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A Concise and Efficient Total Synthesis of Militarinone D

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A highly stereoselective, concise (14 steps longest linear sequence and 20 steps overall), and efficient (15 % overall yield) synthesis of militarinone D has been accomplished. The key reactions utilized in the sequence are enzymatic desymmetrization, *cis*/*trans* isomerization, Horner–Wadsworth–Emmons olefination, and addition of an organolithium species to a highly conjugated chiral aldehyde. The simplicity of the strategy may enable its utilization in the large-scale production of this target. Moreover, the strategy utilized to design the route should be applicable to the preparation of analogs that bear a variety of substituted pyridinone core structures.

Introduction

4-Hydroxy-2-pyridone alkaloids exhibit a diverse range of biological activities, which include antibacterial, antifungal, insecticidal, and cytotoxic activity as well as the ability to induce neurite outgrowth in different cells.[1] Owing to their interesting biological properties, pyridone alkaloids have attracted considerable attention from members of the organic synthesis community. Militarinone D (**1**), a representative member of this natural product family, was isolated from a mycelial extract of the entomopathogenic fungus *Paecilomyces Militaris* by Hamburger et al. in 2003.[2] Two new 3-acyl tetramic acids, militarinone B (**10**) and C (**11**), were also isolated from the same species by this group. Since that time, studies have led to the isolation and characterization of other structurally related 4-hydroxy-2-pyridone natural products including pretenellin (**2**), tenellin (**3**), bassianin (**4**), farinosone A and B (**5** and **6**), *N*-deoxymilitarinone A (**7**), militarinone A (**8**), and pyridovericin (**9**;

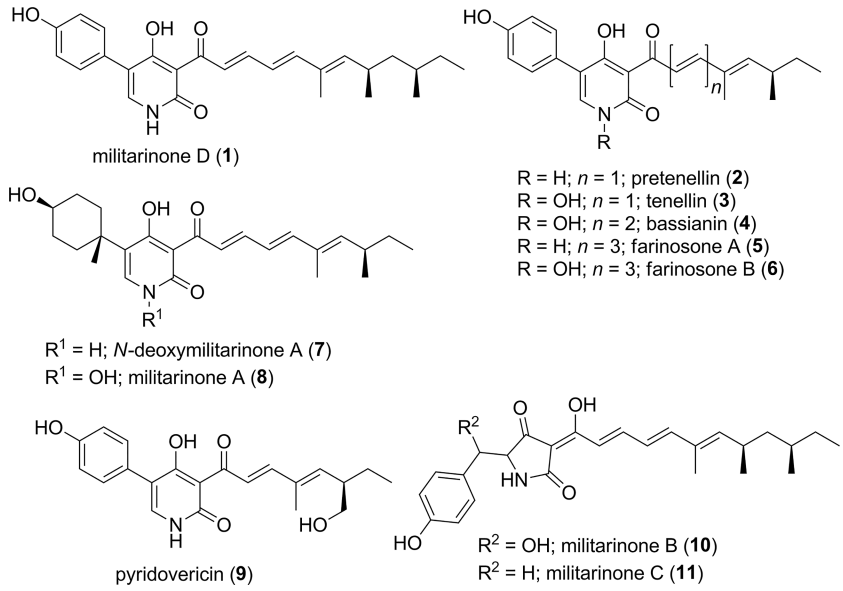

Figure 1. Pyridone alkaloids.

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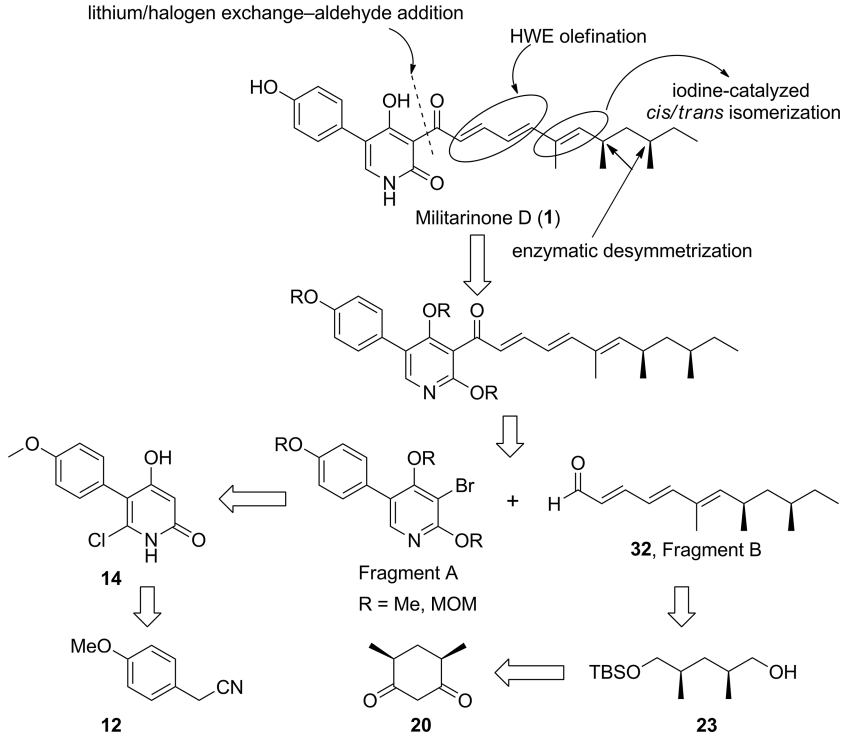


Scheme 1.

Figure 1).[3] Among this group of alkaloids, pretenellin, *N*-deoxymilitarinone A, militarinone A, and farinosone A display neuritogenic activity and pyridovericin inhibits protein tyrosine kinase at high concentrations.[1] In contrast to militarinone A (**8**), structurally related 2-pyridones militarinone B, C and D have only negligible neuritogenic activities in PC-12 cells, whereas militarinone D is cytotoxic.[2]

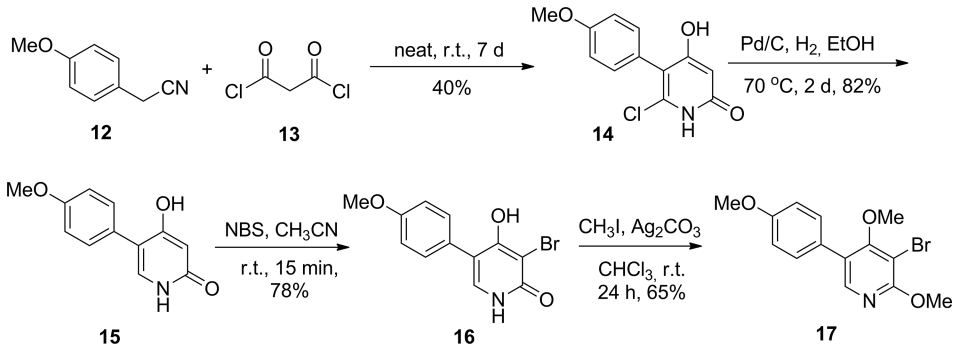
The structure of militarinone D was determined by extensive analysis of spectroscopic data and confirmed by its first total synthesis by Gademann and co-workers.[4a] This sole synthesis of the target, which employed a sequence that featured a Horner–Wadsworth–Emmons (HWE) olefination of a conjugated aldehyde with the pyridone β-ketophosphonate, was accomplished in a total of 22 steps (longest linear sequence of 14 steps) and in 5% overall yield from a known intermediate.[4a] Recently, another synthesis of militarinone D has been reported by Liu and co-workers.[4b]

As a part of an ongoing program focused on the synthesis of biologically active natural products,[5] we have developed an efficient, asymmetric total synthesis of militarinone D (**1**) of which retrosynthetic route and key steps are distinct from those of the previously reported[4a] one. The convergent route designed for preparation of **1** consists of construction and fusion of functionalized pyridone and ketotriene precursors. As can be seen by viewing the retrosynthetic analysis depicted in Scheme 1, the key feature of the synthetic strategy is coupling of a bromopyridine fragment A with triene-aldehyde **32**, fragment B by utilizing metal-halogen exchange and organolithium alkylation. In the plan, a known enzymatic desymmetrization process is employed to furnish mono-protected diol **22**, which contains the two stereogenic centers present in the target with correct absolute configurations. A HWE olefination based sequence is then utilized to generate fragment B triene-aldehyde **32**. Pyridine fragment A is prepared by a coupling reaction of commercially available *p*-methoxyphenyl acetonitrile **12** and malonyl chloride through known 2-pyridone derivative **14** (Scheme 1).

Results and Discussion

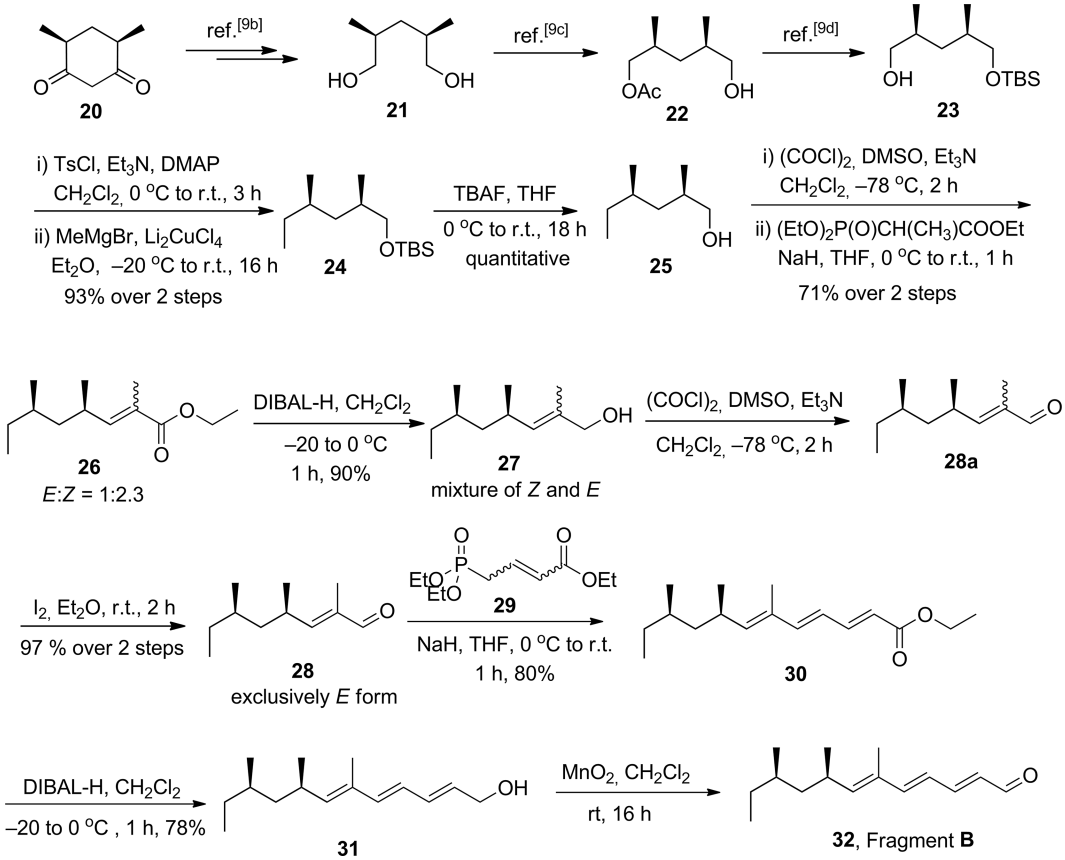
The synthesis of militarinone D (**1**) began with preparation of fragment **A** by starting with commercially available *p*-methoxyphenyl acetonitrile **12** and malonyl chloride **13** (Scheme 2). Reaction of these substances generated known[6] chloro-2-pyridone **14** in 40% yield. Dechlorination of **14** under hydrogenolysis conditions by using 10% Pd/C at 70 °C provided pyridone **15** (82%).[7] The 3-bromo group in fragment A was regioselectively introduced by reaction of **15** with *N*-bromosuccinimide (NBS) at room temperature to form bromopyridone **16** (78% following crystallization). The hydroxyl and 2-pyridone groups in **16** were then converted into the corresponding methyl ethers by using MeI in presence of Ag_2CO_3[8] to form **17** (65%) as the tris-methoxy protected form of Fragment A.

The next task was to synthesize chiral triene-aldehyde **32** (Fragment B). Previously described methods[9] were utilized to prepare known mono-protected diol **23** (>95% *ee*) that had the correct absolute configurations at the two methyl-

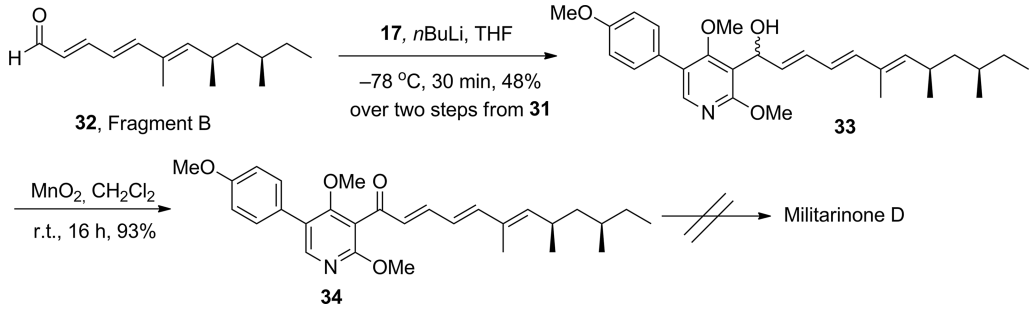


Scheme 2.

substituted stereogenic centers (Scheme 3). The primary hydroxyl group in **23** was subjected to tosylation (TsCl/Et_3N, cat. DMAP) followed by treatment of the resulting tosylate with MeMgBr in the presence of 20 mol-% Li_2CuCl_4 to yield **24** (93% over two steps).[10] Removal of the *O*-silyl group in **24** [tetra-*n*-butylammonium fluoride (TBAF)] produced primary alcohol **25** (quantitative) for which the spectroscopic properties were in good agreement with those reported earlier.[11] Alcohol **25** was then subjected to Swern oxidation that generated a crude aldehyde, which was directly reacted with triethyl 2-phosphonopropionate under HWE olefination conditions to produce α,β-unsaturated ester **26** as a 1:2.3 mixture of *E*/*Z* isomers (determined by ^1H NMR spectroscopy). Reduction of the ester moiety in **26** with diisobutylaluminium hydride (DIBAL-H) generated corresponding alcohol **27**, which was subsequently oxidized under Swern conditions to form aldehyde **28a** (1:2.3 *E*/*Z* isomer mixture). To transform the *Z*-stereoisomer to its *E*-isomer, **28a** was subjected to *cis*/*trans* isomerization by treatment with catalytic iodine in Et_2O at room temperature. This process produced aldehyde **28** as a single *E*-isomer (determined by ^1H NMR spectroscopy). Stereochemically pure aldehyde **28** was then subjected to HWE olefination with phosphonate **29**[12] in presence of NaH to



Scheme 3.

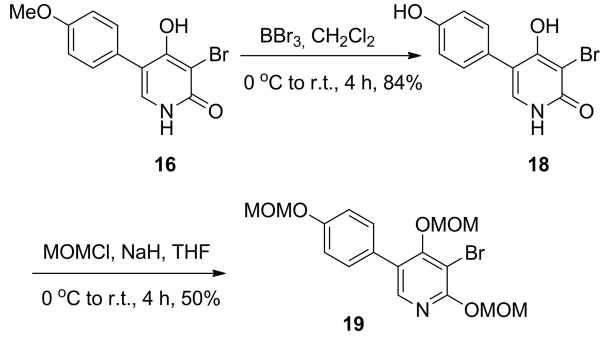


Scheme 4.

yield conjugated *E*,*E*,*E*-triene ester **30** (80%). Ester **30** was then reduced by using DIBAL-H to give corresponding alcohol **31**, which was oxidized with MnO_2 to afford desired aldehyde **32** (Fragment B).

Attention next focused on the crucial coupling reaction of bromo-pyridine **17** (Fragment A) and aldehyde **32** (Fragment B; Scheme 4). Treatment of **17** with *n*BuLi at –78 °C, followed by addition of trienal **32** (Fragment B) led to formation of desired alcohol **33** (48%).[13] Allylic oxidation of alcohol **33** with MnO_2 provided **34**, the tris-methoxy protected derivative of the target, militarinone D. At the final stage of the synthetic route, problems were encountered with removal of the *O*-methyl protecting groups. We first chose a method that involved reaction of in situ generated TMSI (TMSCl, NaI, CH_3CN) by following the literature protocol.[13] Unfortunately, under these conditions as well as a number of others often utilized for this purpose, **34** either underwent decomposition or reactions were sluggish.

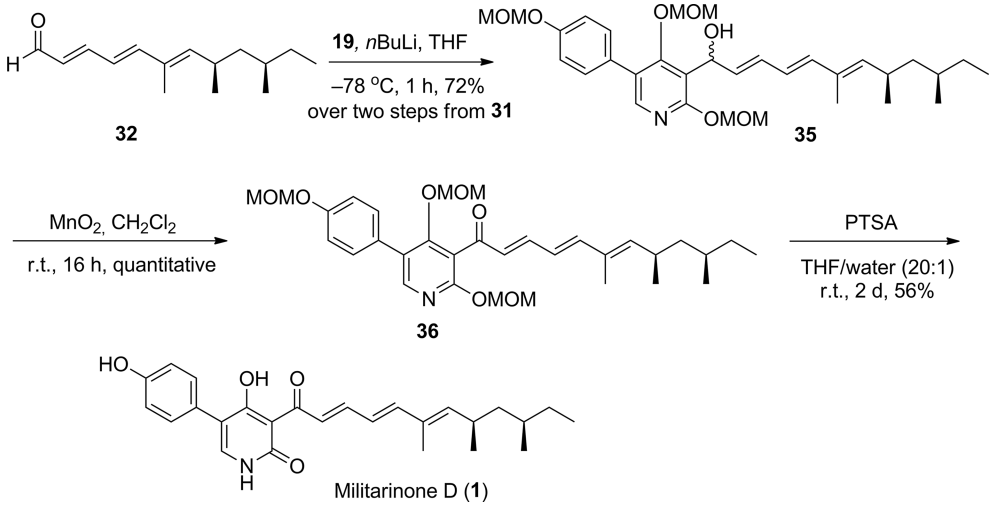
To facilitate the final deblocking process, we prepared tris-methoxymethyl ether (MOM) protected bromo-pyridine **19** (new Fragment A) by treatment of **16** with BBr_3 to afford pyridone **18** (84%). Protection of the hydroxyl and 2-pyridone groups in **18** by reaction with MOMCl [NaH, dimethylformamide (DMF)] provided required tri-*O*-MOM protected pyridine **19** (50%; Scheme 5).



Scheme 5.

In a sequence that mimicked the one used to transform methoxy analogs (see above), **19** was lithiated with *n*BuLi at –78 °C followed by treatment with aldehyde **32** to generate alcohol **35** (72%; Scheme 6). Allylic oxidation of **35** with MnO_2 provided tri-*O*-MOM-protected militarinone D **36** (quantitative).

Finally, the MOM protecting groups in **36** were removed by using excess *p*-toluenesulfonic acid (PTSA) in THF/water/hexane[11] to yield (56%) militarinone D (**1**) as a yellow solid. All spectroscopic properties of synthetic **1** matched those reported for the natural product.[4]



Scheme 6.

Conclusions

The route developed for the synthesis of militarinone D in the effort described above is stereoselective, concise (longest linear sequence of 14 steps and 20 steps total from known intermediate), and efficient (15% overall). The simplicity of the strategy may enable its utilization in the large-scale production of militarinone D (**1**). It is of note that the previously reported[4a] synthesis of militarinone D was accomplished in a total of 22 steps (longest linear sequence of 14 steps) and in 5% overall yield from a known intermediate. Moreover, the synthetic strategy described in this report should be applicable to the preparation of analogs that bear a variety of substituted pyridinone core structures. The synthesis and biological activity screening of various new derivatives of militarinone D (**1**) that contain differently substituted pyridone moieties are currently in progress.

Experimental Section

General: All reactions were carried out under an inert atmosphere of argon or nitrogen by using standard syringe, septa, and cannula techniques unless otherwise mentioned. Reactions were monitored by TLC with 0.25 mm E. Merck pre-coated silica gel plates (60 F254). Reaction progress was monitored by TLC analysis and a UV lamp or *p*-anisaldehyde stain for compound detection. Commercially available reagents were used without further purification. All solvents were purified by using standard techniques. Purification of reaction products was carried out by using silica gel column chromatography with Kieselgel 60 Art. 9385 (230–400 mesh). The purity of all compounds was >95% as determined with a Waters LCMS system (Waters 2998 Photodiode Array Detector, Waters 3100 Mass Detector, Waters SFO System Fluidics Organizer, Water 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) by using a SunFireTM C18 column (4.6 × 50 mm, 5 μm particle size): solvent gradient = 60% (or 95%) A at 0 min, 1% A at 5 min. Solvent A = 0.035% trifluoroacetic acid (TFA) in H_2O; Solvent B = 0.035% TFA in MeOH; flow rate: 3.0 (or 2.5) mL/min. ^1H and ^{13}C NMR spectra were recorded with a Bruker 400 MHz FT NMR (400 MHz for ^1H, and 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to $CHCl_3$ (δ = 7.26 ppm) and [D_6]DMSO (δ = 2.49 ppm) for ^1H NMR spectroscopy, and to $CHCl_3$ (δ = 77.0 ppm) and [D_6]DMSO (δ = 39.5 ppm) for ^{13}C NMR spectroscopy. Standard abbreviations are used for denoting the signal multiplicities. Infrared spectra were recorded with a FTIR Nicolet iS10 spectrometer as neat samples or as KBr mixes. High-resolution mass spectra were recorded with a QTOF mass spectrometer. Optical rotations were measured with a Rudolph Autopol III polarimeter at the wavelength of sodium D-line (589 nm) at room temperature.

6-Chloro-4-hydroxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (14):[6] (*p*-Methoxyphenyl)acetonitrile (**12**; 12.5 g, 85 mmol) and malonyl chloride (**13**; 25 g, 178 mmol) were stirred together under anhydrous conditions at room temperature for 1 week. The solid cake formed was then dissolved in NaOH (2 N aq., 250 mL) and washed with diethyl ether (5 × 100 mL). The aq. layer was then acidified with conc. hydrochloric acid. The precipitate was separated by filtration and washed successively with water (100 mL) and ether (2 × 50 mL). The solid was recrystallized from ethyl acetate to afford **14** (8.5 g, 40%) as a light brown solid. R_f = 0.5 (10% MeOH/CH_2Cl_2). ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.05 (br. s, 1 H), 10.80 (s, 1 H), 7.15 (d, J = 8.8 Hz, 2 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.09 (s, 1 H), 3.77 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 167.0, 162.5, 158.5, 144.6, 131.7, 125.5, 117.1, 113.4, 94.3, 55.1 ppm. ESI-MS: m/z = 252.25 $[M + H]^+$.

4-Hydroxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (15): A solution of chloropyridone **14** (1.7 g, 6.7 mmol) and 10% Pd/C (300 mg) in absolute EtOH (200 mL) was heated at 70 °C under a hydrogen pressure (≈ 2 bar) for 2 d. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give a solid that was recrystallized from acetone to afford pyridone **15** (1.2 g, 82%) as a buff solid. R_f = 0.4 (10% MeOH/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3386, 2923, 1631, 1384, 1041, 875, 445 cm^{-1}. ^1H NMR (400 MHz, [D_6]-DMSO): δ = 7.85 (s, 1 H), 7.44 (d, J = 8.9 Hz, 2 H), 6.99 (d, J = 8.9 Hz, 2 H), 6.81 (s, 1 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 169.1, 160.8, 158.9, 136.0, 130.2, 124.5, 119.0, 113.7, 96.6, 55.1 ppm. ESI-MS: m/z = 218.09 $[M + H]^+$.

3-Bromo-4-hydroxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (16): To a suspension of pyridone **15** (500 mg, 2.3 mmol) in acetonitrile (85 mL) was added NBS (410 mg, 2.3 mmol) portionwise with stirring at room temperature for 15 min. The mixture was then filtered through Celite and the filtrate was concentrated in vacuo giving a crude solid that was recrystallized from ethyl acetate/ether to afford **16** (530 mg, 78%) as an off-white solid. R_f = 0.5 (10% MeOH/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3387, 2923, 1657, 1630, 1502, 1042, 612 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.67 (br. s, 1 H), 10.22 (br. s, 1 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.21 (s, 1 H), 6.95 (d, J = 8.8 Hz, 2 H), 3.76 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]-DMSO): δ = 161.5, 159.2, 158.4, 132.5, 130.2, 126.2, 113.6, 113.1, 97.5, 55.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{10}BrNNaO_3$ $[M + Na]^+$ 317.9742; found 317.9741.

3-Bromo-2,4-dimethoxy-5-(4-methoxyphenyl)pyridine (17): A mixture of bromopyridone **16** (625 mg, 2.11 mmol), Ag_2CO_3 (2.33 g, 8.44 mmol), and CH_3I (2.6 mL, 42.2 mmol) in chloroform (75 mL) was stirred for 2 d at room temperature. The mixture was filtered and the filtrate was successively washed with water and brine then concentrated in vacuo to give a residue that was subjected to column chromatography (SiO_2, EtOAc/hexane = 7:93) to afford **17** (450 mg, 65%) as white solid. R_f = 0.5 (10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2959, 1712, 1614, 1384, 1235, 1137, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.43 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 4.03 (s, 3 H), 3.85 (s, 3 H), 3.53 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 160.7, 159.3, 146.1, 130.0, 126.7, 125.8, 114.0, 101.2, 60.2, 55.2, 54.6 ppm. ESI-MS: m/z = 324.04 $[M + H]^+$.

3-Bromo-4-hydroxy-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (18): To a stirred suspension bromopyridone **16** (1.0 g, 3.39 mmol) in dry CH_2Cl_2 (40 mL) was added BBr_3 (1 M in CH_2Cl_2; 17 mL, 17 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h and diluted with water at 0 °C and saturated aq. solution of $NaHCO_3$. The aqueous layer was separated and then acidified with conc. HCl at 0 °C with vigorous stirring. The resulting solid was separated by filtration, successively washed with water (3 × 50 mL) and ether (2 × 50 mL), and dried under vacuum to afford **18** (0.8 g, 84%) as an off white solid. R_f = 0.2 (10% MeOH/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3362, 2922, 2850, 1631, 1427, 1225, 1108, 1030, 829 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.65 (br. s, 1 H), 10.18 (br. s, 1 H), 9.47 (s, 1 H), 7.22–7.13 (m, 3 H), 6.76 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 161.6, 159.2, 156.6, 130.2, 132.3, 124.5, 114.9, 113.5, 97.5 ppm. HRMS (ESI): calcd. for $C_{11}H_8BrNNaO_3$ $[M + Na]^+$ 303.9585; found 303.9579.

3-Bromo-2,4-bis(methoxymethoxy)-5-[4-(methoxymethoxy)phenyl]-pyridine (19): To a stirred suspension of NaH (0.65 g, 16.27 mmol)

in DMF (10 mL) was added a solution of pyridone **18** (0.4 g, 1.36 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 4 h and then diluted with iced water and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (10% EtOAc/hexane) to afford **19** (0.28 g, 50% yield) as a colorless oil. R_f = 0.6 (30% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 2923, 2828, 1584, 1455, 1436, 1391, 1235, 1153, 1080, 1029, 890 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.09 (d, J = 8.8 Hz, 2 H), 5.61 (s, 2 H), 5.20 (s, 2 H), 4.85 (s, 2 H), 3.57 (s, 3 H), 3.49 (s, 3 H), 3.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 158.5, 156.9, 145.2, 130.3, 128.0, 126.9, 116.3, 111.9, 98.8, 94.3, 92.4, 57.6, 57.2, 56.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{20}BrNNaO_6$ $[M + Na]^+$ 436.0372; found 436.0366.

***tert*-Butyl{[(2*R*,4*R*)-2,4-dimethylhexyl]oxy}dimethylsilane (24):** To a solution of alcohol **23** (7.8 g, 31.64 mmol) in dry CH_2Cl_2 (100 mL) was added Et_3N (6.67 mL, 47.46 mmol) followed by *p*TsCl (7.24 g, 37.96 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature and then diluted with water and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (10 mL) and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (4% EtOAc/hexane) to afford the desired tosylate (11.93 g) as a colorless oil, which was used for the next step without further characterization.

To a solution of MeMgBr (3 M in THF, 40 mL, 120 mmol) in dry ether (80 mL) was slowly added a solution of the tosylate prepared above (11.93 g, 29.81 mmol) in diethyl ether (20 mL) at –20 °C. After 10 min, a solution of Li_2CuCl_4 (0.1 M in THF, 60 mL, 5.96 mmol) was added at same temperature and the resulting mixture was stirred at room temperature for 16 h before dilution with saturated aq. solution of NH_4Cl and water. The organic layer was separated, washed with brine (50 mL) and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (2% EtOAc/hexane) to afford **24** (7.1 g, 93% over 2 steps) as a colorless oil. R_f = 0.8 (10% EtOAc/hexane). $[\alpha]_D^{19}$ = –2.6 (c = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1384, 1032, 811, 626, 495, 483 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.45 (dd, J = 9.7, 5.3 Hz, 1 H), 3.31 (dd, J = 9.7, 6.7 Hz, 1 H), 1.73–1.61 (m, 1 H), 1.48–1.25 (m, 3 H), 1.13–1.03 (m, 1 H), 0.89 (s, 9 H), 0.88–0.81 (m, 9 H), 0.35 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.4, 40.7, 33.2, 31.7, 29.1, 26.0, 19.9, 18.3, 17.6, 11.1, –5.3 ppm. ESI-MS: m/z = 245.2 $[M + H]^+$.

(2*R*,4*R*)-2,4-Dimethylhexan-1-ol (25):[11] To a stirred solution of silyl compound **24** (8 g, 32.72 mmol) in dry THF (100 mL), TBAF (39.3 mL, 39.3 mmol, 1 M in THF) was added at 0 °C. The resulting mixture was stirred for 18 h at room temperature, diluted with saturated $NaHCO_3$ solution (50 mL). The separated organic layer was washed with brine (25 mL), dried with $MgSO_4$ and concentrated in vacuo to give a residue that was subjected to silica-gel column chromatography (10% EtOAc/hexane) to furnish **25** (4.2 g, quantitative) as a colorless oil. R_f = 0.4 (20% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.54–3.48 (m, 1 H), 3.40–3.35 (m, 1 H), 1.75–1.67 (m, 1 H), 1.48–1.23 (m, 4 H), 1.12–1.03 (m, 1 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.91–0.83 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.4, 40.6, 33.1, 31.6, 29.0, 19.7, 17.3, 11.1 ppm.

Ethyl (4*R*,6*R*)-2,4,6-Trimethyloct-2-enoate (26):[11] To a solution of oxalyl chloride (5.9 mL, 69.1 mmol) in anhydrous CH_2Cl_2 (120 mL) was added dimethyl sulfoxide (DMSO; 8.2 mL, 115.1 mmol) dropwise at –78 °C. The reaction mixture was stirred for 30 min at –78 °C and then treated with a solution of alcohol **25** (4.2 g, 46.07 mmol) in CH_2Cl_2 (30 mL) at –78 °C. After 1 h, Et_3N (32.4 mL, 230.35 mmol) was added dropwise at –78 °C. The resulting mixture was stirred for 30 min at –78 °C, warmed to room temperature, stirred for 2 h, and then diluted with water. The separated CH_2Cl_2 layer was washed with aqueous HCl (2%), dried with $MgSO_4$, filtered, and concentrated in vacuo to afford the crude aldehyde as a colorless oil, which was used for next step without further purification.

To a stirred suspension of NaH (7.75 g, 68.8 mmol) in THF (130 mL) was added triethyl 2-phosphonopropionate (16.7 g, 70.2 mmol) at 0 °C and stirred for 30 min at room temperature. The mixture was cooled to 0 °C and treated slowly with a solution of aldehyde (crude, 46.07 mmol). The mixture was stirred at room temperature for 4 h, diluted with iced water (50 mL), and extracted with diethyl ether (3 × 50 mL). The extracts were washed with brine (1 × 50 mL), dried with Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (2% EtOAc/hexane) to afford **25** (4.8 g, 71%, E/Z = 1:2.3) as a colorless oil. R_f = 0.7 (10% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.49 (dq, J = 10.1, 1.3 Hz, 0.3 H), 5.58 (dq, J = 10.1, 1.3 Hz, 0.7 H), 4.19 (q, J = 7.1 Hz, 1.4 H), 4.17 (q, J = 7.1 Hz, 0.6 H), 3.29–3.18 (m, 0.7 H), 2.66–2.54 (m, 0.3 H), 1.88 (d, J = 1.5 Hz, 2 H), 1.84 (d, J = 1.5 Hz, 1 H), 1.38–1.20 (m, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.17–0.99 (m, 2 H), 0.98 (d, J = 6.6 Hz, 1 H), 0.94 (d, J = 6.6 Hz, 2 H), 0.89–0.80 (m, 6 H) ppm.

(4*R*,6*R*)-2,4,6-Trimethyloct-2-en-1-ol (27):[11] DIBAL-H (7 mL, 7.06 mmol, 1 M in toluene) was added to a solution of ester **26** (0.5 g, 2.35 mmol) in dry CH_2Cl_2 (10 mL) at –20 °C. The mixture was stirred at 0 °C for 1 h and diluted by slow addition of a saturated solution of potassium sodium tartrate and then stirred for 30 min at room temperature. The organic layer was separated, washed with brine (1 × 30 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (5% EtOAc/hexane) to afford **27** (0.36 g, 90%). R_f = 0.3 (20% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.11 (dq, J = 9.5, 1.2 Hz, 0.3 H), 4.99 (d, J = 9.9 Hz, 0.7 H), 4.12 (d, J = 4.2 Hz, 1.4 H), 3.98 (d, J = 5.3 Hz, 0.6 H), 2.57–2.43 (m, 1 H), 1.78 (d, J = 1.5 Hz, 2 H), 1.67 (d, J = 1.4 Hz, 1 H), 1.34–0.99 (m, 5 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.86–0.77 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 132.9, 132.8, 132.6, 68.7, 61.6, 44.9, 44.7, 31.9, 29.9, 29.5, 22.24, 21.4, 21.0, 19.0, 18.9, 13.6, 11.1 ppm. ESI-MS: m/z = 171.2 $[M + H]^+$.

(4*R*,6*R*,*E*)-2,4,6-Trimethyloct-2-enal (28): To a solution of oxalyl chloride (0.38 mL, 4.40 mmol) in anhydrous CH_2Cl_2 (10 mL) was added DMSO (0.52 mL, 7.32 mmol) dropwise at –78 °C. The reaction mixture was stirred for 30 min at –78 °C and then treated with a solution of alcohol **27** (500 mg, 2.93 mmol) in CH_2Cl_2 (2 mL) at –78 °C. After 1 h, Et_3N (2.06 mL, 14.65 mmol) was added dropwise. The resulting mixture was stirred for 30 min at –78 °C, warmed to room temperature, stirred for 2 h, and then diluted with water. The separated organic phase was washed with aqueous HCl (2%), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to silica gel column chromatography (hexane) to afford an E/Z mixture of aldehyde **28a** (quantitative, E/Z = 1:2.3) as a colorless oil. R_f = 0.7 (10% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 0.7 H), 9.38 (s, 0.3 H), 6.23–6.20 (m, 1 H), 3.35–3.24 (m, 0.7 H), 2.86–2.76 (m, 0.3 H), 1.76 (d, J = 1.2 Hz, 2 H), 1.75 (d, J = 1.2 Hz, 1 H), 1.35–1.10 (m, 5 H), 1.04 (d, J = 5.7 Hz, 3 H), 1.03 (d, J = 5.7 Hz, 1 H), 0.87–0.82 (m, 6 H) ppm.

To a solution of **28a** in anhydrous Et_2O (50 mL) was added a small quantity of iodine and the resulting mixture was stirred for 2 h,

diluted with aq. $Na_2S_3O_3$ solution and extracted with diethyl ether. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to afford **28** (480 mg, 97%, only *E* isomer). The crude was sufficiently pure to be used in the next step. $[\alpha]_D^{19}$ = –28.2 (*c* = 2, $CHCl_3$), (ref.[11] $[\alpha]_D^{20}$ = –26.0, *c* 2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2961, 2928, 1690, 1642, 1461, 1379, 1278, 1172, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 6.20 (dq, *J* = 10.0, 1.2 Hz, 1 H), 2.86–2.76 (m, 1 H), 1.75 (d, *J* = 1.2 Hz, 3 H), 1.40 (t, *J* = 9.1 Hz, 1 H), 1.33–1.09 (m, 4 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.87–0.80 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 160.8, 137.8, 44.0, 32.4, 31.2, 30.0, 20.4, 19.0, 11.2, 9.3 ppm. ESI-MS: *m*/*z* = 169.2 $[M + H]^+$.

Ethyl (2*E*,4*E*,6*E*,8*R*,10*R*)-6,8,10-Trimethyldodeca-2,4,6-trienoate (30): To a stirred suspension of NaH (207 mg, 5.2 mmol) in THF (10 mL) was added triethyl 4-phosphonocrotonate **29** (1.66 g, 6.65 mmol) at 0 °C and the resulting mixture was stirred for 30 min at room temperature, cooled to 0 °C, and then treated slowly with a solution of aldehyde (350 mg, 2.08 mmol) in THF at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h, diluted with ice water (10 mL) at 0 °C, and extracted with ethyl acetate (3 × 25 mL). The organics extracts were washed with brine (1 × 10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (hexane) to afford **30** (440 mg, 80%, *E*/*Z* = 20:1) as a viscous colorless oil. R_f = 0.2 (10% toluene/hexane). $[\alpha]_D^{19}$ = –41.8 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2959, 2930, 1712, 1614, 1384, 1235, 1137, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 15.1, 11.1 Hz, 1 H), 6.54 (d, *J* = 15.2 Hz, 1 H), 6.21 (dd, *J* = 15.2, 11.1 Hz, 1 H), 5.85 (d, *J* = 15.1 Hz, 1 H), 5.42 (d, *J* = 9.7 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 2.67–2.56 (m, 1 H), 1.79 (d, *J* = 1.1 Hz, 3 H), 1.33–1.19 (m, 6 H), 1.17–1.03 (m, 2 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.87–0.80 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 146.2, 145.4, 145.2, 132.0, 123.6, 119.5, 60.0, 44.6, 32.2, 30.6, 30.0, 21.2, 19.0, 14.3, 12.3, 11.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{28}NaO_2$ $[M + Na]^+$ 287.1987; found 287.1987.

(2*E*,4*E*,6*E*,8*R*,10*R*)-6,8,10-Trimethyldodeca-2,4,6-trien-1-ol (31): DIBAL-H (4.5 mL, 4.5 mmol, 1 M in toluene) was added to a solution of ester **30** (0.4 g, 1.51 mmol) in dry CH_2Cl_2 (15 mL) at –20 °C. The mixture was stirred at 0 °C for 1 h, diluted by slow addition of a saturated solution of potassium sodium tartrate, stirred at room temperature for 30 min, and separated. The organic layer was washed with brine (1 × 30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane = 1:10) to afford **31** (0.26 g, 78%). R_f = 0.3 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –28.8 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3334, 2960, 2923, 2872, 1656, 1376, 983 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.33–6.10 (m, 3 H), 5.82 (dt, *J* = 8.8, 6.2 Hz, 1 H), 5.42 (d, *J* = 9.6 Hz, 1 H), 4.19 (t, *J* = 5.0 Hz, 2 H), 2.65–2.52 (m, 1 H), 1.77 (d, *J* = 1.22 Hz, 3 H), 1.33–1.19 (m, 3 H), 1.16–1.03 (m, 2 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.87–0.80 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 138.7, 132.5, 131.9, 130.4, 125.1, 63.6, 44.8, 32.2, 30.4, 30.1, 21.5, 19.1, 12.5, 11.2 ppm. ESI-MS: *m*/*z* = 223.2 $[M + H]^+$.

(2*E*,4*E*,6*E*,8*R*,10*R*)-6,8,10-Trimethyldodeca-2,4,6-trienal (32, Fragment B): To a solution of alcohol **31** (50 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) was added MnO_2 (197 mg, 22.7 mmol) at room temperature. The mixture was stirred for 16 h and filtered through Celite. The filtrate was concentrated in vacuo to afford crude aldehyde **32** (Fragment B, 0.22 mmol) as a colorless oil, which was used for the next step without further purification.

(2*E*,4*E*,6*E*,8*R*,10*R*)-1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]-6,8,10-trimethyldodeca-2,4,6-trien-1-ol (33): To a solution of pyridine **17** (80 mg, 0.246 mmol) in freshly dried THF (3 mL) was added *n*BuLi (0.3 mL, 0.49 mmol, 1.6 M in THF) at –78 °C. The resulting mixture was stirred for 15 min, treated with a solution of crude aldehyde **32** (0.22 mmol) in THF (1 mL) dropwise, stirred for 1 h, and then diluted with saturated aq. NH_4Cl solution. The separated organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane = 1:9) to afford **33** (50 mg, 48% over two steps) as a light yellow oil. R_f = 0.2 (20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3416, 2957, 2923, 1589, 1469, 1387, 1298, 1247, 1082, 985, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 6.96 (d, *J* = 8.7 Hz, 2 H), 6.30–5.98 (m, 4 H), 5.66–5.57 (m, 1 H), 5.21 (d, *J* = 9.6 Hz, 1 H), 4.01 (s, 3 H), 3.85 (s, 3 H), 3.74 (d, *J* = 11.3 Hz, 1 H), 3.39 (s, 3 H), 2.64–2.52 (m, 1 H), 1.74 (d, *J* = 1.1 Hz, 3 H), 1.30–1.19 (m, 3 H), 1.15–1.02 (m, 2 H), 0.93–0.89 (m, 3 H), 0.84–0.78 9 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 161.3, 159.1, 147.0, 140.9, 138.6, 132.9, 131.9, 131.1, 130.0, 129.8, 127.5, 125.3, 124.8, 117.1, 114.1, 67.7, 60.7, 55.2, 53.8, 44.8, 32.2, 30.3, 30.0, 21.5, 21.0, 19.0, 14.1, 12.4, 11.2 ppm. ESI-MS: *m*/*z* = 466.35 $[M + H]^+$.

(2*E*,4*E*,6*E*,8*R*,10*R*)-1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]-6,8,10-trimethyldodeca-2,4,6-trien-1-one (34): To a solution of alcohol **33** (25 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was added MnO_2 (47 mg, 0.53 mmol) at room temperature. The resulting mixture was stirred for 16 h and filtered through Celite. The filtrate was concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane = 1:9) to afford **34** (23 mg, 93%) as a light yellow oil. R_f = 0.3 (20% EtOAc/hexane). $[\alpha]_D^{19}$ = –41.7 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2958, 2924, 1726, 1649, 1604, 1585, 1515, 1466, 1409, 1272, 1247, 1094, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.06 (dd, *J* = 15.2, 11.0 Hz, 1 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 6.6 (d, *J* = 15.2 Hz, 1 H), 6.45 (d, *J* = 15.2 Hz, 1 H), 6.34 (dd, *J* = 15.2, 11.0 Hz, 1 H), 5.48 (d, *J* = 9.8 Hz, 1 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.49 (s, 3 H), 2.69–2.56 (m, 1 H), 1.81 (s, 3 H), 1.36–1.10 (m, 5 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.88–0.76 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5, 162.9, 161.1, 159.1, 148.3, 148.1, 147.4, 146.6, 132.3, 130.1, 130.0, 127.1, 124.2, 124.1, 115.3, 114.0, 60.9, 55.2, 53.9, 44.5, 32.3, 30.7, 30.0, 21.2, 19.0, 12.3, 11.2 ppm. ESI MS: *m*/*z* = 466.35 $[M + H]^+$.

(2*E*,4*E*,6*E*,8*R*,10*R*)-1-{2,4-Bis(methoxymethoxy)-5-[4-(methoxymethoxy)phenyl]pyridin-3-yl}-6,8,10-trimethyldodeca-2,4,6-trien-1-ol (35): To a solution of pyridone **19** (100 mg, 0.30 mmol) in THF (4 mL) was added *n*BuLi (0.38 mL, 0.60 mmol, 1.6 M in THF) at –78 °C. The resulting mixture was stirred for 15 min, treated with a solution of crude aldehyde **32** (0.22 mmol) in THF (1 mL) dropwise, stirred for 1 h, and then diluted with saturated aq. NH_4Cl solution. The separated organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (20% EtOAc/Hexane) to afford **35** (85 mg, 72%) as a light yellow oil. R_f = 0.3 (30% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3440, 2958, 2924, 1589, 1460, 1383, 1235, 1154, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.36 (d, *J* = 8.6 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 6.37–6.05 (m, 4 H), 5.73 (dd, *J* = 11.0, 5.8 Hz, 1 H), 5.67 (dd, *J* = 6.0, 1.5 Hz, 1 H), 5.54 (dd, *J* = 6.0, 1.5 Hz, 1 H), 5.21 (d, *J* = 10.5 Hz, 1 H), 5.20 (s, 2 H), 4.64 (s, 2 H), 3.69 (d, *J* = 11.0 Hz, 1 H), 3.52 (s, 3 H), 3.49 (s, 3 H), 3.32 (d, *J* = 1.1 Hz, 3 H), 2.64–2.52 (m, 1 H), 1.74 (s, 3 H), 1.32–1.18 (m, 3 H), 1.16–1.02 (m, 2 H), 0.96–0.90 (m, 3 H), 0.84–0.78 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 160.1, 156.8, 147.1, 140.8, 138.6, 132.5, 131.9, 131.3, 130.1, 128.8, 125.5, 125.2, 117.9, 117.8, 116.4, 99.2, 94.3,

91.9, 67.3, 57.7, 57.4, 56.0, 44.8, 32.2, 30.3, 30.0, 21.5, 19.1, 19.0, 12.4, 11.2 ppm. HRMS (ESI): calcd. for $C_{32}H_{45}NNaO_7$ $[M + Na]^+$ 578.3094; found 578.3094.

(2*E*,4*E*,6*E*,8*R*,10*R*)-1-{2,4-Bis(methoxymethoxy)-5-[4-(methoxymethoxy)phenyl]pyridin-3-yl}-6,8,10-trimethyldodeca-2,4,6-trien-1-one (36): To a solution of alcohol **35** (50 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was added MnO_2 (79 mg, 0.9 mmol) at room temperature. The resulting mixture was stirred for 16 h and filtered through Celite. The filtrate was concentrated in vacuo to afford **36** (45 mg, quantitative) as a light yellow oil. R_f = 0.4 (30% EtOAc/hexane). $[\alpha]_D^{19}$ = –151.8 (c = 0.15, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2922, 2851, 1721, 1657, 1579, 1454, 1264, 1236, 1154, 1033, 905 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.39 (d, J = 8.7 Hz, 2 H), 7.12 (dd, J = 15.4, 11.1 Hz, 1 H), 7.07 (d, J = 8.7 Hz, 2 H), 6.62 (d, J = 15.1 Hz, 1 H), 6.44 (d, J = 15.4 Hz, 1 H), 6.33 (dd, J = 15.1, 11.1 Hz, 1 H), 5.51 (s, 2 H), 5.46 (d, J = 9.7 Hz, 1 H), 5.19 (s, 2 H), 4.67 (s, 2 H), 3.49 (s, 3 H), 3.44 (s, 3 H), 3.14 (s, 3 H), 2.67–2.57 (m, 1 H), 1.81 (s, 3 H), 1.31–1.16 (m, 3 H), 1.15–1.06 (m, 2 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.86–0.77 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6, 160.6, 159.4, 156.9, 148.8, 148.2, 147.4, 146.7, 132.3, 130.2, 129.8, 128.3, 125.5, 124.1, 117.4, 116.3, 98.8, 94.3, 91.6, 57.3, 57.0, 56.0, 44.5, 32.3, 30.8, 30.0, 21.1, 19.0, 12.3, 11.2 ppm. HRMS (ESI): calcd. for $C_{32}H_{43}NNaO_7$ $[M + Na]^+$ 576.2937; found 576.2937.

Militarinone D (1): To a solution of **36** (35 mg, 0.06 mmol) in THF/H_2O (7 mL, v/v = 20:1) was added TsOH (4.4 mL, 4.4 mmol, 1 M in hexane) at room temperature. The mixture was stirred for 2 d, and diluted with aqueous sodium hydrogen carbonate solution (10 mL) and ethyl acetate (20 mL). The separated organic layer was washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give a residue that was subjected to silica gel flash column chromatography (MeOH/CH_2Cl_2 = 3:97) to afford militarinone D (**1**; 15 mg, 56%) as a yellow solid. R_f = 0.4 (10% MeOH/CH_2Cl_2). $[\alpha]_D^{19}$ = –46.2 [c = 0.25, MeOH, (ref.[4] $[\alpha]_D^{20}$ = –47,, c 0.25, MeOH)]. IR (KBr): $\tilde{\nu}$ = 3357, 2932, 1648, 1610, 1521, 1466, 1383, 1243, 1124, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.02 (br. s, 1 H), 8.00 (d, J = 14.9 Hz, 2 H), 7.71 (dd, J = 14.9, 11.2 Hz, 1 H), 7.40 (s, 1 H), 7.34 (d, J = 8.3 Hz, 2 H), 6.90 (d, J = 8.3 Hz, 2 H), 6.73 (d, J = 15.0 Hz, 1 H), 6.45 (dd, J = 15.0, 11.2 Hz, 1 H), 5.54 (d, J = 9.8 Hz, 1 H), 2.72–2.57 (m, 1 H), 1.82 (s, 3 H), 1.35–1.20 (m, 3 H), 1.18–1.05 (m, 2 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.85 (t, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5, 177.8, 163.5, 155.6, 149.4, 147.7, 147.3, 137.7, 132.7, 130.4, 126.4, 125.3, 124.7, 116.7, 115.5, 106.4, 44.6, 32.3, 30.9, 30.0, 21.1, 19.1, 12.4, 11.2 ppm. HRMS (ESI): calcd. for $C_{26}H_{31}NNaO_4$ $[M + Na]^+$ 444.2151; found 444.2134.

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