First Synthesis of Marine Sponge Alkaloid Niphatoxin B

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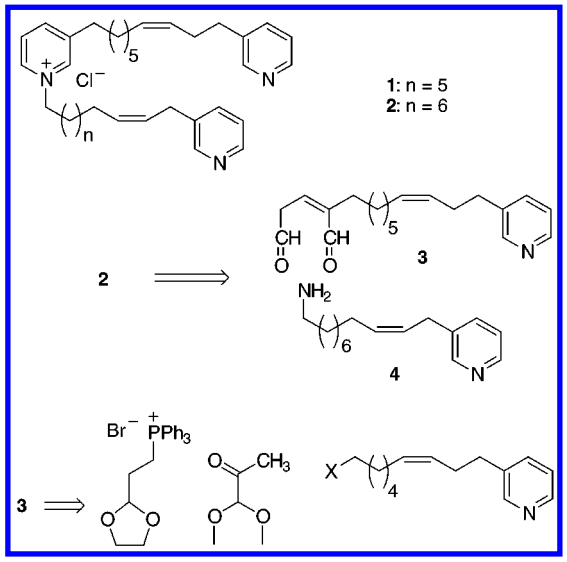
In 1992, Talpir et al. reported the isolation and structure elucidation of niphatoxins A (**1**) and B (**2**), two ichthyo- and cytotoxic (IC_{50} = 0.1 μg/mL, P388) tripyridine alkaloids.[1,2] These Red Sea sponge alkaloids, isolated from a Niphates sp., belong to an emerging and intriguing class of marine secondary metabolites which are related to each other by their apparent biogenetic origin from 3-alkylpyridine or reduced 3-alkylpyridine units.[3] Among them niphatoxins are unique in having three pyridine units and a substructure in which two pyridine rings are linked through their 3 positions to the same alkyl chain. Whereas other members of this group have become subjects of total syntheses or synthetic studies,[4] no synthesis of niphatoxins has been reported up to now. Herein we report the first total synthesis of niphatoxin B (**2**) based on a novel approach to glutaconaldehyde bisacetals.[5] The retrosynthetic analysis for our approach is outlined in Scheme 1. Disconnections of the two C−N bonds in the pyridinium moiety lead to a 3-(ω-aminoalkyl)-pyridine **4** and 2-substituted glutaconaldehyde **3** which in turn could be divided via its bisacetal into two commercially available three carbon fragments and a 3-alkylpyridine unit. Na^+- and K^+-salts of glutaconaldehyde enolates have been used as starting materials to prepare pyridines by reaction with ammonium salts.[5] These glutaconaldehyde salts, however, have been obtained from pyridine by ring opening reactions, and not from acyclic starting materials. In a new biogenetic hypothesis, amino derivatives of glutaconaldehyde were proposed as key intermediates in the biosynthesis of manzamine alkaloids.[6]

Scheme 1



Our efforts were first directed to exploring the feasibility of the envisioned key reactions with simple model compounds. Phosphonium salt **5** was deprotonated with *n*-BuLi in THF at −20 °C, and the resulting ylide was reacted with 1,1-dimethoxy-2-propanone (**6**) to give olefination product **7** in 54% yield as a 9:1 mixture of *E*/*Z*-isomers. Bearing in mind the low stability of glutaconaldehyde in its free form,[5] we planned to subject intermediate **3** to the cyclocondensation with the amine **4** without prior isolation. Acid treatment of **7** until disappearance of the starting material (TLC), addition of cyclohexylamine and Et_3N, and reflux in *n*-butanol gave disappointing results, probably due to decomposition of the resulting 2-methylglutaconaldehyde under the conditions of acetal hydrolysis. Finally, short treatment of **7** with $FeCl_3$,[7] adsorbed on silica gel, in CH_2Cl_2 prior to addition of cyclohexylamine hydrochloride and Et_3N, removal of CH_2Cl_2, and reflux in *n*-butanol afforded pyridinium salt **8** in 39% yield after column chromatography.

We next turned our attention to the preparation of the required glutaconaldehyde bisacetal. Known aldehyde[8] **10** was prepared in 38% and 90% yields by oxidation of THP-protected bromo alcohol **9** using pyridine *N*-oxide or trimethyamine *N*-oxide,[9] respectively. (*Z*)-Selective Wittig olefination of aldehyde **10** with phosphonium salt

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(1) Talpir, R.; Rudi, A.; Ilan, M.; Kashman, Y. *Tetrahedron Lett.* **1992**, *33*, 3033−3034.

(2) The structural formula given in ref 1 on page 3034 appears to be incorrect in respect to the molecular formulas in the text. Structural formula given on page 3034 corresponds to molecular masses of 524 and 538 u, whereas molecular masses given in the text are 510 and 524 u. Comparison of the masses of pyridinealkyl fragments resulting from cleavage of the C−N bond in the text (216 and 230) with the masses of these units in the structural formula (230 and 244) shows that one methylene unit in the N^+-alkyl chain should be omitted. The same incorrect structural formula appears also in ref 3.

(3) For an excellent recent review, see: Andersen, R. J.; Van Soest, R. W. M.; Kong, F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: Elsevier Science: Oxford, U.K., 1996; Vol. 10, pp 301−355.

(4) Manzamines, ircinol A, and ircinal A: (a) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425−6426. (b) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201−6258 and references therein. Xestospongines: (c) Baldwin, J. E.; Melman, A.; Lee, V.; Firkin, C. R.; Whitehead, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 8559−8560 and references therein. Petrosines: (d) Heathcock, C. H.; Brown, R. C. D.; Norman, T. C. *J. Org. Chem.* **1998**, *63*, 5013−5030 and references therein. Sarains: (e) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 8096−8097 and references therein. Mandangamin: (f) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 1920−1921. Cyclostellettamines: (g) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026−8034. (h) Baldwin, J. E.; Spring, D. R.; Atkinson, C. E.; Lee, V. *Tetrahedron* **1998**, *54*, 13655−13680 and references therein. Haliclamines: (i) Morimoto, Y.; Yokoe, C.; Kurihara, H.; Kinoshita, T. *Tetrahedron* **1998**, *54*, 12197−12214 and references therein. Halicyclamine A and keramaphidine B: (j) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem.* **1998**, *110*, 2806−2808 and references therein. Niphatesines and theonelladins: (k) Bracher, F.; Papke, T. *Monatsh. Chem.* **1996**, *127*, 91−95 and references therein. (l) Teubner, A.; Gerlach, H. *Liebigs Ann. Chem.* **1993**, 161−165. Polymeric 3-alkylpyridinium alkaloids: (m) ref 4g and references therein.

(5) For glutaconaldehyde and its derivatives, including glutaconaldehyde bisacetals, see: Becher, J. *Synthesis* **1980**, 589−612.

(6) Reference 4g.

(7) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404−407.

(8) Mancini et al. prepared aldehyde **10** from bromide **9** using DMSO as an oxidant: Mancini, I.; Guella, G.; Pietra, F. *Helv. Chim. Acta* **1991**, *74*, 941−950.

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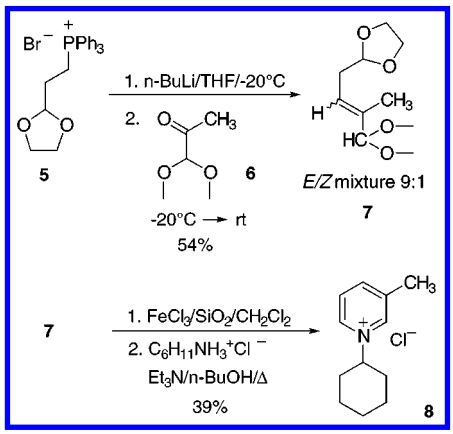
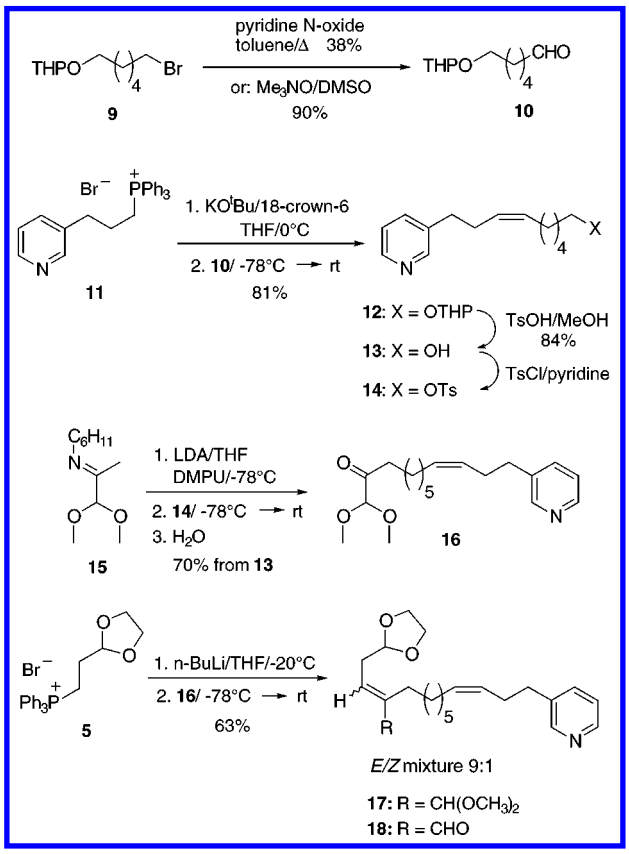
Scheme 2



Scheme 3



11,[10] using potassium *tert*-butoxide in the presence of 18-crown-6 as a base, afforded (*Z*)-alkene **12** nearly as a single geometrical isomer (*E*-isomer < 2%). Deprotection to alcohol **13** and subsequent treatment with TsCl/pyridine led to tosylate **14** which was used immediately without purification for the next step to prevent polymerization. Imine **15**[11] was deprotonated with LDA in THF at −78 °C, and the resulting lithio enamine was alkylated with tosylate **14**. Hydrolysis of the imine functionality upon aqueous workup provided ketone **16** in 70% yield. Wittig reaction of **16** with the ylide generated from phosphonium salt **5** furnished glutaconaldehyde precursor **17** as a 9:1 mixture of *E*/*Z*-isomers in 63% yield. In contrast to ketone **6** (Scheme 2), the use of an excess (4.7 equiv) of ylide and a modified temperature protocol were found essential to achieve this result. In some experiments **17** was accompanied by minor amounts (<15%) of aldehyde **18** arising from dimethyl acetal hydrolysis which was of no consequence for the subsequent reaction. This sequence allowed us to obtain glutaconaldehyde precursor **17** in 27% overall yield in six steps starting from **9** (Scheme 3).

For the construction of the amine component **4**, propyn-1-ol was deprotonated with *n*-BuLi, and the resulting dianion was alkylated with THP-protected bromo alcohol **19**, giving the known propargyl alcohol **20**[12] which was treated with CBr_4/PPh_3[13] to provide bromide **21** (Scheme 4). Generation of the enolate[14] from ester **22**, followed by addition of bromide **21**, afforded alkylation product **23** which was reduced with $LiAlH_4$ to alcohol **24**. Partial hydrogenation using Lindlar catalyst and subsequent Swern oxidation gave glutaraldehyde monoacetal **26**. Glutaraldehyde−pyridine cyclization[15] and THP deprotection to pyridine alcohol **27** were achieved in one laboratory step by treatment with hydroxylammonium chloride in refluxing ethanol. Tosylation, azide substitution, and reduction afforded amine **4** which was isolated as its dihydrochloride salt **4a**. The overall yield of this 10-step sequence starting from **19** was 4.3%.

With both components in hand, the stage was set for the condensation of **17** and **4** to niphatoxin B. Glutaconaldehyde **3** (Scheme 1) was liberated by hydrolysis of the acetal functionalities, applying the conditions found in the model reaction with bisacetal **7**, and cyclized in situ with amine **4** to give niphatoxin B (**2**) in 45% yield after column chromatography.

^1H and ^{13}C NMR data[16] of synthetic niphatoxin B (**2**) were identical with those reported for the natural product.[1] In the FAB-MS, synthetic **2** revealed a base peak at *m*/*z* 524 and prominent peaks at *m*/*z* 295 and 230 which were assigned to $[M^+]$ and the fragments of C−N cleavage, respectively. The dimethylation product of synthetic niphatoxin B showed the same behavior in ^1H and ^{13}C NMR experiments[17] as that of natural niphatoxin.[1]

In conclusion, the first synthesis of niphatoxin B has been accomplished. We have shown that the reaction of primary amines with 2-substituted glutaconaldehydes, generated in situ from the corresponding bisacetals, provides a practical entry to 3-substituted pyridinium salts for which classical approaches, i.e., halide or sulfonate displacement by pyridines, are not considered convenient. Our protocol allows the synthesis of pyri-

(9) For oxidation with pyridine *N*-oxide: (a) Waugh, K. M.; Berlin, K. D. *J. Org. Chem.* **1984**, *49*, 873−878. With trimethylamine *N*-oxide: (b) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825−4826.

(10) Prepared in one step from commercially available 3-(3-pyridyl)-1-propanol in 80% yield: Staab, H. A.; Zipplies, M. F.; Müller, T.; Storch, M.; Krieger, C. *Chem. Ber.* **1994**, *127*, 1667−1680.

(11) Cuvigny, T.; Normant, H. *Synthesis* **1977**, 198−200.

(12) Vig et al. used $LiNH_2$/liquid NH_3 for this conversion: Vig, O. P.; Sharma, M. L.; Kapur, J.; Thapar, S.; Gupta, R. *Indian J. Chem. Sect. B* **1990**, *29*, 606−610.

(13) Harnden, M. R.; Jarvest, R. L. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2777−2784

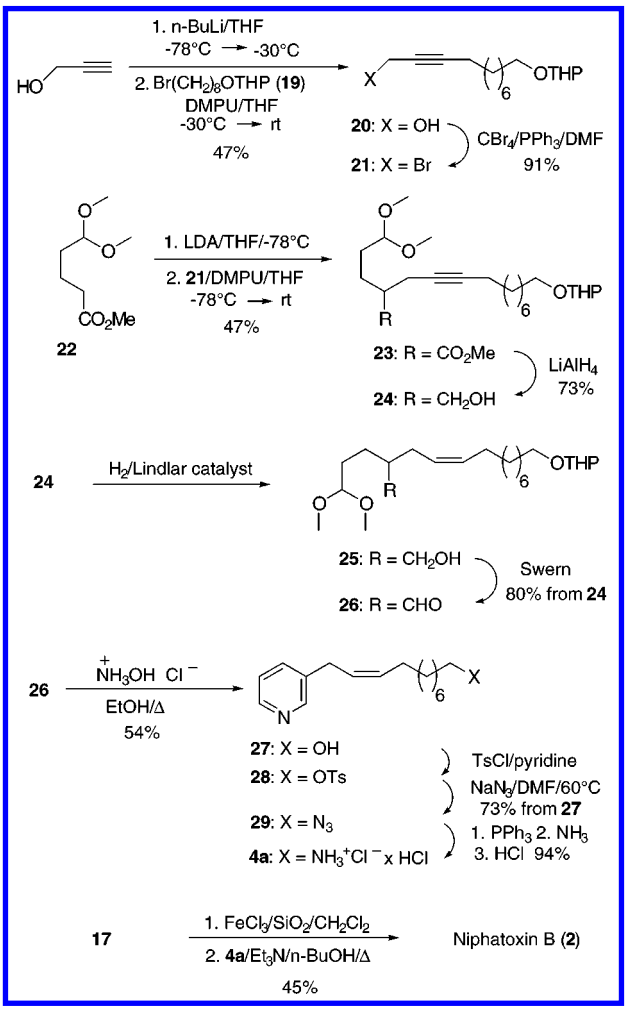
(14) Cooke, M. P., Jr.; Gopal, D. *J. Org. Chem.* **1994**, *59*, 260−263.

(15) Spitzner, D. In *Houben-Weyl−Methoden der Organischen Chemie*, 4th ed.; Kreher, R. P., Ed.; Thieme: Stuttgart, 1992; Vol. E7b, pp 301−304.

(16) Since our ^1H and ^{13}C NMR data of synthetic **2** matched exactly those reported for the natural product when recorded in CD_3OD, we assume that also Talpir et al. used CD_3OD as the solvent for their NMR experiments and not $CDCl_3$ as stated in ref 1. Especially the ^1H NMR chemical shifts of the pyridinium protons show strong solvent dependence. For details, see the Experimental Section.

(17) See the Supporting Information.

Scheme 4



dinium salts in only three steps from acyclic starting materials[18] by the sequence of (a) alkylation of 1,1-dimethoxy-2-propanone via its azaenolate, (b) Wittig olefination with 2-(1,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide, and (c) cyclization with a primary amine. It should be equally useful for making a range of analogues for biological investigations.

Experimental Section

General. Compounds **9** and **19** were prepared according to literature procedures[8,19,20] from the corresponding diols. Commercial reagent grade solvents and chemicals were used as obtained except as indicated below. DMPU (absolute, puriss. over molecular sieve) was purchased from Fluka and DMSO (dried) from Merck. THF was distilled from sodium benzophenone ketyl. Pyridine and Et_3N were stored over KOH pellets. Prior to use in Swern oxidation, CH_2Cl_2 was distilled from P_2O_5. Petroleum ether refers to the 40−60 °C boiling fraction. Solvents used for column chromatography were distilled prior to use. All metallorganic reactions were run in flame-dried glassware under nitrogen. Organic extracts were dried over anhydrous Na_2SO_4. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Merck Kieselgel 60 F_{254} and Merck aluminum oxide 60 F_{254} neutral) were used, and column chromatography was done by using Merck Kieselgel 60 and Merck aluminum oxide 90 (70−230 mesh, activity II−III). Spots were visualized with ultraviolet light (254 nm) or detected by exposure to iodine fumes. Infrared spectra were recorded with an FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained at 250 and 62 MHz, respectively. Compounds which were not submitted for or did not pass elemental analysis were judged to be of >95% purity on the basis of TLC homogenity and ^{1}H NMR analyses (see Supporting Information).

1,1-Dimethoxy-4-(1,3-dioxolan-2-yl)-2-methylbut-2-ene (7) (*E*/*Z*-mixture). Phosphonium salt **5** (8.87 g, 20 mmol) was suspended in THF (60 mL) and cooled to −20 °C. *n*-BuLi (12.5 mL, 20 mmol, 1.6 M in hexane) was added dropwise under a nitrogen atmosphere. After 1 h at this temperature, ketone **6** (2.48 g, 21 mmol) in THF (10 mL) was added. The cooling bath was removed, and stirring was continued for 16 h. Water (300 mL) was added, the layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (0.05 Torr, ot 50 °C) to afford **7** (2.2 g, 54%, 9:1 mixture of *E*/*Z*-isomers) as colorless oil. IR (film): 2890, 2830 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.64 (m, 0.1 H) and 5.52 (m, 0.9 H), 4.93 (d, J = 0.9 Hz, 1 H), 4.89 (t, J = 4.8 Hz, 1 H), 3.80−4.05 (m, 4 H), 3.34 (s, 5.4 H) and 3.29 (s, 0.6 H), 2.49−2.57 (m, 2 H), 1.70−1.75 (m, 2.7 H), and 1.62−1.65 (m, 0.3 H). ^{13}C NMR ($CDCl_3$): δ 135.6 (major), 134.9 (minor), 123.5 (major), 122.5 (minor), 103.9, 102.4, 64.9 (2C), 54.0 (minor, 2C), 53.5 (major, 2C), 32.55 (minor), 32.38 (major), 17.9.

***N*-Cyclohexyl-3-methylpyridinium Chloride (8). 7** (440 mg, 2.2 mmol) was dissolved in CH_2Cl_2 (4 mL), $FeCl_3/SiO_2$ catalyst[7] (100 mg) was added, and the mixture was stirred for 5 min. Then cyclohexylamine hydrochloride (400 mg, 2.9 mmol) in methanol (0.5 mL) was added. After 1 h *n*-butanol (5 mL) and Et_3N (300 mg, 3.0 mmol) were added and CH_2Cl_2 was removed in vacuo. The solution was refluxed for 16 h. Then the solvent was removed in vacuo, and water (5 mL), a concentrated Na_2CO_3 solution (5 mL), and ether (5 mL) were added. The layers were separated, and the aqueous layer was extracted with ether. The aqueous phase was concentrated in vacuo to dryness, and **8** was extracted from the residue with CH_2Cl_2. The crude product was further purified by column chromatography (SiO_2, gradient CH_2Cl_2/methanol: 0−15% methanol) to afford **8** (180 mg, 39%) as a light brown oil. IR (film): 3039, 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.71 (br s, 1 H), 9.52 (d, J = 6.1 Hz, 1 H), 8.27 (br d, J = 7.8 Hz, 1 H), 8.12 (dd, J = 7.8, 6.1 Hz, 1 H), 5.19 (tt, J = 12.0, 4.0 Hz, 1 H), 2.70 (s, 3 H), 1.90−2.31 (m, 6 H), 1.31−1.83 (m, 4 H). ^{1}H NMR (CD_3OD): δ 9.00 (s, 1 H), 8.92 (d, J = 5.9 Hz, 1 H), 8.42 (d, J = 7.9 Hz, 1 H), 7.93−8.06 (m, 1 H), 4.57−4.79 (m, 1 H), 2.60 (s, 3 H), 1.26−2.28 (m, 10 H). ^{13}C NMR (CD_3OD): δ 147.4, 144.1, 141.6, 141.5, 128.9, 73.3, 34.5 (2C), 26.5 (2C), 25.7, 18.5.

6-(Tetrahydro-2-pyranyloxy)hexanal (10). With Pyridine *N*-Oxide. A mixture of 1-bromo-6-(tetrahydro-2-pyranyloxy)hexane (**9**) (16.3 g, 90 mmol), $NaHCO_3$ (16.8 g, 200 mmol), and pyridine *N*-oxide (19.0 g, 200 mmol) in toluene (150 mL) was refluxed for 4 h, using a Dean−Stark water trap, to remove the water formed in the reaction. After cooling, the mixture was filtered and the solution was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, EtOAc/petroleum ether 8/2) to afford **10** (6.88 g, 38%) as a colorless oil. Analytical data were in agreement with those in the literature.[8]

With Trimethylamine *N*-Oxide (TMANO). 1-Bromo-6-(tetrahydro-2-pyranyloxy)hexane (**9**) (0.53 g, 2 mmol) was dissolved in DMSO (4 mL). TMANO (0.60 g, 8 mmol) was added, and the mixture was stirred for 5 h. The mixture was poured into a half-saturated NaCl solution and extracted with ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified as indicated above to give **10** (0.36 g, 90%) as a colorless oil.

(*Z*)-3-[9-(Tetrahydro-2-pyranyloxy)non-3-en-1-yl]pyridine (12). To a stirred suspension of phosphonium salt[10] **11** (23.4 g, 50.5 mmol) and 18-crown-6 (0.9 g, 3.4 mmol) in THF (60 mL) was added a solution of potassium *tert*-butylate (8.5 g, 75.8 mmol) in THF (60 mL) dropwise under a nitrogen atmosphere at 0 °C. After 30 min at 0 °C, the solution was cooled to −78 °C and aldehyde **10** (6.75 g, 33.7 mmol) in THF (30 mL) was added over a period of 30 min. After 30 min, the cooling bath was

(18) For a recent example and references for the preparation of pyridinium salts from acyclic starting materials, see: Yu, L.-B.; Chen, D.; Li, J.; Ramirez, J.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 208−211.

(19) Kang, S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis* **1985**, 1161−1162.

(20) Chapman, O. L.; Mattes, K. C.; Sheridan, R. S.; Klun, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 4878−4884.

removed and the mixture was stirred for additional 2 h. The reaction was quenched with water (100 mL), the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ether) to afford **12** (7.3 g, 81%) as pale yellow oil. IR (film): 3006, 2938, 2860 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (br s, 1H), 8.42 (dd, J = 4.9, 1.7 Hz, 1 H), 7.48 (ddd, J = 7.7, 2.2, 1.7 Hz, 1 H), 7.18 (ddd, J = 7.7, 4.8, 0.8 Hz, 1 H), 5.38 (m, 2 H), 4.57 (m, 1 H), 3.80−3.92 (m, 1 H), 3.65−3.78 (m, 1 H), 3.43−3.55 (m, 1 H), 3.30−3.42 (m, 1 H), 2.66 (t, J = 7.6 Hz, 2 H), 2.35 (dt, J = 7.1, 7.0 Hz, 2 H), 1.20−2.02 (m, 14 H). ^{13}C NMR ($CDCl_3$): δ 150.1, 147.3, 137.2, 135.8, 131.2, 127.9, 123.1, 98.9, 67.5, 62.3, 33.0, 30.8, 29.6, 29.4, 28.7, 27.2, 25.9, 25.5, 19.7.

(*Z*)-9-(3-Pyridyl)non-6-en-1-ol (13). To a stirred solution of **12** (1.9 g, 6.3 mmol) in methanol (35 mL) was added TsOH (1.24 g, 6.5 mmol). Stirring was continued for 4 h. A saturated $NaHCO_3$ solution (45 mL) and water (90 mL) were added, and the mixture was extracted with EtOAc. The combined organic phases were washed with a saturated $NaHCO_3$ solution and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/methanol 9/1) to afford **13** (1.16 g, 84%) as pale yellow oil. IR (film): 3315 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (d, J = 2.2 Hz, 1 H), 8.42 (dd, J = 4.8, 1.7 Hz, 1 H), 7.49 (ddd, J = 7.7, 2.2, 1.7 Hz, 1 H), 7.19 (ddd, J = 7.7, 4.8, 0.8 Hz, 1 H), 5.29−5.47 (m, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 2.67 (t, J = 7.5 Hz, 2 H), 2.36 (dt, J = 7.5. 6.7 Hz, 2 H), 1.83−2.13 (m, 3 H), 1.44−1.62 (m, 2 H), 1.17−1.37 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 149.9, 147.2, 137.2, 136.1, 131.2, 127.9, 123.2, 62.6, 33.0, 32.7, 29.3, 28.6, 27.1, 25.4. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.23; H, 9.65; N, 6.39.

(*Z*)-1,1-Dimethoxy-12-(3-pyridyl)dodec-9-en-2-one (16). Alcohol **13** (1.06 g, 5.0 mmol) was dissolved in pyridine (15 mL) and cooled to −10 °C, and *p*-toluenesulfonyl chloride (1.05 g, 5.5 mmol) was added. After 15 min, the cooling bath was removed and the mixture stirred for 2 h at room temperature. Water (20 mL) and a saturated $NaHCO_3$ solution (2 mL) were added, and the solution was extracted with ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The unstable product **14** was used immediately for the following reaction without further purification.

A solution of diisopropylamine (3.04 g, 30 mmol) in THF (50 mL) was cooled to −78 °C, and *n*-BuLi (15.6 mL, 25 mmol, 1.6 M in hexane) was added dropwise. After 30 min at −78 °C, imine[11] **15** (4.98 g, 25 mmol) in DMPU (5 mL) was added, and the solution was stirred for 1 h at −78 °C. Then tosylate **14** (5.0 mmol, crude) in THF (15 mL) was added. After 2 h, the cooling bath was removed and stirring was continued for 16 h at room temperature. The reaction was quenched with water (50 mL), the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc) to afford **16** (1.12 g, 70% from **13**) as a pale yellow oil. IR (film): 1728 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (br d, J = 2.2 Hz, 1 H), 8.42 (dd, J = 4.8, 1.7 Hz, 1 H), 7.49 (ddd, J = 7.8, 2.2, 1.7 Hz, 1 H), 7.19 (ddd, J = 7.8, 4.8, 0.8 Hz, 1 H), 5.37 (m, 2 H), 4.45 (s, 1 H), 3.40 (s, 6 H), 2.65 (t, J = 7.6 Hz, 2 H), 2.53 (t, J = 7.3 Hz, 2 H), 2.34 (m, 2 H), 1.91 (m, 2 H), 1.55 (m, 2 H), 1.24 (br s, 6 H).^{13}C NMR ($CDCl_3$): δ 205.6, 150.1, 147.3, 137.2, 135.8, 131.2, 127.8, 123.1, 104.3, 54.7 (2 C), 37.2, 33.0, 29.3, 29.0, 28.9, 28.7, 27.1, 22.9.

(*3Z*)-3-[11-Dimethoxymethyl-13-(1,3-dioxolan-2-yl)tridec-3,11-dien-1-yl]pyridine (17). Phosphonium salt **5** (7.27 g, 16.4 mmol) was suspended in THF (100 mL) and cooled to −20 °C. *n*-BuLi (11.0 mL, 17.6 mmol, 1.6 M in hexane) was added dropwise, and the solution was stirred for 1 h at −20 °C. Then the reaction was cooled to −78 °C and ketone **16** (1.12 g, 3.51 mmol) in THF (15 mL) was added dropwise. The solution was allowed to reach room temperature over a period of 16 h. Water (150 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, ether) to afford **17** (0.88 g, 63%, *E*/*Z*-mixture 9:1) as pale yellow oil. IR (film): 2929, 2857 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (br d, J = 2.2 Hz, 1 H), 8.43 (dd, J = 4.8, 1.7 Hz, 1 H), 7.50 (ddd, J = 7.8, 2.2, 1.7 Hz, 1 H), 7.20 (ddd, J = 7.8, 4.8, 0.8 Hz, 1 H), 5.67 (t, J = 7.1 Hz, 0.1 H), 5.48 (t, J = 7.1 Hz, 0.9 H), 5.37 (m, 2 H), 4.92 (s, 1 H), 5.03 (t, J = 4.4 Hz, 0.9 H), 4.89 (t, J = 4.4 Hz, 0.1 H), 3.81−4.04 (m, 4 H), 3.33 (s, 5.4 H), 3.27 (s, 0.6 H), 2.66 (t, J = 7.8 Hz, 2 H), 2.54 (m, 2 H), 2.35 (m, 2 H), 1.84−2.09 (m, 4 H), 1.19−1.49 (m, 7 H). ^{13}C NMR ($CDCl_3$): δ 149.6, 146.8, 139.5, 137.5, 136.3, 131.5, 127.6, 123.2, 122.7, 104.0, 103.2, 64.9 (2C), 54.2 (2C), 33.1, 32.5, 31.3, 29.5, 29.2, 29.0, 28.7 (2C), 27.3.

11-(Tetrahydro-2-pyranyloxy)undec-2-yn-1-ol (20). In a three-necked flask with a mechanical stirrer, a solution of 2-propyn-1-ol (1.12 g, 20 mmol) in THF (75 mL) was cooled to −78 °C under a nitrogen atmosphere. *n*-BuLi (25 mL, 40 mmol, 1.6 M in hexane) was slowly added. After addition was complete, the temperature was allowed to rise to −30 °C. After 45 min at this temperature, a solution of **19** (2.93 g, 10 mmol) in DMPU (40 mL) and THF (30 mL) was added. The cooling bath was removed, and stirring was continued for an additional 16 h. Water (100 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc 7/3) to give **20** (1.35 g, 47%) as a colorless oil. Analytical data were in agreement with the reported data.[21]

1-Bromo-11-(tetrahydro-2-pyranyloxy)undec-2-yne (21). A stirred solution of **20** (7.0 g, 26.1 mmol) and CBr_4 (13.0 g, 39.1 mmol) in DMF (90 mL) was cooled to 0 °C. PPh_3 (10.3 g, 39.1 mmol) was added in one portion, and the mixture was stirred for 25 min at 0 °C. A half-saturated $NaHCO_3$ solution (80 mL) was added, and the mixture was extracted with petroleum ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc 9/1) to give **21** (7.90 g, 91%) as a colorless oil. IR (film): 2312, 2234 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.53−4.62 (m, 1 H), 3.93 (t, J = 2.4 Hz, 2 H), 3.81−3.98 (m, 1 H), 3.67−3.79 (m, 1 H), 3.44−3.56 (m, 1 H), 3.32−3.44 (m, 1 H), 2.16−2.29 (m, 2 H), 1.20−1.93 (m, 18 H). ^{13}C NMR ($CDCl_3$): δ 98.8, 88.3, 75.3, 67.6, 62.3, 30.8, 29.7, 29.3, 29.0, 28.7, 28.3, 26.2, 25.5, 19.7, 18.9, 15.6.

Methyl 2-(3,3-Dimethoxypropyl)-13-(tetrahydro-2-pyranyloxy)tridec-4-ynoate (23). A solution of diisopropylamine (4.8 g, 47.0 mmol) in THF (100 mL) was cooled to −78 °C, and *n*-BuLi (25 mL, 40 mmol, 1.6 M in hexane) was added slowly. After 30 min at −78 °C, **22** (4.46 g, 25.3 mmol) in THF (20 mL) was added dropwise and the solution was stirred for additional 30 min. **21** in DMPU (50 mL) was added, and after 1 h the cooling bath was removed. After 16 h water (100 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc 8/2) to give **23** (5.14 g, 47%) as a colorless oil. IR (film): 1740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.53−4.62 (m, 1 H), 4.32−4.41 (m, 1 H), 3.81−3.94 (m, 1 H), 3.65−3.79 (m, 1 H), 3.69 (s, 2.7 H, major diastereomer) and 3.67 (s, 0.3 H, minor diastereomer), 3.44−3.56 (m, 1 H), 3.26−3.44 (m, 1 H), 3.32 (minor diastereomer, s, 0.6 H) and 3.30 (major diastereomer, d, J = 2.0 Hz, 5.4 H), 2.49−2.61 (m, 1 H), 2.29−2.47 (m, 2 H), 2.07−2.16 (m, 2 H), 1.22−1.89 (m, 22 H). ^{13}C NMR ($CDCl_3$): δ 174.9, 104.2, 98.8, 67.6, 62.3, 52.8, 52.5, 51.6, 44.7, 33.7, 31.9, 30.8, 30.0, 29.7, 29.3, 29.1, 28.9, 28.7, 26.2 (2C), 25.5, 21.7, 19.7, 18.7.

2-(3,3-Dimethoxypropyl)-13-(tetrahydro-2-pyranyloxy)-tridec-4-yn-1-ol (24). A stirred suspension of $LiAlH_4$ (0.89 g, 23.4 mmol) in THF (65 mL) was cooled to 0 °C. Ester **23** (5.01 g, 11.74 mmol) in THF (30 mL) was added slowly at this temperature, and the mixture was stirred for an additional 3 h at room temperature. Then water (32.5 mL) was added dropwise to quench the reaction upon which a white solid precipitated. The solution was decanted, and the solid was extracted with ether (3 × 100 mL). The combined organic phases were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc 1/1) to afford **24** (3.42 g, 73%) as pale yellow oil. IR

(21) Poulain, S.; Noiret, N.; Nugier-Chauvin, C.; Patin, H. *Liebigs Ann./Recl.* **1997**, 35−40.

(film): 3450, 2362 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.54−4.60 (m, 1 H), 4.35 (t, J = 5.1 Hz, 1 H), 3.81−3.93 (m, 1 H), 3.58−3.79 (m, 1 H), 3.64 (d, 2 H), 3.26−3.56 (m, 2 H), 3.32 (s, 6 H), 2.20−2.31 (m, 2 H), 2.07−2.20 (m, 2 H), 1.20−1.91 (m, 23 H). ^{13}C NMR ($CDCl_3$): δ 104.7, 98.8, 67.6, 62.3, 55.5, 54.5, 35.1, 34.3, 30.8, 29.7, 29.6, 29.3, 29.1, 29.0 (2C), 28.8, 26.2, 26.1, 25.5, 24.2, 22.1, 19.7, 18.7. Anal. Calcd for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62. Found: C, 69.31; H, 10.51.

(*Z*)-2-(3,3-Dimethoxypropyl)-13-(tetrahydro-2-pyranyloxy)tridec-4-en-1-ol (25). Methanol (50 mL), quinoline (200 μL), Lindlar catalyst (250 mg, Fluka), and **24** (500 mg, 1.25 mmol) were placed in a hydrogenation flask and hydrogenated for 15 min at atmospheric pressure. The mixture was filtered, and the filtrate was concentrated in vacuo to afford **25** as a pale yellow oil in quantitative yield. The crude product was used for the subsequent reaction without further purification. An analytical sample was prepared by column chromatography (Al_2O_3, petroleum ether/ether gradient (0% ether−100% ether). IR (film): 3454 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.29−5.53 (m, 2 H), 4.53−4.63 (m, 1 H), 4.33 (t, J = 5.1 Hz, 1 H), 3.81−3.94 (m, 1 H), 3.65−3.79 (m, 1 H), 3.22−3.63 (m, 4 H), 3.30 (s, 6 H), 1.20−2.24 (m, 27 H). ^{13}C NMR ($CDCl_3$): δ 131.6, 126.5, 105.0, 98.9, 67.7, 65.4, 62.4, 52.8, 41.0, 32.6, 30.8, 30.0, 29.8, 29.6, 29.43, 29.41, 29.2, 29.0, 27.3, 26.2, 25.7, 25.5, 19.7. Anal. Calcd for $C_{23}H_{44}O_5$: C, 68.96; H, 11.07. Found: C, 68.83; H, 11.09.

(*Z*)-2-(3,3-Dimethoxypropyl)-13-(tetrahydro-2-pyranyloxy)tridec-4-en-1-al (26). A solution of oxalyl chloride (228 mg, 1.8 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78 °C, and a solution of DMSO (281 mg, 3.6 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise under a nitrogen atmosphere. After 30 min alcohol **25** (600 mg, 1.5 mmol) in dry CH_2Cl_2 (0.5 mL) was added slowly and the mixture was stirred for an additional 30 min. Et_3N (1.05 mL) was added, and the cooling bath was removed. After the reaction mixture reached room temperature, water (3 mL) was added and the solution was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc 7/3) to give **26** (480 mg, 80% from **24**) as a pale yellow oil. IR (film): 1726 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.61 (d, J = 2.0 Hz, 1 H), 5.39−5.55 (m, 1 H), 5.23−5.37 (m, 1 H), 4.53−4.62 (m, 1 H), 4.34 (t, J = 5.3 Hz, 1 H), 3.81−3.94 (m, 1 H), 3.66−3.79 (m, 1 H), 3.44−3.56 (m, 1 H), 3.33−3.44 (m, 1 H), 3.31 (s, 6 H), 2.15−2.46 (m, 3 H), 1.93−2.09 (m, 2 H), 1.21−1.87 (m, 22 H).^{13}C NMR ($CDCl_3$): δ 204.3, 132.6, 125.2, 104.4, 98.8, 67.6, 62.3, 52.9, 52.8, 51.6, 30.8, 30.0, 29.9, 29.5, 29.42, 29.39, 29.2, 27.3, 26.7, 26.2, 25.5, 23.3, 19.7. Anal. Calcd for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62. Found: C, 69.06; H, 10.61.

(*Z*)-11-(3-Pyridyl)undec-9-en-1-ol (27). $NH_2OH{\cdot}HCl$ (770 mg, 11.0 mmol) was added to a solution of aldehyde **26** (880 mg, 2.21 mmol) in 99% EtOH (20 mL), and the mixture was refluxed for 60 min. After the red solution reached room temperature, water (70 mL) and ether (70 mL) were added and the solution was basified with 2 N NaOH. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc) to afford **27** (290 mg, 54%) as a colorless oil. IR (film): 3331 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.42 (dd, J = 2.3, 0.8 Hz, 1 H), 8.40 (dd, J = 4.8, 1.7 Hz, 1 H), 7.48 (ddd, J = 7.8, 2.3, 1.7 Hz, 1 H), 7.19 (ddd, J = 7.8, 4.8, 0.8 Hz, 1 H), 5.44−5.64 (m, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.37 (d, J = 6.1 Hz, 2 H), 2.49 (br s, 1 H), 2.06−2.21 (m, 2 H), 1.16−1.63 (m, 12 H). ^{13}C NMR ($CDCl_3$): δ 149.7, 147.2, 136.6, 135.8, 132.1, 126.5, 123.3, 62.8, 32.8, 30.7, 29.5, 29.4, 29.3, 29.1, 27.2, 25.7.

(*Z*)-3-(11-Azidoundec-2-en-1-yl)pyridine (29). A solution of *p*-toluenesulfonyl chloride (2.0 g, 10.4 mmol) in pyridine (10 mL) was cooled to 0 °C, and alcohol **27** (580 mg, 2.36 mmol) in pyridine (3.4 mL) was added dropwise. The solution was stirred for 1 h at room temperature and cooled to 0 °C, and water (2 mL) was added. After 5 min the solution was diluted with water (200 mL) and extracted with ether. The combined organic phases were washed with water and brine, dried, and evaporated in vacuo. The residue was immediately dissolved in DMF (20 mL), NaN_3 (1.5 g, 23.1 mmol) was added, and the solution was stirred for 16 h at 70 °C. Then water (200 mL) was added, and the solution was extracted with petroleum ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc) to afford **29** (470 mg, 73%) as a colorless oil. IR (film): 2095 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.40 (dd, J = 2.3, 0.7 Hz, 1 H), 8.37 (dd, J = 4.8, 1.7 Hz, 1 H), 7.42 (ddd, J = 7.8, 2.3, 1.7 Hz, 1 H), 7.13 (ddd, J = 7.8, 4.8, 0.7 Hz, 1 H), 5.37−5.58 (m, 2 H), 3.19 (d, J = 5.9 Hz, 2 H), 3.33 (t, J = 6.9 Hz, 2 H), 2.01−2.15 (m, 2 H), 1.42−1.61 (m, 2 H), 1.17−1.42 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 149.9, 147.3, 136.4, 135.6, 131.9, 126.6, 123.2, 51.4, 30.7, 29.4, 29.3, 29.1, 29.0, 28.8, 27.2, 26.6.

(*Z*)-11-(3-Pyridyl)undec-9-en-1-amine Dihydrochloride (4a). PPh_3 (670 mg, 2.54 mmol) was added to a solution of azide **29** (470 mg, 1.72 mmol) in pyridine (1.6 mL) at 0 °C and was stirred for 24 h at room temperature. The solution was then cooled to 0 °C, concentrated NH_3 (430 μL) was added, and the solution was stirred for another 24 h at room temperature. Pyridine was evaporated and the residue mixed with 2 N HCl (10.2 mL). The mixture was extracted with ether (4 × 15 mL). The aqueous phase was concentrated in vacuo to afford **4a** (517 mg, 94%) as a pale yellow oil. IR (film): 3384 cm^{-1}. ^1H NMR (CD_3OD): δ 8.73 (br s, 2 H), 8.52 (br d, J = 8.3 Hz, 1 H), 8.05 (dd, J = 8.3, 6.1 Hz, 1 H), 5.54−5.78 (m, 2 H), 3.70 (br d, J = 7.1 Hz, 2 H), 2.91 (t, J = 7.6 Hz, 2 H), 2.12−2.25 (m, 2 H), 1.60−1.69 (m, 2 H), 1.29−1.37 (m, 10 H). ^{13}C NMR (CD_3OD): δ 148.2, 142.8, 141.9, 140.4, 135.4, 128.5, 125.4, 40.9, 31.1, 30.5, 30.3, 30.2, 30.1, 28.5, 28.3, 27.5.

Niphatoxin B (2). 17 (72 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (2 mL), $FeCl_3/SiO_2$ catalyst (30 mg) was added, and the mixture was stirred for 5 min. Dihydrochloride **4a** (83 mg, 0.26 mmol) in methanol (0.6 mL) was added, and stirring was continued for 30 min. *n*-BuOH (3 mL) was added, and CH_2Cl_2 was removed in vacuo. Et_3N (100 μL) was added, and the solution was refluxed for 16 h. The solvents were evaporated in vacuo, and the residue was purified by column chromatography (SiO_2, gradient CH_2Cl_2/methanol: 0−10% methanol) to afford **2** (45 mg, 45%) as a light brown oil. IR (film): 3010, 2929, 2856, 1632, 1592, 1576, 1507, 1478, 1466, 1424, 1328, 1241, 1192, 1160, 1104, 1044, 1028, 834, 799, 718, 695, 523 cm^{-1}.^1H NMR (CD_3OD): δ 8.94 (br s, 1 H), 8.85 (br d, J = 6.0 Hz, 1 H), 8.46 (br d, J = 8.2 Hz, 1 H), 8.30−8.41 (m, 4 H), 8.02 (dd, J = 7.9, 6.1 Hz, 1 H), 7.63−7.73 (m, 2 H), 7.31−7.39 (m, 2 H), 5.47−5.63 (m, 2 H), 5.30−5.44 (m, 2 H), 4.61 (t, J = 7.5 Hz, 2 H), 3.40−3.47 (m, 2 H), 2.87 (t, J = 7.8 Hz, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 2.31−2.43 (m, 2 H), 2.12−2.23 (m, 2 H), 1.84−2.08 (m, 4 H), 1.61−1.77 (m, 2 H), 1.13−1.48 (m, 16 H). ^1H NMR ($CDCl_3$): δ 9.43 (d, J = 5.7 Hz, 1 H), 9.23 (s, 1 H), 8.43 (br s, 4 H), 8.21 (d, J = 7.8 Hz, 1 H), 7.97−8.10 (m, 1 H), 7.46−7.55 (m, 2 H), 7.16−7.27 (m, 2 H), 5.45−5.61 (m, 2 H), 5.27−5.45 (m, 2 H), 5.00 (t, J = 7.1 Hz, 2 H), 3.39 (d, J = 6.0 Hz, 2 H), 2.87 (t, J = 7.2 Hz, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 1.11−2.53 (m, 26 H). ^{13}C NMR (CD_3OD): δ 150.26, 149.97, 147.65, 147.56, 146.67, 145.83, 145.25, 143.37, 139.57, 138.97, 138.48, 138.13, 133.10, 132.20, 129.05 (2 C), 127.81, 125.20, 125.05, 63.02, 33.79, 33.55, 32.47, 31.46, 31.45, 30.57, 30.49, 30.33, 30.17, 30.03, 29.99, 29.94, 29.74, 28.17, 28.07, 27.17. FAB MS, *m*/*z* (%): 524 (100) [M^+], 431 (9), 391 (7), 349 (7), 335 (15), 295 (15), 230 (15), 160 (8), 146 (13), 132 (20), 106 (28).

Supporting Information Available: ^1H NMR spectra for compounds **2**, **4a**, **7**, **8**, **12**, **16**, **17**, **21**, **23**, **27**, and **29** and for the dimethylation product of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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