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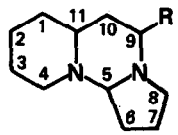
A SHORT TETRAPONERINE SYNTHESIS

Tappey H. Jones

Laboratory of Chemistry
National Heart, Lung, and Blood Institute
Bethesda, MD 20892

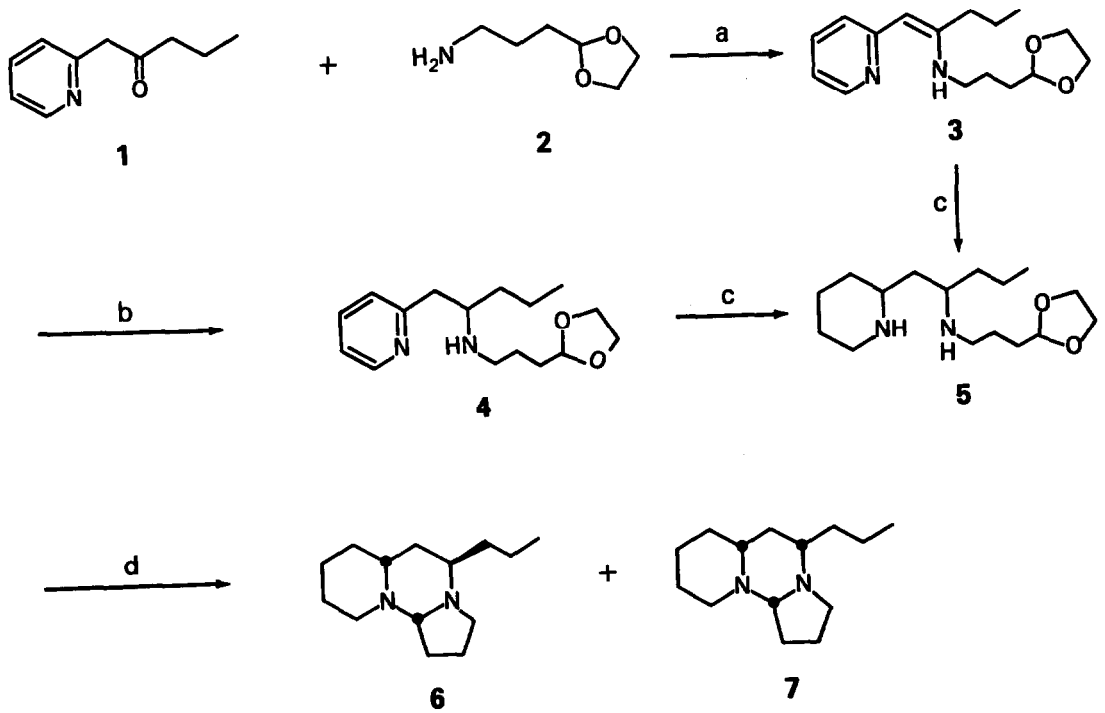
Summary: A short synthesis of (±) tetraponerine T4 **7** and its "unnatural" isomer **6** from the appropriate pyridyl ketone **1** is described. This synthesis includes an investigation of the stereoselectivity of pyridine reduction in the conversion of the amine **4** to **6** and **7**.

The tetraponerines, 9-alkyldecahydropyrido[1,2-c]-pyrrolo[1′,2′-a]pyrimidines, are a group of unique tricyclic alkaloids which are toxic components of the venom of ants in the genus *Tetraponera*.[1,2] Five of the six tetraponerines whose stereochemistry has been established have the configuration in which the C-9 and C-11 hydrogens are *cis*; and while one multistep synthesis of the all-*cis* (9Z,11Z) stereoisomer[3] T-8 (R=n-C_5H_{11}) has been published,[4] we sought a practical route to these compounds to provide material for our ongoing investigation of the relative repellencies and toxicities of the ant venom alkaloids. This report describes a short synthesis of the (9Z,11Z) stereoisomer T-4 (**7**) (R= n-C_3H_7).



It was envisioned that the tetraponerine nucleus could be assembled from the readily available 1-(2-pyridyl)-2-alkanones[5] and a four carbon segment carrying the remaining nitrogen. Thus 1-(2-pyridyl)-2-pentanone **1**[6], the precursor to tetraponerines T3 and T4, was prepared in 87% yield from N,N-dimethylbutyramide and 2-picolyllithium. The remaining nitrogen and four carbons of the tetraponerine nucleus were furnished by 2-(3-aminopropyl)-1,3-dioxolane **2**,[7] prepared in 90% yield by LAH reduction of the corresponding nitrile. The enamine **3**[8] was formed in 90% yield by the condensation of **1** and **2** in benzene with the azeotropic removal of water, and could be reduced to the pyridine amine **4**[8] in 85% yield with sodium borohydride.

Catalytic hydrogenation of **4** provided the piperidyl amine **5** nearly quantitatively as a mixture of diastereomers as indicated by the doubling of many of the ^{13}C nmr resonances.[8] Typical acetal hydrolysis conditions ($HClO_4$, THF, 3 hr, r.t.; followed by neutralization with 10% aqueous NaOH) produced nearly 90% of a mixture (see below) of the (9E,11Z) stereoisomer **6**[9] and the (9Z,11Z) stereoisomer **7** (tetraponerine T4) whose ^1H, and ^{13}C nmr spectra and mass spectra were identical to those reported in the literature.[2] Pure samples of **6** and **7** were conveniently obtained by preparative gas chromatography (2m x 5mm i.d. column packed with 10% SP-1000 on Supelcoport; 150°C, flow rate 60mL/min). It is noteworthy that the same result could be obtained if the enamine **3** was hydrogenated directly to **5**, although in this case, reaction times were much longer and extensive hydrogenolytic cleavages occurred on several occasions.



Reagents: a) benzene, pTSA, reflux; b) $NaBH_4$, MeOH; c) Reduction (see below); d) $HClO_4$, THF, 3 hr. then 10%NaOH.

Since the catalytic hydrogenation of 2-picolyl carbinols analogous to **4** has been reported to be stereoselective,[10] the reduction of **4** under a variety of conditions was investigated to improve the selectivity of this reaction (see Table 1). While rhodium catalysts are widely used since they are not easily poisoned during pyridine hydrogenation in neutral media,[11] both heterogeneous and homogeneous[12] catalysis with rhodium provided no stereoselectivity in the reduction of **4**. Hydrogenation over PtO_2 was somewhat more selective. With acetic acid, GC/MS examination of the reduction mixture prior to hydrolysis revealed the presence of a methylperhydro-pyridopyrimidine (MS m/z=310, $M^{+\cdot}$) incorporating acetaldehyde (from reduction of the acid), along with **5**. This result suggests partial attack of the pyridine or partially reduced pyridine on an initially formed acetaldehyde/amine adduct before the ring is completely hydrogenated. Presumably, reduction of the bicyclic system of this intermediate from the least hindered side increases the amount of the all-*cis* (9Z, 11Z) stereoisomer. Indeed, deliberate addition of one equivalent of acetaldehyde to the hydrogenation mixture provided the same precursor and the best result, a 1/2.3 mixture of **6** to **7**. It is also noteworthy that the stereoselectivity observed in the Na/EtOH reduction of **4** is nearly that obtained by hydrogenation of **4** over PtO_2 in ethanol.

TABLE 1.
Reduction of **4** Followed by Acetal Hydrolysis and Cyclization.

Reagent	Catalyst	Solvent	6/7
H_2	5%Rh/Al_2O_3	EtOH, THF, C_6H_{12}	1/1
"	5%Rh/C	EtOH, C_6H_{12}	1/1
"	$[(py)_3RhCl_3$-$NaBH_4]$	EtOH/DMF	1/1
"	PtO_2	EtOH, C_6H_{12}	1/1.5
"	"	EtOH/1 eq. HOAc	1/2
"	"	EtOH/1 eq. py	1/1.15
"	"	EtOH/1 eq. TFA	1/1.5
"	"	EtOH/1 eq. RCHO	1/2.3
Na		EtOH	1/1.4

While this synthesis is not stereospecific, it does provide (±)-tetraponerine T4 (**7**) conveniently, and potentially its homologue, T8 (R=n-C_5H_{11}). This is also the first preparation of the "unnatural" (9E,11Z) tetraponerine stereoisomer (**6**), the only configuration not found in the ants.

References and Notes

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8. All reactions were followed to completion by gas chromatography. Satisfactory spectral data was obtained for new compounds in accord with their structures. **3**: ^{1}H nmr (200MHz, $CDCl_3$) δ=9.65(1H, br t), 8.29(1H, br d, J=5Hz), 7.38(1H, d of t, J=9, 2Hz), 6.8(1H, d, J=9Hz), 6.7(1H, m), 4.92(1H, m), 3.9(4H,m), 3.27(2H, m), 2.24(2H, t, J=7Hz), 1.77(4H, m), 1.6(2H, quintet, J=7.5H), 1.01(3H, t, J=7.5Hz); ^{13}C nmr δ=160.8(C), 155.0(C), 146.9(CH), 135.0(CH), 120.7(CH), 115.7(CH), 104.4(CH), 92.3(CH), 64.9(2 CH_2), 42.7(CH_2), 35.3(CH_2), 31.4(CH_2), 25.7(CH_2), 22.2(CH_2), 14.1(CH_3); MS m/z(rel. intensity) 276(55,M+), 275(15), 275(15), 215(18), 204(12), 203(15), 186(34), 185(100), 172(15), 171(65), 118(45), 117(40), 115(50), 106(30), 93(55), 73(95), 45(50), 43(35), 41(30). **4**: ^{1}H nmr δ=8.5(1H, br d, J=5Hz), 7.55(1H, d of t, J=9, 2Hz), 7.1(2H, m), 4.8(1H, t, J=6Hz), 3.85(4H, m), 2.95(1H, m), 2.82(2H, d, J=7Hz), 2.55(2H, m), 1.8-1.3(8H, m), 0.85(3H, t, J=7.5Hz); ^{13}C nmr δ= 160.4(C), 149.2(CH), 136.1(CH), 123.9(CH), 121.1(CH), 104.5(CH), 64.8(2 CH_2), 57.9(CH), 46.8(CH_2), 43.1(CH_2), 36.7(CH_2), 31.6(CH_2), 24.8(CH_2), 19.0(CH_2), 14.3(CH_3); MS m/z(rel. intensity) 278(0.5, M+), 277(1), 276(1), 235(10), 187(13), 186(100), 163(20), 148(30), 142(10), 126(20), 124(65), 106(25), 94(23), 93(43), 73(25), 71(24), 70(15), 45(20), 43(22), 41(15). **5**: ^{1}H nmr δ=4.85(1H, t, J=6Hz), 3.87(4H, m), 3.0(2H, m), 2.55(4H, m), 1.8-1.2(16H, m), 0.85(3H, t, 7Hz); ^{13}C nmr δ=104.56, 64.88(2C), 56.20, 56.14, 54.36, 53.88, 47.13, 47.01, 46.77, 46.51, 42.32, 41.55, 36.99, 36.91, 33.84, 33.61, 31.77, 26.62, 26.54, 25.08, 24.95, 19.06, 18.72, 14.37; MS m/z(rel. intensity) 284(0.5,M+), 283(1), 241(2), 222(3), 221(5), 193(9), 186(30), 158(22), 153(15), 124(35), 111(15), 110(35), 98(15), 97(30), 84(100).

9. The **6**/**7** ratios were determined by GLC analysis (30m x 0.53mm id column coated with DB-17, programmed from 60° to 250° at 10°/min). The ^{1}H nmr and ^{13}C nmr spectra for the "unnatural" stereoisomer **6** are as follows: ^{1}H nmr δ= 3.05-2.8(7H, complex m), 1.9-1.2(16H, m), 0.9(3H, t, J=7.0Hz);^{13}C nmr δ=76.1(CH), 56.7(CH), 53.3(CH), 50.9(CH_2),49.0(CH_2), 33.3(CH_2), 33.1(CH_2), 29.9(CH_2), 29.1(CH_2), 25.6(CH_2), 24.6(CH_2), 20.9(CH_2), 20.6(CH_2), 14.3(CH_3); and confirm its assignment as the (9E,11Z) configuration, since they do not show the ^{13}C C-5 resonance at δ=83.4ppm of the (9Z,11E) isomer (T6 type) or the ^{1}H C-5 methine resonance at δ=3.28-3.5ppm of the (9E,11E) isomer (T3, T5, T7 type).[2]

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