Stereoselective Total Synthesis of Atpenins A4 and B, Harzianopyridone, and NBRI23477 B

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The stereoselective total synthesis of atpenins A4 (2) and B (3), harzianopyridone (4), and NBRI23477 B (5) have been developed using a convergent approach involving the coupling reaction of a common iodopyridine with an aldehyde corresponding to the appropriate side chain of the desired compound. Furthermore, the absolute configurations of atpenin B (3), harzianopyridone (4), and NBRI23477 B (5) have been unambiguously determined.

Key words total synthesis; complex II inhibitor; atpenin A4; atpenin B; harzianopyridone; NBRI23477 B

The atpenins, A5 (**1**), A4 (**2**), and B (**3**), contain a highly functionalized pyridine unit and were first isolated in 1988 from the fermentation broth of the atpenin producing strain *Penicillium* sp. FO-125 as growth inhibitors of both fatty acid synthase deficient (A-1) and acyl-CoA synthase I deficient (L-7) mutants of *Candida lipolytica* and **3** was shown to inhibit the ATP-generating system of Raji cells.[1,2] Harzianopyridone (**4**) was originally isolated from *Trichoderma harzianum* in 1989, showing antifungal, antibacterial, and herbicidal activities.[3,4] NBRI23477 B (**5**) was isolated in 2005 from the culture broth of *Penicillium atramentosum* PF1420, as a growth inhibitor of human prostate cancer cells[5] (Fig. 1). The absolute configurations of atpenins A5 (**1**) and A4 (**2**) have been confirmed by X-ray crystallographic analysis.[6,7] The total synthesis of (±)-atpenin B (**3**) was reported by the Quéguiner group in 1994.[8] In 2003, new interest developed in atpenins A5 (**1**) and A4 (**2**) and harzianopyridone (**4**) when the compounds were reported to provide high levels of inhibition in a microbial screening assay against mitochondrial complex II (succinate-ubiquinone oxidoreductase), which is an attractive target for the treatment of helminthiasis.[9] Atpenin A5 (**1**), in particular, proved to be much more potent against bovine heart complex II than any known complex II inhibitors, although the inhibition of **1** was non-selective between helminthes and mammals. Crystal structure analysis of *Escherichia coli* complex II co-crystallized with atpenin A5 (**1**) has also been achieved.[6] It is clear that atpenins and their analogues are useful chemical tools for elucidation of complex II functionality and that they could act as lead compounds for development of novel helminth complex II-specific inhibitors. Recently, we successfully achieved a stereoselective total synthesis of atpenin A5 (**1**) using a convergent approach[10] and the synthetic strategy is amenable to the synthesis of a variety of atpenin analogues. Herein we report the total synthesis of atpenins A4 (**2**) and B (**3**), harzianopyridone (**4**), and NBRI23477 B (**5**) using the synthetic strategy developed for the total synthesis of **1**. Furthermore, the absolute structures of **3**, **4**, and **5** have been determined.

Results and Discussion

Retrosynthetic Analysis of Atpenins A4 (2) and B (3), Harzianopyridone (4), and NBRI23477 B (5) Retrosynthesis of the target compounds is shown in Chart 1. We anticipated that atpenins A4 (**2**) and B (**3**), harzianopyridone (**4**), and NBRI23477 B (**5**) would possess the same configuration as atpenin A5 (**1**), as shown in Fig. 1. It was envisaged that the compounds could be synthesized by coupling of the common iodopyridine **6**[10] with the corresponding aldehydes **7**, **8**, and **9**, which could in turn be derived from a common intermediate **10** or its equivalent **11**, as was the case for compound **9**.

Total Synthesis of Atpenin A4 (2) The synthesis of atpenin A4 (**2**) started from compound **12**, which was prepared

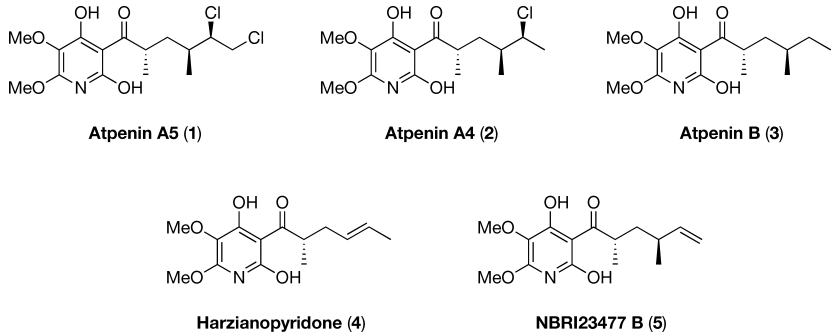

Fig. 1. Structures of Atpenins A5 (**1**), A4 (**2**), and B (**3**), Harzianopyridone (**4**), and NBRI23477 B (**5**)

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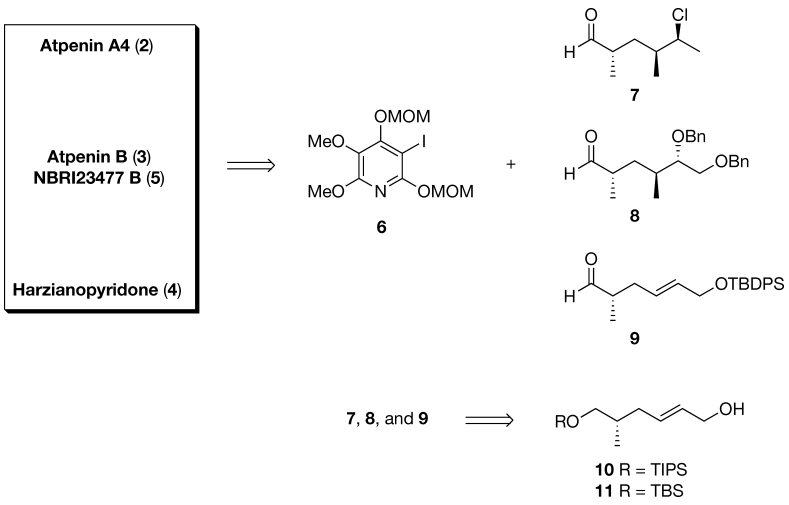
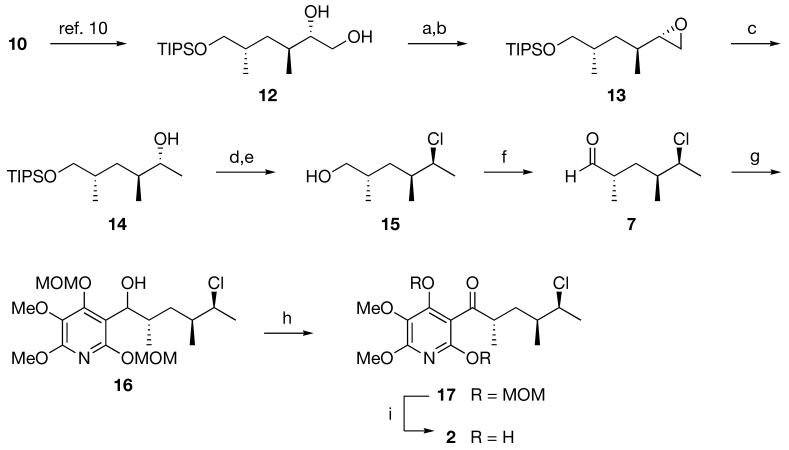


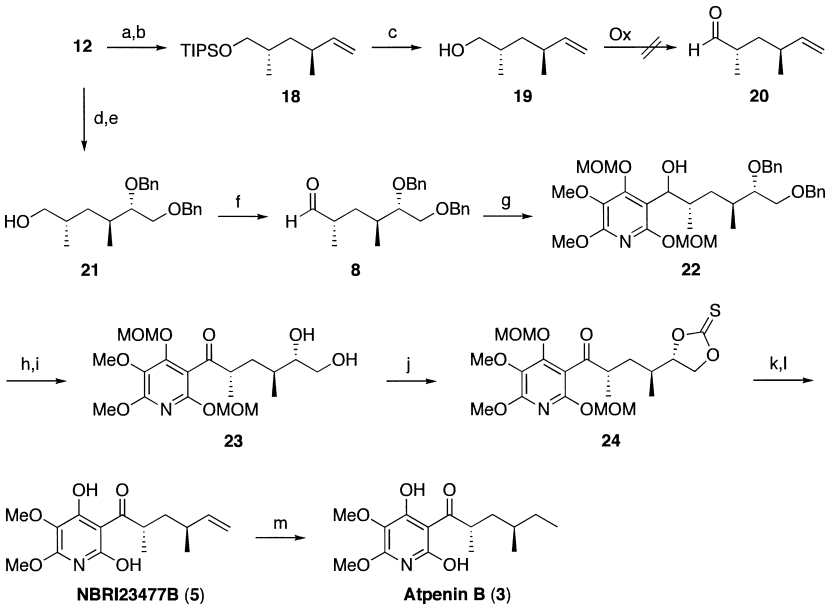
Chart 1. Retrosynthetic Analysis of Atpenins A4 (**2**) and B (**3**), Harzianopyridone (**4**), and NBRI23477 B (**5**)



Reagents and Conditions: (a) *p*-TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, rt, 85%; (b) *n*-BuLi, THF, 0°C, quant.; (c) DIBAL, CH_2Cl_2, −78°C, 97%; (d) NCS, PPh_3, THF, rt; (e) TBAF, THF, rt, 65% (2 steps); (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 75%; (g) **6**, *n*-BuLi, THF, −78°C, 69%; (h) DMP, CH_2Cl_2, rt, 94%; (i) TFA, CH_2Cl_2, 0°C, 97%.
Chart 2

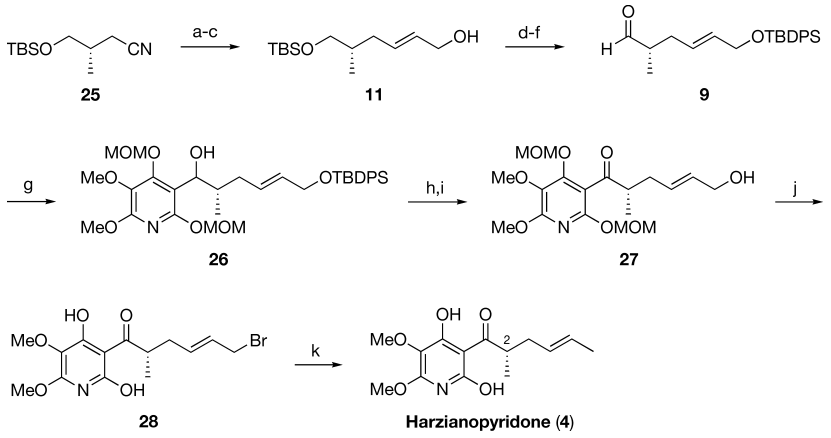
from **10** in four steps[10] (Chart 2). Monotosylation of **12** under standard conditions followed by treatment with *n*-BuLi furnished epoxide **13** in 85% yield over the two steps. Regioselective opening of the epoxide of **13** with bulky reducing agents such as $LiAl(Ot\text{-}Bu)_3H$ proved unsuccessful, whereas reduction with diisobutylaluminium hydride (DIBAL) gave the secondary alcohol **14** in 97% yield. Subsequent chlorination and desilylation furnished a primary alcohol **15** in 65% yield over the two steps. Oxidation of **15** with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) gave the desired aldehyde **7** in 75% yield. Halogen-lithium exchange of iodopyridine **6** with *n*-BuLi followed by a coupling reaction with aldehyde **7** afforded **16** in 65% yield as a diastereomixture. Finally, oxidation of **16** with Dess–Martin periodinane (DMP) gave the ketone **17** in 96% yield, which was subjected to acidic hydrolysis for deprotection of methoxymethyl (MOM) groups to afford the atpenin A4 (**2**) in 97% yield. Synthetic atpenin A4 (**2**) was found to be analytically identical in all respects ($[\alpha]_D$, ^1H- and ^{13}C-NMR, IR, and FAB-MS) to an authentic sample.[1]

Total Synthesis of Atpenin B (3) and NBRI23477 B (5) The synthesis of aldehyde **20** required for the coupling reaction with key intermediate **6** was initially explored as depicted (Chart 3). Diol **12** was heated in toluene with thiocarbonyldiimidazole to give the corresponding cyclic thiocarbonate in 95% yield, which was subsequently converted to **18** in 74% yield by reaction with triethyl phosphite at 100°C.[11] Tetrabutylammonium fluoride (TBAF) mediated triisopropylsilyl (TIPS) deprotection of **18** gave the primary alcohol **19**. Compound **19** was found to have a high volatility and this property was believed to be responsible for the low yields and poor reproducibility observed in the subsequent oxidation reaction. To overcome this problem, an alternative strategy was developed involving the construction of the terminal olefin following the coupling reaction of the aldehyde with the pyridine unit **6**. Benzylation of diol **12** followed by TIPS deprotection gave **21** in 68% yield over the two steps. TEMPO mediated oxidation of **21** gave aldehyde **8** in 92% yield. Halogen-lithium exchange of **6** with *n*-BuLi followed by a coupling reaction with the aldehyde **8** afforded **22** as a diastereomixture in 80% yield. Oxidation of **22** with DMP followed by hydrogenolysis with $Pd(OH)_2/C$ provided the keto-diol **23** in 74% yield over the two steps. Diol **23** was then converted to the cyclic thiocarbonate **24** in 75% yield as described above. Treatment with triethylphosphite at 110°C followed by trifluoroacetic acid (TFA) mediated deprotection of two MOM groups provided NBRI23477 B (**5**) in 47% yield over the two steps. Subsequent



Reagents and Conditions: (a) Thiocarbonyldiimidazole, toluene, 100°C, 95%; (b) $P(OEt)_3$, 100°C, 74%; (c) TBAF, THF, rt; (d) BnBr, NaH, TBAI, THF, 40°C; (e) TBAF, THF, rt, 68% (2 steps); (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 92%; (g) **6**, *n*-BuLi, THF, −78°C, then **8**, 80%; (h) DMP, CH_2Cl_2, rt, 94%; (i) H_2, $Pd(OH)_2$/C, EtOH, rt, 79%; (j) Thiocarbonyldiimidazole, toluene, rt, 75%; (k) $P(OEt)_3$, 110°C, (l) TFA, CH_2Cl_2, 0°C, 47% (2 steps); (m) H_2, Pd/C, EtOH, rt, 92%.

Chart 3



Reagents and Conditions: (a) DIBAL, CH_2Cl_2, −78°C; (b) $Ph_3P{=}CHCO_2Et$, benzene, rt; (c) DIBAL, CH_2Cl_2, 0°C, 73% (3 steps); (d) TBDPSCl, imidazole, DMF, rt, 95%; (e) PPTS, EtOH, rt, 95%; (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 89%; (g) **6**, *n*-BuLi, THF, −78°C, then **9**, 72%; (h) DMP, CH_2Cl_2, rt, 90%; (i) TBAF, THF, rt, 93%; (j) CBr_4, $(CH_2PPh_2)_2$, CH_2Cl_2, 0°C, 56%; (k) $LiEt_3BH$, THF, –78°C, 86%.

Chart 4

hydrogenation of **5** provided atpenin B (**3**) in 92% yield. The analytical properties ($[\alpha]_D$, ^{1}H- and ^{13}C-NMR, IR, and FAB-MS) of synthetic atpenin B (**3**) and NBRI23477 B (**5**) were found to be identical in all respects to those reported for the natural materials,[1,5] confirming that we had successfully achieved the total synthesis of atpenin B (**3**) and NBRI23477 B (**5**) and determined their absolute configurations.

Total Synthesis of Harzianopyridone (4) To avoid the problem encountered above concerning the volatile aldehyde **19** (Chart 4), harzianopyridone (**5**) was synthesized according to the same strategy used in the synthesis of compounds **3** and **5**. Allyl alcohol **11** was prepared from the known nitrile **25**[12] in three steps, according to our total synthesis of **1**.[10] A protection/deprotection sequence followed by TEMPO mediated oxidation gave aldehyde **9** in 80% yield over the three steps. The coupling of the two key segments **6** and **9** was achieved according to the lithium-halogen exchange procedure described above to afford **26** in 72% yield as a diastereomixture. Oxidation of **26** with DMP followed by TBAF mediated *tert*-butyldiphenylsilyl (TBDPS) deprotection afforded allylic alcohol **27** in 84% yield over the two steps.

To complete the total synthesis of harzianopyridone (**4**), removal of the allylic hydroxy group of **27** was required. Unfortunately, our initial attempts to convert **27** to the required allylic compounds by introducing a variety of leaving groups, including mesylate, tosylate, bromide, and iodide under a variety of reaction conditions, led only to no reaction or decomposition. However, treatment of **27** with CBr_4 and $(CH_2PPh_2)_2$[13] provided the required allyl bromide **28** in 56% yield, with concomitant removal of the two MOM groups. Subsequent reduction of the allyl bromide **28** with $LiEt_3BH$ gave the desired product **4** in 86% yield without affecting the carbonyl group probably due to steric hindrance. The synthetic harzianopyridone (**4**) was found to be analytically identical ($[\alpha]_D$, ^{1}H- and

^{13}C-NMR, IR and MS) to the naturally occurring compound[4] in all respects and the absolute stereochemistry was determined to be 2*S*.

Conclusion

The stereoselective total synthesis of atpenins A4 (**2**) and B (**3**), harzianopyridone (**4**), and NBRI23477 B (**5**) have been achieved using a convergent strategy. Furthermore, the absolute stereochemistries of **3**, **4**, and **5** have been unambiguously determined. Evaluation of the associated biological activities and further studies focused on the structure-activity relationships of atpenin analogues are currently underway in our laboratories for the development of novel anthelmintic and anti-tumor agents.

Experimental

General IR spectra were obtained using a Horiba FT-710 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL JNM-EX-270, Agilent Technologies Mercury-300, UNITY-400 and INOVA-600 spectrometers, and chemical shifts were reported on the δ scale and referenced to tetramethylsilane (TMS). Mass spectra were measured with JEOL JMS-700 and JEOL JMS-AX505HA spectrometers. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. Unless otherwise indicated, commercial reagents were used without further purification. Organic solvents were distilled and dried over molecular sieves (3 or 4 Å) prior to use. Reactions were carried out in flame-dried glassware under a positive pressure of argon with magnetic stirring, unless otherwise indicated. Flash column chromatography was carried out on silica gel 60N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 mm Merck silica gel 60 F_{254} plates. Plates were visualized by UV (254 nm) and cerium ammonium molybdate staining.

Triisopropyl-((2*S*,4*S*)-2-methyl-4-((*S*)-oxiran-2-yl)-pentyloxy)silane (13) A solution of **12**[10] (1.03 g, 3.23 mmol) in CH_2Cl_2 (16 mL) was treated with Et_3N (1.34 mL, 9.69 mmol), Me_3N·HCl (30.6 mg, 0.323 mmol), and *p*-toluenesulfonyl chloride (*p*-TsCl) (674 mg, 3.55 mmol). The reaction mixture was stirred at 0°C for 1 h and quenched with water. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (30 : 1 hexanes/EtOAc) to afford the corresponding tosylate (1.29 g, 85%) as a colorless oil: $[\alpha]_D^{27}$ −3.94 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3531, 2917, 1469, 1361, 1247, 1172, 960, 775, 684; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, 2H, *J*=10.7 Hz), 7.35 (d, 2H, *J*=8.4 Hz), 4.12 (dd, 1H, *J*=10.4, 3.0 Hz), 3.98 (dd, 1H, *J*=10.7, 7.4 Hz), 3.65–3.59 (m, 1H), 3.47 (dd, 1H, *J*=8.5, 4.5 Hz), 3.43 (dd, 1H, *J*=9.2, 5.1 Hz), 2.41 (s, 3H), 1.75–1.62 (m, 2H), 1.32–1.16 (m, 2H), 1.10–1.01 (m, 3H), 1.06 (br s, 18H), 0.84 (d, 3H, *J*=7.0 Hz), 0.82 (d, 3H, *J*=6.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 145.2, 133.0, 130.1, 128.2, 74.1, 72.9, 69.5, 35.9, 33.5, 21.9, 18.2, 16.4, 15.4, 12.2; high resolution (HR)-FAB-MS Calcd for $C_{24}H_{45}O_5SSi$: 473.2757, Found: 473.2761.

A solution of the tosylate (545 mg, 1.15 mmol) in tetrahydrofuran (THF) (11 mL) was treated with *n*-BuLi (1.38 M in hexane, 2.74 mL, 2.83 mmol) at −78°C. After stirring for 0.5 h at 0°C, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (100 : 1 hexanes/EtOAc) to afford **13** (348 mg, quant.) as a colorless oil: $[\alpha]_D^{27}$ −23.0 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2942, 2865, 1463, 1367, 1178, 1101, 883, 790, 680; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.51 (d, 2H, *J*=5.2 Hz), 2.72 (dd, 2H, *J*=4.6, 2.7 Hz), 2.50 (dd, 1H, *J*=4.3, 3.4 Hz), 1.81–1.72 (m, 1H), 1.47–1.38 (m, 2H), 1.32–1.28 (m, 1H), 1.11–1.03 (m, 3H), 1.06 (br s, 18H), 0.91 (d, 3H, *J*=6.6 Hz), 0.88 (d, 3H, *J*=7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 68.9, 57.4, 45.8, 37.7, 33.5, 33.2, 18.0, 16.4, 15.4, 12.0; HR-FAB-MS Calcd for $C_{17}H_{37}O_2Si$: 301.2563, Found: 301.2570.

(2*R*,3*S*,5*S*)-3,5-Dimethyl-6-(triisopropylsilyloxy)hexan-2-ol (14) A solution of **13** (0.170 g, 0.565 mmol) in CH_2Cl_2 (6.0 mL) was treated with DIBAL (1.03 M in hexane, 2.74 mL, 2.83 mmol) at −78°C. After stirring for 0.5 h at −78°C, MeOH was added dropwise at −78°C to the resulting solution until the evolution of gas ceased. The mixture was diluted with CH_2Cl_2, treated with Celite (1.0 g) and Na_2SO_4·10H_2O (1.5 g), and then stirred for 2 h at room temperature. The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (30 : 1 hexane/EtOAc) to afford **14** (169 mg, 97%) as a colorless oil: $[\alpha]_D^{27}$ −21.1 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3367, 2944, 2866, 1464, 1383, 1105, 883, 796, 683; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.67–3.59 (m, 1H), 3.48 (d, 2H, *J*=6.5 Hz), 1.78–1.65 (m, 1H), 1.65–1.55 (m, 1H), 1.31–1.16 (m, 2H), 1.13 (d, 3H, *J*=6.1 Hz), 1.10–1.01 (m, 3H), 1.06 (br s, 18H), 0.87 (d, 3H, *J*=1.4 Hz), 0.85 (d, 3H, *J*=2.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 72.2, 69.4, 37.3, 35.9, 33.4, 19.4, 18.0, 16.4, 14.6, 12.0; HR-ESI-MS Calcd for $C_{17}H_{38}O_2SiNa$: 325.2538, Found: 325.2578.

(2*S*,4*S*,5*S*)-5-Chloro-2,4-dimethylhexan-1-ol (15) To a solution of **14** (0.270 g, 0.890 mmol) in THF (4.5 mL) were added *N*-chlorosuccinimide (NCS) (0.180 g, 1.34 mmol) and PPh_3 (0.350 g, 1.34 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched with water, and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was semi-purified by frash silica gel column chromatography (hexane) to afford the crude chloride as a colorless oil.

To a solution of the crude chloride in THF (9.0 mL) was added TBAF (1.0 M THF, 1.68 mL, 1.68 mmol). The reaction mixture was stirred at room temperature for 0.5 h, quenched with a saturated aqueous NH_4Cl solution, and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (30 : 1 hexane/EtOAc) to afford **15** (94.4 mg, 65% over the two steps) as a colorless oil: $[\alpha]_D^{27}$ −24.0 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3352, 2967, 2927, 1458, 1381, 1038, 644; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.16–4.04 (m, 1H), 3.52–3.42 (m, 2H), 1.87–1.78 (m, 1H), 1.75–1.66 (m, 1H), 1.47 (d, 3H, *J*=8.2 Hz), 1.42–1.33 (m, 1H), 1.27–1.21 (m, 1H), 0.95 (d, 3H, *J*=6.8 Hz), 0.91 (d, 3H, *J*=6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 69.0, 64.6, 37.6, 37.4, 33.2, 22.6, 16.4, 14.4.

(2*S*,4*S*,5*S*)-5-Chloro-2,4-dimethylhexanal (7) A solution of **15** (22.0 mg, 0.130 mmol) in CH_2Cl_2 (1.3 mL) was treated with TEMPO (1.6 mg, 10.0 μmol) and $PhI(OAc)_2$ (11.0 mg, 0.330 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with a saturated aqueous $Na_2S_2O_3$ solution, and diluted with CH_2Cl_2. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (100 : 1 hexanes/EtOAc) to afford **7** (15.9 mg, 75%) as a colorless oil: $[\alpha]_D^{27}$ +1.22 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3432, 2970, 2928, 1725, 1457, 1379, 1256, 642, 451; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.69 (d, 1H, *J*=2.6 Hz), 4.16–4.09 (m, 1H), 2.46–2.38 (m, 1H), 1.86–1.77 (m, 1H), 1.77–1.66 (m, 1H), 1.48 (d, 3H, *J*=7.1 Hz), 1.52–1.43 (m, 1H), 1.11 (d, 3H, *J*=7.1 Hz), 0.96 (d, 3H, *J*=6.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.8, 63.0, 43.9, 37.4, 34.5, 22.4, 14.0, 13.5; low resolution-electron ionization (LR-EI)-MS 163 ($[M+H]^+$).

(2*S*,4*S*,5*S*)-5-Chloro-1-(5,6-dimethoxy-2,4-di(methoxymethoxy)pyridin-3-yl)-2,4-dimethylhexan-1-ol (16) A solution of *n*-BuLi (1.57 M in hexane, 1.19 mL, 1.88 mmol) in THF (7.5 mL) was treated with the solution of **6** (289 mg, 0.750 mmol) in THF (3.8 mL) at –78°C, and then the solution of **7** (0.110 g, 0.681 mmol) in THF (3.8 mL) was added. The reaction mixture was stirred for 5 min at –78°C, quenched with a saturated aqueous NH_4Cl solution, and diluted with EtOAc. Then the resulting mixture was allowed to warm to room temperature. After removal of the organic layer, the aqueous layer was extracted with EtOAc, the organic layer was combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (10 : 1 hexane/EtOAc) to afford **16** (198 mg, 69%) as a colorless oil. This material was obtained as a mixture of two diastereomers: $[\alpha]_D^{27}$ −22.0 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3564, 2962, 1590, 1468, 1421, 1159, 1025, 902; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.63–5.48 (m, 2H), 5.37–5.26 (m, 2H), 4.71–4.56 (m, 1H), 4.13–4.01 (m, 1H), 3.94, 3.94 (s, each 3H), 3.75, 3.74 (s, each 3H), 3.57, 3.56 (s, each 3H), 3.52, 3.52 (s, each 3H), 2.17–1.97 (m, 1H), 1.85–1.69 (m, 1H), 1.51, 1.42 (d, each 3H, *J*=7.1, 7.1 Hz), 1.36–1.24 (m, 2H), 1.07 (d, 3H, *J*=6.3 Hz), 0.98 (d, 3H, *J*=5.5 Hz), 0.83 (d, 3H, *J*=6.3 Hz), 0.72 (d, 3H, *J*=8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.1, 157.0, 154.9, 153.0, 152.9, 129.8, 129.7, 110.0, 109.6, 99.2, 91.8, 72.2, 72.0, 64.8, 64.3, 60.6, 60.5, 57.8, 57.4, 57.3, 53.6, 53.5, 38.0, 37.6, 37.4, 37.3, 36.6, 22.4, 22.2, 16.0, 15.8, 14.5, 13.9; HR-electrospray ionization (ESI)-MS Calcd for $C_{19}H_{32}O_7NClNa$: 444.1765, Found: 444.1776.

(2*S*,4*S*,5*S*)-5-Chloro-1-(5,6-dimethoxy-2,4-di(methoxymethoxy)pyridin-3-yl)-2,4-dimethylhexan-1-one (17) A solution of **16** (131 mg, 0.311 mmol) in CH_2Cl_2 (3.1 mL) was treated with Dess–Martin periodinane (198 mg, 0.467 mmol). The reaction mixture was stirred at room temperature for 0.5 h, quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (20 : 1 hexane/EtOAc) to afford **17** (123 mg, 94%) as a colorless oil: $[\alpha]_D^{27}$ −6.4 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2969, 1699, 1585, 1459, 1389, 1114, 897; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.48 (s, 2H), 5.30 (s, 2H), 4.17 (ddd, 1H, *J*=13.4, 6.7, 3.1 Hz), 3.97 (s, 3H), 3.77 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.25–3.12 (m, 1H), 1.91–1.82 (m, 1H), 1.81–1.74 (m, 1H), 1.58–1.52 (m, 1H), 1.47 (d, 3H, *J*=6.4 Hz), 1.15 (d, 3H, *J*=7.1 Hz), 0.95 (d, 3H, *J*=7.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.9, 157.0, 156.0, 152.7, 129.8, 110.7, 98.9, 91.8, 63.3, 60.7, 57.6, 57.3, 53.9, 44.3, 37.4, 36.5, 22.6, 16.1, 14.0; HR-ESI-MS Calcd for $C_{19}H_{30}O_7NClNa$: 442.1608, Found: 442.1601.

Atpenin A4 (2) A solution of **17** (96.0 mg, 0.230 mmol) in CH_2Cl_2 (2.3 mL) was treated with TFA (2.3 mL) at 0°C, and the mixture was stirred at 0°C for 0.5 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (15 : 1 hexane/EtOAc) to afford atpenin A4 (**2**) (73.5 mg, 97%) as a colorless solid: $[\alpha]_D^{27}$ −8.5 (*c*=1.0, EtOH), (lit.[1]) $[\alpha]_D^{22}$ −8.6 (*c*=1.0, EtOH)); IR (KBr) cm^{-1}: 1642, 1606, 1463, 1324, 1191, 1161, 997; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.13 (s, 3H), 4.20–4.11 (m, 1H), 4.10 (dq, 1H, *J*=2.8, 5.5 Hz), 3.79 (s, 3H), 1.86–1.78 (m, 1H), 1.78–1.72 (m, 1H), 1.52 (dt, 1H, *J*=6.4, 12.9 Hz), 1.45 (d, 3H, *J*=5.7 Hz), 1.14 (3H, d, *J*=7.8 Hz), 0.96 (d, 3H, *J*=6.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 210.5, 172.9, 162.2, 155.6, 121.1, 101.0, 63.3, 61.8, 58.4, 39.9, 37.9, 37.3, 23.0, 18.2, 14.4; HR-FAB-MS Calcd for $C_{15}H_{23}O_5NCl$: 332.1265, Found: 332.1274.

(2*S*,4*S*,5*S*)-5,6-Di(benzyloxy)-2,4-dimethylhexan-1-ol (21) A solution of **12** (479 mg, 1.50 mmol) in THF (15 mL) was treated with NaH (192 mg, 4.80 mmol). After stirring for 0.5 h at 0°C, a resulting solution was treated with benzyl bromide (BnBr) (0.534 mL, 4.50 mmol) and tetrabutylammonium iodide (TBAI) (16.6 mg, 45.0 μmol). The reaction mixture was stirred at 40°C for 8 h, quenched with water, and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was semi-purified by frash silica gel column chromatography (60 : 1 hexane/EtOAc) to afford the crude dibenzyl ether as a colorless oil.

A solution of the crude dibenzyl ether in THF (15 mL) was treated with TBAF (1.0 M THF, 2.25 mL, 2.25 mmol). The reaction mixture was stirred at room temperature for 0.5 h, quenched with a saturated aqueous NH_4Cl solution, and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (3 : 1 hexane/EtOAc) to afford **21** (349 mg, 68% over the two steps) as a colorless oil: $[\alpha]_D^{27}$ –22.4 (*c*=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3423, 3063, 3030, 2924, 2869, 1455, 1369, 1097, 738, 698; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38–7.25 (m, 10H), 4.72 (d, 1H, *J*=12.7 Hz), 4.56 (d, 1H, *J*=11.9 Hz), 4.53 (d, 2H, *J*=1.3 Hz) 3.63–3.56 (m, 2H), 3.46–3.37 (m, 3H), 1.95–1.85 (m, 1H), 1.73–1.64 (m, 1H), 1.27–1.19 (m, 2H), 0.90 (d, 3H, *J*=7.2 Hz), 0.86 (d, 3H, *J*=7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 139.0, 138.4, 128.4, 128.3, 128.0–127.7, 127.6, 127.5, 83.1, 73.4, 72.7, 71.2, 68.9, 35.4, 33.3, 32.2, 16.0, 15.7; HR-ESI-MS Calcd for $C_{22}H_{30}O_3Na$: 365.2093, Found: 365.2080.

(2*S*,4*S*,5*S*)-5,6-Di(benzyloxy)-2,4-dimethylhexanal (8) To a solution of **21** (336 mg, 0.982 mmol) in CH_2Cl_2 (10 mL) were added TEMPO (15.0 mg, 0.0982 mmol) and $PhI(OAc)_2$ (788 mg, 2.45 mmol). The reaction mixture was stirred at room temperature for 4.5 h, quenched with a saturated aqueous

$Na_2S_2O_3$ solution, and diluted with CH_2Cl_2. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (60 : 1 hexane/EtOAc) to afford **8** (307 mg, 92%) as a colorless oil: $[\alpha]_D^{27}$ −14.4 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2964, 2929, 2869, 1724, 1456, 1369, 1206, 1097, 739, 699; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.58 (d, 1H, J=2.5 Hz), 7.35–7.25 (m, 10H), 4.70 (d, 1H, J=12.7 Hz), 4.54 (d, 1H, J=7.2 Hz), 4.52 (d, 2H, J=9.0 Hz), 3.63–3.56 (m, 2H), 3.45–3.41 (m, 1H), 2.43–2.33 (m, 1H), 1.96–1.86 (m, 1H), 1.63–1.55 (m, 1H), 1.49–1.41 (m, 1H), 1.04 (d, 3H, J=8.6 Hz), 0.92 (d, 3H, J=6.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 205.2, 139.0, 138.4, 128.5, 128.4, 127.9, 127.8, 127.6, 82.5, 73.5, 72.7, 70.7, 44.3, 32.6, 25.9, 15.8, 13.2; HR-ESI-MS Calcd for $C_{22}H_{28}O_3Na$: 363.1936, Found: 363.1921.

(2*S*,4*S*,5*S*)-5,6-Di(benzyloxy)-1-(5,6-dimethoxy-2,4-di(methoxymethoxy)pyridin-3-yl)-2,4-dimethylhexan-1-ol (22) A solution of *n*-BuLi (1.57 M in hexane, 1.52 mL, 2.40 mmol) in THF (10 mL) was treated with the solution of **6** (367 mg, 0.960 mmol) in THF (5.0 mL) at −78°C, and then the solution of **8** (297 mg, 0.873 mmol) in THF (5.0 mL) was added. The reaction mixture was stirred for 5 min at −78°C, quenched with a saturated aqueous NH_4Cl solution, and diluted with EtOAc. Then the resulting mixture was allowed to warm to room temperature. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (10 : 1 hexane/EtOAc) to afford **22** (0.420 g, 80%) as a colorless oil. This material was obtained as a mixture of two diastereomers: $[\alpha]_D^{27}$ –31.4 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3564, 2956, 1590, 1466, 1391, 1159, 905, 738, 699; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38–7.21 (m, 10H), 5.58–5.43 (m, 2H), 5.34–5.22 (m, 2H), 4.74–4.47 (m, 5H), 3.92, 3.92 (s, each 3H), 3.73, 3.68 (s, each 3H), 3.65–3.61 (m, 1H), 3.45–3.43 (m, 2H), 3.53, 3.51 (s, each 3H), 3.49, 3.46 (s, each 3H), 2.14–2.04 (m, 1H), 1.93–1.81 (m, 1H), 1.39–1.27 (m, 1H), 1.05 (d, 3H, J=5.8 Hz), 0.91 (d, 3H, J=7.2 Hz), 0.97–0.81 (m, 1H), 0.76 (d, 3H, J=8.4 Hz), 0.67 (d, 3H, J=8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.2, 157.1, 154.9, 153.0, 139.2, 138.5, 138.4, 129.8, 128.3, 128.1, 127.6, 127.5, 127.4, 127.2, 110.0, 99.2, 99.1, 91.8, 83.4, 83.2, 73.3, 72.6, 72.5, 72.4, 72.2, 71.2, 60.5, 57.8, 57.4, 53.5, 36.8, 36.7, 35.9, 35.6, 32.6, 32.5, 15.9, 15.8, 15.3, 15.1; HR-ESI-MS Calcd for $C_{33}H_{45}O_9NNa$: 622.2992, Found: 622.2962.

(2*S*,4*S*,5*S*)-1-(5,6-Dimethoxy-2,4-bis(methoxymethoxy)-pyridin-3-yl)-5,6-dihydroxy-2,4-dimethylhexan-1-one (23) A solution of **22** (0.420 g, 0.701 mmol) in CH_2Cl_2 (7.0 mL) was treated with Dess–Martin periodinane (445 mg, 1.05 mmol). The mixture was stirred at room temperature for 0.5 h, quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (5 : 1 hexane/EtOAc) to afford the corresponding ketone (391 mg, 94%) as a colorless oil: $[\alpha]_D^{27}$ −17.7 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2934, 1698, 1585, 1457, 1389, 1158, 1029, 898, 741, 699; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33–7.24 (m, 10H), 5.43 (dd, 2H, J=8.9, 5.8 Hz), 5.25 (dd, 2H, J=8.5, 5.5 Hz), 4.67 (d, 1H, J=11.5 Hz), 4.53 (d, 1H, J=7.4 Hz), 4.52 (d, 2H, J=9.0 Hz), 3.94 (s, 3H), 3.74 (s, 3H), 3.60–3.57 (m, 2H), 3.45 (s, 3H), 3.45–3.43 (m, 1H), 3.43 (s, 3H), 3.15–3.08 (m, 1H), 1.96–1.86 (m, 1H), 1.66–1.54 (m, 2H), 1.11 (d, 3H, J=8.8 Hz), 0.88 (d, 3H, J=5.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.9, 157.1, 156.1, 154.7, 139.1, 138.4, 129.2, 128.4, 128.2, 127.6, 127.5, 127.5, 109.8, 99.0, 91.7, 82.9, 73.4, 72.5, 71.1, 60.7, 57.6, 57.2, 53.9, 44.8, 34.3, 32.7, 15.4, 15.1; HR-ESI-MS Calcd for $C_{33}H_{43}O_9NNa$: 620.2835, Found: 620.2821.

A suspension of the ketone (16.1 mg, 0.0269 mmol) and 20% $Pd(OH)_2$/C (3.2 mg) in EtOH (2.6 mL) was vigorously stirred under a H_2 atmosphere at room temperature for 2 h. The catalyst was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (1 : 2 hexane/EtOAc) to afford **23** (8.9 mg, 79%) as a colorless oil: $[\alpha]_D^{27}$ −6.9 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3479, 2933, 1695, 1587, 1468, 1389, 1212, 1114, 756, 612, 428; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.47 (dd, 2H, J=12.4, 5.8 Hz), 5.28 (s, 2H), 3.95 (s, 3H), 3.76 (s, 3H), 3.71–3.67 (m, 1H), 3.48–3.45 (m, 2H), 3.47 (s, 6H), 3.25–3.17 (m, 1H), 1.82–1.73 (m, 1H), 1.73–1.69 (m, 1H), 1.62–1.51 (m, 1H), 1.14 (d, 3H, J=7.8 Hz), 0.88 (d, 3H, J=7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 210.8, 205.8, 157.0, 156.1, 152.7, 129.8, 110.5, 99.0, 91.9, 75.8, 64.5, 60.8, 57.7, 57.4, 44.4, 34.5, 34.0, 16.1, 15.3; HR-ESI-MS Calcd for $C_{19}H_{31}O_9NNa$: 440.1896, Found: 440.1874.

(2*S*,4*S*)-1-(5,6-Dimethoxy-2,4-di(methoxymethoxy)-pyridin-3-yl)-2-methyl-4-((*S*)-2-thioxo-1,3-dioxolan-4-yl)-pentan-1-one (24) A solution of **23** (34.8 mg, 0.0834 mmol) in toluene (1.6 mL) was treated with thiocarbonyldiimidazole (17.8 mg, 0.100 mmol). The reaction mixture was stirred at room temperature for 4 h, quenched with water, and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (3 : 1 hexane/EtOAc) to afford **24** (29.0 mg, 75%) as a colorless oil: $[\alpha]_D^{27}$ −24.0 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3467, 2931, 2360, 1584, 1458, 1288, 1158, 896; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.50 (d, 1H, J=7.2 Hz), 5.44 (d, 1H, J=5.6 Hz), 5.28 (s, 2H), 4.78 (dd, 1H, J=15.7, 8.3 Hz), 4.64 (t, 1H, J=8.8 Hz), 4.35 (t, 1H, J=8.2 Hz), 3.95 (s, 3H), 3.75 (s, 3H), 3.46 (s, 6H), 3.24–3.15 (m, 1H), 2.11–2.03 (m, 1H), 1.74–1.66 (m, 1H), 1.62–1.54 (m, 1H), 1.14 (d, 3H, J=7.6 Hz), 0.95 (d, 3H, J=9.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.3, 191.9, 157.2, 152.7, 129.7, 110.2, 99.0, 93.2, 91.9, 86.1, 71.0, 60.9, 57.8, 54.3, 44.3, 34.6, 34.0, 33.9, 15.7, 13.8; HR-ESI-MS Calcd for $C_{20}H_{29}O_9NSNa$: 482.1460, Found: 482.1458.

NBRI23477 B (5) A solution of **24** (28.9 mg, 0.0631 mmol) in $P(OEt)_3$ (1.2 mL) was stirred at 110°C for 36 h. The resulting solution was semi-purified by frash silica gel column chromatography (10 : 1 hexane/EtOAc) to afford a mixture of **5** and MOM-protected **5**.

To a solution of the mixture in CH_2Cl_2 (0.4 mL) was added TFA (0.350 mL) at 0°C. The resulting mixture was stirred at 0°C for 15 min and concentrated *in vacuo*. The residue was purified by preparative TLC (2 : 1 hexane/EtOAc) to afford NBRI23477 B (**5**) (8.8 mg, 47% over the two steps) as a white solid: $[\alpha]_D^{27}$ −14.0 (c=0.2, EtOH), (lit.[5] $[\alpha]_D^{20}$ –39.0 (c=0.2, EtOH)); IR (KBr) cm^{-1}: 2928, 1646, 1596, 1455, 1324, 1201,

1162, 996; ^{1}H-NMR (400 MHz, pyridine-d_6) δ: 5.79 (ddd, 1H, J=17.4, 10.2, 7.5 Hz), 4.99 (dd, 1H, J=17.2, 1.2 Hz), 4.94 (dd, 1H, J=10.7, 1.3 Hz), 4.45–4.40 (m, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.35–2.31 (m, 1H), 2.13–2.07 (m, 1H), 1.46–1.39 (m, 1H), 1.33 (d, 3H, J=6.9 Hz), 1.07 (d, 3H, J=6.7 Hz); ^{13}C-NMR (100 MHz, pyridine-d_6) δ: 211.1, 165.6, 162.6, 159.9, 145.0, 124.8, 113.0, 100.8, 60.5, 54.2, 42.1, 40.8, 36.4, 20.3, 18.0; HR-ESI-MS Calcd for $C_{15}H_{21}O_5NNa$: 318.1317, Found: 318.1311.

Atpenin B (3) A suspension of **5** (3.8 mg, 0.0128 mmol) and 5% Pd/C (1.0 mg) in EtOH (1.2 mL) was vigorously stirred under a H_2 atmosphere at room temperature for 4 h. The catalyst was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (2 : 1 hexane/EtOAc) to afford **3** (3.5 mg, 92%) as a white solid: $[\alpha]_D^{27}$ −14.5 (c=0.1, EtOH), (lit.[1]) $[\alpha]_D^{22}$ −27.0 (c=1.0, EtOH)); IR (KBr) cm^{-1}: 1645, 1595, 1456, 1323, 1203, 1159, 996; ^{1}H-NMR (400 MHz, pyridine-d_6) δ: 4.35–4.27 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 1.73 (ddd, 1H, J=13.8, 7.8, 5.0 Hz), 1.43–1.36 (m, 1H), 1.34–1.29 (m, 1H), 1.28–1.20 (m, 1H), 1.20 (d, 3H, J=6.5 Hz), 1.11–1,02 (m, 1H), 0.87 (d, 3H, J=7.2 Hz), 0.72 (t, 3H, J=7.7 Hz); ^{13}C-NMR (100 MHz, pyridine-d_6) δ: 211.6, 165.7, 162.6, 159.9, 124.8, 100.6, 60.6, 54.2, 41.9, 41.0, 30.6, 19.0, 17.0, 20.0, 11.7; HR-ESI-MS Calcd for $C_{15}H_{23}O_5NNa$: 320.1473, Found: 320.1460.

(*S*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-5-methylhex-2-en-1-ol (11) A solution of **25** (4.26 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was treated with DIBAL (1.02 M in hexane, 45.0 mL, 46.0 mmol) at –78°C. After stirring for 1 h at −78°C, 3N aqueous HCl solution was added dropwise to the resulting solution until the evolution of gas ceased. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

A solution of the residue in benzene (200 mL) was treated with (carbethoxymethylene)triphenylphosphorane (13.8 g, 40.0 mmol). After stirring at room temperature for 12 h, the resulting solution was concentrated *in vacuo*. The residue was semi-purified by frash silica gel column chromatography (30 : 1 hexanes/EtOAc) to afford the crude α,β-unsaturated ester.

A solution of the crude ester in CH_2Cl_2 (182 mL) was treated with DIBAL (1.02 M in hexane, 44.8 mL, 45.7 mmol) at 0°C. After stirring for 1 h at 0°C, MeOH was added dropwise to the resulting solution until the evolution of gas ceased. The mixture was diluted with CH_2Cl_2, treated with celite (13.4 g) and $Na_2SO_4 \cdot 10H_2O$ (15.8 g), and then stirred for 2 h at room temperature. The resulting solution was filtered through a pad of celite, the filtrate was concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (20 : 1 hexane/EtOAc) to afford **11** (3.55 g, 73% over the three steps) as a colorless oil: $[\alpha]_D^{27}$ +1.74 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3342, 2954, 2858, 1467, 1254, 1092, 1006, 972, 839, 776, 668; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.70–5.64 (m, 2H), 4.10 (d, 2H, J=4.1 Hz), 3.41 (d, 2H, J=4.1 Hz), 2.25–2.15 (m, 1H), 1.89–1.80 (m, 1H), 1.72–1.63 (m, 1H), 0.89 (s, 9H), 0.87 (d, 3H, J=6.6 Hz), 0.03 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 131.9, 130.6, 68.0, 64.1, 36.2, 36.1, 26.2, 18.6, 16.6, −5.1; HR-FAB-MS Calcd for $C_{13}H_{28}O_2SiNa$: 267.1756, Found: 267.1761.

(*S*,*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhex-4-enal (9) A solution of **11** (3.54 g, 14.5 mmol) in dimethylformamide (DMF) (29 mL) was treated with imidazole (1.98 g, 29.0 mmol) and TBDPSCl (4.10 mL, 16.0 mmol). The reaction mixture was stirred at room temperature for 0.5 h. The resulting solution was diluted with water and EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (70 : 1 hexane/EtOAc) to afford the corresponding TBDPS ether (7.01 g, 95%) as a colorless oil: $[\alpha]_D^{27}$ +4.88 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2955, 2931, 2858, 1468, 1254, 1108, 838, 704, 504; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.73–7.67 (m, 4H), 7.46–7.34 (m, 6H), 5.72–5.51 (m, 2H), 4.16 (dd, 2H, J=4.5, 1.0 Hz), 3.47–3.36 (m, 2H), 2.21–2.11 (m, 1H), 1.88–1.78 (m, 1H), 1.72–1.60 (m, 1H), 1.06 (s, 9H), 0.90 (s, 9H), 0.86 (d, 3H, J=7.1 Hz), 0.03 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 135.9, 134.3, 130.5, 129.9, 129.7, 127.9, 68.1, 64.9, 36.3, 36.2, 27.2, 26.3, 19.6, 18.7, 16.7; HR-ESI-MS Calcd for $C_{29}H_{46}O_2Si_2Na$: 505.2934, Found: 505.2920.

A solution of the TBDPS ether (50.0 mg, 0.104 mmol) in EtOH (1.0 mL) was treated with pyridinium p-toluenesulfonate (PPTS) (13.0 mg, 0.0520 mmol). The mixture was stirred at room temperature for 24 h. The resulting solution was diluted with water and EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (15 : 1 hexane/EtOAc) to afford the corresponding alcohol (36.5 mg, 95%) as a colorless oil: $[\alpha]_D^{27}$ +3.76 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3378, 2932, 2859, 1964, 1467, 1428, 1110, 702, 610, 503; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67–7.61 (m, 4H), 7.41–7.30 (m, 6H), 5.68–5.48 (m, 2H), 4.13 (dd, 2H, J=4.6, 1.1 Hz), 3.49–3.36 (m, 2H), 2.15–2.06 (m, 1H), 1.93–1.83 (m, 1H), 1.72–1.61 (m, 1H), 1.01 (s, 9H), 0.86 (d, 3H, J=7.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 135.6, 133.9, 130.5, 129.7, 129.2, 127.7, 67.7, 64.6, 36.2, 35.9, 27.0, 19.3, 16.5; HR-ESI-MS Calcd for $C_{23}H_{32}O_2SiNa$: 391.2069, Found: 391.2064.

A solution of the alcohol (412 mg, 1.12 mmol) in CH_2Cl_2 (11.2 mL) was treated with TEMPO (17.4 mg, 0.112 mmol) and $PhI(OAc)_2$ (902 mg, 2.80 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with a saturated aqueous $Na_2S_2O_3$ solution, and diluted with CH_2Cl_2. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (60 : 1 hexane/EtOAc) to afford **9** (367 mg, 89%) as a colorless oil: $[\alpha]_D^{27}$ +7.77 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2932, 2858, 1727, 1429, 1110, 822, 741, 704, 505; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.60 (d, 1H, J=1.3 Hz), 7.64–7.60 (m, 4H), 7.38–7.30 (m, 6H), 5.63–5.54 (m, 2H), 4.11 (dd, 2H, J=2.7, 1.6 Hz), 2.44–2.39 (m, 2H), 2.12–2.02 (m, 1H), 1.04 (d, 3H, J=7.7 Hz), 1.01 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.6, 135.6, 133.8, 131.7, 129.7, 127.7, 126.8, 64.2, 46.1, 33.2, 26.8, 19.2, 13.0; HR-ESI-MS Calcd for $C_{23}H_{30}O_2SiNa$: 389.1913, Found: 389.1903.

(2*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-1-(5,6-dimethoxy-2,4-di(methoxymethoxy)pyridin-3-yl)-2-methylhex-4-en-1-ol (26) A solution of *n*-BuLi (1.57 M in hexane, 1.75 mL, 2.75 mmol) in THF (11 mL) was treated with the solution of **6** (423 mg, 1.10 mmol) in THF (5.5 mL) at −78°C, and then the solution of **9** (366 mg, 1.00 mmol) in THF (5.5 mL) was added. The reaction mixture was stirred for 5 min at −78°C, quenched with a saturated aqueous NH_4Cl solution,

and diluted with EtOAc. Then the resulting mixture was allowed to warm to room temperature. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (5 : 1 hexane/EtOAc) to afford **26** (449 mg, 72%) as a colorless oil. This material was obtained as a mixture of two diastereomers: $[\alpha]_D^{27}$ −5.0 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3564, 2931, 1589, 1466, 1390, 1107, 903, 701; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.70–7.64 (m, 4H), 7.44–7.33 (m, 6H), 5.78–5.43 (m, 3H), 5.35–5.24 (m, 2H), 4.68–4.60 (m, 1H), 4.18, 4.11 (d, each 2H, J=4.2, 4.9 Hz), 3.93, 3.92 (s, each 3H), 3.74, 3.73 (s, each 3H), 3.53, 3.53 (s, each 3H), 3.49, 3.49 (s, each 3H), 2.18–1.92 (m, 2H), 1.83–1.72 (m, 1H), 1.07 (d, 3H, J=8.2 Hz), 1.04 (s, 9H), 0.70 (d, 3H, J=7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.2, 157.0, 155.0, 153.1, 135.5, 133.9, 133.8, 130.4, 130.1, 129.9, 129.8, 129.5, 127.6, 110.0, 109.9, 99.1, 91.7, 71.8, 71.4, 64.6, 64.5, 60.5, 57.8, 57.4, 57.3, 53.6, 53.5, 39.4, 39.3, 36.4, 36.1, 26.8, 26.7, 19.2, 16.1, 15.8; HR-ESI-MS Calcd for $C_{34}H_{47}O_8NSiNa$: 648.2968, Found: 648.2963.

(*S*,*E*)-1-(5,6-Dimethoxy-2,4-bis(methoxymethoxy)-pyridin-3-yl)-6-hydroxy-2-methylhex-4-en-1-one (27) A solution of **26** (249 mg, 0.398 mmol) in CH_2Cl_2 (4 mL) was treated with Dess–Martin periodinane (0.250 g, 0.598 mmol). The mixture was stirred at room temperature for 0.5 h, quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (20 : 1 hexane/EtOAc) to afford the corresponding ketone (224 mg, 90%) as a colorless oil: $[\alpha]_D^{27}$ −1.98 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 2934, 1699, 1585, 1466, 1389, 1110, 898, 704, 504; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72–7.62 (m, 4H), 7.46–7.33 (m, 6H), 5.66–5.57 (m, 2H), 5.46 (d, 2H, J=1.1 Hz), 5.26 (d, 2H, J=2.9 Hz), 4.15 (d, 2H, J=3.15 Hz), 3.95 (s, 3H), 3.75 (s, 3H), 3.46 (s, 3H), 3.44 (s, 3H), 3.14–3.07 (m, 1H), 2.57–2.50 (m, 1H), 2.15–2.02 (m, 1H), 1.13 (d, 3H, J=5.8 Hz), 1.04 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.6, 156.9, 156.1, 152.7, 135.5, 133.8, 131.1, 129.9, 129.6, 128.3, 127.6, 110.8, 98.9, 91.7, 64.4, 60.7, 57.6, 57.3, 53.9, 47.0, 35.0, 26.8, 19.2, 15.2; HR-ESI-MS Calcd for $C_{34}H_{45}O_8NSiNa$: 646.2812, Found: 646.2792.

To a solution of the ketone (224 mg, 0.360 mmol) in THF (3.6 mL) was added TBAF (1.0 M THF, 0.540 mL, 0.540 mmol). The reaction mixture was stirred at room temperature for 0.5 h, quenched with water, and diluted with EtOAc. After removal of the organic layer, the aqueous layer was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (3 : 1 hexane/EtOAc) to afford **27** (128 mg, 93%) as a colorless oil: $[\alpha]_D^{27}$ −9.6 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3448, 2080, 1628, 1585, 1456, 1425, 1390, 1118, 919, 755; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.71–5.64 (m, 2H), 5.48 (dd, 2H, J=14.0, 5.7 Hz), 5.27 (s, 2H), 4.09–4.04 (m, 2H), 3.96 (s, 3H), 3.76 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.17 (dd, 1H, J=13.9, 7.7 Hz), 2.58–2.49 (m, 1H), 2.21–2.12 (m, 1H), 1.16 (d, 3H, J=8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.6, 157.0, 156.0, 152.8, 131.2, 129.9, 129.8, 110.7, 99.0, 91.8, 63.5, 60,7, 57.7, 57.3, 53.9, 46.9, 35.2, 15.6; HR-ESI-MS Calcd for $C_{18}H_{27}O_8NNa$: 408.1634, Found: 408.1620.

(*S*,*E*)-6-Bromo-1-(2,4-dihydroxy-5,6-dimethoxypyridin-3-yl)-2-methylhex-4-en-1-one (28) A solution of the **27** (53.0 mg, 0.138 mmol) in CH_2Cl_2 (1.4 mL) was treated with CBr_4 (137 mg, 0.414 mmol) and $(CH_2PPh_2)_2$ (165 mg, 0.414 mmol). The reaction was stirred at 0°C for 0.5 h and concentrated *in vacuo*. The residue was purified by frash silica gel column chromatography (3 : 1 hexane/EtOAc) to afford **28** (27.9 mg, 56%) as a colorless oil: $[\alpha]_D^{27}$ −9.2 (c=1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3448, 2080, 1628, 1585, 1456, 1425, 1390, 1118, 919, 755; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.85–5.65 (m, 2H), 4.18 (s, 3H) 4.06–3.95 (m, 1H), 3.92 (d, 2H, J=6.0 Hz), 3.80 (s, 3H), 2.58–2.50 (m, 1H), 2.19–2.11 (m, 1H), 1.15 (d, 3H, J=7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 209.0, 171.2, 161.7, 155.6, 133.9, 128.4, 121.4, 100.3, 61.5, 57.5, 42.6, 35.5, 32.8, 16.3; HR-FAB-MS Calcd for $C_{14}H_{19}O_5NBr$: 360.0477, Found: 360.0432.

(−)-Harzianopyridone (4) A solution of **28** (25.3 mg, 0.0705 mmol) in THF (1.4 mL) was treated with $LiEt_3BH$ (323 mL, 0.352 mmol, 1.09 M in THF) at −78°C. The mixture was stirred at −78°C for 12 h, quenched with water, and diluted with CH_2Cl_2. Then the resulting mixture was allowed to warm to room temperature. After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (1 : 5 hexane/EtOAc) to afford **4** (17.0 mg, 86%) as a white solid: $[\alpha]_D^{27}$ −8.4 (c=0.1, MeOH), (lit.[4]) $[\alpha]_D^{22}$ −12.3 (c=0.1, MeOH)); IR (KBr) cm^{-1}: 2925, 1645, 1598, 1458, 1375, 1324, 1284, 1199, 1165, 1110, 996, 961, 804, 740, 623; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.50–5.35 (m, 2H), 4.15 (s, 3H), 3.96 (m, 1H), 3.81 (s, 3H), 2.49–2.41 (m, 1H), 2.09–1.99 (m, 1H), 1.63 (d, 3H, J=5.0 Hz), 1.13 (d, 3H, J=6.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 210.0, 172.3, 161.9, 155.4, 128.7, 127.2, 121.3, 100.8, 61.7, 58.0, 43.2, 36.1, 18.1, 16.4; HR-FAB-MS Calcd for $C_{14}H_{20}O_5N$: 282.1341, Found: 282.1353.

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