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A Synthesis of (-) Supinidine and its Regioisomer by Intramolecular Oxime Olefin Cycloaddition.[1]

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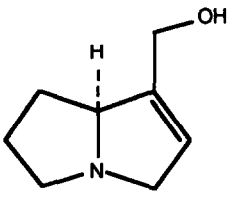
Abstract: A synthesis of (-) supinidine **1** and its regioisomer **2** from L-proline is described. The key step is a thermal intramolecular oxime-olefin cycloaddition, dimerization products resulting from intramolecular nitrone formation were also isolated

The necine alkaloids, comprise a group of pyrrolizidines, many of which exhibit hypotensive, antitumor or antispasmotic properties [2] One of these alkaloids is (-) supinidine, which has been synthesized by several research groups, both in the racemic[3] and optically active form [4] The molecule is reportedly difficult to handle, volatile, unstable to chromatography and decomposes in air [5]

Recently, we have shown that pyrrolidines possessing an olefinic moiety and a properly positioned aldoxime or ketoxime chain undergo thermally induced intramolecular dipolar cycloaddition (via N-H nitrones) to pyrrolizidines or indolizidines fused to an isoxazolidine ring, with stereospecific introduction of stereo centers [6] Thus provides an entry into stereospecifically functionalized pyrrolizidines Alternatively, intramolecular nitrile oxide-olefin cycloaddition[7] may be usable in the synthesis of such systems A possible approach to chiral supinidine is therefore, via intramolecular cycloaddition starting with an unsaturated oxime derived from chiral proline As will be discussed below, the nitrile oxide-olefin cycloaddition route proved to be non-operable We report here the application of intramolecular oxime-olefin cycloadditions (IOOC) to the synthesis of (-) supinidine **1** as well as of its side chain isomer **2.**



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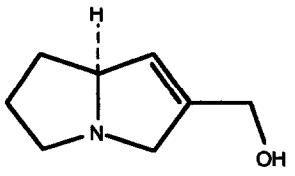
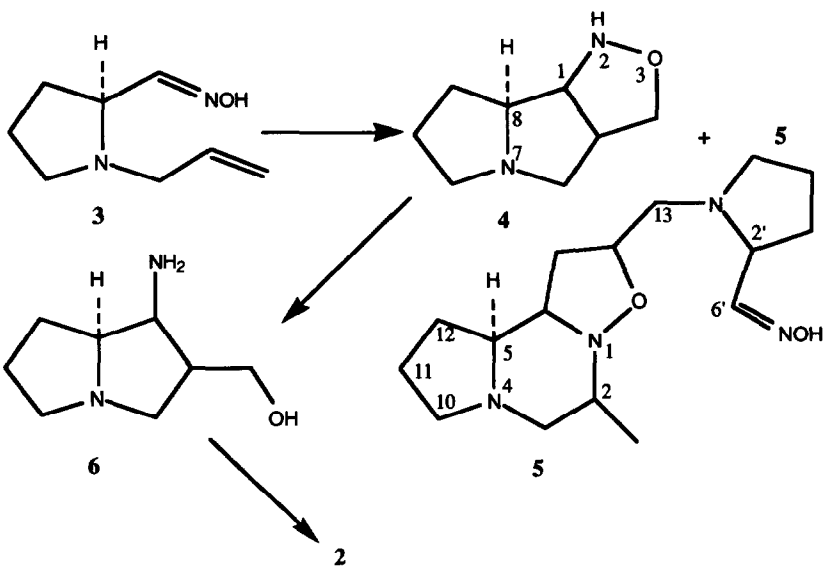


2

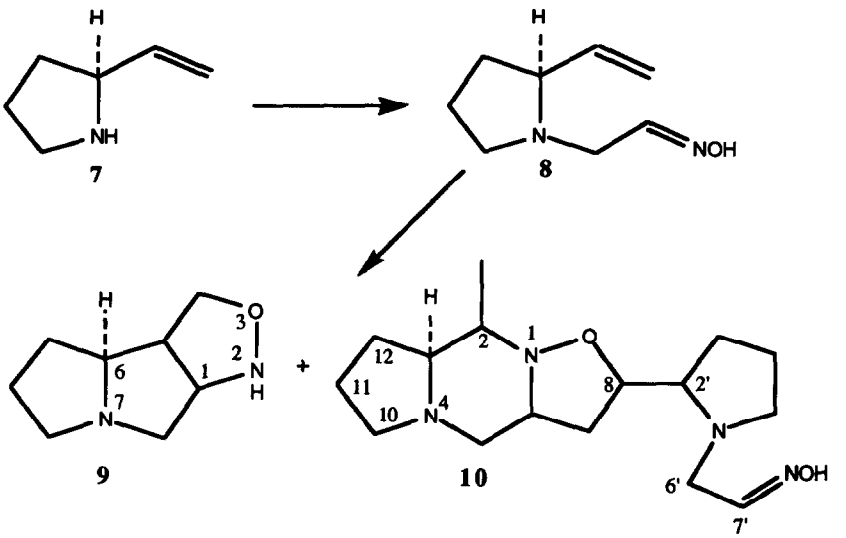
Our approach utilized the conversion of L-proline into either the N-allylpyrrolidine-2-carboxaldoxime **3** or the N-acetoximino-2-vinylpyrrolidine **8**, followed by thermal oxime-olefin cycloaddition [6,8] L-Proline possesses the same absolute configuration as natural (-) supinidine

Because of the instability of supinidine and of the precursor 2-vinylpyrrolidine, we decided to undertake first the synthesis of **2**, the as yet unknown regioisomer of supinidine for comparison of chemical and physiological properties L-Proline was converted via methyl N-allylprolinate and N-allylprolinal to oxime **3**, $[\alpha]_D^{24}$ = -108 2°, (c, 1 65 THF) The latter was heated in a sealed tube in toluene at 180°C for 18 h to afford the tricyclic oxazolidine **4**, $[\alpha]_D^{22}$ = -26 7° (c, 2 7 EtOH) as a single isomer in 81% yield Another product of this reaction was the dimeric species **5** isolated in optically active form in varying yield up to 19% The structure of **5** was confirmed from its ^{1}H- and correlated ^{13}C- NMR and its mode of formation will be discussed below

LAH reduction of oxazolidine **4** led in quantitative yield of the amino alcohol **6**, which on diazotization produced **2** in 60% yield

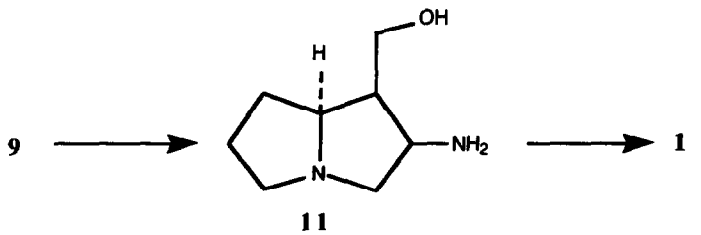


Next the IOOC reaction was applied to the synthesis of (-) supinidine **1**. L-Proline was converted via the unstable 2-vinylpyrrolidine **7** to the oxime **8**, $[\alpha]_D^{22}$= -95 9° (c, 1.45 THF). Heating of **8** at 180°C for 15 h afforded the tricyclic compound **9** $[\alpha]_D^{22}$ = +13 9° (c, 3.5 EtOH) in 56% yield, accompanied sometimes by optically active dimer **10**, up to 24%, (for the structure determination see below) These two products were



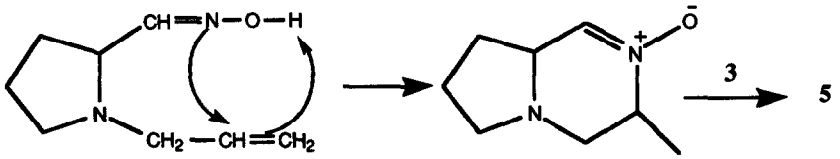
separated by chromatography on silica and elution with MeOH-EtOAc-NH_4OH The success of the oxime-olefin cycloaddition **8** -> **9** contrasts the unsuccessful attempts (tar formation) to have oxime-olefin **8** undergo a nitrile oxide-olefin cycloaddition on treatment with NaOCl or CAT

Reductive cleavage of **9** with LAH followed by diazotization led via amino alcohol **11** to (-) supinidine **1** (53%), $[\alpha]_D^{22}$ = -7 4° (c, 1 35 EtOH), lit.[9] $[\alpha]_D^{18}$ = -10 3° (c, 1 65 EtOH) The compound was identical by PMR and CMR to the authentic material Apparently, the preparation of prolinal, its Wittig reaction to form **7**, as well as the thermolysis of **8** at 180°C to achieve the intramolecular cycloaddition had not led to considerable racemization [4c] Intermediate **11** may also be useful for the synthesis of other necine alkaloids



The formation of dimeric products **5** and **10** deserves comment. Their structures were determined by ^{1}H and ^{13}C-NMR, COSY and hetero COSY experiments and elemental analysis For instance, **10**, present as a mixture of syn- and anti-oximes, showed methyl doublets at 1 11 and 1 13 next to a quartet of doublets at 2 70 ppm, correlated with C absorptions at 16 36 and 59.07 ppm. The other tertiary carbon signals were at 67 80 and pairs at 60.60 and 60 72, 66 31 and 66 78 and next to O at 81 01 and 81 62 ppm. The latter methine carbons were correlated to proton ddd peaks at 4.37 and 4 39 The methylene next to the syn- and anti-aldoxime function was present as four sets of dd signals at 3.13, 3 35, 3.88 and 4 02 with two carbon absorptions at 51.05 and 53 35 ppm Similar correlations permitted the structure assignment to **5**

We propose that **5** is formed via a mechanism resembling the ene reaction[10] and involving an intermediate nitrone **12** as shown in Scheme-1 A similar transformation will convert **8** to **10** An alternative mechanism



Scheme-1

involves tautomerization of the oxime to a N-hydroxyenamine[11a] later disproved.[11b]

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EXPERIMENTAL[6a]

7,8-Trimethylene-3-oxa-2,7-diazabicyclo[3.3.0]octane 4 and 2-methyl-4,5-trimethylene-8-(2'-formyl-1'-pyrrolidin)methyl-9-oxa-1,4-diazabicyclo[4.3.0]nonane oxime 5:

The oxime **3**, obtained as described[6a] but using L-proline, (3.55g, 23 mmol) in 85 ml of dry toluene was heated at 180°C in a sealed ampule for 18 h. The toluene was removed under vacuum and the crude oil was purified on SiO_2 using MeOH· EtOAc 25% NH_3 (1.9 0.4) to afford 2 86 g (81%) of cycloadduct **4** and (2 4%) of dimer **5** as a Z E oxime mixture (30:70) In one case the yield of **5** was 19% and that of **4** was 63%

4, PMR identical to that of racemic **4**,[6a] $[\alpha]_D^{22}$ = -26 67° (c, 2.7 EtOH)

5, Oil, (Z·E; 30·70), $[\alpha]_D^{25}$ = -15 7° (c, 1 19 THF). PMR COSY ($CDCl_3$) δ 9 5 (b, 1H, OH), 7 24 and 6 77 (m, 1H, H-6'), 4 49 (m, 1H, H-8), 3 62 and 3 59 (m, 1H, H-6), 3 29 and 2 26 (m, 1H, H-5'), 3 27 and 2 35 (m, 1H, H-5'), 3 02 and 2 04 (m, 2H, H-10), 3 00 and 2 94 (m ,1H, H-2'), 2 93 (m, 1H, H-2), 2 91 and 1 89 (m, 2H, H-3), 2 85 and 2.46 (m, 1H, H-13), 2 80 and 2 34 (m, 1H, H-13), 2 50 and 2 49 (m, 1H, H-5), 2.47 and 1 67 (m, 1H, H-7), 2 39 and 1 84 (m, 1H, H-7), 1 94 and 1 69 (m, 2H, H-3'), 1.88 and 1 79 (m, 1H, H-

11), 1 85 and 1 48 (m, 1H, H-12),1 83 and 1.78 (m, 1H, H-4'), 1 82 and 1.43 (m, 1H, H-12), 1 80 and 1 76 (m, 1H, H-4'), 1 76 and 1 69 (m, 1H, H-11), 1.13 and 1 12 (m, 3H, CH_3). CMR ($CDCl_3$) δ 153 29 and 153 06 (C-6'), 76.90 and 76 64 (C-8), 64 24 and 63 82 (C-2'), 63 97 and 63.28 (C-6), 62.72 and 62 56 (C-5), 58 65 and 57 16 (C-13), 56.90 (C-3), 55 35 and 54 60 (C-5'), 53.10 and 52 88 (C-2), 52 77 (C-10), 31 47 and 30 56 (C-7), 29.12 and 28 99 (C-3'), 27 63 and 27.60 (C-12), 23 29 and 23 02 (C-4'), 21 74 and 21 77 (C-11), 17 48 and 17 39 (CH_3) MS (CI isobutane) 309 (MH^+, 100), 291 ($MH^+ - H_2O$, 17 2), 264 ($MH^+ - CH_2$=NOH, 14 2), 181 ($MH^+ - C_6H_{12}N_2O$, 21 7) Anal Calcd for $C_{16}H_{28}N_4O_2$ C, 62 20, H, 8 81, N, 17 79 Found C, 62 34, H, 9 09, N, 18 18

1(R)-Amino-2(R)-hydroxymethyl-8(S)-pyrrolizidine 6:

To a stirred solution of lithiumaluminium hydride in 10 mL THF under Ar at -10 to 0°C, a solution of cycloadduct **4** (0 35 g, 2 26 mmol) in 10 mL THF was added dropwise The temperature was slowly raised to 25°C and stirring continued for another 6-8 hours The reaction mixture was quenched by addition of 0 26 mL of water, 0 26 mL of 10% NaOH, 0 5 mL water and 4 g of sodium sulfate, stirred for another 15 min, filtered and washed with THF (2x5 mL) and chloroform (3x5 mL) The combined organic extracts were concentrated to afford 0.34 g (96 2%) of **6**, $[\alpha]_D^{22}$ = -10 64° (c, 2.63 EtOH). PMR ($CDCl_3$) δ· 3 87 (dd, J = 11, 7 Hz, 1H, H-9), 3 74 (dd, J = 11, 4 9 Hz, 1H, H-9), 3 28-3 18 (m, 2H, H-1 and H-8), 3.04 (dd, J = 11, 4 5 Hz, 1H, H-3), 2 97 (dt, J = 10 5, 6 5 Hz, 1H, H-5), 2 68 (dt, J= 11,6 5 Hz, 1H, H-3), 2.54 (dt, J = 10 5, 6 5 Hz, 1H, H-5), 2 40-2 28 (m, 1H, H-2), 2 12-1 93 (m, 1H, H-7), 1 92-1 68 (m, 2H, H-6), 1.63-1 45 (m, 1H, H-7) CMR ($CDCl_3$) δ 72 56 (d, C-8), 62 53 (t, C-9), 60 12 (d, C-1), 56 69 (t, C-3), 55 25 (t, C-5), 44.96 (d, C-2), 30 81 (t, C-7), 25 53(t, C-6) MS (EI) m/z. 157 (MH^+, 16 4), 156 (M^+, 20 6), 140 ($M^+ - NH_2$, 1 6), 125 (5.7), 110 (3 7), 84 (11 6), 83 (100), 82 (14 4), 70 (11) MS (CI isobutane) m/z 157 (MH^+, 100), 199 ($M^+ + C_3H_7$, 3 3), 213 ($M^+ + C_4H_9$, 12 5)

1,2-Dehydro-2-hydroxymethylpyrrolizidine 2:

To amino alcohol **6** (0 077 g, 0 5 mmol) in 2 5 mL of THF was added 3.5 ml of 2N HCl and at 0°C 3.5 mL of 10% sodium nitrite was added dropwise The mixture was stirred in the cold for 1 h and at 25°C for 22 h. Solvent was removed under vacuum and the residue was dissolved in $CHCl_3$ (10 mL) and 3 g of anh K_2CO_3 was added After 24 h stirring at 25°C and filtration, the filtrate was concentrated and purified by chromatography over SiO_2 ($CHCl_3$ MeOH 25% NH_3, 85 15 1) to afford 0 04 g (60%) of **2** as an oil, $[\alpha]_D^{22}$ = +26 72 (c, 1 61 EtOH) PMR ($CDCl_3$) δ 5 57 (bs, 1H, H-1), 4 23 (bm, 1H, H-8), 4 16 (s, 2H, H-9), 3 88 (bd, J = 15 Hz, 1H, H-3), 3 32 (dd, J = 10 5, 4 Hz, 1H, H-3), 3 07 (dt,, J = 10 5, 7 Hz, 1H, H-5), 2 53 (dt, J = 10 5, 7 Hz, 1H, H-5), 2 05-1 86 (m, 1H, H-7), 1 82-1 62 (m, 2H, H-6), 1 58-1 40 (m, 1H, H-7) CMR ($CDCl_3$) δ 140 89 (s, C-2), 125 81 (d, C-1), 71.62 (d, C-8), 62 23 (t, C-3), 59 84 (t, C-9), 56 86 (t, C-5), 31 24 (t, C-7), 25 58 (t, C-6) MS (EI) m/z 140 (MH^+, 15 51), 139 (M^+, 100), 138 (M^+ - H, 21 69), 122 (51 7), 120 (19 89), 11 (20 31), 110 (21 98), 108 (29 97), 94 (11 79), 86 (40 62), 84 (63 48), 81 (10 39), 80 (70 28) If K_2CO_3 was omitted in the work up and the product was extracted with 50% MeOH in ether and chromatographed on cellulose using 50-70% methanol in ether and finally with methanol as eluent, **2.HCL** was obtained as a semi solid in 66%

yield. $[\alpha]_D^{24}$ = +3.26° (c, 0 46 EtOH). PMR (D_2O) δ 5 74 (m, 1H, H-1), 5 07 (bm, 1H, H-8), 4 46 (ddt, J = 15 8, 2 5, 1.2 Hz, 1H, H-3), 4 22 (ddt, J = 2 0, 1.6, 1 1 Hz, 2H, H-9), 3 96 (bm, 1H, H-3), 3.68 (dt, J = 11 5, 6 5 Hz, 1H, H-5), 3 25 (dt, J = 11.5, 6 5 Hz, 1H, H-5), 2.30-1.89 (m, 4H, H-6 and H-7) CMR (D_2O) δ 141 12 (s, C-2), 126.73 (d, C-1), 78.73 (d, C-8), 64 72 (t, C-3), 61 36 (t, C-9), 61 06 (t, C-5), 33 31 (t, C-7), 27.86 (t, C-6) MS (CI isobutane) m/z: 140 (MH^+, 100), 122 ($MH^+ - H_2O$, 40 3), 196 ($MC_4H_9^+$), 178 ($MC_3H_3^+$). Treatment of the hydrochloride of **2** with 25% NH_4OH afforded **2**

6,7-Trimethylene-3-oxa-2,7-diazabicyclo[3.3.0]octane 9 and 2-methyl-3,4-trimethylene-8-{(β-oxo-1'-ethyl)-2'-pyrrolidinyl}-9-oxa-1,4-diazabicyclo[4.3.0]nonane oxime 10:

Oxime **8**, obtained as described[6a] but using L-proline, (0 525 g 3.4 mmol) was dissolved in 24 mL dry toluene, sealed in an ampule under Ar and heated at 180°C for 15 h Work up and purification as described for **4** led to cycloadduct **9**, 0 295 g (56%) as an oil. $[\alpha]_D^{22}$ = +13 9° (c, 3 5 EtOH). PMR ($CDCl_3$) δ: 4 18-4.06 (bm, 1H, H-1), 4.02-3.70 (bm, 2H, H-4), 3 21 (td, J = 7, 3 5 Hz, 1H, H-6), 3 06-2.85 (m, 4H, H-5, H-8 and H-9), 2 75-2.60 (bm, 1H, H-9), 2 12-1 90 (m, 2H, H-10 and H-11), 1 86-1 70 (m, 1H, H-10), 1 65-1 51 (m, 1H, H-11). CMR ($CDCl_3$) δ· 77 72 (t, C-4), 71.36 (d, C-6), 67 08(d, C-1), 56 89 (t, C-8), 54.53 (d, C-5), 52 70 (t, C-9), 30.37 (t, C-11), 24 46 (t, C-10) MS (EI) m/z. 155 (MH^+, 25 45), 154 (M^+, 28.95), 153 M^+ - H, 7 71), 138 (14.47), 124 (11 13), 123 (51 45), 110 (20 65), 109 (7 17), 108 (18 42), 97 (19.74), 96 (100), 95 (19.9), 84 (31 62), 83 (43 65), 82 (24.73), 81 (20 42), 70 (44 28), 68 (20.80) In some experiments up to 24% of dimer **10** along with **9** was obtained on chromatography of the crude product. Dimer **10**, Z·E = 5 6 4 4, $[\alpha]_D^{25}$ = -21 6° (c, 2 07 THF) PMR[12] COSY ($CDCl_3$) δ: 7 51 (dd, J = 7 5, 4 5 Hz, H-7', E isomer), 6 89 (dd, J= 4 5, 3 5 Hz, H-7', Z isomer) 4 39 and 4 37 (ddd, J = 7, 6, 5 Hz, 1H, H-8), 4 02 (dd, J = 16 5, 3 5 Hz, H-6', Z isomer), 3.88 (dd, J = 14, 4 5 Hz, H-6', E isomer), 3 35 (dd, J = 16 6, 4 5 Hz, H-6', Z isomer), 3 13 (dd, J = 14, 7 5 Hz, H-6', E isomer), 3 15 (m, 1H, H-5), 3 00 (m, 1H, H-10), 2 70 (dq, J = 9, 6 Hz, 1H, H-2), 2 63 (m, 1H, H-2'), 2 62 (m, 1H, H-7), 2 60 (m, 1H, H-5), 2 11 (m,1H, H-10), 1 86 (m,1H, H-7), 1.73 (m, 1H, H-3), 1 11 and 1 13 (d, J = 6 Hz, 3H, CH_3) CMR ($CDCl_3$) δ 150.3 and 149 55 (C-7'), 81 62 and 81.01 (C-8), 67 80 (C-3), 66 78 and 66 31 (C-2'), 60 72 and 60 60 (C-6), 59 07 (C-2), 55 63 and 54 92 (C-5'), 53 97 (C-10), 53.35 and 51.05 (C-6'), 51 05 (C-5), 34 37 and 34 21 (C-7), 28 28 and 28 04 (C-3'), 27 82 (C-12), 23 20 and 23.09 (C-4'), 21 87 (C-11), 16 36 (CH_3) MS (CI isobutane) m/z 309 (MH^+, 100), 291 ($MH^+ - H_2O$, 5 5), 268 ($MH^+ - C_2H_3N$, 4 1), 264 ($MH^+ - CH_2{=}NOH$, 8 5), 252 ($MH^+ - C_2H_3NO$, 3 3) Anal Calcd for $C_{16}H_{28}N_4O_2$ C 62 65, H 9 41, N 17.42 Found C 62 34, H 9 09; N 18 08

2(R)-Amino-1(R)-hydroxymethyl-8(S)-pyrrolizidine 11:

LAH reduction of 0 225 g (1.46 mmol) of **9** in 15 mL THF as described for **6** gave 0 2 g (87%) of amino alcohol **11**, $[\alpha]_D^{22}$ = -31 4° (c, 1 15 EtOH) PMR ($CDCl_3$) δ 3 86 (dd, J = 11 5, 4 Hz, 1H, H-9), 3 76 (dd, J = 11 5, 7 Hz, 1H, H-9), 3 65 (ddd, J = 5 5, 4 5, 2 Hz, 1H, H-2), 3 46 (td, J = 7 5, 6Hz 1H, H-8), 2 98 (dt, J = 10 5, 6 Hz, 1H, H-5), 2 95 (dd, J = 10, 2 Hz, 1H, H-3), 2 74 (dd, J = 10, 4 5 Hz, 1H, H-3), 2 58 (dt, J = 10 5, 6 Hz, 1H, H-5), 2 10-1 76 (m, 4H, H-6, H-7 and H-1), 1 60-1 41 (m, 1H, H-7) CMR ($CDCl_3$) δ 64 19 (d, C-8), 63 95 (d, C-3), 61 64 (d, C-9), 55 95 (d, C-2), 54 88 (t, C-5), 50 75 (d, C-1), 31 62 (t, C-7),

25 63 (t, C-6) MS (EI) m/z: 157 (MH^+, 31 47), 156 (M^+, 21 92), 125 (16.41), 108 (11 41), 84 (19 71), 83 (100), 82 (14 31), 70 (10 4)

(-)Supinidine 1:

From 0 04 g (0 26 mmol) of **11** in 1 5 mL THF, 2 mL of 2N HCl and 2 mL of 10% sodium nitrite as described for **2**, there was obtained 0 02 g (53%) of supinidine **1** as an oil, $[\alpha]_D^{22}$ = -7 41°(c, 1.35 EtOH), lit[9] $[\alpha]_D^{18}$ = -10 3° (c, 1 65 EtOH) PMR ($CDCl_3$) δ 5 50 (bs, 1H, H-2), 4 25-4 08 (m, 3H and H-8, H-9), 3 87 (bd, J = 15 Hz, 1H, H-3), 3 31 (ddd, J = 15, 4, 1 5 Hz, 1H, H-3), 3 07 (dt, J = 10 5, 7 Hz, 1H, H-5), 2 57 (dt, J = 10 5, 7 Hz, 1H, H-5), 2 10-1 88 (m, 1H, H-7), 1 85-1 70 (m, 2H, H-6), 1.60-1 40 (m, 1H, H-7) CMR ($CDCl_3$) δ 144 24 (s, C-1), 121 00 (d, C-2), 71 26 (d, C-8), 61 97 (t, C-3), 59.89 (t, C-9), 56 65 (t, C-5), 30 43 (t, C-7), 25.54 (t, C-6) MS (EI) m/z 140 (MH^+, 15 44), 139 (M^+, 100), 138 (M^+ - H, 14 93), 122 (30 95) 120 (15 80), 11 (13 72), 110 (15 84), 109 (9 27), 108 (93 14), 84 (10 29), 183 (30 29), 80 (41 34) PMR and CMR identical to those reported [4]

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