AN ENANTIOSELECTIVE SYNTHESIS OF (+)-INDOLIZIDINE 195B.

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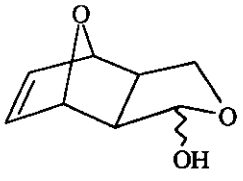
Abstract - A versatile enantioselective synthesis of the dendrobatid alkaloid (+)-indolizidine 195B is described, starting from the readily available lactol (**1**).

The indolizidine alkaloids constitute a family of natural products isolated from the skin secretions of certain neotropical frogs.[1] These substances, available in only very small amounts from natural sources, display interesting biological activities and have been the subject of numerous synthetic studies.[2] In the course of our work related to the control of the stereoselectivity of various reactions by a thermolabile group, we have found that, starting from the lactol (**1**) or its enantiomer, two chelation controlled organometallic additions could lead highly selectively to each of the four stereoisomers of unsymmetrical 1,4-diols (**2**).[3] Such diols are very useful for the synthesis of five membered heterocyclic compounds and the potentiality of the method is illustrated here by the synthesis of enantiomerically pure (+)-indolizidine 195B (**3**). This alkaloid extracted from the skin of the Colombian poison-frog *Dendrobates Histrionicus* [4] has been synthetized three times from synthons coming from the chiral pool : L-diethyl tartrate,[5a] D-mannitol [5b] or L-norleucine. [5c]



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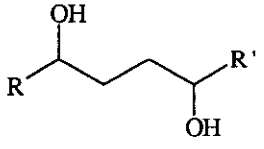

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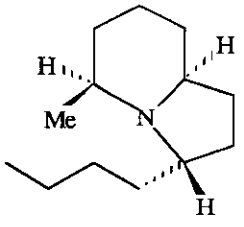

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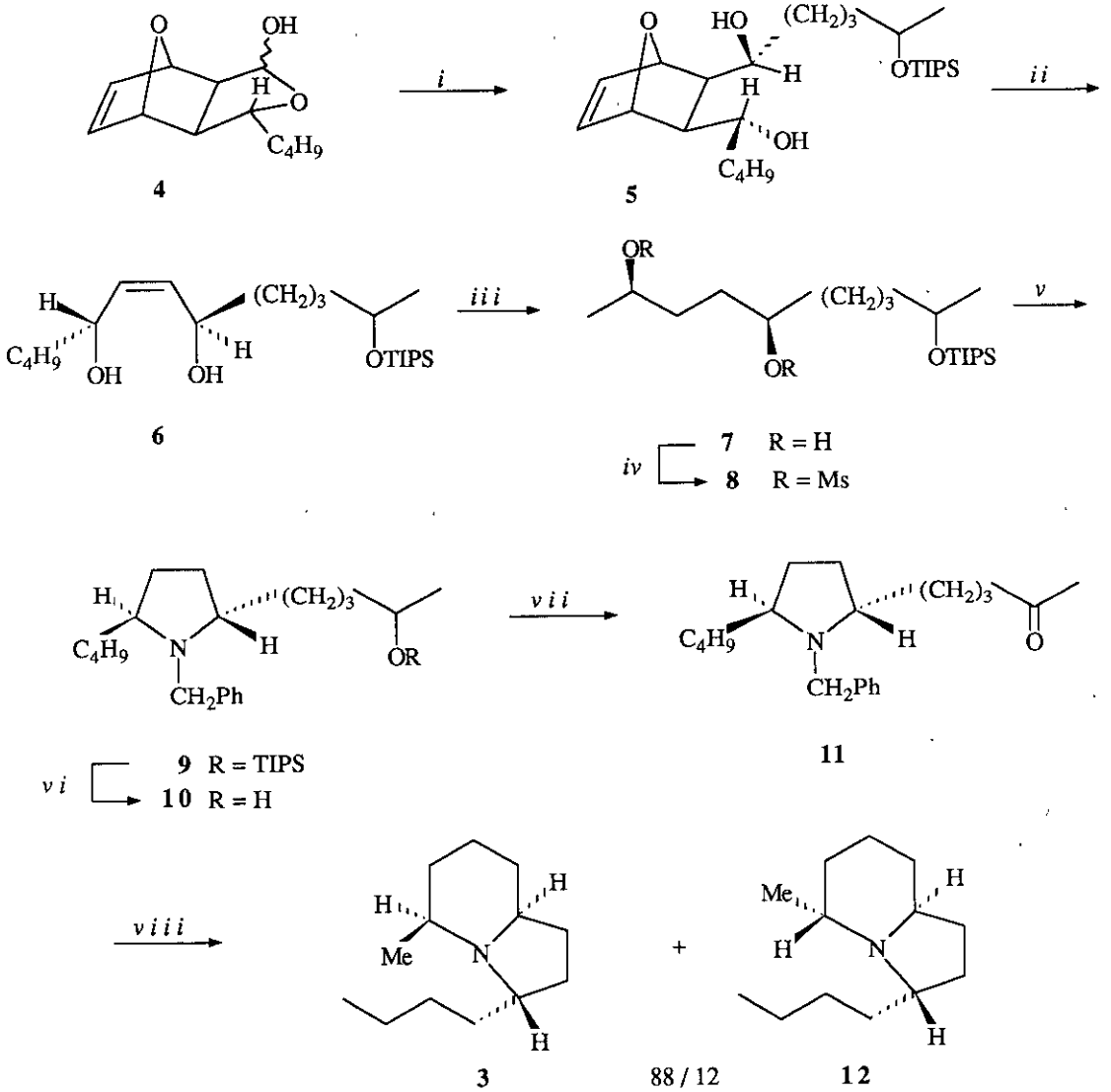
The synthesis started from the lactol (**1**), readily available from the Diels-Alder adduct of furan and maleic anhydride, either *via* an enzymatic resolution [6] or an asymmetric reduction.[7] The stereoselective addition of butylmagnesium bromide to **1** [8] followed by oxidation to the lactone (TPAP-NMO) [9] and DIBAL-H reduction gave rise to the lactol (**4**) in 45% yield for the three steps.



i $CH_3CH(OTIPS)(CH_2)_3MgBr$, THF ; *ii* 500°C, 10^{-3} torr ; *iii* H_2, 5% Pt/C ; *iv* CH_3SO_2Cl, $(C_2H_5)_3N$; *v* $PhCH_2NH_2$ 50°C ; *vi* $(C_4H_9)_4NF$, THF ; *vii* DMSO/$(COCl)_2$/$(C_2H_5)_3N$; *viii* H_2, 10% Pd/C, CO_2

Chelation controlled addition of the Grignard reagent, arising from 5-bromo-2-triisopropylsilyloxypentane, to the lactol (**4**) led to the diol (**5**) with a good yield (88%). It must be noted that the large triisopropylsilyl group is necessary here to achieve an efficient addition ; furthermore, low yields (10 to 20%) were also observed with Grignard reagents prepared from dialkyl acetals of 5-bromo-2-pentanone. Flash thermolysis (500°C, 10-50 ms contact time) of the bicyclo compound (**5**) afforded by retro Diels-Alder reaction the unsaturated diol (**6**) in 87% yield. Hydrogenation by molecular hydrogen catalyzed by 5% platinum on coal gave the diol (**7**) in fair yield (73%) which was quantitatively transformed to the bis-methylsulfonate (**8**) in classical conditions. Treatment of the mesylate (**8**) with an excess of benzylamine at 50°C led with 80% yield to the *trans*-2,5-disubstituted pyrrolidine (**9**) with inversion of the configurations of the two asymmetric carbons implied in the cyclization.[10] After deprotection of the hydroxy group (nBu_4NF, THF), Swern oxidation of **10** afforded the methyl ketone (**11**) (62% yield for the two steps). Hydrogenation of **11** in the presence of a weak acid (CO_2) resulted in cyclization to produce the natural (+)-enantiomer of indolizidine 195B (**3**) {$[\alpha]_D^{20}$ + 95° (c 0.33, MeOH) ; lit.,[5a] : $[\alpha]_D^{24}$ +98° (c 0.3, MeOH)} along with its C_5 epimer in a ratio 88:12 (total yield 73%). Spectral data of **3** were in agreement with the data already reported in the literature.[5]

In summary, (+)-indolizidine 195B has been enantioselectivity synthetized in 11 steps from the lactol (**1**) (8% overall yield) by a new versatile methodology. Effectively this procedure could be applied to the synthesis of the different stereomers of 3,5-disubstituted indolizidines and appears a good alternative to the existing methods.

EXPERIMENTAL

Ir spectra were recorded on a Perkin Elmer 682 spectrophotometer. Nmr spectra were recorded on a Brucker AM250 or AC200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. All reactions were carried out under an inert atmosphere of argon and were monitored by thin-layer chromatography (tlc). Tlc was performed on Merck silica gel 60F-254 precoated on glass.

(1*R*,2*R*,3*S*,4*S*,1'*R*,1"*R*,5'*RS*)-2-(1'-Hydroxy-5'-triisopropyloxyhexyl)-3-(1"-hydroxypentyl)-7-oxabicyclo[2.2.1]hept-5-ene (5). To a solution of the Grignard reagent prepared from 5-bromo-2-triisopropylsilyloxypentane (11.4 g, 35 mmol) and Mg (990 mg) in ether (50 ml) was added at room temperature the lactol (**4**) (780 mg, 3.7 mmol). The solution was refluxed overnight, cooled to room temperature and hydrolyzed by the slow addition of a saturated solution of ammonium chloride (35 ml). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3x100 ml). The combined organic phases were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Flash chromatography of the residue on silica gel (ether/hexane 80/20) afforded 1.48 g (88%) of the diol **5** as a colorless oil. Ir (neat) 3400, 3100, 1470, 1140, 1055 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 0.95 (3 H, t, *J*= 6 7 Hz), 1.0 - 1.90 (17 H, m), 1.08 (18 H, s), 1.19 (3 H, d, *J*= 6.8 Hz), 2.42 - 2.58 (1 H, m), 3.53 - 3.68 (1 H, m), 3.58 - 4.10 (2 H, m), 4.19 - 4.33 (1 H, m), 4.75 (1 H, s), 5.20 (1 H, s), 6.32 - 6.48 (2 H, m); ^{13}C nmr ($CDCl_3$) δ 12.35, 13.96, 15.11, 18.04, 22.16, 22.45, 22.65, 23.23, 23.36, 27.87, 36.63, 37.32,

39.81, 39.96, 44.24, 46.69, 65.70, 66.70, 68.48, 69.15, 72.09, 79.38, 81.14, 135.28, 137.18; CIms (NH_3) m/z (relative intensity) 456 (68), 455 (MH^+, 77), 437 (50), 273 (100), 195 (50), 193 (50), 148 (50).

(5*R*,8*R*,12*RS*)-12-Triisopropylsilyloxy-6-tridecene-5,8-diol (6). The bicyclic diol (**6**) (900 mg, 1.98 mmol) was evaporated through an horizontal mullite tube (500°C, 10^{-3} torr) and the thermolysate was collected on a finger cooled to liquid nitrogen temperature. After warming to room temperature the finger was washed with ether and the resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ether/hexane 40/60) to give 665 mg (87%) of the diol(**6**)as a colorless oil. Ir (neat) 3390, 3010, 1470, 1060 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 0.92 (3 H, t, *J*= 6.7 Hz), 1.06 (18 H, s), 1.17 (3 H, d, *J*= 6.8 Hz), 1.22 - 1.70 (15 H, m), 1.77 (2 H, s), 3.88 - 4.05 (1 H, m), 4.38 - 4.56 (2 H, m), 5.40 - 5.58 (2 H, m); ^{13}C nmr ($CDCl_3$) δ 12.45, 13.99, 21.17, 22.60, 23.43, 23.47, 27.54, 37.26, 37.32, 37.69, 37.83, 39.64, 39.77, 68.20, 68.30, 68.41, 134.00, 134.09, 134.40, 134.44; CIms (NH_3) m/z (relative intensity) 387 (MH^+, 67), 195 (100), 177 (78). Anal. Calcd for $C_{22}H_{46}O_3Si$: C, 68.33; H, 11.99. Found : C, 67.83; H, 11.44.

(5*R*,8*R*,12*RS*)-12-Triisopropylsilyloxy-5,8-tridecanediol (7). A solution of the diol (**6**) (510 mg, 1.32 mmol) in ethyl acetate (25 ml) was hydrogenated over 5% platinum on coal (50 mg) at atmospheric pressure for 30 min. After filtration, the catalyst was washed with ethyl acetate (5 ml) and the filtrate was concentrated at 20 torr. The oily residue was chromatographed on silica gel with ether/hexane (80/20) to give the saturated diol (**7**) (373 mg, 73%) as a colorless oil. Ir (neat) 3340, 1470, 1140, 1060 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) δ 0.91 (3 H, t, *J*= 6.7 Hz), 1.05 (18 H, s), 1.16 (3 H, d, *J*= 6.8 Hz), 1.22 - 1.79 (19 H, m), 2.19 (2 H, s), 3.55 - 3.69 (2 H, m), 3.86 - 3.98 (1 H, m); ^{13}C nmr ($CDCl_3$) δ 12.45, 14.03, 18.11, 21.43, 22.71, 23.41, 27.91, 34.10, 37.47, 37.92, 37.98, 39.83, 39.89, 68.42, 68.48, 72.22, 72.28; CIms (NH_3) m/z (relative intensity) 390 (67), 389 (MH^+, 100), 388 (M^+, 6), 369 (16), 215 (19), 197 (15). Anal. Calcd for $C_{22}H_{48}O_3Si$: C, 67.98; H, 12.45. Found : C, 67.71; H, 11.82.

(5*R*,8*R*,12*RS*)-5,8-Bis[(methylsulfonyl)oxy]-12-triisopropylsilyloxytridecane (8). To a stirred, ice-cold solution of the diol (**7**) (285 mg, 0.73 mmol) and triethylamine (369 mg, 3.65 mmol) in dichloromethane (15 ml) was added a solution of methanesulfonylchloride (128 µl, 1.6 mmol) in dichloromethane (1 ml) *via* syringe. The mixture was stirred for 30 min at 0°C, diluted with dichloromethane (35 ml) and poured on iced-water (6 ml). The organic phase was washed with water (2x5 ml), dried ($MgSO_4$), concentrated in vacuo below 30°C. The residue was chromatographed on silica gel (eluent ether/hexane 70/30) to give 391 mg (98%) of (**8**) as a colorless oil. Ir (neat) 3050, 1360, 1345, 1180, 915 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) δ 0.93 (3 H, t, *J*= 6.7 Hz), 1.06 (18 H, s), 1.17 (3 H, d, *J*= 6.8 Hz), 1.22 - 1.88 (19 H, m), 3.02 (6 H, s), 3.89 - 4.02 (1 H, m), 4.72 - 4.83 (2 H, m); ^{13}C nmr ($CDCl_3$) δ 12.26, 13.67, 17.93, 17.96, 20.43, 20.49, 22.20, 23.25, 26.86, 29.33, 29.39, 33.96, 34.53, 38.42, 39.22, 39.30, 67.93, 67.99, 82.48, 82.54, 82.57. Anal. Calcd for $C_{24}H_{52}O_7S_2Si$: C, 52.90; H, 9.62; S, 11.77. Found : C, 52.66; H, 9.36; S, 11.69.

(2*S*,5*S*,4'*RS*)-N-Benzyl-2-butyl-5-(4'-triisopropylsilyloxypentyl)pyrrolidine (9). A solution of the dimesylate (**8**) (250 mg, 0.46 mmol) in benzylamine (1.23 g, 11.5 mmol) was stirred for 30 h at 50°C. The solution was then poured in iced-water (10 ml) and extracted with ether (4x25 ml). The organic phase

was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent ether/hexane 20/80) to give 169 mg (80%) of the pyrrolidine(**9**)as a colorless oil. Ir (neat) 3100, 3080, 3040, 1470, 1380, 885 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) δ 0.86 (3 H, t, *J*= 6.6 Hz), 1.00 to 1.62 (17 H, m), 1.06 (18 H, s), 1.10 and 1.11 (3 H, 2d, *J*= 5.5 Hz), 1.78 - 1.98 (2 H, m), 2.78 - 2.90 (2 H, m), 3.62 (1 H, 1/2 ABq, *J*= 14.7 Hz), 3.82 (1 H, 1/2 ABq, *J*= 14.7 Hz),3.88 (1 H, m), 7.18 - 7.40 (5 H, m); ^{13}C nmr ($CDCl_3$) δ 12.49, 14.12, 18.15, 22.07, 22.21, 23.02, 23,45, 28.31, 28.68, 30.18, 30.86, 30.96, 40.19, 40.27, 51.35, 60.30, 66.81, 68.52, 126.31, 127.99, 128.40, 140.99; CIms (NH_3) m/e (relative intensity) 460 (MH^+, 100), 370 (47), 369 (46), 368 (85), 324 (28), 216 (20), 108 (39). Anal. Calcd for $C_{29}H_{53}ONSi$: C, 75.75; H, 11.62; N, 3.05. Found : C, 75.39; H, 11.40; N, 2.94.

(2*S*,5*S*,4'*RS*)-N-Benzyl-2-butyl-5-(4'-hydroxypentyl)pyrrolidine (10). To a stirred, ice-cold solution of **9** (103 mg, 0.224 mmol) in THF (2 ml) was added tetrabutylammonium fluoride 1M in THF (390 µl, 0.39 mmol) *via* syringe. The reaction mixture was warmed to ambient temperature and stirred for 5 h. The mixture was poured on water (2 ml) and extracted with ether (4x20 ml). The extract was dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel with dichloromethane/methanol 90/10 gave 56 mg (82%) of pyrrolidine (**10**) as a colorless oil. Ir ($CHCl_3$) 3640, 3370, 1450, 1110 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) δ 0.87 (3 H, t, *J*= 7.3 Hz), 1.05 - 1.68 (15 H, m), 1.16 (3 H, d, *J*= 6 Hz), 1.75 - 1.98 (2 H, m), 2.28 - 2.92 (2 H, m), 3.60 - 3.88 (1 H, m), 3.63 and 3.79 (2 H, ABq, *J*= 13.1 Hz), 7.18 - 7.38 (5 H, m); ^{13}C nmr ($CDCl_3$) δ 14.10, 22.45, 22.57, 22.97, 23.45, 28.27, 28.67, 30.13, 30.59, 30.70, 39.47, 39.52, 51.39, 60.21, 60.28, 60.39, 67.95, 126.36, 128.00, 128.42, 140.82.

(+)-(2S,5S)-N-Benzyl-2-butyl-5-(4-oxopentyl)pyrrolidine (11). To a stirred solution of oxalyl chloride (37 mg, 0.43 mmol) in dichloromethane (1 ml) at -78°C was added dropwise a solution of dimethyl sulfoxide (66 mg, 0.86 mmol) over a period of 5 mn, and the mixture was stirred for another 10 mn at -78°C. To this mixture was added dropwise a solution of **10** (65 mg, 0.214 mmol) in dichloromethane (1 ml) over a period of 5 min, and stirring was continued at -78°C. After 1 h, triethylamine (130 mg, 1.29 mmol) was added to the reaction mixture, and the reaction mixture was warmed to ambient temperature and stirred for 15 min. The solution was diluted with dichloromethane (10 ml) and washed with water (2 ml) and a saturated solution of Na_2CO_3 (5 ml), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by silica gel chromatography with ether/hexane (60/40) then ether/hexane (80/20) gave 48 mg (75%) of **11** as a pale yellow oil. $[\alpha]_D^{20}$ + 64° (c 0.435, $CHCl_3$); ir (neat) 3100, 3080, 3040, 1725 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 0.86 (3 H, t, *J*= 6.4 Hz), 1.00 - 2.05 (14 H, m), 2.10 (3 H, s), 2.35 (2 H, t, *J*= 6.5 Hz), 2.75 - 2.84 (2 H, m), 3.63 (1 H, 1/2 ABq, *J*= 14 Hz), 3.82 (1 H, 1/2 ABq, *J*= 14 Hz), 7.16 - 7.42 (5 H, m); ^{13}C nmr ($CDCl_3$) δ 14.03, 20.48, 22.83, 28.11, 28.16, 28.59, 29.79, 30.02, 43.64, 51.51, 66.83, 126.74, 128.12, 128.65, 208.94; CIms (NH_3) m/z (relative intensity) 301 (M^+, 1), 244 (21), 216 (28), 91 (100).

(+)-Indolizidine 195B (3). A solution of the pyrrolidine (**11**) (34 mg, 0.113 mmol) in methanol saturated with CO_2 (2 ml) was hydrogenated over 10% palladium on coal (40 mg) at atmospheric pressure for 4 h. After filtration, the catalyst was washed with methanol (2 ml) containing methanolic ammonia (1 ml) and the filtrate was concentrated below 30°C at 20 mmHg. The oily residue was diluted with ether, washed with a saturated solution of Na_2CO_3, dried ($MgSO_4$), concentrated in vacuo. The residue was chromatographed on

silica gel with dichloromethane/methanolic ammonia (200:1) (80/20 to 50/50) to give **12** (2 mg) and (+)-**3** (14 mg, 64%) as pale yellow oils. **3** : $[\alpha]_D^{20}$ +95.3° (c 0.33, MeOH); ir (neat) 2960, 2930, 2865, 2858, 2792, 2695, 1450, 1370, 1225, 1190, 1132 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) δ 0.91 (3 H, t, *J*= 7 Hz), 0.98 - 1.98 (16 H, m), 1.12 (3 H d, *J*= 6.2 Hz), 2.32 - 2.48 (1H, m), 2.48 - 2.61 (1 H, m), 3.31 (1 H, br. t, *J*= 8 Hz); ^{13}C nmr ($CDCl_3$) δ 14.14, 20.05, 22.91, 24.48, 25.13, 26.13, 28.97, 29.67, 31.74, 33.96, 52.41, 59.03, 59.24; *ms (70 eV) m/z (relative intensity)* 195 (M^+, 3), 180 (9), 139 (20), 138 (100). **12** : ^1H nmr ($CDCl_3$, 250 MHz) δ 0.91 (3 H, t, *J* = 6.7 Hz), 1.05 - 1.85 (15 H, m), 1.20 (3 H, d, *J* = 6.7 Hz), 1.95 - 2.12 (1 H, m), 2.81 - 3.02 (2 H, m), 3.36 (1 H, br. s).

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