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Formal synthesis of schulzeines B and C

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ABSTRACT

A formal synthesis of schulzeines B and C, marine natural products with inhibitory effect against α-glucosidase, has been achieved. The key reactions of the synthesis are *N*-acyliminium ion cyclization, Sharpless asymmetric dihydroxylation, olefin cross metathesis, and asymmetric allylboration.

1. Introduction

Schulzeines A–C (**1**–**3**) are marine natural products isolated from Japanese sponge, *Penares schulzeii*.[1] These natural products exhibit potent activity against α-glucosidase, an enzyme, which plays pivotal roles in carbohydrate metabolism and cell cycle.[1,2] This intriguing biological activity renders them potential leads for medicinal investigation for treatment of various diseases, such as diabetes, cancers, and viral infections. There have been several synthetic studies[3] of these natural products resulting in three total syntheses of schulzeines B and C[4,5] and one total synthesis of schulzeine A.[5] We have reported a synthesis of the 9,11-dimethyl ether of the tricyclic core of schulzeines utilizing *N*-acyliminium ion cycliaztion.[3a,b] Herein we present a formal synthesis of schulzeines B and C featuring *N*-acyliminium ion cyclization, Sharpless asymmetric dihydroxylation, asymmetric allylboration and olefin cross metathesis as key reactions (Fig. 1).

Our retrosynthetic analysis of schulzeines, as shown in Scheme 1, divides the molecule into two major subunits, namely, the tricyclic core **4** and 28-carbon fatty acid side chain **5**. The tricyclic core **4** could be obtained from intramolecular cyclization of *N*-acyliminium ion **6**, which in turn could be prepared from arylethylamine **7** and benzylated glutamic acid **8**. The 28-carbon fatty acid side chain would be constructed from benzyl 11-dodecenoate (**9**)[6] and C12–C28 subunit **10** via olefin cross metathesis. The

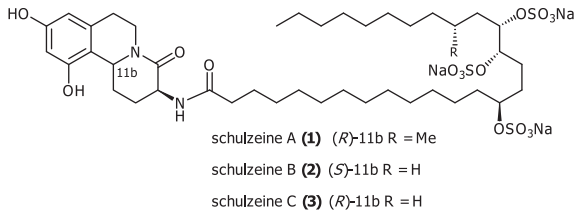

Fig. 1. Schulzeines A–C.

subunit **10** possessing three stereogenic centers at C14, 17, and 18 would be derived from asymmetric allylboration of C14-aldehyde **11**. The C17–18 protected diol functionality could be installed by Sharpless asymmetric dihydroxylation of alkene **12**.

2. Results and discussion

Synthesis of the tricyclic core **4** began with known 2-(3,5-dibenzyloxyphenyl)ethylamine (**7**),[7] prepared in five steps from 3,5-dihydroxybenzoic acid (Scheme 2). This amine was coupled with L-glutamic acid derivative **8** to give amide **13** in good yield. Treatment of this amide with lithium aluminum hydride gave imide **14**.[8] DIBAL-H reduction of the imide occurred selectively at the less hindered carbonyl group to give hydroxylactam **15**.[9] Subsequent treatment of this compound with TMSOTf yielded the protected tricyclic core **16** of schulzeines as an inseparable mixture of two diastereomers at C11b. This mixture was converted into *N*-Boc-carbamates **17a** and **17b** (ca. 3:1) and the two diastereomers were readily separable by flash chromatography and their

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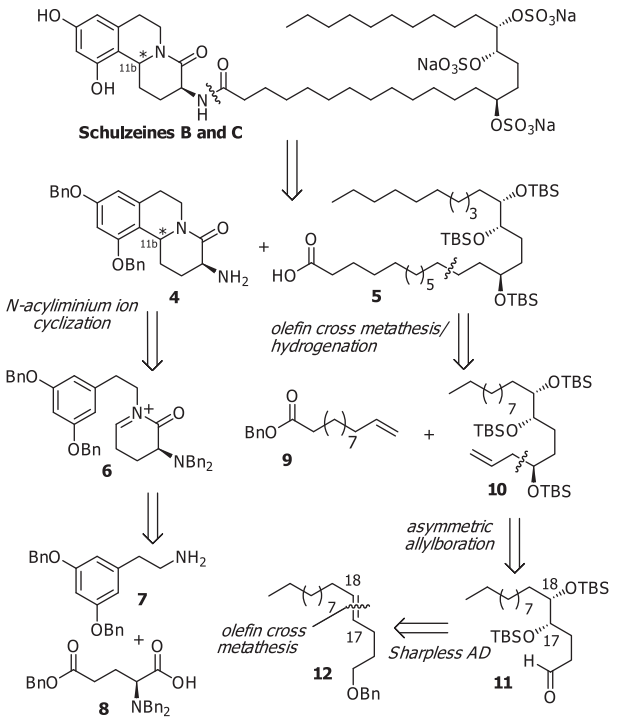
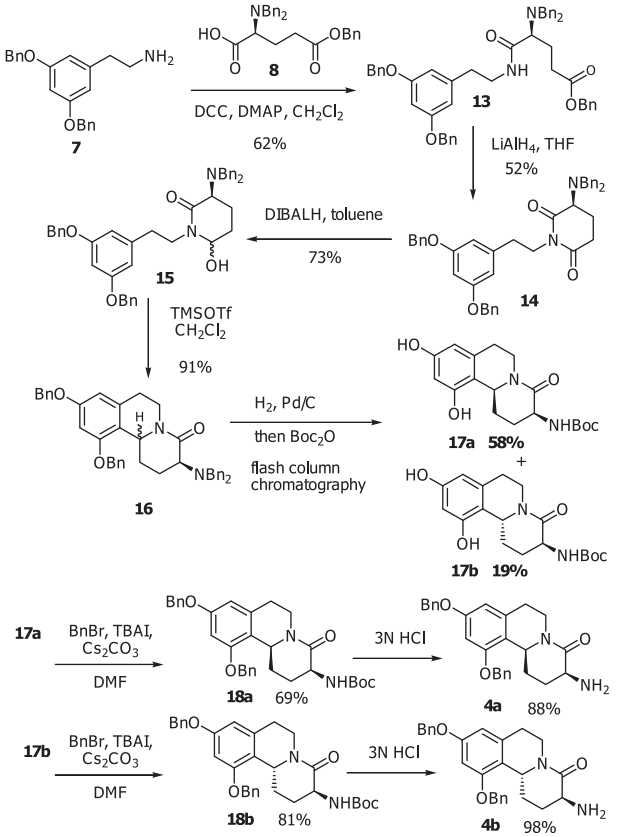


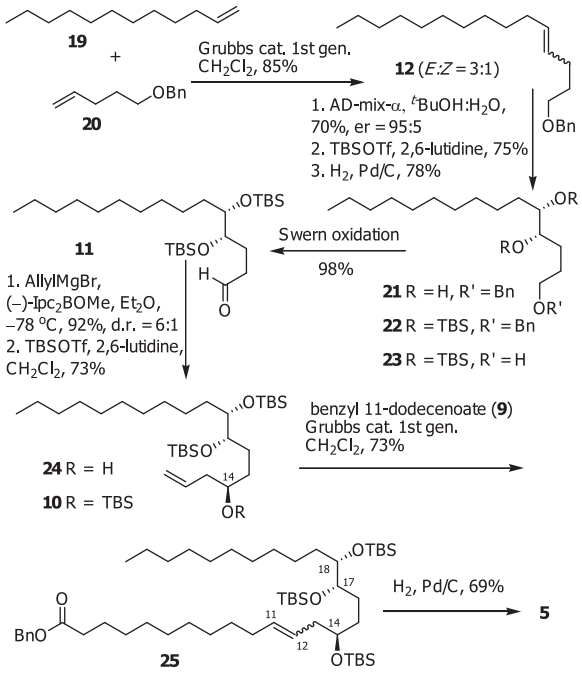
Scheme 1. Retrosynthetic analysis of schulzeines B and C.

configurations at C11b were assigned based on NOESY experiments and comparison of NMR results with a related dimethoxy derivative whose configuration has been confirmed by X-ray crystal analysis.[10,3b] The separated diastereomers were then re-protected as dibenzyl ether **18a** and **18b** and the *N*-Boc-carbamate was removed to give the desired tricyclic core **4a** and **4b** of schulzeines.

The synthesis of C28-fatty acid side chain commenced with olefin cross metathesis of 1-dodecene (**19**) and benzyl-4-pentenyl ether (**20**) in the presence of Grubbs' first generation catalyst (Scheme 3).[11] The product was obtained as a mixture of *E*/*Z* olefin **12** (ca. 3:1) and was treated with AD-mix-α to yield diol **21**.[12] The diol was obtained from Sharpless asymmetric dihydroxylation of *E*-olefin and was separated from the mixture of unreacted mixture of olefin, which had an increased ratio of *Z*-isomer. The diol was protected as bis-TBS ether **22** and the benzyl ether was subsequently removed to give primary alcohol **23**. The alcohol was oxidized to give aldehyde **11** using Swern oxidation and subsequent asymmetric allylboration using Brown's conditions[13] gave the homoallylic alcohol **24** with the desired (*R*)-configuration in a diastereomeric ratio of 6:1. This sets up the stereogenic center at C14 of the 28-carbon fatty acid side chain. The homoallylic alcohol was protected as TBS ether **10**, which subsequently underwent olefin cross metathesis with benzyl 11-dodecenoate (**9**)[6] to give a mixture of inconsequential *E*/*Z* alkene product **25** possessing the full carbon skeleton of C28-fatty acid side chain of schulzeines B and C. Treatment of this mixture with hydrogen gas and palladium on activated carbon resulted in simultaneous reduction of the olefin and hydrogenolysis of the benzyl ester. The resulting 28-carbon fatty acid side chain **5** with the correct absolute configuration of 14*S*, 17*S*, and 18*S* was therefore in hand for coupling with the tricyclic core **4** of schulzeines.

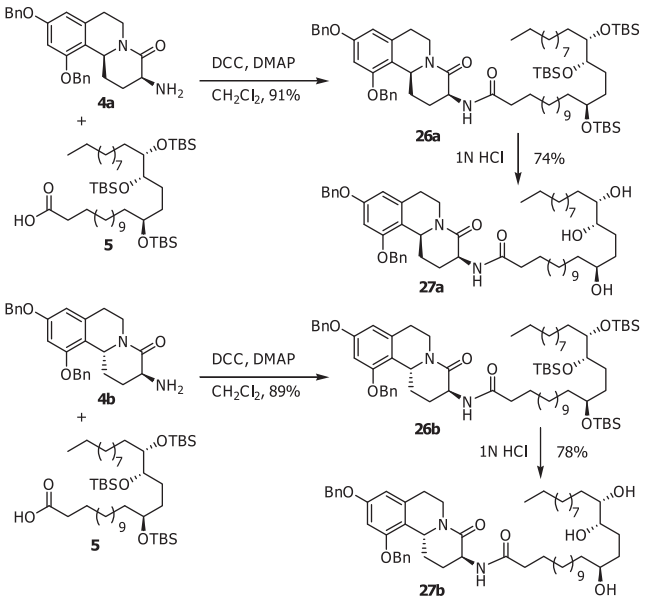


Scheme 2. Synthesis of the tricyclic core **4**.



Scheme 3. Synthesis of the 28-carbon fatty acid side chain **5**.

With both key fragments in hand we proceeded to the coupling of the tricyclic core **4a** or **4b** and the C28-fatty acid side chain **5** (Scheme 4). Amide **26** was obtained from the coupling in good yield in the presence of DCC and DMAP in CH_2Cl_2. The tris-TBS ether was removed using 1 N HCl to furnish the corresponding triol **27**. These advanced intermediates are in common with those in two previously reported syntheses of schulzeines B and C and our spectral data match perfectly with those reported results.[4] Thus a formal synthesis of schulzeines B and C was achieved with the remaining steps for the completion of the synthesis of the natural products being sulfate formation and debenzylation using the reported procedure.[4]



Scheme 4. Fragment coupling and conversion to triol **27**.

3. Conclusion

In summary, the triol intermediates of schulzeines B and C were synthesized with *N*-acyliminium ion cyclization, Sharpless asymmetric dihydroxylation, olefin cross metathesis, and asymmetric allylboration as the key steps. There were 24 total steps with the longest linear sequence of 14 steps from 3,5-dihydroxybenzoic acid and the overall yield of 2.6% and 0.9% for **27a** and **27b**, respectively.

4. Experimental

4.1. General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under argon. Toluene, triethylamine, and dichloromethane were distilled from calcium hydride under argon. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were oven dried at 105 °C overnight. Unless otherwise stated, concentration was performed under reduced pressure using a rotary evaporator at water aspirator pressure. Analytical thin-layer chromatography (TLC) was conducted using Fluka precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in ethanol. Flash chromatography was carried out using Scientific Absorbents Inc. silica gel (40 μm particle size). Optical rotations were measured with a Perkin–Elmer 243 polarimeter at ambient temperature using a 0.9998 dm cell with 1 mL capacity. Infrared (IR) spectra were recorded on a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AC-300 spectrometer.

*4.1.1. Amido-ester **13**.* A mixture of 2-(3,5-dibenzyloxyphenyl)ethylamine (**7**) (1.81 g, 5.43 mmol), *N*,*N*-dibenzyl-L-glutamic acid-5-benzyl ester (**5**) (0.940 g, 2.25 mmol), DCC (1.49 g, 7.22 mmol), and DMAP (55.0 mg, 0.450 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature under argon for 48 h, after which the mixture was filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give amido-ester **13** (1.02 g, 62%) as a yellow-brown oil; R_f (2:1 hexane/ethyl acetate) 0.39; δ_H (300 MHz, $CDCl_3$) 7.50–7.10 (25H, m), 6.50 (1H, t, J=2.2 Hz), 6.40 (2H, d, J=2.2 Hz), 5.24 (1H, d, J=12.2 Hz), 5.13 (1H, d, J=12.2 Hz) 5.00 (4H, s), 3.85 (2H, d, J=13.7 Hz), 3.50 (2H, d, J=13.7 Hz), 3.44–3.10 (3H, m), 2.60 (2H, t, J=7.0 Hz), 2.25–1.70 (4H, m); δ_C (75 MHz, $CDCl_3$) 172.4, 172.3, 160.2 (2C), 141.4, 139.4 (2C), 136.9 (2C), 136.0, 129.0 (4C), 128.7 (2C), 128.6 (4C), 128.5 (2C), 128.4, 128.3 (4C), 128.0 (2C), 127.6 (4C), 127.2 (2C), 108.0 (2C), 100.2, 70.1 (2C), 66.2, 60.3, 54.6 (2C), 40.4, 35.9, 33.1, 25.4; $[\alpha]_D^{25}$ −39.2 (*c* 2.4, $CHCl_3$); ν_{max}(film) 3425, 3033, 2934, 2857, 1727, 1664, 1594, 1519, 1496, 1455, 1265, 1214, 1158, 1070 cm^{-1}; ESI-HRMS calculated for $C_{48}H_{49}N_2O_5$ $[M+H]^+$ 733.3641 found 733.3492.

*4.1.2. Imide **14**.* To a solution of amido-ester **13** (216 mg, 0.295 mmol) in THF (6 mL) was added lithium aluminum hydride (34.0 mg, 0.896 mmol) in one portion at 0 °C. The resulting suspension was stirred at 0 °C under argon for 45 min. The reaction was quenched by drop-wise addition of satd aq $NaHCO_3$ into the mixture until all bubbling subsided. Water (5 mL) was added and the mixture was then extracted with Et_2O (3×20 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 4:1 hexane/ethyl acetate) to give imide **14** (94.0 mg, 52%) as a colorless oil, and the unreacted amide was also recovered; R_f (2:1 hexane/ethyl acetate) 0.66; δ_H (300 MHz, $CDCl_3$) 7.38–7.15 (20H, m), 6.43 (2H, d, J=2.2 Hz), 6.36 (1H, t, J=2.2 Hz), 4.88 (4H, s), 4.07–3.94 (1H, m), 3.91–3.82 (1H, m), 3.82 (2H, d, J=13.9 Hz), 3.55 (2H, d, J=13.9 Hz), 3.39–3.29 (1H, m), 2.80–2.65 (3H, m), 2.37–2.22 (1H, m), 1.94–1.81 (2H, m); δ_C (75 MHz, $CDCl_3$) 173.1, 171.7, 159.9 (2C), 140.7, 139.6 (2C), 136.9 (2C), 128.6 (4C), 128.5 (4C) 128.4 (4C), 127.9 (2C), 127.6 (4C), 127.2 (2C), 108.3 (2C), 100.2, 70.0 (2C), 59.3, 55.0 (2C), 40.5, 34.3, 32.3, 22.7; $[\alpha]_D^{25}$ −39.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2879, 1725, 1674, 1595, 1495, 1455, 1376, 1344, 1264, 1151, 1051, 1027 cm^{-1}; ESI-HRMS calculated for $C_{41}H_{41}N_2O_4$ $[M+H]^+$ 625.3066 found 625.2927.

*4.1.3. Hydroxylactam **15**.* To a solution of imide **14** (93.0 mg, 0.149 mmol) in toluene (2 mL) was added diisobutyl aluminum hydride (1.0 M solution in THF, 0.750 mL, 0.750 mmol) via syringe at −78 °C under argon. The mixture was stirred for 1 h at −78 °C then MeOH (5 mL) was added. The reaction mixture was allowed to warm to room temperature and satd aq $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give hydroxylactam **15** (68.0 mg, 73% mixture of two diastereomers) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.42; δ_H (300 MHz, $CDCl_3$) 7.40–7.10 (20H, m), 6.43 (2H, t, J=2.0 Hz), 6.37 (1H, t, J=2.0 Hz), 4.85 (4H, s), 4.54 (1H, t, J=7.3 Hz), 3.91 (2H, d, J=14.0 Hz), 3.84–3.70 (1H, m), 3.68–3.52 (3H, m), 3.22 (1H, q, J=5.8 Hz), 2.86–2.73 (2H, m), 2.11–1.99 (1H, m), 1.88–1.74 (2H, m), 1.69–1.46 (1H, m); δ_C (75 MHz, $CDCl_3$) 171.2, 159.9 (2C), 141.7, 140.4 (2C), 136.9 (2C), 128.7 (4C), 128.6 (4C), 128.2 (4C), 127.9 (2C), 127.5 (4C), 126.8 (2C), 108.1 (2C), 100.2, 80.4, 70.0 (2C), 58.2, 55.2 (2C), 43.8, 34.4, 31.4, 23.2; ν_{max}(film) 3429, 2832, 1644, 1606, 1552, 1495, 1375, 1265, 1055, 1027 cm^{-1}; ESI-HRMS calculated for $C_{41}H_{43}N_2O_4$ $[M+H]^+$ 627.3223 found 627.3069.

*4.1.4. Tricyclic core **16**.* To a solution of hydroxylactam **15** (68.0 mg, 0.108 mmol) in CH_2Cl_2 (9 mL) was added TMSOTf (39.0 μL, 0.215 mmol) via syringe at 0 °C under argon. The mixture was stirred at this temperature for 4 h and satd aq $NaHCO_3$ was added drop-wise. The mixture was extracted with CH_2Cl_2 (3×10 mL). The

combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to give tricyclic core **16** (inseparable mixture of two diastereomers in approximately 3:1 ratio as determined by ^1H NMR, 60.0 mg, 91%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.68; major product δ_H (300 MHz, $CDCl_3$) 7.50–7.20 (20H, m), 6.47 (1H, d, J=2.0 Hz), 6.37 (1H, d, J=2.0 Hz), 5.05–4.95 (4H, m), 4.85 (1H, dd, J=10.3, 3.9 Hz), 4.57 (1H, dd, J=10.9, 3.2 Hz), 4.26 (2H, d, J=14.6 Hz), 3.89 (2H, d, J=14.6 Hz), 3.55 (1H, dd, J=9.9, 9.1 Hz), 2.88–2.52 (3H, m), 2.01–1.77 (2H, m), 1.30–1.18 (2H, m); δ_C (75 MHz, $CDCl_3$) 171.5, 157.3, 154.9, 140.0 (2C), 136.7, 135.7, 135.6, 127.7 (2C), 127.6 (4C), 127.4 (2C), 127.1 (4C), 127.0, 126.9, 126.5 (2C), 125.7 (2C), 125.6 (2C), 116.8, 104.8, 97.9, 69.1, 68.9, 55.6, 54.2 (2C), 48.9, 37.1, 29.0, 28.6, 22.6; minor product δ_H (300 MHz, $CDCl_3$) 7.50–7.20 (20H, m), 6.38 (1H, d, J=2.1 Hz), 6.34 (1H, d, J=2.1 Hz), 5.05–4.95 (5H, m), 4.70 (1H, dd, J=10.6, 2.1 Hz), 4.08 (2H, d, J=13.9 Hz), 3.84 (2H, d, J=13.9 Hz), 3.42 (1H, dd, J=11.1, 7.3 Hz), 2.87–2.52 (3H, m), 2.47–2.30 (1H, m), 2.19–2.03 (1H, m), 1.99–1.79 (1H, m), 1.46–1.34 (1H, m); δ_C (75 MHz, $CDCl_3$) 169.8, 157.1, 155.5, 139.5 (2C), 137.1, 135.7, 135.5, 127.7 (2C), 127.6 (4C), 127.4 (2C), 127.1 (4C), 127.0, 126.9, 126.5 (2C), 126.0 (2C), 125.7 (2C), 117.5, 105.0, 98.0, 69.1, 69.0, 57.7, 54.4 (2C), 54.2, 37.5, 29.5, 28.4, 26.0; ν_{max}(film) 2874, 2833, 2254, 1703, 1641, 1609, 1542, 1493 cm^{-1}; ESI-HRMS calculated for $C_{41}H_{41}N_2O_3$ $[M+H]^+$ 609.3117 found 609.2977.

*4.1.5. N-Boc debenzylated tricyclic core **17a** and **17b**.* To a solution of tricyclic core **9** (292 mg, 0.480 mmol) in methanol (9 mL) was added palladium on activated carbon (29.0 mg, 10% w/w) and the resulting suspension was stirred under a hydrogen atmosphere for 3 h (a balloon of hydrogen gas was equipped to the reaction flask, ca. 1.1 atm). Then Boc_2O (210 mg, 0.962 mmol) was added and the reaction mixture was stirred for 5 h. The mixture was then filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 2:1 ethyl acetate/hexane) to give two separated diastereomers of the tricyclic core **17a** (97.5 mg, 58%) and **17b** (32.5 mg, 19%) as a colorless oil; **17a** R_f (1:1 hexane/ethyl acetate) 0.19; δ_H (300 MHz, CD_3OD) 6.10 (1H, d, J=2.3 Hz), 6.02 (1H, d, J=2.3 Hz), 4.69 (1H, dd, J=10.8, 3.2 Hz), 4.47 (1H, d, J=6.82 Hz), 4.22 (1H, t, J=10.1 Hz), 2.64–2.49 (3H, m), 2.47–2.32 (1H, m), 2.26–2.11 (1H, m), 1.37–1.31 (1H, m), 1.36 (9H, s), 1.30–1.15 (1H, m); δ_C (75 MHz, CD_3OD) 171.0, 156.7, 156.5, 154.7, 137.0, 113.7, 105.9, 100.6, 79.3, 49.7, 49.4, 39.0, 28.9, 27.8, 27.4 (3C), 24.9; $[\alpha]_D^{25}$ −76.0 (*c* 0.9, MeOH); ν_{max} (film) 3274, 2924, 2854, 1683, 1646, 1511, 1464, 1376, 1277, 1251, 1159, 1055, 947, 842 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{24}N_2NaO_5$ $[M+Na]^+$ 371.1583 found 371.1463; **17b** R_f (2:1 hexane/ethyl acetate) 0.10; δ_H (300 MHz, CD_3OD) 6.08 (1H, d, J=2.3 Hz), 5.99 (1H, d, J=2.3 Hz),4.69 (1H, dd, J=10.8, 3.2 Hz), 4.63 (1H, dd, J=11.0, 2.5 Hz), 3.94–3.77 (1H, m), 2.97 (1H, dd, J=13.8, 3.1 Hz), 2.66–2.37 (3H, m), 2.06–1.94 (1H, m), 1.89–1.73 (1H, m), 1.40 (9H, s), 1.30–1.20 (1H, m); δ_C (75 MHz, CD_3OD) 169.6, 156.7, 156.3, 155.3, 137.3, 114.6, 106.2, 100.7, 79.0, 55.8, 51.8, 39.4, 29.7, 28.1, 27.4 (3C), 27.3; $[\alpha]_D^{25}$ +30.2 (*c* 0.8, MeOH); ν_{max}(film) 3274, 2924, 2854, 1683, 1646, 1511, 1464, 1376, 1277, 1251, 1159, 1055, 947, 842 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{25}N_2O_5$ $[M+H]^+$ 349.1763 found 349.1708.

*4.1.6. N-Boc benzylated tricyclic core **18a**.* To a solution of *N*-Boc debenzylated tricyclic core **17a** (23.0 mg, 66.0 μmol), Cs_2CO_3 (65.0 mg, 0.199 mmol) and TBAI (4.0 mg, 10.8 μmol) in DMF (1 mL) at 0 °C was added benzyl bromide (17.0 μL, 0.143 mmol). This solution was stirred at 0 °C under argon for 1 h. Water was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give dibenzyl ether **18a** (20.0 mg, 69%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.50; δ_H (300 MHz, $CDCl_3$) 7.60–7.18 (10H, m), 6.45 (1H, d, J=2.2 Hz), 6.36 (1H, d, J=2.2 Hz), 5.75 (1H, d, J=5.3 Hz), 5.05 (2H, s), 4.97 (2H, s), 4.89 (1H, dd, J=10.3, 4.0 Hz), 4.69–4.60 (1H, m), 4.32–4.17 (1H, m), 2.79–2.56 (3H, m), 2.54–2.31 (2H, m), 1.50 (9H, s,), 1.34–1.23 (2H, m); δ_C (75 MHz, $CDCl_3$) 170.1, 158.2, 155.7, 155.4, 137.0, 136.5, 136.2, 128.5, 128.3 (2C), 127.9, 127.8 (2C), 127.2 (2C), 126.8 (2C), 117.1, 105.7, 98.8, 79.0, 69.9, 69.8, 49.5, 48.5, 38.6, 29.5, 28.3, 28.2 (3C), 25.9; $[\alpha]_D^{25}$ −83.4 (*c* 1.4, $CHCl_3$); ν_{max}(film) 3413, 2983, 2931, 1710, 1655, 1609, 1497, 1432, 1367, 1162, 1060 cm^{-1}; ESI-HRMS calculated for $C_{32}H_{37}N_2O_5$ $[M+H]^+$ 529.2702 found 529.2624.

*4.1.7. N-Boc benzylated tricyclic core **18b**.* To a solution of *N*-Boc debenzylated tricyclic core **17b** (73.0 mg, 0.210 mmol), Cs_2CO_3 (205 mg, 0.629 mmol), and TBAI (12.0 mg, 32.5 μmol) in DMF (3 mL) at 0 °C was added benzyl bromide (55.0 μL, 0.462 mmol). This solution was stirred at 0 °C under argon for 1 h. Water was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give dibenzyl ether **18b** (74.0 mg, 81%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.30; δ_H (300 MHz, $CDCl_3$) 7.40–7.20 (10H, m), 6.47 (1H, d, J=2.3 Hz), 6.35 (1H, d, J=2.3 Hz), 5.33 (1H, d, J=5.0 Hz), 5.04–4.94 (4H, m), 4.92–4.38 (1H, m), 4.78 (1H, dd, J=11.0, 3.7 Hz), 4.03–3.91 (1H, m) 3.08–2.97 (1H, m), 2.89–2.72 (1H, m), 2.64–2.51 (2H, m), 2.46–2.35 (1H, m), 1.79–1.59 (2H, m), 1.50 (9H, s); δ_C (75 MHz, $CDCl_3$) 168.8, 158.1, 156.7, 156.1, 137.8, 136.6, 136.4, 128.6, 128.5 (2C), 128.0 (2C), 128.1 (2C), 127.4 (2C), 127.1, 118.3, 106.0, 99.0, 79.4, 70.1, 70.0, 56.1, 52.7, 39.4, 30.5, 28.3 (3C), 27.9, 27.8; $[\alpha]_D^{25}$ +96.9 (*c* 2.8, $CHCl_3$); ν_{max}(film) 3413, 2983, 2931, 1710, 1655, 1609, 1497, 1432, 1367, 1162, 1060 cm^1; ESI-HRMS calculated for $C_{32}H_{37}N_2O_5$ $[M+H]^+$ 529.2702 found 529.2556.

*4.1.8. Tricyclic core **4a**.* A solution of *N*-Boc tricyclic core **18a** (62.0 mg, 0.117 mmol) was treated with 3 N HCl in ethyl acetate (1.10 mL) at room temperature. The solution was stirred for 3 h, after which ethyl acetate (5 mL) and satd aq $NaHCO_3$ (10 mL) were added. The phases were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to give amine **4a** (44.0 mg, 88%) as a colorless oil; R_f (1:1 hexane/ethyl acetate) 0.20; δ_H (300 MHz, $CDCl_3$) 7.50–7.30 (10H, m), 6.49 (1H, d, J=2.2 Hz), 6.38 (1H, d, J=2.1 Hz), 5.07 (2H, d, J=2.9 Hz), 5.00 (2H, s), 4.85 (1H, dd, J=11.3, 3.6 Hz), 4.72 (1H, dd, J=8.2, 1.8 Hz), 3.89–3.76 (1H, m), 2.88–2.62 (3H, m), 2.57–2.33 (2H, m), 1.79–1.59 (1H, m), 1.54–1.38 (1H, m); δ_C (75 MHz, $CDCl_3$) 170.9, 158.5, 156.0, 137.4, 136.7, 136.5, 128.8 (2C), 128.6 (2C), 128.1 (2C), 127.5 (2C), 127.0 (2C), 117.0, 105.7, 99.1, 70.2, 70.1, 49.8, 49.2, 39.0, 29.7, 28.2, 25.1. This amine was used immediately, without further purification, in the next step.

*4.1.9. Tricyclic core **4b**.* A solution of *N*-Boc tricyclic core **18b** (74.0 mg, 0.140 mmol) was treated with 3 N HCl in ethyl acetate (1.40 mL) at room temperature. The solution was stirred for 3 h, after which ethyl acetate (5 mL) and satd aq $NaHCO_3$ (10 mL) were added. The phases were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to give amine **4b** (59.0 mg, 98%) as a colorless oil; R_f (1:1 hexane/ethyl acetate) 0.10; δ_H (300 MHz, $CDCl_3$) 7.48–7.30 (10H, m), 6.50 (1H, d, J=2.2 Hz), 6.37 (1H, d, J=2.1 Hz), 5.05 (2H, d, J=3.9 Hz), 5.00 (2H, s), 4.92 (1H, dd, J=11.3, 2.5 Hz), 4.80 (1H, dd, J=8.3, 1.7 Hz), 3.44–3.31 (1H, m), 3.01 (1H, d, J=13.3 Hz), 2.93–2.76 (1H, m), 2.68–2.54 (1H, m), 2.51–2.29 (1H, m), 2.28–2.17 (1H, m), 1.75–1.55 (1H, m), 1.49–1.31 (1H, m); δ_C

(75 MHz, $CDCl_3$) 172.1, 158.2, 156.7, 138.0, 136.8, 136.6, 128.7 (2C), 128.4 (2C), 128.1, 128.0, 127.5 (2C), 127.0 (2C), 118.5, 106.2, 99.1, 70.1 (2C), 56.1, 52.5, 39.2, 30.6, 29.3, 28.5. This amine was used immediately, without further purification, in the next step.

*4.1.10. Benzyl-1-(4-pentadecenyl) ether (**12**).* To a solution of benzyloxy-4-pentene (**20**) (757 mg, 4.28 mmol) and 1-dodecene (**19**) (9.60 mL, 42.8 mmol) in CH_2Cl_2 (150 mL) was added Grubbs' first generation catalyst (176 mg, 0.214 mmol) in CH_2Cl_2 (10 mL). The reaction was heated to reflux under argon for 4 h and then allowed to cool to room temperature. Silica gel was added, and the mixture was concentrated. Purification by flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) gave alkene **12** (1.15 g, 85%, *E*/*Z*=3:1) as a colorless oil; R_f (20:1 hexane/ethyl acetate) 0.61; δ_H (300 MHz, $CDCl_3$) 7.33–7.20 (5H, m), 5.44–5.31 (2H, m), 4.50 (2H, s), 3.50–3.41 (2H, m), 2.17–1.91 (4H, m), 1.72–1.60 (2H, m), 1.39 (16H, br s), 0.88 (3H, t, *J*=6.7 Hz); δ_C (75 MHz, $CDCl_3$) (*E* isomer) 139.2, 131.5, 129.9, 128.8 (2C), 128.1 (2C), 127.9, 73.3, 70.3, 33.1, 32.5, 30.2 (2C), 30.1 (2C), 29.9, 29.7, 29.6, 27.7, 23.2, 14.6; (*Z*-isomer) 139.2, 131.1, 129.4, 128.8 (2C), 128.1 (2C), 127.9, 73.4, 70.4, 33.1, 32.5, 30.3 (2C), 30.1 (2C), 29.9, 29.7, 29.6, 27.7, 24.3, 14.6; ν_{max}(film) 2929, 2856, 1715, 1603, 1467, 1456, 1316, 1099 cm^{-1}; ESI-HRMS calculated for $C_{22}H_{36}NaO$ $[M+Na]^+$ 339.2664 found 339.3338.

*4.1.11. (4S,5S)-1-Benzyloxypentadecane-4,5-diol (**21**).* To a solution of AD-mix-α (0.920 g) and methansulfonamide (60.0 mg) in *tert*-butanol and water (15 mL, 1:1) at 0 °C was added alkene **12** (0.210 g, 0.663 mmol). The reaction mixture was stirred vigorously at 0 °C for 2 days and quenched with sodium sulfite (1.70 g). Ice bath was removed and the mixture was stirred at room temperature for 45 min. The resulting mixture was extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) gave diol **21** (162 mg, 70%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.40; δ_H (300 MHz, $CDCl_3$) 7.34–7.22 (5H, m), 4.50 (2H, s), 3.65 (2H, br s), 3.49 (2H, t, *J*=6.0 Hz), 3.42–3.29 (2H, m), 1.87–1.54 (2H, m), 1.54–1.33 (4H, m), 1.30 (16H br s), 0.88 (3H, t, *J*=6.7 Hz); δ_C (75 MHz, $CDCl_3$) 138.1, 128.4 (2C), 127.7 (3C), 74.7, 74.1, 73.0, 70.4, 33.5, 31.9, 30.6, 29.8 (2C), 29.7 (2C), 29.4, 26.1, 25.8, 22.7, 14.1; $[\alpha]_D^{25}$ −8.1 (*c* 1.1, $CHCl_3$); ν_{max}(film) 3423, 2930, 2856, 1717, 1316, 1279, 1115, 1071, 1001, 892 cm^{-1}; ESI-HRMS calculated for $C_{22}H_{39}O_3$ $[M+H]^+$ 351.2899 found 351.2772.

*4.1.12. (4S,5S)-1-Benzyloxy-4,5-bis-(tert-butyldimethyl silanyl-oxy) pentadecane (**22**).* To an ice-cold solution of diol **21** (690 mg, 1.97 mmol) in dry CH_2Cl_2 (21 mL) under argon atmosphere were added 2,6-lutidine (0.680 mL, 5.93 mmol) and TBSOTf (1.60 mL, 5.93 mmol) The mixture was stirred at room temperature for 2 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) gave bis-TBS ether **22** (853 mg, 75%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.90; δ_H (300 MHz, $CDCl_3$) 7.30–7.10 (5H, m), 4.42 (2H, s), 3.58–3.46 (2H, m), 3.41 (2H, t, *J*=6.1 Hz), 1.84–1.62 (2H, m), 1.62–1.35 (2H, m), 1.22 (18H, br s), 0.84 (21H, br s), 0.00 (12H, s); δ_C (75 MHz, $CDCl_3$) 138.8, 128.3 (2C), 127.6 (2C), 127.4, 75.5, 75.4, 72.8, 70.8, 32.0, 29.8, 29.7 (2C), 29.6, 29.5, 27.2, 26.9, 26.7, 26.1, 26.0 (6C),22.8, 18.1 (2C), 14.2, −4.0 (2C), −4.5 (2C); $[\alpha]_D^{25}$ −22.7 (*c* 1.9, $CHCl_3$); ν_{max} (film) 2928, 2857, 2710, 1716, 1520, 1471, 1463, 1389, 1361, 1256, 1217, 1075, 835, 773 cm^{-1}; ESI-HRMS calculated for $C_{34}H_{67}O_3Si_2$ $[M+H]^+$ 579.4629 found 579.4402.

*4.1.13. (4S,5S)-4,5-Bis-(tert-butyldimethylsilanyloxy) pentadecan-1-ol (**23**).* To a solution of benzyl ether **22** (850 mg, 1.47 mmol) in hexane (17 mL) was added palladium on activated carbon (85.0 mg, 10% w/w) and the resulting suspension was stirred under a hydrogen atmosphere for 3 h (a balloon of hydrogen gas was equipped to the reaction flask, ca. 1.1 atm). The mixture was then filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica gel, 4:1 hexane/ethyl acetate) gave primary alcohol **23** (561 mg, 78%) as a colorless oil; R_f (4:1 hexane/ethyl acetate) 0.75; δ_H (300 MHz, $CDCl_3$) 3.57 (2H, t, *J*=6.2 Hz), 3.53–3.50 (1H, m), 3.50–3.47 (1H, m), 2.30 (1H, br s), 1.75–1.33 (4H, m), 1.21 (18H, br s), 0.84 (21H, br s), 0.06–0.00 (12H, m); δ_C (75 MHz, $CDCl_3$) 75.4, 75.3, 63.1, 30.1, 29.8, 29.7, 29.6 (2C), 29.5, 29.3, 26.6, 26.3, 26.0, 25.8 (6C), 22.6, 17.9 (2C), 14.1, −4.2 (2C), −4.6 (2C); $[\alpha]_D^{25}$ −17.0 (*c* 0.6, $CHCl_3$); ν_{max}(film) 3429, 2955, 2929, 2857, 1471, 1463, 1361, 1258, 1097, 836, 759 cm^{-1}; ESI-HRMS calculated for $C_{27}H_{61}O_3Si_2$ $[M+H]^+$ 489.4159 found 489.4010.

*4.1.14. (4S,5S)-4,5-Bis-(tert-butyldimethylsilanyloxy)penta-decanal (**11**).* To a solution of oxalyl chloride (0.300 mL, 3.49 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C under argon was added DMSO (0.500 mL, 7.04 mmol) drop-wise. After 30 min, alcohol **23** (561 mg, 1.15 mmol) in dry CH_2Cl_2 (5 mL) was added. The mixture was stirred at −78 °C for 1 h. Et_3N (1.44 mL, 10.3 mmol) was added at −78 °C and the reaction mixture was allowed to warm to room temperature over 45 min. The reaction was quenched with water and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated to give aldehyde **11** (550 mg, 98%) as a colorless oil; R_f (10:1 hexane/ethyl acetate) 0.64; δ_H (300 MHz, $CDCl_3$) 9.70 (1H, s), 3.56–3.52 (1H, m), 3.52–3.48 (1H, m), 2.56–2.38 (2H, m), 1.99–1.90 (1H, m), 1.66–1.50 (2H, m), 1.49–1.34 (1H, m), 1.22 (16H br s), 0.82 (21H, br s), 0.00 (12H, s); δ_C (75 MHz, $CDCl_3$) 202.2, 75.1, 74.5, 41.1, 31.9, 29.7, 29.6 (2C), 29.5, 29.3, 26.6, 25.9, 25.8 (6C), 22.8, 22.6, 17.9 (2C), 14.0, −4.2 (2C), −4.7, −5.0; ν_{max}(film) 2928, 2857, 2710, 1716, 1520, 1471, 1463, 1389, 1361, 1256, 1217, 1075, 835, 773 cm^{-1}. This aldehyde was used immediately, without further purification, in the next step.

*4.1.15. (4R,7S,8S)-7,8-Bis-(tert-butyldimethylsilanyloxy)octadec-1-en-4-ol (**24**).* To a solution of (−)-methoxydiisopinocampheylborane (743 mg, 2.35 mmol) in dry Et_2O (25 mL) at 0 °C was added allyl magnesium bromide solution (1 M in THF, 2.10 mL, 2.10 mmol). The mixture was stirred at room temperature for 1 h and then cooled to −78 °C. Aldehyde **11** (564 mg, 1.16 mmol) in dry Et_2O (10 mL) was added drop-wise into the solution. The mixture was stirred at −78 °C for 1 h. MeOH (1.30 mL) was added and the solution was allowed to warm to room temperature. NaOH (3 M, 11.0 mL, 33.0 mmol) and H_2O_2 (30%, 40.0 mL) were added and the solution was stirred overnight. To this mixture was added brine and the layers were separated. The aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (silica gel, 20:1 hexane/ethyl acetate) gave homoallylic secondary alcohol **24** (563 mg, 92%) as a colorless oil; R_f (20:1 hexane/ethyl acetate) 0.38; δ_H (300 MHz, $CDCl_3$) 5.86–5.69 (1H, m), 5.08 (1H, d, *J*=16.2 Hz), 5.07 (1H, d, *J*=11.1 Hz), 3.64–3.52 (1H, m), 3.52–3.49 (1H, m), 3.49–3.46 (1H, m), 2.32–2.19 (1H, m), 2.18–2.05 (1H, m), 1.82–1.51 (4H, m), 1.50–1.25 (3H, m), 1.21 (16H br s), 0.82 (21H, br s), 0.00 (12H, s); δ_C (75 MHz, $CDCl_3$) 134.9, 117.9, 75.7, 75.3, 71.1, 41.8, 34.2, 31.9, 29.7, 29.6 (2C), 29.5, 29.3, 26.6, 26.2, 26.0, 25.8 (6C), 22.7, 18.0 (2C), 14.1, −4.1 (2C), −4.6 (2C); $[\alpha]_D^{25}$ −27.7 (*c* 2.2, $CHCl_3$); ν_{max}(film) 3429, 2929, 2856, 1639, 1520, 1472, 1424, 1361, 1257, 1218, 1006, 928, 771 cm^{-1}; ESI-HRMS calculated for $C_{30}H_{65}O_3Si_2$ $[M+H]^+$ 529.4472 found 529.4292.

*4.1.16. (4R,7S,8S)-4,7,8-Tris-(tert-butyldimethylsilanyloxy)-octadec-1-ene (**10**).* To an ice-cold solution of secondary alcohol **24** (495 mg, 0.936 mmol) in dry CH_2Cl_2 (10 mL) under argon were added 2,6-

lutidine (0.140 mL, 1.22 mmol) and TBSOTf (0.260 mL, 0.964 mmol). The mixture was stirred at room temperature for 2 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (silica gel, hexane) gave tris-TBS ether **10** (590 mg, 73%) as a colorless oil; R_f (20:1 hexane/ethyl acetate) 0.83; δ_H (300 MHz, $CDCl_3$) 5.87–5.69 (1H, m), 5.06–4.92 (2H, m), 3.68–3.57 (1H, m), 3.52–3.36 (2H, m), 2.17 (2H, t, J=6.5 Hz), 1.78–1.49 (4H, m), 1.21 (18H, br s), 0.83 (30H, br s), 0.00 (18H, s); δ_C (75 MHz, $CDCl_3$) 135.5, 116.5, 76.0, 75.4, 72.6, 42.2, 34.4, 31.9, 29.7, 29.6 (2C), 29.5, 29.4, 26.6, 26.3, 25.9, 25.8 (9C), 22.7, 18.1, 18.0 (2C), 14.1, −4.1, −4.2, -4.4, −4.5, −4.6 (2C); $[\alpha]_D^{25}$ −19.5 (*c* 1.8, $CHCl_3$); ν_{max}(film) 2956, 2857, 1639, 1472, 1463, 1361, 1257, 1218, 1091, 1006 cm^{-1}; ESI-HRMS calculated for $C_{36}H_{79}O_3Si_3$ $[M+H]^+$ 643.5337 found 643.5108.

*4.1.17. 28-Carbon alkene **25**.* To a solution of C12–C28 alkene **10** (35.0 mg, 53.0 μmol) and benzyl 11-dodecenoate (**9**) (154 mg, 0.533 mmol) in CH_2Cl_2 (1.8 mL) was added Grubbs' first generation catalyst (4.4 mg, 5.34 μmol) in CH_2Cl_2 (1 mL). The reaction was heated to reflux under argon for 4 h and then allowed to cool to room temperature. Silica gel was added, and the mixture was concentrated. Purification by flash column chromatography (silica gel, 30:1 hexane/ethyl acetate) gave internal alkene **25** (35.0 mg, 73%) as a colorless oil; R_f (30:1 hexane/ethyl acetate) 0.75; δ_H (300 MHz, $CDCl_3$) 7.39–7.27 (5H, m), 5.43–5.32 (2H, m), 5.08 (2H, s), 3.67–3.53 (1H, m), 3.52–3.39 (2H, m), 2.32 (2H, t, J=6.4 Hz), 2.22–2.05 (2H, m), 2.05–1.87 (2H, m), 1.77–1.51 (4H, m), 1.24 (32H, br s), 0.85 (30H, br s), 0.01 (18H, s); δ_C (75 MHz, $CDCl_3$) 173.7, 136.1, 132.7, 132.6, 128.5 (2C), 128.2 (2C), 126.6, 76.0, 75.4, 73.2, 66.0, 41.0, 40.2, 35.6, 34.4, 34.3, 32.7, 31.9, 30.0, 29.7, 29.6 (2C), 29.5, 29.4, 29.3, 29.2, 29.1, 27.5, 26.6, 26.4, 25.9 (9C), 25.0, 22.7, 18.2, 18.0 (2C), 14.1, −4.1, −4.2, −4.4, −4.5 (2C), −4.6; $[\alpha]_D^{25}$ −7.0 (*c* 1.0, $CHCl_3$); ν_{max}(film) 2929, 2856, 1732, 1602, 1520, 1471, 1463, 1434, 1361, 1257, 1218, 1093, 1006, 929, 836, 771 cm^{-1}; ESI-HRMS calculated for $C_{53}H_{103}O_5Si_3$ $[M+H]^+$ 903.7113 found 903.7093.

*4.1.18. 28-Carbon fatty acid side chain **5**.* To a solution of alkene **25** (130 mg, 0.144 mmol) in hexane (2.5 mL) was added palladium on activated carbon (13.0 mg, 10% w/w) and the resulting suspension was stirred under a hydrogen atmosphere for 12 h (a balloon of hydrogen gas was equipped to the reaction flask, ca. 1.1 atm). The mixture was then filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) gave 28-carbon fatty acid **5** (81.0 mg, 69%) as a colorless oil; R_f (20:1 hexane/ethyl acetate) 0.12; δ_H (300 MHz, $CDCl_3$) 3.64–3.53 (1H, m), 3.53–3.40 (2H, m), 2.30 (2H, t, J=7.5 Hz), 1.76–1.49 (6H m), 1.47–1.34 (4H, m), 1.25 (34H, br s), 0.85 (30H, br s), 0.00 (18H, s); δ_C (75 MHz, $CDCl_3$) 180.2, 76.1, 75.4, 72.9, 37.3, 36.6, 34.7 (2C), 34.1, 31.9, 29.9 (2C), 29.8, 29.7, 29.6 (2C), 29.5, 29.4, 29.3, 29.1, 26.6, 26.2, 26.1, 26.0 (3C), 25.9 (6C), 25.5, 25.2, 24.7, 22.7, 18.1, 18.0 (2C), 14.1, −4.1, −4.4, −4.5 (2C), −4.6 (2C); $[\alpha]_D^{25}$ −16.1 (*c* 1.7, $CHCl_3$); ν_{max}(film) 2927, 2856, 1709, 1463, 1388, 1361, 1256, 1215, 1091, 835, 774, 669 cm^{-1}; ESI-HRMS calculated for $C_{46}H_{99}O_5Si_3$ $[M+H]^+$ 815.6800 found 815.6810.

*4.1.19. Amide intermediate **26a** of schulzeine B.* A mixture of tricyclic amine **4a** (40.0 mg, 93.3 μmol), 28-carbon fatty acid side chain **5** (81.5 mg, 0.100 mmol), DCC (62.0 mg, 0.300 mmol), and DMAP (2.5 mg, 20.5 μmol) in CH_2Cl_2 (1 mL) was stirred at room temperature under argon for 48 h after which the mixture was filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give amide **26a** (105 mg, 91%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.62; δ_H (300 MHz, $CDCl_3$) 7.40–7.25 (10H, m), 6.79 (1H, d, J=5.4 Hz), 6.47 (1H, d, J=2.7 Hz), 6.35 (1H, d, J=2.1 Hz), 5.06 (2H, s), 4.96 (2H, s), 4.94–4.86 (1H, m), 4.75–4.65 (1H, m), 4.58–4.46 (1H, m), 3.65–3.53 (1H, m), 3.53–3.38 (2H, m), 2.74–2.62 (2H, m), 2.54–2.42 (2H, m), 2.22 (2H, t, J=7.4 Hz), 1.98–1.82 (2H, m), 1.74–1.49 (10H, m), 1.35 (34H, br s), 0.84 (30H, s), 0.00 (18H, s); δ_C (75 MHz, $CDCl_3$) 173.2, 170.6, 158.5, 155.9, 137.2, 136.7, 136.4, 128.8 (2C), 128.6 (2C), 128.2, 128.1, 127.5 (2C), 127.1 (2C), 117.2, 105.9, 99.1, 76.1, 75.4, 72.9, 70.1 (2C), 48.8, 38.9, 37.1, 36.8, 36.6, 34.7, 33.7, 32.7, 31.9, 30.8, 29.9, 29.7 (4C), 29.6 (4C), 29.5, 29.4, 29.3 (2C), 26.6, 26.1, 25.9 (3C), 25.8 (6C), 25.7, 25.5, 25.2, 22.7, 18.2, 18.0 (2C), 14.1, −4.0, −4.1, −4.4, −4.5 (2C), −4.6; $[\alpha]_D^{25}$ −29.4 (*c* 3.0, $CHCl_3$); ν_{max}(film) 3401, 2928, 2860, 2253, 1790, 1645, 1611, 1499, 1464, 1376, 1257, 1149, 1093, 1010 cm^{-1}; ESI-HRMS calculated for $C_{73}H_{125}N_2O_7Si_3$ $[M+H]^+$ 1225.8795 found 1225.9003.

*4.1.20. Amide intermediate **26b** of schulzeine C.* A mixture of tricyclic amine **4b** (70.0 mg, 0.163 mmol), 28-carbon fatty acid side chain **5** (133 mg, 0.163 mmol), DCC (108 mg, 0.523 mmol), and DMAP (4.0 mg, 32.7 μmol) in CH_2Cl_2 (2 mL) was stirred at room temperature under argon for 48 h after which the mixture was filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give amide **26b** (174 mg, 89%) as a colorless oil; R_f (2:1 hexane/ethyl acetate) 0.38; δ_H (300 MHz, $CDCl_3$) 7.40–7.23 (10H, m), 6.46 (1H, d, J=2.1 Hz), 6.38 (1H, d, J=5.1 Hz), 6.33 (1H, d, J=2.1 Hz), 5.00 (2H, d, J=6.0 Hz), 4.98 (2H, s), 4.88 (1H, dd, J=12.0, 4.1 Hz), 4.77 (1H, dd, J=10.5, 3.0 Hz), 4.24–4.12 (1H, m), 3.65–3.53 (1H, m), 3.54–3.43 (2H, m), 3.04 (1H, d, J=11.4 Hz), 2.81(1H, d, J=12.6 Hz), 2.69–2.44 (3H, m), 2.19 (2H, t, J=7.2 Hz), 1.96–1.83 (2H, m), 1.76–1.49 (10H, m), 1.30 (34H, br s), 0.84 (30H, s), 0.00 (18H, s); δ_C (75 MHz, $CDCl_3$) 173.9, 170.0, 158.3, 156.8, 137.8, 136.7, 136.5, 128.7 (2C), 128.6 (2C), 128.1 (2C), 127.3 (2C), 127.2 (2C), 118.2, 106.1, 99.2, 76.1, 75.4, 72.9, 70.2 (2C), 56.2, 52.0, 49.2, 39.6, 37.3, 36.8, 34.7, 34.1, 31.9, 30.6, 29.7 (2C), 29.6 (2C), 29.5 (2C), 29.4, 29.3 (2C), 29.2, 27.9, 27.2, 26.6, 26.2, 26.1 (3C), 26.0 (6C), 25.7, 25.6, 25.5, 24.7, 22.7, 18.1, 18.0 (2C), 14.1, −4.1 (2C), −4.4, −4.5 (2C), −4.6; $[\alpha]_D^{25}$ +22.5 (*c* 2.0, $CHCl_3$); ν_{max}(film) 3401, 2928, 2856, 2253, 1794, 1645, 1610, 1499, 1464, 1376, 1257, 1149, 1093, 1006 cm^{-1}; ESI-HRMS calculated for $C_{73}H_{125}N_2O_7Si_3$ $[M+H]^+$ 1225.8795 found 1225.9071.

*4.1.21. Triol intermediate **27a** of schulzeine B.* A solution of amide **26a** (13.0 mg, 10.6 μmol) in 1 N HCl in THF (0.500 mL) was stirred at room temperature for 30 min. Ethyl acetate (3 mL) and satd aq $NaHCO_3$ (3 mL) were added and the phases were separated. The aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to give triol **27a** (7.2 mg, 74%) as a colorless oil; δ_H (300 MHz, $CDCl_3$) 7.43–7.29 (10H, m), 6.83 (1H, d, J=5.6 Hz), 6.47 (1H, d, J=2.2 Hz), 6.38 (1H, d, J=2.2 Hz), 5.09 (2H, s), 4.99 (2H, s), 4.93 (1H, dd, J=10.8, 4.0 Hz), 4.77–4.66 (1H, m), 4.60–4.48 (1H, m), 3.79–3.55 (1H, m), 3.49–3.36 (2H, m), 2.86–2.61 (4H, m), 2.57–2.41 (1H, m), 2.26 (2H, t, J=7.9 Hz), 1.77–1.40 (15H, m), 1.37–1.25 (31H, m), 0.88 (3H, t, J=6.3 Hz); δ_C (75 MHz, $CDCl_3$): 173.1, 170.5, 158.5, 155.9, 137.1, 136.7, 136.4, 128.8 (2C), 128.6 (2C), 128.2, 128.1, 127.5 (2C), 127.0 (2C), 117.2, 105.8, 99.1, 74.6, 74.4, 71.9, 70.1 (2C), 48.8, 38.9, 37.5, 36.7, 33.5, 33.0, 31.8, 29.6, 29.5 (6C), 29.5 (5C), 29.4, 29.3 (2C), 29.2, 28.5, 25.7 (2C), 25.6, 25.2, 22.6, 14.0; $[\alpha]_D^{25}$ −47.4 (*c* 2.4, $CHCl_3$); ν_{max}(film) 3430, 3016, 2925, 2853, 1791, 1636, 1608, 1498, 1465, 1375, 1358, 1308, 1271, 1151, 1090, 1048 cm^{-1}; ESI-HRMS calculated for $C_{55}H_{83}N_2O_7$ $[M+H]^+$ 883.6200 found 883.6119.

*4.1.22. Triol intermediate **27b** of schulzeine C.* A solution of amide **26b** (18.0 mg, 14.7 μmol) in 1 N HCl in THF (0.700 mL) was stirred at room temperature for 30 min. Ethyl acetate (3 mL) and satd aq

$NaHCO_3$ (3 mL) were added and the phases were separated. The aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to give triol **27b** (10.1 mg, 78%) as a colorless oil; δ_H (300 MHz, $CDCl_3$) 7.44–7.29 (10H, m), 6.51 (1H, d, J=2.9 Hz), 6.50–6.38 (1H, m), 6.37 (1H, d, J=2.9 Hz), 5.05 (1H, s), 5.03 (1H, s), 5.01 (2H, s), 4.96–4.84 (1H, m), 4.80 (1H, dd, J=11.0, 3.4 Hz), 4.28–4.14 (1H, m), 3.72–3.56 (1H, m), 3.51–3.45 (2H, m), 3.11–2.77 (2H, m), 2.74–2.49 (3H, m), 2.22 (2H, t, J=7.4 Hz), 1.83–1.37 (15H, m), 1.38–1.19 (31H, m), 0.88 (3H, t, J=7.1 Hz); δ_C (75 MHz, $CDCl_3$) 173.7, 168.8, 158.2, 156.8, 137.7, 136.6, 136.4, 128.8 (2C), 128.7 (2C), 128.1 (2C2C), 127.5 (2C), 127.2 (2C), 118.1, 106.1, 99.1, 74.5, 74.4, 71.8, 70.2, 70.1, 56.2, 51.9, 39.5, 37.4, 36.7, 33.5, 33.1, 31.9, 30.6, 29.7, 29.6 (5C), 29.4 (4C), 29.3 (2C), 29,2 (2C), 27.9, 27.2, 25.7, 25.6, 25.5, 22.7, 14.1; $[\alpha]_D^{25}$ +59.1 (c 2.2, $CHCl_3$); ν_{max}(film) 3422, 3016, 2925, 2855, 1790, 1636, 1608, 1498, 1465, 1375, 1358, 1308, 1271, 1151, 1090, 1050 cm^{-1}; ESI-HRMS calculated for $C_{55}H_{83}N_2O_7$ $[M+H]^+$ 883.6200 found 883.6129.

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Supplementary data

Supplementary data containing nuclear magnetic resonance (NMR) spectra of compounds synthesized in this study are available for online publication. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.085.

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8. The use of $LiAlH_4$ as the reagent for the conversion of amido-ester **13** to imide **14** was discovered serendipitously. As reported in Ref. 3a, initially, we planned to reduce the dimethyl ether analog of amido-ester **13** to the corresponding primary alcohol and subsequently oxidize it to yield the hydroxylactam. However, the imide was obtained as the product along with recovered starting material. The intended primary alcohol was not observed.
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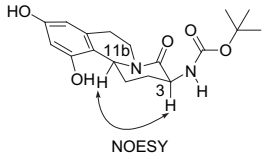
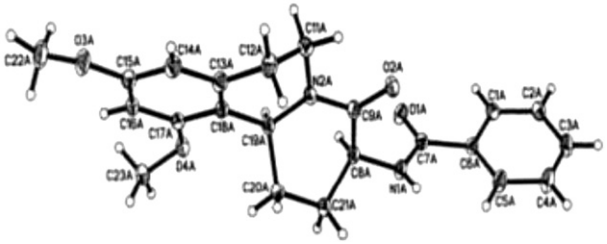
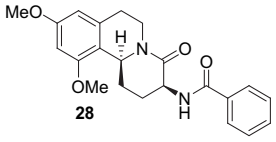


X-ray crystallographic analysis was performed on a related compound dimethyl ether **28** and the relative configuration of H3 and H11b is clearly shown as cis.





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