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A new approach to the C_{28} fatty acid chain of the marine natural products schulzeines B and C: a concise diastereoselective total synthesis of (−)-schulzeine B

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ABSTRACT

An enantioselective approach to the C_{28} fatty acid chain of the marine natural products schulzeines B and C was established based on the L-tartaric acid derived C_4 chiron **11** via successive 1,4-bis-chain elongation reactions and catalytic asymmetric hydrogenation. The chiral tricyclic core **8** was constructed via a diastereoselective Pictet–Spengler cyclization reaction (dr = 89:11) of the L-glutamic acid derived precursor **13**. On this basis, a concise total synthesis of (−)-schulzeine B (**5**) was disclosed.

1. Introduction

Glycosidases play key roles in many biological processes.[1] Many sugar-related natural products, such as azasugars show potent inhibitory activity against glycosidases, and are considered to be promising leads for drug development against metabolites-related diseases.[1] Recently, marine invertebrates have been shown to be a new source of potent α-glucosidase inhibitors.[2] In 2000, two proline-containing macrolide trisulfates penarolide sulfates A_1 (**1**) and A_2 (**2**) were isolated from the marine sponge *Penares* sp. They show potent anti-yeast α-glucosidase activity (IC_{50}=1.2 and 1.5 μg/mL, respectively).[3] Later on, penasulfate A (**3**) (Fig. 1), a pipecolate-containing disulfate was isolated from the same source. It shows ten times more potent than penarolide sulfates A_1 and A_2 against yeast α-glucosidase.[4] Then schulzeines A–C (**4**–**6**), three benzo[*a*]quinolizidine-containing trisulfates were isolated, which exhibit potent inhibitory activities toward yeast α-glucosidase (IC_{50}=48–170 nM) and viral neuraminidase (IC_{50}=60 μM).[5] Noteworthy is that, remarkable inhibitory activities toward α-glucosidase (IC_{50} values of 2.5 and 1.1 μM, respectively) are still retained by the desulfated analogues of schulzeines A and B.[5]

Up to date, the asymmetric total synthesis of penarolide sulfate A_1[6] and schulzeines A–C (**4**–**6**),[7–9] as well as the enantioselective synthesis of the hydroxy acid segment of schulzeines B/C[10] and the 3-aminobenzo[*a*]quinolizidine moiety of schulzeines A–C[11] have been reported. Although Wardrop and Bowen have shown that construction of the tricyclic isoquinoline core by Pictet–Spengler cyclization could reach a 9:1 *cis*/*trans* diastereoselectivity,[9a] however, in all the reported total syntheses of schulzeine B,[7–9] the diastereoselectivities in the construction of the benzo[*a*]quinolizidine core[11] were low, which varied from 1:1 to 2:1.[9b] With a program aiming at the synthesis of glycosidases inhibitors,[12] we now report an efficient and highly diastereoselective synthesis of the C_{28} fatty acid chain of schulzeines B and C, as well as the total synthesis of (−)-schulzeine B via the chiron approach.[13]

2. Results and discussion

Our synthetic approach to schulzeine B (**5**) is displayed retrosynthetically in Scheme 1. As schulzeine B consists of a 3-aminobenzo[*a*]quinolizidine and a C_{28} fatty acid chain, the assembly of two properly protected segments via amide bond formation is the direct and general strategy for its total syntheses.[7–11] For the synthesis of the C_{28} fatty acid chain, a L-tartaric acid-based chiron approach[14] was envisaged. The known tosyl-triflate[15] **11** was chosen as the proper chiron, which includes both the requisite 2,3-diol

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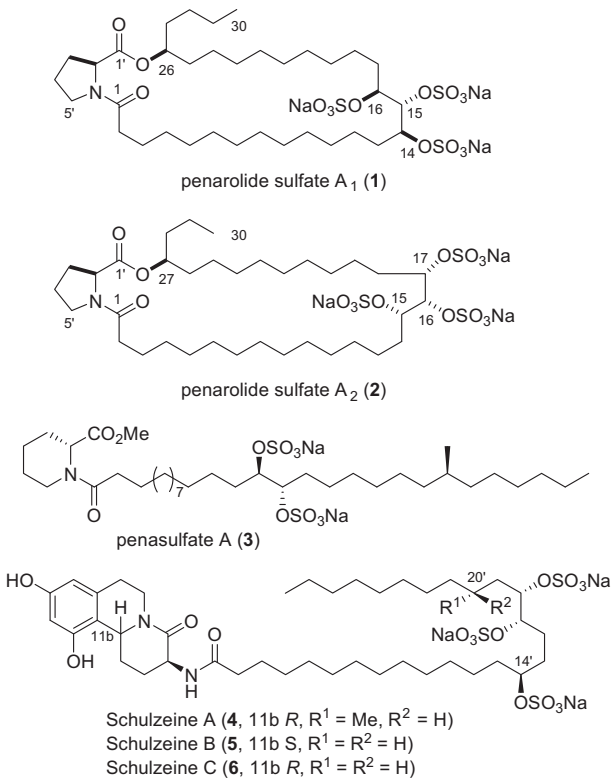
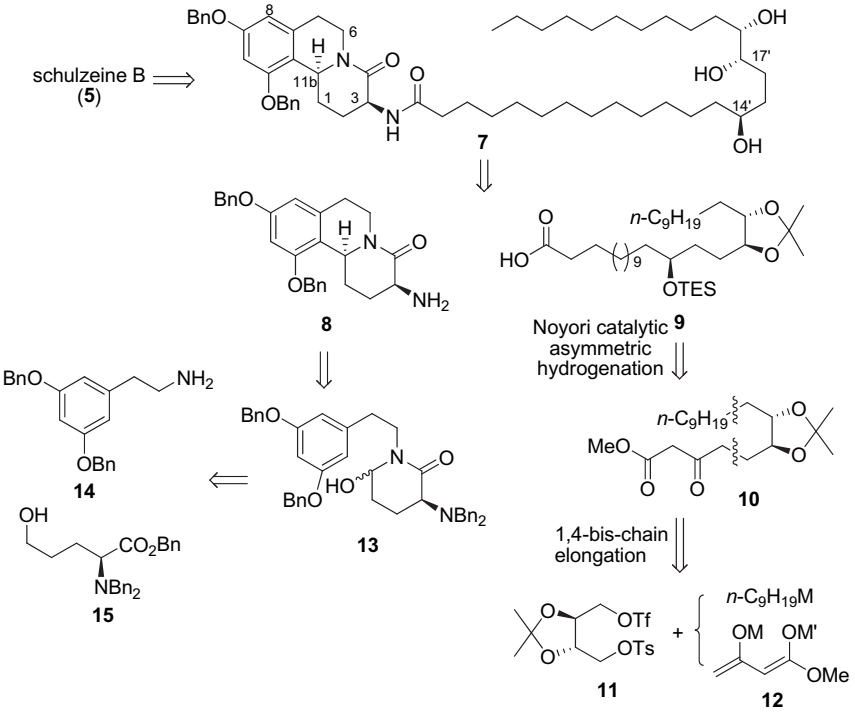


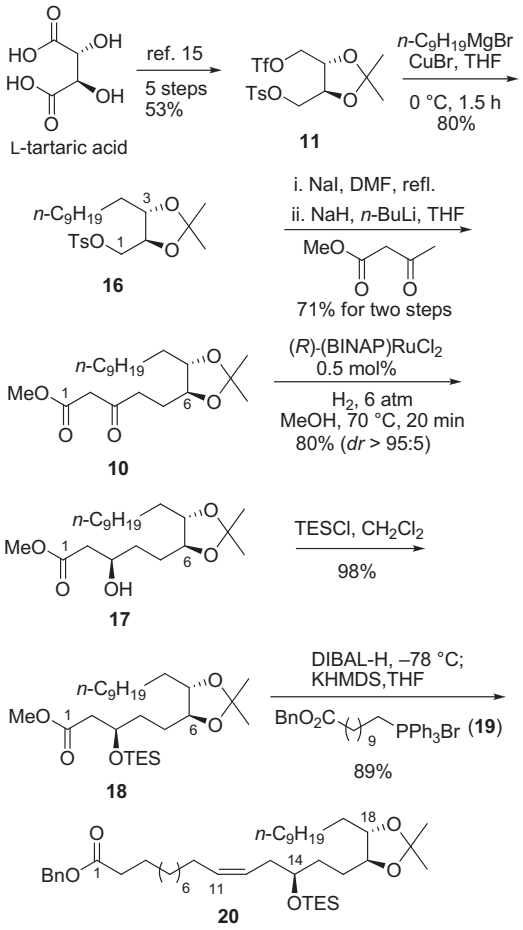
Fig. 1. Marine sulfates exhibiting inhibitory activities toward α-glucosidase.

moiety with *syn*-stereochemistry and 1,4-difunctionalities for a straightforward bis-chain elongation. After coupling with the dienolate **12**, the third carbinolic chiral center could be established by catalytic asymmetric hydrogenation.[8,16] As for the synthesis of the 3-aminobenzo[*a*]quinolizidine moiety, L-glutamic acid-based chiron aproach[7,9,11,17,18] appeared attractive in light of its biogenetic pathway.[5] On the basis of our recent studies on the L-glutamic acid-based synthetic approach to protected 3-amino-6-hydroxy-2-piperidone derivatives,[19] we selected dibenzyl derivative **13** as the precursor for Pictet–Spengler reaction, which could be available from the known compound **14**[7] and **15**.[19] According to recent reports on Pictet–Spengler reactions of *O*,*O*-dimethyl analogue[11] and *N*-Phth protected analogue[9] of **13**, *cis*-diastereoselectivity was expected for Pictet–Spengler reaction of **13**.

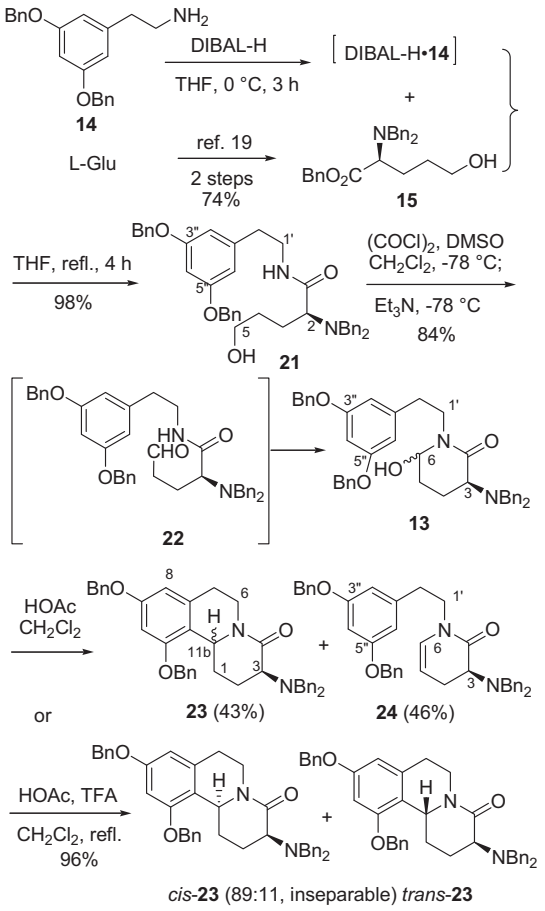
The synthesis of the hydroxy acid segment (**9**) of schulzeines B and C started from the known C_4 building block **11**,[15] readily available from L-tartaric acid in 53% overall yield. Treatment of the tosyl triflate **11** with organocopper reagent, generated in situ from 1.1 equiv of Grignard reagent *n*-C_9H_{19}MgBr and a catalytic amount of CuBr, at 0 °C for 1.5 h produced chemoselectively the desired coupling product **16** in 80% yield (Scheme 2). For the second chain elongation, tosylate **16** was treated with the dianion generated in situ from methyl acetoacetate (NaH; *n*-BuLi).[20] Unfortunately the desired γ-alkylation product was not obtained. Considering the success in the similar γ-alkylation with 4,5-bis(iodomethyl)-2,2-dimethyl-1,3-dioxolane,[21] it was envisioned that both electronic and steric hindrance of the tosyl group might be responsible for the failure of the γ-alkylation with tosylate **16**, and replacement of tosyloxy with iodide as the leaving group would be beneficial. Indeed, after converting the tosylate **16** into the corresponding iodide (NaI, DMF), the alkylation proceeded smoothly to give the desired product **10** in 70% yield. Under the catalytic[8,16] asymmetric hydrogenation conditions (0.5 mol % of (*R*)-(BINAP)$RuCl_2$, H_2, 6 atm, MeOH, 70 °C, 20 min), β-ketoester **10** was reduced to give the β-hydroxyester **17** as the only observable diastereomer in 80% yield. The diastereoselectivity of the reduction was estimated to be higher than 95:5 at the limits of the method (NMR). *O*-Protection of the hydroxyl group with TESCl gave compound **18** in 98% yield. Chemoselective reduction of the ester with DIBAL-H at −78 °C yielded the corresponding aldehyde, which reacted with the Wittig reagent, generated in situ from phosphonium salt **19** and KHMDS in THF to produce the *Z*-olefin **20** in 89% overall yield. The geometry of the olefin could not be determined from the ^{1}H NMR data, but



Scheme 1. Retrosynthetic analysis of schulzeine B.



Scheme 2. Synthesis of the precursor of the C_{28} fatty acid chain of schulzeines B and C.

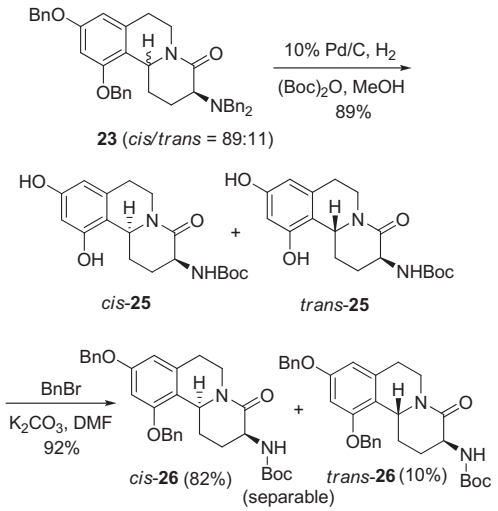


Scheme 3. Diastereoselective construction of the 3-aminobenzo[*a*]quinolizidine moiety *cis*-**23**.

deduced from the observed absorption at 736 and 689 cm^{-1} in the IR spectrum of compound **20**, which is an indication of a *Z*-olefin.[22]

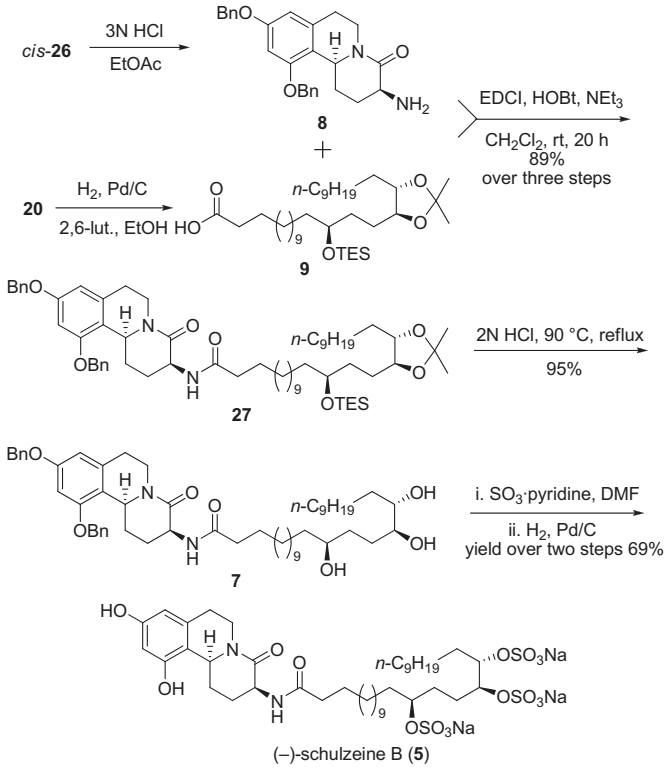
Having accomplished the diastereoselective synthesis of the diastereomer **20** as a precursor of the C_{28} fatty acid residue, we next turned our attention to the synthesis of the *cis*-3-aminobenzo[*a*]quinolizidine moiety **8**. The synthesis started from the known 2-(3,5-bis(benzyloxy)phenyl)ethanamine (**14**)[7] and hydroxylated amino ester **15**[19] (Scheme 3). Using the method developed in our laboratory,[23] the *O*-unprotected hydroxyl ester **15** was treated with a DIBAL-H·amine complex, prepared in situ from amine **14** and DIBAL-H, to afford the desired hydroxy amide **21** in 98% yield. Oxidation of alcohol **21** with either PDC or Dess–Martin periodinane gave aldehyde **22** in only 20–30% and 50–60% yields, respectively. Swern oxidation[24] [$(COCl)_2$, DMSO, CH_2Cl_2; NEt_3] at −78 °C afforded the cyclic tautomer **13** as a separable diastereomeric mixture in 10:1 ratio with a 84% combined yield. Because both diastereomers can be used for the subsequent cyclization, their stereochemistries were not determined. Next, the key diastereoselective Pictet–Spengler cyclization reaction was investigated.[9,11,17] Treatment of the diastereomeric *N*,*O*-acetals **13** with a catalytic amount of HOAc in CH_2Cl_2 at room temperature for 48 h led to the formation of the desired cyclization product **23** as a diastereomeric mixture in 43% yield, along with the dehydrated product **24** in 46% yield. The formation of the enamide **24** might be attributed to the slow rate of the cyclization reaction that makes the dehydration reaction possible. It was thus envisioned that the conditions allowing an enhancement of the cyclization reaction, such as use of a stronger acid and running the reaction at a higher temperature would increase the yield of the cyclization. Indeed, when 2.0 equiv of TFA[17c,9] were added and the reaction run at reflux for 24 h, the desired product **23** was obtained as a diastereomeric mixture in 89:11 ratio with 96% combined yield. The two diastereomers were inseparable by column chromatography and the ratio was determined by ^1H NMR and HPLC analyses. 2D NOESY experiments on the major diastereomer of **23** showed a NOE correlation between the protons at C-3 and C-11b, indicating a cis-relationship between these two protons. The observed *cis*-diastereoselectivity of Pictet–Spengler reaction is in agreement with the reported similar systems,[9,11] but much higher diastereoselectivity was obtained, compared with the corresponding *O*,*O*-dimethyl analogue (8:1 vs 1.7:1 and 2.2:1).[11]

To get two diastereomers separated, a conversion of the *N*-dibenzyl group to a carbamate group[7,9] was envisioned. Thus, selective *N*-monodebenzylation of **23** was first attempted. To our disappointment, treatment of the diastereomeric mixture of **23** with either ceric ammonium nitrate (CAN)[25] or DDQ[26] did not give the desired product. An alternative approach was then investigated. The 8:1 diastereomeric mixture of **23** was subjected to catalytic hydrogenolytic conditions (10% Pd/C, H_2 1 atm, room temperature) in the presence of $(Boc)_2O$, which afforded, in one-pot, the fully debenzylated and *N*-Boc protected compound **25** as an inseparable diastereomeric mixture in 90:10 ratio with a combined yield of 89%. *O*,*O*-Dibenzylation of this diastereomeric mixture with benzyl bromide (K_2CO_3, DMF) at room temperature for 12 h led to the known carbamates[7,9] *cis*-**26** (yield: 82%) and *trans*-**26** (yield: 10%) that were easily separated by flash column chromatography (Scheme 4). Thus, compound *cis*-**26** was synthesized in five steps from the known compound **15** with an overall yield of 58%.



Scheme 4. Synthesis of 3-aminobenzo[*a*]quinolizidine derivative *cis*-**26**.

In order to assemble the benzo[*a*]quinolizidine moiety *cis*-**26** with the protected hydroxy acid segment **20**, *cis*-**26** was deprotected (3 M HCl, EtOAc) to give the free amine **8**,[7] and compound **20** was hydrogenated under basic conditions[8] (H_2, Pd/C, 2,6-lutidine, EtOH) to give the protected C_{28} fatty acid residue of schulzeines B and C (**9**)[8] (Scheme 5). The coupling of the two fragments was undertaken by treatment of carboxylic acid **9** with EDCI, HOBt, and Et_3N to form an activated ester, which reacted with amine **8** to afford the amide **27** in 89% yield. Removal of the acetal and TES protecting groups by heating compound **27** in a 2 N HCl solution in methanol at 90 °C for 2 h gave the desired triol **7** in 95% yield. Sulfation[7–9] of triol **7** using SO_3·pyridine complex in anhydrous DMF provided the trisulfated compound **28**. Finally, hydrogenolysis of the benzyl groups afforded schulzeine B (**5**) (Scheme 5). The spectral data of the synthetic schulzeine B (**5**) are identical with those reported.[5,9]



Scheme 5. Synthesis of (−)-schulzeine B (**5**).

3. Conclusion

In summary, by taking advantage of the multiple functionalities of the L-tartaric acid derived C_4 building block **11**, a flexible and highly diastereoselective approach for the synthesis of the C_{28} fatty acid chain of schulzeines B and C has been achieved. In combination with a highly diastereoselective (*dr* = 89: 11) synthesis of the 3-aminobenzo[*a*]quinolizidine moiety, we have developed a concise and highly diastereoselective total synthesis of the marine natural product (−)-schulzeine B (**5**). The synthesis was achieved in 14 chromatographic separation steps with 12.7% overall yield from the known compounds **15** and **11**.

4. Experimental section

4.1. General methods

Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or in CD_3CN or in CD_3OD with tetramethylsilane as an internal standard. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

4.2. ((4*S*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolan-4-yl)methyl-4-methylbenzenesulfonate (16)

To a suspension of CuBr (76 mg, 0.53 mmol) in THF (10 mL) at 0 °C were added *n*-$C_9H_{19}MgBr$ (0.5 M in THF, 5.2 mL, 2.60 mmol) and a THF solution (3 mL) of the known tosyl triflate **11**.[15] After being stirred at the same temperature for 1.5 h, the reaction was quenched with a saturated NH_4Cl/aqueous NH_3 (9:1) solution (5 mL). The insoluble substance was removed by filtration through Celite. The filtrate was concentrated under vacuum and extracted with ether (10 mL×5). The combined extracts were washed successively with water (3 mL) and brine (1 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Filtration of the residue through a short pad of silica gel column eluting with EtOAc/PE = 1:10 yielded compound **16** (817 mg, yield: 80%) as a colorless oil. $[\alpha]_D^{20}$ −15.8 (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 2986, 2926, 2854, 1598, 1458, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.0 Hz, 2H, Ar), 7.34 (d, *J*=8.0 Hz, 2H, Ar), 4.15–4.04 (m, 2H, OCH), 3.82–3.74 (m, 2H, $-OCH_2$), 2.45 (s, 3H, $PhCH_3$), 1.56–1.48 (m, 2H, CH_2), 1.36 (s, 6H, $C(CH_3)_2$), 1.32–1.24 (m, 19H,), 0.88 (t, *J*=6.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 132.8, 129.8, 128.0, 109.3, 78.2, 77.9, 69.2, 33.1, 31.9, 29.58, 29.55, 29.5, 29.3, 27.3, 26.7, 25.8, 22.7, 21.6, 14.1; MS (ESI) *m*/*z* 427 ($M+H^+$, 100%); HRESIMS calcd for $C_{23}H_{38}O_5SNa$ $(M+Na)^+$: 449.2338; found: 449.2332.

4.3. Methyl 5-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxopentanoate (10)

Compound **16** (1.58 g, 3.70 mmol) was added slowly to a hot (80–90 °C) and vigorously stirred solution of NaI (833 mg, 5.6 mmol) in DMF (7.5 mL). The mixture was stirred at the same temperature for 2 h, then cooled to room temperature and poured into water (75 mL). The resulting mixture was extracted with Et_2O (30 mL×6). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude iodide was used immediately in the next step without further purification.

To a suspension of NaH (178 mg, 7.43 mmol) in THF (25 mL) at 0 °C was added methyl acetoacetate (0.80 mL, 7.43 mmol) and the

mixture was stirred at 0 °C for 15 min before *n*-butyl lithium was added dropwise. After the addition, the mixture was stirred at 0 °C for another 15 min before the solution of the iodide (1.42 g, 3.72 mmol) in THF (2 mL) was added to the reaction mixture. The reaction was allowed to warm to room temperature and stirred for 1 h. Then the reaction was quenched with saturated NH_4Cl (5 mL). The resulting mixture was extracted with ethyl ether (20 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography eluting with 5% EtOAc in PE to give the ketoester **10** as a colorless oil (1.02 g, yield: 74%). $[\alpha]_D^{20}$ −28.5 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 2983, 2929, 2855, 1756, 1714, 1378, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H, OCH_3), 3.62−3.54 (m, 2H, OCH), 3.48 (s, 2H, $OCCH_2CO$), 2.83−2.63 (m, 2H, $COCH_2$), 1.98−1.89 (m, 1H, C*H*H-5), 1.74−1.64 (m, 1H, CH*H*-5), 1.54−1.48 (m, 2H, CH_2-8), 1.36 (s, 6H, $C(CH_3)_2$), 1.31−1.19 (m, 16H), 0.88 (t, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 167.5, 108.0, 80.9, 79.8, 52.3, 49.0, 39.5, 32.7, 31.9, 29.7, 29.6, 29.5, 29.3, 27.3, 27.2, 26.4, 26.0, 22.6, 14.1; MS (ESI): *m*/*z* 393 ($M+Na^+$, 100%); HRESIMS calcd for $C_{21}H_{38}O_5Na$ $(M+Na)^+$: 393.2617; found: 393.2607.

4.4. Methyl (*R*)-5-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxypentanoate (17)

A vial containing catalyst (*R*)-BinapRuCl$_2$ (11 mg, 0.014 mmol, 0.5% equiv) and ketoester **10** (1.00 g, 2.7 mmol) in MeOH (2 mL) was placed in an autoclave and the autoclave was placed in an oil bath pre-warmed to 70 °C. After being purged with hydrogen for 5 min, the pressure of hydrogen was raised to 6 atm, and the mixture was stirred for 20 min. The reaction was stopped and the mixture diluted with CH_2Cl_2, passed through a pad of silica gel, concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2, eluting with 5% EtOAc in hexane) to give the alcohol **17** as a colorless oil (800 mg, yield: 80%). $[\alpha]_D^{20}$ −25.0 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 3469, 2983, 2925, 2851, 1731, 1441, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09−4.01 (m, 1H, HOC*H*), 3.71 (s, 3H, OCH_3), 3.63−3.55 (m, 2H, OCH), 3.21 (d, *J*=4.4 Hz, 1H, OH, D_2O exchangeable), 2.55−2.42 (m, 2H, $OCCH_2CO$), 1.87−1.76 (m, 1H, C*H*H-4), 1.75−1.66 (m, 1H, CH*H*-4), 1.62−1.45 (m, 4H, CH_2-5, CH_2-8), 1.38 (s, 6H, $C(CH_3)_2$), 1.34−1.23 (m, 16H), 0.88 (t, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 108.0, 81.1, 81.0, 67.8, 51.7, 41.3, 33.4, 32.8, 31.9, 29.72, 29.65, 29.6, 29.5, 29.3, 28.9, 27.3, 27.2, 26.1, 22.7, 14.1; MS (ESI): *m*/*z* 395 ($M+Na^+$, 100%); HRESIMS calcd for $C_{21}H_{40}O_5Na$ $(M+Na)^+$: 395.2773; found: 395.2770.

4.5. Methyl 5-(*R*)-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-((triethylsilyl) oxy)pentanoate (18)

To a solution of compound **17** (1.02 g, 2.8 mmol), TESCl (0.94 mL, 5.6 mmol), and DMAP (34 mg, 0.28 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added dropwise triethylamine (0.78 mL, 5.6 mmol). The mixture was then allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with methanol (1 mL) at 0 °C. The mixture was diluted with ether, washed successively with water (1 mL) and brine (1 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography eluting with 2% EtOAc in PE, to give the silyl ether **18** as a colorless oil (1.31 g, yield: 98%). $[\alpha]_D^{20}$ −27.4 (*c* 1.35, $CHCl_3$); IR (film) ν_{max}: 2925, 2876, 2847, 1735, 1457, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22−4.15 (m, 1H, SiOCH), 3.67 (s, 3H, OCH_3), 3.62−3.53 (m, 2H, OCH), 2.53−2.40 (m, 2H, $OCCH_2CO$), 1.79−1.71 (m, 1H, C*H*H-4), 1.68−1.60 (m, 1H, CH*H*-4), 1.59−1.42 (m, 4H, CH_2-5, CH_2-8), 1.37 (s, 6H, $C(CH_3)_2$), 1.30−1.19 (m, 16H), 0.95 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.88 (t, *J*=6.4 Hz, 3H, CH_3), 0.60 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 107.8, 81.0, 80.9, 69.1, 51.4, 42.6, 34.1, 33.0, 31.9, 29.8, 29.6, 29.5, 29.3, 28.5, 27.28, 27.25, 26.1, 22.7, 14.1, 6.8, 4.9; MS (ESI): *m*/*z* 509 ($M+Na^+$, 100%); HRESIMS calcd for $C_{27}H_{54}O_5SiNa$ $(M+Na)^+$: 509.3638; found: 509.3638.

4.6. Benzyl (*R*,*Z*)-16-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-((triethylsilyl)oxy)hexadec-11-enoate (20)

To a solution of ester **18** (186 mg, 0.38 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added a solution of DIBAL-H (0.57 mL of a 1.0 M solution in hexane, 1.0 mmol) dropwise. The reaction mixture was stirred at −78 °C for 0.5 h and then quenched by dropwise addition of methanol (0.6 mL) before the reaction was allowed to warm to 23 °C slowly. To the reaction mixture was added a 1 M solution of Rochelle's salt (4 mL). After being stirred overnight, the mixture was extracted with CH_2Cl_2 (5 mL×3). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the aldehyde as a yellowish oil (164 mg, 94%), which was used as such in the next step.

To a suspension of the phosphonium salt **19** (651 mg, 1.08 mmol) in THF (2.5 mL) at −78 °C was added KHMDS (0.7 M in toluene, 1.2 mL, 0.86 mmol) dropwise. The resulting mixture was stirred at 0 °C for 1 h, and cooled to −78 °C. To the resulting mixture was added dropwise a solution of aldehyde (164 mg, 0.36 mmol) in THF (1 mL). The reaction was allowed to warm to room temperature and stirred for 5 h before quenching with water (1.5 mL). The resulting mixture was extracted with ethyl ether (5 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (eluent: 2% EtOAc in PE) to give *Z*-olefin **20** as a colorless oil (245 mg, yield: 95%). $[\alpha]_D^{20}$ −5.27 (*c* 1.4, $CHCl_3$); IR (film) ν_{max}: 2925, 2851, 1735, 1461, 1096, 736, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.38 (m, 5H, Ar), 5.56−5.51 (m, 2H, CH=CH), 5.19 (s, 2H, OCH_2Ph), 3.81−3.73 (m, 1H, SiOCH), 3.70−3.59 (m, 2H, OCH), 2.42 (t, *J*=7.6 Hz, 2H, $OCCH_2$), 2.35−2.22 (m, 2H, CH_2-13), 2.13−2.04 (m, 2H, CH_2-10), 1.79−1.67 (m, 4H, CH_2-15, CH_2-16), 1.62−1.47 (m, 4H, CH_2-13, CH_2-19), 1.44 (s, 6H, $C(CH_3)_2$), 1.40−1.31 (m, 28H), 1.04 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.95 (t, *J*=6.4 Hz, 3H, CH_3), 0.68 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 136.2, 131.8, 128.5, 128.1, 125.4, 107.7, 81.2, 81.1, 72.2, 66.0, 35.5, 34.3, 33.3, 33.1, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.34, 29.31, 29.2, 29.1, 29.0, 27.5, 27.3, 26.1, 24.9, 22.7, 14.1, 6.9, 5.1, 1.0; MS (ESI): *m*/*z* 737 ($M+Na^+$, 100%); HRESIMS calcd for $C_{44}H_{78}O_3SiNa$ $(M+Na)^+$: 737.5530; found: 737.5516.

4.7. (*S*)-*N*-[3,5-Bis(benzyloxy)phenethyl]-2-(dibenzylamino)-5-hydroxypentanamide (21)

A solution of DIBAL-H (1 M in hexane, 1.33 mL, 1.33 mmol) was added, under a nitrogen atmosphere, to a cooled (0−5 °C) THF solution (0.5 mL) of the known amine **14**[9] (403 mg, 1.2 mmol). The mixture was allowed to warm up and stirred at room temperature for 3 h. The concentration of the thus formed DIBAL-H·**14** complex was about 0.75 M, and was used directly for aminolysis.

To a solution of the known hydroxy amino ester **15**[19] (487 mg, 1.0 mmol) in THF (3 mL) was added the DIBAL-H·**14** complex under nitrogen at room temperature. After being refluxed for 17 h, the reaction was cooled down to 0 °C, and then quenched with 1 M HCl (2 mL). The mixture was extracted with ethyl acetate (3 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluent: ethyl acetate/PE = 1:1) to afford amide **21** (799 mg, yield: 98%) as a colorless oil. $[\alpha]_D^{20}$ −35.9 (*c* 0.7, $CHCl_3$); IR (film) ν_{max}: 3393, 2927, 2869, 2366, 1647, 1588, 1570,

1159, 1110, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.18 (m, 20H, Ar), 7.02 (t, J=5.4 Hz, 1H, NH), 6.60 (t, J=2.0 Hz, 1H, CH-4″), 6.55 (d, J=2.0 Hz, 2H, CH-2″, CH-6″), 5.04 (s, 4H, OCH_2Ph), 3.66 (d, J=13.6 Hz, 2H, NCH_2Ph), 3.69–3.58 (m, 4H, CH_2-5, CH_2-1′), 3.50 (d, J=13.6 Hz, 2H, NCH_2Ph), 3.11 (dd, J=8.3, 3.3 Hz, 1H, CH-2), 2.92–2.73 (m, 3H, CH_2-2′, OH, D_2O exchangeable), 2.04–1.83 (m, 2H, CH_2-3), 1.81–1.64 (m, 2H, CH_2-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 160.4, 141.1, 138.8, 136.8, 130.0, 128.62, 128.60, 128.0, 127.6, 127.3, 108.0, 100.2, 70.1, 61.8, 61.7, 54.4, 39.8, 35.7, 31.5, 20.2; MS (ESI): m/z 629 ($M+H^+$, 100%); HRESIMS calcd for [$C_{41}H_{44}N_2O_4+H^+$]: 629.3379; found: 629.3364.

4.8. (3*S*,6*R*/*S*)-1-[3,5-Bis(benzyloxy)phenethyl]-3-(dibenzylamino)-6-hydroxypiperidin-2-one (13)

To a stirring, cooled (−78 °C) solution of oxalyl chloride (0.13 mL, 1.47 mmol) in CH_2Cl_2 (5 mL) was added dropwise DMSO (0.2 mL, 2.4 mmol). After stirring for 10 min, a solution of compound **21** (739 mg, 1.18 mmol) in CH_2Cl_2 (1.5 mL) was transferred into the reaction mixture via a canula. The resultant mixture was stirred at −78 °C for 40 min, then NEt_3 (1 mL) was added. After stirring for 15 min at −78 °C, an additional NEt_3 (1 mL) was added and the mixture was stirred at 0–5 °C for 15 min. The reaction was quenched with water (1 mL), and the mixture extracted with CH_2Cl_2 (3 mL×3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:5) to give compound **13** (673 mg, yield: 91%) as a pale yellow oil, which is a 10:1 mixture of two diastereomers (determined by ^1H NMR). IR (film) ν_{max}: 3414, 3061, 3024, 2923, 2866, 1634, 1589, 1451, 1381, 1369, 1143, 1049, 1024 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) (data of the major diastereomer) δ 7.48–7.19 (m, 20H, Ar), 6.51 (d, J=6.5 Hz, 2H, CH-2″, CH-6″), 6.49 (t, J=2.2 Hz, 1H, CH-4″), 5.05 (s, 4H, OCH_2Ph), 4.61 (m, 1H, CH-6), 3.97 (d, J=14.1 Hz, 2H, NCH_2Ph), 3.88–3.80 (m, 1H, CH_2-3), 3.75 (d, J=14.1 Hz, 2H, NCH_2Ph), 3.38–3.28 (m, 1H, C*H*H-1′), 3.22–3.13 (m, 1H, CH*H*-1′), 2.89–2.74 (m, 2H, CH_2-2′), 2.22–2.14 (m, 3H, CH_2-4, OH, D_2O exchangeable), 1.80–1.67 (m, 1H, C*H*H-5), 1.54–1.43 (m, 1H, CH*H*-5); ^{13}C NMR (100 MHz, CD_3CN) (data of the major diastereomer) δ 171.8, 160.7, 143.3, 141.6, 138.2, 129.3, 129.2, 128.9, 128.6, 128.4, 127.5, 108.9, 100.9, 80.1, 70.4, 59.7, 55.9, 47.5, 35.0, 30.2, 21.7; MS (ESI): m/z 627 ($M+H^+$, 100%); HRESIMS calcd for [$C_{41}H_{42}N_2O_4+H^+$]: 627.3223; found: 627.3215.

4.9. (3*S*)-9,11-Bis(benzyloxy)-3-(dibenzylamino)-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11*bH*)-one (23)

Acetic acid (4 mL, 70 mmol) was added to a mixture of **13** (622 mg, 0.99 mmol) in anhydrous CH_2Cl_2 (40 mL). After stirring for 10 min, trifluoroacetic acid (0.15 mL, 2.0 mmol) was added. The reaction was heated to reflux for 24 h. After the reaction was allowed to cool down to room temperature, the mixture was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:5) to give compound **23** as a pale yellow solid (580 mg, yield: 96%), which is an inseparable mixture of C-6 epimers (*trans*/*cis* = 11:89, determined by HPLC). IR (film) ν_{max}: 3058, 3021, 2923, 2856, 1655, 1601, 1491, 1448, 1372, 1305, 1265, 1149, 1095, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (data of the major diastereomer) δ 7.51–7.17 (m, 20H, Ar), 6.46 (d, J=2.1 Hz, 1H, CH-10), 6.37 (d, J=2.1 Hz, 1H, CH-8), 5.03–4.96 (m, 4H, OCH_2Ph), 4.86–4.79 (m, 1H, C*H*H-6), 4.62 (dd, J=10.9, 3.4 Hz, 1H, CH-3), 4.23 (d, J=14.6 Hz, 2H, NCH_2Ph), 3.85 (d, J=14.6 Hz, 2H, NCH_2Ph), 3.52 (t, J=9.4 Hz, 1H, CH-11b), 2.85–2.73 (m, 1H, CH*H*-6), 2.73–2.63 (m, 2H, CH_2-7), 2.46–2.34 (m, 1H, C*H*H-2), 2.15–2.01 (m, 1H, C*H*H-1), 1.93–1.81 (m, 1H, CH*H*-1), 1.47–1.33 (m, 1H, CH*H*-2); ^{13}C NMR (100 MHz, $CDCl_3$) (data of the major diastereomer) δ 172.3, 158.2, 155.9, 140.9, 137.6, 136.7, 136.6, 136.5, 128.3, 128.0, 127.9, 127.8, 127.4, 126.9, 126.6, 126.5, 117.8, 105.8, 99.0, 70.0, 69.8, 56.5, 55.1, 49.8, 38.0, 29.9, 29.6, 23.5; MS (ESI): m/z 609 ($M+H^+$, 100%); HRESIMS calcd for [$C_{41}H_{40}N_2O_3+H^+$]: 609.3117; found: 609.3103.

4.10. (*S*)-1-(3,5-Bis(benzyloxy)phenethyl)-3-(dibenzylamino)-3,4-dihydropyridin-2(1*H*)-one (24)

To a solution of **13** (318 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (15 mL) was added acetic acid (2 mL, 35 mmol). After stirring at room temperature for 48 h, the mixture was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:5) to give compound **23** (142 mg, yield: 43%) as a pale yellow solid, and compound **24** (133 mg, yield: 46%) as a pale yellow oil. $[\alpha]_D^{20}$ −93.3 (*c* 0.33, $CHCl_3$); IR (film) ν_{max}: 3061, 3024, 2927, 2853, 1661, 1591, 1448, 1366, 1232, 1146, 1046, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.12 (m, 20H, Ar), 6.45 (s, 3H, CH-2″, CH-4″, CH-6″), 5.68 (dd, J=7.9, 2.6 Hz, 1H, CH-6), 4.95 (s, 5H, OCH_2Ph, CH-5), 4.04 (d, J=14.2 Hz, 2H, NCH_2Ph), 3.88–3.80 (m, 1H, CH-3), 3.78 (d, J=14.2 Hz, 2H, NCH_2Ph), 3.53–3.43 (m, 2H, CH_2-1′), 2.78 (t, J=7.2 Hz, 2H, CH_2-2′), 2.51–2.39 (m, 1H, C*H*H-4), 2.36–2.21 (m, 1H, CH*H*-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 160.0, 140.9, 140.6, 136.9, 129.1, 128.6, 128.5, 128.3, 128.0, 127.6, 126.8, 108.2, 105.1, 100.2, 70.0, 57.3, 55.1, 47.6, 35.3, 25.8; MS (ESI): m/z 609 ($M+H^+$, 100%); HRESIMS calcd for [$C_{41}H_{40}N_2O_3+H^+$]: 609.3117; found: 609.3103.

4.11. *tert*-Butyl (3*S*,11*bS*)-9,11-dihydroxy-4-oxo-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-ylcarbamate (*cis*-25) and *trans*-25

A suspension of the diastereomeric mixture of **23** (188 mg, 0.31 mmol) and 10% Pd/C (19 mg) in methanol (2 mL) was stirred under 1 atm of H_2 at room temperature for 12 h. Boc_2O (0.093 mL, 0.39 mmol) was added and the mixture was stirred for 10 h at room temperature. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to give *cis*-**25** (white gummy paste, 87 mg, yield: 80%), and *trans*-**25** (white gummy paste, 10 mg, yield: 9%). *cis*-**25**: $[\alpha]_D^{20}$ −50.8 (*c* 0.8, MeOH) {lit.[7] $[\alpha]_D^{20}$ −49.1 (*c* 0.9, MeOH)}; IR (film) ν_{max}: 3338, 2975, 2923, 1594, 1466, 1421, 1412, 1381, 1366, 1314, 1116, 1046 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.18 (d, J=2.3 Hz, 1H, CH-10), 6.11 (d, J=2.3 Hz, 1H, CH-8), 4.86–4.74 (br s, 3H, OH, NH), 4.80 (d, J=3.7 Hz, 1H, CH-11b), 4.63–4.52 (m, 1H, C*H*H-6), 4.34–4.26 (m, 1H, CH-3), 2.72–2.55 (m, 3H, C*H*H-1, CH_2-7), 2.53–2.42 (m, 1H, CH*H*-6), 2.34–2.23 (m, 1H, C*H*H-2), 1.46 (s, 9H, CH_3), 1.57–1.27 (m, 2H, CH*H*-2, CH*H*-1); ^{13}C NMR (100 MHz, CD_3OD) δ 172.4, 158.0, 157.9, 156.1, 138.4, 115.0, 107.3, 101.9, 80.5, 51.1, 50.8, 40.4, 30.2, 29.2, 28.7, 26.3; MS (ESI): m/z 349 ($M+H^+$, 72%), 371 ($M+Na^+$, 100%).

Data for *trans*-**25**: $[\alpha]_D^{20}$ +115.8 (*c* 0.2, MeOH) {lit.[7] $[\alpha]_D^{20}$ +122 (*c* 1.4, MeOH)}; IR (film) ν_{max}: 3335, 2972, 2917, 1610, 1427, 1421, 1412, 1381, 1274, 1253, 1146, 1119, 1061 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.17 (d, J=2.2 Hz, 1H, CH-10), 6.08 (d, J=2.2 Hz, 1H, CH-8), 4.89–4.78 (br s, 3H, OH, NH), 4.82–4.70 (m, 2H, CH-11b, C*H*H-6), 3.96 (m, 1H, CH-3), 3.13–3.01 (m, 1H, C*H*H-1), 2.73–2.47 (m, 3H, CH*H*-6, CH_2-7), 2.14–2.04 (m, 1H, C*H*H-2), 2.01–1.85 (m, 1H, CH*H*-2), 1.45 (s, 9H, CH_3), 1.39–1.27 (m, 1H, CH*H*-1); ^{13}C NMR (100 MHz, CD_3OD) δ 171.0, 158.1, 157.6, 156.7, 138.7, 116.0, 107.6, 102.2, 80.4, 57.2, 53.2, 40.8, 31.0, 29.5, 28.8 (2C); MS (ESI): m/z 371 ($M+Na^+$, 100%).

4.12. *tert*-Butyl (3*S*,11*bS*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-ylcarbamate (*cis*-26) and *trans*-26

To a mixture of the above mentioned diastereomeric mixture **25** (400 mg, 1.15 mmol) and K_2CO_3 (635 mg, 4.6 mmol) in dry DMF (6 mL) was added benzyl bromide (0.3 mL, 2.53 mmol) at room

temperature. After stirring for 12 h, the reaction was diluted with ice-water (50 mL) and the resulting mixture extracted with Et_2O (20 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered through a short pad of silica gel column eluting with EtOAc:PE = 1:5 to afford compound *cis*-**26** (498 mg, yield: 82.3%) as a white power, and *trans*-**26** (62 mg, yield: 10.2%) as a pale yellow gummy paste.

Compound *cis*-**26**: mp 117.0–120 °C (EtOAc/PE) {lit.[7] mp 118 °C}; $[\alpha]_D^{20}$ −102.8 (*c* 1.01, $CHCl_3$) {lit. $[\alpha]_D^{20}$ −102 (*c* 1.1, $CHCl_3$);[7] $[\alpha]_D^{24}$ −108.1 (*c* 1.97, $CHCl_3$)[9]}; IR (film) ν_{max}: 3399, 3064, 3033, 2975, 2927, 2869, 1713, 1658, 1610, 1494, 1427, 1363, 1311, 1274, 1162, 1095, 1058, 1024, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.29 (m, 10H, Ar), 6.48 (s, 1H, CH-10), 6.39 (s, 1H, CH-8), 5.75 (d, *J*=5.1 Hz, 1H, NH), 5.09 (d, *J*=12.4 Hz, 1H, OC*H*HPh), 5.05 (d, *J*=12.4 Hz, 1H, OCH*H*Ph), 4.99 (s, 2H, OCH_2Ph), 4.94–4.85 (m, 1H, CH-11b), 4.78–4.67 (m, 1H, C*H*H-6), 4.40–4.26 (m, 1H, CH_2-3), 2.87–2.74 (m, 2H, C*H*H-7, C*H*H-1), 2.74–2.65 (m, 1H, CH*H*-7), 2.62–2.51 (m, 1H, CH*H*-6), 2.51–2.40 (m, 1H, C*H*H-2), 1.46 (s, 9H, CH_3), 1.43–1.33 (m, 2H, CH*H*-1, CH*H*-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.4, 155.9, 155.7, 137.3, 136.7, 136.5, 128.8, 128.6, 128.11, 128.05, 127.5, 127.1, 117.4, 105.9, 99.0, 79.4, 70.2, 49.8, 48.8, 38.8, 29.7, 28.5, 28.4, 25.8; MS (ESI): *m*/*z* 529 ($M+H^+$, 4%), 551 ($M+Na^+$, 100%).

Compound *trans*-**26**: $[\alpha]_D^{20}$ +178.5 (*c* 0.5, $CHCl_3$) {lit. $[\alpha]_D^{20}$ +116 (*c* 1.35, $CHCl_3$);[7] $[\alpha]_D^{24}$ +182.2 (*c* 1.33, $CHCl_3$)[9]}; IR (film) ν_{max}: 3399, 3067, 3027, 2972, 2930, 2863, 1707, 1640, 1607, 1497, 1427, 1363, 1314, 1268, 1247, 1152, 1095, 1046, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.29 (m, 10H, Ar), 6.50 (d, *J*=2.2 Hz, 1H, CH-10), 6.37 (d, *J*=2.2 Hz, 1H, CH-8), 5.37 (s, 1H, NH), 5.06 (d, *J*=11.8 Hz, 1H, OC*H*HPh), 5.02 (d, *J*=11.8 Hz, 1H, OCH*H*Ph), 5.00 (d, *J*=11.8 Hz, 1H, OC*H*HPh), 4.99 (d, *J*=11.8 Hz, 1H, OCH*H*Ph), 4.95–4.88 (m, 1H, C*H*H-6), 4.78 (dd, *J*=11.0, 3.2 Hz, 1H, CH-11b), 4.06–3.96 (m, 1H, CH-3), 3.10–3.02 (m, 1H, C*H*H-1), 2.91–2.81 (m, 1H, C*H*H-7), 2.66–2.55 (m, 2H, CH*H*-6, CH*H*-7), 2.49–2.40 (m, 1H, C*H*H-2), 1.80–1.67 (m, 1H, CH*H*-2), 1.45 (s, 9H, $C(CH_3)_3$), 1.53–1.35 (m, 1H, CH*H*-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 158.1, 156.7, 156.1, 137.8, 136.7, 136.4, 128.6, 128.5, 128.0, 127.4, 127.1, 118.3, 106.0, 99.1, 79.4, 70.1, 70.0, 56.1, 52.7, 39.4, 30.5, 28.3, 28.0, 27.7; MS (ESI): *m*/*z* 551 ($M+Na^+$, 100%).

4.13. (*S*)-*N*-((3*S*,11*bS*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl)-16-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-((triethylsilyl)oxy) hexadecanamide (27)

A mixture of benzyl ester **20** (244 mg, 0.34 mmol), 10% Pd/C (24 mg), and 2,6-lutidine (0.084 mL, 0.72 mmol) in EtOH (1 mL) was stirred under an atmosphere of hydrogen (10 atm) for 3 h. The mixture was then filtered and concentrated under vacuum to give carboxylic acid **9** as a colorless oil, which was used immediately in the next step without further purification.

A mixture of compound *cis*-**26** (168 mg, 0.34 mmol) and 3 M HCl in ethyl acetate (3 mL) was stirred for 30 min at room temperature. The reaction was neutralized with a 1 M NaOH solution. The aqueous phase was extracted with ethyl acetate (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the free amine **8**, which was used directly in the next step without further purification.

A mixture of amine **8** (143 mg, 0.34 mmol), acid **9** (210 mg, 0.34 mmol), HOBt (54 mg, 0.40 mmol), EDCI (77 mg, 0.40 mmol), and NEt_3 (0.08 mL, 0.55 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 20 h. The mixture was then poured into water (2 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2, eluting with 30% EtOAc/PE) to give amide **27** (310 mg, 89% yield over three steps) as a colorless oil: $[\alpha]_D^{20}$ −55.0 (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 3423, 2921, 2855, 1644, 1615, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (m, 10H, Ar), 6.81 (d, *J*=5.2 Hz, 1H, NH), 6.48 (d, *J*=2.4 Hz, 1H, CH-10), 6.38 (d, *J*=2.4 Hz, 1H, CH-8), 5.08 (d, *J*=1.2 Hz, 2H, OCH_2Ph), 4.99 (s, 2H, OCH_2Ph), 4.96–4.91 (m, 1H, CH-11b), 4.76–4.70 (m, 1H, C*H*H-6), 4.58–4.50 (m, 1H, CH-3), 3.70–3.63 (m, 1H, CH-14′), 3.63–3.53 (m, 2H, CH-17′, CH-18′), 2.87–2.64 (m, 4H, CH_2-7, CH*H*-6, C*H*H-2, C*H*H-7), 2.54–2.45 (m, 1H, C*H*H-1), 2.25 (t, *J*=7.2 Hz, 2H, CH_2-2′), 1.71–1.60 (m, 4H), 1.55–1.42 (m, 8H), 1.38 (s, 6H, $C(CH_3)_2$), 1.33–1.24 (m, 34H), 0.97 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.88 (t, *J*=6.8 Hz, 3H, CH_3), 0.60 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 170.5, 158.4, 155.9, 137.1, 136.6, 136.4, 128.7, 128.6, 128.1, 128.0, 127.4, 127.0, 117.2, 107.7, 105.8, 99.0, 81.2, 81.0, 72.2, 70.1, 48.7, 38.8, 37.4, 36.7, 33.5, 33.0, 31.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.24, 29.21, 28.9, 28.5, 27.3, 26.0, 25.7, 25.2, 22.6, 14.0, 6.9, 5.1; MS (ESI): *m*/*z* 1059 ($M+Na^+$, 100%); HRESIMS calcd for $C_{64}H_{100}N_2O_7SiNa$ $(M+Na)^+$: 1059.7198; found: 1059.7182.

4.14. (14*S*,17*S*,18*S*)-*N*-((3*S*,11*bS*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-3-yl)-14,17,18-trihydroxyoctacosanamide (7)

A mixture compound **27** (225 mg, 0.217 mmol) and 2 M HCl (2 mL) in methanol (2 mL) was refluxed at 90 °C for 3 h. The reaction was then quenched with a 2 M NaOH solution (4 mL). The resulting mixture was extracted with EtOAc (5 mL×3). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (SiO_2, eluting with 80% EtOAc in PE) to give triol **7** (180 mg, yield: 95%) as a white solid. Mp 88–89 °C; $[\alpha]_D^{20}$ −61.0 (*c* 2.2, $CHCl_3$) {lit.[9] $[\alpha]_D^{24}$ −60.0 (*c* 7.8, $CHCl_3$)}; IR (film) ν_{max}: 3340, 2917, 2847, 1648, 1602, 1465, 1436, 1146, 1092, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 10H, Ar), 6.86 (d, *J*=4.8 Hz, 1H, NH), 6.47 (d, *J*=1.6 Hz, 1H, CH-10), 6.38 (d, *J*=1.6 Hz, 1H, CH-8), 5.08 (s, 2H, OCH_2Ph), 4.98 (s, 2H, OCH_2Ph), 4.96–4.91 (m, 1H, CH-11b), 4.75–4.69 (m, 1H, C*H*H-6), 4.58–4.51 (m, 1H, CH-3), 3.66–3.59 (m, 1H, CH-14′), 3.42 (d, *J*=4.4 Hz, 2H, CH-17′, CH-18′), 2.96–2.73 (m, 2H, C*H*H-7, CH*H*-6), 2.73–2.62 (m, 2H, C*H*H-2, CH*H*-7), 2.53–2.45 (m, 1H, C*H*H-1), 2.25 (t, *J*=6.4 Hz, 2H, CH_2-2′), 1.70–1.61 (m, 4H,), 1.58–1.40 (m, 8H), 1.35–1.20 (m, 34H), 0.88 (t, *J*=5.6Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.09, 170.45, 158.38, 155.83, 137.03, 136.59, 136.36, 128.68, 128.49, 128.01, 127.95, 127.35, 126.90, 117.08, 105.80, 99.00, 74.27, 74.21, 71.63, 70.03, 48.75, 48.67, 38.79, 37.38, 36.60, 33.41, 32.99, 31.79, 29.65, 29.54, 29.52, 29.48, 29.43, 29.32, 29.22, 29.14, 28.46, 25.66, 25.63, 25.17, 22.56, 14.00; HRESIMS calcd for $C_{55}H_{82}N_2O_7Na$ $(M+Na)^+$: 905.6020; found: 905.6018.

4.15. Schulzeine B (5)

A mixture of triol **7** (54 mg, 0.061 mmol) and sulfur trioxide–pyridine complex (98 mg, 0.61 mmol) in dry DMF (1 mL) was stirred at room temperature for 6 h then quenched with an aqueous NaOH solution (0.5 M, 0.25 mL). After being stirred for 1 h, the reaction mixture was concentrated under vacuum and passed through a Waters C_{18} Sep-Pak Vac® solid phase extraction cartridge and the cartridge was eluted with H_2O (5 mL), H_2O/MeOH (8:1, 5 mL), H_2O/MeOH (4:1, 5 mL), H_2O/MeOH (7:3, 5 mL), H_2O/MeOH (3:2, 5 mL), H_2O/MeOH (1:1, 5 mL), H_2O/MeOH (2:3, 5 mL), H_2O/MeOH (3:7, 5 mL), H_2O/MeOH (1:4, 5 mL), H_2O/MeOH (1:8, 5 mL) and MeOH (5 mL) to give an essentially pure compound **28**, which was immediately dissolved with methanol (3 mL) and 10% Pd/C (15 mg). Then the reaction mixture was placed under an atmosphere of H_2. After being stirred for 3 h, the mixture was then passed through a Waters C_{18} Sep-Pak Vac® solid phase extraction cartridge to remove the catalyst and the filtrate

concentrated under vacuum to give schulzeine B (**5**) (43 mg, 69% over two steps) as a white powder. Mp 183–185 °C; $[\alpha]_D^{20}$ −87.5 (*c* 0.8, MeOH) {lit. $[\alpha]_D^{24}$ −87.1 (*c* 0.10, MeOH);[9] $[\alpha]_D^{22}$ −23 (*c* 0.1, MeOH)[5]}; IR (film) ν_{max}: 3365, 2917, 2847, 1623, 1611, 1470, 1441, 1241, 1063 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 6.20 (d, *J*=1.6 Hz, 1H, CH-10), 6.13 (d, *J*=1.6 Hz, 1H, CH-8), 4.90–4.78 (m, 1H, CH-11b), 4.70–4.60 (m, 4H, CH-3, C*H*H-6, OCH-17′, OCH-18′), 4.42–4.36 (m, 1H, CH-14′), 2.78–2.67 (m, 2H, CH*H*-6, C*H*H-7), 2.67–2.53 (m, 2H, CH*H*-7, C*H*H-1), 2.29 (t, *J*=6.4 Hz, 3H, CH_2-2′, C*H*H-2), 1.98–1.87 (m, 2H, C*H*H-15′, C*H*H-16′), 1.80–1.50 (m, 9H, CH_2-3′, CH_2-13′, CH*H*-15′, CH*H*-16′, CH_2-19′, CH*H*-2), 1.47–1.20 (m, 35H, CH*H*-1, CH_2-4′–12′, CH_2-20′–27′), 0.88 (t, *J*=5.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 176.19, 171.85, 157.94, 156.13, 138.32, 115.01, 107.36, 102.02, 81.27, 80.06, 80.02, 51.74, 49.61, 40.47, 37.02, 35.45, 33.02, 31.64, 30.83, 30.76, 30.73, 30.70, 30.67, 30.64, 30.56, 30.43, 30.39, 30.33, 30.32, 30.25, 29.89, 28.96, 26.88, 26.84, 26.10, 25.89, 25.86, 23.67, 14.41; HRESIMS calcd for $C_{41}H_{67}N_2O_{16}S_3Na_2$ $(M-Na)^-$: 985.3448; found: 985.3440.

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