Enantioselective Synthesis of Tetraponerines by Pd- and Ru-Catalyzed Domino Reactions

Roland Stragies and Siegfried Blechert*

Contribution from the Institut für Organische Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany

Received May 16, 2000

Abstract: An enantioselective synthesis of tetraponerines **T4**, **T6**, **T7**, and **T8** in 24−36% overall yield is described. Key steps in this synthesis are a Pd-catalyzed domino allylation and a Ru-catalyzed ring rearrangement. The effect of different substituents on the equilibrium of the metathesis rearrangement has been investigated. To complete the synthesis a sequence of Wacker oxidation and Takai olefination was used. The preparation of four representative tetraponerines differing in stereochemistry, ring size, and side chain employing five metal-organic reactions clearly demonstrates the efficiency of transition metals in organic synthesis.

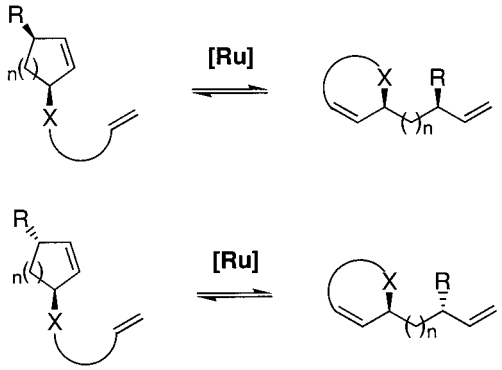
Introduction

Olefin metathesis has proven its synthetic use in many applications.[1] The potential of ring-closing metathesis (RCM) has fully been recognized and was demonstrated in the synthesis of numerous carbo- and heterocycles. An alternative access to this class of compounds is the ruthenium-catalyzed ring rearrangement,[2] in which a carbocycle is transformed into a heterocyclic product by an intramolecular ring-opening−ring-closing domino metathesis (Scheme 1).

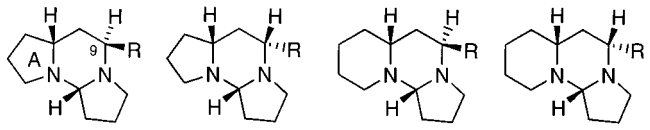
The ratio of starting material to rearrangement product depends on thermodynamic effects, e.g., ring strain and configuration of the substituents. Starting from enantiomerically pure carbocycles, the metathesis rearrangement transfers the chirality into the heterocycle and the formed side chain. Enantiomerically pure carbocycles with several stereocenters can be prepared more conveniently compared to the substituted heterocycles with stereodefined side chains obtained by the metathesis rearrangement. The palladium-catalyzed allylic substitution of cyclopentene derivatives is one possibility for the synthesis of these carbocycles.[3] Herein we report on the flexible synthesis of naturally occurring tetraponerines applying a combination of enantioselective palladium-catalyzed allylation and a domino metathesis process.

Tetraponerines **T1**−**T8** were isolated from the venom of the New Guinean ant *Tetraponera sp*. (Scheme 2).[4] These alkaloids represent the major constituents of the contact poison. Contaminated enemies (ants) immediately show symptoms of nervous poisoning. Several diastereo- or enantioselective syntheses targeting single tetraponerines have been published,[5] but there is only one enantioselective approach leading to all tetraponerines.[6] A flexible synthesis of these unusual alkaloids comprises several challenges. Tetraponerines **T1**−**T8** differ in the side chain, the stereochemistry at C-9, and the size of ring A. Our strategy represents a general and enantioselective approach toward all naturally occurring tetraponerines. To prepare the *cis*-configurated precursors for the metathesis reaction, we applied an enantioselective domino allylic alkylation (tetraponerines **T2**, **T4**, **T6**, **T8**). The efficiency of

Scheme 1. Ruthenium-Catalyzed Ring Rearrangement; [**Ru**] = $Cl_2(PCy_3)_2Ru{=}CHPh$ (Cy = Cyclohexyl)



Scheme 2. Tetraponerines **T1**−**T8**



T1 R = C_3H_7 **T2** R = C_3H_7 **T3** R = C_3H_7 **T4** R = C_3H_7

T5 R = C_5H_{11} **T6** R = C_5H_{11} **T7** R = C_5H_{11} **T8** R = C_5H_{11}

* Corresponding author. Fax: 49-30-31423619. E-mail: blechert@chem.tu-berlin.de.

(1) General reviews on olefin metathesis: (a) Blechert, S.; Schuster, M. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Hashmi A. S. K. *J. Prakt. Chem.* **1997**, *339*, 195. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) Grubbs, R. H.; Chang, S.; *Tetrahedron* **1998**, *54*, 4413. (e) Fürstner, A. *Topics in Organometallic Chemistry*; Springer: Berlin, 1997; Vol. 1.

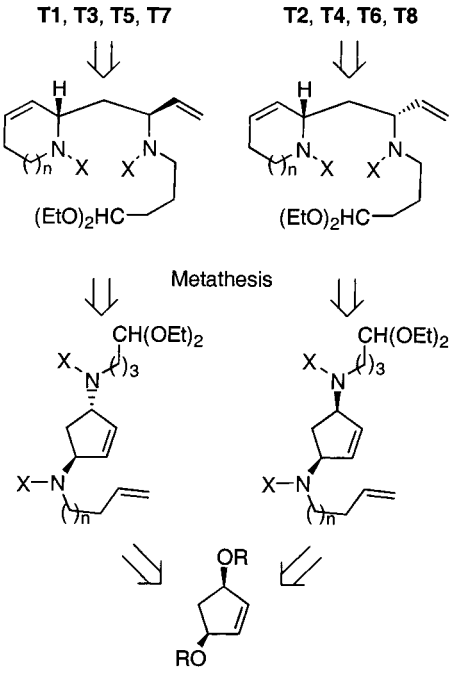
(2) (a) Stragies, R.; Blechert, S. *Synlett* **1998**, 169. (b) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179. (c) Schuster, M.; Stragies, R.; Blechert, S. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Societa Chimica Italiana: Roma, 1998; Vol. 2, p 193. (d) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343. (e) Adams, J. A.; Ford, J. G.; Stamatos, P. J.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 9690.

(3) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*. 395. (c) Gibson, S. E. *Transition Metals in Organic Synthesis*; Oxford University Press: Oxford 1997. (d) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley, New York, 1995.

(4) Brakman, J. C.; Daloze, D.; Pasteels, J. M.; Van Hecke, P.;. Declercq, J. M.; Stinwell, V.; Francke W. *Z. Naturforsch.* **1987**, *42c*, 627.

10.1021/ja001688i CCC: $19.00 © 2000 American Chemical Society
Published on Web 09/26/2000

Scheme 3. Synthesis of Tetraponerines (X = Protecting Group)

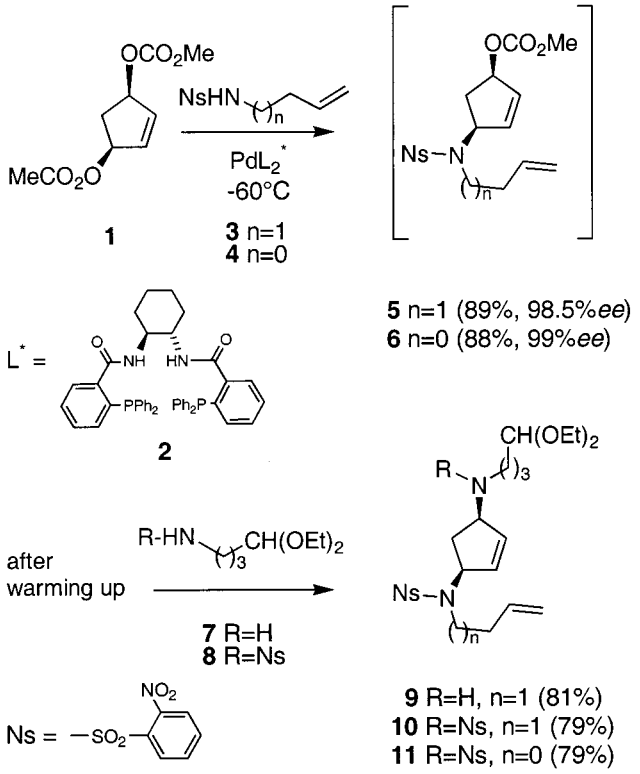


asymmetric allylations[7] has been demonstrated by Trost in the synthesis of (+)-polyoxamic acid[8] and the glycosidase inhibitors[9] allosamizoline and mannostatin A. The *trans*-configurated metathesis precursors can be prepared by a sequence of palladium-catalyzed allylation and Mitsunobu reaction (tetraponerines **T1**, **T3**, **T5**, **T7**). Introduction of either allyl- or butenylamine as nucleophile gives rise to the five- and six-membered ring A formed in the subsequent metathesis reaction (Scheme 3). The different C_3- and C_5-side chains (R) can be incorporated by functionalization of the terminal double bond of the metathesis products. Deprotection, hydrogenation, and acidic cyclization gave the tetraponerines **T4**, and **T6**−**T8**.

Results and Discussion

The results of the domino allylic alkylations are given in Scheme 4. The reaction of dicarbonate **1** with 1.5 mol % of the palladium catalyst and 1 equiv of the nucleophile[10] **3** or **4** gives the compounds **5** and **6** in 89% and 88% yield, respectively. The catalyst was prepared from ligand **2** and tris(dibenzylideneacetone)dipalladium(0) chloroform complex in THF. As

Scheme 4



the N-protecting group we chose the *o*-nitrobenzosulfonyl group Ns,[11] which can be removed much easier compared to the tosyl group. HPLC analysis of the corresponding alcohols **12** and **13** showed an enantiomeric excess (*ee*) of at least 98.5%.[12] Owing to the high reactivity of allyl carbonates, the reaction was carried out at −60 °C followed by slow warming to −35 °C. Performing the reaction at room temperature resulted in decreased enantioselectivity (<80%). The addition of 3 equiv of Et_3N was essential in this allylation to obtain good yields and enantioselectivities. Only 10% conversion of dicarbonate **1** was observed in the absence of Et_3N. We assume that the base acts as a cosolvent and has a stabilizing effect on the formed palladium allyl complex. Byproducts resulting from double allylic amination were found in only 5−9% yield.

On the basis of these results, we extended the allylation to a tandem process. However, initial experiments showed that addition of 2 equiv of the second nucleophile **7** at low temperature only results in decomposition of the starting material. Therefore, the reaction mixture was allowed to warm to room temperature before adding **7**. Amine **9** was isolated in 81% yield. Many attempts to protect the free amine **9** failed, and introduction of the Ns-protected amine **8** in the second amination resulted in decomposition. In similar disubstitutions of functionalized cycloalkenes, 3,4-di(bisphenylphosphino)-butane (dppb) was used successfully.[13] Therefore, we decided to exchange the palladium ligand **2** against dppb after the first amination. This reaction was performed in a one-pot procedure. After warming to room temperature **8** was added to the reaction mixture, and the diaminated products **10** and **11** were isolated in 79% yield.

These domino allylations gave access to all tetraponerines with all-*cis* stereochemistry and to all desired ring sizes. To

(5) Synthesis: (a) Jones, T. H. *Tetrahedron Lett.* **1990**, *32*, 4543. (b) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 1140. (c) Barluenga, J.; Tomás, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699. (d) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691. (e) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1991**, *47*, 3805. (f) Devijver, C.; Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 10913. (g) Macours, P.; Braekman, J. C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415. Biosynthesis of **T1**−**T8**: Renson, B.; Merlin, P.; Braekman, J. C.; Daloze, D.; Roisin, Y.; Pasteels, J. M. *Can. J. Chem.* **1994**, *72*, 105. Mass spectra of **T1**−**T8**: Merlin, P.; Braekman, J. C.; Daloze, D.; Flammang, R.; Maquestiau, A. *Org. Mass Spectrom.* **1989**, *24*, 837.

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

(7) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(8) Trost, B. M.; Krueger, A. C.; Bant, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6521.

(9) Trost, B. M.; Van Vranken, D. L. J. *J. Am. Chem. Soc.* **1993**, *115*, 444.

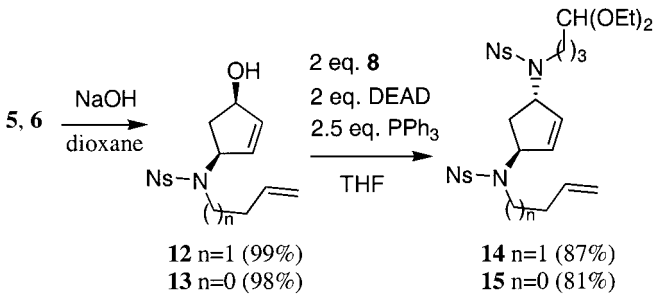
(10) Baker, S. R.; Parsons, A. F.; Pons, J.-F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 7197.

(11) Fukuyama, T.; Joe, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6737.

(12) For the preparation of ligand **2** (1*S*,2*S*)-cyclohexyldiamine from Aldrich, (99% *ee*) was used.

(13) Sirisoms, N. S.; Woster, P. M. *Tetrahedron Lett.* **1998**, *39*, 1489.

Scheme 5



synthesize metathesis precursors with *trans* stereochemistry, we utilized a Mitsunobu reaction[14] introducing the alcohols **12** and **13**, which were quantitatively obtained by basic hydrolysis of the carbonates **5** and **6** (Scheme 5).

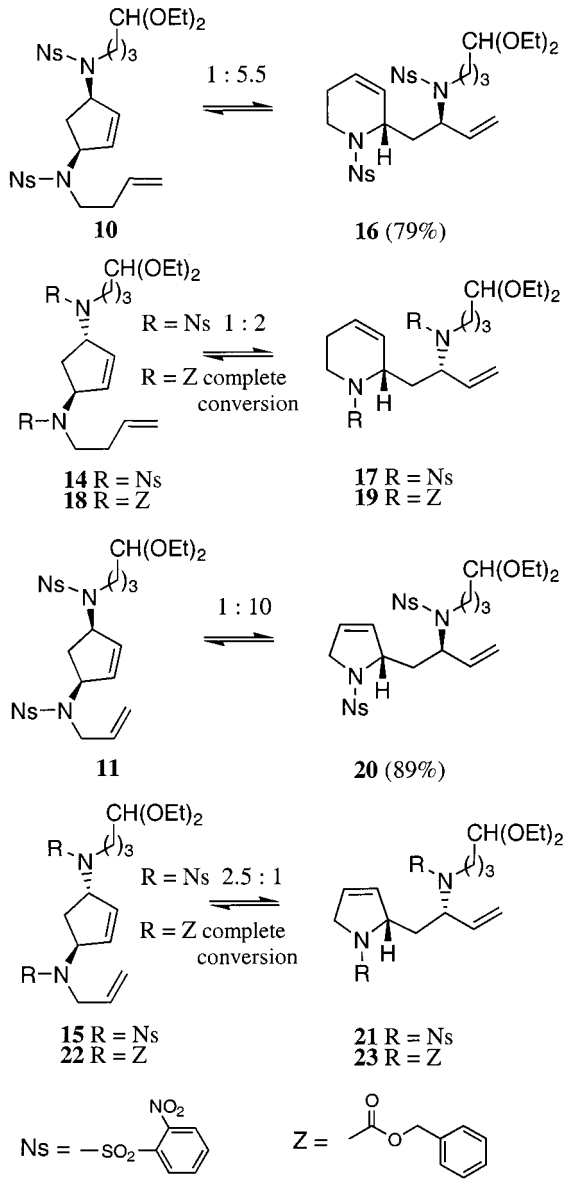
The Mitsunobu reaction was performed with 2 equiv of **8**, 2 equiv of diethyldiazodicarboxylate (DEAD), and 2.5 equiv of PPh_3 in THF. The *trans* diamides **14** and **15** were isolated in 87% and 81% yield, respectively.

After having all metathesis precursors available, the synthesis was continued by detailed investigations of the metathesis ring rearrangements. All reactions were carried out in CH_2Cl_2 using 5 mol % of the Grubbs' catalyst[15] **[Ru]** = $Cl_2(PCy_3)_2Ru{=}CHPh$ (Cy = cyclohexyl). To accelerate the metathesis reaction and to avoid formation of side products, the reactions were performed in the presence of an excess of ethylene.

First experiments with **10** under these conditions at room temperature showed slow conversion into the dihydropyridine derivative **16** (Scheme 6). The conversion could be accelerated by performing the reaction at 35 °C yielding **16** (79%) after 2 days. The ratio of **10**:**16** was 1:5.5 as determined by ^{1}H NMR. No other products were identified. Adding **[Ru]** to the purified metathesis product **16** in CH_2Cl_2 also resulted in a 1:5.5 ratio of starting material **10** to product **16**. When running the reaction with the trans-configurated cyclopentene derivative **14** under the same conditions, the ratio of **14**:**17** was only 1:2. These differences in the conversion could be attributed to the different free energies of the formed products. To improve this ratio we investigated the influence of the N-protecting groups on the equilibrium. We decided to use the benzyloxycarbonyl group Z, owing to its compatibility with the metathesis catalyst and subsequent reaction steps. The deprotection−protection sequence of **14** was performed in one pot employing K_2CO_3 and 2.2 equiv of thiophenol in DMF at 70 °C followed by addition of benzylchloroformate to yield **18** in 95% yield. The metathesis reaction of **18** proceeded quantitatively in 12 h even at room temperature. The starting material was completely consumed, and **19** was isolated in 97% yield. The higher conversion of the Z-protected metathesis precursor might be attributed to a changed complexation behavior.

After the synthesis of the six-membered heterocycles **16** and **19,** we continued with investigations of the synthesis of the dihydropyrrole derivatives. The metathesis reaction of **11** gave **20** in 89% yield. Compared to the metathesis of **10**:**16** (1:5.5), the ratio of **11**:**20** was 1:10. However, a ratio of only 2.5:1 was observed in the metathesis reaction of **15**. According to the synthesis of **19,** the Ns protecting groups of **15** were exchanged, applying the described one-pot procedure above, to yield **22** (93%). In the subsequent metathesis reaction **23** was isolated quantitatively. The influence of the relative stereochemistry of

Scheme 6. Ruthenium-Catalyzed Ring Rearrangement. Conditions: 5 mol % [**Ru**], CH_2Cl_2, C_2H_4



the substituents on the equilibrium of this metathesis reaction was comparable to those of the six-membered heterocycles **16**, **17,** and **19**. In contrast to the *cis*-configurated derivatives the *trans*-configurated cyclopentene derivatives were less efficiently converted into the corresponding heterocycles. However, the introduction of the benzyloxycarbonyl group in the *trans* derivatives resulted in quantitative conversion into the desired products.

After having completed all rearrangement reactions, we attempted to incorporate the different side chains of the tetraponerines employing a cross metathesis (CM) reaction. First, we decided to use allyltrimethylsilane, since it has previously been proven to be highly active in CM.[16]

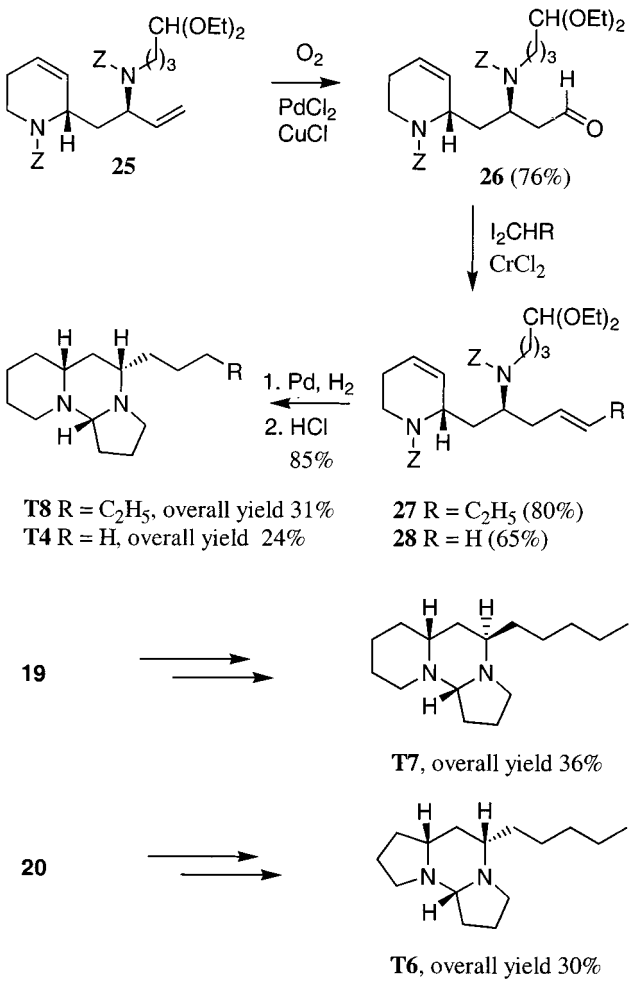
However, no CM products were obtained in the reaction of **16** or **19** with 3 equiv of allyltrimethylsilane and 10 mol % **[Ru]**. We presume that the terminal double bonds of **16** and **19** are too hindered for CM. Also the application of Schrock's molybdenum complex[17] $PhMe_2CCH{=}Mo{=}N[2,6\text{-}(i\text{Pr}_2C_6H_3]\text{-}[OCMe(CF_3)_2]_2$, did not yield any CM product.

(14) Mitsunobu, O. *Synthesis* **1981**, 1.

(15) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(16) (a) Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441. (b) Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117.

Scheme 7: Synthesis of Tetraponerines **T4**, **T6**, **T7,** and **T8**



Thus, a further functionalization of the terminal double bond was necessary to incorporate the different alkyl chains of the tetraponerines. For instance, an aldehyde function should easily be converted into an olefin. We found that under the conditions of the Wacker oxidation[18] the terminal double bonds of the metathesis products were cleanly transformed into the corresponding aldehydes. While the regioselective oxidation of protected allylic alcohols has been reported,[19] the selective Wacker oxidation of an allylic amine derivative to the aldehyde is unprecedented to the best of our knowledge. In the reaction of **19** with 10 mol % $PdCl_2$ and 0.5 equiv of CuCl dissolved in DMF/H_2O (4/1) under oxygen atmosphere, the aldehyde **24** (formula **26**, but (3*S*,4*S*)- instead of (3*R*,4*S*) configuration) was isolated in 79% yield. However, in the reaction of **16** under the same conditions only the amine **8** was isolated. A *retro*-Michael addition of the formed aldehyde would lead to this product. Consequently, we transformed **16** into the Z-protected diamine **25**, utilizing the one-pot procedure mentioned above. **25** was oxidized to the corresponding aldehyde **26** in 76% yield (Scheme 7).

Only 30% yield of the desired olefinated product **27** was isolated after the Wittig reaction of $(Ph)_3P{=}n$Pr with **26** owing to the *retro*-Michael side reaction. To avoid basic conditions during the olefination reaction, the Takai olefination[20] was used. Performing the reaction with $CrCl_2$ and $I_2CHCH_2CH_3$[21] in THF, **27** was obtained in 80% yield. The yield of **28** in the olefination reaction with I_2CH_2 was 65%.

The synthesis was continued with the cleavage of the protecting groups with concomitant hydrogenation of the double bonds employing Pd/C in EtOH. The diethoxy acetal was cleaved under acidic conditions (5% HCl) followed by stereoselective cyclization. The combined yield of hydrogenation and acidic cyclization was 86%. Tetraponerine **T8** was isolated in a remarkable 31% overall yield. Spectroscopical data and optical rotation $[\alpha]_D = +101.0°$ ($c = 2.0$, $CHCl_3$) were in accordance with the data of the natural product $[\alpha]_D = +102°$ ($c = 0.2$, $CHCl_3$).[5g] Tetraponerine **T4** was isolated in 24% overall yield; $[\alpha]_D = +96°$ ($c = 2.0$, $CHCl_3$), $[\alpha]_D = +94°$ ($c = 0.2$, $CHCl_3$).[5g]

Now we turned our attention to the synthesis of tetraponerine **T7** with the inverted stereochemistry at C-9 as compared to **T8** and **T4**. Employing the same reaction sequence to introduce the side chain into **24,** tetraponerine **T7** was isolated with 36% overall yield; $[\alpha]_D = +29.5°$ ($c = 2.2$, $CHCl_3$), $[\alpha]_D = +30°$ ($c = 0.22$, $CHCl_3$).[5g]

To demonstrate the syntheses of tetraponerines having a five-membered ring A, we synthesized **T6** starting from the dihydropyrrole derivative **20**. The synthesis of tetraponerine **T6** also required the exchange of protecting groups. Oxidation and olefination proceeded in comparable yields and tetraponerine **T6** was isolated in 30% overall yield; $[\alpha]_D = +35°$ ($c = 0.15$, $CHCl_3$), $[\alpha]_D = +35°$ ($c = 0.15$, $CHCl_3$).[5g]

The synthesis of four representative tetraponerines demonstrates the high efficiency of the metathesis rearrangement. The palladium-catalyzed tandem allylation was used to efficiently introduce the stereochemical information and gave rise to the metathesis precursors. The powerful combination of these catalytic processes served as the key for the flexible synthesis of four tetraponerines **T4**, **T6**, **T7,** and **T8**, which differ in the side chain, the stereochemistry at C-9, and the size of ring A. We demonstrated that the equilibrium of the metathesis rearrangement can be shifted in favor of the product by exchanging the N-protecting groups. Currently, we are investigating applications of this combination of asymmetric allylic amination and metathesis rearrangement for the synthesis of other alkaloids and heterocycles. Further studies of the effects of substituents and ring sizes in the metathesis rearrangement will be reported in due course.

Experimental Details

^{1}H NMR spectra (400, 500 MHz) and ^{13}C NMR spectra (106.4 MHz) were recorded on a BRUKER AM 400 and BRUKER DIGITAL 500 spectrometer relative to TMS. Mass spectra were recorded on a FINNIGAN MAT 95 SQ and IR spectra on a NICOLET FT-IR 750 spectrometer. Flash chromatography was performed on MERCK Silica Gel 60 (0.040−0.063 mm). MTBE = methyl *tert*-butyl ether. Chiral HPLC analyses were performed with a CHIRACEL OJ column (15% isopropyl alcohol, 85% hexane, flow 0.9 mL/min., 218 nm). Chemicals were purchased from Aldrich or MERCK and were used without further purification. Optical rotations were determined on a PERKIN-ELMER 141 polarimeter.

Methyl (1*R*,4*S*)-4-(But-3-enyl-*N*-nosylamino)cyclopent-2-enyl Carbonate (5). 1.1 g (5.09 mmol) of **1**, 1.3 g (5.09 mmol) of *N*-nosyl-3-butenylamine **3**, and 1.4 g (13.9 mmol) of Et_3N were dissolved in dry THF (15 mL) under nitrogen and cooled to −60 °C. 40 mg (0.038 mmol) of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 106 mg (0.153 mmol) of **2** were dissolved in dry THF (3 mL)

(17) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
(18) Tsuji, J. *Synthesis* **1984**, 369.
(19) Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678.
(20) Okazoe T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.
(21) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989.

under nitrogen and stirred for 30 min until the solution turned red-orange. The catalyst solution was added dropwise to the reaction mixture over 15 min. The solution was stirred for 1 h and was then allowed to warm to −35 °C. Hexane (50 mL) was then added, and the solvent was removed under vacuum. The residue was chromatographed on silica gel using MTBE/hexane (1:1) to yield 1.63 g (4.12 mmol, 89%) of **5** (yellow oil).^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, 1 H, J = 8 Hz, 1 Hz, nosyl), 7.70 (m, 2 H, nosyl), 7.62 (dd, 1 H, J = 8 Hz, 1 Hz, nosyl), 6.07 (ddd, 1 H, J = 6 Hz, 2 Hz, 2 Hz, H2), 5.99 (ddd, 1 H, J = 6 Hz, 2 Hz, 1 Hz, H3), 5.66 (ddt, 1 H, J = 17 Hz, 11 Hz, 7 Hz, H8), 5.43 (m, 1 H, H4), 5.02 (d, 1 H, J = 17 Hz, H9), 5.01 (d, 1 H, J = 11 Hz, H9), 4.98 (m, 1 H, H1), 3.87 (s, 3 H, OMe), 3.32 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz, H6), 3.10 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz, H6), 2.75 (dt, 1 H, J = 15 Hz, 8 Hz, H5), 2.32 (m, 2 H, H7), 1.66 (dt, 1 H, J = 15 Hz, 4 Hz, H5).^{13}C NMR ($CDCl_3$): δ = 155.0 (Cq, carbonyl), 148.0 (Cq, nosyl), 136.4 (CH, C2), 134.3 (CH, nosyl), 133.7 (CH, nosyl), 133.3 (Cq, nosyl), 133.0 (CH, C3), 131.7 (CH, nosyl), 130.9 (CH, nosyl), 124.2 (CH, C8), 117.2 (CH_2, C9), 80.2 (CH, C4), 61.7 (CH, C1), 54.7 (CH_3, OMe), 43.4 (CH_2, C6), 35.4 (CH_2, C5), 34.9 (CH_2, C7). IR (film): 3077, 2955, 1746, 1545, 1442, 1374, 1344, 1265, 1165, 1130, 1061, 954, 898, 779, 653 cm^{-1}. LRMS *m*/*z* (%): 355 (55) [M−$C_3H_5^+$], 321 (80) [M−$C_2H_3O_3^+$], 279 (76), 229 (18), 186 (58) [nosyl$^+$], 141 (100) [M−C_4H_7N-nosyl$^+$], 97 (99), 67 (72). HRMS Calcd for $C_{17}H_{19}N_2O_7S$ [M−H$^+$]: 395.0913. Found: 395.0912. Anal. Calcd for $C_{17}H_{20}N_2O_7S$: C, 51.51%; N, 7.07%; H, 5.09%. Found: C, 51.90%; N, 6.84%; H, 5.14%. $[\alpha]_D^{20}$ = −28.1° (c = 1, $CHCl_3$).

Methyl (1*R*,4*S*)-4-(*N*-Nosyl-1-prop-2-enylamino)cyclopent-2-enyl Carbonate (6). This compound was prepared from 500 mg (2.31 mmol) of **1** in 88% yield (780 mg, 2.04 mmol, yellow oil) by a procedure similar to that employed in the synthesis of **5**. (For data, see Supporting Information.)

(1*S*,4*R*)-1-But-3-enyl-1-[4-(4,4-diethoxybutylamino)cyclopent-2-ene]-*N*-nosylamine (9). 1.5 g (6.94 mmol) of **1**, 1.8 g (6.94 mmol) of *N*-nosyl-3-butenylamine **3**, and 2.1 g (20.8 mmol) of Et_3N were dissolved in dry THF (10 mL) under nitrogen and cooled to −60 °C. 52 mg (0.05 mmol) of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 141 mg (0.204 mmol) of **2** were dissolved in dry THF (3 mL) under nitrogen and stirred for 30 min. until the solution turned red-orange. The catalyst solution was added dropwise to the reaction mixture over 15 min. The solution was then stirred for 1 h and was allowed to warm to −35 °C. The solution was warmed to room temperature, and 2.24 g (13.89 mmol) of **7** dissolved in dry THF (3 mL) were added. After stirring for 1 h, the solvent was removed under vacuum and the residue was chromatographed on silica gel using CH_2Cl_2 (0.5% MeOH) to yield 2.69 g (5.59 mmol, 81%) of **9** (yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, 1 H, J = 8 Hz, 1 Hz, nosyl), 7.79 (m, 2 H, nosyl), 7.71 (dd, 1 H, J = 8 Hz, 1 Hz, nosyl), 6.02 (m, 1 H), 5.90 (m, 1 H), 5.68 (ddt, 1 H, J = 17 Hz, 11 Hz, 7 Hz), 5.43 (m, 1 H), 5.01 (d, 1 H, J = 17 Hz), 5.00 (d, 1 H, J = 11 Hz), 4.92 (m, 1 H), 4.80 (m, 1 H), 4.45 (t, 3 H, J = 7 Hz), 3.62 (m, 2 H), 3.46 (m, 2 H), 3.32 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz), 3.16 (m, 2 H), 2.99 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz), 2.33 (m, 2 H), 1.66−1.50 (m, 5 H), 1.18 (t, 6 H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): δ = 148.1 (Cq, nosyl), 135.1 (CH, olefin), 134.7 (CH, olefin), 134.3 (CH, nosyl), 133.6 (CH, nosyl), 133.5 (Cq, nosyl), 131.6 (CH, nosyl), 130.9 (CH, nosyl), 124.2 (CH, olefin), 116.9 (CH_2, olefin), 102.6 (CH), 76.8 (CH), 61.9 (CH), 61.3 (CH_2), 43.4 (CH_2), 40.7 (CH_2), 35.5 (CH_2), 35.2 (CH_2), 30.9 (CH_2), 24.9 (CH_2), 15.3 (CH_3). IR (film): 3500−3200, 3078, 2975, 2931, 2877, 1717, 1545, 1441, 1373, 1349, 1164, 1131, 1061, 996, 900, 778, 653 cm^{-1}. LRMS *m*/*z* (%): 321 (100) [M−$C_8H_{17}O_2N^+$], 279 (60), 270 (28), 224 (90) [M−C_4H_7N-nosyl$^+$], 186 (76) [nosyl$^+$], 178 (78), 142 (79), 134 (80), 114 (83), 103 (90), 94 (56), 83 (50). HRMS Calcd for $C_{23}H_{35}N_3O_6S$ [M$^+$]: 481.2247. Found: 481.2245. Anal. Calcd for $C_{23}H_{35}N_3O_6S$: C, 57.36%; N, 8.72%; H, 7.33%. Found: C, 55.36%; N, 8.17%; H, 6.93%. $[\alpha]_D^{20}$ = +10.9° (c = 1, $CHCl_3$).

(1*S*,4*R*)-*N*-But-3-enyl-*N*′-(4,4-diethoxybutyl)-*N*,*N*′-dinosylcyclopent-4-ene-1,3-diamine (10). 1.0 g (4.63 mmol) of **1**, 1.2 g (4.63 mmol) of *N*-nosyl-3-butenylamine **3,** and 1.87 g (18.5 mmol) of Et_3N were dissolved in dry THF (10 mL) under nitrogen and cooled to −60 °C. 72 mg (0.069 mmol) of tris(dibenzylideneacetone)dipalladium(0) chloroform complex and 192 mg (0.278 mmol) of **2** were dissolved in dry THF (3 mL) under nitrogen and stirred for 30 min. until the solution turned red-orange. The catalyst solution was then added dropwise to the reaction mixture over a period of 15 min. The solution was stirred for 1 h and was allowed to warm to −35 °C. Then the solution was warmed to room temperature. 119 mg (0.278 mmol) of dppb was then added, and after stirring for 10 min 1.6 g (4.63 mmol) of **8** dissolved in dry THF (5 mL) was added. After stirring for 3 h, the solvent was removed under vacuum and the residue was chromatographed on silica gel using MTBE/hexane (4:1) to yield 2.49 g (3.74 mmol, 79%) of **10** (yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, 2 H, J = 8 Hz, nosyl), 7.67 (m, 4 H, nosyl), 7.59 (d, 2 H, J = 8 Hz, nosyl), 5.82 (dm, 1 H, J = 6 Hz, H2), 5.78 (dm, 1 H, J = 6 Hz, H3), 5.65 (ddt, 1 H, J = 17 Hz, 12 Hz, 7 Hz, H8), 5.00 (d, 1 H, J = 17 Hz, H9), 4.99 (d, 1 H, J = 12 Hz, H9), 4.79 (m, 2 H, H4, H1), 4.38 (t, 1 H, J = 7 Hz, H13), 3.55 (m, 2 H, OCH_2CH$_3$), 3.41 (m, 2 H, OCH_2CH$_3$), 3.31 (m, 2 H, H6), 3.12 (m, 2 H, H7), 2.40 (dt, 1 H, J = 16 Hz, 8 Hz, H5), 2.32 (m, 2 H, H10), 1.62 (m, 3 H, H11, H5), 1.51 (m, 2 H, H12), 1.13 (t, 6 H, J = 7 Hz, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 147.8 (Cq, nosyl), 134.2 (CH, nosyl), 134.0 (CH, C2), 133.9 (CH, C3), 133.8 (CH, nosyl), 133.7 (CH, nosyl), 133.5 (Cq, nosyl), 133.3 (Cq, nosyl), 131.8 (CH, nosyl), 130.7 (CH, nosyl), 124.1 (CH, C8), 117.3 (CH_2, C9), 102.1 (CH, C13), 61.7 (CH, C4), 61.6 (CH, C1), 61.3 (CH_2, OCH_2CH$_3$), 61.2 (CH_2, OCH_2CH$_3$), 44.7 (CH_2, C6), 44.1 (CH_2, C10), 35.4 (CH_2, C7), 33.7 (CH_2, C11), 30.9 (CH_2, C12), 26.4 (CH_2, C5), 15.2 (CH_3, OCH$_2$CH_3). IR (film): 3095, 3078, 2975, 1726, 1544, 1440, 1373, 1348, 1163, 1125, 1060, 852, 779, 741, 653 cm^{-1}. LRMS *m*/*z* (%): 435 (23), 365 (13), 337 (12), 321 (36) [M−$C_8H_{17}O_2$N−nosyl$^+$], 215 (43) [CH$_3$N−nosyl$^+$], 186 (100) [nosyl$^+$], 94 (33). HRMS Calcd for $C_{29}H_{38}N_4O_{10}S_2$ [M$^+$]: 666.2029. Found: 666.2028. Anal. Calcd for $C_{29}H_{38}N_4O_{10}S_2$: C, 52.24%; N, 8.41%; H, 5.75%. Found: C, 52.16%; N, 8.14%; H, 6.01%. $[\alpha]_D^{20}$ = −5.2° (c = 1, $CHCl_3$).

(1*S*,4*R*)-*N*′-(4,4-Diethoxybutyl)-*N*,*N*′-dinosyl-*N*-prop-2-enylcyclopent-4-ene-1,3-diamine (11). This compound was prepared from 1.5 g (6.94 mmol) of **1** in 79% yield (3.56 g, 5.46 mmol) by a procedure similar to that employed in the synthesis of **10**. (For data, see Supporting Information.)

(1*R*,4*S*)-4-(But-3-enyl-*N*-nosylamino)cyclopent-2-enol (12). 1.45 g (3.66 mmol) of **5** was dissolved in 0.5 M NaOH/Dioxan (1:1) (30 mL) and stirred for 1 h at room temperature. Ethyl acetate (100 mL) and a saturated NaCl solution (30 mL) were added to the solution, and the aqueous layer was extracted two times with ethyl acetate (100 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed under vacuum. The residue was chromatographed on silica gel using MTBE/hexane (1:1) to yield 1.24 g (3.66 mmol, 99%) of **12** (yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, 1 H, J = 8 Hz, 1 Hz, nosyl), 7.69 (m, 2 H, nosyl), 7.61 (dd, 1 H, J = 8 Hz, 1 Hz, nosyl), 5.99 (ddd, 1 H, J = 6 Hz, 2 Hz, 2 Hz, olefin), 5.78 (ddd, 1 H, J = 6 Hz, 2 Hz, 1 Hz, olefin), 5.68 (ddt, 1 H, J = 17 Hz, 11 Hz, 7 Hz, olefin), 5.02 (d, 1 H, J = 17 Hz, olefin), 5.01 (d, 1 H, J = 11 Hz, olefin), 4.85 (m, 1 H), 4.70 (m, 1 H), 3.36 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz), 3.18 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz), 2.62 (dt, 1 H, J = 15 Hz, 8 Hz), 2.34 (m, 2 H), 2.10 (sbr, 1 H, OH), 1.51 (dt, 1 H, J = 15 Hz, 5 Hz). ^{13}C NMR ($CDCl_3$): δ = 148.0 (Cq, nosyl), 137.3 (CH, olefin), 134.4 (CH, nosyl), 133.6 (CH, olefin), 133.2 (CH, nosyl), 133.2 (Cq, nosyl), 131.6 (CH, nosyl), 130.8 (CH, nosyl), 124.1 (CH, olefin), 117.1 (CH_2, olefin), 74.4 (CH), 62.4 (CH), 44.0 (CH_2), 38.4 (CH_2), 35.4 (CH_2). IR (film): 3600−3200, 3075, 2978, 2943, 1543, 1439, 1372, 1344, 1161, 1130, 1062, 896, 825, 776, 653 cm^{-1}. LRMS *m*/*z* (%): 297 (28) [M−C_4H_7N−nosyl$^+$], 215 (90) [M−CH$_3$N−nosyl$^+$], 186 (100) [nosyl$^+$], 83 (50). HRMS Calcd for $C_{15}H_{18}N_2O_5S$ [M$^+$]: 338.0936. Found: 338.0938. Anal. Calcd for $C_{15}H_{18}N_2O_5S$: C, 53.24%; N, 8.28%; H, 5.36%. Found: C, 53.21%; N, 8.23%; H, 5.32%. $[\alpha]_D^{20}$ = −20.3° (c = 1, $CHCl_3$).

(1*R*,4*S*)-4-(*N*-Nosylprop-2-enylamino)cyclopent-2-enol (13). This compound was prepared from 720 mg (1.89 mmol) of **6** in 98% yield (600 mg, 1.85 mmol, yellow oil) by a procedure similar to that employed in the synthesis of **12**. (For data, see Supporting Information.)

(1*S*,4*S*)-*N*-But-3-enyl-*N*′-(4,4-diethoxybutyl)-*N*,*N*′-dinosylcyclopent-4-ene-1,3-diamine (14). 1.75 g (5.18 mmol) of **12**, 3.6 g (10.36 mmol) of **8**, and 3.4 g (12.94 mmol) of PPh_3 were dissolved in dry THF (150 mL) under nitrogen. 1.8 g (10.36 mmol) of DEAD dissolved in dry

THF (10 mL) was added dropwise to the reaction mixture over 15 min. After stirring for 1 h, the solvent was removed under vacuum and the residue was chromatographed on silica gel using MTBE/hexane (4:1) to yield 2.9 (4.35 mmol, 87%) of **14** (yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2 H, nosyl), 7.67 (m, 4 H, nosyl), 7.59 (d, 2 H, J = 8 Hz, nosyl), 5.87 (m, 2 H, H2, H3), 5.64 (ddt, 1 H, J = 17 Hz, 11 Hz, 7 Hz, H8), 5.19 (m, 2 H, H1, H4), 5.01 (d, 1 H, J = 11 Hz, H9), 5.00 (d, 1 H, J = 17 Hz, H9), 4.40 (t, 1 H, J = 7 Hz, H13), 3.59 (m, 2 H, OCH_2CH$_3$), 3.44 (m, 2 H, OCH_2CH$_3$), 3.22 (m, 2 H, H6), 2.90 (m, 2 H, H10), 2.27 (m, 2 H, H7), 1.96 (t, 2 H, J = 7 Hz, H5), 1.56−1.47 (m, 4 H, H11, H12), 1.16 (t, 6 H, J = 7 Hz, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 148.0 (Cq, nosyl), 135.4 (CH, C2), 135.1 (CH, C3), 134.1 (CH, nosyl), 133.7 (CH, nosyl), 133.6 (CH, nosyl), 133.4 (Cq, nosyl), 133.3 (Cq, nosyl), 131.7 (CH, nosyl), 130.8 (CH, nosyl), 124.1 (CH, C8), 117.4 (CH$_2$, C9), 102.3 (CH, C13), 63.8 (CH, C1), 63.7 (CH, C4), 61.3 (CH$_2$, OCH$_2$CH$_3$), 44.5 (CH$_2$, C6), 44.0 (CH$_2$, C10), 35.3 (CH$_2$, C7), 33.1 (CH$_2$, C11), 31.0 (CH$_2$, C5), 26.3 (CH$_2$, C12), 15.3 (CH$_3$, OCH$_2$CH_3). IR (film): 3074, 2975, 2929, 1734, 1543, 1439, 1372, 1352, 1163, 1121, 1059, 852, 776, 742, 652 cm^{-1}. LRMS *m*/*z* (%): 435 (100) [M−C$_3$H$_5$−nosyl$^+$], 366 (38), 321 (98) [M−C$_8$H$_{17}$O$_2$N−nosyl$^+$], 186 (84) [nosyl$^+$], 179 (50), 103 (49), 94 (75), 85 (51). HRMS Calcd for $C_{29}H_{38}N_4O_{10}S_2$ [M$^+$]: 666.2029. Found: 666.2037. Anal. Calcd for $C_{29}H_{38}N_4O_{10}S_2$: C, 52.24%; N, 8.41%; H, 5.75%. Found: C, 52.03%; N, 8.17%; H, 5.97%. $[\alpha]_D^{20}$ = −36.0° (*c* = 1, $CHCl_3$).

(1*S*,4*S*)-*N*′-(4,4-Diethoxybutyl)-*N*,*N*′-dinosyl-*N*-prop-2-enylcyclopent-4-ene-1,3-diamine (15). This compound was prepared from 625 mg (0.185 mmol) of **13** in 81% yield (978 mg, 0.15 mmol, yellow oil) by a procedure similar to that employed in the synthesis of **14**. (For data, see Supporting Information.)

(2*S*,8*S*)-2-[2-(4,4-Diethoxybutyl)-*N*-nosylamino]but-3-enyl-*N*-nosyl-1,2,5,6 -tetrahydropyridine (16). 1.4 g (2.102 mmol) of **10** was dissolved in dry CH_2Cl_2 (100 mL), and C_2H_4 (50 mL) was slowly bubbled through the solution. 87 mg (0.105 mmol) of **[Ru]** was then added, and the mixture was stirred at 35 °C for 48 h. The solvent was removed under vacuum, and the residue was chromatographed on silica gel using MTBE/hexane (7:3) to yield 1.105 g (1.66 mmol, 79%) of **16** (yellow oil) and 225 mg (0.338 mmol, 15%) of **10**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, 2 H, J = 8 Hz, nosyl), 7.92 (d, 2 H, J = 8 Hz, nosyl), 7.74−7.56 (m, 5 H, nosyl), 7.52 (d, 2 H, J = 8 Hz, nosyl), 5.84−5.59 (m, 3 H, H3, H4, H9), 5.22 (d, 1 H, J = 11 Hz, H10), 5.15 (d, 1 H, J = 17 Hz, H10), 4.45 (t, 1 H, J = 7 Hz, H14), 4.40 (m, 1 H, H12), 4.31 (m, 1 H, H18), 3.94 (dd, 1 H, J = 15 Hz, 7 Hz, H7), 3.60 (m, 2 H, OCH_2CH$_3$), 3.45 (m, 2 H, OCH_2CH$_3$), 3.40−3.20 (m, 3 H, H6, H7), 2.22−2.00 (m, 3 H, H5, H11), 1.82 (dm, 1 H, J = 15 Hz. H5), 1.69 (m, 2 H, H12), 1.58 (m, 2 H, H13), 1.16 (t, 6 H, J = 7 Hz, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 148.0 (Cq, nosyl), 147.8 (Cq, nosyl), 134.2 (CH, nosyl), 133.7 (Cq, nosyl), 133.5 (CH, nosyl), 133.4 (CH, nosyl), 133.1 (Cq, nosyl), 132.0 (CH, nosyl), 131.6 (CH, nosyl), 130.2 (CH, nosyl), 126.9 (CH, nosyl), 125.4 (CH, C9), 124.0 (CH, C3), 123.8 (CH, C4), 119.2 (CH$_2$, C10), 102.4 (CH, C14), 61.4 (CH$_2$, OCH$_2$CH$_3$), 61.2 (CH$_2$, OCH$_2$CH$_3$), 56.1 (CH, C2), 51.6 (CH, C8), 45.0 (CH$_2$, C6), 38.2 (CH$_2$, C11), 37.8 (CH$_2$, C12), 31.0 (CH$_2$, C7), 26.3 (CH$_2$, C5), 23.0 (CH$_2$, C13), 15.3 (CH$_3$, OCH$_2$CH_3). IR (film): 3095, 3074, 2930, 2878, 1543, 1439, 1373, 1351, 1163, 1125, 1059, 999, 852, 779, 729, 678 cm^{-1}. LRMS *m*/*z* (%): 434 (10), 267 (100) [C$_5$H$_7$N−nosyl$^+$], 186 (35) [nosyl$^+$]. HRMS Calcd for $C_{29}H_{37}N_4O_{10}S_2$ [M−H$^+$]: 665.1951. Found: 665.1955. Anal. Calcd for $C_{29}H_{38}N_4O_{10}S_2$: C, 52.24%; N, 8.41%; H, 5.75%. Found: C, 52.59%; N, 8.29%; H, 5.86%. $[\alpha]_D^{20}$ = +82.3° (*c* = 1, $CHCl_3$).

(1*S*,4*S*)-*N*-But-3-enyl-*N*,*N*′-dibenzyloxycarbonyl-*N*′-(4,4-diethoxybutyl)cyclopent-4-ene-1,3-diamine (18). 1.6 g (2.4 mmol) of **14** and 3.3 g (24 mmol) of K_2CO_3 were dissolved in dry DMF (30 mL) and heated to 70 °C. 660 mg (6.0 mmol) of thiophenol was then added and the solution stirred for 30 min. The mixture was cooled to room temperature, and 1.0 g (6.0 mmol) of benzylchloroformiate, dissolved in dry DMF (3 mL), was added. After an additional 10 min of stirring, MTBE (100 mL) was added. The mixture was filtered, and the solvent was removed under vacuum. The residue was chromatographed on silica gel using MTBE/hexane (3:7) to yield 1.29 g (2.29 mmol, 95%) of **18** (clear oil). (For data, see Supporting Information.)

(2*S*,8*R*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-but-3-enyl-1,2,5,6-tetrahydropyridine (19). 1.6 g (2.84 mmol) of **18** was dissolved in dry CH_2Cl_2 (100 mL), and C_2H_4 (50 mL) was bubbled slowly through the solution. 117 mg (0.142 mmol) of **[Ru]** was then added, and the mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, and the residue was chromatographed on silica gel using MTBE/hexane (3:7) to yield 1.55 g (2.75 mmol, 97%) of **19** (clear oil). ^{1}H NMR (500 MHz, C_6D_6): δ = 7.30−7.00 (m, 10 H, phenyl), 6.01−5.88 (m, 1 H), 5.57 (dm, 2 H, J = 6 Hz), 5.52 (dm, 2 H, J = 6 Hz), 5.13 (m, 5 H), 4.97 (d, 1 H, J = 11 Hz), 4.72−4.61 (m, 1 H), 4.54 (m, 1 H), 4.41 (t, 1 H, J = 7 Hz), 4.18−4.00 (m, 1 H), 3.51 (m, 2 H), 3.35 (m, 2 H), 3.33−3.16 (m, 1 H), 2.69 (ddd, 1 H, J = 15 Hz, 6 Hz, 4 Hz), 1.99 (m, 3 H), 1.74 (m, 2 H), 1.60 (m, 2 H), 1.49 (dm, 1 H, J = 17 Hz), 1.10 (t, 6 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 155.7 (Cq), 155.0 (Cq), 137.7 (CH), 137.6 (Cq), 137.4 (Cq), 128.3−127.5 (9 C), 116.2 (CH$_2$), 102.7 (CH), 66.9 (CH$_2$), 66.8 (CH$_2$), 60.8 (CH$_2$), 60.7 (CH$_2$), 57.5 (CH), 50.3 (CH), 45.8 (CH$_2$), 37.2 (CH$_2$), 37.1 (CH$_2$), 31.4 (CH$_2$), 25.3 (CH$_2$), 24.7 (CH$_2$), 15.2 (CH$_3$). IR (film): 3065, 3033, 2974, 2943, 2896, 1695, 1455, 1415, 1287, 1138, 1069, 994, 770, 698 cm^{-1}. LRMS *m*/*z* (%): 518 (14) [M−C$_2$H$_6$O$^+$], 427 (18) [M−Z$^+$], 383 (22), 270 (53), 224 (18), 134 (16), 91 (100) [C$_7$H$_7$+]. HRMS Calcd for $C_{33}H_{44}N_2O_6$ [M$^+$]: 564.3199. Found: 564.3202. Anal. Calcd for $C_{33}H_{44}N_2O_6$: C, 70.19%; N, 4.96%; H, 7.85%. Found: C, 70.49%; N, 5.20%; H, 7.63%. $[\alpha]_D^{20}$ = +82.4° (*c* = 1, $CHCl_3$).

(2*S*,7*R*)-2-[2-(4,4-Diethoxybutyl)-*N*-nosylamino]but-3-enyl-*N*-nosyl-2,5-dihydropyrrole (20). This compound was prepared from 1.3 g (1.98 mmol) of **11** in 89% yield (1.15 g, 1.95 mmol) by a procedure similar to that employed in the synthesis of **19**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (m, 1 H, nosyl), 7.85 (m, 1 H, nosyl), 7.74−7.55 (m, 6 H, nosyl), 5.96 (dd, 1 H, J = 6 Hz, 2 Hz, H3), 5.77 (d, 1 H, J = 6 Hz, H4), 5.96 (ddd, 1 H, J = 17 Hz, 10 Hz, 6 Hz, H8), 5.15 (d, 1 H, J = 10 Hz, H5), 5.11 (d, 1 H, J = 17 Hz, H5), 4.82 (m, 1 H, H7), 4.54 (m, 1 H, H2), 4.46 (t, 1 H, J = 7 Hz, H13), 4.29 (dd, 1 H, J = 16 Hz, 1 Hz, H6), 4.12 (ddd, 1 H, J = 6 Hz, 2 Hz, 1 Hz, H6), 3.60 (m, 2 H, OCH_2CH$_3$), 3.46 (m, 2 H, OCH_2CH$_3$), 3.29 (dd, 2 H, J = 10 Hz, 7 Hz, H6), 2.37 (ddd, 1 H, J = 15 Hz, 9 Hz, 4 Hz, H10), 1.98 (ddd, 1 H, J = 15 Hz, 9 Hz, 6 Hz, H10), 1.77 (m, 2 H, H11), 1.68 (m, 2 H, H12), 1.16 (t, 6 H, J = 7 Hz, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 148.8 (Cq, nosyl), 148.1 (Cq, nosyl), 135.8 (CH, C3), 133.7 (Cq, nosyl), 133.6 (Cq, nosyl), 133.5 (CH, nosyl), 131.8 (CH, nosyl), 131.7 (CH, nosyl), 130.8 (CH, C4), 129.6 (CH, nosyl), 129.4 (CH, nosyl), 125.4 (CH, C8), 124.2 (CH, nosyl), 124.0 (CH, nosyl), 118.5 (CH$_2$, C3), 102.5 (CH, C13), 65.1 (CH, C2), 61.5 (CH$_2$, OCH$_2$CH$_3$), 61.3 (CH$_2$, OCH$_2$-CH$_3$), 56.6 (CH, C7), 55.2 (CH$_2$, C5), 44.9 (CH$_2$, C6), 39.0 (CH$_2$, C10), 31.1 (CH$_2$, C11), 26.2 (CH$_2$, C12), 15.3 (CH$_3$, OCH$_2$CH_3). IR (film): 3093, 2975, 2930, 2881, 1544, 1439, 1373, 1354, 1167, 1127, 1060, 1000, 852, 779, 742, 655 cm^{-1}. LRMS *m*/*z* (%): 420 (36) [M−C$_3$H$_9$N−nosyl$^+$], 253 (100), 186 (92) [nosyl$^+$], 70 (56). HRMS Calcd for $C_{28}H_{35}N_4O_{10}S_2$ [M−H$^+$]: 651.1795. Found: 651.1797. Anal. Calcd for $C_{28}H_{36}N_4O_{10}S_2$: C, 51.25%; N, 8.58%; H, 5.56%. Found: C, 51.77%; N, 8.24%; H, 5.80%. $[\alpha]_D^{20}$ = +86.5° (*c* = 1, $CHCl_3$).

(1*S*,4*S*)-*N*,*N*′-Dibenzyloxycarbonyl-*N*′-(4,4-diethoxybutyl)-*N*-prop-2-enyl-cyclopent-4-ene-1,3-diamine (22). This compound was prepared from 170 mg (0.261 mmol) of **15** in 94% yield (135 mg, 0.245 mmol, clear oil) by a procedure similar to that employed in the synthesis of **18**. (For data, see Supporting Information.)

(2*S*,7*S*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-but-3-enyl-2,5-dihydro-1*H*-pyrrole (23). This compound was prepared from 100 mg (0.182 mmol) of **22** in 99% yield (99 mg, 0.18 mmol) by a procedure similar to that employed in the synthesis of **19**. ^{1}H NMR (500 MHz, C_6D_6): δ = 7.30−7.00 (m, 10 H, phenyl), 5.98−5.81 (m, 1 H), 5.60−5.50 (m, 1 H), 5.27 (m, 1 H), 5.20−5.05 (m, 5 H), 5.03−4.91 (m, 1 H), 4.72−4.53 (m, 1 H), 4.40 (t, 1 H, J = 7 Hz), 4.03−3.86 (m, 1 H), 3.51 (m, 2 H), 3.35 (m, 2 H), 3.26−3.10 (m, 1 H), 2.04−1.88 (m, 1 H), 1.80−1.66 (m, 2 H), 1.58 (m, 2 H), 1.09 (t, 6 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 155.6 (Cq, carbonyl), 154.2 (Cq, carbonyl), 137.7 (Cq, phenyl), 137.5 (Cq, phenyl), 129.7 (CH), 128.3−127.5 (8 C), 125.1 (CH), 116.3 (CH$_2$), 102.7 (CH), 66.8 (CH$_2$), 60.7 (CH$_2$), 56.9 (CH), 48.7 (CH), 45.3 (CH$_2$), 31.4 (CH$_2$), 26.8 (CH$_2$), 25.3 (CH$_2$), 15.2 (CH$_3$). IR (film): 3065, 3032,

2973, 2930, 2875, 1698, 1455, 1413, 1272, 1126, 1062, 1002, 769, 698 cm^{-1}. LRMS *m*/*z* (%): 505 (14) [M−$C_2H_5O^+$], 256 (18), 91 (100) [$C_7H_7^+$]. HRMS Calcd for $C_{30}H_{37}N_2O_5$ [M−$C_2H_5O^+$]: 505.2702. Found: 505.2709. Anal. Calcd for $C_{32}H_{42}N_2O_6$: C, 69.79%; N, 5.09%; H, 7.69%. Found: C, 69.61%; N, 5.16%; H, 7.77%. $[\alpha]_D^{20} = +72.0°$ (c = 1, $CHCl_3$).

Total Synthesis of Tetraponerines T4 and T8. (2*S*,8*R*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-but-3-enyl-1,2,5,6-tetrahydropyridine (25). This compound was prepared from 1 g (0.15 mmol) of **16** in 96% yield (813 mg, 1.44 mmol) by a procedure similar to that employed in the synthesis of **18**. (For data, see Supporting Information.)

(3*R*,4*S*)-3-[*N*-Benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-4-(*N*-benzyloxycarbonyl-1,2,5,6-tetrahydropyridin-2-yl)butyraldehyde (26). 650 mg (1.152 mmol) of **25** was dissolved in DMF/H_2O (4:1) (20 mL) under an oxygen atmosphere. 20 mg (0.115 mmol) of $PdCl_2$ and 57 mg (0.576 mmol) of CuCl were added, and the suspension was stirred for 6 h. MTBE (100 mL) was then added, and the mixture was dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed on silica gel using MTBE/hexane (1:1) to yield 510 mg (0.876 mmol, 76%) of **26** (clear oil). ^{1}H NMR (500 MHz, C_6D_6): δ = 9.43 (sbr, 1 H, aldehyde), 7.30−7.00 (m, 10 H, phenyl), 5.68−5.58 (m, 1 H. olefin), 5.51 (m, 1 H, olefin), 5.19−5.01 (m, 4 H, benzyl), 4.54−4.39 (m, 3 H), 4.19−3.99 (m, 1 H), 3.52 (m, 2 H), 3.40−3.25 (m, 3 H), 3.19−3.07 (m, 1 H), 2.77−2.33 (m, 3 H), 2.02−1.53 (m, 8 H), 1.48 (dm, 1 H, J = 18 Hz), 1.11 (t, 6 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 198.7 (CH, aldehyde), 155.8 (Cq, carbonyl), 155.0 (Cq, carbonyl), 137.3 (Cq, phenyl), 128.4−127.5 (8 C, phenyl), 125.5 (CH, olefin), 102.7 (CH), 102.6 (CH), 102.4 (CH), 67.0 (CH), 67.0 (CH_2), 66.9 (CH_2), 60.9 (CH_2, benzyl), 60.8 (CH_2), 60.4 (CH_2), 49.8 (CH_2), 49.7 (CH_2), 47.2 (CH), 45.6 (CH_2), 45.9 (CH_2), 37.9 (CH_2), 37.1 (CH_2), 31.4 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 24.5 (CH_2), 15.3 (CH_3). IR (film): 3033, 2972, 2929, 2899, 1695, 1424, 1308, 1241, 1111, 1060, 699 cm^{-1}. LRMS *m*/*z* (%): 535 (18) [M−$C_2H_5O^+$], 399 (30), 216 (28) [$C_5H_{10}NZ^+$], 172 (82) [$C_9H_{18}O_2N^+$], 91 (100) [$C_7H_7^+$]. HRMS Calcd for $C_{31}H_{39}N_2O_6$ [M−$C_2H_5O^+$]: 535.2808. Found: 535.2810. Anal. Calcd for $C_{33}H_{44}N_2O_7$: C, 68.25%; N, 4.82%; H, 7.64%. Found: C, 68.38%; N, 5.12%; H, 7.61%. $[\alpha]_D^{20} = +51.8°$ (c = 1, $CHCl_3$).

(2*S*,8*S*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]hept-4-enyl-1,2,5,6-tetrahydropyridine (27). A. Wittig Reaction. 380 mg (0.987 mmol) of $P(Ph)_3(CH_2)_3Br$ and 14 mg (0.987 mmol) of NaH were dissolved in dry THF/DMF (1:1) (4 mL) and stirred at 40 °C for 30 min. The mixture was cooled to 0 °C, and 200 mg (0.394 mmol) of **26** dissolved in dry THF (1 mL) was added. 0.5 mL of saturated NH_4Cl solution was then added, and the mixture was dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed on silica gel using MTBE/hexane (3:7) to yield 90 mg (0.148 mmol, 38%) of **27** (clear oil).

B. Takai Olefination. 250 mg (2.07 mmol) of $CrCl_2$ were dissolved in dry THF (15 mL) under nitrogen, and 150 mg (2.07 mmol) of dry DMF dissolved in THF (1 mL) were added. The suspension was stirred for 30 min. 153 mg (0.517 mmol) of 1,1-diiodopropane dissolved in THF (1 mL) and 150 mg (0.259 mmol) of **26** dissolved in THF (1 mL) were added, and the suspension was stirred for an additional 30 min. The reaction mixture was filtered through silica gel, and the solvent was removed under vacuum. The residue was chromatographed on silica gel using MTBE/hexane (3:7) to yield 126 mg (0.166 mmol, 80%) of **27** (clear oil). ^{1}H NMR (500 MHz, C_6D_6): δ = 7.30−7.00 (m, 10 H, phenyl), 5.57−5.72 (m, 1 H), 5.58−5.32 (m, 3 H), 5.20−5.07(m, 4 H), 4.65−4.42 (m, 2 H), 4.31−4.0 (m, 2 H), 3.53 (m, 2 H), 3.35 (m, 2 H), 3.33−3.05 (m, 2 H), 2.73 (m, 1 H), 2.41−2.19 (m, 2 H), 2.05−1.54 (m, 10 H), 1.50 (dm, 1 H, J = 17 Hz), 1.11 (t, 6 H, J = 7 Hz), 0.91 (t, 3 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 156.2 (Cq, carbonyl), 154.9 (Cq, carbonyl), 137.6 (Cq, phenyl), 137.5 (CH), 134.5 (CH), 133.5 (Cq, phenyl), 128.3−127.5 (8 C, phenyl), 126.0 (CH), 125.2 (CH), 102.8 (CH), 66.9 (CH_2), 66.8 (CH_2), 66.7 (CH_2), 60.8 (CH_2), 60.7 (CH_2), 54.7 (CH), 50.2 (CH), 37.1 (CH_2), 36.9 (CH_2), 31.6 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 20.7 (CH), 20.7 (CH_2), 15.3 (CH_3), 13.6 (CH_3). IR (film): 3032, 2958, 2930, 1693, 1455, 1423, 1310, 1242, 1196, 1100, 1064, 697 cm^{-1}. LRMS *m*/*z* (%): 561 (7) [M−$C_2H_6O^+$], 535 (21), 489 (70), 353 (56), 258 (27), 216 (94) [$C_5H_{10}NZ^+$], 172 (96) [$C_9H_{18}O_2N^+$], 91 (100) [$C_7H_7^+$]. HRMS Calcd for $C_{34}H_{45}N_2O_5$ [M−$C_2H_5O^+$]: 561.3328, Found: 561.3329. Anal. Calcd for $C_{36}H_{50}N_2O_6$: C, 71.02%; N, 4.60%; H, 8.61%. Found: C, 71.16%, N, 4.75%, H, 8.15%. $[\alpha]_D^{20} = +43.4°$ (c = 1, $CHCl_3$).

Tetraponerine T8. 270 mg (0.446 mmol) of **27** and 20 mg of Pd/C (10%) were dissolved in EtOH (10 mL) and stirred for 8 h under hydrogen. The solvent was removed under vacuum, the residue was taken up in 5% HCl (20 mL) and stirred for 12 h. Concentrated NaOH solution was added to reach a final pH of 12. The aqueous layer was extracted twice with ethyl acetate (50 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was filtered with MTBE through silica gel (1 mL) to yield 96 mg (0.384 mmol, 86%) of **T8**. ^{1}H NMR (500 MHz, C_6D_6): δ = 3.14 (ddd, 1 H, J = 8 Hz, 8 Hz, 2 Hz), 2.82 (ddd, 1 H, J = 10 Hz, 3 Hz, 3 Hz), 2.30 (dd, 1 H, J = 8 Hz, 6 Hz), 2.11 (m, 1 H), 2.03 (q, 1 H, J = 8 Hz), 1.8−1.1 (m, 22 H), 0.89 (t, 3 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 85.3 (CH), 62.4 (CH), 61.1 (CH), 51.3 (CH_2), 48.8 (CH_2), 37.7 (CH_2), 34.3 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 22.8 (CH_2), 19.9 (CH_2), 14.1 (CH_3). IR (film): 2953, 2929, 2858, 2793, 2540, 2511, 1490, 1378 cm^{-1}. LRMS *m*/*z* (%): 250 (51) [M$^+$], 249 (81) [M−H$^+$], 235 (81) [M-CH_3^+], 193 (95) [$C_{12}H_{21}N_2$+], 152 (61), 96 (100). HRMS Calcd for $C_{16}H_{30}N_2$ [M$^+$]: 250.2409. Found: 250.2409. $[\alpha]_D^{20} = +101.0°$ (c = 2.0, $CHCl_3$).

Synthesis of Tetraponerine T4. (2*S*,8*S*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]pent-4-enyl-1,2,5,6-tetrahydropyridine (28). 250 mg (2.07 mmol) of $CrCl_2$ was dissolved in dry THF (15 mL) under nitrogen, and 150 mg (2.07 mmol) of dry DMF dissolved in THF (1 mL) was added. The suspension was stirred for 30 min. 140 mg (0.517 mmol) of diiodomethane dissolved in THF (1 mL) and 150 mg (0.259 mmol) of **26** dissolved in THF (1 mL) were added, and the suspension was stirred for an additional 30 min. The reaction mixture was filtered through silica gel, and the solvent was removed under vacuum. The residue was chromatographed on silica gel using MTBE/hexane (3:7) to yield 97 mg (0.168 mmol, 65%) of **28** (clear oil). (For data, see Supporting Information.)

Tetraponerine T4 was prepared in 80% yield (57 mg, 0.257 mmol) from **28** by a procedure similar to that employed in the synthesis of **T8**. ^{1}H NMR (500 MHz, C_6D_6): δ = 3.11 (ddd, 1 H, J = 8 Hz, 8 Hz, 3 Hz), 2.82 (ddd, 1 H, J = 10 Hz, 3 Hz, 3 Hz), 2.29 (dd, 1 H, J = 8 Hz, 6 Hz), 2.11 (m, 1 H), 2.01 (q, 1 H, J = 8 Hz), 1.8−1.1 (m, 18 H), 0.88 (t, 3 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 85.3 (CH), 62.4 (CH), 60.9 (CH), 51.3 (CH_2), 48.7 (CH_2), 37.7 (CH_2), 36.6 (CH_2), 32.7 (CH_2), 29.4 (CH_2), 26.0 (CH_2), 24.8 (CH_2), 19.9 (CH_2), 18.4 (CH_2), 14.5 (CH_3). IR (film): 2955, 2931, 2871, 2857, 1790, 1705, 2510, 1460, 1378, 1191 cm^{-1}. LRMS *m*/*z* (%): 222 (43) [M$^+$], 221 (85) [M−H$^+$], 193 (100) [$C_{12}H_{21}N_2^+$], 152 (96), 96 (90). HRMS Calcd for $C_{14}H_{26}N_2$ [M$^+$]: 222.2096. Found: 222.2099. $[\alpha]_D^{20} = +96°$ (c = 2.0, $CHCl_3$).

Total Synthesis of Tetraponerine T7. (3*S*,4*S*)-3-[*N*-Benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-4-(*N*-benzyloxycarbonyl-1,2,5,6-tetrahydropyridin-2-yl)butyraldehyde (24). This compound was prepared from 350 mg (0.636 mmol) of **19** in 79% yield (280 mg, 0.483 mmol) by a procedure similar to that employed in the synthesis of **26**. (For data, see Supporting Information.)

(2*S*,8*S*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-hept-4-enyl-1,2,5,6-tetrahydropyridine. This compound was prepared from 150 mg (0.248 mmol) of **24** in 77% yield (121 mg, 0.20 mmol, clear oil) by a procedure similar to that employed in the synthesis of **27**. (For data, see Supporting Information.)

Tetraponerine T7 was prepared from 300 mg (0.493 mmol) of the olefin in 84% yield (103 mg, 0.412 mmol) by a procedure similar to that employed in the synthesis of **T8**. ^{1}H NMR (500 MHz, C_6D_6): δ = 3.31 (dd, 1 H, J = 6 Hz, 2 Hz), 3.13 (m, 1 H), 2.86−2.75 (m, 3 H), 2.05 (tm, 1 H, J = 11 Hz), 1.90 (ddd, 1 H, J = 12 H, 12 H, 5 H), 1.82−1.1 (m, 20 H), 0.92 (t, 3 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 75.6 (CH), 56.9 (CH), 53.5 (CH), 51.1 (CH_2), 50.8 (CH_2), 34.4 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 31.2 (CH_2), 30.7 (CH_2), 27.5 (CH_2), 26.7 (CH_2), 25.4 (CH_2), 23.4 (CH_2), 22.3 (CH_2), 14.5 (CH_3). IR (film): 2953, 2927, 2856, 2748, 2624, 1455, 1352, 1130 cm^{-1}. LRMS *m*/*z* (%): 250 (76) [M$^+$], 249 (96) [M−H$^+$], 193 (100) [$C_{12}H_{21}N_2$+], 152 (59), 96 (57).

HRMS Calcd for $C_{16}H_{30}N_2$ [M^+]: 250.2409. Found: 250.2407. $[\alpha]_D^{20} = +29.5°$ ($c = 2.2$, $CHCl_3$).

Total Synthesis of Tetraponerine T6. (2*S*,7*R*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-but-3-enyl-2,5-dihydropyrrole. This compound was prepared from 810 mg (1.24 mmol) of **20** in 91% yield (620 mg, 1.13 mmol) by a procedure similar to that employed in the synthesis of **18**. (For data, see Supporting Information.)

(3*R*,4*S*)-3-[*N*-Benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-4-[*N*-benzyloxycarbonyl-2,5-dihydropyrrol-2-yl)butyraldehyde. This compound was prepared from 280 mg (0.515 mmol) of the metathesis product in 72% yield (210 mg, 0.371 mmol) by a procedure similar to that employed in the synthesis of **26**. (For data, see Supporting Information.)

(2*S*,7*R*)-*N*-Benzyloxycarbonyl-2-[2-*N*-benzyloxycarbonyl-(4,4-diethoxybutyl)amino]-hept-4-enyl-2,5-dihydropyrrole. This compound was prepared from 90 mg (0.159 mmol) of the aldehyde in 70% yield (65 mg, 0.11 mmol) by a procedure similar to that employed in the synthesis of **27**. (For data, see Supporting Information.)

Tetraponerine T6 was prepared from 60 mg (0.101 mmol) of the olefin in 89% yield (21.4 mg, 0.091 mmol) by a procedure similar to that employed in the synthesis of **T8**. ^{1}H NMR (500 MHz, C_6D_6): δ = 3.51 (m, 1 H), 2.89 (ddd, 1 H, J = 9 Hz, 9 Hz, 2 Hz), 2.71 (dd, 1 H, J = 7 Hz, 5 Hz), 2.42 (m, 1 H), 2.34 (m, 1 H), 1.98−1.85 (m, 2 H), 1.85−1.22 (m, 18 H), 0.91 (t, 3 H, J = 7 Hz). ^{13}C NMR (C_6D_6): δ = 83.2 (CH), 64.0 (CH), 59.5 (CH), 48.9 (CH_2), 45.7 (CH_2), 34.5 (CH_2), 33.3 (CH_2), 32.4 (CH_2), 30.3 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.9 (CH_2), 21.1 (CH_2), 20.7 (CH_2), 14.1 (CH_3). IR (film): 2956, 2929, 2857, 2787, 1738, 1702, 1459, 1378 cm^{-1}. LRMS *m*/*z* (%): 236 (56) [M^+], 235 (100) [$M-H^+$], 193 (18) [$C_{12}H_{21}N_2+$], 179 (68), 166 (45), 96 (47), 70 (30). HRMS Calcd for $C_{15}H_{28}N_2$ [M^+]: 236.2252. Found: 236.2255. $[\alpha]_D^{20} = +35°$ ($c = 0.15$, $CHCl_3$).

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie.

Supporting Information Available: Data of compounds **6**, **11**, **13**, **15**, **18**, **22**, **24**, **25**, **28** and the precursors of **T6** and **T7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001688I