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Total Syntheses of Schulzeines B and C

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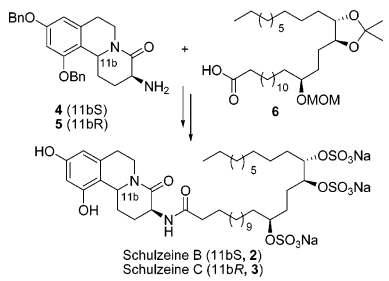
Received March 22, 2007



Schulzeines B (**2**) and C (**3**) were synthesized by a convergent strategy using epimeric tricyclic lactam building blocks, **4** and **5**, and the C28 fatty acid side chain **6**. Syntheses of tricyclic lactams (**4**/**5**) were achieved by Bischler−Napieralski reaction. Sharpless asymmetric dihydroxylation and BINAL-H-mediated asymmetric reduction of an enone was employed to prepare the key fatty acid side chain **6**. The spectral as well as analytical data of **2** and **3** were in good agreement with the reported data for the natural products, thus confirming their assigned structures.

In 2004, Fusetani and co-workers isolated three novel tetrahydroisoquinoline alkaloids designated schulzeines A−C (**1**−**3**) from a bioassay-guided isolation of hydrophilic extract of marine sponge *Penares schulzei* which inhibit yeast α-glucosidase at concentrations as low as 48 nM.[1] The constitution and the relative stereochemistry of schluzeines were elucidated by chemical degradation and by extensive 2D-NMR studies and the absolute configuration by application of Mosher method. Schluzeines encompass the 9,11-tetrahydroisoquinoline constellation and are characterized by a fused δ-lactam ring and a C28 sulfated fatty acid side chain linked via an amide bond.[2] The structural complexity and important biological activity of schulzeines A−C drew our attention with regards to their total synthesis. Apart from a recent synthesis of the tetrahydroisoquinoline subunit, no report has yet appeared on the total synthesis of any of these natural products.[3] Herein, we report the total syntheses of schulzeines B (**2**) and C (**3**) (Figure 1)

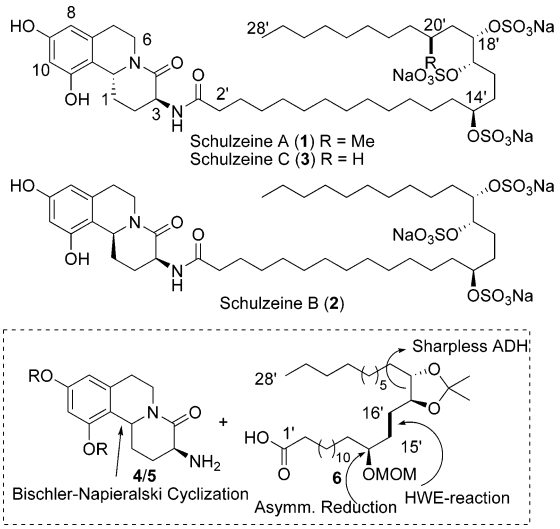


FIGURE 1. Schulzeines B and C

through a convergent strategy that features the Bischler−Napieralski reaction[4] to construct the key tetrahydroisoquinoline moiety of these molecules.

Inspection of structures **2** and **3** reveals that they have a common C28 fatty acid side chain and are epimeric at C11b of the tetrahydroisoquinoline unit. Retrosynthetically, we sought to address the synthesis of the tetrahydroisoquinoline unit by using the Bischler−Napieralski[4] reaction followed by a nonstereoselective reduction of the resulting dihydroisoquinoline. A convergent strategy toward the suitably protected C28 fatty acid was envisaged by the coupling of C1′−C15′ (**18**) and C16′−C28′ (**22**) building blocks via a HWE-reaction. The resulting enone en route should additionally provide access to the C14′−OH group. Our plan for the synthesis of C16′−C28′ subunit is founded upon the Sharpless asymmetric dihydroxylation.

The synthesis began with the EDC-HOBt-mediated coupling reaction between **7**[5] and **8**[6] to afford the amide derivative **9** in 84% yield (Scheme 1). Treatment of **9** with $POCl_3$ in $CHCl_3$ at 70 °C afforded **10**.[4b] Interestingly, the attempted reduction[7] of **10** with $NaCNBH_3$ and subsequent stirring with aq $NaHCO_3$ also brought requisite cyclization resulting in the tricyclic derivatives **11** and **12** (2:3), which are separated by simple column chromatography and characterized by 2D-NMR spectral studies. The observed n*O*es between H-3 and H-11b in the NOESY spectrum of **11** clearly indicated a *cis*-relationship. Following a sequence of simple protecting group manipulations,

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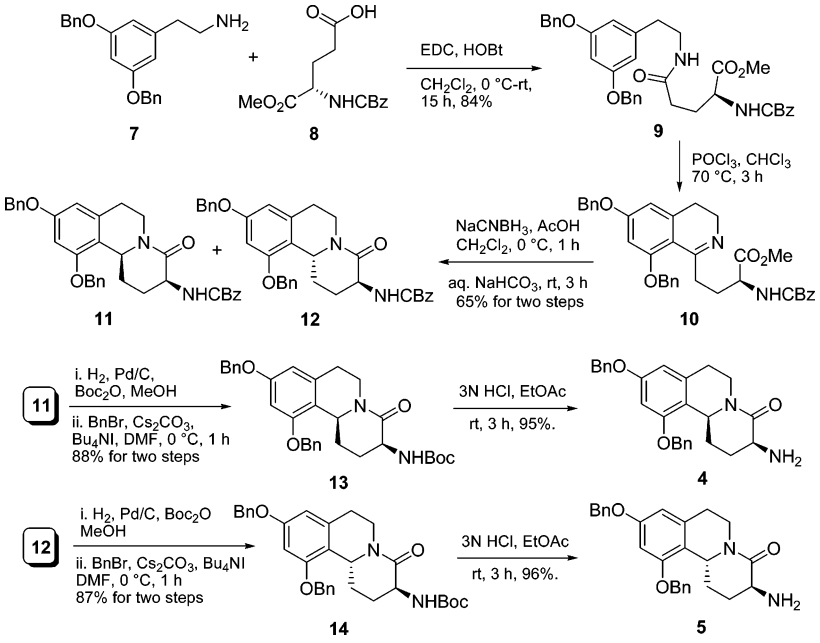
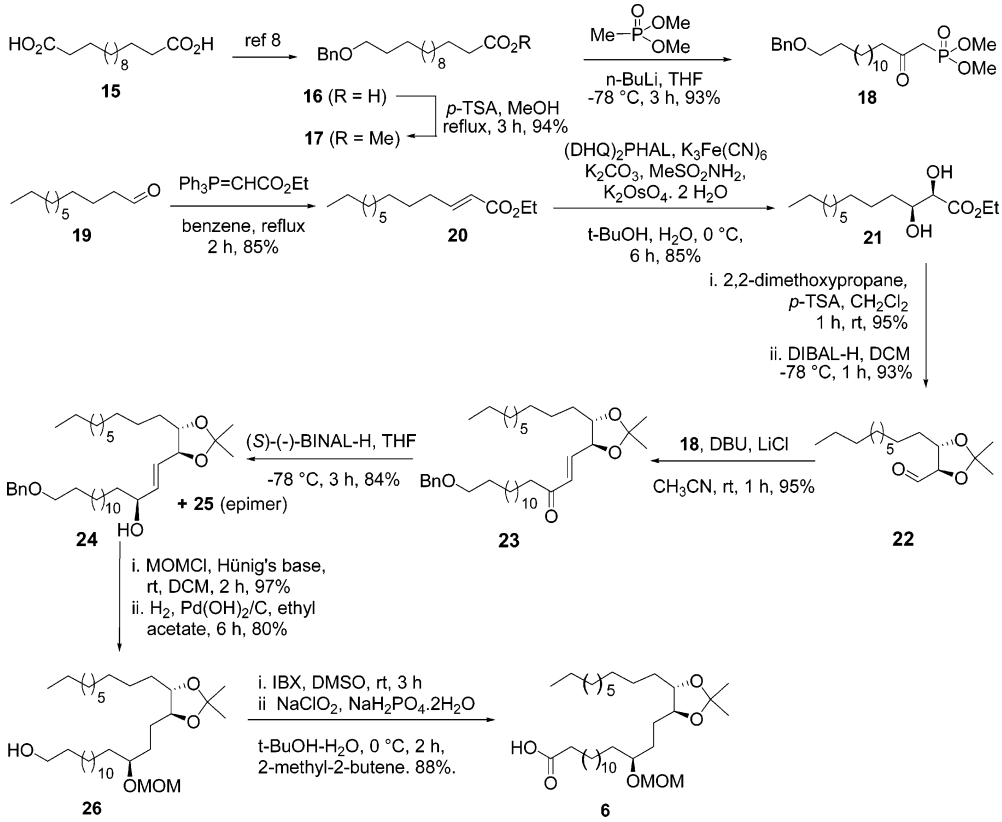
10.1021/jo070560h CCC: $37.00
Published on Web 07/14/2007

SCHEME 1. Synthesis of 4 and Its 11-*epi*-Diastereomer 5



SCHEME 2. Synthesis of C28 Fatty Acid 6



11 and **12** were transformed to requisite amines **4** and **5**, respectively.

The construction of the C28 fatty acid side chain began with the syntheses of the C15 and C13 subunits. Following the available literature protocol,[8] commercially available 1,12-dodecanedicarboxylic acid (**15**) was converted to the acid **16**, and subjected to acid-catalyzed esterification to afford the methyl ester **17**. Treatment of **17** with lithiated methyldimethylphosphonate provided the requisite C15 subunit **18** in excellent yield (Scheme 2).[9] Synthesis of the C13 subunit started with the two-carbon homologation of undecan-1-al (**19**)[10] using ethoxycar-

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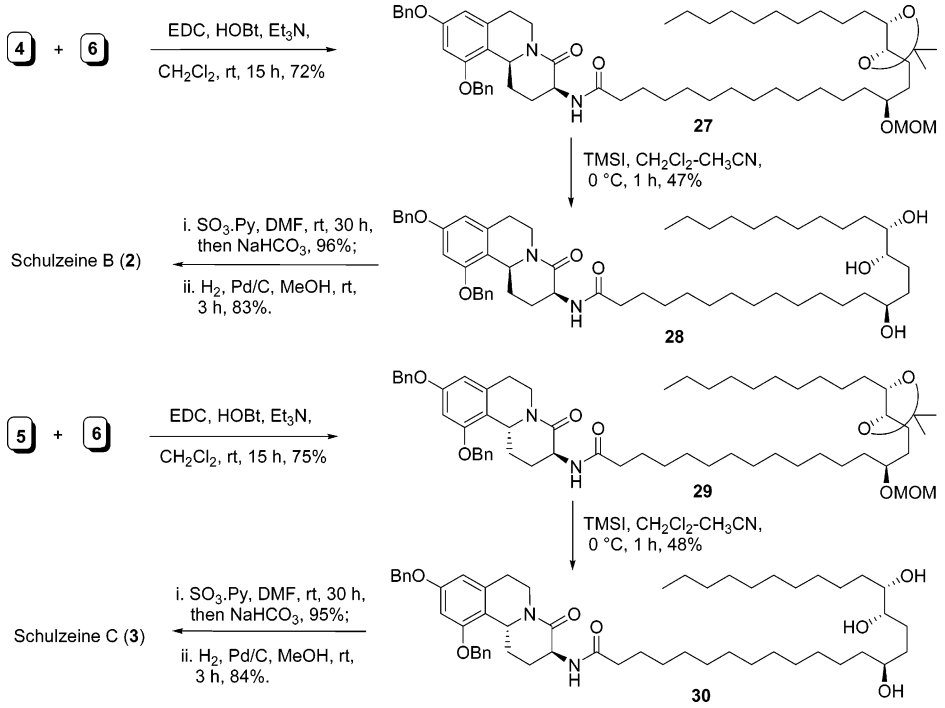
SCHEME 3. Synthesis of Schulzeines B (2) and C (3)



bonyl-methylene-triphenylphosphorane in CH_2Cl_2, affording **20** as a mixture of *E*/*Z*-isomers (85:15). Asymmetric dihydroxylation of **20***E* using $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, and $K_2OsO_4{\cdot}2H_2O$ in ^{t}BuOH:H_2O (1:1) at 0 °C for 6 h gave the dihydroxy derivative **21** in 85% yield.[10,11] Protection of **21** as an isopropylidene derivative followed by controlled reduction with DIBAL-H gave the C13 aldehyde **22**.

With both the C15 and C13 subunits in hand, we addressed the HWE coupling which would provide the side chain fatty acid unit. After exploring a variety of bases, we concluded that the key HWE-reaction between **18** and **22** can be successfully carried out using DBU−LiCl[12] and resulted exclusively with formation of enone **23** with *E*-configuration. In the ^{1}H NMR spectrum of **23**, the olefinic protons appeared at δ 6.36 and δ 6.70 as doublet of doublets ($J_{15,16}$ = 15.8 Hz) thus confirming the assigned *E*-configuration. The resulting enone **23** was reduced with (*S*)-(−)-BINAL-H in THF at −78 °C to afford **24** and its (14′*R*)-isomer **25** in 11:1 ratio.[13] The absolute configuration of the newly created center in major isomer **24** was established by application of Mosher method.[14] In order to avoid the use of (*S*)-(−)-BINAL-H, which is required in stoichiometric quantities, the reduction of enone **23** was attempted under Luche's conditions[15] to afford a 2:3 mixture of **24** and its epimer **25**. Interestingly, when the aforementioned ketone reduction was attempted with K-Selectride,[16] the diastereoselectivity was reversed, and the undesired diastereomer **25** was obtained as the major product. Protection of the free hydroxyl group in **24** as its MOM ether followed by hydrogenolysis gave **26** in 78% over the two steps. Oxidation of **26** to the corresponding aldehyde with IBX followed by further oxidation with $NaClO_2$ in ^{t}BuOH at 0 °C gave the C28 fatty acid **6**.With all three required fragments **4**−**6** now available, their assembly into the target molecules **2** and **3** became our next task. EDC−HOBt-mediated coupling of amine **4** with the free carboxylic acid **6**, was facile and afforded the coupled product **27**. TMSI[17] mediated deprotection of the acetonide and MOM-protecting groups in **27** gave the triol **28** in 47% yield. To this end, persulfation of triol **28** using $SO_3{\cdot}$Py in DMF[18] followed by debenzylation afforded schulzeine B (**2**) in 80% yield over two steps. Similarly, starting with **5** and following a same sequence of reactions, the synthesis of schulzeine C (**3**) was completed. The spectral as well as the analytical data of

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(17) (a) Jung, M. A.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. (b) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *48*, 4175. (c) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron. Lett.* **1984**, *25*, 2515.

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synthetic **2** and **3** nicely matched with the reported data of the natural products, thus confirming the assigned relative and absolute stereochemistry of schulzeines B and C.

In summary, the first total syntheses of schulzeines B and C are documented. Bischler−Napieralski reaction for the construction of key tetrahydroisoquinoline moieties, Sharpless asymmetric dihydroxylation and BINAL-H-mediated asymmetric reduction of an enone for the preparation of side chain C28 fatty acid, were employed. The reported approach is convergent in nature and provides considerable flexibility for the synthesis of related nonnatural analogues.

Experimental Section

Benzyl (3*S*,11b*S*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido-[2,1-*a*]isoquinolin-3-ylcarbamate (11) and Benzyl (3*S*,11b*R*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido-[2,1-*a*]isoquinolin-3-ylcarbamate (12). A mixture of compound **9** (3.6 g, 5.90 mmol), $POCl_3$ (10 mL), and dry $CHCl_3$ (10 mL) was heated under reflux for 3 h, concentrated, and co-distilled with benzene. The residue was triturated with cold hexane (30 mL) and decanted. The reddish gum was dissolved in glacial acetic acid (5 mL) and methylene chloride (30 mL) and cooled to 0 °C, and then solid sodium cyanoborohydride (1.30 g, 20.68 mmol) was added. After 1.5 h, saturated sodium bicarbonate solution was introduced until the reaction mixture rendered basic. After 3 h of stirring at room temperature, it was diluted with dichloromethane, and the layers were separated. The aqueous layer was extracted with dichloromethane (30 mL × 3). The combined layers were washed with water, dried over Na_2SO_4, and evaporated, and the orange residue was purified on silica gel column using ethyl acetate and light petroleum (1:3) to give the *cis*-isomer **11** (860 mg, 26%) as a solid; mp 130 °C, $[\alpha]_D = -82.2$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) υ_{max} (cm^{-1}): 3408, 3019, 1797, 1718, 1655, 1609, 1499, 1441, 1147; ^1H NMR (200 MHz, $CDCl_3$): δ 7.40−7.29 (m, 15H), 6.45 (d, $J = 2.1$ Hz, 1H), 6.37 (d, $J = 2.1$ Hz, 1H), 6.05 (d, $J = 5.3$ Hz, 1H), 5.12 (s, 2H), 5.08 (s, 2H), 4.99 (s, 2H), 4.90 (dd, $J = 10.6$, 4.0 Hz, 1H), 4.75−4.69 (m, 1H), 4.36 (m, 1H), 2.89−2.40 (m, 5H), 1.48−1.34 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): δ 170.0, 158.4, 156.0, 155.8, 137.2, 136.6, 136.4, 136.4, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.4, 127.0, 117.1, 105.7, 98.9, 70.0, 66.6, 50.0, 48.7, 38.8, 29.6, 28.3, 25.5; MS (ESI) *m*/*z*: Calcd for (M^+ + Na) 585.25. Found: 585.63; Anal. Calcd for $C_{35}H_{34}N_2O_5$: C, 74.71; H, 6.09; N, 4.98. Found: C, 74.93; H, 6.02; N, 4.88.

Further elution gave the *trans*-isomer **12** (1.3 g, 39%) as a liquid, $[\alpha]_D = +93.6$ (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) υ_{max} (cm^{-1}) 3405, 3019, 1797, 1720, 1650, 1609, 1499, 1441, 1147; ^1H NMR (200 MHz, $CDCl_3$): δ 7.42−7.26 (m, 15 H), 6.47 (d, $J = 2.2$ Hz, 1H), 6.34 (d, $J = 2.2$ Hz, 1H), 5.70 (br s, 1H), 5.09 (s, 2H), 5.02 (d, $J = 2.5$ Hz, 2H), 5.00 (s, 2H), 4.96−4.87 (m, 1H), 4.77 (dd, $J = 10.9$, 3.4 Hz, 1H), 4.04 (m, 1H), 3.08−3.02 (m, 1H), 2.93−2.73 (m, 1H), 2.66−2.43 (m, 3H), 1.77 (dt, $J = 13.5$, 12.3 Hz, 1H), 1.54−1.34 (m, 1H); ^{13}C (50 MHz, $CDCl_3$): δ 168.3, 158.0, 156.6, 156.3, 137.7, 136.6, 136.4, 136.3, 128.5, 128.4, 128.4, 128.2, 127.9, 127.9, 127.7, 127.3, 126.9, 118.1, 106.0, 99.0, 70.0, 69.9, 66.4, 55.8, 52.7, 39.3, 30.4, 27.9, 27.3; MS (ESI) *m*/*z*: Calcd for (M^+ + Na) 585.25. Found: 585.63; Anal. Calcd for $C_{35}H_{34}N_2O_5$: C, 74.71; H, 6.09; N, 4.98. Found: C, 74.85; H, 5.95; N, 4.76.

(*S*)-16-((4*S*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-(methoxymethoxy)hexadecanoic Acid (6). Iodoxybenzoic acid (IBX) (140 mg, 0.5 mmol) and **26** (200 mg, 0.4 mmol) in DMSO (4 mL) were stirred at room temperature for 3 h, diluted with H_2O (3 mL), and filtered. The filtrate was extracted with diethyl ether (10 mL × 2), washed with $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and concentrated. To the crude aldehyde (200 mg, 0.4 mmol), ^{t}BuOH (2 mL), $NaH_2PO_4{\cdot}2H_2O$ (190 mg, 1.2 mmol), 2-methyl-2-butene (0.2 mL) was added dropwise a solution of $NaClO_2$ (110 mg, 1.2 mmol) in water (1 mL). After 2 h, the reaction mixture was diluted with water, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified on silica gel by eluting with ethyl acetate and light petroleum (1:4) to give **6** (180 mg, 88%) as light-yellow oil. $[\alpha]_D = -15.1$ (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) υ_{max} (cm^{-1}) 3012, 2987, 2855, 2928, 1710, 1465, 1379; ^1H NMR (200 MHz, $CDCl_3$): δ 4.65 (s, 2H), 3.62−3.52 (m, 3H), 3.38 (s, 3H), 2.34 (t, $J = 7.3$ Hz, 2H), 1.73−1.48 (m, 10H), 1.37 (s, 6H), 1.26 (m, 34H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.3, 107.8, 95.4, 81.2, 81.0, 77.6, 55.5, 34.4, 34.0, 33.0, 31.9, 29.8 (2C), 29.6 (2C), 29.4, 29.3, 29.2, 29.1, 28.8, 27.3, 26.1, 25.2, 24.7, 22.7, 14.1; MS (ESI) *m*/*z*: Calcd for (M^+ + Na) 579.47. Found: 579.19; Anal. Calcd for $C_{33}H_{64}O_6$: C, 71.18; H, 11.58. Found: C, 71.00; H, 11.75.

Schulzeine B (2). Sulfur trioxide−pyridine complex (110 mg, 0.69 mmol) was added to a solution of the **28** (20 mg, 0.023 mmol) in dry DMF (3 mL) under nitrogen and then stirred at room temperature for 30 h. The reaction mixture was basified by adding saturated $NaHCO_3$ solution. After stirring for 30 min, the resulting solution was concentrated in vacuo. The residue was triturated with ethyl acetate and filtered. The residue was purified on a silica gel column using methanol and ethyl acetate (1:4) to afford the sulfate salt (27 mg, 96%). $[\alpha]_D = -24.0$ (*c* 0.5, CH_3OH); IR (Nujol) υ_{max} (cm^{-1}) 2923, 2853, 1631, 1464, 1378, 1221, 1109, 1090, 824; ^1H NMR (400 MHz, CD_3OD): δ 7.42−7.28 (m, 10 H), 6.57 (d, $J = 2.1$ Hz, 1H), 6.45 (d, $J = 2.1$ Hz, 1H), 5.09 (d, $J = 6.8$ Hz, 2H), 5.03 (s, 2H), 4.90 (dd, $J = 11.0$, 3.8 Hz, 2H), 4.65 (m, 2H), 4.59 (dd, $J = 9.7$, 7.9 Hz, 1H), 4.36 (m, 1H), 2.78−2.69 (m, 3H), 2.50 (m, 1H), 2.26 (t, $J = 7.4$ Hz, 2H), 2.21 (m, 1H), 1.95−1.90 (m, 2H), 1.87−1.81 (m, 1H), 1.75−1.50 (m, 10H), 1.45−1.36 (m, 3H), 1.30−1.22 (m, 30H), 0.87 (t, $J = 6.6$ Hz, 3H); ^{13}C (100 MHz, CD_3OD): δ 176.1, 171.7, 159.8, 157.3, 138.6, 138.4, 138.2, 129.6, 129.4, 129.0, 128.8, 128.4, 128.3, 118.1, 107.4, 100.1, 81.1, 79.9, 78.8, 71.2, 71.0, 51.3, 49.5, 40.1, 36.9, 35.3, 32.9, 31.5, 30.8, 30.7, 30.7, 30.6, 30.5, 30.4, 30.3, 30.2, 29.7, 29.3, 26.8, 25.9, 25.8, 25.7, 24.2, 23.6, 14.4; MS (ESI) *m*/*z*: Calcd for (M^+ + Na) 1211.43. Found: 1211.48.

A solution of resulting sulfate salt (24 mg) and 10% Pd/C in methanol (4 mL) was hydrogenated at normal temperature and pressure for 3 h and filtered. The catalyst was washed with methanol (2 × 2 mL), and the combined filtrate was concentrated to obtain schulzeine B (**2**) (17 mg, 83%). $[\alpha]_D = -24.4$ (*c* 0.6, CH_3OH); lit. $[\alpha]_D = -23$ (*c* 0.1, CH_3OH), IR (Nujol) υ_{max} (cm^{-1}) 3416, 2923, 2853, 1628, 1460, 1376, 1220, 1063, 1002, 773; ^1H NMR (400 MHz, CD_3OD): δ 6.21 (d, $J = 2.3$ Hz, 1H), 6.13 (d, $J = 2.3$ Hz, 1H), 4.84 (m, 1H), 4.64 (m, 4H), 4.36 (m, 1H), 2.74−2.53 (m, 4H), 2.28 (t, $J = 7.5$ Hz, 2H), 2.24 (m, 1H), 1.93 (m, 2H), 1.85 (m, 1H), 1.77−1.53 (m, 10H), 1.45−1.37 (m, 3H), 1.28 (m, 30H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C (100 MHz, CD_3OD): δ 176.2, 171.8, 157.9, 156.1, 138.3, 115.0, 107.3, 101.9, 81.2, 80.0, 80.0, 51.7, 49.6, 40.4 37.0, 35.4, 31.6, 30.8, 30.7, 30.7, 30.5, 30.4, 30.3, 30.3, 30.2, 29.8, 28.9, 26.9, 26.8, 26.0, 25.9, 23.6, 14.4; ^1H NMR (400 MHz, pyridine-d_5): δ 8.26 (d, 1H, $J = 6.85$ Hz), 6.89 (d, 1H, $J = 2.03$ Hz), 6.61 (d, 1H, $J = 2.03$ Hz), 5.79 (m, 1H), 5.47 (m, 1H), 5.25 (dd, 1H, $J = 11.0$, 4.0 Hz), 5.17−5.09 (m, 2H), 5.99 (m, 1H), 2.91−2.62 (m, 4H), 2.50 (t, 2H, $J = 7.34$ Hz), 2.40 (m, 1H), 2.16 (m, 2H), 1.96 (m, 1H), 1.91−1.55 (m, 10 H), 1.45 (m, 3H), 1.31−1.22 (m, 30 H), 0.92 (t, 3H, $J = 6.8$ Hz). MS (ESI) *m*/*z*: Calcd for (M^+ + Na) 1031.33. Found: 1031.71.

Acknowledgment. C.P. and D.B. thank CSIR (New Delhi) for financial assistance in the form of a research fellowship.

Supporting Information Available: Experimental procedures, spectral and analytical data for all new compounds (**9**, **13**−**14**, **17**−**18**, **21**−**30**, and **3**) and representative ^1H and ^{13}C spectra of (**2**−**3**, **6**, **9**, **11**−**14**, **17**−**18**, **21**, and **23**−**30**) and NOESY (**11**−**12**). This material is available for free of charge via the Internet at http://pubs.acs.org.

JO070560H