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Stereoselective Preparation Of Tri And Tetracyclic Amines As Potential Intermediates In *Aspidosperma* Alkaloid Synthesis

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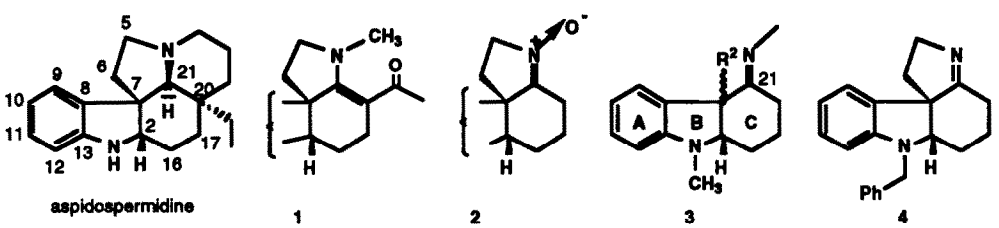
Abstract: *The stereoselectivity of the reduction of tri and tetracyclic imines 3 and 4, easily prepared from hexahydrocarbazolone 5 is studied.*

In our program directed toward the synthesis of *Aspidosperma* alkaloids framework (*e.g.* aspidospermidine),[1,2,3] most of the key intermediates were obtained by reduction of unsaturated compounds such as enaminoketones **1**, nitrones **2**, imines **3** and **4** to the corresponding amines (Scheme 1). This reduction step is crucial because it establishes definitively the stereochemistry at the C-21[4] position.



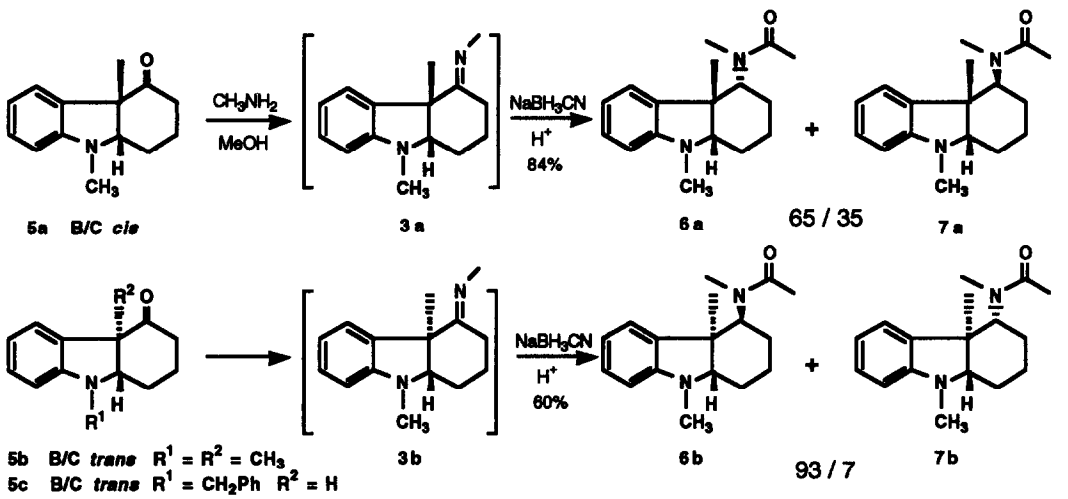
Scheme 1

Herein, we report a systematic study of the reduction of tricyclic model imines **3** and tetracyclic compound **4**[5] to saturated amines.Tricyclic imines **3a** (B/C *cis*) and **3b** (B/C) *trans* were easily prepared by amination of hexahydrobazolones **5** followed by *in situ* reduction using $NaBH_3CN$[6] to the corresponding unstable amines which were immediately acylated and characterized as their acetamido derivatives **6a/7a** and **6b/7b** (Scheme 2).

Reduction of compound **3a** (B/C *cis)* followed by *N*-acylation led to a mixture of two products **6a/7a** in a 65/35 ratio (84% yield). Their structure and stereochemistry were deduced from NMR spectra (^1H, ^{13}C and ROESY experiment). Since no ROE was observed between H-21 and H-2 or H-9 we deduced that both compounds **6a**[7] and **7a**[7] adopt a conformation in which the C ring is a flattened chair with the acetamido func-

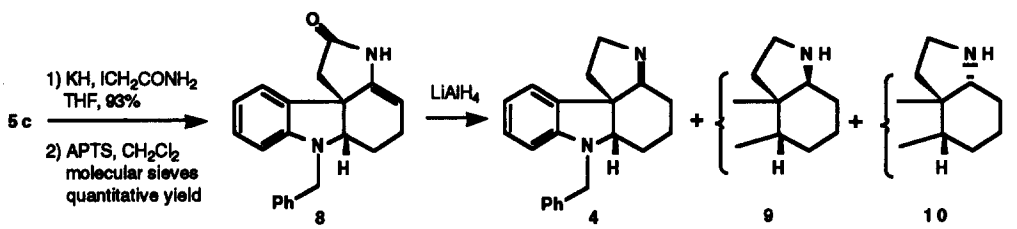
tion in a pseudo-equatorial position. These results were confirmed by molecular modelling and calculations.

The reduction and acylation of compound **3b** (B/C *trans*) led to a mixture of **6b** and **7b** (60% yield) in a 93/7 ratio. The ROE between H-21 and H-9 in the major product **6b**[7] and the lack of a ROE in this compound between H-21 and H-2 is in agreement with a chair C ring bearing an axial acetamido function . In compound **7b**[7] H-21 and H-2 showed a ROE which confirms the equatorial stereochemistry of the acetamido group.



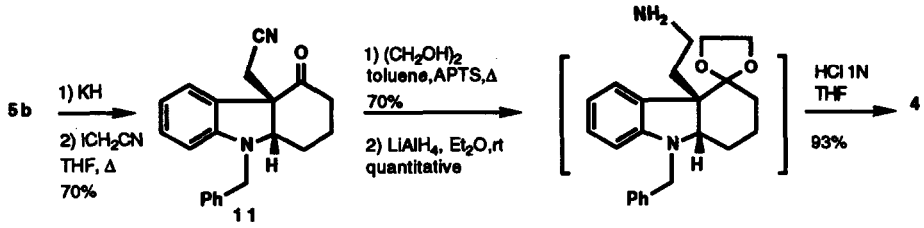
Scheme 2

Preparation of imine **4** from hexahydrocarbazolone **5c** on a larger scale than previously described[5] failed : Reduction of enamide **8** led invariably to a mixture of the desired imine **4** together with amines **9** and **10**, the result of further reduction of **4** (Scheme 3).



Scheme 3

We therefore developed an alternative method to prepare the imine **4**. Thus, nitrile **11** was reduced to amine after protection of the carbonyl group. Deprotection was followed by spontaneous cyclization into imine **4** (Scheme 4).



Scheme 4

Chemical reduction of imine **4** (Table 1) provided the amines **9**[8] and **10**[8] in good yield with a preponderance of the *cis* amine. Their ratio was determined by quantitative ^{13}C NMR. $LiAlH_4$ (run 1) led to a 70/30 ratio of com-pounds **9/10** (quantitative yield). Attempts to improve this ratio using hindered hydride such as *L*-selectride or Superhydride failed. In fact no reduction was observed, due to the steric hindrance. Chemical reduction with $NaBH_3CN$ (run 5) and catalytic reduction (run 13) led to interesting results : chemical yields were good to quantitative and only the amine of natural configuration (B/C *cis* and E/C *cis)* was obtained. The outcome of dissolving metal reduction was of particular interest. The reduction using Na in EtOH failed and had to be performed at higher temperature in *n*BuOH (run 11). It led to a mixture of amines **9** and **10** in a 88/12 ratio. These conditions are thought to allow thermodynamic control[9] and show the greater stability of the natural isomer.

Table 1. Reduction of imine **4**

Run	Conditions	Temp	Yield (%)	amine *cis* **9**/amine *trans***10**
1	$LiAlH_4$, THF	reflux	quantitative	70/30
2	*L*-selectride, THF	rt to reflux	no reaction	
3	Superhydride, THF	rt to reflux	no reaction	
4	DIBAL, toluene	-78°C to reflux	no reaction	
5	$NaBH_3CN$,MeOH/HCl	rt	75%	100/0
6	$NaBH_4$, MeOH	rt	58%	67/33
7	KBH_4, MeOH	reflux	71 %	77/23
8	PtO_2, EtOH	rt	quantitative	59/41
9	Pd/C, EtOH	rt	no reaction	
10	Na, EtOH	rt to reflux	no reaction	
11	Na, *n*BuOH	reflux	75%	88/12
12	Na, NH_3	-40°C	60%	debenzylated imine
13	Ni Raney, EtOH	rt	quantitative	100/0
14	BH_3, THF	0°C to rt	no reaction	
15	9-BBN, THF or Toluene	rt to reflux	no reaction	

The rather unstable amines **9** and **10** were well characterized by their NMR ^1H and ^{13}C spectra . The assignment of the*cis* or*trans* stereochemistry was verified unambigously by 2D H^1-H^1 ROESY NMR. In amine **9** H-21 appears at δ 3.10 ppm as a doublet of doublet (J = 9 and 5 Hz) and has a ROE with H-2 at δ 3.50 ppm which is resolved as a triplet (J = 4Hz). No ROE between H-21 (doublet of doublet) at δ 3.2 ppm (J = 12 and 4 Hz) and the H-2 multiplet at δ 3.3-3.5 ppm was observed in amine **10** indicating a *trans* E/C ring junction .

In conclusion, dissolving metal reduction led to the thermodynamic product and gave mainly the *cis* amine. $NaBH_3CN$ and catalytic hydrogenation (H_2, Ni Raney) led stereospecifically with excellent yield to the amine with the natural configuration showing the validity of this synthetic approach.

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7 - **6a** : oil. ^{1}H-NMR ($CDCl_3$, 300MHz) δ = 1.40 (s, 3H, CH_3) ; 1.60-2.10 (m, 6H, H-16, H-17 and H-20) ; 2.10 (s, 3H, $COCH_3$) ; 2.40 (s, 3H, $CONCH_3$) ; 2.65 (s, 3H, NCH_3) ; 3.12 (dd, 1H, J = 2 and 3 Hz, H-2) ; 4.78 (dd, 1H, J = 11 and 4 Hz, H-21) ; 6.50 (d, 1H, J = 8 Hz, H-12) ; 6.65 (t, 1H, J = 8Hz, H-10) ; 6.92 (d, 1H, J = 8 Hz, H-9) ; 7.10 (t, 1H, J = 8 Hz, H-11). IR (CCl_4) 1650 cm^{-1}. ^{13}C-NMR ($CDCl_3$, 100 Hz) δ 18.1 (C-17), 18.9 (C-16), 22.7 ($\underline{C}H_3CO$), 23.1 (C-20), 26.4 (CH_3), 33.6 ($\underline{N}CH_3$), 47.9 (C-7), 55.3 (C-21), 74.9 (C-2), 107.4 (C-12), 117.7 (C-10), 125.1 (C-9), 128.2 (C-11), 133.4 (C-8), 153.9 (C-13), 172.2 (CO). Anal Calcd for $C_{17}H_{24}N_{20}$: C, 74.96 ; H, 8.88 ; N, 10.29. Found : C, 74.69 ; H, 8.85 ; N, 10.46.

7a : F = 140°C (ether). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 1.00 (s, 3H, $COCH_3$) ; 1.32 (s, 3H, CH_3) ; 1.40-1.60 (m, 2H, H-16 and H-20) ; 1.60-1.85 (m, 2H, H-17) ; 1.85-2.05 (m, 1H, H-20) ; 2.60 (s, 3H, NCH_3) ; 2.82 (t, 1H, J = 3 Hz, H-2) ; 2.82 (s, 3H, $CONCH_3$) ; 3.52 (dd, 1H, J = 11 and 3Hz, H-21) ; 6.52 (d, 1H, J = 8Hz, H-12) ; 6.68 (t, 1H, J = 8Hz, H-10) ; 6.82 (d,1H, J = 8Hz, H-9) ; 7.05 (t, 1H, J = 8 Hz, H-11). IR (CCl_4) 1642 cm^{-1}. ^{13}C-NMR ($CDCl_3$, 100 MHz) 17.2 (CH_3), 20.5 ($CO\underline{C}H_3$), 21.9 (C-17), 22.6 (C-16), 26.8 (C-20), 31.3 ($CON\underline{C}H_3$), 33.7 (NCH_3), 48.3 (C-7), 59.7 (C-21), 76.4 (C-2), 108.9 (C-12), 119.1 (C-10), 123.1 (C-9), 128.2 (C-11), 135.9 (C-8), 152.2 (C-13), 172.6 (CO). Anal Calcd for $C_{17}H_{24}N_2O$: C 74.96 ; H, 8.88 ; N, 10.29. Found : C, 74.16 ; H, 8.49 ; N, 9.09.

6b : oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 1.16 (s, 3H, CH_3) ; 1.65-2.10 (m, 6H, H-20, H-17 and H-16) ; 2.06 (s, 3H, $COCH_3$) ; 2.68 (s, 3H, $CONCH_3$) ; 2.87 (s, 3H, NCH_3) ; 3.0 (dd, 1H, J = 12 and 4 Hz, H-2) ; 5.35 (dd, 1H, J = 5 and 7 Hz, H-21) ; 6.10 (d, 1H, J = 8Hz, H-8) ; 6.75 (t, 1H, J = 8Hz, H-10) ; 7.10 (d,1H, J = 7Hz, H-5) ; 7.12 (t, 1H, J = 7Hz, H-11). IR (CCl_4) 1630 cm^{-1}. ^{13}C-NMR ($CDCl_3$, 100 Hz) δ 20.6 (C-16 and C-20), 22.3 ($CO\underline{C}H_3$), 22.9 (CH_3), 23.6 (C-17), 34.1 (NCH_3), 47.6 (C-7), 52.3 (C-21), 70.8 (C-2), 108.7 (C-12), 119.2 (C-10), 122.3 (C-9), 126.7 (C-11), 136.3 (C-8), 152.2 (C-13), 171.3 (CO). Anal Calcd for $C_{17}H_{24}N_2O$: C, 74.96 ; H, 8.88 ; N, 10.29. Found : C, 74.58; H, 8.78 ; N, 10.37.

7b : oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 1.15 (s, 3H, CH_3) ; 1.45-1.75 (m, 2H, H-16 and H-20) ; 1.80-2.20 (m, 4H, H-16, H-17 and H-20) ; 2.25 (s, 3H, $COCH_3$) ; 2.45 (dd, 1H, J = 12 and 3 Hz, H-21) ; 2.66 (s, 3H, NCH_3) ; 4.02 (dd, 1H, J = 12 and 3 Hz, H-2) ; 6.68 (d, 1H, J = 8Hz, H-12) ; 6.78 (t, 1H, J = 8Hz, H-10) ; 7.00 (d,1H, J = 8Hz, H-9) ; 7.20 (t, 1H, J = 8 Hz, H-11). IR (CCl_4) 1630 cm^{-1}. ^{13}C-NMR ($CDCl_3$, 100 Hz) δ 18.5 (CH_3), 22.8 (C-16), 23.5 ($CO\underline{C}H_3$), 23.8 (C*-17), 28.5 (C*-20), 30.4 ($CON\underline{C}H_3$), 34.1 (NCH_3), 48.0 (C-7), 62.4 (C-21), 76.5 (C-2), 109.5 (C-12), 118.6 (C-10), 122.6(C-9), 127.5 (C-11), 137.5 (C-8), 152.5 (C-13), 171.6 (CO).

8 - **9** : oil. ^{1}H-NMR ($CDCl_3$, 300MHz) δ = 1.30-1.70 (m, 6H, H-20, H-17 and H-16) ; 1.90-2.21 (m, 2H, H-6) ; 3.10 (dd, 1H, J = 9 Hz and J = 5 Hz, H-21) ; 3.20-3.41 (m, 2H, H-5) ; 3.5 (t, 1H, J = 4 Hz, H-2) ; 3.90 (s, 1H, NH) ; 4.25 (AB spectra, 2H, J = 16 Hz, Δν = 85 Hz, $N\underline{C}H_2Ph$) ; 6.40 (d, 1H, J = 7 Hz, H-12) ; 6.71 (t, 1H, J = 7 Hz, H-10) ; 7 .00 (t, 1H, J = 7 Hz, H-11) ; 7.05 (d, 1H, J = 7 Hz, H-9) ; 7.2-7.4 (m, 5H, H aromatic). IR ($CHCl_3$) 3420 cm^{-1}. ^{13}C-NMR ($CDCl_3$, 75 Hz) δ 18.2 (C-20), 23.6 (C-17), 27.3 (C-16), 35.0 (C-6), 43.7 (C-5), 50.6 ($N\underline{C}H_2Ph$), 53.2 (C-7), 62.0 (C-21), 67.6 (C-2), 107.8 (C-12), 118.1 (C-10), 121.1 (C-9), 127.7 (C-11), 136.5 (C-8), 138.8 (C-*ipso*), 151.0 (C-13).

10 : oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 1.1-1.4 (m, 2H, H-16 and H-17) ; 1.5-1.8 (m, 3H, H-16, H-17 and H-20) ; 1.9-2.1 (m, 3H, H-6 and H-20) ; 3.2 (dd, 1H, J = 12 and 4 Hz, H-21) ; 3.3-3.5 (m, 3H, H-5 and H-2) ; 4.3 (AB spectra, 2H, J = 15 Hz, Δν = 88 Hz, $N\underline{C}H_2Ph$) ; 6.4 (d, 1H, J = 8 Hz, H-12) ; 6.8 (t, 1H, J = 8 Hz, H-10) ; 6.8 (s,1H, NH) ; 7.1 (t, 1H, J = 8 Hz, H-11) ; 7.2-7.4 (m, 5H, H aromatic) ; 7.5 (d, 1H, J = 8 Hz, H-9). IR ($CHCl_3$) 3425 cm^{-1}. ^{13}C-NMR ($CDCl_3$, 75 Hz) δ 21.7 (C-20), 24.3 (C-16), 37.9 (C-17), 42.4 (C-5), 48.9 ($N\underline{C}H_2Ph$), 54.1 (C-7), 61.6 (C-21), 68.0 (C-2), 107.9 (C-12), 118.0 (C-10), 124.3 (C-9), 128.0 (C-11), 131.2 (C-8), 138.1 (C-*ipso*), 150.6 (C-13).

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