Enantioselective Synthesis of (−)-Anaferine Dihydrochloride by a Ruthenium-Catalysed Tandem Ring Rearrangement Metathesis

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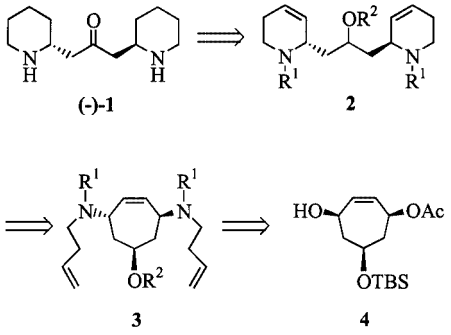
A stereoselective synthesis of (–)-anaferine dihydrochloride has been developed. The bis(tetrahydropyridine) system **10** was formed by a tandem ring rearrangement metathesis of the chiral bis(but-3-enylamino)cycloheptene derivative **9**. (–)-Anaferine dihydrochloride was obtained in 23% overall yield in eleven steps and its absolute configuration was confirmed as (*R*,*R*) by this total synthesis.

Introduction

(−)-Anaferine **1** was first isolated in 1962 by Schwarting et al. from *Withania somnifera* Dunal as a mixture of diastereomers.[1] The pure compound is rather labile in neutral or basic media, due to easy epimerisation via a retro-Michael−Michael reaction sequence. Acid solutions and salts, such as dihydrochlorides of **1**, however, are configurationally stable. Moerman et al. resolved a mixture of (±)-**1** with (*R*)-6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid[2] and isolated the enantiomers as salts, for example hydrochlorides. ORD spectroscopic analysis of the enantiomerically pure salts demonstrated that (−)-anaferine **1** is the (*R*,*R*)-enantiomer. We report here the first enantioselective synthesis of (−)-anaferine dihydrochloride **1·2HCl** with a tandem ring rearrangement metathesis as the key step.

Our plan was to synthesise **1** from the unsaturated precursor **2** by hydrogenation of the double bonds, O- and N-deprotection and oxidation of the secondary alcohol (Scheme 1). Compound **2** could be obtained from **3** by a tandem ring rearrangement metathesis, i.e. a combination of a ring-opening metathesis (ROM) and two ring-closing metatheses (RCM).[3] The chirality embedded in the carbocyclic starting material **3** is transferred into the two piperidine rings of the bis-heterocyclic system **2**. The two but-3-enylamino side chains of **3** could be introduced sequentially by diastereoselective nucleophilic substitution of the hydroxyl and the acetoxy groups of enantiomerically pure cycloheptene derivative **4**. This, in turn, is easily accessible in five steps from commercially available tropone.[4]



Scheme 1. Retrosynthetic approach to (−)-anaferine **1**

Results and Discussion

The first amino side chain was introduced into **4** by a Mitsunobu reaction using *N*-but-3-enyl-*N*-nosylamine with inversion of the configuration (Scheme 2). The amine **5** was obtained in 89% yield after chromatography. In the next step another but-3-enylamino side chain had to be introduced with retention of the configuration. An η^3-allylpalladium substitution with a suitable N-nucleophile should yield the desired product. Several attempts with different nucleophiles (e.g. but-3-enylamine, sodium azide, *N*-but-3-enyl-*N*-nosylamine) and catalyst systems [e.g. $Pd(PPh_3)_4$, $Pd_2(dba)_3$·chloroform complex/PPh_3 or dppb, $Pd(OAc)_2$/PPh_3 or dppb][5] were unsuccessful. We then envisaged a double inversion strategy to introduce the second but-3-enylamino side chain with net retention. Cleavage of the acetate **5** with potassium cyanide in methanol gave alcohol **6** in 86% yield. Among several methods to transform the alcohol **6** into the chloride **7** with inversion of the configuration, mesyl chloride turned out to be the reagent of choice. The diastereomerically pure chloride **7** (>95% *de* determined by

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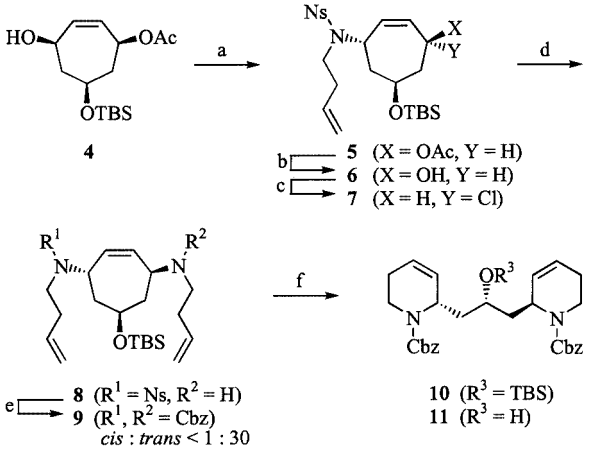
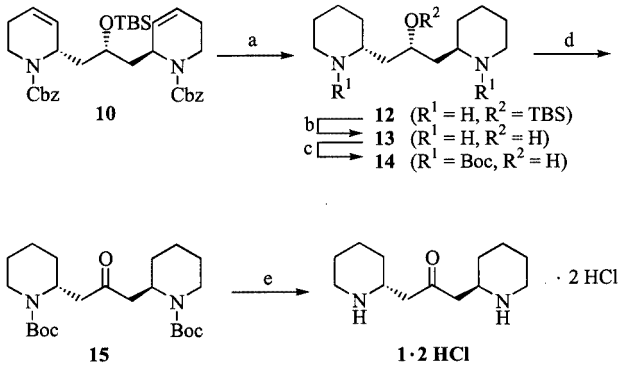


Scheme 2. Reagents and conditions: (a) *N*-nosyl-*N*-but-3-enylamine, PPh_3, DEAD, THF, room temp., 89%; (b) KCN, MeOH, room temp., 86%; (c) MsCl, pyridine, room temp., 82%, (d) but-3-enylamine, K_2CO_3, MeCN, 70 °C, 86%; (e) (i) PhSH, K_2CO_3, DMF, 70 °C; (ii) benzyl chloroformate, 0 °C, 86%; (f) $[Cl_2(Cy_3P)_2Ru{=}CHPh]$, CH_2Cl_2, reflux, 87%

^{1}H NMR spectroscopy) was obtained in 82% yield. Conversion of **7** into the bis-amine **8** with repeated inversion (S_N2) of the configuration was effected by heating **7** in acetonitrile with a sixfold excess of but-3-enylamine and an excess of potassium carbonate.

Under these conditions the amine **8** was obtained in 86% yield with a 96:4 diastereoselectivity (determined by ^{1}H NMR spectroscopy). A change of the N-protecting groups from Ns to Cbz would enable us to cleave the protective groups in the course of the hydrogenation of the double bonds at a later stage of the synthesis. The deprotection-protection sequence was performed with 1.5 equivalents of thiophenol and an excess of potassium carbonate in DMF at 70 °C followed by the addition of three equivalents of benzyl chloroformate at 0 °C, affording **9** in 86% yield.[6] The subsequent tandem ring rearrangement metathesis was carried out under an inert atmosphere with Grubbs catalyst $[Cl_2(Cy_3P)_2Ru{=}CHPh]$ in refluxing dichloromethane. This afforded the bis-tetrahydropyridine derivative **10** in 87% yield. It was planned to cleave the TBS ether and to oxidise the resulting *N*-Cbz-protected alcohol **11** to the ketone (in similar cases β-amino alcohols bearing electron-withdrawing N-protective groups could be oxidised to the corresponding β-amino ketones with conservation of the configuration. The syntheses of ruspolinone[7] and febrifugine[8] are recent examples of this strategy.). The subsequent hydrogenation in an acidic medium should give the dihydrochloride of (−)-anaferine **1**. Several attempts to cleave the TBS ether **10** with fluoride (TBAF/THF, pyridinium fluoride/H_2O/THF) failed. Careful deprotection in acidic medium (TFA in dichloromethane) resulted in very low yields and isomerisation of the double bonds. This isomerisation is probably caused by decomposition products of the ruthenium catalyst. Attempts to remove the catalyst by oxidation with lead tetraacetate[9] also gave isomerisation products.



Scheme 3. Reagents and conditions: (a) H_2, Pd/C (10%), MeOH, room temp., 87%; (b) conc. HCl, EtOH, room temp., 90%; (c) $(Boc)_2O$, NEt_3, MeOH, 50 °C, 98%; (d) PCC, molecular sieves (4 Å), CH_2Cl_2, room temp., quant.; (e) 3 N HCl, MeOH, room temp., quant.

Therefore, the hydrogenation was carried out first giving **12** in 87% yield. O-deprotection in acidic medium gave alcohol **13** in 90% yield, which was protected as its di-*tert*-butylcarbamate **14** (Scheme 3). Subsequent oxidation with pyridinium chlorochromate gave di-Boc-anaferine **15** in quantitative yield. Deprotection of **15** was quantitatively effected in dilute hydrochloric acid affording (−)-anaferine dihydrochloride **1·2HCl**. The analytical data of **1·2HCl** ($[\alpha]_D^{20}$ = −47.9 (*c* = 0.65; MeOH/H_2O, 1:1); m.p. 241 °C) were consistent with the literature data[1] ($[\alpha]_D^{20}$ = −49.8 ± 2 (*c* = 0.529; MeOH/H_2O, 1:1); m.p. 242.5−243.5 °C).

Conclusion

The development of methods for the preparation of chiral heterocyclic ring systems is a challenge in natural product synthesis. In this field, olefin metathesis has gained increasing importance during the last decade. Thus, (−)-anaferine dihydrochloride **1·2HCl** was synthesised in 23% overall yield in eleven steps. In conclusion, the absolute configuration assigned to (*R*,*R*)-anaferine **1** by Moerman et al.[2] could be confirmed by this stereoselective total synthesis.

Experimental Section

General: ^{1}H (200, 500 MHz) and ^{13}C NMR spectra (50, 125 MHz) were recorded as solutions (solvents are given) on either a Bruker AC 200 or a Bruker DRX 500 spectrometer relative to TMS. Mass spectra were obtained by electron impact (EI) at 70 eV on a Finnigan mat 95 SQ. IR spectra were measured by attenuated total reflectance (ATR) on a Perkin−Elmer 881 spectrometer. Optical rotations were determined on a Perkin−Elmer 341 polarimeter using a 10 cm path-length cell. Flash chromatography (FC) was performed on Merck silica gel 60 (0.040−0.063 mm). Air- and moisture-sensitive reactions were performed under N_2 in a Braun MB 120 BG glove box. MTBE = methyl *tert*-butyl ether. Chemicals were purchased from Aldrich or Merck and were used without further purification.

***N*-Nosylamine 5:** DEAD (1.80 g, 10.3 mmol) was added dropwise at 0 °C to a solution of acetate **4** (1.79 g, 5.95 mmol, prepared according

to ref.[4]), *N*-nosyl-*N*-but-3-enylamine (2.00 g, 7.75 mmol) and PPh_3 (3.10 g, 11.8 mmol) in THF (60 mL). After stirring for 18 h at room temperature the solution was concentrated in vacuo and the residue was purified by FC (cyclohexane/MTBE, 4:1) to give **5** as a light yellow oil (2.80 g, 89% yield). R_f = 0.54 (cyclohexane/MTBE, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.02−8.11 (m, 1 H), 7.58−7.72 (m, 3 H), 5.52−5.84 (m, 3 H), 5.24−5.36 (m, 1 H), 5.00−5.13 (m, 2 H), 4.74−4.87 (m, 1 H), 4.17−4.30 (m, 1 H), 3.18−3.48 (m, 2 H), 1.96−2.58 (m, 5 H), 2.05 (s, 3 H), 1.76−1.94 (m, 1 H), 0.84 (s, 9 H), 0.02 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.1 (C_q), 148.1 (C_q), 134.4 (2 CH), 133.7 (CH), 133.5 (C_q), 133.4 (CH), 131.6 (CH), 131.2 (CH), 124.1 (CH), 117.2 (CH_2), 68.1 (CH), 64.4 (CH), 52.8 (CH), 45.0 (CH_2), 42.2 (CH_2), 41.9 (CH_2), 35.5 (CH_2), 25.7 (3 CH_3), 21.2 (CH_3), 18.0 (C_q), −4.9 (2 CH_3) ppm. IR: ṽ = 3078 (w), 1739 (s), 1546 (vs), 1372 (s), 1240 (s), 1164 (s), 837 (s), 777 (s) cm^{-1}. MS (210 °C): *m*/*z* (%) = 481 (12) [$M^+ - C_4H_9$], 421 (17), 347 (33), 283 (33), 223 (69), 186 (86), 161 (46), 160 (38), 117 (84), 91 (70), 75 (100). HRMS ($C_{21}H_{29}N_2O_7SSi$ [$M^+ - C_4H_9$]): calcd. 481.1465; found 481.1461. $C_{25}H_{38}N_2O_7SSi$ (538.3): calcd. C 55.76, H 7.06, N 5.20; found C 55.51, H 7.18, N 5.47. $[\alpha]_D^{20}$ = −26 (*c* = 0.90, $CHCl_3$).

Alcohol 6: *N*-Nosylamine **5** (1.70 g, 3.16 mmol) and KCN (20 mg, 0.3 mmol) were dissolved in MeOH (20 mL) and stirred for 15 h at room temperature. The solution was concentrated in vacuo. Purification of the residue by FC (cyclohexane/MTBE, 1:1) afforded **6** as pale yellow oil (1.50 g, 96% yield). R_f = 0.14 (cyclohexane/MTBE, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (m, 1 H), 7.61−7.70 (m, 2 H), 7.58 (m, 1 H), 5.77−5.84 (m, 1 H), 5.72 (ddt, *J* = 7, 10, 17 Hz, 1 H), 5.44−5.49 (m, 1 H), 5.00−5.10 (m, 2 H), 4.89−4.94 (m, 1 H), 4.22−4.34 (m, 2 H), 3.39−3.46 (m, 1 H), 3.16−3.23 (m, 1 H), 2.95 (br., s, 1 H), 2.42−2.51 (m, 1 H), 2.28−2.37 (m, 1 H), 1.93−2.12 (m, 4 H), 0.87 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.2 (C_q), 136.4 (CH), 134.6 (CH), 133.6 (CH), 133.6 (C_q), 133.3 (CH), 131.7 (CH), 131.2 (CH), 124.2 (CH), 117.2 (CH_2), 67.3 (CH), 66.9 (CH), 53.7 (CH), 45.3 (CH_2), 42.8 (CH_2), 42.0 (CH_2), 35.8 (CH_2), 25.9 (3 CH_3), 18.1 (C_q), −4.9 (CH_3), −5.0 (CH_3) ppm. IR: ṽ = 3540 (br), 3409 (br), 3079 (w), 1545 (vs), 1371 (s), 1348 (s), 1256 (s), 1162 (s), 833 (s), 777 (s) cm^{-1}. MS (140 °C): *m*/*z* (%) = 479 (10) [M^+ − OH], 440 (4) [$M^+ - C_4H_9$], 347 (32), 186 (100), 161 (44), 120 (86), 109 (40), 73 (88). HRMS ($C_{23}H_{35}N_2O_5SSi$ [M^+ − OH]): calcd. 479.2036; found 479.2033. $C_{23}H_{36}N_2O_6SSi$ (496.2): calcd. C 55.65, H 7.26, N 5.65; found C 55.62, H 6.97, N 5.47. $[\alpha]_D^{20}$ = −31 (*c* = 0.46, $CHCl_3$).

Chloride 7: Mesyl chloride (1.21 g, 10.6 mmol) was added dropwise to a cold (ice bath), stirring solution of alcohol **6** (2.59 g, 5.22 mmol) in pyridine (25 mL). After stirring at room temperature for 18 h the mixture was concentrated in vacuo, the residue was suspended in ethyl acetate (100 mL) and filtered through silica. The filtrate was concentrated in vacuo to give **7** as a light yellow solid (2.20 g, 82% yield). R_f = 0.51 (cyclohexane/MTBE, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98−8.06 (m, 1 H), 7.56−7.74 (m, 3 H), 5.62−5.84 (m, 2 H), 5.50−5.62 (m, 1 H), 5.00−5.14 (m, 2 H), 4.80−4.96 (m, 2 H), 4.20−4.34 (m, 1 H), 3.37−3.56 (m, 1 H), 3.14−3.32 (m, 1 H), 1.96−2.40 (m, 6 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.1 (C_q), 134.7 (CH), 134.4 (CH), 134.1 (CH), 133.6 (C_q), 133.4 (CH), 131.6 (CH), 131.0 (CH), 124.1 (CH), 117.3 (CH_2), 66.7 (CH), 53.8 (CH), 53.1 (CH), 45.4 (CH_2), 44.0 (CH_2), 41.7 (CH_2), 35.6 (CH_2), 25.7 (3 CH_3), 18.00 (C_q), −4.92 (CH_3), −5.07 (CH_3) ppm. IR: ṽ = 3078 (w), 1546 (vs), 1372 (s), 1348 (s), 1165 (s), 1077 (s), 837 (s), 777 (s) cm^{-1}. MS (180 °C): *m*/*z* (%) = 457 (11) [$M^+ - C_4H_9$], 383 (20), 186 (86), 160 (11), 127 (40), 91 (71), 73 (100). HRMS ($C_{19}H_{26}ClN_2O_5SSi$ [$M^+ - C_4H_9$]): calcd. 457.1020; found 457.1029. $C_{23}H_{35}ClN_2O_5SSi$ (514.6): calcd. C 53.64, H 6.80, N 5.44; found C 53.61, H 6.88, N 5.63. $[\alpha]_D^{20}$ = +45 (*c* = 0.61, $CHCl_3$).

Diamine 8: Chloride **7** (2.10 g, 4.08 mmol), but-3-enylamine (1.80 g, 25 mmol) and K_2CO_3 (1.30 g, 9.42 mmol) were stirred in acetonitrile (25 mL) at 70 °C for 18 h. Then brine (100 mL) was added and the solution was extracted with MTBE (3 × 50 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, concentrated in vacuo and the residue was purified by FC [cyclohexane/MTBE, 1:1 (+2% Et_2NH)] giving **8** as pale yellow oil (1.93 g, 86% yield). R_f = 0.18 (cyclohexane/MTBE/Et_2NH, 5:5:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.00−8.08 (m, 1 H), 7.54−7.71 (m, 3 H), 5.63−5.88 (m, 3 H), 5.42−5.52 (m, 1 H), 4.98−5.15 (m, 4 H), 4.70−4.82 (m, 1 H), 4.12−4.24 (m, 1 H), 3.14−3.50 (m, 3 H), 2.58−2.72 (m, 2 H), 1.93−2.56 (m, 7 H), 1.59−1.79 (m, 1 H), 1.50 (br., s, 1 H), 0.85 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.1 (C_q), 137.9 (CH), 136.1 (CH), 134.6 (CH), 133.7 (C_q), 133.4 (CH), 132.8 (CH), 131.5 (CH), 131.2 (CH), 124.2 (CH), 117.0 (CH_2), 116.6 (CH_2), 66.5 (CH), 53.3 (CH), 52.7 (CH), 45.7 (CH_2), 45.0 (CH_2), 42.6 (CH_2), 41.8 (CH_2), 35.7 (CH_2), 34.8 (CH_2), 25.9 (3 CH_3), 18.1 (C_q), −4.82 (CH_3), −4.85 (CH_3) ppm. IR: ṽ = 3077 (w), 1546 (vs), 1372 (s), 1164 (s), 1078 (s), 836 (s), 776 (s) cm^{-1}. MS (170 °C): *m*/*z* (%) = 550 (1) [MH^+], 508 (6) [$M^+ - C_3H_5$], 421 (30), 347 (55), 231 (100), 120 (100), 73 (100). HRMS ($C_{27}H_{44}N_3O_5SSi$ [MH^+]): calcd. 550.2771; found 550.2778. $C_{27}H_{43}N_3O_5SSi$ (549.4): calcd. C 58.99, H 7.89, N 7.65; found C 58.65, H 7.50, N 7.51. $[\alpha]_D^{20}$ = +42 (*c* = 0.24, $CHCl_3$).

Dicarbamate 9: Diamine **8** (1.93 g, 3.52 mmol) and K_2CO_3 (2.80 g, 20.2 mmol) were suspended in DMF (15 mL). PhSH (670 mg, 6.10 mmol) was added and the suspension was stirred at 70 °C for 30 min. The mixture was then cooled to 0 °C and benzyl chloroformate (2.10 g, 12.4 mmol) was added dropwise over 25 min whilst stirring. The mixture was stirred for 30 min at 0 °C, then for a further 2 h at room temperature. The mixture was poured into water (150 mL) and extracted with MTBE (50 mL). The aqueous phase was saturated with NaCl and extracted with MTBE (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by FC (cyclohexane/MTBE, 7:1 to 3:1) yielded dicarbamate **9** as a light yellow oil (1.91 g, 86% yield). R_f = 0.40 (cyclohexane/MTBE, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20−7.42 (m, 10 H), 5.40−5.88 (m, 4 H), 4.95−5.22 (m, 8 H), 4.02−4.82 (m, 3 H), 3.04−3.40 (m, 4 H), 2.20−2.60 (m, 5 H), 1.90−2.13 (m, 2 H), 1.70−1.87 (m, 1 H), 0.87 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.6 (br., C=O), 136.7 (C_q), 135.1 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 116.5 (CH_2), 67.0 (br,. CH_2), 66.3 (br., CH), 52.3 (br., CH), 42.3 (br., CH_2), 33.7 (br., CH_2), 25.6 (3 CH_3), 17.8 (C_q), −4.8 (CH_3), −4.9 (CH_3) ppm. IR: ṽ = 3067 (w), 3032 (w), 1699 (vs), 1416 (m), 1288 (m), 1258 (s), 835 (m), 773 (s) cm^{-1}. MS (160 °C): *m*/*z* (%) = 632 (1) [M^+], 591 (4) [$M^+ - C_3H_5$], 575 (17) [$M^+ - C_4H_9$], 428 (14), 167 (11), 91 (100), 69 (16). HRMS ($C_{37}H_{52}N_2O_5Si$ [M^+]): calcd. 632.3645; found 632.3641. $[\alpha]_D^{20}$ = −54.7 (*c* = 1.33, $CHCl_3$).

Bis(tetrahydropyridine)dicarbamate 10: Dicarbamate **9** (1.80 g, 2.85 mmol) and $[Cl_2(Cy_3P)_2Ru{=}CHPh]$ (230 mg, 0.28 mmol, 10 mol %) were refluxed under N_2 (glove box) in dry CH_2Cl_2 (100 mL) for 48 h. The solution was concentrated in vacuo and the residue was purified by FC (cyclohexane/MTBE, 3:1) to afford **10** as a light brown oil (1.42 g, 82% yield). An analytical sample (30 mg) of the crude material was dissolved in CH_2Cl_2 (1 mL) and $Pb(OAc)_4$ (15 mg, 90%) was added. The suspension was stirred overnight and filtered through silica affording colourless **10** (26 mg, 87%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20−7.42 (m, 10 H), 5.40−5.88 (m, 4 H), 4.98−5.24 (br., s, 4 H), 3.72−4.72 (m, 5 H), 2.64−3.10 (m, 2 H), 1.61−2.40 (m, 8 H), 0.72−0.99 (br., s, 9 H), −0.05, −0.17 (2s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.0 (br., C=O), 136.9 (C_q), 128.4 (CH), 128.3 (CH),

127.8 (CH), 125.5 (CH), 124.9 (CH), 67.3 (br., CH), 66.9 (br., CH_2), 49.8, 49.1 (2 br., CH), 41.5 (br., CH_2), 37.0 (br., CH_2), 25.8 (3 CH_3), 24.8 (br., CH_2), 18.0 (C_q), −4.1 (CH_3), −4.6 (CH_3) ppm. IR: $\tilde{\nu}$ = 3066 (w), 3032 (w), 1700 (vs), 1425 (s), 1253 (s), 1100 (m), 1080 (m), 836 (m), 775 (m), 697 (m) cm^{-1}. MS (130 °C): *m/z* (%) = 547 (2) [$M^+ - C_4H_9$], 503 (3), 459 (3), 350 (24), 268 (57), 120 (24), 91 (100), 73 (89). HRMS ($C_{31}H_{39}N_2O_5Si$ [$M^+ - C_4H_9$]): calcd. 547.2628; found 547.2629. $C_{35}H_{48}N_2O_5Si$ (604.8): calcd. C 69.54, H 7.95, N 4.64; found C 69.84, H 8.27, N 4.89. $[\alpha]_D^{20}$ = +178 (*c* = 0.51, $CHCl_3$).

Piperidine Derivative 12: Dicarbamate **10** (1.40 g, 2.32 mmol) was dissolved in MeOH (20 mL). Pd on charcoal (10%) was added and the suspension was stirred under H_2 at room temperature overnight. The catalyst was filtered off, the filtrate was concentrated in vacuo and the residue was purified by FC [MTBE (+5% Et_2NH)] to afford **12** (690 mg, 87%) as a light brown oil. R_f = 0.37 (MTBE/Et_2NH, 10:1). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.72−3.84 (m, 1 H), 2.82−2.96 (m, 2 H), 2.33−2.57 (m, 4 H), 2.05 (br., s, 2 H), 0.85−1.70 (m, 16 H), 0.75 (s, 9 H), −0.05 (s, 3 H), −0.06 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 67.9 (CH), 54.5, 53.3 (2 CH), 46.9, 46.8 (2 CH_2), 45.1, 45.0 (2 CH_2), 33.4, 33.35 (2 CH_2), 26.2 (2 CH_2), 25.8 (3 CH_3), 24.9, 24.8 (2 CH_2), 17.9 (C_q), −4.4 (2 CH_3) ppm. IR: $\tilde{\nu}$ = 1472 (m), 1425 (m), 1255 (m), 1066 (m), 836 (s), 774 (s) cm^{-1}. MS (130 °C): *m/z* (%) = 340 (6) [M^+], 325 (6) [$M^+ - CH_3$], 283 (44) [$M^+ - C_4H_9$], 240 (17), 208 (21), 124 (54), 97 (30), 84 (100) [$C_5H_{10}N^+$]. HRMS ($C_{19}H_{40}N_2OSi$ [M^+]): calcd. 340.2910; found 340.2911. $C_{19}H_{40}N_2OSi{\cdot}0.5H_2O$ (349.5): calcd. C 65.33, H 11.46, N 8.02; found C 65.51, H 11.31, N 8.02. $[\alpha]_D^{20}$ = +15.8 (*c* = 0.55, $CHCl_3$).

Alcohol 13: Ether **12** (900 mg, 2.65 mmol) was stirred in EtOH/conc. HCl (2:1, 10 mL) overnight. The solution was diluted with water (40 mL) and washed with MTBE (3 × 15 mL). Then the aqueous solution was brought to pH 14 with 30% NaOH and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to give **13** as a colourless oil (540 mg, 90% yield). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.47 (br. s, 3 H), 3.94−4.12 (m, 1 H), 2.96−3.14 (m, 2 H), 2.44−2.94 (m, 4 H), 1.00−1.89 (m, 16 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 68.8 (CH), 57.4, 53.7 (2 CH), 46.3, 45.9 (2 CH_2), 42.9, 42.6 (2 CH_2), 33.0, 31.8 (2 CH_2), 26.0, 25.8 (2 CH_2), 24.2, 24.1 (2 CH_2) ppm. IR: $\tilde{\nu}$ = 3306 (br.), 3256 (br.), 1442 (m), 1330 (m), 1120 (m), 1053 (m), 775 (s) cm^{-1}. MS (110 °C): *m/z* (%) = 226 (5) [M^+], 154 (6), 126 (11), 98 (15), 84 (100) [$C_5H_{10}N^+$]. HRMS ($C_{13}H_{26}N_2O$ [M^+]): calcd. 226.2045; found 226.2050. $[\alpha]_D^{20}$ = −11.7 (*c* = 0.75, $CHCl_3$).

Piperidine Derivative 14: A solution of alcohol **13** (220 mg, 0.97 mmol), Boc_2O (500 mg, 2.29 mmol) and NEt_3 (200 mg, 1.98 mmol) was stirred in MeOH (5 mL) at 70 °C for 5 h. The solution was then concentrated in vacuo and the residue was purified by FC (cyclohexane/MTBE, 2:1) affording **14** (404 mg, 98%) as a white solid. R_f = 0.19 (cyclohexane/MTBE, 3:1). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.28−4.52 (m, 2 H), 3.70−3.98 (m, 2 H), 3.08−3.34 (m, 1 H), 2.60−2.92 (m, 2 H), 1.80−2.38 (m, 2 H), 1.00−1.74 (m, 14 H), 1.42 (s, 18 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.5, 155.0 (2 C=O), 79.9, 79.0 (2 C_q), 64.7 (2 CH), 47.4, 46.3 (2 CH), 39.3, 39.0 (2 CH_2), 37.0, 36.7 (2 CH_2), 29.7, 29.4 (2 CH_2), 28.5, 28.3 (2 CH_3), 25.6, 25.5 (2 CH_2), 19.1 (2 CH_2) ppm. IR: $\tilde{\nu}$ = 3445 (br), 1687 (vs), 1660 (s), 1417 (vs), 1365 (vs), 1274 (s), 1252 (s), 1165 (vs), 1145 (s), 1076 (m), 864 (w), 769 (m) cm^{-1}. MS (100 °C): *m/z* (%) = 426 (4) [M^+], 325 (24), 253 (10), 225 (12), 128 (74), 84 (100), 57 (73). HRMS ($C_{23}H_{42}N_2O_5$ [M^+]): calcd. 426.3094; found 426.3097. $C_{23}H_{42}N_2O_5$ (426.3): calcd. C 64.79, H 9.86, N 6.57; found C 64.51, H 9.67, N 6.75. $[\alpha]_D^{20}$ = +41.4 (*c* = 0.725, $CHCl_3$).

Di-Boc-anaferine 15: Alcohol **14** (42 mg, 0.1 mmol), pyridinium chlorochromate (124 mg, 0.58 mmol) and molecular sieves (4 Å) were suspended in CH_2Cl_2 (5 mL) and stirred for 15 h at room temp. MTBE (10 mL) was added and the suspension was filtered through silica. Washing the silica with MTBE (100 mL), and concentrating the filtrate in vacuo, followed by FC of the residue (cyclohexane/MTBE, 3:1), gave di-Boc-anaferine **15** (42 mg, 100%) as a colourless solid. R_f = 0.19 (CH/MTBE, 3:1). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.60−4.76 (m, 2 H), 3.82−4.02 (m, 2 H), 2.50−2.86 (m, 6 H), 1.20−1.71 (m, 12 H), 1.41 (s, 18 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 207.2 (C=O), 154.8 (C=O), 79.6 (C_q), 47.3 (CH), 43.4 (CH_2), 39.6 (CH_2), 28.5 (CH_3), 28.4 (CH_2), 25.4 (CH_2), 19.1 (2 CH_2) ppm. IR: $\tilde{\nu}$ = 1689 (vs), 1411 (s), 1365 (s), 1272 (s), 1254 (s), 1163 (s), 869 (w), 770 (m) cm^{-1}. MS (130 °C): *m/z* (%) = 424 (2) [M^+], 324 (11), 323 (38), 223 (46), 140 (89), 128 (87), 84 (100), 57 (79). HRMS ($C_{23}H_{40}N_2O_5$ [M^+]): calcd. 424.2937; found 424.2937. $C_{23}H_{40}N_2O_5$ (424.3): calcd. C 65.09, H 9.43, N 6.60; found C 64.86, H 9.22, N 6.58. $[\alpha]_D^{20}$ = +19.9 (*c* = 0.765, $CHCl_3$).

(−)-Anaferine Dihydrochloride 1·2HCl: Ketone **15** (42 mg, 0.1 mmol) was dissolved in MeOH (1 mL) and 3 N HCl (2 mL) and stirred for 15 h at room temp. Concentration of the solution in vacuo gave **1·2HCl** (29 mg, 100%) as a colourless solid. m.p. 241°C (ref.[1] m.p. 242.5−243.5 °C). ^1H NMR (500 MHz, [D_4]MeOH): δ = 3.50−3.61 (m, 2 H), 3.32−3.40 (m, 2 H), 2.88−3.05 (m, 6 H), 1.82−1.95 (m, 6 H), 1.00−1.74 (m, 6 H) ppm. ^{13}C NMR ([D_4]MeOH): δ = 205.0 (C=O), 52.3 (CH), 44.8 (CH_2), 44.7 (CH_2), 28.3 (CH_2), 22.0 (CH_2), 21.6 (CH_2) ppm. IR: $\tilde{\nu}$ = 3392 (br), 1720 (s), 1588 (s), 1439 (m), 1383 (m), 1309 (m), 1112 (m), 1078 (m), 1027 (m), 982 (m), 939 (m) cm^{-1}. MS (210 °C): *m/z* (%) = 224 (6) [M^+], 223 (8), 140 (46), 128 (17), 98 (30), 84 (100), 56 (30). HRMS ($C_{13}H_{24}N_2O$ [M^+]): calcd. 224.1889; found 224.1891. $C_{13}H_{26}Cl_2N_2O{\cdot}0.5H_2O$ (305.3): calcd. C 50.98, H 8.82, N 9.15; found C 50.72, H 8.61, N 9.18. $[\alpha]_D^{20}$ = −47.9 (*c* = 0.65, MeOH/H_2O, 1:1) {ref.[1] $[\alpha]_D^{20}$ = −49.8 ± 2 (*c* = 0.529, MeOH/H_2O, 1:1)}.

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