Concise and Stereoselective Syntheses of the Eight Natural Ant Defense Alkaloids (+)-Tetraponerine-1 to (+)-Tetraponerine-8 According to the CN(*R,S*) Strategy

Chongwei Yue, Isabelle Gauthier, Jacques Royer,* and Henri-Philippe Husson

Institut de Chimie des Substances Naturelles du CNRS, 91198 Gif-sur-Yvette, France

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The asymmetric syntheses of all the known defense alkaloids of the ant Tetraponera sp. tetraponerines **T-1** to **T-8** have been accomplished in five or six steps with 20−45% overall yields**.** The synthesis involved in the cross-condensation of (*R*)-piperidin-2-ylacetaldehyde with 4-aminobutyraldehyde which upon quenching by cyanide ion gave a stable tricyclic amino nitrile **3** with both a high yield and complete diastereoselectivity. This amino nitrile is the common precursor of four tetraponerines. A similar synthesis using (*R*)-pyrrolidine-2-ylacetaldehyde provided the tricyclic amino nitrile **2** precursor of the four other tetraponerines.

Ants often use powerful defensive stings; although most of the venoms are of proteinic nature, some of them consist of alkaloids. This is the case for some Myrmicinae species as *solenopsis* or *monomorium* genus whose venoms contain dialkylated-piperidine, -pyrrolidine, or -indolizidine derivatives.[1] All these substances exhibit interesting insecticide properties. It was reported in 1988 by Braeckman, Daloze, and co-workers that the venom of pseudomyrmecine ants *Tetraponera* sp. consists of eight toxic alkaloids with an original tricyclic structure and which have been named tetraponerine-1 to tetraponerine-8 (**T-1** to **T-8**).[2]

Among these toxic substances, the structure and the relative configuration of the major component, tetraponerine-8, has been established by X-ray diffraction analysis.[2b] Although erroneous structures were first published for **T-3**, **T-5**, **T-6**, and **T-7**,[2a] very recently reported studies[3] fully established that the structures of tetraponerines, as deduced from their spectroscopic characteristics together with syntheses (**T-5** and **T-6**)[3a] and X-ray analysis (**T-8**),[2b] are those represented in Figure 1. A doubt remains for the structures of **T-1** and **T-2** which were isolated in very small amounts, and indeed no NMR data have been reported for these compounds.

The unprecedented tricyclic skeleton along with the interesting insecticidal activities of the tetraponerines ($LD_{50} = 2 \times 10^{-9}$ mol/ant mg[2b]) have made them attractive targets for total synthesis. Indeed, very soon after their isolation, a total synthesis of the racemic form of the major alkaloid (+)-tetraponerine-8 was published by Merlin *et al.*,[4] and its first asymmetric total synthesis was accomplished by our group.[5] Other total syntheses of (±)-**T-8** have also appeared[6] as well as those of (±)-**T-4**,[6b] (±)-**T-5**, (±)-**T-6**.[3b] An asymmetric synthesis of (+)-**T-8** and (+)-**T-7** was recently described.[3a] Nevertheless, no synthesis of **T-1** and **T-2**, nor asymmetric synthesis of **T-4**, **T-5**, and **T-6** has yet been accomplished.

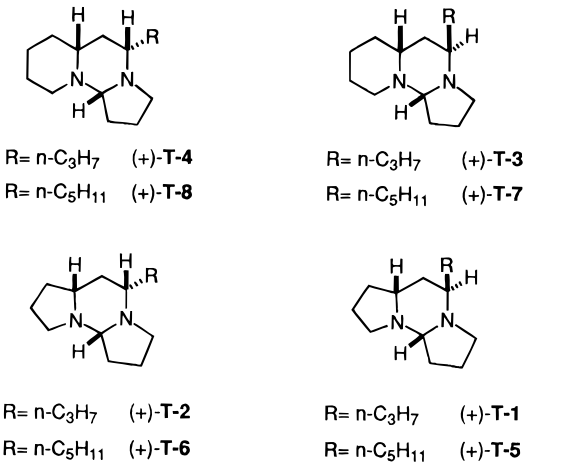

Figure 1.

The asymmetric synthesis of (+)-**T-8**, described in a preliminary report,[5] enabled us to determine the absolute configuration of the natural enantiomer as that depicted in Figure 1. The absolute configuration of **T-3**, **T-4** and **T-7** have been determined by circular dichroism.[3a]

From the recently revised structures,[3] it appears that the strategy we used for the asymmetric synthesis of **T-8**[5] would allow us to synthesize the eight tetraponerines **T-1** to **T-8** in a convergent and concise approach. We describe herein these diastereoselective asymmetric syntheses.

Results and Discussion

The structure of the tetraponerines is characterized by a 1,3-diaza tricyclic system. The construction of this kind of system has been already reported in the literature using the Hofmann−Löfler photocyclization,[7] the intramolecular condensation of secondary amines with aldehydes,[8] the reductive intramolecular cyclization of

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(1) Braekman, J.-C.; Daloze, D. In *Studies in Natural Products Chemistry*; Atta-ur-Rhaman Ed., Elsevier: New York, 1990; Vol. 6, p 421.

(2) (a) Merlin, P.; Braekman, J.-C.; Daloze, D.; Pasteels, J.-M. *J. Chem. Ecol.* **1988**, *14*, 517. (b) Braekman, J.-C.; Daloze, D.; Pasteels, J.-M.; Vanhecke, P.; Declercq, J.-P.; Sinnwell, V.; Franke, W. *Z. Naturforsch.* **1987**, *42c*, 627.

(3) (a) Marcours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron*, **1995**, *51*, 1415. (b) Devijver, C.; Marcours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. *Tetrahedron* **1995**, *51*, 10913.

(4) (a) Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691. (b) Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron* **1991**, *47*, 3805.

(5) Yue, C.; Royer, J; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 1140.

(6) (a) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 1535. (b) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 4543. (c) Barluenga, J.; Tomàs, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699.

(7) (a) Ban, Y.; Kimura, M.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1490. (b) Kimura, M.; Ban, Y. *Synthesis* **1976**, 201.

(8) (a) Winterfeld, K.; Göbel, W. *Chem. Ber.* **1959**, *92*, 637. (b) Ayer, W.; Piers, K. *Can. J. Chem.* **1967**, *45*, 451.

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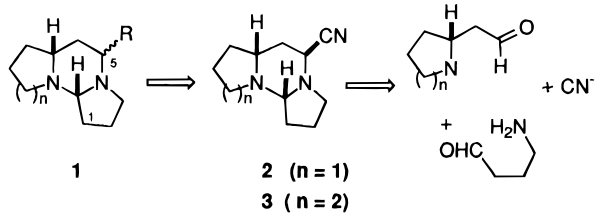
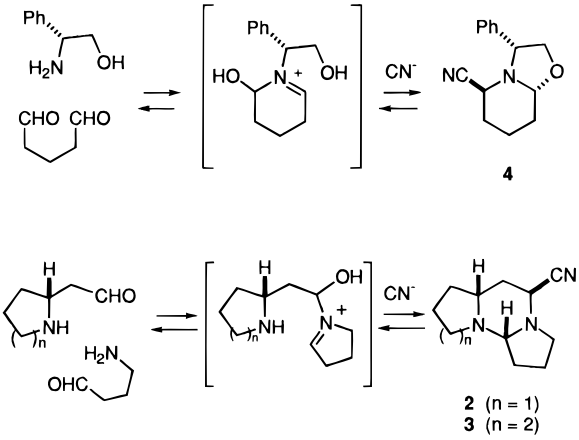
Scheme 1



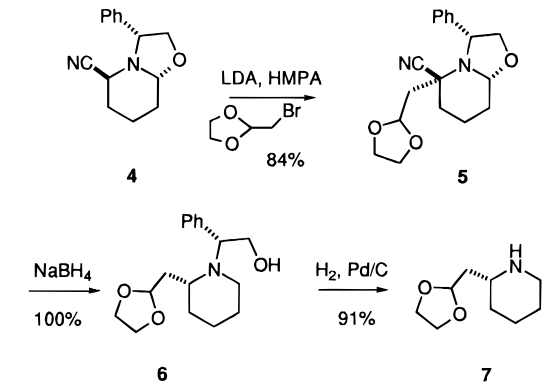
Scheme 2



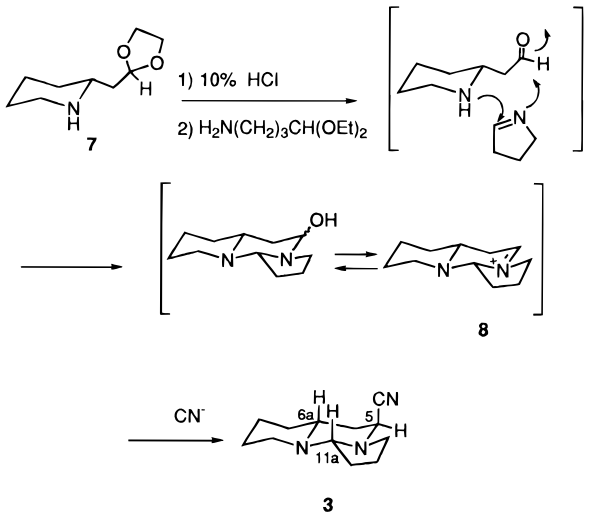
secondary amines with lactams or imides,[9] and the condensation of diamines with dialdehydes.[10] Our strategy is based on a cross-condensation of two different amino aldehydes to give cyano aminals **2** or **3** (Scheme 1).

Tetraponerines **T-1** to **T-8** may be represented by the general formula **1** with (i) $n = 1$ or 2, (ii) a *R*- or *S*-configuration at C-5, and (iii) R = *n*-propyl or *n*-pentyl. A general access to all the tetraponerines will thus be possible starting from amino nitriles **2** or **3** if we are able to introduce the alkyl groups in the proper configuration. Previous studies from this laboratory have shown that alkylation of amino nitriles can be stereoselectively controlled which constitutes the basis of the so-called CN-(*R*,*S*) method.[11,12] The synthesis of amino nitriles **2** or **3** might appear as a rather difficult task; nevertheless, structural similarities with chiral 2-cyano-6-oxazolopiperidine **4** suggested a preparation according to a similar route. We have already shown[11] that **4** can be obtained as a single isomer through a second-order asymmetric induction (namely a series of equilibria leading to the more stable isomer **4**) by the condensation of a dialdehyde with a chiral amino alcohol in the presence of cyanide (Scheme 2). It was thus assumed that the cross-condensation of two amino aldehydes would also lead through equilibrated reactions to the more stable stereomer of amino nitriles **2** or **3** in which the rings have stable *trans*-junctions and the CN group is axial as imposed by the anomeric effect. The asymmetric synthesis of all the tetraponerines was therefore undertaken with this strategy.

Scheme 3



Scheme 4



Synthesis of (+)-T-3, (+)-T-4, (+)-T-7, and (+)-T-8. The asymmetric synthesis of these four alkaloids started with cyanooxazolidine **4** which was converted to amino acetal **7** in three steps and 76% overall yield as previously described[5] and shown in Scheme 3. The hydride reduction step permitted the total diastereoselective preparation of acetal **6**: only one diastereomer was found in the reaction mixture as indicated by NMR and chromatographic analyses. A *2R* configuration was assigned to **7** on the basis of our previous work.[11b]

Amino acetal **7**, after hydrolysis with aqueous 10% HCl at room temperature to liberate the aldehyde, was treated in the same pot with the commercially available 4-aminobutyraldehyde diethyl acetal and potassium cyanide to afford cyano aminal **3**. The formation of the compound can be explained as follows: a cross-condensation between these amino aldehydes occurred instantly to give probably the unstable tricyclic N,O-acetal intermediate which is in equilibrium with the corresponding iminium **8** (Scheme 4). The latter was trapped by cyanide to form the cyano aminal **3** in 84% yield. The presence of the aminal function and amino nitrile group was clearly proved by the ^{13}C NMR analysis, showing two signals at 79.0 and 116.2 ppm.

It should be noted that this reaction is thermodynamically controlled and is pH-dependent. After several experiments using a variety of pH conditions, it was eventually found that the trapping is favored at pH 2−3. Furthermore, in the basification step, the pH should not

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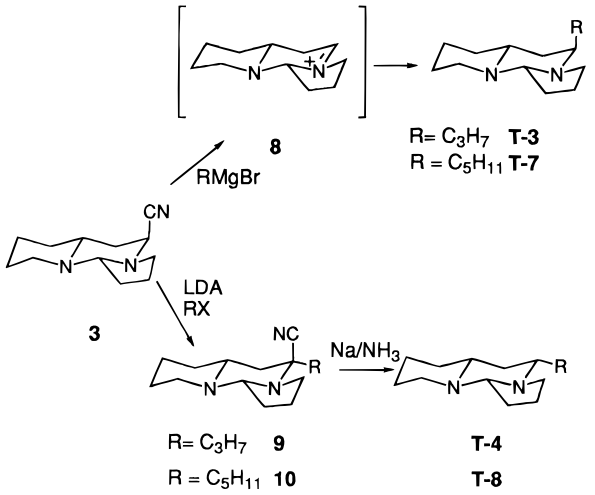
(10) (a) Kukla, M.-J.; Breslin, H.-J. *J. Org.Chem.* **1987**, *52*, 5046. (b) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5137.

(11) (a) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Syntheses* **1991**, *70*, 54. (b) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (c) Royer, J.; Husson, H.-P. *Janssen Chim. Acta* **1993**, *11*, 3.

(12) CN(*R*,*S*) method refers to the desire to obtain a *R* or *S* configuration α to the nitrogen by substitution of the CN group.

Scheme 5



exceed pH 9. At higher pH values elimination of HCN and formation of the corresponding enamine becomes the main reaction. In this cross-condensation step, two new chiral centers and three bonds were created, nevertheless, only one single diastereomer could be isolated. It was assumed that the thermodynamically more stable product **3** was obtained (second-order asymmetric induction), and the relative configuration was confirmed by careful NMR analysis. This analysis revealed that the protons at C-6a and C-11a are both axial (exhibiting ^3J coupling constants of 8 and 10 Hz, respectively) and that the cyano group occupies an axial position at C-5 (anomeric effect).

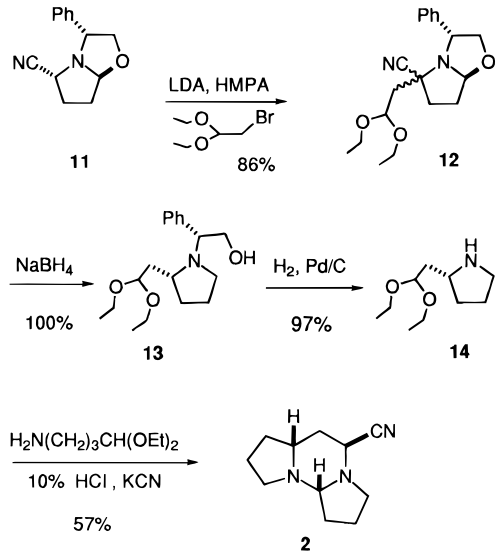
After ensuring the correct configuration of **3**, it was necessary to introduce the alkyl side chain at C-5 in the proper position to obtain the desired isomer.

It has been previously shown, according to the CN(*R*, *S*) method,[11] that replacement of CN group of the synthon **4** by an alkyl chain could be directed to produce either equatorial or axial α-alkyl piperidine derivatives as required.

Introduction of the alkyl side chain in the equatorial position necessitates two steps. The alkylation of cyano aminal **3** was achieved *via* its anion (LDA−HMPA, and then *n*-$C_5H_{11}Br$) to give **10** in 62% yield (Scheme 5). This compound was obtained as a single isomer, and its configuration was tentatively assigned to that one depicted on Scheme 5 (with CN axial by comparison with the starting material). The stereoselective decyanation of **10** using Na in liquid ammonia yielded (97%) exclusively *all-cis* tetraponerine-8 (+)-**T-8** ($[\alpha]^{20}_D$ +99°, lit.: $[\alpha]^{20}_D$ +102°) (Scheme 5). Using a similar procedure tetraponerine-4 (+)-**T-4** was prepared from **3** via **9** in 65% yield for the two steps. Synthetic (+)-**T-4** had identical spectral data of those of natural material and has a $[\alpha]_D$ +105° ($CHCl_3$, *c* 0.3), lit.[3a] +94° ($CHCl_3$, *c* 0.2).

As expected, the direct nucleophilic alkylation of cyano aminal **3** with propylmagnesium bromide in ether at −20 °C led, *via* iminium ion **8**, to the introduction of the side chain in an axial position to give tetraponerine (+)-**T-3** in 77% yield. Careful examination of the crude reaction mixture allowed us to assess a 97% de for this alkylation step; the minute amount of C-5 epimeric material ((+)-**T-4**) was easily removed and pure (+)-**T3** $[\alpha]_D$ +31°, $CHCl_3$, *c* 3.1) was obtained in 70% yield. Alkylation of **3** with pentylmagnesium bromide in the same conditions gave (+)-**T-7** ($[\alpha]_D$ +30°, $CHCl_3$, *c* 2.8) in 69% yield (75% yield of crude mixture with 97% de).

Scheme 6



Synthesis of (+)-T-1, (+)-T-2, (+)-T-5, and (+)-T-6. For the asymmetric synthesis of these alkaloids, the same strategy as above was applied starting from the 2-cyano-5-oxazapyrrolidine **11**. This compound has received less attention than the piperidine analogue; nevertheless, it can be easily prepared[13] and has already been shown to undergo highly diastereoselective alkylations.[14]

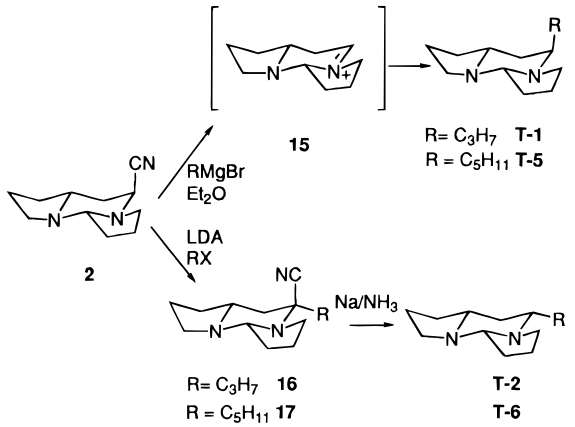
Cyanooxazolidine **11** was diastereoselectively transformed into the pyrrolidine acetal derivative **14** in three steps and 83% overall yield (Scheme 6). It should be noted that the alkylation of the anion of **11** gave amino nitrile **12** as a mixture of two diastereomers in a 7:3 ratio.[15] These diastereomers could be easily separated by flash chromatography, but were reduced as a mixture using $NaBH_4$ to give a single[14] amino alcohol **13** in a quantitative yield. Removal of the chiral appendage of **13** by hydrogenolysis gave **14** in high yield. The cross-condensation of **14** with aminobutyraldehyde was then attempted, and we were pleased to obtain the amino nitrile **2** upon quenching with cyanide ion as a single diastereomer (albeit with a lower yield, 57%, compared to the piperidine series). The relative configuration of **2** was assigned as that depicted in Scheme 6 on the basis of ^1H NMR analysis and thermodynamic hypotheses. As already reported for the pyridopyrrolopyrimidine series (*vide supra*), the thermodynamically more stable compound was formed, in which the rings are fused with a *trans*-junction and the CN group occupies an axial position.

Amino nitrile **2** was the precursor of the four remaining tetraponerines, using our methodology to introduce the alkyl (propyl or pentyl) group in the correct configuration (Scheme 7).

Treatment of **2** in ether at −20 °C by *n*-propyl Grignard reagent gave (+)-**T-1** ($[\alpha]^{20}_D$ +11° ($CHCl_3$, *c* 0.14)), as an unique isomer in 51% yield after purification. In a similar fashion, *n*-pentylmagnesium bromide added stereoselectively to **2** to give (+)-**T-5** ($[\alpha]^{20}_D$ +10° ($CHCl_3$, *c* 0.24); lit. [3a]$[\alpha]^{20}_D$ +10° ($CHCl_3$, *c* 0.2)) identical in all aspects to the natural compound.[3b] In this case no trace of the epimeric compound could be found.

(13) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 6175.
(14) Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 2457.
(15) The cheaper bromoacetaldehyde diethyl acetal was used in this case.

Scheme 7



Alkylation of the anion of **2** (LDA−HMPA, THF, −78 °C) with propyl bromide or pentyl bromide gave the corresponding amino nitriles **16** and **17** which were decyanated, respectively, to (+)-**T-2**($[\alpha]^{20}_D$ +36° ($CHCl_3$, *c* 1,8)) and (+)-**T-6** ($[\alpha]^{20}_D$ +35° ($CHCl_3$, *c* 0.31); lit.[3a] $[\alpha]^{20}_D$ +35° ($CHCl_3$, *c* 0.15)).

As only minute amounts of tetraponerines (+)-**T-1** and (+)-**T-2** had been isolated from the natural source,[3a] physical data were scarce and indeed no optical rotations or NMR data was reported. The authenticity of these two compounds has been obtained by comparison of synthetic and natural material by GC.[16] Identical retention times in separate as well as in coinjections experiments were further evidences for their structures.

We have thus prepared all eight natural tetraponerines through a concise, convergent, and efficient synthesis in five or six steps and 20−45% overall yields. The CN-(*R,S*) strategy was used twice in these syntheses: firstly in the diastereoselective preparation of the chiral piperidine or pyrrolidine acetaldehyde, which allowed the incorporation of the first asymetric center, and secondly in the diastereoselective alkylation of the tricyclic amino nitriles **2** or **3** leading to the final alkaloids.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl immediately prior to use. Diisopropylamine was distilled from and stored over KOH. Final solutions before rotary evaporation were dried over Na_2SO_4, and flash chromatography was carried out using 230−400 mesh silica gel. Melting points are uncorrected. Optical rotations werte recorded at 20 °C in a 1 dm cell. Microanalyses were carried out at the Service de Microanalyse at the Institut de Chimie des Substances Naturelles.

5-([1,3]Dioxolan-2-ylmethyl)-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-5-carbonitrile (5). To a stirred solution of LDA [prepared from 6.1 mL (43.3 mmol) of diisopropylamine and 27.1 mL (43.4 mmol) of 1.6M n-BuLi in hexane] in THF (15 mL) and HMPA (15 mL, 86.6 mmol) was added dropwise a solution of **4** (3.94 g, 17.3 mmol) in THF (30 mL) at −78 °C. After 20 min, a solution of 2-(bromomethyl)-1,3-dioxolane (2.6 mL, 25 mmol) in THF (2.5 mL) was added. After stirring for 2 h at −78 °C, the mixture was quenched by saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic phases were dried and evaporated *in vacuo* to give a residue which was purified by flash chromatography (hexane/Et_2O 2:1) to afford **5** (4.6 g, 85%) as a colorless oil: $[\alpha]^{20}_D$ −156° ($CHCl_3$, *c* 1.2); IR (neat) 2953, 2880, 2100, 1134 cm^{-1}; MS (EI) *m/z* 314 (M^+, 30), 313 (31), 288 (19), 287 (73), 244 (82), 227 (39), 214 (100), 148 (74); ^1H NMR (200 MHz, $CDCl_3$) δ 7.2−7.5 (m, 5 H), 4.85 (dd, *J* = 5, 6 Hz, 1 H), 4.21 (m, 2 H), 4.05 (dd, *J* = 5, 9 Hz, 1 H), 3.7−3.9 (m, 5 H), 2.2 (brd, *J* = 9 Hz, 2 H), 1.95 (dd, *J* = 5, 14 Hz, 1 H), 1.6, 1.75 (m, 4 H), 1.5 (dd, *J* = 6, 14 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 29 4, 35.1, 43.4, 59.7, 62.2, 64.4, 64.8, 74.8, 92.0, 100.8, 118.4, 127.0, 127.7, 128.9, 144.0. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.55; H, 7.23; N, 8.69.

2-[2-([1,3]Dioxolan-2-ylmethyl)piperidin-1-yl]-2-phenylethanol (6). To a suspension of $NaBH_4$ (5.5 g, 140 mmol) in ethanol (180 mL) was added a solution of **5** (3.66 g, 11.6 mmol) in ethanol (20 mL); the mixture was refluxed for 2 h and then cooled to room temperature. Water (*ca.* 100 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried and evaporated to give **6** (3.39 g, 100%) as a colorless oil which can be used in the next step without purification. Flash chromatography on silica gel (CH_2Cl_2/CH_3OH 20:1) furnished analytical sample: $[\alpha]^{20}_D$ −74° ($CHCl_3$, c 0.44); MS (EI) *m/z* 291 (M^+, 1), 260 (52), 204 (11), 174 (100); ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 4.85 (dd, *J* = 5, 6 Hz, 1 H), 3.6−4.0 (m, 7 H), 3.25 (m, 1 H), 2.33−2.67 (m, 2 H), 1.28−2.0 (m, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5, 25.7, 29.3, 30.4, 43.6, 52.7, 62.6, 64.8, 67.9, 103.8, 127.6, 128.4, 128.8, 155.9. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.11; H, 8.51; N, 4.75.

(2*R*)-2-([1,3]Dioxolan-2-ylmethyl)piperidine (7). Compound **6** (3.2 g, 11.0 mmol) in methanol (150 mL) was hydrogenated in the presence of 10% Pd/C at atmospheric pressure and room temperature for 40 min. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo.* Purification by flash chromatography on silica gel (CH_2Cl_2/CH_3OH/NH_4OH 20:1:0.1) gave **7** (1.71 g, 91%) as a colorless oil: $[\alpha]^{20}_D$ +9° ($CHCl_3$, *c* 0.1); IR (neat) 3330, 2931, 1140 cm^{-1}; MS (CI) *m/z* 172 $(MH)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 5.0 (t, *J* = 5 Hz, 1 H), 3.92 (m, 4 H), 3.05 (brd, *J* = 11.5 Hz, 1 H), 2.50−2.77 (m, 3 H), 1.10−1.78 (m, 8 H); ^{13}C NMR (50 Mz, $CDCl_3$) δ 24.7, 26.0, 33.2, 40.9, 46.8, 53.2, 64.5, 64.7, 103.3. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.15; H, 9.76; N, 7.94.

Decahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine-5-carbonitrile (3). Piperidine **7** (1.62 g, 9.47 mmol) in 5% aqueous HCl (30 mL) was stirred at room temperature overnight. Then, to the above solution were added successively aminobutyraldehyde diethyl acetal (3 mL, 15 mmol) and KCN (1.8 g, 17.4 mmol) while the pH was controlled between 2 and 3 by the addition of diluted aqueous HCl. After 2 h at room temperature the mixture was basified by slow addition of a saturated $NaHCO_3$ to pH 8 and then extracted with CH_2Cl_2. The organic phase was dried and concentrated to dryness to a orange colored oil which was purified by flash chromatography (CH_2Cl_2/CH_3OH 20:1) to give **3** (1.63 g, 84%) as a colorless oil that crystallized upon standing: mp 75 °C (CH_2Cl_2); $[\alpha]^{20}_D$ +9.5° ($CHCl_3$, *c* 0.4); IR (neat) 3040, 221 0, 1210 cm^{-1}; MS (CI) *m/z* 206 $(MH)^+$, 179 $(MH - HCN)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.1 (dd, *J* = 2.1, 4.9 Hz, 1 H), 3.0 (dt, *J* = 2.5, 8.5 Hz, 1 H), 2.9 (brd, *J* = 11.5 Hz, 2 H), 2.78 (dd, *J* = 6.1, 8.5 Hz, 1 H), 2.6 (q, *J* = 8.5 Hz, 1 H), 2.2 (tt, *J* = 2.5, 10 Hz, 1 H), 1.20, 2.10 (m, 13 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3, 23.8, 25.1, 28.7, 31.5, 34.8, 49.3, 49.8, 50.4, 57.5, 79.0, 116.2. Anal. Calcd for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 70.28; H, 9.21; N, 20.52.

(+)-T-3. To a cooled (−20 °C) solution of cyano aminal **3** (410 mg, 2 mmol) in Et_2O (15 mL) was added 2 M *n*-propylmagnesium bromide in Et_2O (2.5 mL, 5 mmol). The resulted suspension was stirred at −20 °C for 90 min, and then saturated aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried and evaporated to give crude product that was purified (CH_2Cl_2−MeOH−NH_4OH 96:4:0.05) to afford (310 mg, 70%) of pure (+)-**T-3** as a colorless oil. $[\alpha]^{20}_D$ +31° ($CHCl_3$, *c* 3.1); lit.[3a] $[\alpha]^{20}_D$ +27° ($CHCl_3$, *c* 0.07) Anal. Calcd for $C_{14}H_{26}N_2$: C, 75.61; H, 11.78; N, 12.59, Found: C, 75.17; H, 11.85; N, 12.97. The first column chromatography fractions (40 mg) showed the presence of *ca.* 15% of epimeric tetraponerine (T-4) as

(16) This experiment has kindly been carried out by Prof. Daloze and Braekman at the University of Brussels.

determined by ^{13}C NMR, corresponding to a 97% de for the crude reaction mixture.

(+)-T-7. According to the same procedure, **3** (410 mg, 2 mmol) was treated with 2 M *n*-pentylmagnesium bromide to give (+)-**T-7** (305 mg, 69%) as a colorless oil: $[\alpha]^{20}_D$ +30° ($CHCl_3$, *c* 2.8); lit.[3a] $[\alpha]^{20}_D$ +30° ($CHCl_3$, *c* 0.22) Anal. Calcd for $C_{16}H_{30}N_2$: C, 76.74; H, 12.07; N, 11.18, Found: C, 76.95; H, 11.91; N, 11.46. The first chromatography fractions (32 mg) showed the presence of *ca.* 15% of epimeric tetraponerine (T-8) as determined by ^{13}C NMR, corresponding to a 97% de for the crude reaction mixture.

5-Pentyl-decahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine-5-carbonitrile (10). To a solution of LDA (prepared with 0.9 mL (6.43 mol) of diisopropylamine and 4 mL (6.4 mmol) of 1.6 M n-BuLi in hexane) in THF (6 mL) and HMPA (1.5 mL, 8.6 mmol) was added a solution of **3** (440 mg, 2.15 mmol) in THF (20 mL) at −78 °C. The resulted yellow-brown solution was stirred at −78 °C for 30 min, and then pentyl bromide (0.55 mL, 4.3 mmol) in THF (5 mL) was added. After 30 min, the reaction was quenched by saturated aqueous NH_4Cl and extracted by CH_2Cl_2. The combined extracts were dried and concentrated *in vacuo*. The crude product was purified by flash chromatography (Et_2O−hexane 5:1) to afford **10** (364 mg, 62%) as a colorless oil. $[\alpha]^{20}_D$ +61° ($CHCl_3$, *c* 1.0); IR (neat) 2954, 2305 cm^{-1}; MS (CI) *m/z* 276 (MH^+), 249, 206; ^1H NMR (200 MHz, $CDCl_3$) δ 3.1 (ddd, J = 2, 8, 8.5 Hz, 1 H), 2.90 (brd, J = 12 Hz, 1 H), 2.81 (dd, J = 6, 8 Hz, 1 H), 2.45 (q, J = 8.5 Hz, 1 H), 2.18 (tt, J = 2.5, 10 Hz, 1 H), 1.20−2.10 (m, 21 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 19.1, 22.3, 22.9, 24.0, 25.2, 29.0, 31.6, 31.7, 38.3, 40.4, 46.1, 50.6, 58.9, 61.2, 80.4, 118.7. Anal. Calcd for $C_{17}H_{29}N_3$: C, 74.13; H, 10.61; N, 15.26. Found: C, 74.08; H, 10.40; N, 15.34.

5-Propyl-decahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine-5-carbonitrile (9). Following the procedure described above for the preparation of **10**, amino nitrile **3** (220 mg, 1.07 mmol) was reacted with C_3H_7Br to give **9** as a colorless oil (183mg, 69%): $[\alpha]^{20}_D$ +38° ($CHCl_3$, *c* 0.66); MS (EI) *m/z* 248, 247 (M^+), 246, 219, 218, 179, 177; ^1H NMR (200 MHz, $CDCl_3$) δ 3.13 (dt, J = 2, 8.5 Hz, 1 H), 2.90 (brd, J = 12 Hz, 1 H), 2.83 (dd, J = 6, 8 Hz, 1 H), 2.45 (t, J = 8.5 Hz, 1 H), 2.20 (tt, J = 2.5, 10 Hz, 1 H), 1.20-2.10 (m, 17 H), 0.77 (t, J = 7 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 16.7, 19.2, 24.1, 25.3, 29.0, 31.7, 40.6 (2 carbons), 46.8, 50.7, 50.9, 61.3, 80.5, 118.8. Anal. Calcd for $C_{15}H_{25}N_3$: C, 72.83; H, 10.19; N, 16.99. Found: C, 72.59; H, 10.24; N, 17.15.

Tetraponerine-8 (T-8). To 30 mL of liquid ammonia was added sodium metal (140 mg, 6.1 mmol) at −78 °C. After 30 min, a deep blue colored solution was obtained to which was added a solution of **10** (194 mg, 0.71 mmol) in THF at −78 °C. After stirring for 20 min, the reaction was quenched by the addition of methanol (1 mL), the mixture was then warmed to room temperature to evaporate excess of ammonia. After addition of saturated aqueous NH_4Cl and extraction with CH_2Cl_2, the combined extracts were dried and concentrated to give crude product. After flash chromatography (hexane−acetone 4:1 saturated by NH_4OH), (+)-tetraponerine-8 (171 mg, 97%) was obtained as a white solid: mp 40 °C (hexane−acetone); $[\alpha]^{20}_D$ +99° ($CHCl_3$, *c* 0.6), lit.[1b] $[\alpha]^{20}_D$ +102° ($CHCl_3$, *c* 0.15). Anal. Calcd for $C_{16}H_{30}N_2$: C, 76.74; H, 12.07; 11.19. Found: C, 76.40; H, 12.12; N, 11.08.

Tetraponerine-4 (T-4). According to the same procedure described above for (+)-tetraponerine-8, amino nitrile **9** (140 mg) produced (+)-**T-4** (120 mg, 95% yield) as a colorless oil: $[\alpha]^{20}_D$ +105° ($CHCl_3$, *c* 0 3), lit.[3a] $[\alpha]^{20}_D$ +94° ($CHCl_3$, *c* 0 2). Anal. Calcd for $C_{14}H_{26}N_2$: C, 75.62; H, 11.78; N, 12.60. Found: C, 75.60; H, 11.58; N, 12.52.

5-(2,2-Diethoxyethyl)-3-phenyl-hexahydro-pyrrolo[2,1-*b*]oxazole-5-carbonitrile (12). To a stirred solution of LDA [prepared from 4 mL (28.5 mmol) of diisopropylamine and 17.8 mL (28.4 mmol) of 1.6 M n-BuLi in hexane] in THF (30 mL) and HMPA (7.9 mL, 45.1 mmol) was added dropwise a solution of **11** (2 g, 9.3 mmol) in THF (10 mL) at −78 °C. After 30 min, a solution of bromoacetaldehyde diethyl acetal (2.8 mL, 18.7 mmol) in THF (2.5 mL) was added. After stirring for 4 h at −78 °C, the mixture was quenched by saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were combined, dried, and concentrated *in vacuo*. The crude oil was then purified by flash chromatography (heptane/EtOAc 7:3) to afford **12** (2.7 g, 86%) as a colorless oil and a 7:3 mixture of diastereoisomers. They can be separated to furnish analytical sample of each epimer.

Major compound (less polar): $[\alpha]^{20}_D$ −147° ($CHCl_3$, *c* 2.38); IR (neat) 2988, 2880, 2224, 1131 cm^{-1}; MS (CI) *m/z* 331 (MH^+); ^1H NMR (250 MHz, $CDCl_3$) δ 7.0−7.5 (m, 5 H), 5.06 (dd, J = 2.5, 6 Hz, 1 H), 4.69 (t, J = 8 Hz, 1 H), 4.65 (dd, J = 4, 7 Hz, 1 H), 4.54 (t, J = 7 Hz, 1 H), 3.3−3.6 (m, 4 H), 3.62 (dd, J = 7, 8 Hz, 1 H), 1.8−2.6 (m, 6 H), 1.14 (t, J = 7 Hz, 3 H), 1.11 (t, J = 7 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 15.2, 15.3, 29.2, 38.4, 42.8, 61.3, 62.1, 62.7, 63.9, 75.8, 97.9, 99.8, 120.6, 126.3, 127.5; 128.8, 141.7. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.47. Found: C, 68.75; H, 7.67; N, 8.19.

Minor compound (more polar): ^1H NMR (250 MHz, $CDCl_3$) δ 7.0−7.5 (m, 5 H), 5.05 (d, J = 4.6 Hz, 1 H), 4.71 (dd, J = 3.5, 7.4 Hz, 1 H), 4.50 (t, J = 7.5 Hz, 1 H), 4.29 (t, J = 7.5, 8.2 Hz, 1 H), 3.4−3.8 (m with t, J = 8.2 Hz at 3.54, 5 H), 2−2.5 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), 1.16 (t, J = 7 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 15.0 (2 carbons), 29.4, 36.2, 38.2, 61.3, 61.9, 62.5, 63.6, 74.3, 97.6, 101.0, 121.6, 126.3, 127.5; 128.8, 141.2; HRMS (CI) calcd for $C_{19}H_{25}N_2O_3 + H^+$: 331.2022; found 331.2028.

2-[2-(2,2-Diethoxyethyl)pyrrolidin-1-yl]-2-phenylethanol (13). Following the procedure described above for preparation of **6**, amino nitrile **12** (2.65 g, 8 mmol, as a mixture of diastereomers) afforded **13** (2.4 g, 100%) as a colorless oil which can be purified by flash chromatography ($CH_2Cl_2/CH_3OH/NH_4OH$ 20:1:0.1), but was pure enough for the next step: $[\alpha]^{20}_D$ +7° ($CHCl_3$, *c* 1.67); IR (neat) 3394, 2988, 2880, 1131 cm^{-1}; MS (CI) *m/z* 308 (MH^+); ^1H NMR (250 MHz, $CDCl_3$) δ 7.0−7.5 (m, 5 H), 4.37 (dd, J = 4.2, 6.8 Hz, 1 H), 3.96 (dd, J = 9.0, 12.4Hz, 1 H), 3.8 (m, 2 H), 3.3−3.6 (m, 4 H), 3.08 (m, 3 H), 2.8 (m, 1 H), 1.4−1.8 (m, 6 H), 1.11 (t, J = 7 Hz, 3 H), 1.08 (t, J = 7 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 15.3, 23.1, 30.6, 38.4, 52.3, 56.8, 60.7, 61.3, 63.4, 68.2, 101.4, 127.7, 128.3, 128.8, 138.9. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.50; N, 4.55. Found: C, 70.14; H, 9.31; N, 4.52.

(2*R*)-2-(2,2-Diethoxyethyl)pyrrolidine (14). Following the procedure described for **7**, compound **13** (2.4 g, 7.81 mmol) was hydrogenated to give **14** (1.41 g, 97%) as a colorless oil: $[\alpha]^{20}_D$ +2° ($CHCl_3$, *c* 4.07); IR (neat) 3387, 2975, 1131 cm^{-1}; MS (CI) *m/z* 188 (MH^+); ^1H NMR (250 MHz, $CDCl_3$) δ 4.65 (t, J = 4.6 Hz, 1 H), 3.67 (dq, J = 7.0, 9.3 Hz, 2 H), 3.52 (dq, J = 7.0, 9.1 Hz, 2 H), 3.35 (m, 1 H), 3.1 (m, 1 H), 3.02 (ddd, J = 6.1, 8.4, 10.8 Hz, 1 H), 1.8−2 (m, 6 H), 1.45 (m, 1 H), 1.21 (t, J = 7 Hz, 6 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 15.3 (2 carbons), 24.2, 31.4, 38.2, 45.4, 55.9, 61.6, 61.7, 101.3; HRMS (CI) calcd for $C_{10}H_{21}NO_2 + H^+$ 188.1650; found: 188.1652.

Decahydro-5*H*-dipyrrolo[1,2-*a*:1′,2′-*c*]pyrimidine-5-carbonitrile (2). Following the procedure outlined for compound **3**, pyrrolidine **14** (1.18 g, 6.32 mmol) was reacted with aminobutyraldehyde diethyl acetal (2 mL, 10.1 mmol) and KCN (784 mg, 11.56 mmol) to provide **2** (688 mg, 57%) as a colorless oil: $[\alpha]^{20}_D$ +41° ($CHCl_3$, *c* 0.75); IR (neat) 3409, 2966, 2804, 2221, 1390 cm^{-1}; MS (CI) *m/z* 192 (MH^+); ^1H NMR (250 MHz, $CDCl_3$) δ 4.14 (dd, J = 2.0, 4.9 Hz, 1 H), 3.04 (dt, J = 3.0, 8.5 Hz, 1 H), 3.02 (dt, J = 3.0, 8.5 Hz, 1 H), 2.92 (dd, J = 6.0, 8.3 Hz, 1 H), 2.64 (q, J = 8.5 Hz, 1 H), 2.3 (m,1 H), 2.2 (q, J = 8.7 Hz, 1 H), 2.1−2.2 (m, 10 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 19.8, 20.9, 28.5, 29.2, 32.2, 48.5, 48.8, 49.2, 59.8, 78.7, 116.4. Anal. Calcd for $C_{11}H_{17}N_3$: C, 69.07; H, 8.95; N, 21.96. Found: C, 68.77; H, 8.71; N, 21.68.

5-Propyl-decahydro-5*H*-dipyrrolo[1,2-*a*:1′,2′-*c*]pyrimidine-5-carbonitrile (16). To a solution of LDA [prepared with 0.3 mL (2.19 mmol) of diisopropylamine and 1.36 mL (2.18 mmol) of 1.6 M n-BuLi in hexane] in THF (2 mL) and HMPA (0.51 mL, 2.92 mmol) was added a solution of **2** (140 mg, 0,73 mmol) in THF (3.5 mL) at −78 °C. The resulted brown solution was stirred at −78 °C for 30 min, and then *n*-propyl bromide (0.33 mL, 1.46 mmol) in THF (1.7 mL) was added. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted by CH_2Cl_2. The combined extracts were dried and concentrated *in*

vacuo. The crude product was purified by flash chromatography (EtOAc/heptane 8:2) to give **16** (78 mg, 46%) as a colorless oil: IR (neat) 3409, 2964, 2818, 2214, 1390 cm^{-1}; MS (CI) *m/z* 234 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 3.12 (dt, J = 2.7, 8.5 Hz, 1 H), 3.04 (dt, J = 2.5, 8.5 Hz, 1 H), 2.88 (dd, J = 5.8, 6.8 Hz, 1 H), 2.48 (q, J = 8.5 Hz, 1 H), 2.3 (m, 1 H), 2.22 (q, J = 8.5 Hz, 1 H), 1.2−2.1 (m, 14 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.1, 16.6, 19.4, 21.1, 28.7, 29.4, 37.7, 40.5, 45.4, 48.8, 60.7, 79.5, 118.5; HRMS (CI) calcd for $C_{14}H_{23}N_3 + H^+$ 234.1970; found: 234.1979.

5-Pentyl-decahydro-5*H*-dipyrrolo[1,2-*a*:1′,2′-*c*]pyrimidine-5-carbonitrile (17). According to the same procedure, amino nitrile **2** (140 mg, 0.73 mmol) reacted with *n*-pentyl bromide to give **17** as a colorless oil (109 mg, 57%): IR (neat) 3409, 2964, 2818, 2214, 1390 cm^{-1}; MS (CI) *m/z* 262 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 3.10 (dt, J = 2.3, 8.5 Hz, 1 H), 3.04 (dt, J = 2.6, 8.5 Hz, 1 H), 2.88 (dd, J = 5.8, 9.2 Hz, 1 H), 2.47 (q, J = 8.5 Hz, 1 H), 2.31 (m, 1 H), 2.20 (q, J = 8.5 Hz, 1 H), 1.3−2.1 (m, 18 H), 0.89 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 13.8, 19.5, 21.1, 22.4, 22.9, 28.8, 29.3, 31.7, 37.8, 38.3, 45.4, 48.9, 60.8, 79.6, 118.7; HRMS (CI) calcd for $C_{16}H_{27}N_3 + H^+$ 262.2283; found: 262.2281.

(+)-Tetraponerine-2 (T-2). According to the procedure described for the preparation of **T-8**, tetraponerine (+)-**T-2**(65 mg) was obtained as a colorless oil in 92% yield: $[\alpha]^{20}_D$ +36° ($CHCl_3$, *c* 1.79); IR (neat) 3368, 2956, 2868, 1375 cm^{-1}; MS (EI) *m/z* 208 ($M^{\bullet+}$, 50), 207 (100), 179 (47); ^1H NMR (250 MHz, $CDCl_3$) δ 3.14 (dt, J = 3.2, 8.5 Hz, 1 H), 3.03 (dt, J = 2.8, 8.5 Hz, 1 H), 2.76 (t, J = 6.0 Hz, 1 H), 2.29 (m, 2 H), 2.11 (q, J = 8.5 Hz, 1 H), 2 (m, 1 H), 1.2−1.9 (m, 14 H), 0.91 (t, J = 5.9 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.5, 18.8, 20.2, 21.1, 28.7, 29.9, 33.7, 36.3, 47.2, 48.8, 60.3, 63.9, 83.6; HRMS (EI) calcd for $C_{13}H_{24}N_2$ 208.1940; found: 208.1930.

(+)-Tetraponerine-6 (T-6). (+)-**T-6** was obtained in an identical fashion with a yield of 75%: $[\alpha]^{20}_D$ +35° ($CHCl_3$, *c* 0.31); lit. $[\alpha]^{20}_D$ +35° ($CHCl_3$, *c* 0.15); IR (neat) 3368, 2956, 2868, 1375 cm^{-1}; MS (CI) *m/z* 236 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 3.13 (dt, J = 3.1, 8.5 Hz, 1 H), 3 (dt, J = 2.5, 8.5 Hz, 1 H), 2.58 (t, J = 6.5 Hz, 1 H), 2.19 (m, 2 H), 2.06 (q, J = 8.5 Hz, 1 H), 1.95 (m, 1 H), 1.2−1.9 (m, 18 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.2, 20.2, 21.2, 22.8, 25.3, 28.9, 29.9, 32.4, 33.9, 34.0, 47.7, 49.1, 60.7, 64.2, 83.8. Anal. Calcd for $C_{15}H_{28}N_2$: C, 76.21; H, 11.94; N, 11.85; found: C, 75.91; H, 11.51; N, 11.11.

(+)-Tetraponerine-1 (T-1). According to the procedure described for **T-3**, cyanoaminal **2** (300 mg, 1.57 mmol) was reacted with *n*-propylmagnesium bromide to afford (+)-**T-1** (167 mg, 51%) as a colorless oil: $[\alpha]^{20}_D$ +11° ($CHCl_3$, *c* 0.14); IR (neat) 3400, 2950, 2881, 1375 cm^{-1}; MS (CI) *m/z* 209 $(MH)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 3.39 (brd J = 4.5 Hz, 1 H), 3.09 (q, J = 7.4 Hz, 1 H), 2.96 (m, 2 H), 2.81 (dd, J = 4.9, 6.7 Hz, 1 H), 2.06 (m, 1 H), 1.25−1.95 (m, 15 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.2, 20.1, 20.5, 21.2, 29.4, 29.6, 30.9, 33.9, 49.9, 50.2, 53.5, 58.3, 76.8; HRMS (CI) calcd for $C_{13}H_{24}N_2 + H^+$ 209.2018; found: 209.2028.

(+)-Tetraponerine-5 (T-5). According to the procedure described for **T-3**, cyano aminal **2** (140 mg,0.73 mmol) was treated with *n*-pentylmagnesium bromide to give (+)-**T-5** (107 mg, 62%) as a colorless oil: $[\alpha]^{20}_D$ +10° ($CHCl_3$, *c* 0.24); lit. $[\alpha]^{20}_D$ +10° ($CHCl_3$, *c* 0.2); IR (neat) 3400, 2950, 2881, 1375 cm^{-1}; MS (EI) *m/z* 236 ($M^{\bullet+}$,87), 179 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 3.39 (brd, J = 3.3 Hz, 1 H), 3.08 (q, J = 8.0 Hz, 1 H), 2.97 (dt, J = 2.4, 8.7 Hz, 1 H), 2.90 (q, J = 7.2 Hz, 1 H), 2.82 (m, 1 H), 2.18 (m, 1 H), 2.05 (m, 1 H), 1.2−2 (m, 18 H), 0.95 (t, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.2, 20.2, 21.3, 22.8, 27.2, 29.4, 29.7, 30.9, 31.6, 32.1, 50.0, 50.3, 53.9, 58.3, 76.8. Anal. Calcd for $C_{15}H_{28}N_2$: C, 76.21; H, 11.94; N, 11.85. Found: C, 75.84; H, 11.43; N, 11.09.

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