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Concise Asymmetric Syntheses of (+)- and (-)-Tetraponerine-8, (+)- and (-)-Tetraponerine-7, and their Ethyl Homologues. A Correction of the Structures of Tetraponerine-3, and -7.

P. Macours, J. C. Braekman, and D. Daloze.

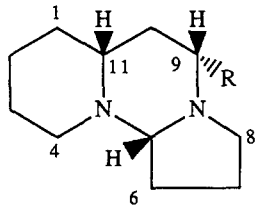
Laboratory of Bio-organic Chemistry, Faculty of Sciences, University of Brussels, CP 160/07, Av. F. D. Roosevelt 50, B-1050 Brussels, Belgium.

Abstract: (+)- and (-)-T-8, (+)- and (-)-9-epi-T-8, and their ethyl homologues were synthesized in six steps and 27% overall yield from chiral acetylenic sulfoxide (+)-**7a** or (+)-**7b**, *via* a cycloaddition reaction with 3,4,5,6-tetrahydropyridine-1-oxide, and chromatographic separation of the resulting diastereoisomeric Δ^4-isoxazolines. Comparison of the spectral properties of the synthetic (+)-9-epi-T-8 with those of natural (+)-T-7 and (+)-T-3 led us to correct the structures of the latter two compounds. The absolute configuration of (+)-T-4 was determined to be 5R,9S,11R, and those of (+)-T-7 and (+)-T-3 to be 5R,9R,11R by comparison of their CD curves with those of the synthetic compounds.

The tetraponerines are a new class of toxic alkaloids which were isolated from the venom of the New Guinean ant *Tetraponera* sp.[1] The structure and relative configuration of the major component, (+)-tetraponerine-8 [(+)-T-8], was established as 6-pentyldecahydropyrido[1,2-c]pyrrolo[1',2'-a]pyrimidine [(+)-**1a**] by an X-ray diffraction analysis.[1] The absolute configuration of (+)-T-8 was determined to be 5R, 9S, 11R by chemical degradation into (R)-(+)-pipecolic acid[2] and by enantioselective synthesis.[3]

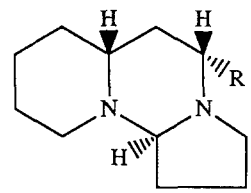
The structure and relative configuration of tetraponerines, (+)-T-3 (**2**), (+)-T-4 (**3**), and (+)-T-7 (**4**) (Figure 1), were subsequently proposed by comparison of their one-dimensional ^1H and ^{13}C NMR spectra at 250 and 62.8 MHz, respectively, with those of (+)-T-8.[4] Several syntheses of this class of alkaloids have already been published. Our diastereoselective synthesis of (±)-T-8[5,6] was followed by an enantioselective synthesis of (+)-T-8, based on the CN(R,S) method.[3] Concise syntheses of (±)-T-8 and its propyl homologue (±)-T-4 were also described.[7,8,9]

The unusual structures and biological properties[1] of the tetraponerines prompted us to study their biosynthesis[10] and their pharmacological activities, and to establish their absolute configuration by application of chiroptical methods. To this end, enantiomerically pure (+)- and (-)-tetraponerines of known absolute configuration were needed. It was also desirable to obtain C-9 epimers in order to investigate the possible influence of the configuration at that centre on the chiroptical properties of the tetraponerine skeleton. To meet all these requirements, we devised a scheme that allows to selectively synthesize both enantiomers of a tetraponerine, starting from one and the same chiral acetylenic sulfoxide *via* a cycloaddition reaction with 3,4,5,6-tetrahydropyridine-1-oxide.[11] (+)- and (-)-T-8, (+)- and (-)-9-epi-T-8, and their ethyl homologues were first selected as synthetic targets, because their comparison could shed some light on the influence of the side chain length on both the biological activities and the chiroptical properties of the tetraponerines and,



1a, R = n-C_5H_{11}: T-8

3, R = n-C_3H_7: T-4



4, R = n-C_5H_{11}: T-7

2, R = n-C_3H_7: T-3

Figure 1. Structures proposed for T-3, T-4, T-7 and T-8.[4]

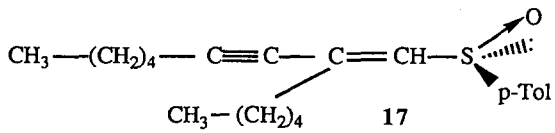
perhaps, on the structures of tetraponerine-1 and -2 (T-1 and T-2).[4] It should be mentioned that the structures of the latter are still not determined because of the small amounts available from natural sources. On the basis of GCMS data, it was hypothesized that T-1 and T-2 could possess the tricyclic skeleton characteristic of the tetraponerines with an ethyl side chain at C-9.

We also report herein a correction of the structures previously proposed for (+)-T-3 and (+)-T-7, a complete assignment of the ^1H and ^{13}C NMR spectra of T-3, T-4, T-7, T-8, and their synthetic ethyl homologues **1b** and **16b** and, finally, a study of their chiroptical properties which allowed us to determine the absolute configuration of natural (+)-T-3, (+)-T-4, and (+)-T-7.

RESULTS AND DISCUSSION

The asymmetric synthesis which is outlined in scheme 1 meets the requirements mentioned above, since it allowed us to easily obtain (+)- and (-)-tetraponerines in high enantiomeric purity. We will only detail the synthesis of (5R,9S,11R)-(+)-T-8 [(+)-**1a**] and (5R,9R,11R)-(+)-9-epi-T-8 [(+)-**16a**] which used hept-1-ynylmagnesium bromide (**5a**) as starting material and β-aminoketone (R)-(-)-**11a**[11] as key intermediate. The synthesis of their ethyl homologues [(+)-**1b** and (+)-**16b**] was performed in the same way, except that we used as starting material but-1-ynylmagnesium bromide (**5b**), obtained by treatment of 1,2-dibromobutane with $NaNH_2$ in liquid NH_3,[12] followed by reaction of the resulting but-1-yne with C_2H_5MgBr. The synthesis of the four (-) enantiomers, (-)-**1a**, (-)-**16a**, (-)-**1b** and (-)-**16b**, will not be discussed, since they were obtained from β-aminoketones (S)-(+)-**11a** and (S)-(+)-**11b** respectively as described hereunder for the (+) enantiomers.

Chiral acetylenic sulfoxide (S)-(+)-**7a** was prepared in a 72% yield by addition of acetylenic Grignard reagent **5a** (1.5 eq.) to (S)-(-)-menthyl-p-toluenesulfinate **6**. In our hands, the "normal" addition of (S)-(-)-**6** to **5a** described by Kosugi *et al.*[13] afforded mainly **17**, arising from the addition of **5a** to the triple bond of (S)-(+)-**7a**. The key step of our synthesis was the cycloaddition reaction[11] of sulfoxide (S)-(+)-**7a** with 3,4,5,6-tetrahydropyridine-1-oxide (**8**), itself produced by HgO oxidation of N-hydroxypiperidine.[14] This cycloaddition afforded an approximately 1 : 1 mixture of diastereoisomeric Δ^4-isoxazolines (R,S)-(+)-**9a** and



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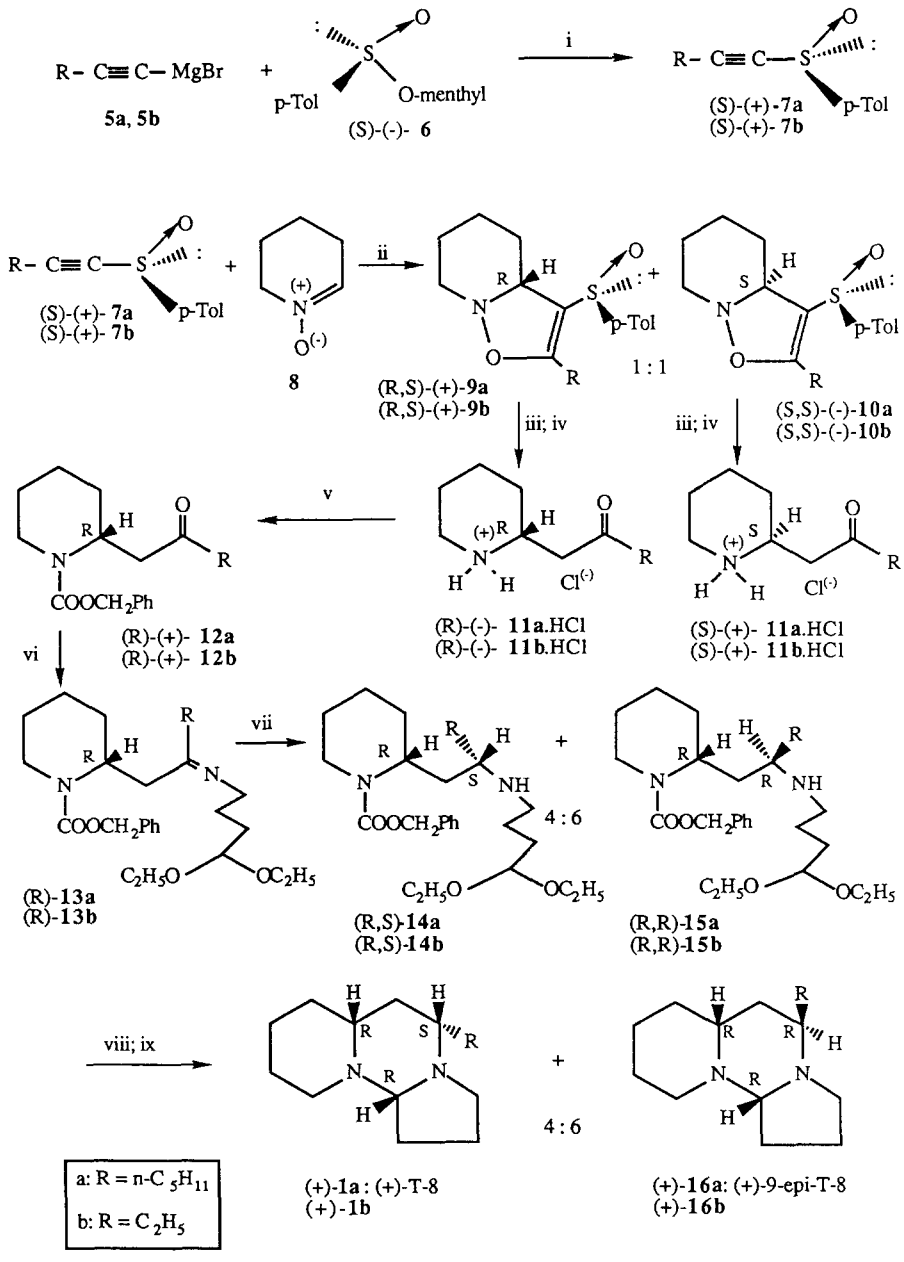
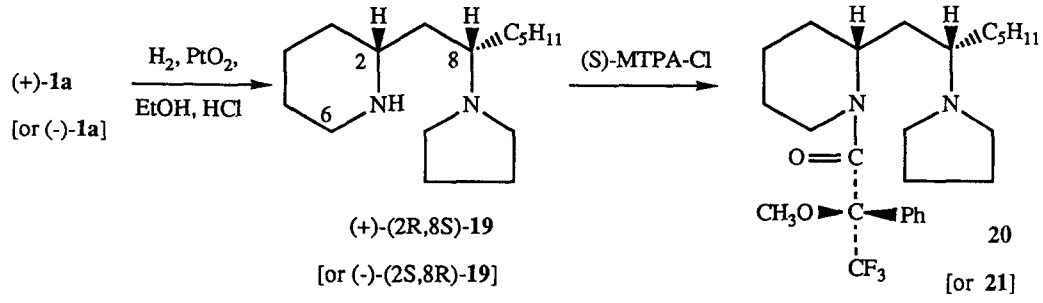


Scheme 1. Reagents and conditions: i. Et_2O/toluene, -23 °C, 1.5 h, 72%; ii. $CHCl_3$, r. t., 25 h, 87%; iii. SiO_2 chomatogr.; iv. a) H_2, PtO_2, citric acid, CH_3OH, r. t., 24 h; b) elution on Sephadex DEAE A-25 (Cl^-), 70%; v. $ClCOOCH_2Ph$, aq. K_2CO_3, 0 °C, 1.5 h, 95%; vi. Excess of 4,4-diethoxybutylamine, Amberlyst A-15, 3 Å mol. sieves, r. t., 25 h; vii. $NaBH_4$, CH_3OH, 90% for vi -vii; viii. H_2, Pd-C, CH_3OH, r. t., 7 h; ix. a) 3% HCl overnight; b) 10% NaOH to pH = 8, 2 h, 73% for viii-ix.

(S,S)-(-)-**10a** in a 87% yield. These results confirm the low asymmetric induction power of chiral sulfoxide groups in this type of cycloaddition reactions.[11] Fortunately, the presence of the *p*-tolylsulfoxide moiety in **9a** and **10a** permitted to easily separate them from each other by simple flash chromatography on silica gel (yield: 41% of (R,S)-(+)-**9a** and 46% of (S,S)-(-)-**10a**). The two Δ^4-isoxazolines were then transformed into β-aminoketones (R)-(-)-**11a** and (S)-(+)-**11a**, respectively, by hydrogenolysis with H_2/PtO_2 in MeOH, in the presence of citric acid.[11] To prevent their racemization, they were isolated as their hydrochloride salt by elution of the reaction mixture on a Sephadex DEAE A-25 column (yield: 70%). Next, the amino group of (R)-(-)-**11a** was protected by reaction with benzylchloroformate to afford N-benzyloxycarbonyl derivative (R)-(+)-**12a** in a 95% yield. The last steps of our scheme are based on the tetraponerine synthesis described by Jones.[7] Carbamate (R)-(+)-**12a** was treated with an excess of 4,4-diethoxybutylamine, in the presence of Amberlyst A-15 and 3 Å molecular sieves. Isolation of the resulting unstable imine (R)-**13a** proved troublesome and did only succeed by rapid filtration on Florisil. Accordingly, in all subsequent syntheses, this imine was immediately reduced without purification to afford a mixture of diastereoisomeric amines (R,S)-**14a** and (R,R)-**15a**. Several reducing agents were investigated with the aim to increase the yield and/or the diastereoselectivity of the reduction of the imino group. Best yields were obtained with $NaBH_4$ in MeOH which furnished **14a** and **15a** in a 90% yield from **12a**. The stereoselectivity of the reduction (but not the yield) was temperature-dependent (ratio **14a/15a** = 4 : 6 at room temperature and 2 : 8 at -78 °C, as determined by ^1H NMR). It is worth mentioning that bulky reducing agents [e. g., L-Selectride, $(t\text{-}BuO)_3AlLiH$] were totally inefficient for the reduction of **13a**.[15] Since amines (R,S)-**14a** and (R,R)-**15a** could not be separated from each other, the last steps of the synthesis were performed on the 4 : 6 mixture. Deprotection of the carbamate group with H_2, Pd/C, and treatment of the resulting diaminoacetals first with 3% HCl to regenerate the aldehyde group, then with 10% NaOH to effect the cyclization,[7] afforded a mixture of the expected tricyclic derivatives (+)-**1a** and (+)-**16a** in an average 73% yield [83% for (+)-**1b** and (+)-**16b**]. Silica gel chromatography on a Lobar column afforded (+)-**1a**, identical in all respects with natural (+)-T-8[1] and (+)-**16a** [(+)-9-epi-T-8], in a 4 : 6 ratio, in agreement with that measured by ^1H NMR for the mixture of (R,S)-**14a** and (R,R)-**15a**.

Synthetic (+)-**1a** and (-)-**1a** were hydrogenolyzed into the corresponding diamines[6,10] (+)-(2R,8S)-**19** and (-)-(2S,8R)-**19**, which were derivatized with (S)-2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid chloride [(S)-MTPA-Cl][16], to afford the diastereoisomeric MTPA amides **20** and **21**, respectively (scheme 2). The same hydrogenolysis/derivatization procedure was also applied to a sample of (±)-**1a**. Capillary GC analyses and ^1H NMR (250 and 600 MHz) comparison of the different MTPA amide samples showed that the enantiomeric excess of synthetic (+)-**1a** and (-)-**1a** was at least 99%. These results demonstrate that the racemization[11] of β-aminoketones (R)-(-)-**11a** and (S)-(+)-**11a** was indeed very low.



Scheme 2. Synthesis of MTPA Amides **20** and **21**.

In parallel with these synthetic studies, we had the opportunity to re-isolate natural tetraponerines from a new sample of *Tetraponera* sp. ants. This, coupled to the availability of synthetic material, allowed us to make a complete assignment of the ^{1}H and ^{13}C NMR spectra of these compounds, using one and two-dimensional techniques (COSY $^{1}H/^{1}H$, HMQC, HMBC, nOe difference spectra). The ^{13}C (150.87 MHz) and ^{1}H (600 MHz) NMR spectra of natural (+)-T-8, (+)-T-7, (+)-T-4, (+)-T-3, and synthetic (+)-**1b** and (+)-**16b**, are reported in Table 1 and 2, respectively. Natural (+)-T-7 had the same ^{1}H and ^{13}C NMR spectra as synthetic (+)-9-epi-T-8 [(+)-**16a**]. Moreover, a careful comparison of the two compounds indeed showed that they were identical (IR, optical rotation, and same retention time in capillary GC on two different columns). It follows that T-7 is not 5-epi-T-8 (**4**), as previously proposed,[4] but 9-epi-T-8 (**16a**). Comparison of the ^{1}H and ^{13}C NMR spectra of the natural propyl homologue (+)-T-4 with those of (+)-T-8 (Tables 1 and 2) showed that the two compounds have the same relative configuration, and, consequently, that structure **3** proposed[4] for (+)-T-4 is indeed correct. Likewise, comparison of the spectral data of natural (+)-T-3 and (+)-T-7 confirmed[4] that they have the same relative configuration. Thus, T-3 must be represented by structure **18** instead of **2**.

Table 1. ^{13}C NMR of Natural and Synthetic Tetraponerines (150.87 MHz, C_6D_6).

C	(+)-T-8 (**1a**)	(+)-T-7 (**16a**)	(+)-T-4 (**3**)	(+)-T-3 (**18**)	(+)-**1b**	(+)-**16b**
CH_2-1	34.2	34.0	33.0	34.3	32.6	34.2
CH_2-2	24.7	25.1	25.1	25.2	24.7	25.2
CH_2-3	25.8	26.4	26.2	26.6	25.7	26.6
CH_2-4	51.3	50.9	51.5	51.0	51.3	51.0
CH-5	85.4	75.6	85.5	75.5	85.6	75.3
CH_2-6	29.3	30.5	29.7	30.6	29.3	30.6
CH_2-7	19.9	22.2	20.3	22.2	19.8	22.2
CH_2-8	49.7	50.7	48.9	50.6	49.5	50.7
CH-9	61.6	53.3	61.1	53.0	62.5	55.0
CH_2-10	37.6	32.2	37.9	32.2	37.4	31.7
CH-11	62.6	56.8	62.7	56.7	62.9	56.6
CH_2-12	32.6	31.0	36.9	33.3	26.7	23.9
$CH_{2(3)}$-13	24.9	27.4	18.7	20.7	9.6	11.9
$CH_{2(3)}$-14	32.2	32.5	14.8	14.5	-	-
CH_2-15	22.9	23.2	-	-	-	-
CH_3-16	14.2	14.4	-	-	-	-

In the absence of any NMR data for natural T-1 and T-2, we could only compare their retention times in capillary GC with those of the synthetic ethyl derivatives **1b** and **16b**, and found them to be different in both cases. The structures of T-1 and T-2 are still under investigation, as are those of (+)-T-5 and (+)-T-6.[4]

The availability of synthetic (+)- and (-)-tetraponerines of known absolute configuration allowed us to address the problem of the absolute configuration of the natural compounds which, except for that of (+)-T-8,[2,3] was still undetermined. Since these molecules contain two tertiary amino functional groups, chiroptical methods seemed to be well suited to solve that problem. Indeed, it has been reported that tertiary aliphatic amines usually give rise to two absorption bands in circular dichroism around 195-205 nm and 220-230 nm.[17,18,19] The mirror-image CD curves obtained for synthetic (+)- and (-)-T-8, as well as (+)- and (-)-T-7,

Table 2. ^1H NMR spectra of natural and synthetic tetraponerines (600 MHz, C_6D_6, J in Hz).

Proton	(+)-T-8 (**1a**)	(+)-T-7 (**16a**)	(+)-T-4 (**3**)	(+)-T-3 (**18**)	(+)-**1b**	(+)-**16b**[a]
H_2C-1	1.43; 1.60	1.34; 1.42	1.32; 1.44	1.28; 1.32	1.30; 1.42	
H_2C-2	1.18; 1.60	1.16; 1.58	1.15; 1.60	1.17; 1.55	1.15; 1.60	
H_2C-3	1.50; 1.65	1.44; 1.48	1.48; 1.65	1.45; 1.55	1.48; 1.60	
HC-4_{ax}	1.72	1.52	1.70	1.55	1.70	
HC-4_{eq}	2.83, ddd (10, 2.5, 2.5)	2.76[b]	2.80, ddd (9.5, 2.5, 2.5)	2.76[b]	2.82, ddd (9.5, 2, 2)	2.76[b]
HC-5	2.32, dd (8, 6)	3.31, dd (5.5, 2)	2.29, dd (8, 6)	3.28, dd (4.9, 2)	2.28, dd (8, 6)	3.26, bt (3)
H_2C-6	1.74	1.72; 1.82	1.72	1.75	1.70	
H_2C-7	1.48; 1.70	1.65; 1.82	1.46; 1.70	1.66; 1.78	1.44; 1.68	
HC-8_a	2.05, q (8)	3.22, bq (8)	2.0, q (8)	3.15, bq (6.5)	1.97, q (8)	3.15, m
HC-8_b	3.16, ddd (8, 8, 2)	2.78, ddd (8, 8, 2)	3.12, ddd (8, 8, 2.5)	2.77[b]	3.10, ddd (8, 8, 2)	2.66, m
HC-9	2.12, m,	2.80[b]	2.09, m	2.80, bq (6.5)	2.00, m	2.76[b]
HC-10_{ax}	1.35	1.98, bddd (12, 12, 5.4)	1.30	1.90, bddd (12.5, 12.5, 5.5)	1.30	1.90[b]
HC-10_{eq}	1.50	1.10, bd (12)	1.43	1.09, bd (12.5)	1.44	1.10, bd (12.5)
HC-11	1.72	2.05, bt (11)	1.68	2.0, m	1.66	1.95[b]
H_2C-12	1.38; 1.46	1.34; 1.74	1.32; 1.50	1.32; 1.74	1.36; 1.55	
$H_{2(3)}C$-13	1.25; 1.45	1.28; 1.40	1.22; 1.36	1.33; 1.43	0.86, t (6.5)	0.92, t (7.2)
$H_{2(3)}C$-14	1.25	1.28	0.89, t (6.5)	0.90, t (6.5)		
H_2C-15	1.28	1.30				
H_3C-16	0.90, t (6.5)	0.92, t (6.5)				

[a] Spectrum incompletely assigned due to degradation of sample.
[b] Multiplicity not determined due to superposition of signals

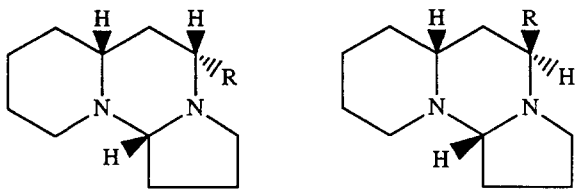
Table 3. CD of Natural and Synthetic Tetraponerines (CH_3CN)

	Synthetic Tetraponerines		Natural Tetraponerines	
Compound	λ_{max} (nm)	[Θ]	λ_{max} (nm)	[Θ]
(5R,9S,11R)-(+)-T-8	207	+ 8,860	206	+ 8,460
(5S,9R,11S)-(-)-T-8	205	- 8,250		
(5R,9S,11R)-(+)-T-4			205	+ 6,210
(5R,9S,11R)-(+)-**1b**	205	+ 6,530		
(5S,9R,11S)-(-)-**1b**	203	- 6,020		
(5R,9R,11R)-(+)-T-7	200[a]	+ 3,300	200[a]	+ 3,300
	222	- 3,100	221	- 2,900
(5S,9S,11S)-(-)-T-7	200[a]	- 3,330		
	224	+ 2,910		
(5R,9R,11R)-(+)-T-3			203[a]	+ 1,470
			224	- 2,280
(5R,9R,11R)-(+)-**16b**	200[a]	+ 2,890		
	220	- 1,930		
(5S,9S,11S)-(-)-**16b**	200[a]	- 2,580		
	223	+ 2,230		

[a] CD absorption could not be measured accurately beyond this wavelength.

in CH_3CN (Table 3) allowed us to use the sign of the Cotton effect to determine the absolute configuration of the tetraponerines. Moreover, the 5R*,9S*,11R* relative configuration is characterized by a CD curve having one Cotton effect around 195-205 nm, whereas the 5R*,9R*,11R* configuration affords CD curves with two Cotton effects of opposite signs around 200 and 220 nm. We also obtained CD curves of natural (+)-T-8, (+)-T-7, (+)-T-4 and (+)-T-3 as well as those of the synthetic derivatives (+)- and (-)-**1b** and (+)- and (-)-**16b**. Comparison of the data in Table 3 unambiguously demonstrates that natural (+)-T-4 has the same (5R,9S,11R) absolute configuration as (+)-T-8, and that both (+)-T-3 and (+)-T-7 have the (5R,9R,11R) absolute configuration. Our results also indicate that the length of the C-9 alkyl chain has little influence on the chiroptical properties of the tetraponerines. Circular dichroism thus appears to be a rapid and reliable method to determine the absolute configuration of homologous tetraponerines.

In conclusion, four enantiomerically pure (+)-tetraponerines as well as their (-) enantiomers were easily synthesized in six steps and 27% overall yield through a cycloaddition reaction of chiral acetylenic sulfoxides with 3,4,5,6-tetrahydropyridine-1-oxide. The synthetic compounds thus obtained allowed us to correct the structures previously proposed for (+)-T-3 and (+)-T-7, to assign the absolute configuration of (+)-T-3 (**18**), (+)-T-4 (**3**) and (+)-T-7 (**16a**) and to confirm that of (+)-T-8 (**1a**) (Figure 2). The pharmacological properties of these compounds are currently under investigation.



1a, R = n-C_5H_{11}: (+)-T-8 **16a**, R = n-C_5H_{11}: (+)-T-7

3, R = n-C_3H_7: (+)-T-4 **18**, R = n-C_3H_7: (+)-T-3

Figure 2. Structures and absolute configuration of natural (+)-T-3, (+)-T-4, (+)-T-7, and (+)-T-8.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a BRUKER WM 250 spectrometer (at 250 and 62.8 MHz, respectively) or 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. Data are reported as follows: chemical shift [multiplicity (s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, t: triplet, q: quartet, m: 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 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 = 1.10^{-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.). Preparative GC separations were realized on a DELSI 200 chromatograph, using an 3% OV-1 on Chromosorb W packed column (length, 150 cm; i. d., 0.5 cm). During work up, organic solutions were dried over $MgSO_4$.

p-Tolylalkynylsulfoxides (S)-(+)-(7a) and (S)-(+)-(7b). Hept-1-yne (1.7 ml, 13.0 mmol) was added dropwise at 0 °C to EtMgBr (prepared from 7.87 mmol of Mg and 8.15 mmol of EtBr) and the reaction mixture refluxed for 80 min. Then, this solution, which contained a blackish suspension, was added rapidly and under N_2 to a solution of menthyl p-toluenesulfinate (S)-(-)-(6)[20] (1.544 g, 5.24 mmol) in 15.5 ml of dry toluene, and the reaction mixture kept at -23 °C for 90 min. The reaction was quenched by addition of 16 ml of a saturated NH_4Cl solution and the aqueous phase extracted with a mixture of Et_2O : AcOEt : CH_2Cl_2 (2 : 2 : 1). The combined organic extracts were washed with a saturated NaCl solution, dried and evaporated *in vacuo*. A silica gel flash chromatography (hexane : AcOEt, 95 : 5 to 85 : 15) led to the isolation of unreacted (S)-(-)-**6** (0.263 g, 17%), (-)-menthol (0.590 g) and (S)-(+)-**7a** (0.883 g, 72%). (S)-(+)-**7a**: oil. $[\alpha]_D$ +74.3° (c=1.8, $CHCl_3$); lit.[13]: $[\alpha]_D$ +73.8° (c=0.47, $CHCl_3$). UV (CH_3OH): λ_{max} 208 nm, ε=16,600;

235 nm, ε=10,500. EIMS: m/z 234 ($M^{+\cdot}$, 6%); 218 ($M^{+\cdot}$- O, 6); 186 ($M^{+\cdot}$- SO, 21); 185 (21); 175 [$M^{+\cdot}$-(C_3H_7+O), 29]; 157 (87); 131 (84); 129 (100); 91 ($C_7H_7^+$, 61). IR (film): 2956-2930, 2180, 1490-1460, 1090-1060, 810 cm^{-1}. ^1H NMR ($CDCl_3$): 7.67 and 7.28 (AA'XX', 4H); 2.41 (s, 3H); 2.40 (t, 7 Hz, 2H); 1.62-1.51 (m, 2H); 1.38-1.29 (m, 4H); 0.87 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 142.6; 142.0; 130.5 (2C); 125.6 (2C); 106.3; 78.9; 31.4; 27.7; 22.4; 21.9; 20.2; 14.2.

When sufinate (S)-(-)-**6** was added to hept-1-ynylmagnesium bromide (**5a**) as described,[13] compound **17** was the major derivative synthesized. **17**: UV(CH_3OH): λ_{max} 255 nm, ε=19,500. CIMS (NH_3): m/z 331 [(M+H)$^+$, 100]; 317 (90); 315 [(M+H)$^+$-O, 88]; 268 [(M+H)$^+$-SO-CH_3, 17]; 266 (18). IR (film): 2956-2860, 2207, 1585, 1462, 1080, 1044, 808 cm^{-1}. ^1H NMR ($CDCl_3$): 7.56 and 7.30 (AA'XX', 4H); 6.27 (s, 1H); 2.44 (t, 7 Hz, 2H); 2.40 (s, 3H); 2.19 (t, 7.5 Hz, 2H); 1.62-1.23 (m, 12H); 0.91 (t, 6.5 Hz, 3H); 0.86 (t, 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): 142.2; 141.0; 140.1; 135.5; 129.9 (2C); 124.0 (2C); 101.7; 37.8; 31.1; 31.0; 28.1; 27.3; 22.3; 22.2; 21.3; 19.6; 13.94; 13.88.

In an analogous manner, p-tolylbutynylsulfoxide (S)-(+)-**7b** was synthesized in a 53% yield by addition to sulfinate (S)-(-)-**6** of but-1-ynylmagnesium bromide (**5b**), prepared by dehydrohalogenation of 1,2-dibromobutane[12] followed by treatment of the resulting but-1-yne with C_2H_5MgBr. (S)-(+)-**7b**: oil. $[\alpha]_D$ +103° (c=0.9, $CHCl_3$). EIMS: m/z 192 ($M^{+\cdot}$, 3%); 177 ($M^{+\cdot}$- CH_3, 5), 176 ($M^{+\cdot}$- O, 3), 144 ($M^{+\cdot}$- SO, 64); 143 ($M^{+\cdot}$- SOH, 22); 129 ($M^{+\cdot}$- SO - CH_3, 100); 119 (34); 91 ($C_7H_7^+$, 21). IR (film): 2981-2879, 2181, 1596, 1493, 1455, 1087, 1058, 810 cm^{-1}. ^1H NMR ($CDCl_3$): 7.69 and 7.34 (AA'XX', 4H); 2.43 (q, 7.5 Hz, 2H); 2.42 (s, 3H); 1.19 (t, 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): 142.6; 141.9; 130.6 (2C); 125.6 (2C); 107.2; 78.3; 21.9; 13.9; 13.0.

Δ^4-Isoxazolines (R,S)-(+)-9a, (S,S)-(-)-10a, (R,S)-(+)-9b and (S,S)-(-)-10b. To a solution of 1-hydroxypiperidine (0.407 g, 4.03 mmol) in 20 ml of freshly distilled, ethanol-free $CHCl_3$, yellow HgO (1.73 g, 7.97 mmol) was added at 0 °C and the stirring was maintained for 25 min at room temperature. The mixture was filtered on Celite, the latter was washed several times with $CHCl_3$, and the volume of $CHCl_3$ reduced *in vacuo* to 25 ml. Then, a solution of (S)-(+)-**7a** (0.84 g, 3.6 mmol) dissolved in a minimum of $CHCl_3$ was added and the reaction mixture stirred at room temperature for 25 h. The solvent was evaporated and the residue submitted to a silica gel flash chromatography (hexane : AcOEt, 9 : 1 to 7 : 3), to afford, in order of increasing polarity, (R,S)-(+)-**9a** (0.497 g, 41%) and (S,S)-(-)-**10a** (0.550 g, 46%). (R,S)-(+)-**9a**: oil. $[\alpha]_D$ +161° (c=0.57, CH_3OH); lit.[11]: $[\alpha]_D$ +162° (c=1.6, CH_3OH). EIMS: m/z 333 ($M^{+\cdot}$, 2%); 332 ($M^{+\cdot}$- H, 4); 316 ($M^{+\cdot}$- OH, 5); 278 (2%); 260 ($M^{+\cdot}$- C_4H_9O, 3); 246 ($M^{+\cdot}$- $C_5H_{11}O$, 6); 234 (5); 222 (16); 210 (24); 194 (11); 139 (CH_3PhSO^+, 35); 124 (53); 123 (CH_3PhS^+, 24); 99 (100); 96 ($C_6H_{10}N^+$, 27); 91 ($C_7H_7^+$, 34). IR (film): 2953-2861, 1634, 1494, 1455, 1082-1016, 810 cm^{-1}. ^1H NMR ($CDCl_3$): 7.43 and 7.30 (AA'XX', 4H); 4.06 (m, 1H); 3.17 (m, 1H); 3.03 (ddd, 10, 10, 3 Hz, 1H); 2.69-2.54 (m, 2H); 2.40 (s, 3H); 1.93 (m, 1H); 1.65 (m, 5H); 1.40 (m, 6H); 0.93 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 168.1; 140.3; 138.9; 129.9 (2C); 124.5 (2C); 112.2; 64.0; 51.7; 31.5; 26.8; 26.1; 25.8; 22.4; 22.3; 21.3; 19.5; 13.9. (S,S)-(-)-**10a**: oil. $[\alpha]_D$ -54° (c=0.48, CH_3OH); lit.[11]: $[\alpha]_D$ -60° (c=1.6, CH_3OH). EIMS: m/z 333 ($M^{+\cdot}$, 10%); 332 ($M^{+\cdot}$- H, 5); 316 ($M^{+\cdot}$- OH, 22); 278 (5); 260 ($M^{+\cdot}$- C_4H_9O, 8); 246 ($M^{+\cdot}$- $C_5H_{11}O$, 66); 234 (11); 222 (20); 210 ($M^{+\cdot}$- CH_3PhS, 25); 194 ($M^{+\cdot}$- CH_3PhSO, 36); 172 (21); 139 (CH_3PhSO^+, 100); 124 (60); 123 (CH_3PhS^+, 63); 99 (88); 96 ($C_6H_{10}N^+$, 39); 91 ($C_7H_7^+$, 46). IR (film): 2952-2860, 1630, 1492, 1454, 1082-1018, 954, 810 cm^{-1}. ^1H NMR ($CDCl_3$): 7.50 and 7.31 (AA'XX', 4H); 4.62 (m, 1H); 3.08 (m, 1H); 2.74-2.43 (m, 3H); 2.41 (s, 3H); 1.72-1.26 (m, 11H); 0.94 (t, 7 Hz, 3H and m, 1H). ^{13}C NMR ($CDCl_3$): 167.0; 140.4 (2C); 129.6 (2C); 124.6 (2C); 111.4; 63.9; 52.2; 31.5 ; 27.0; 25.7; 25.1; 23.0; 22.3; 21.3; 19.7; 13.9.

The same reaction performed on 0.502 g of (S)-(+)-**7b** afforded a mixture of Δ^4-isoxazolines which were separated by flash chromatography as described above to afford 0.335 g of (R,S)-(+)-**9b** (44%) and

0.397 g of (S,S)-(-)-**10b** (52%). (R,S)-(+)-**9b**: m. p.: 75-79 °C. $[\alpha]_D$ +211° (c=0.67, CH_3OH). EIMS: m/z 291 ($M^{+\cdot}$, 27%); 274 ($M^{+\cdot}$- OH, 50); 246 ($M^{+\cdot}$- O - C_2H_5, 63); 243 ($M^{+\cdot}$- SO, 33); 218 (56); 217 (55); 214 ($M^{+\cdot}$- SO - C_2H_5, 88); 168 (32); 152 ($M^{+\cdot}$- SO - C_7H_7, 60); 139 ($C_7H_7SO^+$, 80); 124 (68); 123 ($C_7H_7S^+$, 86); 112 (82); 96 ($C_6H_{10}N^+$, 55); 91 ($C_7H_7^+$, 100). IR (film): 2977-2857, 1633, 1492-1435, 1273-1214, 1091-1016, 983, 843-812 cm^{-1}. ^1H NMR ($CDCl_3$): 7.42 and 7.30 (AA'MM', 4H); 4.06 (bm, 1H); 3.18 (m, 1H); 3.02 (ddd, 10, 10, 3 Hz, 1H); 2.66 (AB part of ABM_3X, J_{AB}=15 Hz, J_{AM}=J_{BM}=7.5 Hz, J_{AX}=0.8 Hz, J_{BX}=1.4 Hz, 2H); 2.40 (s, 3H); 1.96 (m, 1H); 1.69-1.39 (m, 5H); 1.27 (t, 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): 169.3; 140.7; 139.3; 130.3 (2C); 124.8 (2C); 111.8; 64.4; 52.0; 26.4; 22.8; 21.7; 19.9; 19.7; 12.2. (S,S)-(-)-**10b**: m. p.: 48-51 °C. $[\alpha]_D$ -35° (c=0.68, CH_3OH). EIMS: m/z 291 ($M^{+\cdot}$, 5%); 274 ($M^{+\cdot}$- OH, 10); 273 (12); 246 ($M^{+\cdot}$- O - C_2H_5, 55); 243 ($M^{+\cdot}$- SO, 7); 214 ($M^{+\cdot}$- SO - C_2H_5, 14); 168 (30); 152 ($M^{+\cdot}$- SO - C_7H_7, 21); 140 (27); 139 ($C_7H_7SO^+$, 60); 124 (94); 123 ($C_7H_7S^+$, 100); 112 (28); 96 ($C_6H_{10}N^+$, 29); 91 ($C_7H_7^+$, 94). IR (film): 2973-2857, 1633, 1492-1446, 1276-1214, 1080-1015, 983, 812 cm^{-1}. ^1H NMR ($CDCl_3$): 7.51 and 7.31 (AA'MM', 4H); 4.63 (bm, 1H); 3.07 (m, 1H); 2.81-2.49 (m, 3H); 2.41 (s, 3H); 1.92-1.40 (m, 4H); 1.27 (t, 7.5 Hz, 3H); 0.96 (m, 1H); 0.25 (bm, 1H). ^{13}C NMR ($CDCl_3$): 168.2; 140.9 (2C); 130.1 (2C); 125.0 (2C); 111.2; 64.6; 52.6; 25.5; 23.4; 21.7; 20.0; 19.7; 12.3.

β-Aminoketone hydrochlorides (R)-(-)-11a.HCl, (R)-(-)-11b.HCl, and their enantiomers. Δ^4-Isoxazoline (R,S)-(+)-**9a** (0.497 g, 1.49 mmol) in 36 ml of CH_3OH was reduced catalytically by H_2 at atmospheric pressure, in the presence of 0.04 g of PtO_2 and 0.94 g (4.47 mmol) of citric acid at room temperature. After 24 h, the reaction mixture was filtered on Celite, and the latter repeatedly washed with CH_3OH. The solvent was evaporated *in vacuo* and the residue was deposited on a Sephadex DEAE A-25 column, conditioned with aqueous NaCl and eluted with H_2O : CH_3OH, 1 : 4. The hydrochloride of (R)-(-)-**11a** thus obtained was recrystallized in a mixture of acetone and Et_2O, to afford 0.24 g of white crystals (yield: 69%). (R)-(-)-**11a**.HCl: m. p. 108-110 °C. $[\alpha]_D$ -27° (c=0.54, CH_3OH). EIMS: m/z 197 ($M^{+\cdot}$, 4%); 196 ($M^{+\cdot}$- H, 2); 140 ($M^{+\cdot}$- $CH_3(CH_2)_3$, 5); 126 ($M^{+\cdot}$- $CH_3(CH_2)_4$, 7); 98 ($M^{+\cdot}$- $CH_3(CH_2)_4CO$, 13); 84 ($C_5H_{10}N^+$, 100). IR ($CHCl_3$): 3300, 2961, 2860-2350, 1712 cm^{-1}. ^1H NMR ($CDCl_3$): 9.40 (bs, 2H); 3.50 (m, 2H); 3.27 (dd, 18, 4 Hz, 1H); 3.02-2.86 (m, 2H); 2.45 (m, 2H); 2.06-1.51 (m, 8H); 1.28 (m, 4H); 0.89 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 207.2; 53.1; 45.0; 44.8; 43.3; 31.2; 28.3; 23.1; 22.3; 22.2; 22.1; 13.8.

The same procedure was applied to (S,S)-(-)-**10a**, (R,S)-(+)-**9b** and (S,S)-(-)-**10b**, affording the corresponding β-aminoketone hydrochlorides (S)-(+)-**11a**.HCl, (R)-(-)-**11b**.HCl and (S)-(+)-**11b**.HCl, respectively. (S)-(+)-**11a**.HCl: $[\alpha]_D$ +26° (c=0.39, CH_3OH). Same spectral properties as (R)-(-)-**11a**.HCl. (R)-(-)-**11b**.HCl: m. p.: 154-155 °C. $[\alpha]_D$ -31° (c=0.44, CH_3OH). EIMS: m/z 155 ($M^{+\cdot}$, 7%); 154 ($M^{+\cdot}$- H, 3); 140 ($M^{+\cdot}$- CH_3, 3); 126 ($M^{+\cdot}$- C_2H_5, 5); 98 ($M^{+\cdot}$- COC_2H_5, 19); 84 ($C_5H_{10}N^+$, 100). IR ($CHCl_3$): 3200, 2958, 2840-2350, 1713 cm^{-1}. ^1H NMR ($CDCl_3$): 9.39 (bs, 2H); 3.56-3.48 (m, 2H); 3.27 (dd, 18, 4 Hz, 1H); 3.02-2.86 (m, 2H); 2.50 (m, 2H); 2.0-1.51 (m, 6H); 1.06 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 207.9; 53.4; 45.3; 45.2; 36.9; 28.7; 22.6; 22.4; 7.9. (S)-(+)-**11b**.HCl: $[\alpha]_D$ +32° (c=0.57, CH_3OH). Same spectral properties as (R)-(-)-**11b**.HCl.

β-Aminoketone (R)-(-)-11a. (R)-(-)-**11a**.HCl (8 mg) was dissolved in CH_2Cl_2 (2 ml) and the resulting solution was shaken with an aqueous 2% NH_4OH solution. Drying and evaporation of the CH_2Cl_2 *in vacuo* afforded (R)-(-)-**11a**, $[\alpha]_D$ -26° (c=0.22, CH_3OH); lit.[11]: $[\alpha]_D$ -23° (c=1.1, CH_3OH).

Carbamates (R)-(+)-12a, (R)-(+)-12b, and their enantiomers. To a solution of (R)-(-)-**11a**.HCl (0.206 g, 0.88 mmol) in 3 ml H_2O were added 0.304 g (2.2 mmol) of K_2CO_3 and 252 µl (1.76 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 3 ml of CH_2Cl_2. The organic extracts were dried, filtered and evaporated *in vacuo*. A chromatography of the residue on neutral alumina (eluent: CH_2Cl_2) afforded 0.278 g of (R)-(+)-**12a** (95%), as a colorless oil. (R)-(+)-**12a**: $[\alpha]_D$ +4.4° (c=1.54, $CHCl_3$). UV (CH_3OH): λ_{max} 206 nm, ε = 10,430. EIMS: m/z 331 ($M^{+\cdot}$, <1%); 330 ($M^{+\cdot}$- H, <1); 328 (<1); 285 (<1); 240 ($M^{+\cdot}$- $PhCH_2$, 4); 224 ($M^{+\cdot}$- $PhCH_2O$, <1); 218 ($M^{+\cdot}$- $CH_3(CH_2)_4COCH_2$, 2); 197 (9); 196 ($M^{+\cdot}$- $PhCH_2CO_2$, 62); 174 (23); 98 ($C_6H_{12}N^+$, 8); 91 ($C_7H_7^+$, 100). IR (film): 2935-2861, 1713-1683, 1447, 1435, 1418, 1354, 1261, 1091, 1072 cm^{-1}. ^1H NMR ($CDCl_3$): 7.35-7.27 (m, 5H); 5.11 (s, 2H); 4.80 (m, 1H); 4.05 (bd, 13 Hz, 1H); 2.86 (ddd, 13, 13, 2 Hz, 1H); 2.69 and 2.61 (AB part of ABX; J_{AB}: 15 Hz, J_{AX}: 7 Hz, J_{BX}: 8 Hz, 2H); 2.39 (bdd, 7, 7 Hz, 2H); 1.65-1.19 (m, 12H); 0.89 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 209.6; 156.0; 137.6; 129.1 (2C); 128.5; 128.4 (2C); 67.6; 48.2; 43.8; 43.5; 40.4; 31.8; 28.8; 25.8; 23.9; 22.9; 19.4; 14.3. (S)-(-)-**12a**, synthesized from (S)-(+)-**11a**, had $[\alpha]_D$ -4.7° (c=0.9, $CHCl_3$).

Similarly, (R)-(+)-**12b** was obtained from (R)-(-)-**11b** in a 96% yield. (R)-(+)-**12b**: oil. $[\alpha]_D$ +9.5° (c=0.64; $CHCl_3$). EIMS: m/z 289 ($M^{+\cdot}$, <1%); 260 ($M^{+\cdot}$- C_2H_5, <1); 218 ($M^{+\cdot}$- $C_2H_5COCH_2$, 2); 198 ($M^{+\cdot}$- $PhCH_2$, 8); 174 (21); 154 ($M^{+\cdot}$- $PhCH_2CO_2$, 49); 98 ($C_6H_{12}N^+$, 8.5); 91 ($C_7H_7^+$, 100). IR (film): 2939, 1713-1683, 1455, 1447, 1423, 1354, 1263, 1145, 1075, 699 cm^{-1}. ^1H NMR ($CDCl_3$): 7.36-7.28 (m, 5H); 5.11 (s, 2H); 4.79 (m, 1H); 4.05 (bd, 14 Hz, 1H); 2.86 (bdd, 12, 12 Hz, 1H); 2.65 (m, 2H); 2.45-2.37 (m, 2H); 1.68-1.43 (m, 6H); 1.0 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 209.4; 155.8; 137.4; 128.9 (2C); 128.4; 128.3 (2C); 67.5; 48.2; 43.5; 40.3; 36.5; 28.8; 25.7; 19.3; 8.1. (S)-(-)-**12b**, obtained from (S)-(+)-**11b**, had $[\alpha]_D$ -10° (c=1.0, $CHCl_3$).

Amines (R,S)-14a/(R,R)-15a, (R,S)-14b/(R,R)-15b, and their enantiomers. Carbamate (R)-(+)-**12a** (0.248 g, 0.75 mmol) was dissolved in 2.5 ml (14.1 mmol, 19 eq.) of 4,4-diethoxybutylamine and the mixture stirred at room temperature under nitrogen for 25 h, in the presence of 0.246 g of Amberlyst A-15 resin and 3 Å molecular sieves. In one assay, the resulting unstable imine (R)-**13a** was isolated in moderate yield by rapid filtration on Florisil. Usually, however, the reaction mixture containing imine (R)-**13a** was filtered to remove the resin and the molecular sieves, 13 ml of anhydrous CH_3OH were added and the solution cooled at 0 °C. $NaBH_4$ (0.117 g, 3.1 mmol, 4 eq.) was added and the mixture was 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 3 ml of CH_2Cl_2. Evaporation of the solvent and flash chromatography on silica gel (CH_2Cl_2 : CH_3OH, 95 : 5) furnished 0.323 g (90%) of a mixture of the two amines (R,S)-**14a** and (R,R)-**15a**, that could not be separated under these conditions. (R)-**13a**: EIMS: m/z 474 ($M^{+\cdot}$, 47%); 445 ($M^{+\cdot}$- C_2H_5, 53); 429 ($M^{+\cdot}$- C_2H_5O, 52); 399 (28); 389 (75); 383 ($M^{+\cdot}$- $PhCH_2$, 42); 382 (41); 339 ($M^{+\cdot}$- $PhCH_2CO_2$, 38); 329 (84); 247 (88); 218 ($C_5H_9NCO_2CH_2Ph^+$, 90); 210 (85); 174 (100). ^1H NMR ($CDCl_3$): 7.35-7.29 (m, 5H); 5.11 (s, 2H); 4.78 (m, 1H); 4.68 (t, 5 Hz, 1H); 4.05 (bd, 13 Hz, 1H); 3.77-3.47 (m, 5H); 2.86 (bdd, 13, 13 Hz, 1H); 2.75-2.51 (m, 3H); 2.39 (bdd, 7, 7 Hz, 2H); 1.92-1.18 (22H); 0.87 (t, 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): C=N not detected; 155.3; 136.9; 128.5 (2C); 127.9; 127.8 (2C); 102.8; 67.1; 61.9 (2C); 59.3; 47.7; 43.3; 43.0; 39.9; 35.9; 31.4; 29.7; 28.3; 25.3; 23.4; 22.5; 18.9; 15.4 (2C); 13.9. (R,S)-**14a** + (R,R)-**15a**: EIMS: m/z 476 ($M^{+\cdot}$, 1.5%); 447 ($M^{+\cdot}$- C_2H_5, 22); 431 ($M^{+\cdot}$- C_2H_5O, 8); 405 ($M^{+\cdot}$- C_5H_{11}, 5); 385 ($M^{+\cdot}$- $PhCH_2$, 10); 345 (8); 331 (7); 313 (17); 244 (17); 218 ($C_5H_9NCO_2CH_2Ph^+$, 47); 198 (56); 174 (82); 91 (100). IR (film): 3450, 2953-2931, 1704-1683, 1661, 1455, 1353, 1266, 1128, 1062 cm^{-1}. ^1H NMR ($CDCl_3$): 7.36-7.29 (m, 5H); 5.15-5.07 (m, 2H); 4.48-4.32 (m, 2H); 4.06 (m, 1H); 3.70-3.31 (m, 4H); 2.97-1.96 (6H); 1.75-1.16 (19H); 1.20 (two superimposed t, 7 Hz, 6H); 0.89 (t, 7 Hz , 3H).

The mixture of (S,R)-**14a** and (S,S)-**15a** was obtained in the same manner, starting from (S)-(-)-**12a**. Its spectral properties were identical to those of the mixture of (R,S)-**14a** and (R,R)-**15a**.

The mixture of amines (R,S)-**14b** and (R,R)-**15b** were synthesized as described above but starting from (R)-(+)-**12b**. (R,S)-**14b** + (R,R)-**15b**: EIMS: m/z 434 ($M^{+\bullet}$, 1.5%); 405 ($M^{+\bullet}$- C_2H_5, 13); 389 ($M^{+\bullet}$- C_2H_5O, 4); 343 ($M^{+\bullet}$- C_7H_7, 7); 313 (8); 303 ($M^{+\bullet}$- $C_3H_5(OC_2H_5)_2$, 6); 289 ($M^{+\bullet}$- $C_4H_7(OC_2H_5)_2$, 4); 218 ($C_5H_9NCO_2CH_2Ph^+$, 27); 174 (64); 156 (31); 110 (30); 91 ($C_7H_7^+$, 100). IR (film): 3440, 2972-2934, 1703-1683, 1455, 1418, 1353, 1263, 1068 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40-7.29 (m, 5H); 5.20-5.07 (m, 2H); 4.50-4.40 (m, 2H); 4.08 (m, 1H); 3.70-3.43 (m, 4H); 2.97-1.42 (19H); 1.19 (two superimposed t, 7 Hz, 6H); 0.93 (t, 7 Hz, 3H). The mixture of amines (S,R)-**14b** and (S,S)-**15b** was synthesized from (S)-(-)-**12b**, and had spectral properties identical to those of (R,S)-**14b** + (R,R)-**15b**.

(+)-1a, (+)-16a, (+)-1b, (+)-16b, and their enantiomers. The mixture of diastereoisomeric amines (R,S)-**14a** and (R,R)-**15a** (0.318 g, 0.67 mmol) was dissolved in 15 ml of CH_3OH and submitted to a hydrogenolysis reaction at room temperature, at a hydrogen pressure slightly over 1 atmosphere, in the presence of 0.119 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 1.7 ml of a 10% HCl solution and 3.4 ml of water, and stirred at room temperature overnight. The mixture was then basified by slow addition of a 10% NaOH solution (up to pH 8) and stirred for a further 2 h at room temperature. Finally, the reaction mixture was brought to pH 10 and extracted three times with 5 ml of CH_2Cl_2. Evaporation of the solvent afforded 0.14 g of a yellow oil, containing the two expected tricyclic derivatives (+)-**1a** and (+)-**16a** in a 4 : 6 ratio, by capillary GC (OV-1, 25 m, 165°C, isothermal). These two compounds were cleanly separated by chromatography on a silica gel Lobar column (Merck, size A) ($CHCl_3$ to $CHCl_3$: EtOH, 95 : 5). By this procedure, 0.052 g of (+)-**1a** and 0.07 g of (+)-**16a** were obtained (yield: 73% for the deprotection-cyclization steps). (+)-**1a**: $[\alpha]_D$ +101° (c=0.3, $CHCl_3$); lit.[1]: $[\alpha]_{579}$ +102° (c=0.15, $CHCl_3$); lit.[3]: $[\alpha]_D$ +99° (c=0.6, $CHCl_3$); IR, EIMS, ^1H and ^{13}C NMR identical to the published data[1,4]. Complete ^1H and ^{13}C assignments: tables 1 and 2. CD: table 3. (+)-**16a**: $[\alpha]_D$ +31° (c=0.43, $CHCl_3$); natural (+)-T-7: $[\alpha]_D$ +30° (c=0.22, $CHCl_3$); IR, EIMS, ^1H and ^{13}C NMR identical to the data published for (+)-T-7.[4] Complete ^1H and ^{13}C assignments: tables 1 and 2. CD: table 3. (+)-T-7 and synthetic (+)-**16a** were indistinguishable in capillary GC on both OV-1 and OV-1701 columns (isothermal at 165 °C).

The enantiomers (-)-**1a** and (-)-**16a** were obtained by application of the same procedure to the mixture of amines (S,R)-**14a** and (S,S)-**15a**. (-)-**1a**: $[\alpha]_D$ -99° (c=0.3, $CHCl_3$). (-)-**16a**: $[\alpha]_D$ -31° (c=0.25, $CHCl_3$). CD: table 3.

The ethyl homologues (+)-**1b** and (+)-**16b** were obtained as described for (+)-**1a** and (+)-**16a**, starting from the mixture of (R,S)-**14b** and (R,R)-**15b**, but in a 65% yield . This lower yield was due to separation problems of the two epimers on the Lobar column. (+)-**1b**: $[\alpha]_D$ +78° (c=0.14; $CHCl_3$). EIMS: m/z 208 ($M^{+\bullet}$, 60%); 207 ($M^{+\bullet}$- H, 100); 193 ($M^{+\bullet}$- CH_3, 50); 180 (12); 165 (20); 152 (36); 137 (25), 110 ($C_7H_{12}N^+$, 28); 96 ($C_6H_{10}N^+$, 44); 84 ($C_5H_{10}N^+$, 46); 70 ($C_4H_8N^+$, 35). IR (film): 2958-2875, 2865, 2791, 2776, 1192, 1114 cm^{-1}. ^1H and ^{13}C NMR spectra: tables 1 and 2. CD: table 3. (+)-**16b**: $[\alpha]_D$ +34° (c=0.6, $CHCl_3$). EIMS: m/z 208 ($M^{+\bullet}$, 71%); 207 ($M^{+\bullet}$- H, 100); 193 ($M^{+\bullet}$- CH_3, 72); 180 (16); 165 (28); 152 (34); 137 (28), 110 ($C_7H_{12}N^+$, 13); 96 ($C_6H_{10}N^+$, 57); 84 ($C_5H_{10}N^+$, 35); 70 ($C_4H_8N^+$, 14). IR (film): 2956, 2871, 2860, 2804, 2749, 1226, 1117 cm^{-1}. ^1H and ^{13}C NMR spectra: tables 1 and 2. CD: table 3.

The enantiomers (-)-**1b** and (-)-**16b** were obtained by application of the same procedure to the mixture of amines (S,R)-**14b** and (S,S)-**15b**. (-)-**1b**: $[\alpha]_D$ -77° (c=0.1, $CHCl_3$). (-)-**16b**: $[\alpha]_D$ -35° (c=0.5, $CHCl_3$). CD: table 3.

MTPA amides 20 and 21. Synthetic (+)-**1a** (4 mg) in 4 ml of C_2H_5OH was hydrogenolyzed under 1 atmosphere of H_2, in the presence of PtO_2 and HCl, according to the procedure of Renson *et al.*[10] After usual work up, the reaction mixture was purified by chromatography on alumina (AcOEt to AcOEt : C_2H_5OH,

1 : 2), affording diamine (+)-(2R,8S)-**19** (3.5 mg), $[\alpha]_D$ +14° (c=0.17, $CHCl_3$), which had spectroscopic data identical to those reported.[6] To (+)-(2R,8S)-**19** (3 mg) in 350 µl of anhydrous pyridine were added Et_3N (22 µl) and (S)-MTPA-Cl (30.3 mg), prepared from (R)-MTPA acid according to Ward and Rhee.[21] After 90 min at 90 °C, the same amounts of Et_3N and (S)-MTPA-Cl were added and the reaction maintained at 90 °C for 3 h. Usual work up and rapid filtration on silica gel (CH_2Cl_2 : CH_3OH, 95 : 5) afforded MTPA amide **20** in a 70% yield. **20**: EIMS: m/z 468 ($M^{+\bullet}$, 7%), 398 (12), 397 (47), 300 (34), 189 (38), 154 (100). IR (film): 2935-2794, 1652, 1265, 1181, 1156, 720 cm^{-1}. ^1H NMR: 7.55 (m, 2H) and 7.38 (m, 3H) (phenyl); 4.97 (m, 1H, CH-N-CO); 3.69 (q, 2 Hz, 3H, OCH_3).

By the same procedure, MTPA amide **21** was obtained from (-)-**1a**, via diamine (-)-(2S,8R)-**19**, $[\alpha]_D$ -16° (c=0.2, $CHCl_3$). **21**: EIMS and IR identical to those of **20**. ^1H NMR: 7.47 (m, 2H) and 7.39 (m, 3H) (phenyl); 4.86 (m, 1H, CH-N-CO); 3.76 (q, 2 Hz, 3H, OCH_3).

The three MTPA amide samples coming from (±)-**1a**, (+)-**1a**, and (-)-**1a** were analyzed, before filtration on silica gel, on a 25 m OV 1 capillary column, programmed from 250 °C (1 min) to 280 °C (15 min) with a rate of 6 °C/min. The peaks corresponding to amides **20** and **21** were well resolved and identified by GCMS. Under these conditions, the samples of **20** [from (+)-**1a**] and **21** [from (-)-**1a**] were shown to contain less than 1% of the other diastereoisomer.

Isolation of natural tetraponerines from *Tetraponera* sp. 1,500 Individuals of *Tetraponera* sp. collected at Laing Island (Papua-New Guinea) were extracted with CH_2Cl_2/CH_3OH, and the alkaloidic fraction submitted to the separation scheme described in ref. 4. This afforded (+)-T-3 (1.6 mg), (+)-T-4 (3.6 mg), (+)-T-5 (4.6 mg), (+)-T-6 (3.0 mg), (+)-T-7 (6.6 mg), and (+)-T-8 (10.5 mg), identical in all respects (IR, EIMS, ^1H and ^{13}C NMR) with the compounds originally described.[4] The optical rotations which were not reported in ref. 4 are as follows: (+)-T-3: $[\alpha]_D$ + 27° (c=0.07, $CHCl_3$); (+)-T-4: $[\alpha]_D$ + 94° (c=0.2, $CHCl_3$); (+)-T-5: $[\alpha]_D$ + 10° (c=0.2, $CHCl_3$); (+)-T-6: $[\alpha]_D$ + 35° (c=0.15, $CHCl_3$); (+)-T-7: $[\alpha]_D$ + 30° (c=0.22, $CHCl_3$); (+)-T-8: $[\alpha]_D$ + 102° (c=0.2, $CHCl_3$); ^1H and ^{13}C NMR of T-3, T-4, T-7 and T-8: tables 1 and 2.

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