Synthesis of 3-alkylpyridines. Part 2.[1] Synthesis of both enantiomers of niphatesine C[2]

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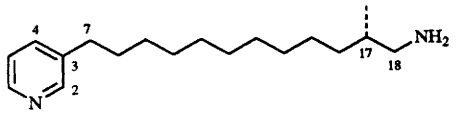
Both enantiomers of the pyridine alkaloid niphatesine C **1** have been prepared in a convergent synthesis by acylation of the nonracemic thiophenes **3** and *ent*-**3**, reductive desulfurization, and functional group transformation. The absolute configuration of the natural product was established as (*S*) based on comparison of the sense of optical rotation with that of synthetic **1**.

Niphatesine C **1** is an alkaloid isolated from the Okinawan marine sponge *Niphates sp.* found near Kerama Islands.[3] It belongs to a large group of natural products with 3-alkylpyridine structure[4] showing antimicrobial and cytostatic activities.[3]



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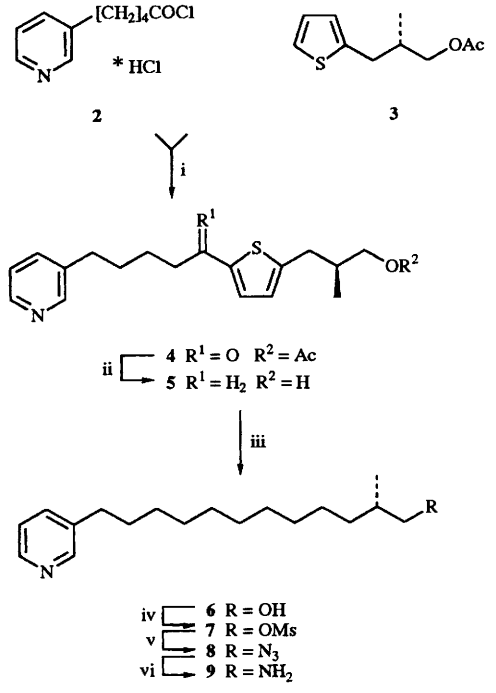
Results and discussion

For the enantioselective synthesis of **1** a route was developed which permits the convenient introduction of the chiral centre. Unfortunately, at the beginning of our work the absolute configuration of the natural product was unknown. Therefore, we used a chiral building block which is available in both enantiomeric forms (**3** and *ent*-**3**) in high optical purity. Both enantiomers of this chiral thiophene are available by esterification of (*R*)- or (*S*)-2-methyl-3-(2-thienyl)propan-1-ol,[5,6] respectively. The chiral, non-racemic thiophenes **3** and *ent*-**3** can be connected with a pyridinealkanoic acid chloride by regioselective acylation, allow the introduction of the nitrogen function by transformation of the terminal functional group, and can be converted into a part of the alkyl chain by reductive desulfurization of the thiophene ring.

This strategy has been utilized successfully for the total synthesis of racemic ikimine A in our previous work[1] and has now been employed for the enantioselective synthesis of niphatesine C **1**.

5-(3-Pyridyl)pentanoic acid chloride hydrochloride[1] **2** was obtained from the carboxylic acid[7] with oxalyl chloride. Friedel–Crafts acylation of the (*S*)-thiophene **3** (enantiomeric excess 92%) with the crude acid chloride **2** gave the thienyl ketone **4**. Huang–Minlon reduction and simultaneous ester cleavage of **4** gave the alcohol **5** smoothly (Scheme 1).

To effect desulfurization of the thiophene **5** it was stirred with an excess of freshly prepared Raney nickel W7 under a hydrogen atmosphere at room temperature. Though GLC analysis showed nearly complete desulfurization, **6** was isolated in only 62% yield. The poor yield is probably due to chemisorption of the highly polarizable nitrogen compounds on the nickel surface. Comparable difficulties with reductive desulfurization have been published,[8] whereas other authors observed good yields in this crucial step.[5,9] A minor decrease of optical purity during the reductive desulfurization of related compounds was prevented by acetylation of the alcohol moiety.[5] However, in our case there was no need for protection of **5** because the enantiomeric excess was not altered during the course of this reaction.

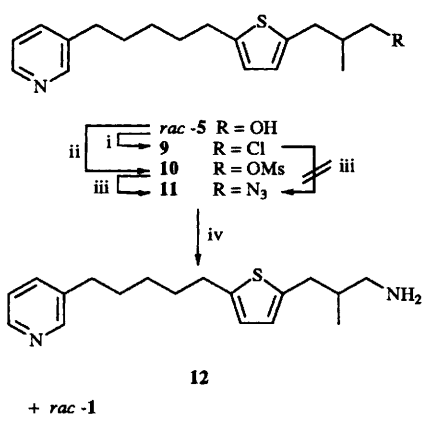


Scheme 1 Total synthesis of the alkaloid niphatesine C **1**. *Reagents:* i, $SnCl_4$, CH_2Cl_2, ii, KOH, N_2H_4, diethylene glycol; iii, Raney nickel, H_2, THF; iv, MsCl, pyridine; v, NaN_3, DMF; vi, Pd/C, H_2, EtOH

For the introduction of the terminal nitrogen function the hydroxy group of **6** was transformed into a leaving group by mesylation and converted into the azide **8** by treatment with sodium azide in DMF. Finally, the amine **1** was obtained by hydrogenation of the azide with palladium on charcoal catalyst under medium pressure.

Moreover, we examined two alternative routes to **1**. For economical reasons these experiments were performed starting from racemic thiophene *rac*-**3**. Initially, we attempted to realize a considerably shorter synthetic route to **1** by simultaneous reduction of the thiophene ring and the terminal azido group. Therefore, the azide **11** was synthesized by substitution of *rac*-**5** with sodium or lithium azide in DMF *via* mesylate **10**. In contrast, under the same conditions the chloride **9** completely failed to give the azido compound **11**. Unfortunately, the attempted simultaneous desulfurization and reduction of the

azido group of **11** with Raney nickel W7 gave no satisfactory results. GC–MS analysis of the reaction showed a mixture composed of 40% of *rac*-**1**, 40% of the aminoalkyl thiophene **12** and 20% of olefinic compounds as the result of incomplete reduction of the thiophene ring (Scheme 2). Similar incomplete



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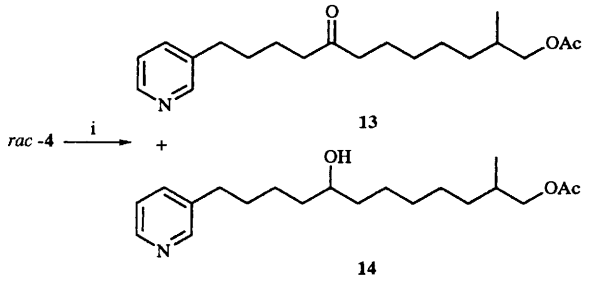
+ *rac*-**1**

Scheme 2 Synthesis and reductive desulfurization of **11**. *Reagents:* i, $SOCl_2$, toluene; ii, MsCl, pyridine; iii, NaN_3, DMF; iv, Raney nickel W7, H_2, THF

reductions to give alkenes were described earlier for other thiophenes.[9] For comparison, **12** was prepared by reduction of **11** with lithium tetrahydroaluminate.

In a further approach to *rac*-**1** we examined the reductive desulfurization of the thiophene ring prior to Huang–Minlon reduction (Scheme 3). However, treatment of *rac*-**4** with Raney



Scheme 3 Reductive desulfurization of *rac*-**4**. *Reagents:* i, Raney nickel W7, H_2, THF

nickel W7 yielded, besides a minor amount of ketone **13** (identified by GC–MS), mainly the secondary alcohol **14**. Consequently, the strategy outlined in Scheme 1 remains the most convenient one.

The spectroscopic data of synthetic **1** are in full agreement with the values[3] reported for natural niphatesine C. The ^1H and ^{13}C spectra of the natural product were reported for the trifluoroacetate, though not indicated by the authors.[3]

As synthetic (*S*)-**1** and natural **1** show dextrorotary optical rotation, the natural product was established to have the (*S*) configuration. The levorotary unnatural amine *ent*-**1** was obtained in an analogous manner to the synthetic route outlined in Scheme 1 starting from the (*R*)-ester *ent*-**3**[6] (enantiomeric excess 96%).

Since completion of this work a further enantioselective synthesis of **1** based on a commercially available building block has been described.[10]

In preliminary investigations alkaloid **1** showed no activity against grampositive nor gramnegative bacteria, but a moderate action against fungi and mycobacteria was found. Structural variations of the natural product **1** for an improvement of the antimicrobial and also cytostatic activities[3] are under investigation.

Experimental

General

Elemental analyses were performed on a Labormatic CH analyser (Wösthoff) for C and H and a Hewlett-Packard CHN autoanalyser for N. FTIR spectra were recorded on a Nicolet 51-P spectrometer, UV spectra on a Shimadzu UV–PC 2105 photometer. NMR spectra were recorded in $CDCl_3$, unless otherwise stated, with tetramethylsilane as internal standard on a JEOL GX-400 (400.1 MHz ^1H, 100.5 MHz ^{13}C) spectrometer. *J* Values are given in Hz. Mass spectra, exact masses, and GC–MS were recorded on VG 7070H, Finnigan MAT-8430, and MAT-4515 spectrometers, respectively. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was carried out on Merck silica (230–400 mesh). Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Raney nickel W7[11] was freshly prepared from nickel–aluminium alloy and used immediately for the reductions. The organic extracts were dried over anhydrous sodium sulfate which was later removed by filtration. The solvent used was concentrated using a rotary evaporator under reduced pressure. Dichloromethane was distilled from phosphorus pentoxide and stored over 4 Å molecular sieves. GLC was performed on a phenylmethylsilicon stationary phase AT-50 (Alltech) (30 m, 0.225 mm i.d. 0.25 μm film) on a Shimadzu GC-14 A gas chromatograph equipped with FID.

Synthesis of niphatesine C 1

The synthesis of (*S*)-niphatesine C **1** is outlined below. (*R*)-Niphatesine C *ent*-**3** and racemic niphatesine C *rac*-**1** were prepared in an analogous manner starting from *ent*-**3** or *rac*-**3**.

2-Methyl-3-{5-[5-(3-pyridyl)pentanoyl]-2-thienyl}propyl acetate 4

Tin tetrachloride (9.8 g, 37.8 mmol) was added slowly to a stirred mixture of 5-(3-pyridyl)pentanoic acid chloride hydrochloride **2**[7] (3.2 g, 13.7 mmol) and (*S*)-2-methyl-3-(2-thienyl)propyl acetate **3**[5,6] (2.5 g, 12.6 mmol) in dry dichloromethane (70 cm^3) under nitrogen at 0 °C. After 1 h the red resin was dissolved in hydrochloric acid (6 mol dm^{-3}, 60 cm^3), the solution was poured into a concentrated solution of potassium hydroxide (**CAUTION!**) and extracted with ethyl acetate. Purification by flash chromatography gave *compound* **4** (3.6 g, 79%) as an oil (Found: C, 66.8; H, 7.3; N, 3.9. $C_{20}H_{25}NO_3S$ requires C, 66.82; H, 7.01; N, 3.90%); ν_{max}(KBr)/cm^{-1} 3418, 2932, 1737, 1656, 1455, 1242, 1041, 804 and 714; δ_H 8.33 (1 H, d, *J* 1.6, 2-H), 8.30 (1 H, dd, *J* 4.7 and 1.6, 6-H), 7.45 (1 H, d, *J* 3.8, 13-H), 7.38 (1 H, dd, *J* 1.6 and 7.6, 4-H), 7.08 (1 H, dd, *J* 4.7 and 7.6, 5-H), 6.71 (1 H, d, *J* 3.8, 14-H), 3.83 (2 H, d, *J* 6.0, 18-H_2), 2.84 (1 H, dd, *J* 6.0 and 14.8, 16-H[a]), 2.77 (2 H, t, *J* 7.3, 10-H_2), 2.60 (1 H, dd, *J* 7.9 and 14.8, 16-H[b]), 2.54 (2 H, t, *J* 7.3, 7-H_2), 2.05 (1 H, m, 17-H), 1.95 (3 H, s, CO–CH_3), 1.60 (2 H, m, 9-H_2), 1.67 (2 H, m, 8-H_2) and 0.87 (3 H, d, *J* 6.7, CH_3); δ_C 192.1 (s, C-11), 170.5 (s, *C*O–CH_3), 151.7 (s, C-12), 149.4 (d, C-2), 146.9 (d, C-6), 142.1 (s, C-15), 136.9 (s, C-3), 135.9 (d, C-4), 131.7 (d, C-13), 126.5 (d, C-14), 122.9 (d, C-5), 67.5 (t, C-18), 38.1 (t, C-10), 34.3 (d, C-17), 33.9 (t, C-16), 32.4 (t, C-7), 30.2 (t, C-8), 23.8 (t, C-9), 20.4 (q, CO–*C*H_3) and 16.1 (q, CH_3); *m*/*z* (EI) 359 (M^+, 71%), 299 (11), 287 (20), 286 (100), 225 (15), 165 (31), 139 (11), 107 (14), 106 (72), 97 (14), 93 (12) and 92 (20).

4. $[\alpha]_D^{20}$ +6.9 (*c* 3.26, $CHCl_3$); ee 92% (GLC); (*S*).

***ent*-4.** $[\alpha]_D^{20}$ −7.7 (*c* 3.27, $CHCl_3$); ee 96% (GLC); (*R*).

2-Methyl-3-{5-[5-(3-pyridyl)pentyl]-2-thienyl}propan-1-ol 5

A mixture of compound **4** (3.6 g, 10.0 mmol), potassium hydroxide (3.5 g, 62.4 mmol) and 80% hydrazinium hydroxide

(1.8 g, 27.2 mmol) was heated slowly to 120 °C with stirring and was refluxed for 2 h. The excess of hydrazine was distilled off and then the temperature was slowly raised to 210 °C. After being kept at 210 °C for 4 h the mixture was poured into water and extracted with ethyl acetate. Purification by flash chromatography yielded *compound* **5** (2.4 g, 79%) as an oil (Found: C, 71.0; H, 8.7; N, 4.45. $C_{18}H_{25}NOS$ requires C, 71.24; H, 8.30; N, 4.62%); ν_{max}(KBr)/cm^{-1} 3310, 2930, 2856, 1479, 1423, 1103, 794 and 713; δ_H 8.39 (2 H, br s, 2-H and 6-H),† 7.47 (1 H, ddd, *J* 1.9, 1.9 and 7.8, 4-H), 7.19 (1 H, dd, *J* 4.9 and 7.8, 5-H), 6.55 (1 H, d, *J* 3.2, ArH), 6.53 (1 H, d, *J* 3.2, ArH), 3.54 (1 H, dd, *J* 5.7 and 10.4, 18-H^a), 3.47 (1 H, dd, *J* 6.0 and 10.4, 18-H^b), 3.11 (1 H, br s, OH), 2.88 (1 H, dd, *J* 6.3, 14.5, 16-H^a), 2.73 (2 H, t, *J* 7.4, 10-H$_2$), 2.60 (1 H, m, 16-H^b), 2.59 (2 H, t, *J* 7.6, 7-H$_2$), 1.92 (1 H, m, 17-H), 1.70–1.59 (4 H, m, 8-H$_2$ and 10-H$_2$), 1.38 (2 H, m, 9-H$_2$) and 0.96 (3 H, d, *J* 7.0, CH$_3$); δ_C 149.6 (d, C-2), 146.9 (d, C-6), 143.2 (s), 140.9 (s) 137.8 (s, C-3), 136.0 (d, C-4) 124.7 (d), 123.5 (d), 123.4 (d, C-5), 66.9 (t, C-18), 38.1 (d, C-17), 33.8 (t, C-16), 32.8 (t, C-7), 31.3 (t), 30.7 (t), 29.9 (t), 28.3 (t) and 16.6 (q, CH$_3$); *m*/*z* (EI) 303 (M$^+$, 32%), 274 (18), 273 (79), 272 (100), 244 (15), 137 (11), 123 (17), 111 (26), 106 (15), 97 (11), 93 (14) and 92 (26).

5. $[\alpha]_D^{20}$ −5.8 (*c* 4.26, $CHCl_3$); ee 92% (GLC): (*S*).

***ent*-5.** $[\alpha]_D^{20}$ +5.8 (*c* 4.06, $CHCl_3$); ee 96% (GLC); (*R*).

2-Methyl-12-(3-pyridyl)dodecan-1-ol 6

To a stirred suspension of **5** (1.58 g, 5.2 mmol) in dry THF (10 cm^3) under hydrogen Raney nickel W7 was added in several portions every 2 h until GLC showed that no starting material remained. Filtration and purification by flash chromatography gave *compound* **6** (0.90 g, 62%) as an oil (Found: C, 77.9; H, 11.8; N, 4.75. $C_{18}H_{31}NO$ requires C, 77.89; H, 11.26; N, 5.05%); ν_{max}(KBr)/cm^{-1} 3333, 2925, 2854, 1466, 1424, 1045, 1030 and 714; δ_H 8.42 (2 H, br s, 2-H and 6-H), 7.49 (1 H, d, *J* 7.6, 4-H), 7.20 (1 H, dd, *J* 4.7 and 7.6, 5-H), 3.50 (1 H, dd, *J* 5.8 and 10.4, 18-H^a), 3.40 (1 H, dd, *J* 6.7 and 10.4, 18-H^b), 2.64 (1 H, br s, OH), 2.59 (2 H, t, *J* 7.7, 7-H$_2$), 1.60 (3 H, br m, 8-H$_2$ and 17-H), 1.36–1.23 (15 H, br m, 9-H$_2$–16-H^a), 1.09 (1 H, m, 16-H^b) and 0.91 (3 H, d, *J* 6.6, CH$_3$); δ_C 149.8 (d, C-2), 147.0 (d, C-6), 138.1 (s, C-3), 135.9 (d, C-4), 123.3 (d, C-5), 68.2 (t, C-18), 35.8 (d, C-17), 33.2 (t), 33.0 (t), 31.1 (t), 29.9 (t), 29.58 (t), 29.56 (t), 29.5 (t), 29.3 (t), 29.1 (t), 27.0 (t) and 16.7 (q, CH$_3$); *m*/*z* (EI) 277 (M$^+$, 8%), 276 (12), 247 (17), 246 (35), 218 (21), 204 (19), 190 (12), 176 (10), 162 (12), 148 (13), 120 (16), 107 (22), 106 (100), 93 (85), 92 (39) and 57 (11).

6. $[\alpha]_D^{20}$ −5.4 (*c* 3.19, $CHCl_3$); ee 92% (GLC); (*S*).

***ent*-6.** $[\alpha]_D^{20}$ +5.6 (*c* 3.20, $CHCl_3$); ee 96% (GLC); (*R*).

3-(12-Azido-11-methyldodecyl)pyridine 8

To a solution of compound **6** (0.30 g, 1.1 mmol) in dry pyridine (0.2 g, 2.5 mmol) methanesulfonyl chloride (0.2 g, 1.7 mmol) was added dropwise at 0 °C under nitrogen. After 2 h ice–water was added to it and the mixture was extracted with precooled dichloromethane, washed with a cold aqueous solution of sodium carbonate and the solvent evaporated under reduced pressure. Further purification by flash chromatography gave *compound* **7** (0.20 g) as an oil. The mesylate **7** and sodium azide (0.2 g, 3.1 mmol) in dry DMF (3 cm^3) were stirred under nitrogen at 80 °C for 2 h. Dilution with water, extraction with ethyl acetate and column chromatography gave *compound* **8** (0.10 g, 31% from **6**) as an oil (Found: C, 71.3, H, 10.3; N, 18.5. $C_{18}H_{30}N_4$ requires C, 71.48; H, 10.00; N, 18.52%); ν_{max}(KBr)/cm^{-1} 2928, 2855, 2096, 1464, 1421 and 714; δ_H 8.44 (2 H, br s, 2-H and 6-H), 7.48 (1 H, d, *J* 7.8, 4-H), 7.20 (1 H, dd, *J* 4.8 and 7.8, 5-H), 3.20 (1 H, dd, *J* 5.9 and 12.0, 18-H^a), 3.09 (1 H, dd, *J* 6.9 and 12.0, 18-H^b), 2.59 (2 H, t, *J* 7.7, 7-H$_2$), 1.70 (1 H, m, 17-H), 1.61 (2 H, m, 8-H$_2$), 1.40–1.18 (15 H, br m, 9-H$_2$–16-H^a), 1.11 (1 H, m, 16-H^b) and 0.94 (3 H, d, *J* 6.6, CH$_3$); δ_C 149.9 (d, C-2), 147.1 (d, C-6), 138.0 (s, C-3), 135.7 (d, C-4), 123.2 (d, C-5), 57.8 (t), 34.0 (t), 33.5 (d, C-17), 33.0 (t), 31.1 (t), 29.7 (t), 29.5 (t), 29.47 (t), 29.4 (t), 29.3 (t), 29.1 (t), 26.7 (t) and 17.6 (q, CH$_3$); *m*/*z* (EI) 302 (M$^+$, 3%), 260 (83), 247 (28), 246 (93), 218 (24), 204 (20), 190 (23), 120 (20), 107 (22), 106 (100), 93 (80) and 92 (40).

8. $[\alpha]_D^{20}$ +1.7 (*c* 5.10, $CHCl_3$); ee 92% (GLC); (*S*).

***ent*-8.** $[\alpha]_D^{20}$ −1.9 (*c* 5.10, $CHCl_3$); ee 96% (GLC); (*R*).

Niphatesine C 1

A mixture of compound **8** (36 mg, 0.12 mmol) and 5% palladium on charcoal catalyst (30 mg) was hydrogenated for 3 h under 1.5 atm at 20 °C in methanol (3 cm^3). Filtration and evaporation gave *compound* **1** (25 mg, 76%) as an oil, λ_{max}(MeOH–CF_3CO_2H)/nm 202 (ε/dm^3 mol^{-1} cm^{-1} 52 600), 259sh (36 500), 263 (40 400) and 268sh (31 900); ν_{max}(KBr)/cm^{-1} 1679 and 1471; δ_H(CD_3OD–CF_3CO_2D) 8.76 (1 H, br s, 2-H), 8.72 (1 H, br s, 6-H), 8.51 (1 H, d, *J* 8.1, 4-H), 8.03 (1 H, m, 5-H), 2.89 (3 H, m, 7-H$_2$ and 18-H^a), 2.70 (1 H, m, 18-H^b), 1.77–1.70 (3 H, m, 17-H and 8-H$_2$), 1.42–1.19 (15 H, m, 9-H$_2$–16-H^a), 1.20 (1 H, m, 16-H^b) and 1.00 (3 H, d, *J* 6.7, CH$_3$); δ_C(CD_3OD–CF_3CO_2D) 147.8 (d, C-4), 144.9 (s, C-3), 142.1 (d, C-2), 140.3 (d, C-6), 128.3 (d, C-5), 46.5 (t, C-18), 35.0 (t), 33.5 (t), 32.9 (d, C-17), 31.6 (t), 30.7 (t), 30.63 (t), 30.60 (t), 30.55 (t), 30.4 (t), 30.1 (t), 27.7 (t) and 17.3 (q, CH$_3$); *m*/*z* (GC–MS, EI) 276 (M$^+$, 2%), 247 (35), 218 (14), 204 (10), 190 (11), 162 (12), 148 (10), 120 (15), 107 (20), 106 (95), 93 (100) and 92 (20) [Found: *m*/*z* (EI), 276.2565. Calc. for $C_{18}H_{32}N_2$ (M$^+$), 276.2565].

1. $[\alpha]_D^{20}$ +2.4 (*c* 0.5, MeOH); ee 92% (GLC); (*S*).

***ent*-1.** $[\alpha]_D^{20}$ −3.2 (*c* 3.2, MeOH); ee 96% (GLC); (*R*).

The following compounds were prepared only in racemic forms.

3-{5-[5-(3-Chloro-2-methylpropyl)-2-thienyl]pentyl}pyridine 9

To a solution of *rac*-**5** (0.60 g, 1.98 mmol) in dry toluene (2 cm^3) a solution of thionyl chloride (0.3 g, 2.6 mmol) in dry toluene (3 cm^3) was added at 0 °C. After being stirred for 30 min the solution was warmed to gentle reflux for an additional 150 min. The solvent was evaporated and the residue partitioned between dilute ammonia and ethyl acetate. Several extractions, washing with brine and drying gave the crude product, which was further purified by chromatography on silica gel to yield *compound* **9** (0.50 g, 78%) as an oil (Found: C, 67.1; H, 7.4; N, 4.3. $C_{18}H_{24}ClNS$ requires C, 67.16; H, 7.51; N, 4.35%); ν_{max}(KBr)/cm^{-1} 2932, 2857, 2361, 1575, 1422, 1026, 797 and 714; δ_H 8.43 (1 H, s, 2-H), 8.42 (1 H, d, *J* 1.6, 6-H), 7.46 (1 H, m, 4-H), 7.19 (1 H, m, 5-H), 6.59 (1 H, d, *J* 3.4, ArH), 6.56 (1 H, d, *J* 3.4, ArH), 3.49 (1 H, dd, *J* 10.8 and 5.1, 18-H^a), 3.44 (1 H, dd, *J* 10.8 and 5.7, 18-H^b), 2.88 (1 H, dd, *J* 7.2 and 14.7, 16-H^a), 2.74 (2 H, t, *J* 7.6, 11-H$_2$), 2.71 (1 H, m, 16-H^b), 2.60 (2 H, t, *J* 7.8, 7-H$_2$), 2.10 (1 H, m, 17-H), 1.71–1.61 (4 H, br m, 8-H$_2$ and 10-H$_2$), 1.41 (2 H, br m, 9-H$_2$) and 1.05 (3 H, d, *J* 6.7, CH$_3$); δ_C 149.9 (d, C-2), 147.2 (d, C-6), 143.7 (s), 139.5 (s), 137.7 (s, C-3), 135.8 (d, C-4), 125.2 (d), 123.6 (d), 123.2 (d), 50.0 (t, C-18), 37.5 (d, C-17), 34.2 (t, C-16), 32.9 (t, C-7), 31.4 (t), 30.8 (t), 30.0 (t), 28.5 (t) and 17.6 (q, CH$_3$); *m*/*z* (EI) 321 (M$^+$, 6%), 286 (23), 285 (100), 272 (45), 270 (13), 244 (16), 151 (32), 137 (10), 134 (10), 123 (13), 111 (44), 110 (17), 106 (30), 93 (27) and 92 (30).

3-{5-[5-(3-Azido-2-methylpropyl)-2-thienyl]pentyl}pyridine 11

The same procedure as described above for the preparation of compound **8** was used. Reaction of *rac*-**5** (2.4 g, 7.9 mmol) with methanesulfonyl chloride (1.0 g, 8.9 mol) gave the mesylate **10** (3.2 g, 94%). Treatment of **10** (0.50 g, 1.3 mmol) with sodium

† In most of the 3-substituted pyridines described here, 6-H appears as a broad singlet and not, as expected, as a doublet. Similar observations were made by other authors in this series of alkaloids.[3,12]

azide gave compound **11** (270 mg, 65%) as an oil (Found: C, 66.0; H, 7.5; N, 16.8. $C_{18}H_{24}N_4S$ requires C, 65.82; H, 7.36; N, 17.06%); ν_{max}(KBr)/cm^{-1} 2932, 2856, 2099, 1423, 796 and 713; δ_H 8.43 (2 H, br s, 2-H and 6-H), 7.47 (1 H, d, *J* 7.8, 4-H), 7.19 (1 H, dd, *J* 4.7 and 7.8, 5-H), 6.56 (2 H, s, 13-H and 14-H), 3.25 (1 H, dd, *J* 5.7 and 12.0, 18-H^a), 3.17 (1 H, dd, *J* 6.4 and 12.0, 18-H^b), 2.80 (1 H, dd, *J* 6.8 and 14.7, 16-H^a), 2.74 (2 H, t, *J* 7.5, 11-H_2), 2.65 (1 H, dd, *J* 7.3 and 14.7, 16-H^b), 2.60 (2 H, t, *J* 7.5, 7-H_2), 1.98 (1 H, m, 17-H), 1.71–1.61 (4 H, m, 8-H_2 and 10-H_2), 1.40 (2 H, m, 9-H_2) and 1.00 (3 H, d, *J* 6.8, CH_3); δ_C 150.0 (d, C-2), 147.2 (d, C-6), 143.8 (s), 139.6 (s), 137.7 (s, C-3), 135.7 (d, C-4), 125.2 (d), 123.6 (d), 123.2 (d, C-5), 56.6 (t, C-18), 35.7 (d, C-17), 34.4 (t, C-16), 32.9 (t, C-7), 31.4 (t), 30.8 (t), 30.0 (t), 28.5 (t) and 17.6 (q, CH_3); *m/z* (EI) 328 (M^+, 4%), 273 (27), 272 (100), 271 (64), 258 (38), 257 (40), 166 (44), 137 (26), 110 (14), 106 (17), 93 (14) and 92 (20).

Reductive desulfurization of compound 11

The same procedure as described for the preparation of **6** was used for the reduction of **11** with Raney nickel W7 to give a mixture of *rac*-**1** (40%), **12** (40%) and olefinic products (20%) (GC–MS analysis).

2-Methyl-3-{5-[5-(3-pyridyl)pentyl]-2-thienyl}propylamine 12. A solution of **11** (100 mg, 0.30 mmol) in anhydrous THF (1 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (27 mg, 0.71 mmol) in anhydrous THF and the mixture was refluxed for 2 h. Then the mixture was cooled to room temperature, diluted with diethyl ether (2 cm^3) and treated with $Na_2SO_4 \cdot 10H_2O$ with stirring for 30 min. The solid was filtered off and washed with ethanol (3 × 5 cm^3). The combined filtrates were evaporated to give **12** (50 mg, 54%) as an oil; ν_{max}(KBr)/cm^{-1} 3140, 3045, 2812, 1406, 1207, 1074, 788 and 559; δ_H 8.34 (1 H, br s, 2-H), 8.32 (1 H, br s, 6-H), 7.65 (1 H, d, *J* 7.5, 4-H), 7.33 (1 H, dd, *J* 4.8 and 7.5, 5-H), 6.57 (1 H, d, *J* 3.3, ArH), 6.54 (1 H, d, *J* 3.3, ArH), 2.83–2.50 (8 H, br m), 1.85 (1 H, m, 17-H), 1.64 (4 H, m, 8-H_2 and 10-H_2), 1.38 (2 H, m, 9-H_2) and 0.94 (3 H, d, *J* 6.7, CH_3); δ_C 150.0 (d, C-2), 147.4 (d, C-4), 144.6 (s), 141.5 (s), 140.1 (s, C-3), 138.2 (d, C-4), 126.1 (d), 125.1 (d, C-5), 124.8 (d), 47.5 (t, C-18), 38.3 (d, C-17), 35.8 (t), 33.6 (t, C-16), 32.6 (t), 31.9 (t), 30.8 (t), 29.4 (t) and 17.6 (q, CH_3); *m/z* (EI; GC–MS) 302 (M^+, 30%), 285 (47), 273 (40), 272 (100), 258 (28), 245 (12), 244 (12), 232 (12), 151 (57), 137 (25), 134 (29), 123 (27), 111 (40), 110 (12), 107 (22), 106 (95), 97 (28), 93 (70) and 92 (60) [Found: *m/z* 302.1817. Calc. for $C_{18}H_{26}N_2S$ (M^+) 302.1817].

Reductive desulfurization of ketone *rac*-4

The same procedure as described for the preparation of **6** was used for the desulfurization of *rac*-**4** to give a mixture of mainly the alcohol **14** (49%) and a trace of ketone **13**.

2-Methyl-8-oxo-12-(3-pyridyl)dodecyl acetate 13. *m/z* (EI; GC–MS) 333 (M^+, 5%), 274 (14), 190 (12), 134 (15), 120 (16), 107 (20), 106 (100), 93 (11) and 92 (27).

8-Hydroxy-2-methyl-12-(3-pyridyl)dodecyl acetate 14. (Found: C, 71.9; H, 10.75; N, 4.1. $C_{20}H_{33}NO_3$ requires C, 71.60; H, 9.91, N, 4.18%); ν_{max}(KBr)/cm^{-1} 3395, 2932, 2857, 1738, 1242, 1035 and 714; δ_H 8.43 (1 H, br s, 2-H), 8.42 (1 H, br s, 6-H), 7.49 (1 H, d, *J* 7.7, 4-H), 7.20 (1 H, dd, *J* 4.7 and 7.7, 5-H), 3.94 (1 H, dd, *J* 5.9 and 10.7, 18-H^a), 3.83 (1 H, dd, *J* 6.9 and 10.7, 18-H^b), 3.58 (1 H, m, 11-H), 2.62 (2 H, t, *J* 7.7, 7-H_2), 2.05 (3 H, s, CO–CH_3), 1.77 (1 H, m, 17-H), 1.64 (2 H, m, 8-H_2), 1.53–1.29 (14 H, br m, 6 CH_2, 16-H^a and OH), 1.13 (1 H, br m, 16-H^b) and 0.91 (3 H, d, *J* 6.6, CH_3); δ_C 171.2 (s, *C*O–CH_3), 149.8 (d, C-2), 147.1 (d, C-6), 137.7 (s, C-3), 135.8 (d, C-4), 123.2 (d, C-5), 71.6 (d, C-11), 69.4 (t, C-18), 37.5 (t), 37.2 (t), 33.2 (t), 32.9 (t), 32.4 (d, C-17), 31.1 (t), 29.8 (t), 26.7 (t), 25.5 (t), 25.2 (t), 20.9 (q, CO–*C*H_3) and 16.8 (q, CH_3); *m/z* (EI; GC–MS) 335 (M^+, 8%), 334 (10), 276 (12), 165 (10), 164 (78), 135 (16), 134 (20), 107 (28), 106 (100), 105 (27) and 93 (58).

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References

1 Part 1: F. Bracher and T. Papke, *Nat. Prod. Lett.*, 1994, **4**, 223.
2 F. Bracher and T. Papke, presented in part at the Annual Meeting of the German Pharmaceutical Society, Saarbrücken 1993; Abstract: *Arch. Pharm. (Weinheim, Ger.)*, 1993, **326**, 589.
3 J. Kobayashi, C. Zeng, M. Ishibashi, H. Shigemori, T. Sasaki and Y. Mikami, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1291.
4 A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 491.
5 H.-E. Högberg, E. Hedenström, J. Fägerhag and S. Servi, *J. Org. Chem.*, 1992, **57**, 2052; O. Nordin, E. Hedenström and H.-E. Högberg, *Tetrahedron: Asymmetry*, 1994, **5**, 785.
6 F. Bracher and T. Papke, *Tetrahedron: Asymmetry*, 1994, **5**, 1653.
7 T. Tanouchi, M. Kawamura, I. Ohyama, I. Kajiwara, Y. Iguchi, T. Okada, T. Miyamoto, K. Taniguchi and M. Hayashi, *J. Med. Chem.*, 1981, **24**, 1149.
8 E. J. Modest and J. Szmuszkobicz, *J. Am. Chem. Soc.*, 1950, **72**, 577; S. Bernstein and L. Dorfmann, *J. Am. Chem. Soc.*, 1946, **68**, 1152.
9 C. R. Noe, M. Knollmüller, K. Dungler, C. Mikulka and P. Gärtner, *Monatsh. Chem.*, 1991, **122**, 705.
10 A. V. R. Rao and G. R. Reddy, *Tetrahedron Lett.*, 1993, **34**, 8329.
11 H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, 1948, **70**, 655.
12 J. Kobayashi, T. Murayama, S. Kosuge, F. Kanda, M. Ishibashi, H. Kobayashi, Y. Ohizumi, T. Ohta, S. Nozoe and T. Sasaki, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3301; A. R. Carroll and P. J. Scheuer, *Tetrahedron*, 1990, **46**, 6637.

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