Total Synthesis and Determination of Structure of the Pyrrolizidine Alkaloid Curassanecine

Jean-Claude Gramain, Roland Remuson, Danielle Vallee-Goyet, Jean Guilhem, and Catherine Lavaud

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TOTAL SYNTHESIS AND DETERMINATION OF STRUCTURE OF THE PYRROLIZIDINE ALKALOID CURASSANECINE

JEAN-CLAUDE GRAMAIN,* ROLAND REMUSON, DANIELLE VALLEE-GOYET,

Laboratoire de Chimie des Substances Naturelles, Université Blaise Pascal (Clermont-II), URA 485 du CNRS, 63177 Aubiere Cedex, France

JEAN GUILHEM,

Laboratoire de Cristallographie, Institut de Chimie des Substances Naturelles, Avenue de la Terrasse, 91198 Gif sur Yvette Cedex, France

and CATHERINE LAVAUD

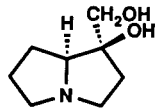
Laboratoire de Pharmacognosie, Faculté de Pharmacie, URA 492 du CNRS, 51, rue Cognacq-Jay, 51096 Reims, France

ABSTRACT.—The first total synthesis of curassanecine [**1**], a new bicyclic alkaloid recently isolated from *Heliotropium curassavicum*, was realized in three steps from *N*-acetylpyrrolidine in 48% overall yield. Pulsed methods in 2D liquid phase nmr, in particular heteronuclear multiple bond correlation (HMBC) and correlation with a compound the structure of which was determined by X-ray crystallography, were used to confirm without ambiguity the structure and relative stereochemistry of this alkaloid.

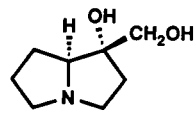
The chemistry of the pyrrolizidine alkaloids is of considerable interest because of their wide range of physiological properties (1–4) and their wide distribution in nature.

Following our recently described five-step synthesis of isoretronecanol (*Senecio* alkaloid) using a strategy based on the intramolecular photoreduction of an α-ketoester (5), we now describe the first total synthesis of curassanecine [**1**] and of its diastereoisomer **2** using a similar approach. Curassanecine [**1**] is a saturated amino alcohol pyrrolizidine alkaloid, recently isolated from *Heliotropium curassavicum*, a glaucous fleshy herb found in south west North America, in India, in Australia, and in Europe (6). This molecule is the first alkaloid in the series with a quaternary carbon atom at C-1 (numbering of pyrrolizidine alkaloids was used in this paper for nitrogen bicyclic compounds) that bears a tertiary alcohol functional group. The difficulties in establishing the stereochemistry of such alcohols are well known (7), and Mohanraj *et al.* (6) suggested its stereochemistry by comparison of its ^{13}C chemical shifts with those of other necine bases that have no tertiary alcohol functional group (8). Thus, as stated by Robins in a recent review, "confirmation of this structure by synthesis would be desirable (9)." Therefore, we undertook the synthesis of both diasteroisomers of curassanecine in order to assign stereochemistry without ambiguity. We took advantage of the easy synthesis of diastereoisomers **4a** and **4b** which constitute close precursors of curassanecine [**1**] and of its isomer **2**. Moreover, the separation and the determination of the stereochemistry could be done.

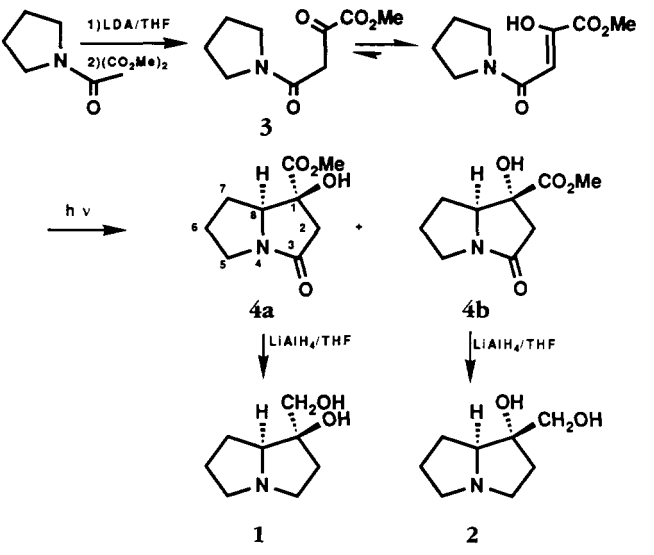
The photocyclization of α-keto ester **3** (medium pressure mercury lamp, Pyrex), obtained by condensation of methyl oxalate on the anion of *N*-acetylpyrrolidine, led to the mixture of hydroxy esters **4a** and **4b** in 70% yield (5) (Scheme 1). Separation by flash chromatography afforded **4a** and **4b** as pure products in a 1 to 1 ratio.



1



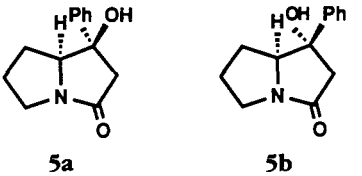
2



SCHEME 1

The direct determination of the stereochemistry of hydroxy esters **4** was not possible by solvent effect experiments in ^{1}H nmr (10, 11) due to the presence of several functional groups in the molecule.

However, the synthesis of diastereoisomeric alcohols **5a** and **5b**, which present a structural analogy with **4a** and **4b**, was recently described (12). Their stereochemistry was established by using solvent effect experiments in ^{1}H nmr. Using the pair of solvents $CDCl_3$ and pyridine, these effects are negative and are larger when the hydroxyl group is closer to the observed proton (10).



The solvent effects induced by the tertiary alcohol on the bridgehead position were 0 ppm for **5a** (H and OH in trans position) and −0.14 ppm for **5b** (H and OH in cis position).

In order to confirm the stereochemistry, which was assigned on the basis of the solvent effects in ^{1}H nmr, the crystal structure of **5b** was determined by X-ray crystallography and was in agreement with the nmr results. Table 1 gives the atomic coordinates and Table 2 the bond lengths and interbond angle.[1] The X-ray structure is shown in Figure 1.

Attempted transformations of **5** into **4**, using ozonolysis on Si gel (13) or RuO_4 oxidation (14, 15), were unsuccessful. Nevertheless, heteronuclear multiple bond correlation (HMBC) (16) demonstrated a correlation between **4a** and **5a** on one hand and **4b** and **5b** on the other.

[1]Atomic coordinates for this structure have been deposited at the Cambridge Crystallographic Data Centre, and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

TABLE 1. Atomic coordinates of **5b**.

Atom	x	y	z	U
N-1	2820 (1)	5448 (3)	5843 (2)	34 (1)
C-2	3345 (1)	6683 (4)	6176 (3)	36 (2)
O-2	3310 (1)	8531 (3)	6148 (3)	55 (2)
C-3	3965 (1)	5415 (4)	6566 (3)	38 (2)
C-4	3808 (1)	3353 (3)	5830 (3)	32 (2)
O-4	4093 (1)	1861 (3)	6820 (2)	45 (1)
C-5	3004 (1)	3329 (3)	5857 (3)	33 (2)
C-6	2564 (1)	2467 (4)	4539 (4)	50 (2)
C-7	1967 (3)	3878 (6)	4402 (6)	98 (5)
C-8	2177 (1)	5863 (4)	5012 (3)	47 (2)
C-41	4083 (1)	3188 (3)	4175 (3)	35 (2)
C-42	4359 (1)	1390 (4)	3645 (3)	42 (2)
C-43	4573 (2)	1204 (5)	2118 (4)	54 (2)
C-44	4505 (2)	2771 (6)	1088 (4)	58 (3)
C-45	4241 (2)	4564 (5)	1613 (4)	58 (3)
C-46	4037 (2)	4785 (4)	3134 (3)	49 (2)

The absence of protons linked to C-1 in **4a**, **4b** and **5a**, **5b** precluded comparison of interproton couplings between the series. $^2J_{CH}$ in *CCH fragments depend on the angle between the C-4 bond and the orientation of orbitals on the starred carbons (17). In rigid systems, it is therefore possible to link $^2J_{CH}$ couplings with substituent orientation. $^2J_{CH}$ may be directly detected on proton-coupled carbon spectra (but this is complicated by the multiplication of long range couplings) or by using selective *J*-resolved experiments (18). For the sake of sensitivity, HMBC experiments (16) were chosen and run on compounds **4** and **5**. The most striking difference between **4a** and **4b** is

TABLE 2. Bond distances (Å) and angles (°) for **5b**.

N-1–C-2	1.338 (3)	C-5–C-6	1.523 (4)
N-1–C-5	1.458 (3)	C-6–C-7	1.495 (5)
N-1–C-8	1.457 (3)	C-7–C-8	1.480 (5)
C-2–O-2	1.235 (3)	C-41–C-42	1.392 (3)
C-2–C-3	1.505 (3)	C-41–C-46	1.394 (4)
C-3–C-4	1.542 (3)	C-42–C-43	1.387 (4)
C-4–O-4	1.417 (3)	C-43–C-44	1.375 (5)
C-4–C-5	1.561 (3)	C-44–C-45	1.379 (5)
C-4–C-41	1.528 (3)	C-45–C-46	1.378 (4)
C-2–N-1–C-5	114.2 (2)	N-1–C-5–C-4	103.5 (2)
C-2–N-1–C-8	129.3 (2)	N-1–C-5–C-6	103.0 (2)
C-5–N-1–C-8	113.3 (2)	C-4–C-5–C-6	123.0 (2)
N-1–C-2–O-2	124.7 (2)	C-5–C-6–C-7	104.3 (3)
N-1–C-2–C-3	107.8 (2)	C-6–C-7–C-8	109.1 (3)
O-2–C-2–C-3	127.6 (2)	N-1–C-8–C-7	103.5 (3)
C-2–C-3–C-4	104.9 (2)	C-4–C-41–C-42	120.4 (2)
C-3–C-4–O-4	107.9 (2)	C-4–C-41–C-46	121.4 (2)
C-3–C-4–C-5	101.2 (2)	C-42–C-41–C-46	118.1 (2)
C-3–C-4–C-41	112.1 (2)	C-41–C-42–C-43	120.5 (2)
O-4–C-4–C-5	111.4 (2)	C-42–C-43–C-44	120.8 (3)
O-4–C-4–C-41	111.8 (2)	C-43–C-44–C-45	118.8 (3)
C-5–C-4–C-41	111.9 (2)	C-44–C-45–C-46	121.0 (3)
C-4–O-4–HO-4	110.3 (29)	C-41–C-46–C-45	120.7 (3)

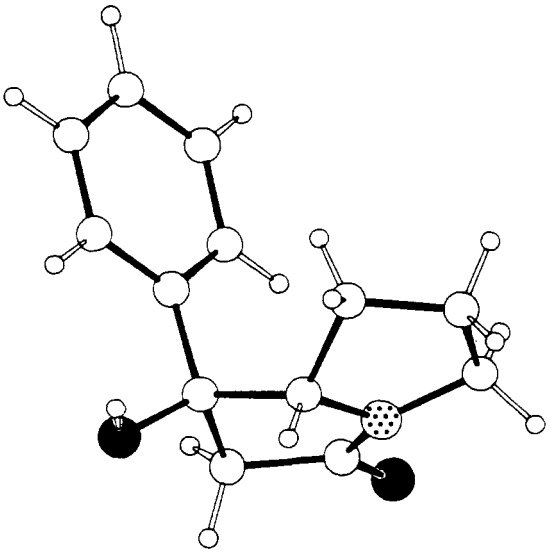


FIGURE 1. X-ray structure of **5b**.

found on the couplings between CH_2-2 and C-1: in **4b** the two protons of the methylene couple to C-1, while in **4a** only the upfield proton couples to C-1.

In the **5a**, **5b** pair, the same phenomenon is observed: two couplings between CH_2-2 and C-1 in **5b** and only one in **5a**. Compound **5b** is therefore assigned the configuration of **4b**. Surprisingly, $^3J_{CH}$ couplings which are Karplus dependent (18) were of no use in this determination.

Other similarities were observed in high field ^{1}H nmr: the proton in the C-8 position appeared as a triplet in **4a** and **5a** ($J = 7$ Hz) and as a doublet of doublets in **4b** and **5b** ($J_1 = 6.5$ Hz, $J_2 = 9$ Hz); the methylene group in the C-2 position appeared as AB spectra in **4** and **5**, but the nonequivalence is much higher for **4a** and **5a** ($\Delta\nu = 240$ Hz at 300 MHz) than for **4b** and **5b** ($\Delta\nu = 60$ Hz at 300 MHz).

Reduction ($LiAlH_4$, THF) of the carbonyl groups of ester and lactam functions in **4a** and **4b** afforded alcohols **1** and **2**, respectively, in 80% yield each. ^{1}H-nmr and ^{13}C-nmr spectra of **1**, which is obtained from **4a**, were identical to those described in the literature by Mohanraj and Herz (8) for curassanecine (Table 3). Consequently, the structure and stereochemistry of curassanecine are those of compound **1**.

TABLE 3. Proton and Carbon Chemical Shifts in C_5D_5N.

Proton	Compound		Carbon	Compound		
	Curassanecine[a]	**1**		Curassanecine[a]	**1**	**2**
H-2 . . .	2.30, 2.22	2.20, 2.30	C-1	80.32	80.17	82.53
H-3 . . .	3.35, 3.00	3.45, 3.00	C-2	39.15	38.92	33.29
H-5 . . .	3.11, 2.78	3.15, 2.80	C-3	55.66	55.46	64.10
H-6 . . .	1.79	1.78	C-5	53.29	53.17	64.00
H-7 . . .	2.39, 2.03	2.39, 1.98	C-6	25.42	25.11	25.10
H-8 . . .	4.19	4.05	C-7	27.84	27.71	28.53
			C-8	70.80	70.89	70.91
H-9 . . .	3.98	3.98	C-9	68.38	67.77	65.63

[a]Values in this column are from Mohanraj and Herz (8).

Examination of Table 3 shows a similarity concerning ^{1}H-nmr as well as ^{13}C-nmr chemical shifts; moreover, ^{1}H- and ^{13}C-nmr spectra of the isomer **2** are quite different, thus confirming the structural assignment of **1**.

In conclusion, we achieved the first total synthesis of (+/−) curassanecine, in three steps, from *N*-acetylpyrrolidine, in a 48% overall yield. The structure and relative stereochemistry of this alkaloid and of its diastereoisomer are thus determined without ambiguity.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr and ^{13}C-nmr spectra were determined in $CDCl_3$ and C_5D_5N solution with TMS as internal standard using JEOL C 60H, JEOL FX 60 and BRUKER MSL 300 spectrometers. HMBC experiments were run on a BRUKER AC 300 modified for reverse detection. 90° ^{1}H pulses (decoupler) were 18.5 μsec, 90° ^{13}C pulses were 5.6 μsec; delays for evolution of long range couplings were 60 msec. Experiments consisted of 256 × 2K experiments, FIDs were multiplied by a squared sine bell with a 60° shift in both directions, and spectra were presented in the power mode.

Ir spectra were recorded on a Perkin-Elmer 377 spectrometer, Mass spectra were recorded on a Varian CH_5 spectrometer. Analytical chromatography was performed on Merck Si gel plates with fluorescent irradiation and were developed by I_2 vapor exposure or uv irradiation. Flash chromatography was conducted with Merck 40–63 μm Si gel. Reagent grade THF was distilled from sodium benzophenone prior to use. Other anhydrous solvents were distilled from CaH_2 and stored over 4Å molecular sieves until use. Irradiation was performed in a Pyrex glass vessel using a medium pressure mercury lamp (Philips 400 W). The reaction mixture was flushed with a stream of dry N_2 to remove O_2.

2-OXO-4-HYDROXY-4-CARBOMETHOXY-1-AZABICYCLO [3.3.0] OCTANE [**4a**, **4b**].—A solution of **3** (1 g, 10 mmol) in *t*-BuOH (200 ml) was irradiated under N_2 for 48 h. Solvent was distilled thoroughly, and purification by flash chromatography afforded **4a** and **4b**. Compound **4a** (0.44 g, 44%): ir ν (CCl_4) 3540, 1740, 1710 cm^{-1}; ^{1}H nmr δ ($CDCl_3$) 1.70 (m, 1H), 2.1 (m, 3H), 3.0 (m, 1H), 3.6 (m, 1H), 2.9 (AX spectra, J_{AX} = 16 Hz, Δν 224 Hz), 3.85 (s, 3H), 4.25 (t, 1H, J = 7 Hz); ^{13}C nmr δ ($CDCl_3$) 21.1 (C-6), 25.0 (C-7), 40.2 (C-2), 46.1 (C-5), 51.45 (C-10), 66.7 (C-8), 75.7 (C-1), 170.1 (C-9), 171.7 (C-3); exact mass calcd for $C_9H_{13}NO_4$, 199.0845, found $[M]^+$ 199.0846. Compound **4b** (0.48 g, 48%): ir ν (CCl_4) 3540, 1740, 1710 cm^{-1}; ^{1}H nmr δ ($CDCl_3$) 1.35 (m, 1H), 1.9 (m, 2H), 2.9 (AB spectra, J_{AB} = 16 Hz, Δν 224 Hz), 3.1 (m, 1H), 3.6 (m, 1H), 3.8 (s, 3H), 4.05 (dd, J_1 = 10 Hz, J_2 = 6.5 Hz); ^{13}C nmr δ ($CDCl_3$) 24.1 (C-6, C-7), 39.9 (C-2), 44.2 (C-5), 50.6 (C-10), 69.1 (C-8), 76.6 (C-1), 170.2 (C-9), 171.3 (C-3); exact mass calcd for $C_9H_{13}NO_4$, 199.0845, found $[M]^+$ 199.0846.

REDUCTION OF **4a** AND **4b**.—To a solution of **4a** (0.2 g, 1 mmol) in anhydrous THF (17 ml) was added $LiAlH_4$ (0.15 g, 3.9 mmol), and the system was heated under reflux for 18 h. Then H_2O (0.16 ml), 15% aqueous NaOH (0.16 ml), and H_2O (0.16 ml) were successively added. Evaporation of volatiles left a residue, which was leached with Et_2O, and the resulting solution was dried ($MgSO_4$). Evaporation and purification on alumina gave (±)-curassanecine [**1**] (0.11 g, 72%) as a yellow oil: ir ν (CCl_4) 3700, 3400 cm^{-1}; ^{1}H nmr δ (C_5D_5N) 1.8 (m, 2H, H-6), 2.0 (m, 1H, H-7), 2.2–2.4 (m, 3H, H-2 and H-7), 2.9 (m, 1H, H-5β), 3.0 (m, 1H, H-3β), 3.1 (m, 1H, H-5α), 3.39 (t, J = 8 Hz, 1H, H-3α), 4.0 (s, 2H, H-9), 5.4 (broad s, 1H, OH); ^{13}C nmr δ (C_5D_5N) 25.11 (C-6), 27.71 (C-7), 38.92 (C-2), 53.17 (C-5), 55.46 (C-3), 67.77 (C-9), 70.89 (C-8), 80.17 (C-1).

According to the previous procedure, reduction of **4b** (0.2 g, 1 mmol) gave **2** (0.05 g, 30%) as a yellow oil: ir ν (CCl_4) 3700, 3400, cm^{-1}; ^{1}H nmr δ (C_5D_5N) 1.8 (m, 2H), 2.0 (m, 1H), 2.2 (m, 3H), 2.4–2.6 (m, 1H), 2.8–3.2 (m, 2H), 3.8–4.4 (m, 3H), 5.4 (broad s, 1H, OH); ^{13}C nmr δ (C_5D_5N) 25.10 (C-6), 28.53 (C-7), 33.29 (C-2), 64.20 (C-5 or C-3), 64.42 (C-3 or C-5), 65.63 (C-9), 70.98 (C-8), 82.53 (C-1).

CRYSTAL STRUCTURE OF **5b**.—Monoclinic $P2_1/n$; Z = 4; a = 19.394 (10), b = 6.671 (3), c = 8.592 (5) Å; b = 90.67 (8); V = 1112 Å^3; μ (CuKα) = 6.2 cm^{-1}; d_x = 1.3 $|h|<24$, $|k|<8$, $|l|<11$. Three standards every 3 h; no decay; scan speed 0.0375° sec^{-1}, scan width 2.3°; 4002 measured, 2006 unique reflexions, 1674 used [$(I>3\sigma(I)$, σ from counting statistics]. Direct methods (19), full-matrix least-squares (20). H-atoms refined (U_{iso} fixed equal to that of holder), C,N,O anisotropic. Final R = 5.8% (R_w = 7.6%), with $w = [\sigma 2(F) + 0.002F^2]^{-1}$.

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