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Short Syntheses of (±)-Tetraponerines-5 and -6. The Structures of Tetraponerines-1 and -2, and a Revision of the Structures of (+)-Tetraponerines-5 and -6.

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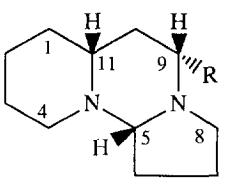
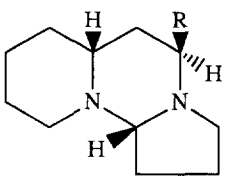
Abstract: The structures and absolute configurations of (+)-tetraponerines-5 and -6 [(+)-T-5 and (+)-T-6], from the poison gland of the ant *Tetraponera* sp., were reassigned as **7** and **8**, respectively, on the basis of extensive two-dimensional NMR and CD studies. These results led to structure proposals **9** for T-1 and **10** for T-2, the two minor alkaloids of the venom. The structures and relative configurations of T-5 and T-6 were subsequently confirmed by short stereoselective syntheses.

INTRODUCTION

The poison gland of the New Guinean ant *Tetraponera* sp. produces a mixture of eight toxic alkaloids, for which the name tetraponerines has been coined.[1] The structure and relative configuration of the major derivative, (+)-tetraponerine-8 [(+)-T-8] was established as **1** (Figure 1) by an X-ray diffraction analysis,[1] whereas the structures of (+)-tetraponerines-3, -4, -5, -6, and -7 [(+)-T-3 to (+)-T-7] were proposed on the basis of a comparison of their spectral properties, in particular one-dimensional NMR spectra at 250 MHz, with those of (+)-T-8.[2] The structures proposed for (+)-T-8 (**1**) and (+)-T-4 (**2**) were confirmed by several syntheses,[3-9] whereas the relative configurations of (+)-T-7 and (+)-T-3 were revised to (**3**) and (**4**), respectively.[3] The absolute configuration of (+)-T-8 was established by Yue *et al.*,[6] by asymmetric synthesis. The absolute configurations of (+)-T-7, (+)-T-4 and (+)-T-3 were determined by circular dichroism (Figure 1).[3]





1, R = n-C_5H_{11}: (+)-T-8

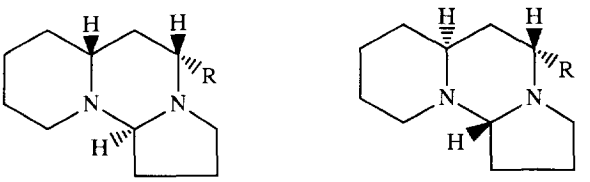
2, R = n-C_3H_7: (+)-T-4

3, R = n-C_5H_{11}: (+)-T-7

4, R = n-C_3H_7: (+)-T-3

Figure 1. Structures and absolute configurations of (+)-T-8, (+)-T-7, (+)-T-4, and (+)-T-3.[3]

On the other hand, the structures and relative configurations originally proposed[2] for (+)-T-5 (**5**) and (+)-T-6 (**6**) are represented in Figure 2. In addition, it is worth mentioning that the structures of the two minor naturally-occurring tetraponerines, T-1 and T-2, are still undetermined owing to the small amounts available from natural sources.



5, R = n-C_4H_9 **6**, R = n-C_4H_9

Figure 2. Structures and relative configurations originally proposed for (+)-T-5 and (+)-T-6.[2]

In the course of our work on the biosynthesis of the tetraponerines,[10] we needed a supply of "cold" material in order to perform the degradation of ^{14}C-labelled (+)-T-6 obtained from incorporation experiments. As the relative stereochemistry that was proposed for (+)-T-6 at C-5 and C-11 (see **6**) cannot be attained by using the methodologies currently developed[3-9] for the synthesis of the tetraponerine skeleton, we chose to synthesize two racemic epimers of **6**, namely (±)-11-epi-**6** and (±)-9,11-diepi-**6**. However, comparison of the spectral data of these synthetic epimers[11] with those of natural (+)-T-6 casted doubts on the structure proposed for the latter. This prompted us to re-isolate[3] this compound and the related (+)-T-5 from *Tetraponera* sp. and to re-examine their structure by modern two-dimensional NMR methods at 600 MHz.

In this paper, we report on the results of this spectroscopic study which led us to revise the structures and relative configurations of (+)-T-5 and (+)-T-6 from **5** and **6** to **7** and **8**, respectively, and to propose structures **9** for T-1 and **10** for T-2. The corrected structures and relative configurations of T-5 (**7**) and T-6 (**8**) were subsequently confirmed by short diastereoselective syntheses which are reported in this paper.

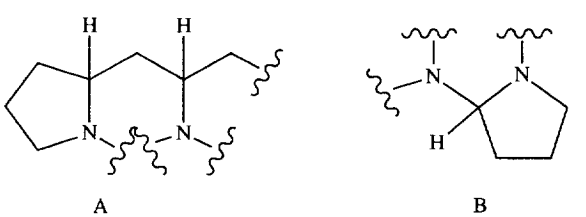
RESULTS AND DISCUSSION

The two alkaloids, (+)-T-5 (4.6 mg) and (+)-T-6 (3.0 mg), were isolated along with the other tetraponerines from a sample of 1,500 *Tetraponera* sp.workers.[3] Both compounds have the same $C_{15}H_{28}N_2$ molecular formula by HRMS, and thus possess one methylene less than (+)-T-7 and (+)-T-8. Complete assignment of their ^1H and ^{13}C NMR spectra using one- and two-dimensional methods (COSY $^1H/^1H$, HMQC, HMBC, nOe difference spectra) was performed and the results are reported in Table 1. These data immediately disclosed that the structures proposed[2] for these two compounds should be revised. In particular, the COSY $^1H/^1H$ and HMBC spectra of (+)-T-5 and (+)-T-6 clearly showed the presence of substructures A and B (Figure 3), thus implying that these compounds possess a tricyclic 5-6-5 ring system with a pentyl side chain at C-8, instead of the tricyclic 6-6-5 ring system with a butyl side chain at C-9, as previously proposed by analogy with (+)-T-8. These conclusions were also supported by mass spectral data. Indeed, the mass spectra of (+)-T-7 (**3**) and (+)-T-8 (**1**) both display[2] a prominent fragment ion at m/z 193 ($C_{12}H_{21}N_2$ by HRMS), corresponding to the loss of a C_4H_9 radical from the $M^{+\cdot}$ at m/z 250. In contrast, in the MS of (+)-T-5 and (+)-T-6 the most intense fragment peak is at m/z 179 ($C_{11}H_{19}N_2$ by HRMS) again arising from the loss of a C_4H_9 radical from $M^{+\cdot}$ at m/z 236, thus confirming that the tricyclic system of (+)-T-5 and (+)-T-6 contains one carbon atom less

Table 1. ^{1}H and ^{13}C NMR data of natural (+)-T-5 and (+)-T-6 (600 and 150.87 MHz, C_6D_6, δ, J in Hz)

	(+)-T-6 (**8**)		(+)-T-5 (**7**)	
Position	^{13}C	^{1}H	^{13}C	^{1}H
H_2C-1	30.5	1.40; 1.70	31.5	1.34; 1.62
H_2C-2	21.1	1.48; 1.68	20.4	1.37; 1.58
H_2C-3	49.1	1.93, q (8.5)	50.0	1.73, m
		2.93, ddd (8.5, 8.5, 2.2)		2.86*
HC-4	83.2	2.86, dd (6.5, 4.5)	76.0	3.50, dd (1.8, 1.8)
H_2C-5	29.2	1.77	30.1	1.35; 1.79
H_2C-6	20.8	1.60; 1.80	22.0	1.75; 1.85
H_2C-7	45.9	2.34, m	51.0	2.87*
		3.05, m		3.22, q (8.0)
HC-8	59.6	2.42, m	54.1	2.84*
H_2C-9	33.3	1.34	30.0	1.34
		1.43		1.80
HC-10	64.0	1.88, m	58.3	1.98, m
H_2C-11	34.6	1.37; 1.60	33.1	1.32; 1.76
H_2C-12	25.9	1.38; 1.40	27.4	1.32; 1.52
H_2C-13	32.5	1.27	32.5	1.24; 1.32
H_2C-14	23.0	1.30	23.2	1.30
H_3C-15	14.3	0.90, t (6.5)	14.4	0.90, t (6.5)

* Multiplicity not determined due to superposition of signals



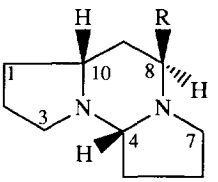
A B

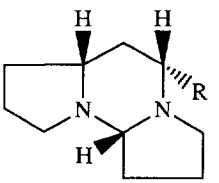
Figure 3. Partial structures deduced for (+)-T-5 and (+)-T-6 from $^{1}H/^{1}H$ COSY and HMQC experiments.

than that of (+)-T-7 and (+)-T-8. It follows that the previous interpretation[12] of the mass spectra of these derivatives should also be revised.

The relative configuration of (+)-T 6 was determined by nOe difference spectra. Indeed, strong nOes were observed between H-4, H-8 and H-10 (see numbering in Figure 4), indicating that this compound has the same all-cis relative configuration as (+)-T-8 and (+)-T-4, and thus possesses structure **8** (Figure 4). This assignment was also supported by comparison of the ^{13}C NMR spectra of (+)-T-8[3] and (+)-T-6 (Table 1). In (+)-T-8, C-5, C-9 and C-11 appear at δ 85.4, 61.6 and 62.6, respectively, whereas the corresponding carbon atoms of (+)-T 6, namely C-4, C-8 and C-10, appear at δ 83.2, 59.6 and 64.0, respectively. On the other hand, no nOes could be observed for (+)-T-5 and thus the relative configuration of the latter rested on the comparison of its ^{13}C and ^{1}H NMR spectra with those of (+)-T-6 and of their homologues (+)-T-7 and (+)-T-8.[3] It may be seen that C-4 (76.0), C-8 (54.1) and C-10 (58.3) of (+)-T-5 experience approximately the same shielding with respect to the corresponding carbon atoms in (+)-T-6 than do C-5 (75.6), C-9 (53.3) and C-11 (56.8) of (+)-T-7 with respect

to the corresponding carbon atoms of (+)-T-8 (see above).[3] All these arguments showed that (+)-T-5 is (+)-8-epi-T-6 (**7**). We also measured the CD curves of (+)-T-5 and (+)-T-6 (see Experimental). The CD curves of (+)-T-8[3] and (+)-T-6 on one hand, and of (+)-T-7[3] and (+)-T-5 on the other hand, show similar characteristics. Thus, if the correlations between chiroptical properties and absolute configuration which were established[3] for the 6-6-5 tricyclic series remain valid for the 5-6-5 series, the absolute configurations of (+)-T-5 and (+)-T-6 should be the same as those of (+)-T-7 and (+)-T-8, respectively (Figure 4).





7 R = n-C_5H_{11}: (+)-T-5

8 R = n-C_5H_{11}: (+)-T-6

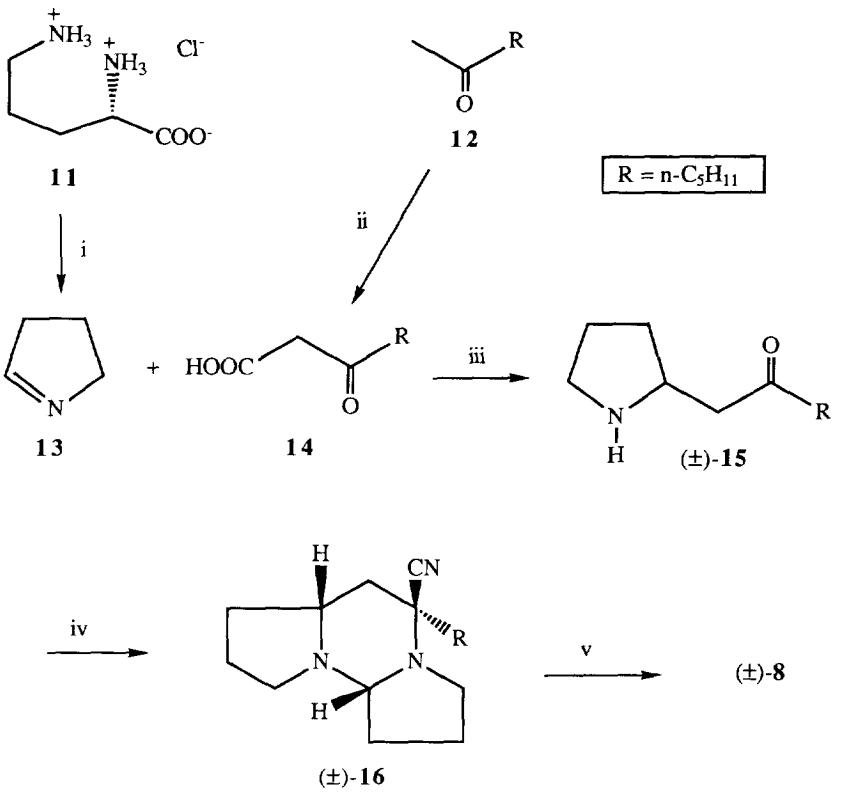
9 R = n-C_3H_7: T-1

10 R = n-C_3H_7: T-2

Figure 4. Structures of T-1, T-2, (+)-T-5, and (+)-T-6 (absolute configurations for **7** and **8**).

With these results in hand, we turned to the two last members of the series, the minor components T-1 and T-2. It should be recalled that these two compounds were found to be different from synthetic derivatives having a 6-6-5 ring system and an ethyl side chain at C-9.[3] We have now been able to isolate for the first time a small amount (about 0.1 mg) of T-2 ($M^{+\cdot}$ at m/z 208). Its ^1H NMR spectrum is very similar to that of (+)-T-6. In particular, the signals of H_2C-3, HC-4, H_2C-7, HC-8 and HC-10 exhibit nearly the same δ and J (Table 1 and Experimental). Moreover, both compounds display a prominent fragment peak at m/z 179 in their MS. Accordingly, we propose that T-2 also possesses the 5-6-5 ring system of T-6, but bearing a propyl instead of a pentyl side chain. Thus T-2 should be represented by structure **10** (Figure 4). The trace component T-1 was isolated in too small amounts to get an NMR spectrum. However, its GC/EIMS spectrum is identical to that of T-2, thus suggesting the same structural relationship between these two compounds as between (+)-T-5 and (+)-T-6. This is supported by the comparison of the Kovats indexes[2] in GC of the two pairs of compounds: (+)-T-5 is eluting faster than (+)-T-6 and T-1 faster than T-2. A similar relationship exists between the compounds of the 6-6-5 series.[2] All these arguments point to structure **9** for T-1 (Figure 4).

In order to unambiguously prove the new structures proposed for T-5 and T-6, we have realized expeditious syntheses of (±)-**7** and (±)-**8** by a strategy which utilizes β-aminoketone (±)-**15** as pivotal intermediate. The stereoselective synthesis of (±)-**8** is outlined in Scheme 1. A Schöpf condensation[13,14] of the trimer of Δ^1-pyrroline (**13**), obtained by NBS oxidation of L-ornithine hydrochloride (**11**)[13], with 3-oxooctanoic acid (**14**), obtained by treatment of heptan-2-one (**12**) with methylmagnesium carbonate in DMF[15], led in a 44 % yield to β-aminoketone (±)-**15**. The latter could easily be transformed into (±)-**8** following the procedure of Yue *et al.*[7] Thus, treatment of (±)-**15** with 1,1-diethoxy-4-aminobutane in the presence of HCl and KCN stereoselectively led in an 82% yield to the tricyclic diaminonitrile (±)-**16** which was cleanly transformed into (±)-**8** by reduction with Na in liquid NH_3 (yield: 70%). The spectral properties (^1H and ^{13}C NMR, IR, MS) of natural (+)-T-6[2] and synthetic (±)-**8** were identical, as were their retention times in capillary GC. The next synthetic target, (±)-**7**, can also be constructed from β-aminoketone (±)-**15**, by adapting the procedure of Jones (Scheme 2).[7] Thus, β-aminoketone (±)-**15** was protected as its N-benzyloxycarbonyl derivative (±)-**17**



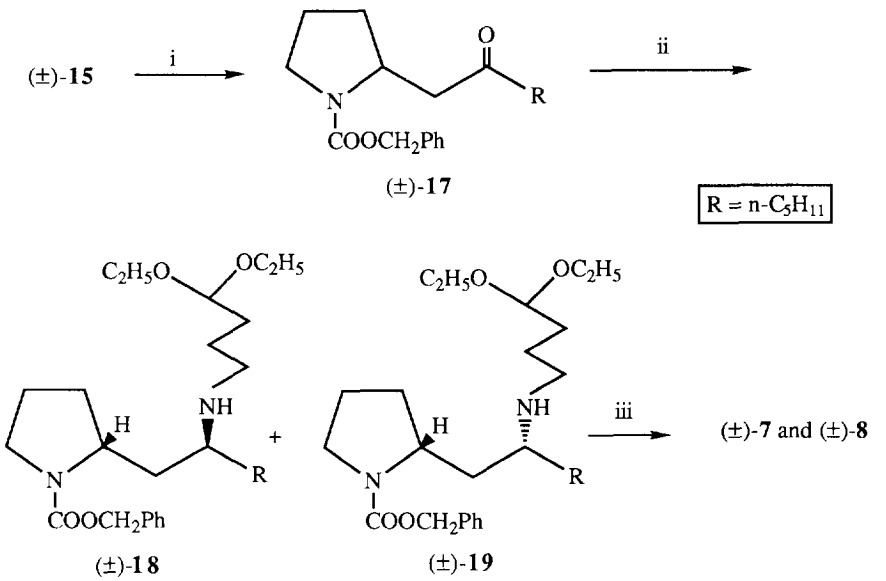
Scheme 1: Reagents and conditions: i) NBS, H_2O, r.t., p < 1 atm; ii) Methyl magnesiumcarbonate, DMF, 120 °C, 24 h; iii) pH = 6.9 (44% for i-iii); iv) Excess of 1,1-diethoxy-4-aminobutane, excess of KCN, pH = 3-4, r.t., 3 h (82%); v) Na/NH_3, -78 °C, 1.5 h (70%).

(86%), which was reacted with 1,1-diethoxy-4-aminobutane. The resulting imine was immediately reduced[3] with $NaBH_4$, to afford a mixture of the two diastereomeric aminocarbamates, (±)-**18** and (±)-**19** (68% for the two steps). This mixture was cyclized under the previously described conditions[3] to afford (±)-**7** and (±)-**8** in a 55:45 ratio (yield: 76%). These two epimers were easily separated by silica gel chromatography. The spectral properties (^1H and ^{13}C NMR, IR, MS) and GC retention time of (±)-**7** matched those of natural (+)-T-5.[2]

Finally, a careful reanalysis of the CIP descriptors of the tetraponerines by using the "tree graph " recommended by Prelog and Helmchen[16] prompted us to change the *R* descriptor assigned previously[2,3,6] to C-5 of T 8 and analogues into *S*. Thus, the absolute configuration of (+)-T-3 and (+)-T-7 is 5*S*, 9*R*, 11*R*, that of (+)-T-4 and (+)-T-8 is 5*S*, 9*S*, 11*R*, whereas those of (+)-T-5 and (+)-T-6 are 4*S*, 8*R*, 10*R* and 4*S*, 8*S*, 10*R*, respectively.

In conclusion, a two dimensional NMR study allowed us to assign to (+)-T-5 and (+)-T-6 structures **7** and **8**, respectively, that were confirmed by short diastereoselective syntheses. The absolute configurations of these compounds have also been tentatively assigned by comparison of their CD curves with those of (+)-T-7 and (+)-T-8. For the first time, we also assign structures to the two minor components of the *Tetraponera* sp. venom, T-1 and T-2. The four compounds discussed in this paper are the first representatives of a novel class of

alkaloids. The co-occurrence of alkaloids based on two different, albeit closely related, ring systems in the venom of *Tetraponera* sp. poses intriguing biosynthetic problems that are currently under investigation in our laboratories.



Scheme 2: Reagents and conditions: i) $ClCOOCH_2Ph$, aq. K_2CO_3, 0 °C, 2 h (86%); ii) a) Excess of 1,1-diethoxy-4-aminobutane, Amberlyst A-15, 3Å molecular sieves, r.t., 24 h; b) $NaBH_4$, CH_3OH (68%); iii) a) H_2, Pd-C, CH_3OH, r.t., 7 h; b) 1N HCl overnight; c) 2N NaOH to pH = 8.0, 2 h (76%).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a BRUKER WM 250 spectrometer (at 250 and 62.8 MHz, respectively) or, when stated, on a VARIAN UNITY 600 spectrometer (at 600 and 150.87 MHz, respectively), and are reported in ppm from internal TMS on the δ scale. All the spectra were recorded in $CDCl_3$, unless otherwise stated. Data are reported as follows: chemical shift [multiplicity (s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, t: triplet, q: quartet, m: multiplet, bm: broad multiplet), coupling constants in Hertz]. Ultraviolet spectra were taken on a PHILIPS PU 8700 spectrometer. Infrared spectra were taken with a BRUKER IFS 25 instrument either as a film on a NaCl disk, or in $CHCl_3$ solution. EIMS were recorded on a VG Micromass 7070, HREIMS on a FISONS VG AUTOSPEC spectrometer and GCMS analyses on a FINNIGAN ITD 800 apparatus, coupled to a TRACOR gas chromatograph. In both cases, peak intensities are expressed as % relative to the base peak. Optical rotations were measured on a PERKIN-ELMER 141 polarimeter at 589 nm (sodium D line), in a 10 cm cell at 20 °C. Circular dichroic curves were measured in CH_3CN solutions on a JOBIN-YVON Mark 5 dichrograph in quartz cells of 1 cm length; $c = 2.10^{-4}$ M. Thin layer chromatography analyses were performed on 0.25 mm POLYGRAM silica gel $SILG/UV_{254}$ precoated

plates (MACHEREY NAGEL) or on 0.2 mm neutral alumina 60 F_{254} precoated plates (MERCK, type E). Unless otherwise stated, column chromatographies were performed over silica gel (MN Kieselgel 0.04-0.063 mm), using the flash technique or over MN neutral alumina (activity 1). GC analyses were performed on a VARIAN 3700 apparatus equipped with an OV-1 or an OV-1701 column (RESCOM, 25 m, 0.32 mm i. d.). During work up, organic solutions were dried over $MgSO_4$.

Isolation of natural tetraponerines from *Tetraponera* sp.

The isolation procedure was described in ref. 2 and 3. The complete ^1H and ^{13}C NMR assignments and the CD data of (+)-T-3, (+)-T-4, (+)-T-7, and (+)-T-8 were reported in ref. 3, as well as the optical rotations of (+)-T-3 to (+)-T-8. HREIMS: (+)-T-5: m/z 236.2246 (calc. for $C_{15}H_{28}N_2$: 236.2252); 179.1542 (calc. for $C_{11}H_{19}N_2$: 179.1548); (+)-T-6: HREIMS: m/z 236.2259; 179.1545; (+)-T-7: m/z 250.2436 (calc. for $C_{16}H_{30}N_2$: 250.2409); 193.1716 (calc. for $C_{12}H_{21}N_2$: 193.1704); (+)-T-8: m/z 250.2399; 193.1715. The ^1H and ^{13}C NMR spectra of (+)-T-5 and (+)-T-6 are reported in Table 1. CD: (+)-T-5: λ_{max} 203 nm, [θ] = - 700 and λ_{max} 217 nm, [θ] = - 4,090; (+)-T-6: λ_{max} 209 nm, [θ] = + 2,920. T-2: GC/EIMS: $M^{+\cdot}$ at m/z 208 (22); 207 (44); 193 (2); 179 (33); 138 (47); 96 (56); 70 (48); 41 (100). ^1H NMR (600 MHz, C_6D_6): δ 3.03 (1H, m, H-7e); 2.92 (1H, ddd, 9.0, 9.0, 2.5 Hz, H-3e); 2.87 (1H, dd, 7.0, 4.0 Hz, H-4); 2.43 (1H, m, H-8); 2.31 (1H, m, H-7a); 1.92 (1H, q, 8.5 Hz, H-3a); 1.88 (1H, m, H-10); 1.8-1.2 (14H); 0.90 (3H, t, 6.5 Hz, H-13). T-1: GC/EIMS: $M^{+\cdot}$ at m/z 208 (27); 207 (51); 193 (2), 179 (58); 138 (42); 96 (69); 70 (38); 41 (100).

3-Oxooctanoic acid (14).

Heptan-2-one (**12**) (0.910 g, 8.0 mmol) was heated in the presence of 9 ml of methyl magnesiumcarbonate (18 mmol) in DMF at 120 °C under nitrogen for 24h. After cooling, the reaction mixture was poured under vigourous stirring into a mixture of 10 ml of 1N HCl and 10 g of ice covered with 8 ml of pentane. The pentane layer was separated and the aqueous layer extracted three times with 10 ml of pentane. The combinated pentane extracts were evaporated *in vacuo* and the residue was engaged without any purification into the Schöpf condensation.

β-Aminoketone [(±)-15].

N-bromosuccinimide (0.727 g, 4.0 mmol) was added to a solution of L-ornithine monohydrochloride (**11**) (0.339 g, 1.97 mmol) in 20 ml of water in a small flask. The flask was rotated by means of a rotary evaporator under mild suction, while immersed in a water bath at 40 °C. When the solution had become colorless (1 h) it was transferred quantitatively with repeated washings (2x1 ml of water) into a dropping funnel. This mixture was then added at room temperature over a period of 4 h to a solution of 3-oxooctanoic acid (**14**) in a citrate buffer (pH = 6.9). After completion of the addition, the reaction mixture was stirred for 20 h, then cooled (5 °C), basified with cold potassium hydroxide (10% w/v) and the product was extracted three times into $CHCl_3$ (5 ml). The organic extracts were dried, filtered and evaporated *in vacuo*. A chromatography of the oily residue on neutral alumina (eluent: AcOEt) afforded 0.161 g (44%) of (±)-**15** as a pale yellow oil, which was stored and characterized as its hydrochloride. (±)-**15**.HCl: oil; EIMS: $C_{11}H_{21}NO$ (M=183); m/z 183 (20, $M^{+\cdot}$); 182 (10, $M^{+\cdot}$ - H·); 126 (26, $M^{+\cdot}$ - C_4H_9·); 112 (64, $M^{+\cdot}$ - C_5H_{11}·); 99 (10); 84 (88, $C_5H_{10}N^+$); 70 (100, $C_4H_8N^+$). IR: 3362, 2911-2811, 1710, 1458, 1373 cm^{-1}. ^1H NMR: 9.49 (2H, bs, NH_2^+); 3.94 (1H, m, H-2); 3.40 (2H, m, H_2-5); 3.35 (1H, dd, 18.4, 7.1 Hz, H-6); 2.95 (1H, dd, 18.4, 6.5 Hz, H-6); 2.49 (2H, m, H_2-8); 2.26 (1H, m); 2.02 (2H, m); 1.74-1.52 (3H, m); 1.36-1.22 (4H, m); 0.88 (3H, t, 6.8 Hz, H_3-12). ^{13}C NMR: 208.1 (C-7); 55.4 (C-2); 45.1; 44.5; 43.0; 31.4; 30.6; 23.7; 23.3; 22.5; 13.9 (C-12).

Aminonitrile (±)-16.

β-Aminoketone (±)-**15** (0.325 g, 1.78 mmol) was dissolved in a solution of 10% HCl (1.2 ml) and water (40 ml). To this solution were added 682 µl (4.0 mmol) of commercially available 1,1-diethoxy-4-aminobutane and 0.229 g (3.5 mmol) of potassium cyanide, and the solution pH was kept between 3 and 4 by addition of 1N HCl. The resulting mixture was stirred for 3 h at room temperature, after which it was basified with 25% NH_4OH and extracted four times with 10 ml of CH_2Cl_2. The organic extracts were dried, filtered and evaporated *in vacuo*. A chromatography on silica gel (eluent: ether : hexane 5:1) afforded 0.378 g (82%) of (±)-**16**, as a colourless oil. (±)-**16**: oil; EIMS: $C_{16}H_{27}N_3$ (M=261); m/z 260 (5, $M^{+\cdot}$ - H·); 234 (7, $M^{+\cdot}$ - HCN); 233 (11, $M^{+\cdot}$ - H· - HCN); 191 (7, $M^{+\cdot}$ - HCN - C_3H_7·); 177 (6, $M^{+\cdot}$ - HCN - C_4H_9·); 163 (8, $M^{+\cdot}$ - HCN - C_5H_{11}·); 152 (46); 134 (100). IR: 2952, 2872, 2232, 1455, 1340, 1136, 1056, 884 cm^{-1}. ^1H NMR: 3.11 (1H, ddd, 8.5, 8.5, 2.5 Hz, H-7a or H-3a); 3.04 (1H, ddd, 8.4, 8.4, 2.6 Hz, H-3a or H-7a); 2.89 (1H, dd, 8.5, 6.0 Hz, H-4); 2.47 (1H, q, 8.5 Hz, H-7b or H-3b); 2.32 (1H, m); 2.22 (1H, q, 8.6 Hz, H-3b or H-7b); 2.07-1.20 (18H); 0.90 (3H, t, 6.5 Hz, H_3-15). ^{13}C NMR: 119.2 (CN); 80.1 (C-4); 61.4; 61.3; 49.3; 46.0; 38.9; 38.4; 32.3; 29.9; 29.3; 23.5; 22.9; 21.7; 20.0; 14.3 (C-15).

(±)-Tetraponerine-6 [(±)-8].

Aminonitrile (±)-**16** (0.02 g, 0.08 mmol) in 3 ml of anhydrous THF was slowly added to 5 ml of freshly distilled ammonia containing 0.025 g of Na. The mixture was stirred at -78°C for 1h30, after which the reaction was quenched by the addition of 2x1 ml of CH_3OH. The mixture was warmed to 25 °C, diluted with water and extracted three times with 5 ml of CH_2Cl_2. The organic layer were dried, filtered and purified by chromatography on neutral alumina (eluent: CH_2Cl_2 to CH_2Cl_2 : CH_3OH 98:2) to afford 0.013 g (70%) of (±)-**8**. The spectral properties of this material were identical to those of natural T-6 (Table 1 and ref.2). The natural and synthetic samples had the same retention times in capillary GC on an OV 1 column at 165 °C.

Carbamate (±)-17.

To a solution of (±)-**15** (0.127 g, 0.69 mmol) in 3 ml of an EtOH:H_2O (1:1) mixture were added 0.274 g (1.4 mmol) of K_2CO_3 and 119 µl (0.83 mmol) of freshly distilled benzylchloroformate. The resulting mixture was stirred at 0 °C for 2 h after which it was basified with 25% NH_4OH and extracted four times with 7 ml of CH_2Cl_2. The organic extracts were dried, filtered and evaporated *in vacuo*. A chromatography of the residue on silica gel (eluent: hexane : AcOEt 7:3) afforded 0.188g of (±)-**17** (86%) as a colourless oil. (±)-**17**: EIMS: $C_{19}H_{27}NO_3$ (M=317); m/z 318 (<1, M+H^+); 317 (<1, $M^{+\cdot}$); 226 (7, $M^{+\cdot}$ - $CH_2C_6H_5$·); 210 (<1, $M^{+\cdot}$ - $OCH_2C_6H_5$·); 204 (<1); 183 (6); 182 (48, $M^{+\cdot}$ - $COOCH_2C_6H_5$·); 179 (19); 91 (100, $CH_2C_6H_5^+$). IR: 2955, 2925, 2875, 1709, 1694, 1454, 1414, 1353, 1333, 1182, 1101, 769, 698 cm^{-1}. ^1H NMR (60 °C): 7.31 (5H, m, phenyl); 5.11 (2H, AB, J_{AB} = 12.4 Hz, $COOCH_2Ph$); 4.22 (1H, m, H-2); 3.41 (2H, m, H_2-5); 3.0 (1H, m, H-6a); 2.40 (3H, m, H-6b + H_2-8); 2.09 (1H, m, H-3a); 1.84 (2H, m, H_2-4); 1.68 (1H, m, H-3b); 1.53 (2H, m, H_2-9); 1.26 (4H, m, H_2-10 + H_2-11); 0.87 (3H, t, 6.8 Hz, H_3-12). ^{13}C NMR (60 °C, 150.87 MHz): 209.5; 154.6; 137.1; 128.5 (2C); 127.9 (2C); 127.6; 66.6; 54.1; 46.6 (2C); 43.3; 31.4 (2C); 23.4 (2C); 22.4; 13.9.

Aminocarbamates (±)-18 and (±)-19.

Carbamate (±)-**17** (0.164 g, 0.52 mmol) was dissolved in 1.3 ml (7.8 mmol) of 1,1-diethoxy-4-aminobutane and the mixture stirred at room temperature under nitrogen for 24 h, in the presence of 0.164 g of Amberlyst A-15 resin and a 3Å molecular sieves. The reaction mixture was filtered, 4 ml of anhydrous CH_3OH were added and the solution cooled at 0 °C. $NaBH_4$ (0.08 g, 2.1 mmol) was added and the mixture stirred at room temperature under nitrogen for 4 h. The CH_3OH was evaporated *in vacuo*, water was added, the solution basified with 25% NH_4OH and extracted four times with 5 ml of CH_2Cl_2. Evaporation of the solvent and chromatography on silica gel (eluent: CH_2Cl_2 : CH_3OH 95:5) furnished 0.164 g (68%) of a mixture of the two aminocarbamates (±)-**18** and (±)-**19**, that could not be separated under these conditions. Mixture of (±)-**18** and (±)-**19**: oil; EIMS; $C_{27}H_{46}N_2O_4$ (M=462); m/z at 462 (2, $M^{+\cdot}$); 433 (35, $M^{+\cdot}$ - $C_2H_5\cdot$); 417 (13, $M^{+\cdot}$ - $OC_2H_5\cdot$); 391 (12, $M^{+\cdot}$ - $C_5H_{11}\cdot$); 371 (14, $M^{+\cdot}$ - $CH_2Ph\cdot$); 345 (4, $M^{+\cdot}$ - $C_6H_{13}O_2\cdot$); 331 (9, $M^{+\cdot}$ - $C_7H_{15}O_2\cdot$); 317 (21, $M^{+\cdot}$ - $C_8H_{17}O_2\cdot$); 299 (100); 244 (22); 212 (13); 204 (34); 198 (88); 160 (99); 91 (94). IR: 3320, 2971-2873, 1699, 1455, 1415, 1357, 1105, 1062, 996, 769, 698 cm^{-1}. ^1H NMR (60 °C): 7.33 (5H, m, phenyl); 5.12 (2H, s, $COOCH_2Ph$); 4.47 (1H, m, O-CH-O); 3.99 (1H, m, H-2); 3.61 (2H, m, CH_2-O); 3.45 (4H, m, CH_2O + H_2-5); 2.75 (3H, bm); 1.88 (4H, m); 1.67-1.50 (9H); 1.28 (6H, bs); 1.18 (6H, t, 7.0 Hz, $\underline{CH_3}$-CH_2-O); 0.88 (3H, t, 6.8 Hz, H_3-12). ^{13}C NMR (60 °C): 136.9; 128.5 (2C); 127.9 (3C); 102.9; 67.1; 61.6 (2C); 56.6; 55.8; 46.4; 45.7; 38.5; 31.9; 31.8; 31.5; 25.5; 23.5; 22.4; 15.3 (2C); 13.8 (three of the carbon signals were not detected, because of superposition or of broadening as a consequence of rotamer interconversion).

(±)-Tetraponerines-5 and -6 [(±)-7 and (±)-8].

The mixture of amines (±)-**18** and (±)-**19** (0.082 g, 0.18 mmol) was dissolved in 13 ml of CH_3OH and submitted to a hydrogenolysis reaction at room temperature, at a hydrogen pressure of 1 atm, in the presence of 0.015 g of Pd-C. After 7 h, the catalyst was removed by filtration on Celite. After evaporation of the CH_3OH *in vacuo*, the residue was taken in 3 ml of a 1N HCl solution and stirred at room temperature overnight. The mixture was then basified by slow addition of a 2N NaOH solution (up to pH = 8.0) and stirred for a further 2 h at room temperature. Finally, the reaction mixture was brought to pH = 10.0 and extracted five times with 8 ml of CH_2Cl_2. Evaporation of the solvent and chromatography on neutral alumina (eluent: CH_2Cl_2 to CH_2Cl_2 : AcOEt 5:5) afforded 0.032 g (76%) of a pale yellow oil, containing the two expected tricyclic derivatives (±)-**7** and (±)-**8** in a 55:45 ratio, by capillary GC (OV 17, 25 m, 165 °C, isothermal). The two compounds were partially separated by successive chromatographies on silica gel (eluent: CH_2Cl_2 : EtOH 95:5). By this procedure 0.007 g of (±)-**7** and 0.009 g of (±)-**8** were obtained. Their spectroscopic properties (IR, EIMS, ^1H and ^{13}C NMR) were identical to those reported in Table 1 and to the published data.[2]

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