemic mixture.

Discussion

Formation of cis (+) amine **2** as the only product showed the total stereospecificity of the Pictet-Spengler reaction. This result also confirmed the enantiomeric purity of α-aminoaldehyde **8** obtained from L-glutamic acid derivative **6**.

Reversible formation of the spiro intermediate in the Pictet-Spengler reaction has been postulated and in some instances confirmed[7]. In our case, equilibration between spiro compounds **10a**, **10b** and iminium **9** is expected to favor **10a** owing to the attack on the lower face of **9** [anti to the $(CH_2)_2COOtBu$ group] which is maintained in a pseudocyclic conformation[8] due to hydrogen bonding (Scheme 5).



Scheme 5

In the absence of such hydrogen bonding, the facial selectivity of nucleophilic addition to iminium **9** will depend upon the Cram-Felkin-Ahn rules, and thus the Pictet-Spengler cyclocondensation reaction through the rearrangement of the spiro compound **10b** should lead to a *trans* carboline[9]. Further work to test this proposal is in progress.

By using an enantiomerically pure α-aminoaldehyde obtained from L-glutamic acid derivative, we were able to prepare enantioselectively and diastereoselectively the cis (+)-1-(S)-amino-1,2,3,4,6,7,12,12b-(R)-octahydroindolo[2,3]quinolizidine in three steps. Its enantiomer should be obtainable from the corresponding D-glutamic acid derivative.

Acknowledgments

We wish to thank the Groupe de Recherches Servier for financial support and Pr. P. Potier for his interest during this work.

Experimental

Flash chromatography was performed using silica gel (Merck, 230-400 Mesh). Melting points were determined on a Tottoli apparatus. IR spectra were recorded on a Nicolet 250 FT-IR instrument. Proton NMR spectra were determined on a Bruker AC 200-MHz or 250-MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Mass spectral measurements were made on an AEI MS9 spectrometer. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

t-Butyl-4-(S)-benzyloxycarbonylamino-4-(N-methoxy-N-methyl) carbamoyl n-butyrate 7

To a solution of N-CBz-L-glutamic γ-t-butylester **6** (505 mg; 1.50 mmol) and N-methylmorpholine (330 µl; 3.00 mmol) in dry dichloromethane (10 ml) at -15°C, isobutyl chloroformate (200 µl; 1.50 mmol) was added. After a 15 min of stirring, N,O-dimethylhydroxylamine hydrochloride (145 mg; 1.50 mmol) was added, the mixture was stirred at -15°C for 1 hour and a further 2 hours at room temperature. Water (10 ml) was added and the resulting mixture was extracted with dichloromethane (3x10 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), evaporated and flash chromatographied. Elution with dichloromethane yielded hydroxamate **7** (560 mg; 98%) as a colorless oil ($[\alpha]_D^{24}$ = -12.4° (MeOH; c 0.6)). IR (CH_3Cl) ν_{max} = 3015; 1720; 1510; 1370. ^1H n.m.r. (200 MHz, $CDCl_3$) : 7.5 - 7.2 (m, 5H, Ph); 5.90 (d, 1H, NH-CBz; J_{NH-4} = 8 Hz); 5.10 (s, 2H, CH_2-Ph); 4.8 - 4.7 (m, 1H, H_4); 3.80 (s, 3H, OCH_3); 3.20 (s, 3H, N-CH_3); 2.20 (t, 2H, 2 H_2; J_{2-3} = 7 Hz); 2.1 - 1.7 (m, 2H, 2 H_3); 1.30 (s, 9H, $C(CH_3)_3$). ^{13}C n.m.r. (50,3 MHz, $CDCl_3$) : 172.0 (C_1); 168.3 (CO-N-OMe); 156.3 (CO CBz); 136.5 (C Ph); 126.0 (2 C_o + 2 C_m + C_p); 80.5 (O-$C(CH_3)_3$); 66.8 (CH_2-Ph); 61.6 (OCH_3); 50.6 (N-CH_3); 32.2 (C_4); 31.3 (C_2); 28.1 (3 CH_3); 27.8 (C_3). (CI^+) m / z = 381 (MH^+, 100%); 325; 217; 91; 57.

t-Butyl-4-(S)-4-benzyloxycarbonylamino-4-formyl n-butyrate 8

To a solution of hydroxamate **7** (5.31 g; 14.0 mmol) in dry diethylether (160 ml) under argon at -20°C, lithium aluminium hydride (665 mg; 17.5 mmol) was added portionwise. After a 2 hours stirring at -20°C, the mixture was hydrolysed with a 5% solution of KH_2SO_4 (70 ml) and filtred. The filtrate was extracted with diethylether (3x80 ml). The combined organic layers were washed with HCl 1M (3x80 ml), a satured solution of $NaHCO_3$ (3x80 ml) then with brine, dried and evaporated to yielded pure crude aldehyde **8** (3.98 g; 90%) as a colorless oil ($[\alpha]_D^{24}$ = -23.3° (MeOH; c 0.9)). IR (CH_3Cl) ν_{max} = 3430; 3025; 2965; 1700 - 1710; 1510. ^1H n.m.r. (200 MHz, $CDCl_3$) : 9.55 (s, 1H, CHO); 7.30 (s, 5H, Ph); 5.80 (d, 1H, NH-CBz; J_{NH-4} = 8 Hz); 5.05 (s, 2H, CH_2-Ph); 4.4 - 4.3 (m, 1H, H_4); 2.30 (t, 2H, 2 H_2; J_{2-3} = 7 Hz); 1.7 - 2.1

(m, 2H, 2 H_3); 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) : 198.9 (CHO); 172.0 (CO ester); 156.2 (CO CBz); 136.2 (C Ph); 128.5 (2 C_o); 128.2 (C_p); 128.0 (2 C_m); 80.9 (O-C$(CH_3)_3$); 67.1 (C_4); 30.9 (C_2); 28.0 (3 CH_3); 24.1 (C_3). (CI^+) m / z = 322 (MH^+, 100%); 304; 266; 107; 91; 57.

1-(R)-[1'-(S)-Benzyloxycarbonylamino-3'-t-butoxycarbonyl propyl]β-carboline 11

A solution of aminoaldehyde **8** (1.67 g; 5.20 mmol) in dry dichloromethane (100 ml) was cooled to -40°C under argon and tryptamine (1.25 g; 7.80 mmol) in dichloromethane (20 ml) was added. A solution of dry trifluoroacetic acid (0.79 ml; 10.4 mmol) in dichloromethane (10 ml) was then added dropwise. After 4 hours stirring at -40°C, the mixture was neutralised with a 5% solution of $NaHCO_3$. Aqueous layer was extracted with dichloromethane (3x150 ml) and the combined organic layers were washed with brine, dried (Na_2SO_4), evaporated and flash chromatographied. Elution with ethyl acetate / heptane (50 / 50) yielded carboline **11** (1.93 g; 80%) as a white powder ($[\alpha]_D^{24}$ = +20.2° (MeOH; c 1.0) found C 69.60; H 7.26; N 9.12 $C_{27}H_{33}N_3O_4$ requires C 69.98; H 7.13; N 9.07). HRMS found 463.2458 $C_{27}H_{33}N_3O_4$ requires 463.2463. IR (CH_3Cl) ν_{max} = 3300; 3020 - 2980 - 2970; 1700; 1510. ^1H n.m.r. (200 MHz, $CDCl_3$) : 8.55 (br s, 1H, H_9); 7.0 - 7.6 (m, 9H, aromatic); 5.6 - 7.9 (m, 1H, H_2); 5.10 (s, 2H, CH_2-Ph); 4.95 (d, 1H, H_1; $J_{1-1'}$ = 7 Hz); 4.60 (d, 1H, NH-CBz; $J_{NH-1'}$ = 7 Hz); 4.1 - 4.4 (m, 2H, 2 H_3); 3.5 - 3.4 (m, 1H, $H_{1'}$); 2.43 (t, 2H, 2 $H_{3'}$; $J_{3'-2'}$ = 7 Hz); 1.6 - 1.9 (m, 4H, 2 $H_{2'}$, 2 H_4); 1.45 (s, 9H, $C(CH_3)_3$). ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) : 172.7 (CO ester); 156.9 (CO CBz); 136.3 - 136.6 (C_{8a} + C Ph); 132.8 (C_{9a}); 128.2 - 127.2 (2 C_o + 2 C_m + C_p + C_{4b}); 121.3 (C_7); 118.9 (C_6); 117.7 (C_8); 110.5 (C_{4a}); 80.4 (O-C$(CH_3)_3$); 66.2 (CH_2-Ph); 56.1 (C_1); 52.6 ($C_{1'}$); 43.3 (C_3); 32.2 ($C_{3'}$); 27.9 (3 CH_3); 27.2 (C_4); 22.5 ($C_{2'}$). (EI) m / z = 463 (M); 390; 298; 171 (100%); 143; 130; 117; 91.

1-(S)-(N-Carbobenzyloxy)amino-1,2,3,4,6,7,12,12b-(R)-octahydroindolo[2,3-a]quinolizidin-4-one 12

To a solution of carboline **11** (345 mg; 0.74 mmol) in dry methanol (20 ml) at room temperature, sodium methylate (44 mg; 0.81 mmol) was added under argon. After 24 hours stirring, the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate, washed with HCl 1M (50 ml), aqueous solution of $NaHCO_3$ (50 ml) then with brine, dried (Na_2SO_4), evaporated and flash chromatographied. Elution with ethyl acetate / heptane (90 / 10) yielded compound **12** (232 mg; 81%) as a white powder ($[\alpha]_D^{24}$ = +59.0° (MeOH; c 0.6) found 389.1751 $C_{23}H_{23}N_3O_3$ requires 389.1734). IR (CH_3Cl) ν_{max} = 3435; 3320; 3015 - 2980 - 2950; 1710; 1635; 1510; 1125. ^1H n.m.r. (200 MHz, $CDCl_3$) : 9.54 (s, 1H, H_{12}); 6.9 - 7.5 (m, 9H, aromatic); 6.20 (d, 1H, NH-CBz; J_{NH-1} = 6 Hz); 5.20 (d, 2H, CH_2-Ph; J = 6 Hz); 4.45 (sl, 1H, H_{12b}); 2.70 (m, 5H, 2 H_6, 2 H_3, H_1); 2.40 (m, 4H, 2 H_7, 2 H_2). ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) : 169.3 (C_4); 157.0 (CO CBz); 137.1 (C_{11a}); 136.6 (C Ph); 136.0 (C_{12a}); 129.8 (C_{7b}); 128.4 (2 C_o); 127.9 (C_p); 127.4 (2 C_m); 122.3 (C_{10}); 119.5 (C_9); 118.4 (C_8); 111.4 (C_{11}); 111.2 (C_{7a}); 66.8 (CH_2-Ph); 58.2 (C_{12b}); 46.7 (C_1); 40.2 (C_6); 28.2 (C_3); 23.3 (C_2); 20.7 (C_7). (EI) m / z = 389 (M); 298 : 281; 238 (100%); 171; 170; 169; 107; 91; 77.

1-(S)-Amino-1,2,3,4,6,7,12,12b-(R)-octahydroindolo[2,3-a]quinolizidin-4-one 14

To a solution of lactame **12** (485 mg; 1.25 mmol) in dry degassed methanol, ammonium formate (336 mg; 6.22 mmol) and 10% palladium on charcoal (49 mg) were added. The whole was stirred 2 hours under argon at room temperature, filtred (celite) and evaporated. Precipitation from diethylether gave compound **14** (216 mg; 68%) as a white powder. IR (CH_3Cl) ν_{max} = 3440; 1715; 1630; 1505. ^1H n.m.r. (200 MHz, $CDCl_3$) : 8.47 (br s, 1H, H_{12}); 7.52 (dd, 1H, H_8; J_{8-9} = 7 Hz; J_{8-10} = 2 Hz); 7.41 (dd, 1H, H_{11}; J_{11-10} = 7 Hz; J_{11-9} = 2 Hz); 7.20 (td, 1H, H_{10}; J_{10-9} = J_{10-11} = 7 Hz; J_{10-8} = 2 Hz); 7.09 (td, 1H, H_9; J_{9-10} = J_{9-8} = 7 Hz; J_{9-11} = 2 Hz); 5.11 (d, 2H, NH_2; J_{NH2-1} = 5 Hz); 4.04 (br s, 1H, H_{12b}); 3.4 - 3.3 (m, 2H, 2 H_6); 3.0 - 2.8 (m, 3H, H_1, 2 H_3); 2.7 - 2.1 (m, 4H, 2 H_2, 2 H_7). (CI^+) m / z = 256 (MH^+).

1-(S)-(N-Benzyloxycarbonyl)-amino-1,2,3,4,6,7,12,12b-(R)-octahydroindolo[2,3-a] quinolizidine 13

To a solution of lactame **12** (386 mg; 0.99 mmol) in dry tetrahydrofuran, lithium aluminium hydride (45 mg; 1.2 mmol) was added under argon. After 24 hours stirring, the whole was cooled to -20°C then ethyl acetate (2 ml) and a saturated solution of ammonium chloride (2 ml) were added dropwise. The mixture was washed with brine. The organic layer was dried (Na_2SO_4), evaporated and flash chromatographied. Elution with heptane / ethyl acetate (60 / 40) yielded compound **13** (249 mg; 67%) as a white powder. IR (CH_3Cl) ν_{max} = 3420 - 3280; 2980 - 2850 - 2820 - 2760; 1710; 1615; 1460. ^1H n.m.r. (200 MHz, $CDCl_3$) : 9.05 (br s, 1H, H_{12}); 7.2 - 7.0 (m, 9H, aromatic); 5.2 - 5.0 (m, 3H, CH_2-Ph, NHCBz); 3.90 (d, 1H, H_{12b}; J_{12b-1} = 2.5 Hz); 3.2 - 2.8 (m, 4H, 2 H_4, 2 H_6); 2.70 (td, 1H, H_1; J_{1-2} = 3 Hz; J_{1-12b} = 2.5 Hz); 1.5 - 1.2 (m, 6H, 2 H_2, 2 H_3, 2 H_7). (EI) m / z = 375 (M); 374; 324; 284; 224 (100%); 197; 170; 143; 130; 117; 91; 77.

1-(S)-Amino-1,2,3,4,6,7,12,12b-(R)-octahydroindolo[2,3-a]quinolizidine 2

To a solution of carbamate **13** (50 mg; 0.13 mmol) in dry degassed methanol, ammonium formate (18 mg; 0.25 mmol) and 10% palladium on charcoal (42 mg) were added. The mixture was refluxed 2 hours under argon, filtred (celite), evaporated and flash chromatographied. Elution with dichloromethane / methanol (90 / 10) and recrystallisation from isopropanol gave amine cis **2** (22 mg; 70%) as white crystals m.p. = 137-139°C ($[\alpha]_D^{24}$ = +144.6° (MeOH; c 0.1); found C 74.8; H 7.7 $C_{15}H_{19}N_3$ requires C 74.7; H 7.9; N 17.4).IR (CH_3Cl) ν_{max} = 3420 - 3275; 2975 - 2850 - 2820 - 2760; 1615; 1455. ^1H n.m.r. (200 MHz, $CDCl_3$) : 8.90 (br s, 1H, H_{12}); 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 (td, 1H, H_{10}; J_{10-9} = J_{10-11} = 7 Hz; J_{10-8} = 2 Hz); 7.11 (td, 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); 3.1 - 2.5 (m, 6H, H_{7a}, H_{7e}, H_1, H_{6a}, H_{6e}, H_{4e}); 2.37 (td, 1H, H_{4a}; J_{4a-4e} = 11 Hz; J_{4a-3a} = 11 Hz; J_{4a-3e} = 2.5 Hz); 2.0 - 1.5 (m, 4H, H_{2a}, H_{2e}, H_{3a}, H_{3e}). ^{13}C n.m.r. (50.3 MHz, $CDCl_3$) : 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). (EI) m / z = 241 (M); 240; 225; 197; 170; 169; 168 (100%); 140; 133; 117. (HPLC) column: cellulose carbamate, mobile layer: heptane / i-propanol / triethylamine (90 / 10 / 0.5), detection: 280 nm, e.e.> 98.

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6 Separation from **2** racemic mixture:
i) monobenzylation: BrBn, NaH, THF, reflux 85%,
ii) R(+)-α-methylbenzylisocyanate, $CHCl_3$, r.t.. 64%,
iii) diastereomers 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%.
Circular dichroism spectra and correlation with known compound enabled us to determine absolute configurations (Husson, H.P.; Imbert, T.; Thal, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1973**, 2013 and references cited therein).

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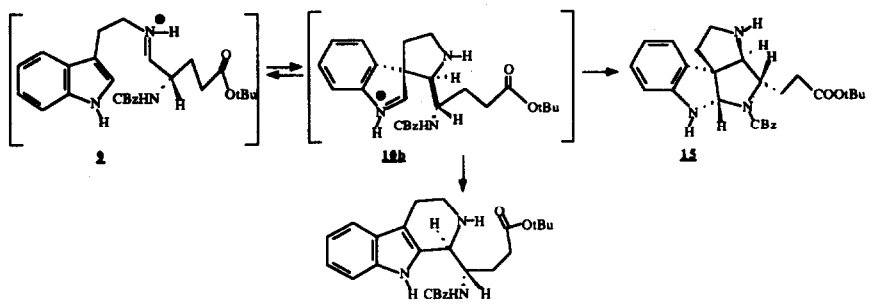
9 Tetracycle **15**, coming from intramolecular trapping of spiro compound **10b**, could probably be isolated in higher temperature conditions. A similar case has been described in a study of Eudistomine compounds[3].



2 **10b** **15**