Combining Two-Directional Synthesis and Tandem Reactions : New access to 3,5-disubstituted pyrrolizidines and first total synthesis of alkaloid *cis*-223B.

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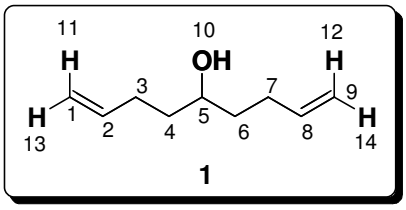
Supplementary Information.

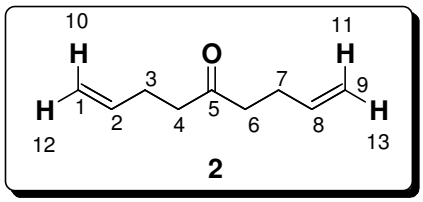
Experimental details for compounds **1**, **2**, **3**, **7**, **8**, **9**, **10**, **12**, **13**, **14** and alkaloid *cis*-**223B,** ^{1}H and ^{13}C NMR spectra for these compounds.



1

Nona-1,8-dien-5-ol **1 :** (M. Nagai, J. Lazor, C. S. Wilcox, *J. Org. Chem.* 1990, **55**, 3440.)

To a dry nitrogen flask equipped with a reflux condenser was added magnesium (2.43 g, 99.9 mmol) and a single iodine crystal in dry diethyl ether (30 cm^3). Then a solution of 4-Bromobutene (10.06 cm^3, 96.1 mmol) in dry diethyl ether (40 cm^3) was added dropwise. The mixture is allowed to reflux for 2 h. Then the reaction mixture was cooled down to 0°C and a solution of ethyl formate (4 cm^3, 48 mmol) was added dropwise over 2 h, then the resulting mixture was stirred at room temperature overnight. The reaction was quenched with saturated ammonium chloride and extracted with diethyl ether. The solvent was evaporated and the crude mixture was refluxed in 15% aqueous potassium hydroxide for 3 h to hydrolyse any formate ester. The mixture was cooled and extracted with diethyl ether, dried over anhydrous sodium sulphate, filtered and evaporated to afford compound **1** (5.52 g, 82%) as a colourless oil. $\nu_{max}(CH_2Cl_2/cm^{-1})$ 3319, 2932, 2859, 1641, 1415 and 908; δ_H(400 MHz; $CDCl_3$) 1.63-1.48 (5H, m, 4-H_2, 6-H_2 and 10-H), 2.28-2.06 (4H, m, 3-H_2 and 7-H_2), 3.65 (1H, m, 5-H), 4.97 (2H, ddt, *J* 10.2, 3.1 and 1.3, 13-H and 14-H), 5.04 (2H, ddt, *J* 17.1, 3.1 and 1.7, 11-H and 12-H), 5.83 (2H, m, 15-H and 16-H).



2

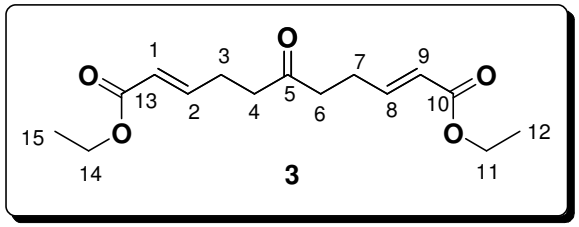
nona-1,8-dien-5-one **2** : (a) M. Nagai, J. Lazor, C. S. Wilcox, *J. Org. Chem.* 1990, **55**, 3440; b) R. B. Mitra, G. B. Reddy, *Synthesis* 1989, 694.)

To a solution of alcohol **1** (1.98, 14.07 mmol) in dichloromethane (30 cm^3) was added silica gel (4g) followed by PCC (3.48 g, 15.81 mmol).

Then the reaction mixture was stirred at room temperature for 18 h.

More silica gel (4 g) was added and the mixture was filtered on a short pad of silica gel and washed with diethyl ether.

The organic phase was concentrated to give pure ketone **2** (1.94 g, 99%) as a yellow oil. $\nu_{max}(CH_2Cl_2/cm^{-1})$ 2979, 2920, 1714, 1641, 1413 and 911; δ_H(400 MHz; $CDCl_3$) 2.32 (4H, m, 3-H_2, 7-H_2), 2.51 (4H, t, *J* 7.6, 4-H_2 and 6-H_2), 4.97 (2H, dq, *J* 10.2 and 1.7, 13-H and 12-H), 5.03 (2H, dq, *J* 17.1 and 1.7, 11-H and H-10), 5.80 (2H, m, 2-H and 8-H); δ_C(75 MHz, $CDCl_3$) 27.6 (3-C and 7-C), 41.7 (4-C and 6-C), 115.1 (1-C and 9-C), 137.0 (2-C and 8-C), 209.1 (5-C).

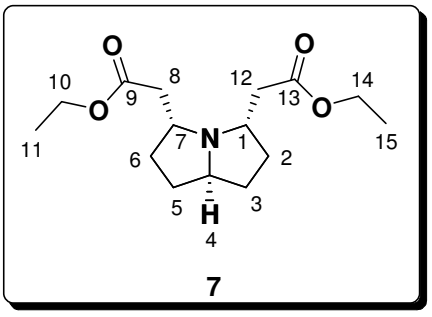


3

Diethyl (2E,9E)-6-oxoundeca-2,9-dienedioate **3** :

To a solution of ketone **2** (1.54 g, 11.09 mmol) in dichloromethane (60 cm^3) under inert N_2 atmosphere, was added sequentially ethyl acrylate (7.25 cm^3, 66.6 mmol) and Hoveyda-Grubbs second generation catalyst (174 mg, .28 mmol). The mixture was stirred at room temperature for 5 days. More catalyst (90 mg, 0.14 mmol) was then added and the reaction was stirred for further 2 days. After TLC monitoring, more catalyst (40 mg, 0.06 mmol) was added and the reaction mixture was allowed to stir for 2 days.

Then the solvent was evaporated and the resulting brown oil was purified by column chromatography on silica, using a mixture of petroleum ether and ethyl acetate (75:25) as eluent, to afford compound **3** (2.07 g, 66%) as a clear oil. $\nu_{max}(CH_2Cl_2/cm^{-1})$ 2983, 2906, 1710, 1654, 1312, 1176 and 1040; δ_H(400 MHz; $CDCl_3$) 1.28 (6H, t, *J* 7.1, 12-H and 15-H), 2.48 (4H, m, 3-H_2 and 7-H_2), 2.58 (4H, t, *J* 6.8, 4-H_2 and 6-H_2), 4.18 (4H, q, *J* 7.1, 14-H_2 and 11-H_2), 5.82 (2H, dt, *J* 15.7 and 1.6, 1-H and 9-H), 6.91 (2H, dt, *J* 15.6 and 6.7, 2-H and 8-H); δ_C(101 MHz, $CDCl_3$) 14.1 (12-C and 15-C), 25.8 (3-C and 7-C), 40.5 (4-C and 6-C), 60.2 (11-C and 14-C), 122.1 (1-C and 9-C), 146.8 (2-C and 8-C), 166.2 (13-C and 10-C), 206.8 (5-C).*m/z* (ESI) 305.1360 ($M^{+\cdot}$. $C_{15}H_{22}NaO_5$ requires 305.1359).



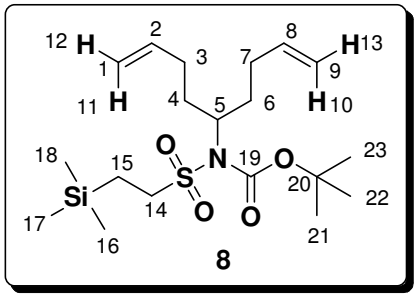
7

Diethyl 2,2'-(3R,5S)-hexahydro-1H-pyrrolizine-3,5-diyldiacetate **7** :

To ketone **3** (1.34 g, 4.76 mmol) was added, at room temperature, under N_2 atmosphere, 12 cm^3 (24 mmol) of ammonia in ethanol solution (2M) followed by titanium ethoxide (2.52 cm^3, 12 mmol) as dessicant. The reaction mixture was stirred for 18 h. Then sodium borohydride (284 mg, 7.50 mmol) was added in one portion and the reaction mixture was stirred for 8 h. Excess of sodium borohydride was removed by addition of an aliquot of acetone (2.4 cm^3) and glacial acetic acid (8.6 cm^3) is added to the reaction. Finally the mixture was heated at 75°C for 48 h.

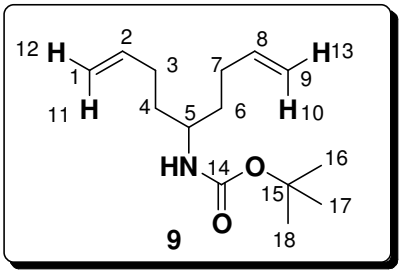
The reaction mixture was cooled down and the solvent were evaporated. The reaction was neutralised with saturated potassium carbonate solution. Then the reaction was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated to give crude mixture as a brown oil.

The product was then purified by column chromatography on alumina using a mixture of petroleum ether and ethyl acetate (8:2) as eluent, to give pyrrolizidine **7** (952 mg, 71%) as a yellow oil. $\nu_{max}(CH_2Cl_2/cm^{-1})$ 2960, 2159, 2027, 1976, 1732 and 1266; δ_H(400 MHz; $CDCl_3$) 1.26 (6H, t, *J* 7.1, 11-H and 15-H), 1.46 (4H, m) and 1.97 (4H, m): 2-H_2, 3-H_2, 5-H_2 and 6-H_2, 2.24 (2H, dd, *J* 14.9 and 8.2) and 2.54 (2H, dd, 14.9 and 6.0): 8-H_2 and 12-H_2, 3.18 (2H, m, 7-H and 1-H), 3.59 (1H, quintet, *J* 6.5, 4-H), 4.13 (4H, q, *J* 7.1, 14-H_2 and 10-H_2); δ_C(101 MHz, $CDCl_3$) 14.2 (11-C and 15-C), 31.1 (3-C and 5-C), 31.3 (6-C and 2-C), 41.4 (8-C and 12-C), 60.2 (10-C and 14-C), 62.9 (1-C and 7-C), 64.3 (4-C), 172.2 (9-C and 13-C).*m/z* (ESI) 284.1863 ($[M+H]^+$. $C_{15}H_{26}NO_4$ requires 284.1856).



5-{N-(ter-Butoxycarbonyl)-N-[[2'-(trimethylsilyl)ethyl]sulfonyl]}-1,8-nonadiene **8 :**

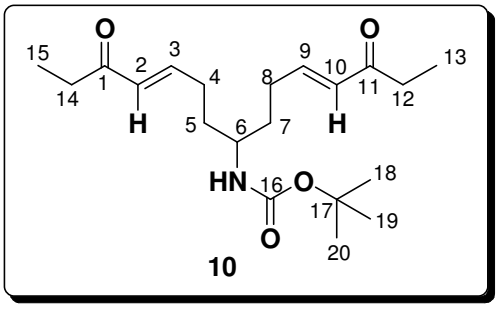
DIAD (1.87 cm^3, 8.93 mmol) was added dropwise to a solution of alcohol **1** (1.00 g, 7.13 mmol), triphenylphosphine (2.81 g, 10.71 mmol), and SES(NH)Boc (2.41 g, 8.56 mmol) in anhydrous THF, over 2.5 h. The solvent was then removed *in vacuo* and the resulting slurry was filtered through a pad of silica eluting with diethyl ether. After concentration of the filtrates *in vacuo*, the crude mixture was purified by column chromatography on silica gel using dichloromethane and hexane (2:1) as eluent, to give pure compound **8** as a viscous pale yellow oil (2.51 g, 87%). $\nu_{max}(CH_2Cl_2/cm^{-1})$ 1724; δ_H(400 MHz; $CDCl_3$) 0.06 (9H, s, 16-H_3, 17-H_3 and 18-H_3), 1.04 (2H, m, 15-H_2), 1.52 (9H, s, 21-H_3, 22-H_3 and 23-H_3), 2.03-1.70 (4H, m, 4-H_2 and 6-H_2), 2.08 (4H, dt, *J* 7.7 and 6.5, 3-H_2 and 7-H_2), 3.41 (2H, m, 14-H_2), 4.20 (1H, quintet, *J* 7.7, 5-H), 5.00 (2H, ddt, *J* 10.2, 1.4 and 1.0, 12-H and 13-H), 5.03 (2H, dd, *J* 16.9 and 1.4, 10-H and 11-H), 5.81 (2H, ddt, *J* 16.9, 10.2 and 6.5, 2-H and 8-H); δ_C(101 MHz, $CDCl_3$) -2.1 (16-C, 17-C and 18-C), 10.1 (15-C), 28.0 (21-C, 22-C and 23-C), 31.0 (3-C and 7-C), 32.8 (4-C and 6-C), 51.4 (14-C), 58.2 (5-C), 84.0 (20-C), 115.0 (1-C and 9-C), 137.6 (2-C and 8-C), 151.7 (19-C); *m/z* (CI) 404.2285 ($[M+H]^+$. $C_{19}H_{38}NO_4SSi$ requires 404.2285).



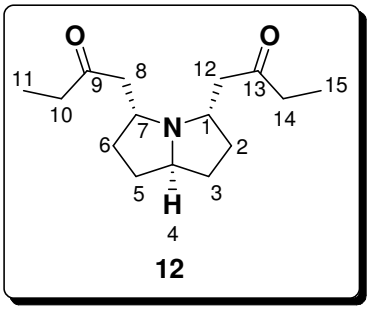
Tert-butyl nona-1,8-dien-5-ylcarbamate **9** :

Method 1 :
To a solution of nonadiene **8** (1.19 g, 2.95 mmol) in THF (20 cm^3), was added, under N_2 atmosphere, 1M TBAF solution (7.1 cm^3, 7.1 mmol) . The reaction is then stirred and heated at 70°C for 18 h. The solvent were evaporated and the crude mixture was purified by column chromatography on silica gel, using petroleum ether and ethyl acetate (95:5) as eluent, to give the carbamate **9** as a waxy white solid (477.0 mg, 68%).

Method 2:
To the solution of nonadiene **8** (1.00 g, 2.48 mmol) in acetonitrile (20 cm^3) was added cesium fluoride (3.76 g, 24.8 mmol) and the reaction mixture was stirred at room temperature for 18 h and at reflux for 1 h. The reaction was quenched with water (20 cm^3) and extracted with dichloromethane (4 × 10 cm^3). The combined organic layers were dried over anhydrous sodium sulphate, filtered, then concentrated *in vacuo* to give the carbamate **9** as a waxy white solid (550.0 mg, 94%).
$\nu_{max}(CDCl_3/cm^{-1})$ 3348, 1692, 1641; δ_H(400 MHz; $CDCl_3$) 1.44 (9H, s, 16-H_3, 17-H_3 and 18-H_3), 1.38-1.61 (4H, m, 4-H_2 and 6-H_2), 2.10 (4H, m, 3-H_2 and 7-H_2), 3.60 (1H, m, 5-H), 4.25 (1H, d, *J* 7.9, NH), 4.94-4.98 (2H, m, 12-H and 13-H), 5.02 (2H, dq, *J* 17.1, 1.6, 10-H and 11-H), 5.81 (2H, m, 2-H and 8-H); δ_C(101 MHz, $CDCl_3$) 28.4 (16-C, 17-C and 18-C), 30.1 (4-C and 6-C), 34.8 (3-C and 7-C), 49.9 (5-C), 78.9 (15-C), 114.7 (1-C and 9-C), 138.1 (2-C and 8-C), 155.5 (14-C); *m/z* (ESI) 262.1787 ($[M+Na]^+$. $C_{14}H_{25}NNaO_2$ requires 262.1778).



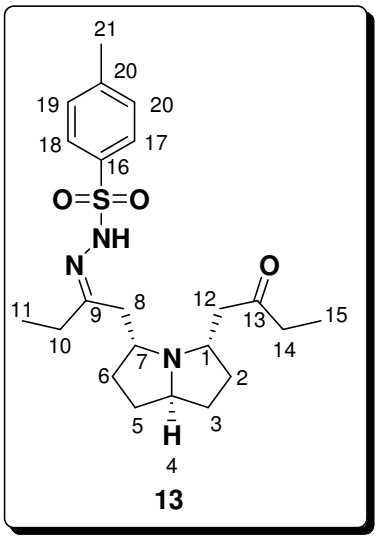
Tert-butyl (4E,11E)-3,13-dioxopentadeca-4,11-dien-8-ylcarbamate **10**
To the solution of carbamate **9** (201.8 mg, 0.84 mmol) in dichloromethane (7 cm^3), under inert N_2 atmosphere, was added sequentially 1-penten-3-one (0.50 cm^3, 5.06 mmol) and Hoveyda-Grubbs second generation catalyst (26 mg, 0.04 mmol). The mixture was stirred at room temperature for 3 days. More catalyst (15 mg, 0.02 mmol) was then added and the reaction was stirred for further 3 days. Then the solvent was evaporated and the resulting brown oil was purified by column chromatography on silica, using a mixture of petroleum ether and ethyl acetate (8:2) as eluent, to afford compound **10** (99.9 mg, 34%) as a brown oil along with some already cyclised pyrrolidine **11** (184 mg, 62%) as a brown oil as well.
$\nu_{max}(CH_2Cl_2/cm^{-1})$ 2973, 2201, 2035, 1711, 1687, 1632, 1391 and 1266; δ_H(400 MHz; $CDCl_3$) 1.09 (6H, t, *J* 7.2, 13-H_3 and 15-H_3), 1.44 (9H, s, 18-H_3, 19-H_3 and 20-H_3), 1.46-1.64 (4H, m, 5-H_2 and 7-H_2), 2.27 (4H, m, 4-H_2 and 8-H_2), 2.55 (4H, q, *J* 7.2, 12-H_2 and 14-H_2), 3.61 (1H, m, 6-H), 4.24 (1H, d, *J* 9.6, NH), 6.10 (2H, d, *J* 16, 2-H and 10-H), 6.81 (2H, m, 3-H and 9-H); δ_C(101 MHz, $CDCl_3$) 7.9 (13-C and 15-C), 28.2 (18-C, 19-C and 20-C), 28.9 (4-C and 8-C), 33.2 (12-C and 14-C), 34.12 (5-C and 7-C), 49.9 (6-C), 79.2 (17-C), 130.2 (10-C and 2-C), 145.6 (3-C and 9-C), 155.5 (16-C), 200.9 (1-C and 11-C); *m/z* (ESI) 352.2486 ($[M+H]^+$. $C_{20}H_{34}NO_4$ requires 352.2482).



12

1,1'-(3R,5S,7as)-hexahydro-1H-pyrrolizine-3,5-diyldibutan-2-one **12** :

To the mixture of compound 1**0** and **11** (308.0 mg, 0.87 mmol) in solution in dichloromethane (15 cm^3), was added, under N_2 atmosphere, TFA (1.35 cm^3, 17.52 mmol). The reaction mixture was heated at 55°C for 24 h. Then the reaction media was neutralised with saturated potassium carbonate solution and extracted with dichloromethane. The organic phases were dried over sodium sulphate, filtered and evaporated. The crude mixture was then purified by column chromatography on alumina, using petroleum ether and ethyl acetate (7:3) as eluent, to afford the pyrrolizidine **12** (164.7 mg, 75 %) as an orange oil.
$\nu_{max}(CH_2Cl_2/cm^{-1})$ 2937, 2159, 2029, 1976, 1711 and 1266; δ_H(400 MHz; $CDCl_3$) 1.04 (6H, t, *J* 7.3, 11-H_3 and 15-H_3), 1.40 (4H, m) and 1.95 (4H, m): 2-H_2, 3-H_2, 5-H_2 and 6-H_2, 2.31 (2H, dd, *J* 16.1 and 7.6) and 2.67 (2H, dd, 15.9 and 6.2): 8-H_2 and 12-H_2, 2.43 (4H, m, 10-H_2 and 14-H_2), 3.2 (2H, quintet, *J* 6.5, 1-H and 7-H), 3.53 (1H, quintet, *J* 6.4, 4-H); δ_C(101 MHz, $CDCl_3$) 7.6 (11-C and 15-C), 31.1 (3-C and 5-C), 31.5 (6-C and 2-C), 36.9 (10-C and 14-C), 49.0 (8-C and 12-C), 61.9 (1-C and 7-C), 63.9 (4-C), 211.1 (9-C and 13-C).*m/z* (ESI) 274.1767 ($[M+Na]^+$. $C_{15}H_{25}NNaO_2$ requires 274.1778).



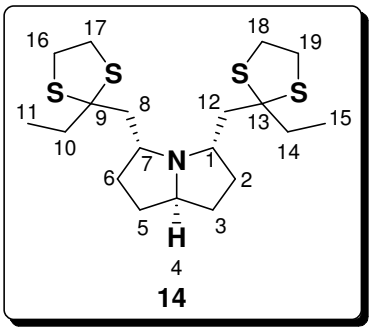
13

Mono tosylhydrazone **13** :

To a solution of pyrrolizidine **12** (13.0 mg, 0.05 mmol) in absolute ethanol (0.5 cm^3) was added tosylhydrazine (22.0 mg, 0.11 mmol), under N_2 atmosphere. Then the reaction mixture was heated at 88°C for 4 h and was the cooled to room temperature and stirred overnight.

Then the solvent are evaporated and the crude mixture was purified by column chromatography on alumina, using petroleum ether and ethyl acetate (7:3) as eluent, to give product **13** (10.7 mg, 49%) as a colorless solid.

$\nu_{max}(CH_2Cl_2/cm^{-1})$ 2968, 2221, 2029, 1711, 1332, 1160 and 911; δ_H(400 MHz; $CDCl_3$) 0.96 (3H, t, *J* 7.3, 11-H_3), 1.04 (3H, t, *J* 7.3, 15-H_3), 1.31-1.45 (4H, m) and 1.80-2.01 (4H, m): 2-H_2, 3-H_2, 5-H_2 and 6-H_2, 2.16-2.47 (8H, m, 8-H_2, 10-H_2, 14-H_2, 12-H and NH), 2.42 (3H, s, 22-H_3), 2.70 (1H, dd, *J* 17.9 and 6.1, 12-H), 3.19 (2H, m, 1-H and 7-H), 3.44 (1H, quintet, *J* 6.2, 4-H); 7.28 (2H, d, *J* 8.3, 19-H and 20-H), 7.90 (2H, d, *J* 8.2, 17-H and 18-H); δ_C(101 MHz, $CDCl_3$) 7.60 (11-C), 10.5 (15-C), 21.5 (22-C), 29.7, 30.9, 31.1, 32 and 32.2 (2-C, 3-C, 5-C, 6-C and 10-C), 36.5 and 36.7 (8-C and 14-C), 46.6 (12-C), 62.0 (1-C), 63.7 (4-C), 65.6 (7-C), 127.8 (17-C and 18-C), 129.0 (19-C and 20-C), 137.4 (16-C), 142.7 (21-C), 159.0 (9-C), 210.4 (13-C) *.m/z* (ESI) 420.2307 ($[M+H]^+$. $C_{22}H_{34}N_3O_3S$ requires 420.2315).

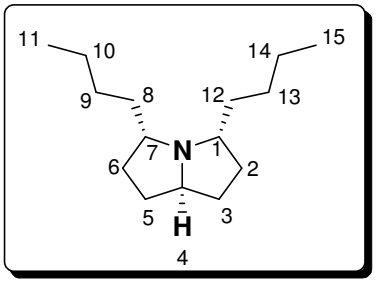


14

(3S,5R,7as)-3,5-bis((2-ethyl-1,3-dithiolan-2-yl)methyl)-hexahydro-1H-pyrrolizine **14** :

To a solution of pyrrolizidine **12** (61 mg, 0.24 mmol) in dry dichloromethane (1.5 cm^3), was added, under N_2 atmosphere, 1,2-ethanedithiol (.41 cm^3, 4.8 mmol) in presence of $BF_3{\cdot}Et_2O$ (0.4 cm^3, 3.2 mmol). The reaction was then stirred at room temperature for 18 h.
Acetone (0.6 cm^3) was then added to remove excess of 1,2-ethanedithiol. The reaction mixture was washed with a saturated sodium bicarbonate solution and extracted with dichloromethane. The organic phase was dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude mixture was then purified by column chromatography on alumina, using petroleum ether and ethyl acetate (8:2) as eluent, to give pyrrolizidine **14** (83.1 mg, 85%) as a yellow oil.

$\nu_{max}(CH_2Cl_2/cm^{-1})$ 2959, 2920, 2159, 1435, 1371, 1275 and 1095; δ_H(400 MHz; $CDCl_3$) 1.07 (6H, t, *J* 7.3, 11-H_3 and 15-H_3), 1.41 (2H, m) and 1.99 (2H, m): 3-H_2 and 5-H_2, 1.63 (2H, m) and 2.10 (2H, m): 6-H_2 and 2-H_2, 1.97 (4H, m, 14-H_2 and 10-H_2), 1.98 (2H, dd, *J* 14.2 and 2.1) and 2.39 (2H, dd, *J* 14.6 and 2.8): 8-H_2 and 12-H_2, 3.05 (2H, m, 1-H and 7-H), 3.27 (8H, m , 16-H_2, 17-H_2, 18-H_2 and 19-H_2), 3.50 (1H, quintet, *J* 6.7, 4-H); δ_C(101 MHz, $CDCl_3$) 11.2 (11-C and 15-C), 32.2 (3-C and 5-C), 32.7 (6-C and 2-C), 37.6 (10-C and 14-C), 39.27 (16-C and 19-C), 39.52 (18-C and 17-C), 48.5 (8-C and 12-C), 62.3 (4-C), 63.7 (7-C and 1-C), 71.5 (9-C and 13-C).*m/z* (ESI) 404.1561 ($[M+H]^+$. $C_{19}H_{34}NS_4$ requires 404.1569).



(3R,5S,7ar)-3,5-dibutyl-hexahydro-1H-pyrrolizine **Alkaloid *cis*-223B** :

To a suspension of Raney Nickel (1 g) in absolute ethanol (1.5 cm^3), was added, under N_2 nitrogen, a solution of pyrrolizidine **14** (45.9 mg, 0.11 mmol) in absolute ethanol.
The reaction mixture was heated at 78°C for 3 h and then filtered through a pad of celite, rinced with dichloromethane and ethyl acetate.
Alkaloid *cis*-223B was obtained, after a purification by column chromatography on alumina, using petroleum ether and ethyl acetate (8:2) as eluent, as a yellow oil (25 mg, 98%).

$\nu_{max}(CH_2Cl_2/cm^{-1})$ 2928, 2857, 1421, 1264 and 1045; δ_H(400 MHz; $CDCl_3$) 0.90 (6H, t, *J* 7.1, 11-H_3 and 15-H_3), 1.26-1.60 (12H, m, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2), 1.40 (m, 4H) and 1.94 (4H, m): 2-H_2, 3-H_2, 5-H_2 and 6-H_2, 2.61 (2H, m, 1-H and 7-H) 3.56 (1H, m, 4-H); δ_C(101 MHz, $CDCl_3$) 14.1 (11-C and 15-C), 22.9 (10-C and 14-C), 29.3 (9-C and 13-C), 31.6 and 31.7 (2-C, 3-C, 5-C and 6-C), 36.6 (8-C and 12-C), 64.6 (4-C), 66.8 (7-C and 1C).*m/z* (ESI) 224.2368 ($[M+H]^+$. $C_{15}H_{30}N$ requires 224.2373).