Natural Tetraponerines: A General Synthesis and Antiproliferative Activity

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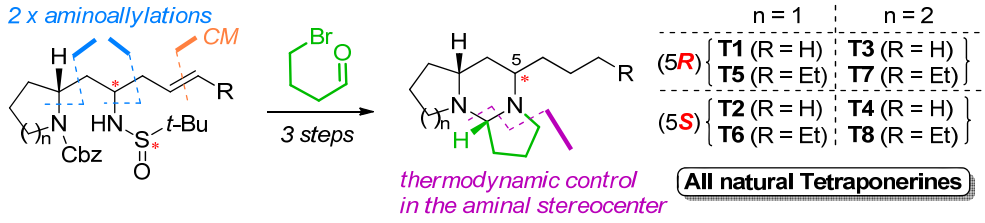


ABSTRACT: A stereocontrolled general methodology to access all natural tetraponerines from (+)−**T1** to (+)−**T8** is detailed. Two consecutive indium-mediated aminoallylations with the appropriate enantiomer of chiral *N*-*tert*-butylsulfinamide and a thermodynamic control at the aminal stereocenter, allow the formation of each natural tetraponerine with excellent stereoselectivity. The use of 4-bromobutanal in the first aminoallylation leads to the formation of 5-6-5 tetraponerines whilst 5-bromopentanal is required to build the scaffold of 6-6-5 tetraponerines. A cross-metathesis reaction of the second aminoallylation product with *cis*-3-hexene is used to elongate the side chain up to 5 carbons so as to prepare the tetraponerines **T5** to **T8**. The anticancer activity of these heavier tetraponerines against four different carcinoma human cell lines is examined, observing a promising cytotoxic activity of (+)−**T7** against breast carcinoma cell line MCF-7.

INTRODUCTION

Azaheterocycles with nitrogen atoms at the junction of two rings constitute a large group of natural alkaloids that commonly exhibit a quinolizidine or an indolizidine framework and display a wide range of biological activities.[1] The complexity of these compounds is further increased by the stereochemistry of the pyramidal nitrogen at the ring junction, with important consequences in their bioactivities.[2] Tetraponerine alkaloids form a unique family of such compounds which share a quinolizidine or an indolizidine fragment with another indolizidine framework. These tricyclic alkaloids, named tetraponerines **T1** to **T8**, possess a very uncommon aminal structure in alkaloids[3] and can be divided in two groups depending on the size of the rings: 5-6-5 or 6-6-5. In each group, the tetraponerines differ in the length of the alkyl chain located in C_5 (propyl or pentyl) and in the configuration of this stereocenter (Figure 1).

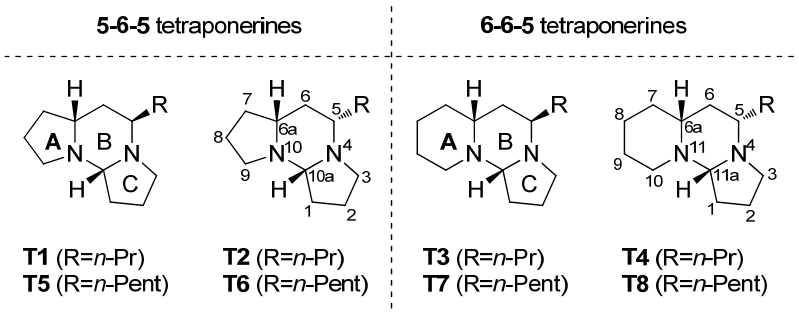


Figure 1. Structures of natural tetraponerines.

Tetraponerines are secreted by *Pseudomyrmecine* ants of the genus *Tetraponera*, for which more than 80 species can be found in Asia, Africa or Australia; being **T8** the major tetraponerine isolated from the New Guinean ant *Tetraponera*, whilst **T1** and **T2** are very minor naturally occurring products. It was early recognized that tetraponerines are paralyzing venoms segregated by the host ants against their enemies. Not surprisingly, it was found that they exhibit important insecticidal and neurotoxic

biological activities.[4] Recent studies categorize them as efficient inhibitors of a range of nAChRs (nicotinic acetylcholine receptors).[5] However, despite their interesting biological profile, the actual mechanisms of interaction with their corresponding receptors are still unknown. More recently, cytotoxic activities have also been described for these natural products as well as for some synthetic analogs containing long hydrocarbon chains at C_5 position.[6]

In 1987 Braekman and co-workers reported the first isolation and structural elucidation of these natural products.[4] The structure of **T8** was unequivocally assigned by X-ray diffraction analysis,[4] whilst the structures of the other natural tetraponerines were proposed by comparison of their spectroscopical data, in particular one-dimensional ^{1}H- and ^{13}C-NMR spectra, with those of **T8**.[7] However, structures of **T3**, **T5**, **T6** and **T7** were mistakenly described at first and corrected then by further studies involving nuclear magnetic resonance and circular dicroism.[8] More recently, the combined use of infrared spectroscopy (IR) and mass spectrometry (MS) have also been described to easily identify each tetraponerine from its natural source.[9] In this study it was observed that tetraponerines with 5-(*S*) configuration show more intense Bohlmann bands in the infrared spectra at lower vibrational frequencies than the 5-(*R*) isomers.

The origin of natural tetraponerines has been studied by the Braekman's group with **T6**[10] and **T8**[11] and different biosynthetic routes were proposed depending on the A ring size. Importantly, upon studies of its biochemical pathway, **T8** was submitted to catalytic hydrogenation under acidic conditions and the N_{11}-C_{11a} bond was selectively cleaved, suggesting that the aminal core is in equilibrium with the corresponding iminium ion.

The first enantioselective synthesis of (+)-**T8** was achieved in 1990, providing a firm evidence of the absolute configuration of this natural alkaloid.[12] The singular tricyclic

skeleton of these alkaloids which holds an aminal moiety along with their interesting biological activities have made the tetraponerines very attractive targets for total synthesis.[13] The group of Royer applied its CN (*R*,*S*) strategy[14] to the synthesis of all natural tetraponerines known, being the only general method reported to prepare this entire family of alkaloids up to date.[15]

Aware of the lack of detailed structural information of tetraponerines we have recently examined the conformational and configurational space of **T3** and **T4**. [16] For this study we fixed the known configurations at C_{6a} (*R*) and at C_5 [(*R*)-for **T3** and (*S*)- for **T4**] and considered all possible configurations at nitrogen atoms (N_4 and N_{11}) as well as at the aminal carbon center (C_{11a}). The geometry of the resulting twelve configurational isomers (for each tetraponerine) was optimized by DFT calculations and their populations were estimated from the calculated energies. The first conclusion from these calculations is that for both **T3** and **T4**, at least 99% of the population is represented by either its *ttc*- or *ttt*- isomer (Figure 2).[17] A closer examination of these two configurational isomers shows that, despite the different fusions at the indolizidine frameworks, the same (*S*)-configuration at the aminal carbon center is observed. Remarkably, this configuration at C_{11a} is observed not only for natural **T3** and **T4**, but also for all the other natural tetraponerines. On the other hand, tetraponerine **T3** slightly prefers a *cis*-configuration at ring C (65% of *ttc*-**T3**) while **T4** is clearly dominated by a *trans*-configuration at the indolizidine framework (95% of *ttt*-**T4**). Importantly, low activation barriers were found for inversion of **T3** and **T4** at N_4, which allows a fast equilibration between the two most populated isomers (*ttc* and *ttt*). Interestingly, tetraponerine analogues with a 5-5-6 tricyclic skeleton have recently been prepared in racemic form.[18] The relative stereochemistry of these latter analogues was assigned as *cis* (fusion A/B)-*transoid-trans* (fusion B/C), according to NOE correlations.

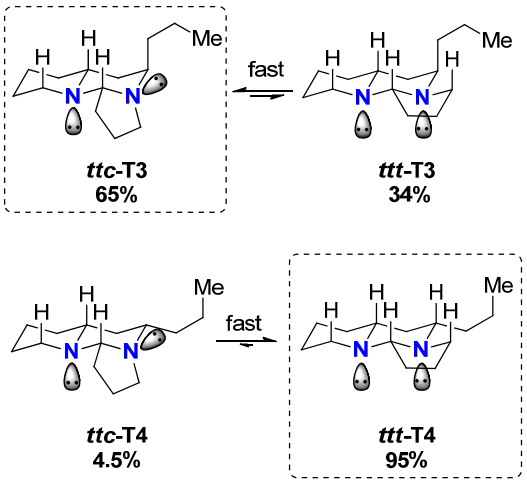


Figure 2. Main configurational isomers previously found by DFT calculations of **T3** and **T4**.[16]

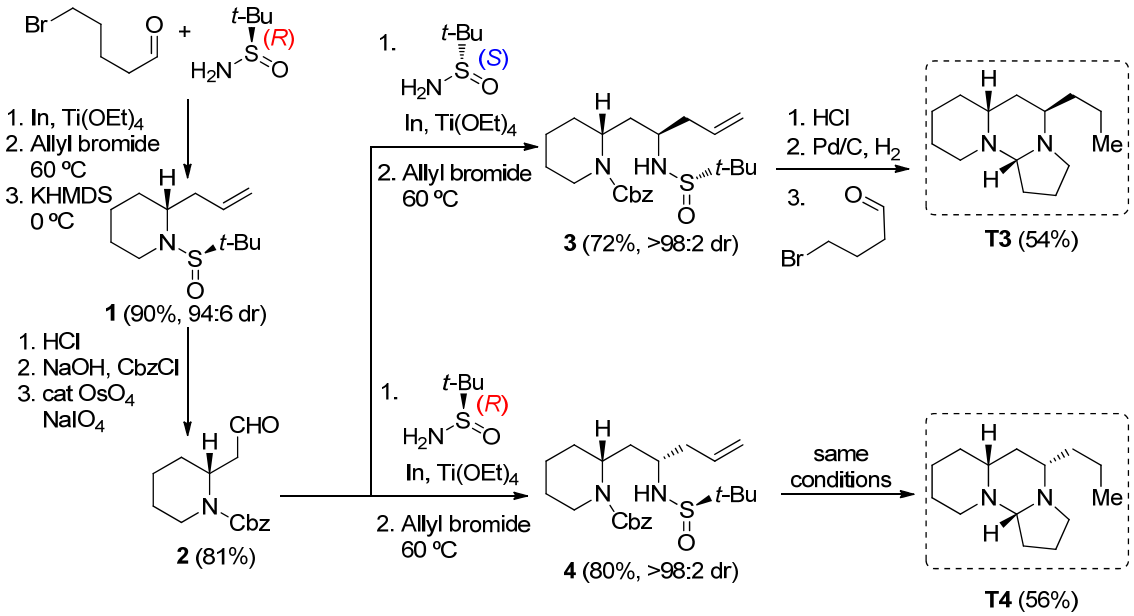
In the present work we describe a detailed account of our stereoselective total synthesis of all known tetraponerines, from (+)-**T1** to (+)-**T8**. We also provide the anticancer activity of C_5-pentyl tetraponerines (**T5** to **T8**) against four human cell lines.

RESULTS AND DISCUSSION

In a previous work,[16] we described the total synthesis of natural tetraponerines **T3** and **T4** using a divergent approach from simple starting materials: 4-bromobutanal, 5-bromopentanal, allylbromide and both enantiomeric forms of *N*-*tert*-butylsulfinamide.[19] As depicted in Scheme 1, the synthesis started with a 2-allylpiperidine derivative, which was prepared by aminoallylation of 5-bromopentanal with (*R*)-*tert*-butylsulfinamide and *in situ* generated allylindium reagent, followed by intramolecular *N*-alkylation.[20] Oxidative cleavage of the double bond gave rise to the corresponding aldehyde **2**, which was submitted to a second aminoallylation where the configuration at the new stereogenic center in products **3** and **4** was mainly controlled by the chiral sulfinyl group regardless the chirality of the aldehyde.[21] This issue was crucial to prepare the

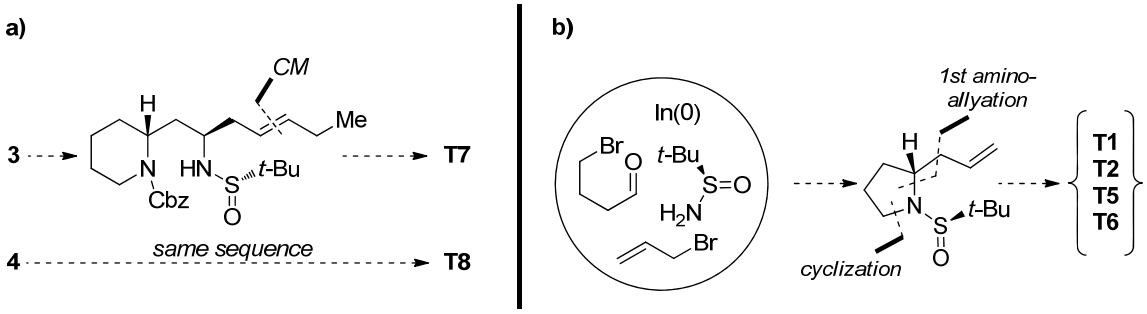
required diamines from the same chiral aldehyde, using the appropriate enantiomer of chiral *tert*-butylsulfinamide. Acidic deprotection of the homoallylic diamines, followed by hydrogenation of the allyl moiety with concomitant hydrogenolysis of the carbamate afforded the corresponding free diamines. Without purification, these intermediates were put into react with 4-bromobutanal to initiate a cascade of reactions where the aminal formation is presumably followed by intramolecular alkylation of N_4.[22] This route allowed the preparation in good overall yields of enantiomerically pure tetraponerines (+)−**T3** and (+)−**T4** with identical spectral and physical data to the one reported in the literature for the natural compounds.[8] Importantly, the aminal formation with the right stereochemistry at C_{11a} for both compounds clearly supports the hypothesis of a thermodynamic control to afford the most stable aminal possible through equilibration with an iminium form. This idea was essential in our synthetic plan and comes from the following observations: a) all natural tetraponerines are proposed to exhibit the same configuration at the aminal carbon center, regardless the configuration at C_5; b) during the biosynthetic studies of **T8**, the C_{11a}-N_{11} bond was selectively cleaved under hydrogenation conditions.[11] Moreover, our stereochemical analysis of tetraponerines **T3** and **T4** by DFT calculations indicated that both tetraponerines are mainly populated (> 99%) by configurational isomers (*ttt* and *ttc*) with (*S*)- configuration at C_{11a}.

Scheme 1. Synthesis of Tetraponerines (+)−T3 and (+)−T4



Prompted by these results we decided to implement the appropriate modifications to use the same general strategy in the synthesis of all known natural tetraponerines. As depicted in Scheme 2a, we recognized that the allyl group in the intermediates **3** and **4** provides a handle to enlarge the hydrocarbonated side-chain up to 5 carbon atoms by cross-metathesis with an appropriate partner. Therefore, tetraponerine **T7** could be obtained from intermediate **3** and following the same route, compound **4** could be carried forward to the synthesis of **T8**. The rest of natural tetraponerines (**T1**, **T2**, **T5** and **T6**) have a 5-membered ring A. Accordingly, we decided to use 4-bromobutanal in our aminoallylation-cyclization sequence to prepare the key 2-allylpyrrolidine intermediate that could be submitted to the same reaction sequence followed for the synthesis of 6-6-5 tetraponerines (Scheme 2b).

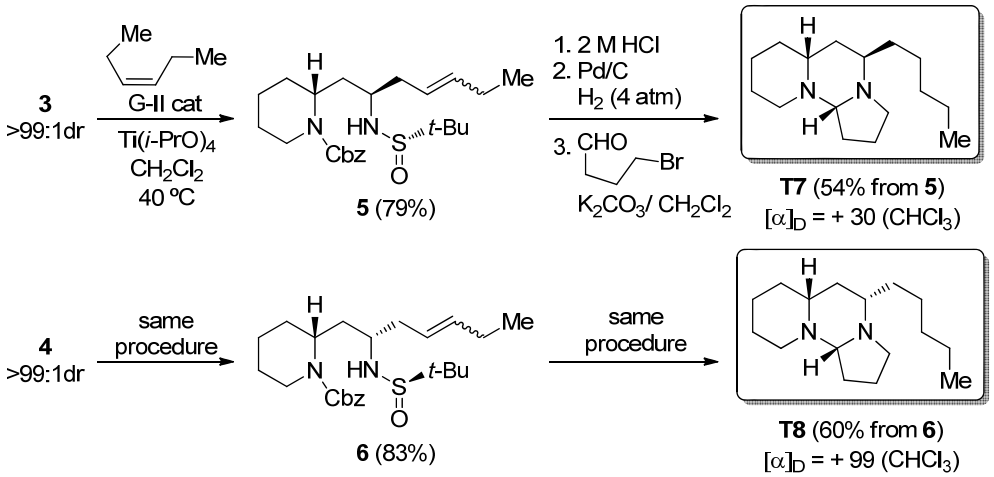
Scheme 2. **Modifications for the Synthesis of the other Tetraponerines**



*Synthesis of tetraponerines **(+)−T7** and **(+)−T8**.*

Cross-metathesis is a very useful synthetic tool in the preparation of bioactive compounds from alkene intermediates. In this context, we [23] and others [24] have demonstrated that sulfinamines are tolerated by Grubbs 2nd generation catalyst particularly when Ti(O*i*-Pr)$_4$ is used as additive to accelerate the reaction. With these precedents we decided to use *cis*-3-hexene as cross metathesis partner[25] to elongate the side-chain up to 5 carbons of intermediates **3** and **4**, *in route* to the preparation of **T7** and **T8**, respectively. We were pleased to observe that the reaction took place smoothly in CH_2Cl_2 at 40 ºC with both protected diamines, obtaining the expected compounds in good yields (Scheme 3).[26] After this single modification, the reaction sequence proceed as for compounds **T3** and **T4**, obtaining good overall yields and excellent diasteroselectivities (>99:1 dr by GC) for both tetraponerines **T7** and **T8**. NMR spectra were compared with the data of **T3** and **T4**, finding the same signal pattern distinctive of these 6-6-5 skeletons. More importantly, the physical and spectral data of the synthesized (+)−**T7** and (+)−**T8** were in full agreement with reported values for these naturally occurring compounds.[13b and 13c]

Scheme 3. Synthesis of (+)−T7 and (+)−T8

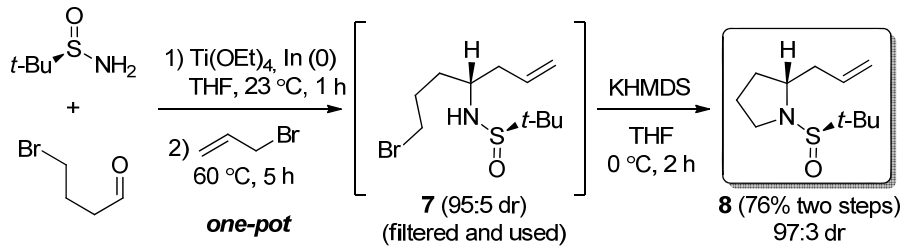


Synthesis of tetraponerines ***(+)−T1, (+)−T2, (+)−T5*** *and* ***(+)−T6.***

Our next goal was to extend this methodology to the synthesis of the remaining natural 5-6-5-tetraponerines (**T1**, **T2**, **T5** and **T6**) which differ from the others in the size of ring A. It is worth saying that this extension is not straightforward and our DFT configurational analysis was only performed for tetraponerines **T3** and **T4**, with a 6-6-5 pattern. The subgroup of tetraponerines with two indolizidine moieties fused in the core has a more flexible scaffold and the contribution of several configurational isomers could complicate the stereochemical landscape of these compounds. This issue has been so far overlooked in the literature.

Our synthesis began with the indium-mediated aminoallylation of 4-bromobutanal with (R_S)-*tert*-butylsulfinamide, followed by cyclization with KHMDS at 0 ºC. The corresponding 2-allylpyrrolidine **8** was obtained in good diastereoselectivity and good overall yield after only one purification step (Scheme 4).

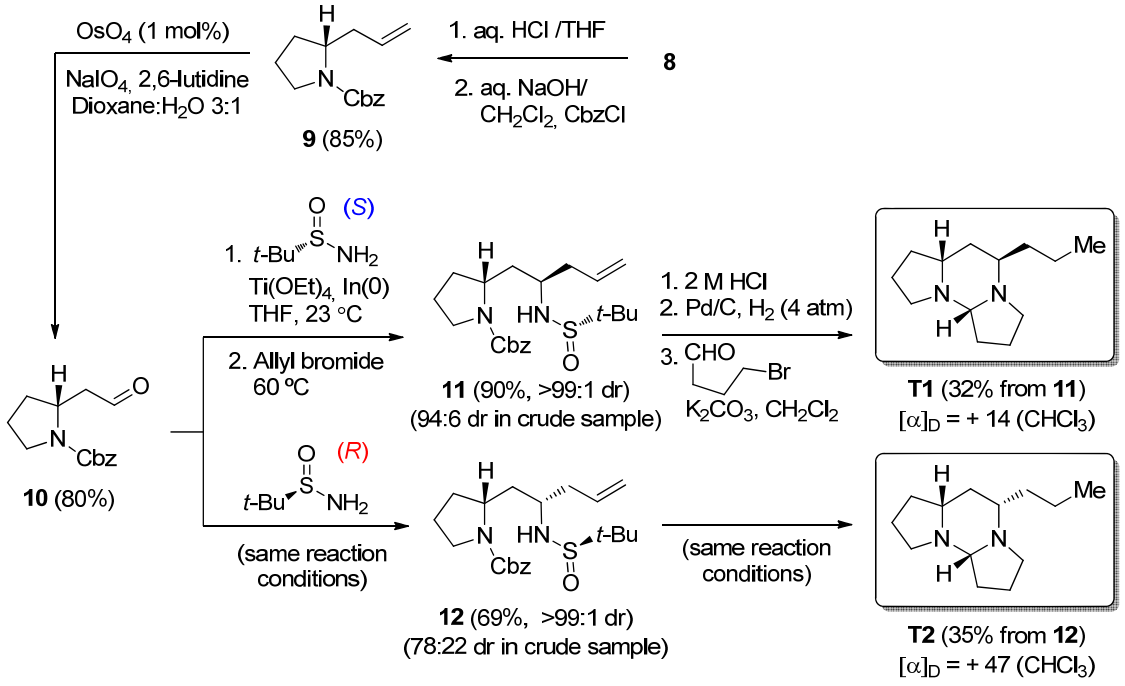
Scheme 4. Synthesis of 2-Allylpyrrolidine Intermediate 8



Compound **8** was a common intermediate in the synthesis of all 5-6-5 tetraponerines. Eventually, the nitrogen protecting group was exchange in a one-pot procedure by Cbz to accomplish the oxidative cleavage of the terminal double bond under modified Johnson-Lemieux conditions (Scheme 5). The obtained aldehyde **10** was submitted to a second aminoallylation reaction with (*R*)- or (*S*)-*N*-*tert*-butylsulfinamides. Gratifyingly, as occurred in the case of the 6-6-5-tetraponerines, the stereocontrol exerted by the sulfinyl group overcomes the influences of the chiral aldehyde moiety. Consequently, protected diamines **11** and **12** could be obtained in good isolated yields and excellent diastereoselectivities after column chromatography (>99:1 dr by HPLC). In this case the match-mismatched effect was stronger than with piperidine-derivative substrates, achieving a 90% yield of diasteromerically pure **11** after purification (94:6 dr before chromatography) and a 69% yield of **12** isolated as a single isomer after purification (only 78:22 dr before chromatography). Contrary to what was observed for the piperidine aldehyde **2**, in this case the matched product was obtained when (*S*)-*N*-*tert*-butylsulfinamide was used. Importantly, we were able to confirm the absolute configuration of diamine derivative **12** by single crystal X-ray analysis[27] and it was found to be consistent with the stereochemistry predicted by our working model for the aminoallylation step.[20] Finally, the syntheses of (+)−**T1** and (+)−**T2** were completed after acidic deprotection, catalytic hydrogenation and reaction of both free diamines with 4-bromobutanal. The GC-MS data obtained shows essentially one peak with a fragmentation pattern that perfectly matched with the one reported for **T1** and **T2**.[9]

Moreover, the ^{1}H and ^{13}C-NMR of the obtained **T2** also shows a good correlation with the data described in the literature.[15] However, the NMR spectral data obtained for **T1** shows more signals that the ones described in the literature for this tetraponerine (a very minor component in the natural source).[28] Contrary to what has been observed for the other tetraponerines prepared, this *worst NMR correlation* could be explained if different isomers of **T1** with different configurations at C_{11a} are under equilibrium.

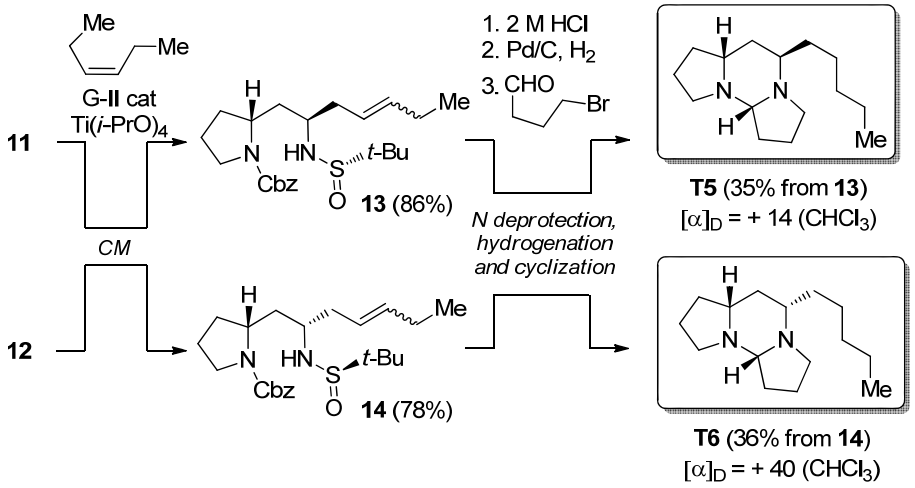
Scheme 5. Synthesis of Tetraponerines (+)−T1 and (+)−T2



Finally, tetraponerines **T5** and **T6** were prepared by including in the reaction sequence the cross-metathesis step of diamine derivatives **11** of **12**, respectively, with *cis*-3-hexene (Scheme 6). After acidic treatment and catalytic hydrogenation, the obtained free diamines were treated, as in other cases, with 4-bromobutanal to obtain the corresponding tetraponerines in moderate overall yields. Once again, the GC-MS of compounds **T5** and **T6**,[9] as well as the NMR data for **T6**,[13b and 29] were in good agreement with the literature. However, the NMR data obtained for compound **T5** showed more signals than the previously reported[30]. Since the same disagreement was

found for **T1** we hypothesized that these 5-6-5 tetraponerines with (*S*)-configuration at C_5 are actually a mixture of different aminal isomers in equilibrium with comparable energies. However, this hypothesis was not further confirmed.

Scheme 6. Synthesis of Tetraponerines (+)−T5 and (+)−T6



The Bolhmann Bands in IR Spectra of Tetraponerines.

A brief comment is in order here related to the use of the Bohlmann bands to assign the configuration at C_5 of tetraponerines.[31] The relevant region of the IR spectra obtained for the synthesized tetraponerines are shown in Figure 3. The presence of bands for C-H stretching at relatively low vibrational frequencies (2780-2810 cm^{-1}) can be observed for the IR spectra obtained for the synthesized tetraponerines. The origin of these so called Bohlmann bands is not accurately known but has been related to the lengthening of $C\text{-}H_{axial}$ bonds due to the hyperconjugation of the adjacent nitrogen lone pair with the antiperiplanar antibonding C-H orbitals (n → σ* C-H).[32]

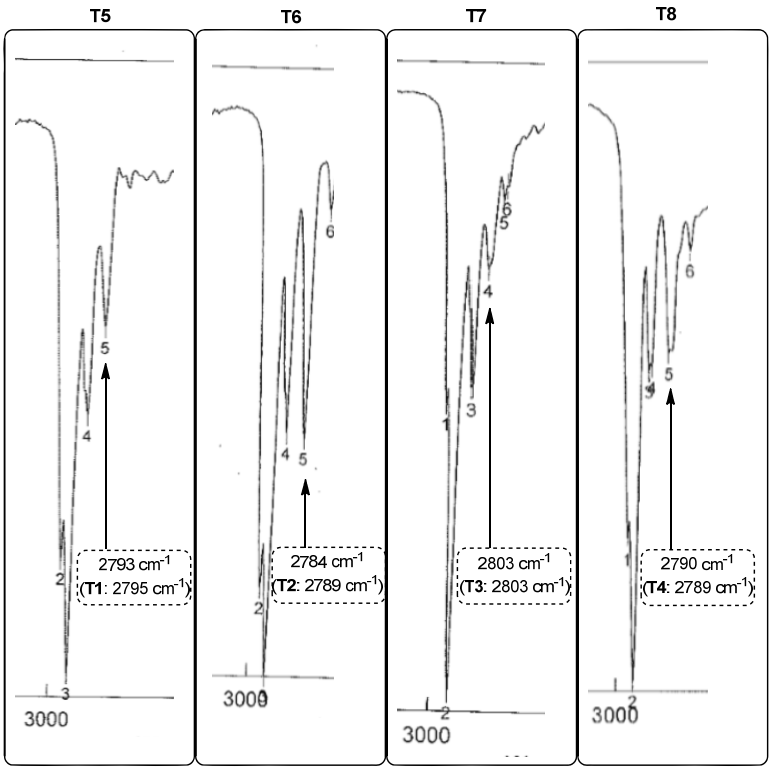


Figure 3. Bohlmann bands in the IR spectra of tetraponerines.

As reported,[9] the even-numbered tetraponerines (**T2**, **T4**, **T6** and **T8**) with (*S*)-configuration at C_5 show a more severe deviation on this C-H bands which appear at lower vibrational frequencies and more intense, compare to the odd-numbered tetraponerines (**T1**, **T3**, **T5** and **T7**). It is reasonable to consider that the configurational analyses performed for **T3** and **T4** by DFT calculations[16] can be extrapolated to **T7** and **T8**. Consequently, the even-numbered tetraponerines (**T4** and **T8**) must be mainly populated by a *ttt*-isomer while the *ttc* is the major isomer for **T3** and **T7**. As depicted in Figure 2, *ttt*-**T4** and *ttt*-**T8** exhibit two nitrogen atoms with electron pairs antiperiplanar to 5 C-H bonds, whereas *ttc*-isomers exhibit only one N−lone pair antiperiplanar to 3 C−H bonds. Consequently, the Bohlmann bands pattern of the 6-6-5-tetraponerines can be rationalized in terms of the facility for hyperconjugation of nitrogen lone pairs with antiperiplanar C-H bonds. Extrapolation of this explanation to the 5-6-5-tetraponerines is not straightforward, especially to the light of our NMR data for **T1** and **T5**. However,

the same pattern is observed for the Bohlmann bands and their use to predict the configuration at C_5 of tetraponerines is still valid.

Biological assays

The biological activities of tetraponerines have been only briefly examined probably due to their poor availability either by isolation from their natural source or by chemical synthesis. Among the few studies accomplished, an assessment of the anticancer activity of some natural tetraponerines and their analogues against HT-29 cell line (colorectal carcinoma), showed that the larger hydrocarbonated chain at the C_5, the lower IC_{50} values were obtained.[6] With this precedents we decided to evaluate the cytoxicity of pentyl-side-chain tetraponerines ((+)−**T5** to (+)−**T8**) at 4 different human carcinoma cell lines from different origins (A2780 from ovary carcinoma, NCI-H460 from lung, Caco-2 from colon and MCF-7 from breast). In order to predict the therapeutic range, we also screened these compounds over a non-tumoral cell line (MRC-5, lung fibroblasts). At a first step, all the compounds were assayed at 100 μM and for those compounds showing a decrease in cell viability higher than 50%, a concentration-response curve was assayed in order to evaluate their cytotoxic potency (IC_{50}). Unfortunately, in most of the cases the cellular growth inhibition was not enough to calculate the IC_{50} value, nevertheless, (+)−**T7** showed promising results against A2780, MCF-7 (cellular growth inhibition > 50%), being more efficient against MCF-7 cancer cells. However, (+)−**T7** also showed a good percentage of inhibition at MRC-5 cell lines which could lead to non-specific toxic effects (Table 1).

Table 1. Cellular Growth Inhibition Percentage of (+)−T5, (+)−T6, (+)−T7 and (+)−T8 at 100 μM against Human Cell Lines[a]

Compound	Cell line				
	NCI-H460[b]	Caco-2[c]	A2780[c]	MCF-7[c]	MRC-5[d]
CDDP	68	58	96	89	90
(+)-**T5**	29	20	40	49	43
(+)-**T6**	40	28	30	27	26
(+)-**T7**	48	41	**62**	**82**	**55**
(+)-**T8**	21	12	49	49	35

[a] Cell lines: NCI-H460, lung carcinoma; Caco-2, colon carcinoma; A2780, ovary carcinoma; MCF-7, breast carcinoma; MRC-5, human lung fibroblast cells. [b]48 h cellular growth inhibition (%) as determined by MTT. [c] 96 h cellular growth inhibition (%) as determined by MTT. [d] 7 d cellular growth inhibition (%) as determined by MTT. MTT = (3-[4,5-dimethylthiazol-2-yl]-2,5- diphenyltetrazolium bromide). CDDP (*cis*-diaminedichloroplatinum(II)) was used as control.

The inhibition/concentration curves were obtained for (+)−**T7** against the cell lines where the cellular growth inhibition was above 50% in order to calculate the IC_{50} values (Table 2). [33] For A2780 and MRC-5 cell lines, the obtained IC_{50} values were above 100 μM and solubility problems did not allow achieving the maximum inhibitory concentration. However, an acceptable value of IC_{50} (45 ± 3 μM) was obtained against MCF-7 cancer cells.

Table 2. Assessment of Cytotoxicity (IC_{50}, μM) of (+)−T7 against Human Cell Lines[a]

Compound	Cell line		
	A2780[b]	MCF-7[b]	MRC-5[c]
CDDP	0.86 ± 0.01	8.18 ± 0.56	5.72 ± 0.14
(+)-**T7**	>100	45 ± 3	>100

[a] Cell lines: A2780, ovary carcinoma; MCF-7, breast carcinoma; MRC-5, human lung fibroblast cells. [b] Determined after 96 h using the MTT method. [c] Determided after 7 d using the MTT method. MTT = (3-[4,5-dimethylthiazol-2-yl]-2,5- diphenyltetrazolium bromide). CDDP (*cis*-diaminedichloroplatinum(II)) was used as control.

It is worth mentioning that in previous studies it was concluded that the cytotoxicity of tetraponerine analogs against HT29 cancer cells was independent of the configuration at

C_5.[6] In this study we have found that the antiproliferative activity of (+)-**T7** is consistently bigger than that of (+)-**T8** against another three different human cell lines.

CONCLUSION

In summary, the iterative use of stereoselective aminoallylation of aldehydes with chiral *N-tert*-butylsulfinamide and *in situ* generated allyl indium reagent provides a convenient access to all natural tetraponerines from easily available starting materials. The formation of the tricyclic aminal scaffold was achieved by reaction of the corresponding free enantioenriched diamines with 4-bromobutanal, with concomitant N_4 alkylation. The configuration at the aminal carbon center was thermodynamically controlled with excellent selectivity in the synthesis of any natural tetraponerine, except for (+)−**T1** and (+)−**T5**. Interestingly, this methodology allows the access not only to the eight natural tetraponerines, but also to their eight enantiomers, by only changing the (*R*)-*tert*-butylsulfinamide for the also commercially available (*S*)-enantiomer in the first aminoallylation step. Importantly, the cross metathesis step could be extended to the use of other alkenes, being possible the synthesis of a wide range of tetraponerine analogues for their biological evaluation. The antiproliferative activity of (+)−**T5** to (+)−**T8** against four different carcinoma cell lines show that the configuration at C_5 could be important in their potency. Compound (+)−**T7** showed a promising cytotoxic profile at breast carcinoma cell line MCF-7 when compared with its effect at non-tumoral cell lines. With these results we think that further evaluation of tetraponerines (+)−**T7** and (+)−**T8** -or analogues with the same scaffold- against other cancer cell lines is pertinent in future works.

EXPERIMENTAL SECTION

General Remarks. TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230 − 400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 ºC and concentrations (c) are given in g/100 mL. Infrared analysis was performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. Mass spectra (EI) were obtained at 70 eV; and fragment ions in m/z with relative intensities (%) in parentheses. HRMS analyses were carried out using the Electron Impact (EI) mode at 70 eV or by Q-TOF using Electro Spray Ionization (ESI) mode. GC analyses were obtained with an HP-5 column (30 m × 0.25 mm, ID × 0.25 μm) and an EI (70 EV) detector. The temperature program: hold at 60 ºC for 3 min, ramp from 60 ºC to 270 ºC at 15 ºC/min, hold at 270 ºC for 10 min. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ or C_6D_6 as the solvent and TMS as an internal Standard (0.00 ppm). The data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm and to C_6D_6 at 127.00 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

Biological procedures: Procedures used for biological assays are described in the Supporting Information.

Experimental procedures and full characterization data for previously reported compounds. Procedure as well as complete characterization data for compounds **1**,[20a] **2**, **3**, **4**, **T3** and **T4** were previously described by our group.[16]

(2*R*,2'*R*,S_S)-(*N*-Benzyloxycarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-heptenyl]piperidine (5). The corresponding homoallylamine **3** (464 mg, 1.16 mmol) was placed in four different dry

Schlenck tubes under Argon atmosphere (116 mg each).[34] In each flask, the homoallylamine was disolved in dry CH_2Cl_2 (5 mL). Then Ti(O*i*-Pr)$_4$ (27 μL, 0.09 mmol), *cis*-3-hexene (143 μL, 1.16 mmol) and Grubbs-II catalyst (7 mg, 0.009 mmol) were added sequentially. The reaction mixtures were heated at 40 ºC for 6 h. After that time, all reactions were collected together and the solvent removed under reduced pressure. The residue obtained was purified by column chromatography (3:2 hexane/EtOAc). The expected product **5** was obtained as a colorless wax (391 mg, 79%). Rotamers are present: $[\alpha]^{20}_D$ + 50.5 (*c* 1.01, $CHCl_3$); R_f 0.21 (1:1 hexane/EtOAc); IR ν 3242, 2935, 2867, 1677, 1421, 1352, 1260, 1173, 1142, 1064, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 5.62 – 5.42 (m, 1H), 5.37 – 5.26 (m, 1H), 5.14 (t, *J* = 12.5 Hz, 2H), 4.91 – 4.33 (m, 2H), 4.05 (br d, *J* = 12.9 Hz, 1H), 2.91 (br s, 1H), 2.77 (t, *J* = 12.4 Hz, 1H), 2.39 (br s, 1H), 2.35 – 2.19 (m, 1H), 2.11 – 1.89 (m, 3H), 1.82 – 1.33 (m, 7H), 1.20 (s, 9H), 1.02 – 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C), 136.9 (C), 135.4 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 125.4 (CH), 67.1 (CH_2), 55.6 (C), 53.4 (CH_3), 47.6 (CH), 39.3 (CH_2), 39.2 (CH_2), 36.2 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 22.8 (CH), 19.2 (CH_2), 13.9 (CH_3); GC t_R = 20.0 min; LRMS (EI) *m/z* (%) 378 (M^+ - C_4H_8, 0.1), 328 (3), 241 (8), 218 (31), 175 (8), 174 (58), 92 (8), 91 (100); HRMS (ESI) calcd for $C_{24}H_{39}N_2O_3S$ (M^++1) 435.2681, found 435.2670.

(2*R*,2'*S*,*R*$_S$)-(*N*-Benzyloxycarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-heptenyl]piperidine (6). The expected product **6** was obtained from **4** (337 mg, 0.83 mmol) as a colorless wax (299 mg, 83%) following the same procedure described for **5**. Rotamers are present: $[\alpha]^{20}_D$ – 17.6 (*c* 1.05, $CHCl_3$); R_f 0.21 (1:1 hexane/EtOAc); IR ν 3239, 2932, 2867, 1692, 1422, 1259, 1172, 1065, 1053, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.70 – 5.47 (m, 1H), 5.41 – 5.24 (m, 1H), 5.20 – 5.03 (m, 2H), 4.48 (s, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 12.4, 6.1 Hz, 1H), 2.89 (t, *J* = 13.1 Hz, 1H), 2.40 (s, 1H), 2.29 (s, 1H), 2.11 – 1.91 (m, 3H), 1.88 – 1.53 (m, 7H), 1.50 – 1.32 (m, 1H), 1.17 (s, 9H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 137.4 (C), 136.9 (CH), 128.6 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 67.1 (CH_2), 55.9 (C), 52.9 (CH), 47.8 (CH), 39.5 (CH_2), 39.3 (CH_2), 34.5 (CH_2), 27.9 (CH_2),

25.8 (CH_2), 25.6 (CH_2), 22.7 (CH_3), 18.9 (CH_2), 14.1 (CH_3); GC t_R = 19.9 min; LRMS (EI) *m/z* (%) 378 (M^+ - C_4H_8, 0.1), 328 (3), 241 (8), 218 (31), 175 (8), 174 (58), 92 (8), 91 (100); HRMS (ESI) calcd for $C_{24}H_{39}N_2O_3S$ (M^++1) 435.2681, found 435.2671.

Tetraponerine T7. To a solution of compound **5** (300 mg, 0.765 mmol) in THF (2 mL) was added aqueous 6 M HCl (383 μL, 2.30 mmol) at 0 ºC under Ar. The reaction mixture was stirred for 1 h while reaching 23 ºC. Aqueous 2 M NaOH (3 mL) was added to the reaction mixture and the free amine was extracted with EtOAc (3 x 10 mL) and washed with brine (1 x 10 mL). The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then dissolved in dry MeOH (15 mL) and Pd/C 10% (256 mg) was added to the mixture. The suspension was shacked under hydrogen atmosphere (4 atm.) for 12 h at 23 ºC, filtered through Celite and the obtained solution was concentrated under reduced pressure. The residue (free diamine) was then dissolved in dry CH_2Cl_2 (8 mL) and K_2CO_3 (317 mg, 2.30 mmol) was added, followed by 4-bromobutanal[35] (207 mg, 1.377 mmol). The reaction mixture was stirred at 23 ºC for 4 h, after which time inorganic salts were removed by filtration. The filtrate was washed twice with aqueous $NaHCO_3$, followed by brine and then dried over $MgSO_4$. The organics were concentrated under reduced pressure and the residue was purified by column chromatography (96:4:0.05 CH_2Cl_2/ MeOH/ 20% NH_4OH) to provide the desired product as an oil (102 mg, 54%): $[\alpha]^{20}_D$ + 30 (*c* 0.82, $CHCl_3$), [lit.[13b] $[\alpha]^{20}_D$ + 29.5 (*c* 2.2, $CHCl_3$)]; R_f 0.50 (9:1 CH_2Cl_2/MeOH); IR ν 2954, 2926, 2855, 2803, 1455, 1389, 1346, 1156, 1129, 1118 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.03 (dd, *J* = 4.4, 2.7 Hz, 1H), 2.90 (dd, *J* = 14.6, 7.5 Hz, 1H), 2.57 – 2.46 (m, 3H), 1.83 – 1.73 (m, 1H), 1.68 (dd, *J* = 12.5, 5.2 Hz, 1H), 1.58 – 1.20 (m, 9H), 1.16 – 0.90 (m, 10H), 0.87 – 0.81 (m, 1H), 0.64 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 75.5 (CH), 56.7 (CH), 53.3 (CH), 50.9 (CH_2), 50.6 (CH_2), 34.1 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 31.0 (CH_2), 30.5 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 25.1 (CH_2), 23.2 (CH_2), 22.2 (CH_2), 14.4 (CH_3); GC t_R = 13.8 min; LRMS (EI) *m/z* (%) 251 (M+1, 6), 250 (M^+, 44), 249 (82), 207 (19), 194 (14), 193 (100), 180 (14), 179 (10), 165 (6), 152 (34), 151 (11), 138 (10), 110 (12), 96 (30), 84 (10), 55 (6); HRMS (ESI) calcd for $C_{16}H_{31}N_2$ (M^++1) 251.2487, found 251.2486.

Tetraponerine T8. Tetraponerine **T8** was obtained from **6** (205 mg, 0.49 mmol) as a yellow oil (74 mg, 60%) following the same procedure described for **T7**: $[\alpha]^{20}_{D}$ + 99 (*c* 0.70, $CHCl_3$), [lit.[13b] $[\alpha]^{20}_{D}$ + 101 (*c* 2.0, $CHCl_3$)]; R_f 0.40 (9:1 CH_2Cl_2/MeOH); IR ν 2928, 2857, 2790, 2775, 1631, 1454, 1377, 1338, 1188, 1156, 1035 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.26 (td, *J* = 8.1, 2.2 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.42 (t, *J* = 6.8 Hz, 1H), 2.23 (ddd, *J* = 11.0, 7.3, 3.7 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.91 – 1.66 (m, 8H), 1.65 – 1.24 (m, 14H), 1.01 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.6 (CH), 62.7 (CH), 61.4 (CH), 51.5 (CH_2), 49.0 (CH_2), 38.0 (CH_2), 34.6 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 29.7 (CH_2), 26.2 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 23.1 (CH_2), 20.2 (CH_2), 14.3 (CH_3); GC t_R = 14.2 min; LRMS (EI) *m/z* (%) 251 (M+1, 6), 250 (M^+, 45), 249 (100), 207 (19), 194 (13), 193 (95), 180 (20), 179 (11), 165 (12), 152 (45), 151 (15), 138 (12), 137 (10), 110 (14), 96 (30), 84 (16), 55 (9); HRMS (ESI) calcd for $C_{16}H_{31}N_2$ (M^++1) 251.2487, found 251.2493.

(4*R*,*R*$_S$)-*N*-(*tert*-Butylsulfinyl)-7-bromohept-1-en-4-amine (7). To a dry flask were added (*R*$_S$)-*N*-*tert*-butylsulfinamide (829 mg, 6.79 mmol) followed by indium powder (968 g, 8.489 mmol) under Ar. Then a solution of 4-bromobutyraldehyde (1.121 g, 7.470 mmol) in dry THF (15.9 ml) and $Ti(OEt)_4$ (3.1 mL, 13.582 mmol,) were added successively and the reaction mixture was stirred under Ar for 1 h at 23 ºC. At this time allyl bromide (897 µL, 10.186 mmol) was added to the mixture and the reaction was allowed to reach 60 ºC and stirred at that temperature for 5 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (100 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/hexane (50 mL) and filtered again through Celite. Organics were concentrated to afford the expected compound **7** (1.783 g, 89%, 95:5 dr according to ^1H NMR) as a colorless wax, pure enough to be used in the next step. To provide the spectroscopy data, a sample of homoallylamine **7** was purified by column chromatography: R_f 0.13 (7:3 hexane/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 19.6, 9.4, 7.2 Hz, 1H), 5.20 (d, *J* = 0.7 Hz, 1H), 5.16 (d, *J* = 3.6 Hz, 1H), 3.41 (t, *J* = 6.6 Hz,

3H), 3.27 (d, *J* = 6.2 Hz, 1H), 2.55 – 2.25 (m, 2H), 2.03 – 1.82 (m, 2H), 1.82 – 1.56 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (CH), 119.5 (CH_2), 56.2 (C), 54.5 (CH), 40.7 (CH_2), 33.7 (CH_2), 33.6 (CH_2), 29.0 (CH_2), 22.8 (CH_3); GC t_R = 14.1 min; LRMS (EI) *m/z* (%) 200 (40), 199 (100), 198 (39), 197 (95), 118 (15), 91 (13), 70 (80), 68 (16), 57 (66).

(2*R*,*R*s)-2-Allyl-(*N*-*tert*-butylsulfinyl)pyrrolidine (8). A titrated solution of KHMDS in THF (7.9 mL, 1.03 M, 8.136 mmol) was added via syringe to a cold solution (0 ºC) of crude **7** (1.600 g, 5.424 mmol) in dry THF (13.8 mL). The reaction mixture was stirred for 1.5 h at 0 ºC under Ar, quenched with saturated NH_4Cl solution and allowed to reach room temperature. The aqueous phase was extracted with EtOAc (3 times) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (80:20 hexane/EtOAc) to provide the product as a colorless oil (1.008 g, 86%, 97:3 dr according to the ^{1}H-NMR): $[\alpha]_D^{20}$ – 17.1 (*c* 1.038, $CHCl_3$); R_f 0.30 (7:3 hexane/EtOAc); IR ν 3076, 2658, 2871, 1639, 1474, 1456, 1361, 1065, 994, 911 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 – 5.66 (m, 1H), 5.11 – 5.01 (m, 2H), 3.74 (ddd, *J* = 10.1, 6.6, 3.7 Hz, 1H), 3.51 – 3.43 (m, 1H), 3.14 (dt, *J* = 10.7, 7.0 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.17 (ddd, *J* = 14.0, 9.4, 8.2 Hz, 1H), 1.87 – 1.73 (m, 3H), 1.71 –1.60 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (CH), 117.3 (CH_2), 58.1 (C), 57.5 (CH), 48.6 (CH_2), 39.0 (CH_2), 30.4 (CH_2), 24.2 (CH_2), 23.7 (CH_3); GC t_R = 11.9 min; LRMS (EI) *m/z* (%) 215 (M^+, 0.1), 159 (16), 118 (100), 117 (29), 70 (10), 57 (13); HRMS (EI) calcd for $C_{11}H_{21}NOS$ 215.1344, found 215.1348.

(*R*)-2-Allyl-(*N*-benzyloxycarbonyl)pyrrolidine (9). An aqueous 6 M solution of HCl (2 mL, 12.00 mmol) was added to a solution of **8** (860 mg, 4.0 mmol) in dry THF (4 mL) at 0 ºC under Ar. The solution was allowed to reach 23 ºC and was stirred for 2 h. After cooled again to 0 ºC, an aqueous 2 M solution of NaOH (14 mL, 27.00 mmol) was carefully added and the resulting mixture was stirred at the same temperature. After 5 min, a solution of benzyloxicarbonyl chloride (670 μL, 4.70 mmol) in CH_2Cl_2 (12 mL) was added to the stirring solution. The resulting mixture was then allowed to reach 23 ºC and stirred for 3 h. The reaction mixture was

extracted with EtOAc (3 times) and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatograpy (95:5 hexane/EtOAc) to provide the desired product **9** as a colorless oil (831 mg, 85%). Rotamers are present: $[\alpha]_D^{20}$ + 53.1 (*c* 0.617, $CHCl_3$); R_f 0.60 (7:3 hexane/EtOAc); IR ν 3035, 2972, 2876, 1696, 1639, 1446, 1407, 1355, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.83 – 5.64 (m, 1H), 5.21 – 4.96 (m, 4H), 3.92 (br s, 1H), 3.52 – 3.35 (m, 2H), 2.51 (br d, *J* = 54.4 Hz, 1H), 2.15 (td, *J* = 14.8, 8.1 Hz, 1H), 1.96 – 1.70 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (C), 154.9 (C), 137.3 (C), 137.1 (C), 135.2 (CH), 135.0 (CH), 128.6 (CH), 127.9 (CH), 117.4 (CH_2), 66.8 (CH_2), 66.6 (CH_2), 57.4 (CH), 56.9 (CH), 47.0 (CH_2), 46.7 (CH_2), 39.1 (CH_2), 38.2 (CH_2), 30.2 (CH_2), 29.3 (CH_2), 23.8 (CH_2), 23.0 (CH_2); GC t_R = 14.6 min; LRMS (EI) *m/z* (%) 245 (M^+, 0.1), 204 (26), 160 (28), 91 (100); HRMS (EI) calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1427.

(*R*)-(*N*-Benzyloxycarbonyl)-2-(2-oxoethyl)pyrrolidine (10). To a solution of **9** (790 mg, 3.224 mmol) in 1,4-dioxane:H_2O (3:1, 30 mL) were successively added 2,6-lutidine (751 µL, 6.45 mmol), $NaIO_4$ (2.8 g, 12.90 mmol) and a solution of OsO_4 in *t*-BuOH (2.5 % wt in *t*-BuOH, 317 µL). The mixture was stirred at 23 ºC for 1.5 h before being quenched with water (20 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the collected organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatograpy (4:1 hexane/EtOAc) to provide the pure product as a colorless oil (639 mg, 80%). Rotamers are present: $[\alpha]_D^{20}$ + 40.4 (*c* 1.44, $CHCl_3$); R_f 0.24 (7:3 hexane/EtOAc); IR ν 3031, 2956, 2879, 2726, 1718, 1692, 1497, 1448, 1409, 1356, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (br s, 0.6H), 9.67 (br s, 0.4H), 7.44 – 7.29 (m, 5H), 5.24 – 5.01 (m, 2H), 4.32 (dt, *J* = 12.1, 5.9 Hz, 1H), 3.58 – 3.27 (m, 2H), 2.99 (dd, *J* = 16.5, 3.1 Hz, 0.6H), 2.83 (br d, *J* = 16.8 Hz, 0.4H), 2.53 (d, *J* = 7.6 Hz, 0.6H), 2.48 (d, *J* = 7.6 Hz, 0.4H), 2.14 (dq, *J* = 12.5, 7.9 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.74 – 1.61 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (CH), 200.6 (CH), 155.0 (C), 154.7 (C), 136.9 (C), 136.6 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 67.1 (CH_2), 66.9 (CH_2), 53.1 (CH), 52.3 (CH), 49.4 (CH_2),

48.7 (CH_2), 46.9 (CH_2), 46.5 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 23.9 (CH_2), 23.1 (CH_2); GC t_R = 15.4 min; LRMS (EI) *m/z* (%) 247 (M^+, 0.6), 219 (10), 160 (10), 156 (10), 112 (10), 91 (100), 65 (10); HRMS (EI) calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1213.

(2*R*,2'*R*,*S*$_S$)-(*N*-Benzyloxycarbonyl)-2-[2'-(*tert*-butylsulfinamine)-4'-pentenyl]pyrrolidine (11). To a dry flask were added (S_S)- *N*-*tert*-butylsulfinamide (134 mg, 1.107 mmol) and indium powder (158 mg, 1.38 mmol) under Ar. Then was added a solution of aldehyde **10** (301 mg, 1.218 mmol) in dry THF (2.7 ml) followed by $Ti(OEt)_4$ (500 µL, 2.22 mmol) and the reaction mixture was stirred under Ar for 1 h at 23 ºC . At this time allyl bromide (143 µL, 1.66 mmol) was added to the mixture and it was heated to 60 ºC for 5 h. The mixture was allowed to reach 23 ºC and was carefully added over a stirring mixture of 4:1 EtOAc/brine (15 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and the organics were concentrated under reduced pressure. According to HPLC analysis (Chiralcel AD-H column 25 cm x 0.46 cm, isocratic elution with 95:5 *n*-hexane/*i*-PrOH, 1.0 mL/min, UV detection at 217 nm), the crude reaction mixture showed a major diastereoisomer at 16.17 min (94%) and other diastereoisomers at 20.80 - 23.50 min (6%). After column chromatography (3:2 hexane/EtOAc), the major isomer was isolated pure (>99:1 dr according to HPLC) as a colorless wax product as a unique diastereoisomer after purification by column chromatography (391 mg, 90%). Rotamers are present: $[\alpha]_D^{20}$ + 83.2 (*c* 1.220, $CHCl_3$); R_f 0.20 (1:1 hexane/EtOAc); IR ν 3243, 3065, 2957, 2888, 1685, 1452, 1409, 1360, 1099, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 5.80 (dq, *J* = 10.0, 6.9 Hz, 0.8H), 5.62 (dd, *J* = 15.8, 8.3 Hz, 0.2H), 5.27 – 5.00 (m, 5H), 4.34 (dd, *J* = 13.0, 7.6 Hz, 0.8H), 3.99 (br s, 0.2H), 3.42 (dt, *J* = 11.4, 8.5 Hz, 2H), 3.20 (qd, *J* = 10.1, 5.5 Hz, 1H), 2.52 (dt, *J* = 14.5, 7.4 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.09 – 1.81 (m, 3H), 1.81 – 1.54 (m, 3H), 1.24 (s, 7H), 1.12 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C), 137.0 (C), 135.6 (CH), 134.1 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 119.0 (CH_2), 117.5 (CH_2), 67.3 (CH_2), 66.9 (CH_2), 55.6 (C), 54.9 (CH), 53.3 (CH), 46.6 (CH_2), 42.4 (CH_2), 41.3 (CH_2), 39.8 (CH_2), 39.2 (CH_2), 31.4 (CH_2), 23.8 (CH_2), 23.0 (CH_3), 22.7 (CH_3); GC t_R = 22.7 min; LRMS (EI) *m/z* (%) 336 (M^+, 0.8), 287 (6), 218 (14), 204 (10), 174 (10), 160

(20), 114 (6), 91 (100), 70 (23); HRMS (EI) calcd for $C_{21}H_{32}N_2O_3S - C_4H_8$ 336.1508, found 336.1510.

(2*R*,2'*S*,R_S)-(*N*-Benzyloxycarbonyl)-2-[(2'-*tert*-butylsulfinamine)-4'-pentenyl]pyrrolidine (12). Compound **12** was prepared from aldehyde **10** (301 mg, 1.218 mmol) and (R_S)-*N*-*tert*-butylsulfinamide (134 mg, 1.107 mmol) following the same procedure described above for compound **11**. According to HPLC analysis (Chiralcel AD-H column 25 cm x 0.46 cm, isocratic elution with 95:5 *n*-hexane/*i*-PrOH, 1.0 mL/min, UV detection at 217 nm), the crude reaction mixture showed a major diastereoisomer at 21.4 min (78%) and other diastereoisomers at 14.4 - 17.0 min (22%). After column chromatography (3:2 hexane/EtOAc), the major isomer was isolated pure (>99:1 dr according to HPLC) as a colorless wax (301 mg, 69%): mp 76.5 – 77.1 °C; $[\alpha]_D^{20}$ - 31.8 (*c* 0.929, $CHCl_3$); R_f 0.16 (1:1 hexane/EtOAc); IR ν 3203, 3075, 2958, 2883, 1689, 1471, 1453, 1407, 1096, 1045, 1032 cm^{-1}; Rotamers are present (as shown in the X-ray at the Supporting Information) ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.32 (m, 5H), 5.94 – 5.58 (m, 1H), 5.27 – 4.94 (m, 4H), 4.04 (br d, *J* = 35.6 Hz, 1H), 3.58 – 3.36 (m, 2.6H), 3.28 (br d, *J* = 32.9 Hz, 1H), 3.02 (d, *J* = 8.4 Hz, 0.4H), 2.58 – 2.31 (m, 2H), 2.09 – 1.80 (m, 4H), 1.68 (br d, *J* = 5.1 Hz, 1H), 1.51 – 1.35 (m, 1H), 1.22 (s, 5H), 1.06 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (C), 137.1 (C), 137.0 (C), 134.0 (CH), 133.3 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 119.8 (CH_2), 119.2 (CH_2), 67.2 (CH_2), 66.6 (CH_2) 56.4 (C), 56.2 (C), 55.2 (CH), 54.6 (CH), 54.5 (CH), 54.3 (CH), 46.7 (CH_2), 46.4 (CH_2), 42.2 (CH_2), 42.0 (CH_2), 40.3 (CH_2), 39.5 (CH_2), 30.5 (CH_2), 30.1 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 22.9 (CH_3), 22.7 (CH_3); GC t_R = 22.9 min; LRMS (EI) *m/z* (%) 336 (M^+, 0.8), 287 (6), 218 (14), 204 (10), 174 (10), 160 (25), 114 (12), 91 (100), 70 (23); HRMS (EI) calcd for $C_{21}H_{32}N_2O_3S - C_4H_8$ 336.1508, found 336.1509.

Tetraponerine T1. Tetraponerine **T1** was prepared from **11** (300 mg, 0.765 mmol) and 4-bromobutanal (207 mg, 1.377 mmol) following the same procedure described above for compound **T7**, affording the expected product as an oil (51 mg, 32 % from **11**). Configurational isomers must be present:[36] $[\alpha]_D^{20}$ + 14 (*c* 0.498, $CHCl_3$) [lit.[15] $[\alpha]^{20}_D$ + 11 (*c* 0.14, $CHCl_3$)]; R_f

0.15 (95:5 CH_2Cl_2/MeOH); IR ν 2954, 2928, 2871, 2792, 2639, 2585, 1457, 1381, 1349, 1191, 1167, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 – 3.74 (m, 1H), 3.46 – 3.15 (m, 2H), 3.14 – 2.88 (m, 2H), 2.77 – 2.36 (m, 1H), 2.31 – 1.78 (m, 8H), 1.79 – 1.16 (m, 7H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 77.0 (CH), 58.4 (CH), 53.7 (CH), 50.4 (CH_2), 49.8 (CH_2), 33.8 (CH_2), 30.8 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 21.3 (CH_2), 20.5 (CH_2), 20.1 (CH_2), 14.3 (CH_3); GC t_R = 11.6 min; LRMS (EI) *m/z* (%) 208 (M^+, 46), 207 (100), 180 (12), 179 (91), 165 (10), 138 (51), 137 (19), 124 (23), 110 (17), 96 (64), 70 (29); HRMS (EI) calcd for $C_{13}H_{24}N_2$ 208.1939, found 208.1929.

Tetraponerine T2. Tetraponerine **T2** was prepared from **12** (230 mg, 0.587 mmol), and 4-bromobutanal (159 mg, 1.057 mmol) following the same procedure described above for compound **T7**, affording the expected product as an oil (42 mg, 35 % from **12**); $[\alpha]_D^{20}$ + 47 (*c* 0.232, $CHCl_3$), [lit.[15] $[\alpha]^{20}_D$ + 36 (*c* 1.79, $CHCl_3$)]; R_f 0.15 (95:5 CH_2Cl_2/MeOH); IR ν 2955, 2931, 2871, 2787, 2695, 1457, 1379, 1362, 1190, 1162, 1099 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.17 – 2.93 (m, 3H), 2.60 – 2.51 (m, 1H), 2.43 (td, *J* = 8.7, 5.1 Hz, 1H), 2.07 – 1.83 (m, 5H), 1.83 – 1.60 (m, 4H), 1.60 – 1.25 (m, 7H), 1.01 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 83.0 (CH), 63.8 (CH), 59.1 (CH), 48.6 (CH_2), 45.5 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 21.1 (CH_2), 20.8 (CH_2), 19.3 (CH_2), 14.6 (CH_3); GC t_R = 11.9 min; LRMS (EI) *m/z* (%) 208 (M^+, 41), 207 (100), 180 (8), 179 (53), 165 (11), 138 (59), 137 (20), 124 (25), 110 (18), 96 (47), 70 (37); HRMS (EI) calcd for $C_{13}H_{24}N_2$ 208.1939, found 208.1932.

(2*R*,2'*R*,*S*$_S$)-(*N*-Benzyloxycarbonyl)-2-[(2'-*tert*-butylsulfinamine)-4'-heptenyl]pyrrolidine (13). Compound **13** was prepared from **11** (513 mg, 1.31 mmol) following the same procedure described above for compound **5**, affording the corresponding product as a colorless wax (473 mg, 86%). Rotamers are present: $[\alpha]^{20}_D$ + 81.6 (*c* 1.20, $CHCl_3$); R_f 0.31 (1:1 hexane/EtOAc); IR ν 3248, 3031, 2958, 2931, 1685, 1453, 1409, 1359, 1099, 1062, 968, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 5H), 5.66 – 5.48 (m, 1H), 5.47 – 5.29 (m, 1H), 5.29 – 5.03 (m, 2H), 4.42 – 3.89 (m, 1H), 3.56 – 3.05 (m, 3H), 2.42 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.34 – 2.19 (m, 1H), 1.23 (s, 7H), 1.12 (s, 2H), 1.18 (d, *J* = 34.3 Hz, 9H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 156.1 (C), 137.0 (C), 135.4 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 125.6 (CH), 66.9 (CH_2), 55.7 (C), 55.0 (CH), 53.5 (CH), 46.5 (CH_2), 42.2 (CH_2), 38.0 (CH_2), 31.3 (CH_2), 25.8 (CH_2), 23.8 (CH_2), 22.9 (CH_3), 22.7 (CH_3), 14.3 (CH_3), 13.9 (CH_3); GC t_R = 19.4 min; LRMS (EI) *m/z* (%) 314 (3), 227 (3), 204 (12), 173 (4), 161 (3), 160 (23), 145 (24), 92 (8), 91 (100), 70 (6), 69 (3), 65 (5); HRMS (ESI) calcd for $C_{23}H_{37}N_2O_3S$ (M^++1) 421.2525, found 421.2521.

(2*R*,2'*S*,*R*$_S$)-(*N*-Benzyloxycarbonyl)-2-[(2'-*tert*-butylsulfinamine)-4'-heptenyl]pyrrolidine (14). Compound **14** was prepared from **12** (358 mg, 0.90 mmol) following the same procedure described above for compound **5**, affording the corresponding product as a colorless wax (295 mg, 78%). Rotamers are present: $[\alpha]^{20}_D$ – 20.5 (*c* 0.99, $CHCl_3$); R_f 0.30 (1:1 hexane/EtOAc); IR ν 3232, 3030, 2959, 2873, 1691, 1454, 1412, 1359, 1102, 1057, 970, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 5.59 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.47 – 5.22 (m, 1H), 5.22 – 4.97 (m, 2H), 4.18 – 3.87 (m, 1H), 3.59 – 3.00 (m, 4H), 2.34 (br d, *J* = 21.0 Hz, 2H), 2.11 – 1.92 (m, 4H), 1.92 – 1.59 (m, 3H), 1.37 (dd, *J* = 24.1, 12.3 Hz, 1H), 1.23 (s, 5H), 1.05 (s, 4H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (C), 137.7 (CH), 137.2 (CH), 136.9 (C), 136.8 (C), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 123.8 (CH), 123.1 (CH), 67.0 (CH_2), 66.5 (CH_2), 56.1 (C), 55.9 (C), 55.1 (CH), 54.6 (CH), 54.4 (CH), 46.6 (CH_2), 46.2 (CH_2), 40.6 (CH_2), 40.5 (CH_2), 40.2 (CH_2), 39.3 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 14.2 (CH_3), 13.9 (CH_3); GC t_R = 19.4 min; LRMS (EI) *m/z* (%) 314 (3), 227 (3), 207 (3), 204 (11), 179 (3), 174 (4), 173 (4), 161 (3), 160 (23), 145 (9), 92 (8), 91 (100), 70 (6), 65 (4); HRMS (ESI) calcd for $C_{23}H_{37}N_2O_3S$ (M^++1) 421.2525, found 421.2519.

Tetraponerine T5. Tetraponerine **T5** was prepared from **13** (460 mg, 1.10 mmol), and 4-bromobutanal following the same procedure described above for compound **T7**, affording the expected product as a yellow oil (90 mg, 35%). Configurational isomers must be present:[36] $[\alpha]^{20}_D$ + 14 (*c* 1.60, $CHCl_3$), [lit.[15] $[\alpha]^{20}_D$ + 10 (*c* 0.24, $CHCl_3$)]; R_f 0.35 (9:1 CH_2Cl_2/MeOH); IR ν 3414, 2953, 2927, 2857, 2793, 1457, 1384, 1348, 1233, 1162, 1114, 1064 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 3.75 – 3.45 (m, 1H), 3.40 – 2.64 (m, 4H), 2.62 – 2.15 (m, 1H), 2.16 – 1.43 (m, 12H), 1.40 – 0.98 (m, 7H), 0.89 (dd, *J* = 9.0, 4.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.9 (CH), 58.3 (CH), 53.9 (CH), 50.3 (CH_2), 49.5 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 21.1 (CH_2), 20.0 (CH_2), 14.1 (CH_3); GC t_R = 13.0 min; LRMS (EI) *m/z* (%) 237 (5), 236 (M^+, 42), 235 (100), 193 (13), 180 (12), 179 (81), 166 (15), 165 (6), 152 (11), 138 (27), 137 (12), 124 (10), 110 (21), 96 (43), 70 (18), 55 (7); HRMS (ESI) calcd for $C_{15}H_{29}N_2$ (M^++1) 237.2331, found 237.2324.

Tetraponerine T6. Tetraponerine **T6** was prepared from **14** (255 mg, 0.61 mmol), and 4-bromobutanal following the same procedure described above for compound **T7**, affording the expected product as a yellow oil (52 g, 36%); $[\alpha]^{20}_D$ + 40 (*c* 0.75, $CHCl_3$), [lit.[15] $[\alpha]^{20}_D$ + 35 (*c* 0.31, $CHCl_3$)]; R_f 0.50 (9:1 CH_2Cl_2/MeOH); IR ν 3395, 2954, 2928, 2858, 2784, 1458, 1378, 1204, 1188, 1161, 1064 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.11 – 3.01 (m, 1H), 2.94 (td, *J* = 8.4, 2.5 Hz, 1H), 2.85 (t, *J* = 5.3 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.32 (dd, *J* = 8.4, 5.3 Hz, 1H), 2.00 – 1.84 (m, 2H), 1.83 – 1.52 (m, 7H), 1.50 – 1.19 (m, 11H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.4 (CH), 64.2 (CH), 59.7 (CH), 49.1 (CH_2), 45.9 (CH_2), 34.7 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 25.9 (CH_2), 23.1 (CH_2), 21.3 (CH_2), 20.9 (CH_2), 14.4 (CH_3); GC t_R = 13.3 min; LRMS (EI) *m/z* (%) 237 (M+1, 5), 236 (M^+, 40), 235 (100), 207 (5), 193 (15), 180 (8), 179 (54), 166 (17), 165 (10), 152 (13), 151 (10), 138 (38), 137 (14), 124 (12), 123 (5), 110 (14), 97 (7), 96 (35), 70 (24), 68 (7), 55 (6); HRMS (ESI) calcd for $C_{15}H_{29}N_2$ (M^++1) 237.2331, found 237.2333.

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Supporting Information: Copies of ^{1}H and ^{13}C NMR spectra for compounds **5-14**, **T1**, **T2** and **T5-T8** are provided. GC-MS for **T1-T8**, HPLC traces of compounds **11** and **12**, crystallographic data for compound **12**; as well as cytotoxic data for **T5-T8** against four different carcinoma cell lines are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

(1) (a) Wang, K.; Su, B.; Wang, Z.; Wu, M.; Li, Z.; Hu, Y.; Fan, Z.; Mi, N.; Wang, Q. *J. Agric. Food Chem.* **2010**, *58*, 2703−2709. (b) Chemler, S. R. *Curr. Bioact. Compd*. **2009**, *5*, 2. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165; and references there in. (d) Wei, L-: Shi, Q.; Bastow, K. F.; Brossi, A.; Morris-Natschke, S. L.; Nakagawa-Goto, K.; Wu, T. S.; Pan, S. L.; Teng, C. M.; Lee, K. H. *J. Med. Chem*. **2007**, *50*, 3674 − 3680.

(2) (a) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311 − 2352. (b) Hanessian, S.; Parthasarathy, S.; Mauduit, M.; Payza, K. *J. Med. Chem*. **2003**, *46*, 34 − 48. (c) Casy, A. F.; Parfitt, R. T. Opioid Alkaloids; Springer: Heidelberg, 1989, p 465. (d) Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. *J. Med. Chem*. **1978**, *21*, 153 − 154. (e) Belleau, B.; Conway, T.; Ahmed, F. R.; Hardy, A. D. *J. Med. Chem.* **1974**, *17*, 907 − 908. (f) Portoghese, P. S. *J. Med. Chem*. **1965**, *8*, 609 − 616.

(3) Very few alkaloids possess an aminal carbon: Ban, Y.; Kimura, M.; Oishi, T. *Heterocycles* **1974**, *2*, 323 − 328.

(4) Braekman, J. C.; Daloze, D.; Pasteels, J. M.; Vanhecke, P.; Declercq, J. P.; Sinnwell, V.; Francke, W.; *Z Naturforschung. Teil C* **1987**, *42*, 627 − 630.

(5) Kem, W. R.; Wildeboer, K.; LeFrancois, S.; Raja, M.; Marszalec, W.; Braekman, J. C. *Cell Mol. Neurobiol.* **2004**, *24*, 535 − 551.

(6) Rouchaud, A.; Braekman, J. C. *Eur. J. Org. Chem.* **2009**, 2666 − 2674.

(7) Merlin, P., Braekman, J. C., Daloze, D., Pasteels, J. M. *J. Chem. Ecol.* **1988**, *14*, 517 − 527.

(8) Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 1415 − 1428.

(9) Garraffo, M. H.; Spande, T. F.; Jain, P.; Kaneko, T.; Jones, T. H.; Blum, M. S.; Ali, T. M. M.; Snelling, R. R.; Isabell, L. A.; Robertson, H. G.; Daly, J. W. *Rapid Commun Mass Spectrom*. **2001**, *15*, 1409 − 1415.

(10) Devijver, C.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Chem. Comm*. **1997**, 661 − 662.

(11) Renson, B.; Merlin, P.; Daloze, D.; Braekman, J. C.; Roisin, Y.; Pasteels, J. M. *Can J. Chem*. **1994**, *72*, 105 − 109.

(12) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem*. **1990**, *55*, 1140 − 1141.

(13) For selected syntheses of enantioenriched tetraponerines: (a) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, M.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670-8673. (b) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584 − 9591. (c) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594 − 8601.

(14) Guerrier, L.; Roger, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc*. **1983**, *105*, 7754 − 7755.

(15) Yue, C. W.; Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem*. **1996**, *61*, 4949 − 4954.

(16) Bosque, I.; Gonzalez-Gomez, J. C.; Guijarro, A.; Foubelo, F.; Yus, M. *J. Org. Chem*. **2012**, *77*, 10340 − 10346.

(17) A definition of the stereochemical descriptors used is in order here. The first descriptor refers to the configuration of the nitrogen N_{11}, with its lone pair either *cis*- or *trans*-to H_{6a}. Next, the relative stereochemistry of the quinolizidine and indolizidine frameworks (i.e., the rings AB and BC) was defined as either *cisoid*- or *transoid*-. Finally the indolizidine ring fusion BC was again defined as either *cis*- or *trans*-. Thus, as depicted in the example, the *ttc*-isomer would correspond to a *trans* quinolizidine-*transoide-cis* indolizidine.

(18) Rouchaud, A.; Braekman, J.-C. *Eur. J. Org. Chem.* **2011**, 2346 – 2353.

(19) For a comprehensive review on the application of *tert*-butylsulfinamides, see: Ellman, J. A.; Robak, M. T.; Herbage, M. A. *Chem. Rev.* **2010**, *110*, 3600 – 3740.

(20) (a) Bosque, I.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem*., **2012**, *77*, 780 – 784. (b) Gonzalez-Gomez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem*. **2010**, *75*, 6308 − 6311.

(21) For a review on diastereoselective allylation of imines and its application to the synthesis of natural products, see: Yus, M. ; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.*, **2013**, *113*, 5595.

(22) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699 – 3700.

(23) (a) Medjahdi, M.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Heterocycles* **2012**, *86*, 727 − 734. (b) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Synlett.* **2008**, *18*, 2777 − 2780.

(24) Fustero, S.; Monteagudo, S.; Sanchez-Rosello, M.; Flores, S.; Barrio, P.; del Pozo, C. *Chem. Eur. J*. **2010**, *16*, 9835 − 9845.

(25) It is reported that *cis*-olefins are more sterically accessible to ruthenium alkylidene catalysts in the cross-metathesis reaction. See: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484 – 2489.

(26) The presence of rotamers made difficult the determination of the alkene double bond stereochemistry; however this issue has no consequences in the present synthetic approach.

(27) The crystallographic data of this compound (CDCC 971540) can be found in the Supporting Information.

(28) The NMR data was compared to the one reported in reference 15; however, to the best of our knowledge, the NMR traces of **T1** or **T2** are not reported in the literature.

(29) Kim, J. T.; Butt, J.; Gevorgyan, V. *J. Org. Chem*. **2004**, *69*, 5638 − 5645.

(30) The NMR data was compared to the one reported in reference 15; however, to the best of our knowledge, the NMR traces of **T5** are not reported in the literature.

(31) These bands are commonly used to elucidate the structure of alkaloids, see for example: Gribble, G. W.; Nelson, R. B. *J. Org. Chem.* **1973**, *38*, 2831 − 2834.

(32) Wolfe, S.; Schlegel, B.; Whangbo, M.-H. *Can. J. Chem.* **1974**, *52*, 3787 − 3792.

(33) See inhibition *vs* concentration curves in the Supporting Information.

(34) The reactions were run in parallel at the scale of 0.3 mmol maximum each because we observed lower conversion at higher scale.

(35) 4-Bromobutanal is commercially available, but we prepared it by DIBAL-H reduction of the corresponding methyl ester.

(36) To ensure that the amine was not partially protonated, the sample was washed with saturated solution of $NaHCO_3$ before submitting to NMR experiments. Similar NMR spectra were obtained in $CDCl_3$ and CD_2Cl_2 (where traces of HCl are less likely).