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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-TETRAPONERINE-8

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Abstract: A stereocontrolled total synthesis of the ant alkaloid (±)-tetraponerine-8 (**1**) has been achieved in 7 steps and 28% overall yield, starting from 1-hydroxypiperidine. Key steps are a 1,3-dipolar cycloaddition (**3** + **4** -> **5**), a nucleophilic substitution (**14** -> **15**), and a reductive cyclization affording the tricyclic skeleton of tetraponerine-8 (**15** -> **17**).

Résumé: Une synthèse stéréocontrôlée de la tetraponérine-8 (**1**), alcaloïde de fourmi, a été réalisée en 7 étapes avec un rendement global de 28% au départ de la 1-hydroxypipéridine. Les étapes clés sont une cycloaddition 1,3-dipolaire (**3** + **4** -> **5**) une substitution nucléophile (**14** -> **15**) et une cyclisation réductrice (**15** -> **17**) conduisant au squelette tricyclique de la tetraponérine-8.

Introduction

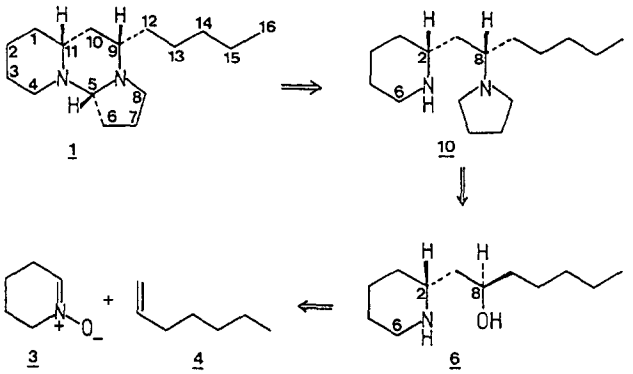
The tetraponerines, 6-alkyldecahydropyrido[1,2-c]pyrrolo[1',2'-a]pyrimidines, are a new class of toxic alkaloids which were isolated from the venom of the New-Guinean ant Tetraponera sp. The structure and relative configuration of the major component of the venom, tetraponerine-8, has been established as **1** by an X-ray diffraction analysis[1]. The structures of five other tetraponerines (T_3 to T_7) have been deduced on the basis of their spectroscopic properties[2]. They differ from each other by the length of the alkyl side chain at C-9 and/or by the relative stereochemistry of the three asymmetric carbon atoms.

The unusual structures and insecticidal activities[1] of the tetraponerines have made them attractive targets for total synthesis. Indeed, after we reported in a short communication a stereoselective total synthesis of (±)-T_8[3], Yue et al.[4] published an enantioselective synthesis of natural (+)-T_8, which was shown to have the (5R,9S,11R) configuration. Recently, Jones[5] synthesized (±)-T_4, a lower homolog of T_8 and (±)-T_8 by two different ways both starting from a 2-alkylpyridine.

In this paper, we provide full details of our earlier synthesis of (±)-T_8 and describe a modification of the original synthetic scheme allowing to increase the overall yield from 11 to 28%.

Results and discussion

Scheme I



Our approach to (±)-T_8 is outlined antithetically in scheme I.

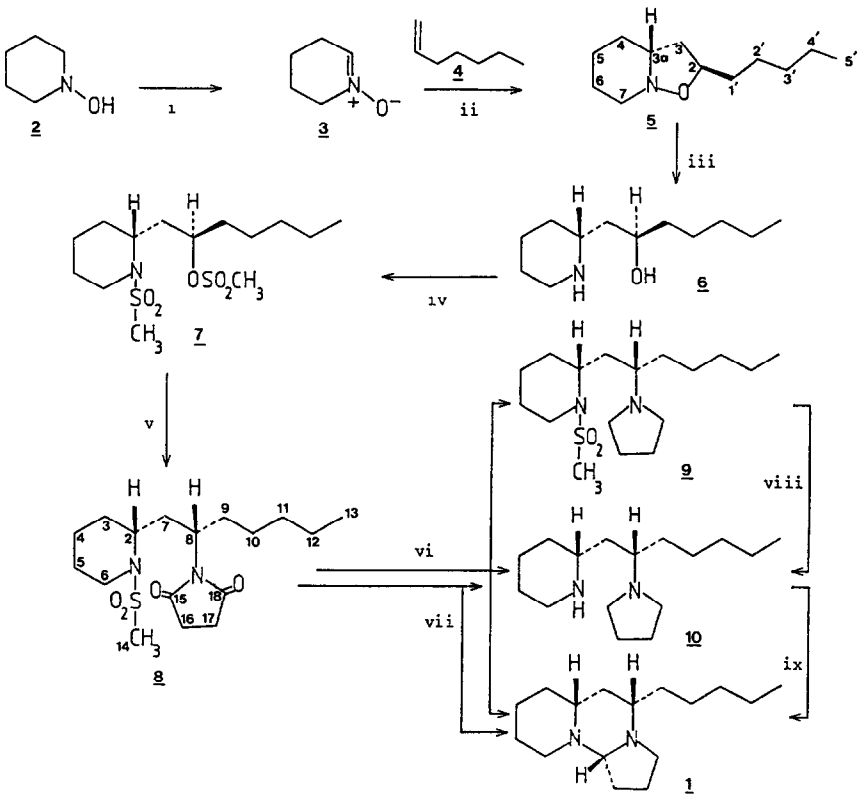
The key steps are: i) the 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydropyridine-1-oxide (**3**) with 1-heptene (**4**), which is highly regio- and stereoselective[6-10], leading after hydrogenolysis of the isoxazolidine to the (2R*, 8R*) aminoalcohol **6**; ii) the introduction of a pyrrolidine ring at C-8 by a nucleophilic substitution reaction on a suitably N-protected and O-activated derivative of **6**, which affords diamine **10**, having the same 2R*,8S* configuration as T_8; and iii) the photocylization[11] of **10** into (±)-T_8.

Our first synthesis of (±)-T_8 is outlined in scheme II. The initial steps proceeded without complication. Thus, cycloaddition of nitrone **3**, prepared by HgO oxidation[12] of 1-hydroxypiperidine (**2**), with 1-heptene (**4**) afforded isoxazolidine **5** in a 94% yield after chromatography on alumina (compound **5** amounted to at least 96% of the reaction mixture, by capillary GLC). Hydrogenolysis by H_2/Raney-Nickel[13] furnished aminoalcohol **6** in an 88% yield from **2**. After having proved the (2R*,8R*) configuration of **6**[3], we tried to introduce a succinimido group at C-8 through a Mitsunobu reaction[14]. However, under a variety of experimental conditions[14], the reaction always led to complex mixtures.

Thus, we turned to an alternative route based on a selective protection of the amino function of **6**, followed by activation of the OH group and nucleophilic substitution at C-8 (Scheme III). However, our initial attempts in that direction were disappointing. Reaction of **6** with "BOC-ON"[15] afforded the expected N-BOC-aminoalcohol **11** in a 73 % yield. However, when **11** was treated with mesyl chloride in pyridine, the cyclic urethane **13** rather than mesylate **12** was obtained in a 94 % yield. The (2R*, 8S*) relative configuration of **13** was proved by 2D $^1H/^1H$ NMR experiments which allowed assignment of all the signals below δ 2.0 and determination of the coupling constants (experimental). Particularly relevant are the coupling constants of H_{axial}C-7 obtained by a J-resolved experiment, (δ 1.54, J = 11.5, 11.5, 14 Hz) which demonstrate that HC-8 is

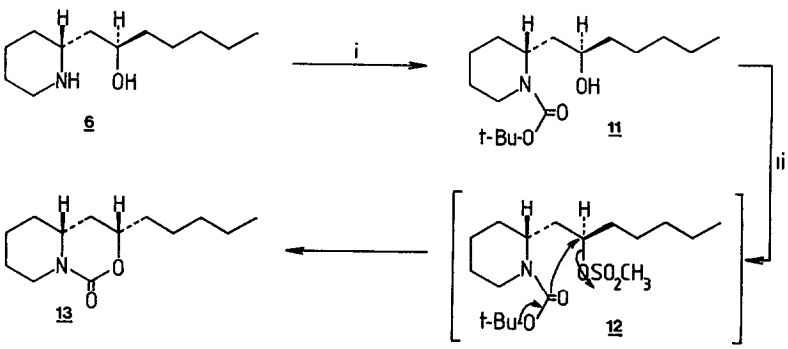
axially oriented. Thus, the formation of **13** may be explained as shown in scheme III: mesylate **12**, which is formed under the reaction conditions, undergoes an intramolecular nucleophilic substitution at C-8 by the t-butyloxycarbonyl group. Analogous cyclization reactions of N-ethoxy-carbonyl-protected aminoalcohols have already been reported[16].

Scheme II



i: $HgO/CHCl_3$; ii: $CHCl_3$, reflux, 94%; iii: H_2, Ra-Ni/CH_3OH, 94%; iv: $(CH_3SO_2)_2O$, NEt_3, CH_2Cl_2, 81%; v: succinimide, K_2CO_3/HMPT-THF, 71%; vi: $LiAlH_4$/THF [**10**: 50%, **9**: 33%, **1**: 5%]; vii: Red-Al/toluene, 51%; viii: Na, t-BuOH/NH_3-HMPT, 64%; ix: N-chlorosuccinimide, NEt_3/ether-THF, hυ, 30%).

Scheme III



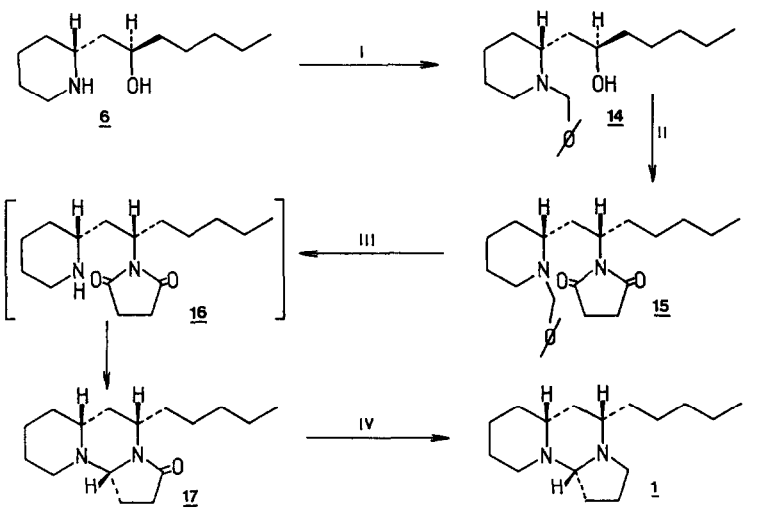
i: BOC-ON, NEt_3/ CH_2Cl_2, 73%; ii: CH_3SO_2Cl/ pyridine, 94%.

Another attempt to selectively protect the nitrogen atom of **6** with tritylsulfenyl chloride[17] also failed. These disappointing results led us to examine the simultaneous N-protection and O-activation of **6** through sulfonylation. Treatment of **6** with TsCl or MsCl under a variety of conditions (CH_2Cl_2 or pyridine as solvent, with or without DMAP, various reaction times) always afforded mixtures containing high proportions (up to 60%) of sulfonamide derivatives bearing a chlorine atom at C-8. Such competitive nucleophilic substitutions by Cl^- during tosylation or mesylation reactions of alcohols are well documented[18,19]. This problem could finally be solved by replacing MsCl by methanesulfonic anhydride[20], a sulfonating agent with a very poor nucleophilic leaving group. Treatment of **6** with 3 equiv. of $(CH_3SO_2)_2O$ in CH_2Cl_2 with NEt_3 as base afforded dimesyl **7** in an 81% yield (scheme II). The next step, nucleophilic substitution of the mesylate group at C-8 to introduce the nitrogen-containing five-membered ring was best accomplished[3] by using succinimide in HMPT/THF with K_2CO_3 as base (yield : 71 %). All other attempts with stronger nucleophiles (pyrrolidine or 2-pyrrolidinone) and/or stronger bases (KOH, NaH) always led to substantial amounts of elimination products. The two last steps of our synthesis proved to be rather troublesome. Indeed, attempted transformation of **8** into aminosulfonamide **9** by refluxing with $LiAlH_4$ in THF afforded three compounds[3]: the expected product **9** (30%), the diamine **10** (51%) and (±)-T_8 (5%). Compound **9** could be subsequently converted to **10** in a 64% yield by treatment with Na/t-BuOH in NH_3/HMPT[21]. We hoped to improve this step by reducing **8** with sodium bis(2-methoxyethoxy)aluminum hydride which is known[22] to cleave alkylsulfonamides. However, under these conditions, a very complex reaction mixture was formed from which diamine **10** could be isolated in only 51% yield. The last step of the synthesis, cyclization of **10** into (±)-T_8 was achieved under conditions described by Kimura and Ban[11] (NCS, hυ, NEt_3 in Et_2O). The best yield initially obtained[3] was 30%. Recent work in our laboratory[23] has shown that the yield of this reaction can be improved by decarbonating diamine **10** just before it is used, and by running the reaction under Ar. However, despite our efforts, reproducibility of this critical step could not be achieved and yields vary widely (from 42 to 76%). This cyclization, however, is highly stereoselective since no trace of T_7, the C-5 epimer of T_8, could be detected in the reaction mixture by capillary GLC.

Thus, this synthetic scheme, although affording stereoselectively T_8 in 6 steps, is flawed by the problems encountered in the reduction of **8** and by the lack of reproducibility of the cyclization reaction.

Our second route started with aminoalcohol **6** and was made possible by a selective, more convenient, protection of the nitrogen atom, as shown in scheme IV. Thus, selective protection of the NH group of **6** could be achieved by treatment with 1.1 equiv. of benzyl bromide and 2 equiv. of KOH in $EtOH/H_2O$[24]. This afforded N-benzylaminoalcohol **14** in a 93% yield. Attempts to mesylate **14** under the conditions developed for **6** (scheme II) were not successful.

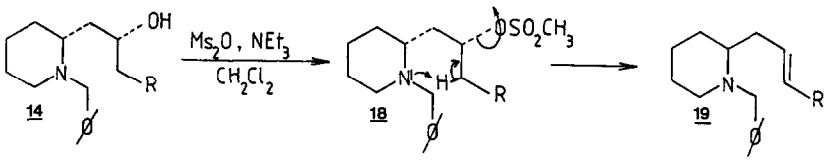
Scheme IV



i: ΦCH_2Br, KOH/EtOH-H_2O, 93% ii: $P\Phi_3$, EtOOC-N=N-COOEt, succinimide/ THF, 58%
iii: H_2-Pd/C,CH_3OH iv: $LiAlH_4$/THF reflux, 59% (two steps)

Although mesylate **18** could be obtained, it underwent extensive degradation, even when kept at room temperature. Among the degradation products, only olefin **19** could be isolated, presumably arising from **18** by intramolecular elimination promoted by the nitrogen lone pair (scheme V).

Scheme V (R= n-butyl).



It is worth mentioning that similar problems were encountered by Carruthers et al.[25] during attempted mesylation of a structurally related N-benzylaminoalcohol. To circumvent this problem, we turned to a Mitsunobu[14] reaction with succinimide as the nucleophile. The optimal yield (58%) was achieved by using 1.5 equiv. of reactants (DEAD, $P\Phi_3$, succinimide). Here again, a mixture of elimination products (olefin **19** and its Δ^7-isomer: 11%) along with a more polar compound (18%), identified by its spectroscopic properties as 8-epi-**14**. The formation of the latter and its apparent lack of reactivity under Mitsunobu conditions are still unexplained.

Conversion of **15** into 8-oxo-T_8(**17**) requires the deprotection of the amino group followed by cyclization of the resulting aminoimide. Literature data[26-28] suggested that both reactions could be performed by catalytic hydrogenation under neutral[27] or acidic[28] conditions. Thus, the transformation was attempted with different catalysts (PtO_2, Pd black, Pd/C) with or without acid, and the reaction monitored by tlc. Under the best conditions (10% Pd/C, H_2, MeOH), only **17** could be detected in the reaction medium after 100 hours. Shorter times of reactions led to mixtures of aminoimide **16** and 8-oxo-T_8 **17**. After elimination of catalyst and solvent, **17** was subjected to $LiAlH_4$ reduction in refluxing THF. This procedure afforded (±)-T_8 in a 59% yield from **15**, identical in all respects (except [α]) with an authentic sample. This reductive cyclization is also highly stereoselective.

Conclusions

The second synthetic scheme described above allows to stereoselectively synthesize (±)-T_8 in 7 steps with a 28% yield, starting from 1-hydroxypiperidine. An excellent level of stereocontrol was achieved at each stage (d.e. > 95%): cycloaddition yielding **5**, Mitsunobu reaction on **14** to afford **15** and reductive cyclization of the latter into **17**.

Experimental Section

^1H magnetic resonance spectra (250 MHz) and ^{13}C magnetic resonance spectra (62.8 MHz) were recorded on a BRUKER WM 250 spectrometer and are reported in parts per million from internal tetramethylsilane on the δ scale ($CDCl_3$). Data are reported as follows: chemical shift [multiplicity (s= singlet, d= doublet, t= triplet, m= multiplet), coupling constants in hertz, integration, interpretation]. Infrared spectra were taken with a BRUKER IFS 25 instrument. Mass spectra were recorded on a V.G. Micromass 7070 F spectrometer. GLC/MS analysis were performed on a FINNIGAN ITD 800 apparatus and GLC analysis on a

VARIAN 3700, using OV-1 or OV-1701 capillary columns (25 m). Analytical thin layer chromatography was performed with MERCK aluminum oxide 60 F-254 (type E) or POLYGRAM silica gel SilG/ UV^{254} 0.25 mm precoated plates. Column chromatography was performed over MACHEREY-NAGEL silica gel (0.04-0.063 mm) or neutral aluminum oxide (activity I).

Preparation of isoxazolidine 5. To a magnetically stirred solution of 1-hydroxypiperidine (5.17 g, 51.1 mmol) in $CHCl_3$ (50 ml) maintained near 0°C was added HgO (34.61 g, 15.9 mmol). The mixture was stirred for 20 min at 0°C then filtered through celite, before adding 1-heptene (22 ml, 15.7 mmol). The solution was brought to reflux overnight. After removal of the volatiles in vacuo, alumina chromatography (hexane/EtOAc 8:2 to EtOAc 100%) led to pure **5** (9.43 g, 47.9 mmol, 94%); MS (EI) m/z 197 ($M^{+\cdot}$,18%), 100 ($M^{+\cdot}$-$C_7H_{13}\cdot$,100), 99 ($M^{+\cdot}$-C_7H_{14},39), 84 ($C_5H_{10}N^+$,45); ^1H NMR δ 0.88 (t:6.5Hz,3H,H_3C-5'), 2.44 (m,H_{ax}C-7), 3.42 (m,1H,H_{eq}C-7), 4.02 (m,1H,HC-2); ^{13}C NMR δ 76.1 (C-2), 66.4 (C-3a), 55.2 (C-7), 40.2 (C-3), 35.4 (C-4), 31.9 (C-3'), 29.5 (C-1'), 25.6 (C-2'), 24.8 (C-6), 24.0 (C-5), 22.6 (C-4'), 14.0 (C-5'); IR (NaCl) 1120 and 1090 cm^{-1} (C-O), 1000 cm^{-1} (C-N).

Preparation of aminoalcohol 6. Isoxazolidine **5** (5.05 g, 25.6 mmol) was reduced by catalytic hydrogenation over Raney-Nickel in methanol (150 ml). Fitration of the catalyst was followed by purification by alumina chromatography ($CHCl_3$/CH_3OH 95:5) which led to isolation of 4.55 g of aminoalcohol **6** (22.8 mmol, 89%) and 0.24 g of isoxazolidine **5** (1.22 mmol, 5%). Recristallization of aminoalcohol **6** from hexane/CH_2Cl_2 gave white needles (F: 104-106°C); MS (EI) m/z 199 ($M^{+\cdot}$,2%), 128 ($M^{+\cdot}$-$C_5H_{11}\cdot$,7), 98 ($M^{+\cdot}$-$C_6H_{13}O\cdot$,2), 84 ($C_5H_{10}N^+$,100); IR (KBr) 3500-3300 cm^{-1} (O-H; N-H); ^1H NMR δ 0.89 (t:6.5Hz,3H,H_3C-13), 2.88 (ddd:12.4;12.4;3Hz,H_{ax}C-6), 3.32 (m,1H,HC-2), 3.48 (m,1H,H_{eq}C-6), 4.01 (m,1H,HC-8); ^{13}C NMR δ 66.5 (C-8), 54.6 (C-2), 45.0 (C-6), 40.0 (C-7), 37.6 (C-9), 31.9 (C-3), 29.0 (C-11), 25.5 (C-5), 22.7 (C-4+C-10), 22.2 (C-12), 14.0 (C-13).

Preparation of N-BOC-aminoalcohol 11. BOC-ON (0.015 g, 6.09 10^{-5} mol) and triethylamine (0.069 g, 6.8 10^{-4} mol) were added to a stirred solution of aminoalcohol **6** (0.01 g, 5.02 10^{-5} mol) in CH_2Cl_2 (0.6 ml) and the solution was stirred for 9 hours. Then, water was added and the mixture was extracted with CH_2Cl_2. The crude product was purified by silica gel flash chromatography (hexane/EtOAc 9:1) to give compound **11** (0.01 g, 3.68 10^{-5} mol, 73%). MS (EI) m/z 299 ($M^{+\cdot}$,7%), 226 ($M^{+\cdot}$-$C_4H_9O\cdot$,2), 198 ($M^{+\cdot}$-$C_5H_9O_2\cdot$,4), 184 ($M^{+\cdot}$-$C_7H_{15}O\cdot$,11), 172 ($M^{+\cdot}$-C_4H_8-$C_5H_{11}\cdot$,5), 128 ($M^{+\cdot}$-C_5H_{10}-$C_4H_9CO_2\cdot$,100), 84 ($C_5H_{10}N^+$,56); IR (NaCl) 3440 cm^{-1} (O-H), 1660 cm^{-1} (C=O); ^1H NMR δ 0.88 (t:6.5Hz,3H,H_3C-13), 1.47 (s,9H,C(CH_3)$_3$), 1.99 (ddd:13;13;2Hz,1H), 2.67 (ddd:11.7;11.7;2.5Hz,1H,H_{ax}C-6), 3.30 (m,1H,HC-2), 3.95 (m,H_{eq}C-6), 4.46 (m,1H,HC-8); ^{13}C NMR δ 80.1 (C-15); 67.4 (C-8); 46.6 (C-2); 39.3 (C-6); 37.6, 36.7 (C-3,C-7); 32.0, 29.5 (C-9,C-11); 28.4 (C-16+C-17+C-18); 25.7, 25.6 (C-5,C-10); 22.7 (C-12); 19.2 (C-4); 14.1 (C-13).

Mesylation of N-BOC-aminoalcohol 11. Mesyl chloride (0.058 g, 5.9 10^{-4} mol) was added at -78°C to a solution of **11** (8.2 mg, 2.74 10^{-5} mol) in pyridine (1 ml). The mixture was stirred for 19 hours at room temperature, then water was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml). Silicagel flash chromatography (hexane/EtOAc 8:2) gave urethane **13** (5.8 mg, 2.58 10^{-5} mol, 94%) as the major product. MS (EI) m/z 225 ($M^{+\cdot}$,16%), 182 ($M^{+\cdot}$-$C_3H_7\cdot$,16), 168 ($M^{+\cdot}$-$C_4H_9\cdot$,11), 154 ($M^{+\cdot}$-$C_5H_{11}\cdot$,14), 127 ($M^{+\cdot}$-C_7H_{14},42), 84 ($C_5H_{10}N^+$,100); IR (NaCl) 1680 cm^{-1} (C=O); ^1H NMR δ 0.89 (t:6.7Hz,3H,H_3C-13), 2.04 (ddd:14;5.5;2Hz,1H,H_{eq}C-7), 2.64 (ddd:12.8;12.8;3.2Hz,1H,H_{ax}C-6), 3.26 (dddd:11.5;11.5;5.5;2.5Hz,

1H,HC-2), 4.11 (dddd:11.5;6.6;4.5;1.9Hz,1H,HC-8), 4.47 (dddd:13.5;1.5;1.5;<1Hz,H_{eq}C-6); ^{13}C NMR (DEPT) δ 75.0 (C-8); 54.1 (C-2); 44.7 (C-6); 35.8, 34.9, 33.7 (C-3,C-7,C-9); 31.6 (C-11); 25.0, 24.3, 23.7 (C-4,C-5,C-10); 22.5 (C-12); 14.0 (C-13).

Mesylation of aminoalcohol 6. A solution of methanesulfonic anhydride (1.3 g, 7.46 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise to aminoalcohol **6** (0.48 g, 2.41 mmol) and triethylamine (2.8 g, 27.7 mmol) in dry CH_2Cl_2 (10 ml) at -78°C and stirred for one hour. Water was added and the mixture was extracted with CH_2Cl_2 (3 x 10 ml). Silica gel flash chromatography (toluene/EtOAc 9:1) gave N,O-dimesylaminoalcohol **7** (0.695 g, 1.96 mmol, 81%). MS (CI NH_3) m/z 373 ($[M+NH_4]^+$,25%), 277 ($[M+H-CH_3SO_2\cdot]^{+\cdot}$,100), 260 ($M^{+\cdot}$-$CH_3SO_3\cdot$,31), 162 ($M^{+\cdot}$-$C_8H_{17}O_3S\cdot$,31), 84 ($C_5H_{10}N^+$,23); IR: 1330 cm^{-1} and 1150 cm^{-1} (SO_2); ^{1}H NMR δ 0.90 (t:7Hz,3H,H_3C-13), 2.10 (ddd:15;9;4Hz,1H,HC-7), 2.93 (s,3H,H_3C-14), 3.00 (m,1H,H_{ax}C-6), 3.07 (s,3H,H_3C-15), 3.67 (ld,1H,H_{eq}C-6), 4.20 (m,1H,HC-2), 4.73 (m,1H,HC-8); ^{13}C NMR δ 81.4 (C-8); 49.4 (C-2); 40.7 (C-14+C-6); 38.7 (C-15); 35.0, 34.9 (C-7,C-9); 31.5 (C-3); 29.1 (C-11); 24.9, 24.4 (C-5,C-10); 22.5 (C-12); 18.6 (C-4); 13.9 (C-13).

Preparation of imide 8. N,O-dimesylaminoalcohol **7** (0.355 g, 1 mmol), succinimide (0.223 g, 2.25 mmol) and potassium carbonate (0.234 g, 1.63 mmol) were stirred for 5 days at 40°C in THF (5 ml) and HMPT (10 ml). Water (50 ml) was added and the mixture extracted with 1,2-dichloroethane (4 x 25 ml). Silica gel flash chromatography (hexane/EtOAc 8:2) afforded first elimination products (0.021 g, 8.1 10^{-5} mol, 8%) and then imide **8** (0.254 g, 7.1 10^{-4} mol, 71 %). Imide **8**: MS (CI NH_3) m/z 376 ($[M+NH_4]^+$,47%), 359 ($[M+H]^+$,100), 279 ($M^{+\cdot}$-$CH_3SO_2\cdot$,55), 162 ($M^{+\cdot}$-$C_{11}H_{18}NO_2\cdot$,50); IR (NaCl) 1715 cm^{-1} and 1650 cm^{-1} (imide), 1310 cm^{-1} and 1150 cm^{-1} (SO_2); ^{1}H NMR δ 0.86 (t:7Hz,3H,H_3C-13), 1.84 (ddd:15;8;4Hz,1H,HC-7), 2.45 (ddd:15;11;5Hz,1H,H'C-7), 2.68 (s,4H,H_2C-16+H_2C-17), 2.82 (s,3H,H_3C-14), 2.97 (ddd:13;13;2Hz,1H,H_{ax}C-6), 3.60 (ld,1H,H_{eq}C-6), 3.78 (m,1H,HC-8), 4.06 (m,1H,HC-2); ^{13}C NMR δ 178.3 (C-15+C-18); 50.6, 50.3 (C-2,C-8); 40.8 (C-6); 40.0 (C-14); 31.8, 31.6, 31.4 (C-3,C-7,C-9); 28.5 (C-11); 28.1 (C-16+C-17); 26.1 (C-5); 25.0 (C-10); 22.5 (C-12); 18.5 (C-4); 13.9 (C-13).

Reduction of imide 8 with $LiAlH_4$. Imide **8** (4.542 g, 12.7 mmol) in dry THF (50 ml) was added to a solution of $LiAlH_4$ (5.733 g, 173 mmol) in dry THF (50 ml). The mixture was heated to reflux for 5 days then EtOAc was added (50 ml) to destroy excess hydride. Water was added and the mixture was extracted with CH_2Cl_2 (150 ml). Purification of the crude product by alumina chromatography (toluene/EtOAc/MeOH 5:5:1) gave (±)-T_8 (0.150 g, 0.6 mmol, 5%), aminosulfonamide **9** (1.38 g, 5.48 mmol, 33%) and diamine **10** (1.59 g, 6.31 mmol, 50%). Aminosulfonamide **9**: MS (EI) m/z 330 ($M^{+\cdot}$,1%), 259 ($M^{+\cdot}$-C_4H_9N,34), 162 ($M^{+\cdot}$-$C_{11}H_{22}N\cdot$,100), 154 ($M^{+\cdot}$-$C_7H_{14}NO_2S\cdot$,89), 98 ($C_6H_{12}N^+$,5), 84 ($C_5H_{10}N^+$,9), 70 ($C_4H_8N^+$,5); IR (NaCl) 2790 cm^{-1} (Bohlmann), 1340 cm^{-1} and 1140 cm^{-1} (SO_2); ^{1}H NMR δ 0.89 (t:7Hz,3H,H_3C-13), 1.95 (ls,4H, H_2C-16+H_2C-17), 2.19 (m,1H,H-C-7), 2.86 (m,1H,HC-8), 2.93 (s,3H,H_3C-14), 2.98 (ls,4H,H_2C-15 +H_2C-18), 3.10 (ddd:13;13;3Hz,1H,H_{ax}C-6), 3.70 (ld,1H, H_{eq}C-6), 4.09 (m,1H,HC-2); ^{13}C NMR δ 60.9 (C-8); 50.6 (C-15+C-18); 50.4 (C-2); 40.8 (C-14); 40.6 (C-6); 32.1, 31.9, 30.3 (C-3,C-7,C-9); 28.6 (C-10); 25.2, 24.8 (C-5,C-11); 23.5 (C-16+C-17); 22.4 (C-12); 18.5 (C-4); 14.0 (C-13). Diamine **10**: MS (EI) m/z 252 ($M^{+\cdot}$,8%), 181 ($M^{+\cdot}$-$C_5H_{11}\cdot$,24), 154 ($M^{+\cdot}$-$C_6H_{12}N\cdot$,95), 124 ($C_8H_{14}N^+$,20), 110 ($C_7H_{12}N^+$,27), 98 ($C_6H_{12}N^+$,52), 84 ($C_5H_{10}N^+$, 100), 70 ($C_4H_8N^+$,10); IR (NaCl) 3290 cm^{-1} (N-H), 2790 cm^{-1} (Bohlmann), 1140 cm^{-1} (C-N); ^{1}H NMR δ 0.89 (t:7Hz,3H,H_3C-13), 2.75-2.85 (m,3H,H_{ax}C-6+H-C-14+H-C-17), 2.97-3.12 (m,4H,H_{eq}C-6+HC-8+HC-14+HC-17), 3.42 (ld,1H,HC-2), 4.95 (ls,1H,N-H); ^{13}C NMR δ 61.3 (C-8); 59.0

(C-2); 48.4 (C-14+C-17); 44.5 (C-6); 34.2 (C-3); 31.9, 29.1 (C-7,C-9); 28.3 (C-11); 26.6 (C-5); 23.7 (C-15+C-16); 22.8, 22.5, 22.0 (C-4,C-10,C-12); 14.0 (C-13).

Reduction of aminosulfonamide 9 with Na in NH_3-HMPT. Sodium (0.044 g, 1.9 mmol) was dissolved in ammonia (5 ml) at -78°C. Aminosulfonamide **9** (0.154 g, 0.47 mmol), t-BuOH (0.138 g, 1.9 mmol) and HMPT (5 ml) were added in THF solution. The mixture was stirred for 1/2 hour at -78°C and then kept under reflux (-33°C) till the blue color disappeared. Water was added and the mixture was extracted with 1,2-dichloroethane. Alumina chromatography ($CHCl_3/CH_3OH$ 9:1) of the crude product gave diamine **10** (0.075 g, 0.29 mmol, 64%).

Reduction of imide 8 with sodium bis(methoxyethoxy)aluminum hydride (Red-Al). Imide **8** (0.05 g, 0.14 mmol) in dry toluene (3 ml) was added to a 70 % Red-Al solution in toluene (1.3 ml, 4.67 mmol) and the mixture was refluxed for 6 hours. Then 10 % aqueous NaOH was added and the organic phase extracted with CH_2Cl_2 (50 ml). Alumina chromatography gave diamine **10** (0.018 g, 7.14 10^{-5} mol, 51 %) and traces of (±)-T_8.

(±)-T_8 from diamine 10. N-chlorosuccinimide (21 mg, 1.59 10^{-4} mol) was added to diamine **10** (20 mg, 7.94 10^{-5} mol) in dry THF (3 ml). The solution was stirred for 5 minutes. Then, triethylamine was added and the solution was irradiated during 1.5 hour with a high pressure Hg lamp (BAUSCH-LOMB SP-200). Purification of the reaction mixture by silica gel flash chromatography (hexane/acetone 9:1 + NH_4OH) yielded pure (±)-T_8 (6 mg, 2.4 10^{-5} mol, 30 %). MS (EI) m/z 250 ($M^{+\cdot}$,66%), 249 ($M^{+\cdot}$-H·,99), 207 ($M^{+\cdot}$-C_3H_7·,26), 193 ($M^{+\cdot}$-C_4H_9·,100), 180 ($M^{+\cdot}$-C_5H_{10}·, $M^{+\cdot}$-C_5H_8N·,45), 152 ($M^{+\cdot}$-$C_6H_{12}N$·,67), 96 ($C_6H_{10}N^+$,50), 84 ($C_5H_{10}N^+$,44); IR (NaCl) 2790-2700 cm^{-1} (Bohlmann), 1170 cm^{-1} (C-N); ^1H NMR (C_6D_6) δ 0.90 (t:7Hz,3H,H_3C-16), 1.98-2.15 (m,2H,HC-11+HC-8), 2.30 (dd:8;6Hz,1H,HC-5), 2.82 (m,1H,H_{eq}C-4), 3.15 (ddd:9;9;2Hz,1H,H'C-8); ^{13}C NMR (C_6D_6) δ 85.6 (C-5); 62.7, 61.4 (C-9,C-11); 51.5, 49.0 (C-4,C-8); 38.0 (C-10); 34.6 (C-1); 33.0, 32.8 (C-12,C-14); 29.7 (C-6); 26.2 (C-3); 25.2, 25.1 (C-2,C-13); 23.1 (C-15); 20.3 (C-7); 14.3 (C-16).

Preparation of N-benzylaminoalcohol 14. KOH (11 mg, 2 10^{-4} mol), aminoalcohol **6** (920 mg, 1 10^{-4} mol) and benzyl bromide (12 µl, 1.1 10^{-4} mol) were refluxed for 1/2 hour in ethanol/water 1:1 (20 ml). The solution was extracted at basic pH (NH_4OH) with CH_2Cl_2 (3 x 10 ml). Silica gel flash chromatography ($CHCl_3/CH_3OH$ 95:5) gave N-benzylaminoalcohol **14** (27 mg, 9.34 10^{-5} mol, 93 %). MS (EI) m/z 289 ($M^{+\cdot}$,2%), 218 ($M^{+\cdot}$-C_5H_{11}·,3), 174 ($C_{12}H_{16}N^+$,100), 91 ($C_7H_7^+$,24), 84 ($C_5H_{10}N^+$,5); IR (NaCl) 3300 cm^{-1} (O-H), 735 cm^{-1} and 700 cm^{-1} (phenyl group); ^1H NMR δ 0.89 (t:7Hz,3H,H_3C-13), 2.00 (ddd:12;10;3Hz,1H,H_{ax}C-6), 2.60 (m,1H,HC-2), 2.88 (dt:12;3Hz,1H,H_{eq}C-6), 3.10 (d:13Hz,1H,HC-14), 4.06 (m,1H,HC-8), 4.42 (d:13Hz,1H,H'C-14), 7.20-7.32 (m,5H,HC-16,HC-17,HC-18,HC-19,HC-20); ^{13}C NMR (DEPT) δ 129.3, 128.4 (C-16,C-17,C-19,C-20); 127.1 (C-18); 69.4 (C-8); 60.0 (C-2); 58.5 (C-14); 52.0 (C-6); 37.9, 36.6 (C-9,C-7); 32.1 (C-3); 29.3 (C-11); 25.4 (C-5); 24.5 (C-4); 23.9 (C-10); 22.7 (C-12); 14.1 (C-13).

Mesylation of N-benzylaminoalcohol 14. Triethylamine (109 mg, 1.08 10^{-3} mol) and methanesulfonic anhydride (100 mg, 5.75 10^{-4} mol) were added to N-benzylaminoalcohol **14** (30 mg, 1.04 10^{-4} mol) in CH_2Cl_2 (1 ml) at -20°C. The mixture was stirred for 15 hours at room temperature, then poured into water (5 ml) and extracted with CH_2Cl_2 (3 x 2 ml). Silica gel flash chromatography (hexane/EtOAc 98:2 + NH_4OH) furnished as sole product olefin **18** (2 mg, 7.38 10^{-6} mol, 7 %); MS (ITD) m/z 270 ($M^{+\cdot}$-H·,<1%), 174 ($M^{+\cdot}$-C_7H_{13}·,100), 91 ($C_7H_7^+$,73); IR (NaCl) 2790-2750 cm^{-1} (Bohlmann),

1650 cm^{-1} (C=C), 1100-700 cm^{-1} (phenyl group); ^1H NMR δ 0.89 (t:7Hz,3H,H_3C-13), 1.95-2.35 (m,6H, H_2C-7+H_2C-10+HC-2+$H_{ax}C$-6), 2.72 (dt:12;4Hz,1H,$H_{eq}C$-6), 3.25 (d:13.5Hz,1H,HC-14), 4.00 (d:13.5Hz,1H,H'C-14), 5.44 (m,2H,HC-8+HC-9), 7.19-7.34 (m,5H,(CH)phenyl); ^{13}C NMR (DEPT) δ 132.4 (C-9); 129.0, 128.1 (C-16+C-20,C-17+C-19); 127.1, 126.6 (C-8,C-18); 60.7 (C-2); 58.0 (C-14); 51.7 (C-6); 34.9 (C-7); 32.4, 31.8 (C-3,C-10); 30.4 (C-11); 25.5 (C-5); 23.5 (C-4); 22.2 (C-12); 13.9 (C-13).

Preparation of N-benzylaminoimide 15 (Mitsunobu reaction). To N-benzylaminoalcohol **14** (0.3 g, 1.04 mmol) and triphenylphosphine (0.818 g, 3.12 mmol) in 5 ml dry THF at 0°C was added dropwise a THF solution of DEAD (0.54 g, 3.12 mmol in 5 ml THF). Then, succinimide (0.309 g, 3.12 mmol) was added and the reaction mixture was stirred 48 hours at room temperature under Ar. Purification of the crude mixture by silica gel flash chromatography gave elimination products (mixture of **18** and the Δ^7-isomer, 32 mg, 1.2 10^{-4} mol, 11 %), imide **15** (221 mg, 6 10^{-4} mol, 58 %) and 8-epi-**14** (54 mg, 1.9 10^{-4} mol, 18 %). Minor olefin (Δ^7): MS (ITD) m/z 271 ($M^{+\cdot}$,11%), 256 ($M^{+\cdot}$-$CH_3^{\cdot}$,<1), 242 ($M^{+\cdot}$-$C_2H_5^{\cdot}$,1), 228 ($M^{+\cdot}$-$C_3H_7^{\cdot}$,9), 214 ($M^{+\cdot}$-$C_4H_9^{\cdot}$,13), 200 ($M^{+\cdot}$-$C_5H_{11}^{\cdot}$,41), 174 ($M^{+\cdot}$-$C_7H_{13}^{\cdot}$,46), 91 ($C_7H_7^+$,100). Imide **15**: MS (EI) m/z 370 ($M^{+\cdot}$,2%), 299 ($M^{+\cdot}$-$C_5H_{11}^{\cdot}$,<1), 174 ($M^{+\cdot}$-$C_{11}H_{18}NO_2^{\cdot}$,100), 91 ($C_7H_7^+$,30), 84 ($C_5H_{10}N^+$,2); IR (NaCl) 1770 cm^{-1} and 1700 cm^{-1} (imide), 1500 cm^{-1}, 1300-1100 cm^{-1}, 736 cm^{-1} and 700 cm^{-1} (phenyl group); ^1H NMR δ 0.85 (t:6.5Hz,3H,H_3C-13), 2.49 (m,1H,HC-2), 2.50 (s,4H,H_2C-22+H_2C-23), 2.68 (m,1H,$H_{eq}C$-6), 3.33 (d:13.9Hz,1H,HC-14), 3.80 (d:13.9Hz,1H,H'C-14), 4.12 (m,1H,HC-8), 7.16-7.32 (m,5H,(CH)phenyl group); ^{13}C NMR δ 177.5 (C-21+C-24); 140.0 (C-15); 128.7, 128.1 (C-16+C-20, C-17+C-19); 126.6 (C-18); 57.8 (C-14); 55.9 (C-2); 50.3 (C-8); 50.1 (C-6); 32.0, 31.4, 30.3 (C-3,C-7,C-9); 28.7 (C-11); 27.9 (C-22+C-23); 26.3 (C-5); 24.8 (C-4); 22.5 (C-10); 21.7 (C-12); 13.9 (C-13). Alcohol 8-epi-**14**: MS (EI) m/z 289 ($M^{+\cdot}$,2%), 218 ($M^{+\cdot}$-$C_5H_{11}^{\cdot}$,3), 174 ($M^{+\cdot}$-$C_7H_{15}O^{\cdot}$,100), 91 ($C_7H_7^+$,61), 84 ($C_5H_{10}N^+$,3); IR (NaCl) 3320 cm^{-1} (O-H); ^1H NMR (C_6D_6) δ 0.88 (t:6.5Hz,3H,H_3C-13), 1.92 (ddd:14.2;10.2;10.2Hz,1H,$H_{ax}C$-7), 2.28 (ddd:14;4;4Hz,1H,$H_{eq}C$-6), 2.76 (dddd:10.2;4;4;4Hz,1H,HC-2), 2.89 (ddd:14;10;3Hz,1H,$H_{ax}C$-6), 3.57 (d:13.1Hz,1H,HC-14), 3.67 (d:13.1Hz,1H,H'C-14), 3.75 (dddd:10.2;8;4;2.5Hz,1H,HC-8), 5.00 (bs,1H,O-H), 7.05-7.36 (m,5H,(CH)phenyl group); ^{13}C NMR (C_6D_6) δ 139.5 (C-15); 129.3, 128.7 (C-16+C-20,C-17+C-19), 127.4 (C-18); 72.4 (C-8); 59.0 (C-2); 56.7 (C-14); 46.1 (C-6); 38.9 (C-9); 37.2 (C-7), 32.5 (C-3); 25.9, 25.7 (C-10,C-11); 23.1 (C-5); 21.6 (C-12); 20.3 (C-4), 14.3 (C-13).

Reductive cyclization of N-benzylaminoimide 15. Imide **15** (12.5 mg, 3.38 10^{-5} mol) was hydrogenated for 15 hours over 10 % Pd/C in methanol (100 ml). The solution was then filtered through cellulose and the filtrate was concentrated. Silica gel flash chromatography (toluene/acetone/methanol 8:2:0 to 8:2:2) gave 8-oxo-T_8 **17** (1.2 mg, 4.54 10^{-6} mol, 13 %) and aminoimide **16** (3.4 mg, 1.21 10^{-5} mol, 36 %). 8-oxo-T_8 **17**: MS (EI) m/z 264 ($M^{+\cdot}$,31%), 263 ($M^{+\cdot}$-$H^{\cdot}$,90), 235 ($M^{+\cdot}$-$C_2H_5^{\cdot}$,13), 207 ($M^{+\cdot}$-$C_4H_9^{\cdot}$,82), 166 ($C_{10}H_{16}NO^+$,20), 84 ($C_5H_{10}N^+$,$C_4H_6NO^+$,100); IR (NaCl) 2800-2760 cm^{-1} (Bohlmann), 1700 cm^{-1} (C=O lactam); ^1H NMR δ 0.88 (t:6.5Hz,3H,H_3C-16), 2.97 (ld,1H,$H_{eq}C$-4), 3.15 (m,1H,HC-9), 3.50 (dd:6.1;6.1Hz,1H,HC-5); ^{13}C NMR δ 174.7 (C-8); 80.3 (C-5); 61.8 (C-11); 57.1 (C-9); 49.4 (C-4); 38.1 (C-10); 32.4, 31.9, 31.6, 31.0 (C-1,C-12,C-7,C-14); 26.1, 25.2 (C-3,C-2); 24.1, 23.6, 22.6 (C-6,C-13,C-15); 14.0 (C-16). Aminoimide **16**: MS (EI) m/z 281 ($[M+H]^+$), 280 ($M^{+\cdot}$), 279 ($M^{+\cdot}$-$H^{\cdot}$), 265 ($M^{+\cdot}$-$CH_3^{\cdot}$), 251 ($M^{+\cdot}$-$C_2H_5^{\cdot}$), 237 ($M^{+\cdot}$-$C_3H_7^{\cdot}$), 223 ($M^{+\cdot}$-$C_4H_9^{\cdot}$), 209 ($M^{+\cdot}$-$C_5H_{11}^{\cdot}$), 182 ($C_{10}H_{16}NO_2^+$), 180 ($M^{+\cdot}$-$C_4H_5NO_2$-$H^{\cdot}$), 110 ($C_7H_{12}N^+$), 98 ($C_6H_{12}N^+$, $C_4H_4NO_2^+$), 84 ($C_5H_{10}N^+$); IR (NaCl) 3300 cm^{-1} (N-H), 1770 cm^{-1} and 1700 cm^{-1} (imide); ^1H NMR δ 0.85 (t:6.5Hz,3H,H_3C-13), 2.53-2.82 (m,6H,

H_2C-15+H_2C-16+HC-2+H_{ax}C-6), 3.41 (ld,1H,H_{eq}C-6), 4.07 (m,1H,HC-8).

(±)-T_8 from 8-oxo-T_8 17. To $LiAlH_4$ (30 mg, 7.9 10^{-4} mol) in dry THF (2 ml) was added 8-oxo-T_8 **17** (19.7 mg, 7.46 10^{-5} mol) in THF (1 ml). The mixture was refluxed for 6 hours, then excess hydride was quenched with EtOAc and aluminum salts hydrolyzed with NH_4OH 10% (5 ml). After extraction of the product with CH_2Cl_2 (3 x 5 ml) and concentration in vacuo, silica gel flash chromatography ($CHCl_3$/EtOH 9:1) gave pure (±)-T_8 (16.4 mg, 6.56 10^{-5} mol, 88%).

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