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ORIGINAL ARTICLE

Enantioselective total synthesis of atpenin A5

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Enantioselective total synthesis of atpenin A5, a potent mitochondrial complex II (succinate-ubiquinone oxidoreductase) inhibitor, has been achieved by a convergent approach through a coupling reaction between 5-iodo-2,3,4,6-tetraalkoxypyridine and a side-chain aldehyde. The two key segments were synthesized through *ortho*-metalation/boronation with $(MeO)_3B$/oxidation with *m*CPBA, *ortho*-iodination, halogen dance reaction, Sharpless epoxidation and regioselective epoxide-opening reaction. This synthetic study resulted in the revision of the earlier reported ^{1}H-NMR data of the natural atpenin A5 and the confirmation of the stereochemical assignment.
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INTRODUCTION

Atpenins[1,2] were first isolated from the fermentation broth of a fungal 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 atpenin B were shown to inhibit the ATP-generating system of Raji cells (Figure 1). They inhibited the growth of filamentous fungi. The absolute configuration of atpenin A4 (**2**) was confirmed by X-ray crystallographic analysis.[3] The total synthesis of (±)-atpenin B (**1**) was reported by Quéguiner and co-workers.[4] Recently, atpenins were rediscovered as a result of microbial screening for mitochondrial complex II (succinate-ubiquinone oxidoreductase) inhibitors.[5] Among them, atpenin A5 (**3**) proved to be much more potent against bovine heart complex II than known complex II inhibitors. Furthermore, the crystal structure analysis of *Escherichia coli* complex II–atpenin A5 (**3**) complex has been achieved, and catalytic reduction of quinone was suggested to occur at the atpenin-binding site of *E. coli* complex II.[6] As described, atpenins are expected to be useful as biochemical tools in the molecular-biological research of complex II. We report herein the enantioselective total synthesis of atpenin A5 (**3**) by a convergent strategy through a coupling reaction between 2,3,4,6-tetraalkoxypyridine (**4a**) and a side-chain aldehyde (**5**), as shown in Figure 2. The 2,3,4,6-tetraalkoxypyridine (**4a**) would be constructed from 2-chloro-3-pyridinol (**6**) through the modified Quéguiner's procedure as follows: (1) directed *ortho*-lithiation/iodination, (2) halogen dance reaction[7] and (3) installation of a hydroxy group on the pyridine ring through a one-pot procedure by a sequence of reactions, and halo–lithium exchange/quenching with $(MeO)_3B$/oxidation. The side-chain aldehyde **5** could be synthesized from a commercially available chiral ester **7** by Sharpless asymmetric epoxidation[8] and regioselective epoxide opening as key reactions.

RESULTS AND DISCUSSION

The synthesis of **4a** began with the conversion of the commercially available 2-chloro-3-pyridinol **6** into a known 4-hydroxypyridine **8** (51%, 3 steps), according to the Quéguiner's atpenin B synthesis[4] (Scheme 1). In the earlier synthesis, the next key reaction was a directed *ortho*-lithiation, followed by bromination, in which the use of a diisopropyl carbamate group as a protecting group for the 4-hydroxy group was essential for the directed *ortho*-lithiation. However, the treatment required to deprotect the diisopropyl carbamate group in the final stage of total synthesis (5 M solution of KOH in methanol under reflux) would lead to significant epimerization at the C8 position (in atpenin A5 numbering). Therefore, we looked at other approaches to provide 5-halogenation and protection of the 4-hydroxy group. After various unfruitful trials, the problem was solved by a very simple and mild method, in which **8** was treated with K_2CO_3 and I_2 in water (for similar reaction conditions, see Kay *et al.*[9]) to afford the desired 4-hydroxy-5-iodopyridine **9** in 75% yield. This modification allowed the use of an easily removable protecting group and led us to the synthesis of an MOM ether **10** (90% yield). Subsequent halogen dance reaction of **10** with lithium diisopropylamide smoothly proceeded to afford 6-iodopyridine **11** in 75% yield. Treatment of **11** with *n*-butyl lithium for halo–lithium exchange, boronation with $(MeO)_3B$ and oxidation with *m*CPBA (used instead of trifluoroperacetic acid because of its ease in handling) gave 6-hydroxy-5-iodopyridine **13**, not **12**, in 76% yield with good reproducibility. The iodopyridinol **13** would be obtained by *ortho*-iodination of **12** with iodine, which was easily generated *in situ* by oxidation of the iodide with *m*CPBA under

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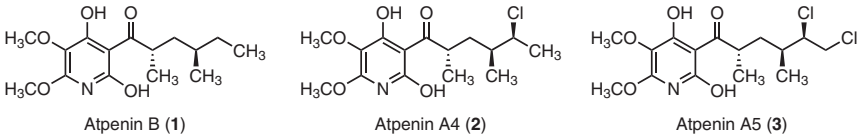


Figure 1 Structures of atpenins B (**1**), A4 (**2**) and A5 (**3**).

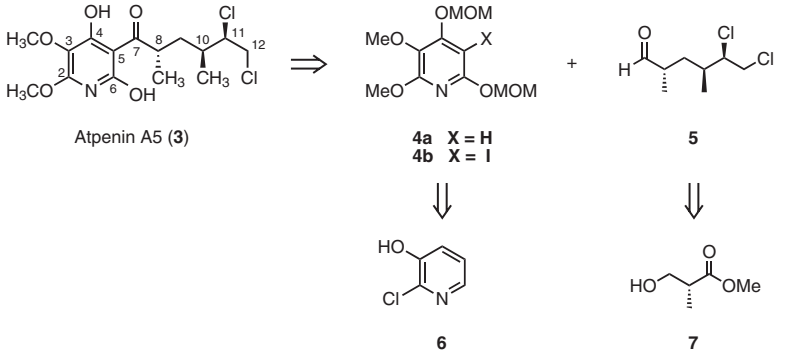
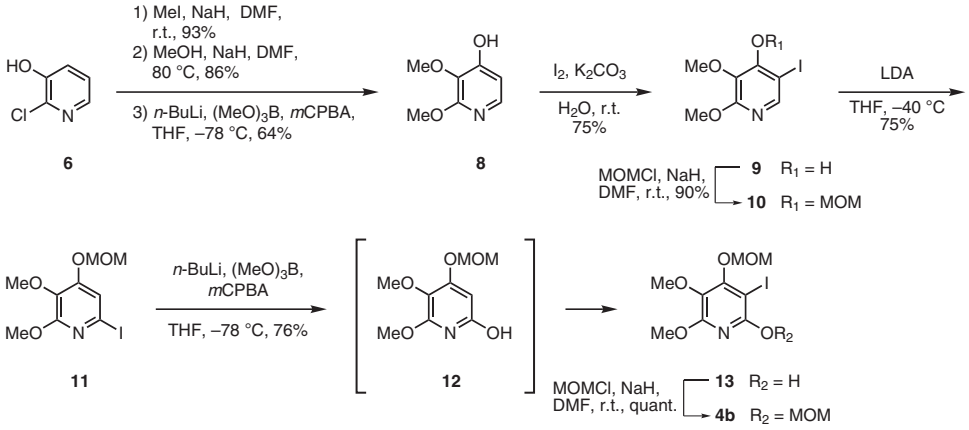


Figure 2 Retrosynthesis of atpenin A5 (**3**).

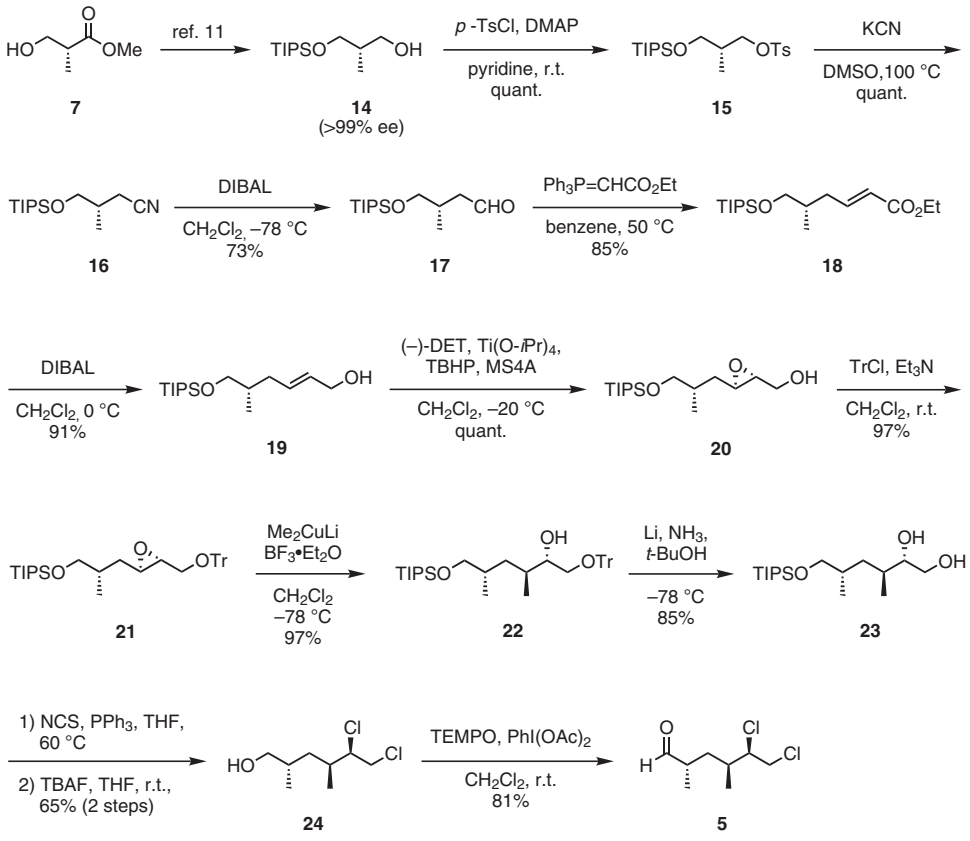


Scheme 1 Synthesis of 5-iodo-2,3,4,6-tetraalkoxypyridine **4b**.

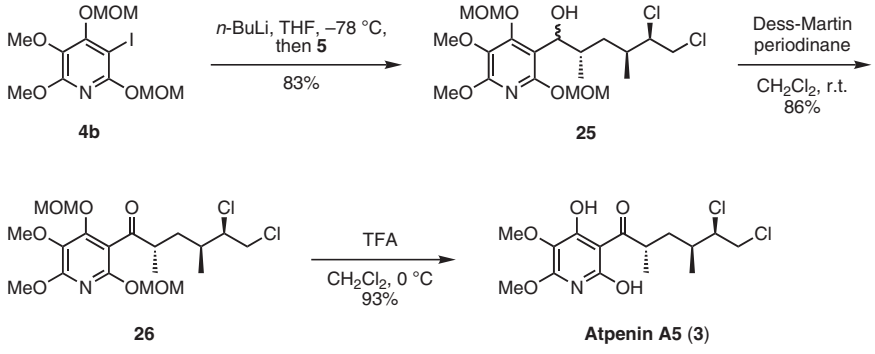
basic conditions. The iodopyridinol **13** was protected as an MOM ether to furnish 5-iodo-2,3,4,6-tetraalkoxypyridine **4b** in a quantitative yield, which is the desirable alternative to 2,3,4,6-tetraalkoxypyridine **4a** in terms of the coupling reaction with the side chain **5**.

The stereoselective construction of the other required fragment, aldehyde **5**, was carried out as summarized in Scheme 2. A readily available alcohol **14** (Komatsu *et al.*,[10] enantiomeric excess was determined by ^{19}F-NMR spectroscopy after esterification with Mosher's acid.), derived from the commercially available ester **7**, was subjected to tosylation, followed by a nucleophilic substitution reaction with potassium cyanide to give nitrile **16** quantitatively over two steps. The cyano group in **16** was reduced with DIBAL to afford a known aldehyde **17** in 73% yield.[11] Subsequent two-carbon elongation with $Ph_3P{=}CHCO_2Et$ provided **18** in 85% yield. Reduction of the ethyl ester **18** with DIBAL, followed by Sharpless asymmetric epoxidation with (−)-DET, afforded the desired epoxy alcohol **20** as a single diastereomer in 91% yield over two steps. (The epoxidation of the corresponding allyl alcohol with *m*CPBA as a simple achiral epoxidizing agent gave a 1:1 diastereomixture of the epoxy alcohol.) Alcohol **20** was protected as a trityl ether and subjected to the regioselective epoxide-opening reaction with Me_2CuLi and $BF_3{\bullet}Et_2O$[12] to furnish alcohol **22** as a single diastereomer in 94% yield over two steps. Birch reduction to remove the trityl group gave diol **23** in 85% yield. Bischlorination by treatment of diol **23** with NCS and PPh_3 followed by deprotection of the TIPS ether with TBAF, gave **24** in 65% yield over two steps.[13] Oxidation of alcohol **24** with TEMPO and $PhI(OAc)_2$ afforded the key fragment **5** in 81% yield.

With the required fragments, **4b** and **5,** in hand, coupling reaction was attempted as the next key step (Scheme 3). Halo–lithium exchange of **4b** with *n*-BuLi, followed by treatment of aldehyde **5** gave the desired coupled product **25** as a diastereomixture in 83% yield. Oxidation of **25** with Dess–Martin periodinane provided **26** in 86% yield. Finally, cleavage of the bis-MOM ether in **26** with TFA afforded atpenin A5 (**3**) in 93% yield. However, the ^{1}H-NMR spectrum of our synthetic atpenin A5 (**3**) had different chemical shifts from those reported in the literature for the natural product, although the peak patterns were quite similar. As a result, we re-measured the ^{1}H-NMR spectrum of the natural atpenin A5 (**3**) and found that the earlier reported data were incorrect. In fact, our synthetic atpenin A5 (**3**) was completely identical to an authentic sample in all respects.



Scheme 2 Synthesis of aldehyde **5**.



Scheme 3 Completion of the total synthesis of atpenin A5 (**3**).

In summary, the first enantioselective total synthesis of atpenin A5 has been achieved by a convergent approach. The syntheses of the other congeners (A4 and B), and the analogs as well as the biological evaluation of **3**, are currently in progress in our laboratories.

EXPERIMENTAL SECTION

General

Melting points were measured with a Yanagimoto MP apparatus (Yanagimoto, Kyoto, Japan) and remain uncorrected. UV and IR spectra were obtained using an Agilent 8453 spectrophotometer (Agilent Technologies, Waldbornn, Germany) and a Horiba FT-710 spectrophotometer (Horiba, Kyoto, Japan) respectively. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL JNM-EX-270 (JEOL, Tokyo, Japan), Mercury-300 (Varian, Palo Alto, CA, USA), UNITY-400 (Varian) and INOVA-600 (Varian) spectrometers, and chemical shifts were reported on the δ scale from internal TMS. MS spectra were measured with JEOL JMS-700 (JEOL) and JEOL JMS-AX505HA (JEOL) spectrometers. Optical rotations were recorded on a JASCO DIP-1000 polarimeter (JASCO, Tokyo, Japan). Elemental analyses were performed on a Yanako-MT5 (Yanako, Kyoto, Japan). Commercial reagents were used without further purification unless otherwise indicated. Organic solvents were distilled and dried over molecular sieves (3 or 4 Å). Reactions were carried out in a flame-dried glassware under positive Ar pressure while stirring with a magnetic stirbar unless otherwise indicated. Flash chromatography was carried out on silica gel 60N (spherical, neutral, particle size 40–50 mm). TLC was performed on 0.25 mm E Merck silica gel 60 F254 plates and visualized by UV (254 nm) and cerium ammonium molybdenate.

5-Iodo-2,3-dimethoxypyridin-4-ol (9)

A solution of 2,3-dimethoxypyridin-4-ol **8** (440 mg, 2.84 mmol) in H_2O (6.3 ml) was treated with K_2CO_3 (785 mg, 5.68 mmol) and I_2 (742 mg, 2.93 mmol). The reaction mixture was stirred at room temperature for 1 h,

quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (10 : 1 hexanes/EtOAc) to afford **9** (598 mg, 75%) as a yellow solid. mp 134–136°C; IR (KBr) 2998, 2942, 1571, 1473, 1403, 1319, 1261, 1191, 1002, 761, 651 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.02 (s, 1H), 3.97 (s, 3H), 3.88 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 157.3, 155.0, 147.2, 130.1, 73.0, 60.7, 53.9; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_7H_9NO_3I$ 281.9627, found 281.9627.

5-Iodo-2,3-dimethoxy-4-(methoxymethoxy)pyridine (10)

A solution of **9** (58.0 mg, 206 μmol) in DMF (2.0 ml) was treated with NaH (60%, 12.4 mg, 309 μmol) and MOMCl (24 μl, 309 μmol). The reaction mixture was stirred at room temperature for 1 h, quenched with H_2O and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **10** (60.3 mg, 90%) as a yellow solid. mp 57–59 °C; IR (KBr) 3062, 2989, 2944, 2836, 1735, 1563, 1467, 1400, 1211, 1164, 1105, 904, 617, 586 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.10 (s, 1H), 5.36 (s, 2H) 3.95 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.6, 155.2, 147.6, 135.6, 98.7, 80.9, 60.5, 58.1, 53.9; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_9H_{13}NO_4I$ 325.9890, found 325.9890.

6-Iodo-2,3-dimethoxy-4-(methoxymethoxy)pyridine (11)

To a solution of iPr$_2$NH (67 μl, 471 μmol) in THF (0.4 ml) was added dropwise *n*-BuLi (1.61 M in hexane, 293 μl, 471 μmol). After stirring for 30 min at 0 °C, a solution of **10** (51.0 mg, 157 μmol) in THF (0.4 ml) was added at −40 °C, and the resulting mixture was further stirred for 1 h at −40 °C. EtOH was added, and the resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (10 : 1 hexanes/EtOAc) to afford **11** (38.3 mg, 75%) as a yellow solid. mp 59–61 °C; IR (KBr) 3097, 2944, 1571, 1479, 1367, 1240, 1162, 1114, 1072, 995, 912, 844, 740, 441 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.15 (s, 1H), 5.21 (s, 2H), 3.95 (s, 3H), 3.82 (s, 3H), 3.48 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 157.8, 156.9, 132.8, 116.5, 105.0, 94.7, 60.7, 56.6, 54.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_9H_{13}NO_4I$ 325.9890, found 325.9894.

3-Iodo-5,6-dimethoxy-4-(methoxymethoxy)pyridin-2-ol (13)

A solution of *n*-BuLi (1.59 M in hexane, 2.38 ml, 1.51 mmol) in THF (15 ml) was treated with a solution of **13** (491 mg, 1.51 mmol) in THF (15 ml) at −78 °C. Trimethylborate (507 μl, 4.53 mmol) was added and the mixture was stirred for 5 min at –78 °C. In addition, *m*CPBA (60%, 1.74 g, 6.04 mmol) was added and the mixture was stirred for 30 min. Saturated aqueous $Na_2S_2O_3$ was added, and the resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **13** (393 mg, 76%) as a white solid. mp 119–121 °C; IR (KBr) 3116, 2987, 2832, 2547, 1600, 1467, 1386, 1112, 894, 819, 767 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.40 (s, 2H), 3.93 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 158.6, 157.6. 155.9, 129.6, 99.0, 61.9, 61.0, 58.5, 54.6; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_9H_{13}NO_5I$ 341.9838, found 341.9843.

3-Iodo-5,6-dimethoxy-2,4-bis(methoxymethoxy)pyridine (4b)

A solution of **13** (29.3 mg, 85.9 μmol) in DMF (1.0 ml) was treated with NaH (60%, 5.0 mg, 129 μmol) and MOMCl (8 μl, 103 μmol), and the mixture was stirred at room temperature for 1 h. The resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (15 : 1 hexanes/EtOAc) to afford **4b** (33.4 mg, quant.) as a yellow oil. mp 62–64 °C; IR (KBr) 2954, 2838, 2362, 1735, 1562, 1467, 1378, 1214, 1159, 1105, 995, 877 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.52 (s, 2H), 5.38 (s, 2H), 3.95 (s, 3H), 3.76 (s, 3H), 3.63 (s, 3H) 3.55 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 158.5, 157.0, 155.2, 130.4, 99.0, 92.7, 65.0, 60.9, 58.4, 57.3, 54.1; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{11}H_{18}NO_6I$ 386.0101, found 386.0107; Anal. calcd for $C_{11}H_{18}NO_6I$: C, 4.19; H, 34.30; O, 3.64, found: C, 4.10; H, 34.51; O, 3.67.

(*R*)-2-Methyl-3-(triisopropylsilyloxy)propyl 4-methylbenzenesulfonate (15)

A solution of **14** (870 mg, 3.45 mmol) in pyridine (6.9 ml) was treated with *p*-TsCl (990 mg, 5.18 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature for 2 h. The resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (50 : 1 hexanes/EtOAc) to afford **15** (1.31 g, quant.) as a colorless oil. $[\alpha]_D^{27}$ −6.31 (*c* 1.0, $CHCl_3$); IR (KBr) 2952, 2867, 1600, 1463, 1367, 1182, 1105, 977, 786, 675, 561 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J*=8.3 Hz), 7.33 (d, 2H, *J*=8.3 Hz), 4.06 (dd, 1H, *J*=9.2, 6.0 Hz), 3.95 (dd, 1H, *J*=9.2, 6.0 Hz), 3.59 (dd, 1H, *J*=9.9, 5.8 Hz), 3.49 (dd, 1H, *J*=9.9, 5.8 Hz), 2.43 (s, 3H), 2.00−1.94 (m, 1H), 1.05−0.94 (m, 3H), 0.99 (bs, 18H), 0.90 (d, 3H, *J*=6.9 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 144.5, 133.0, 129.7, 127.8, 72.2, 64.2, 35.9, 21.6, 17.9, 13.2, 11.8; LRMS (FAB, *m*-NBA) $[M+H]^+$ 401, $[M+Na]^+$ 423.

(*S*)-3-Methyl-4-(triisopropylsilyloxy)butanenitrile (16)

A solution of **15** (1.31 g, 3.25 mmol) in DMSO (3.3 ml) was treated with KCN (210 mg, 3.25 mmol). After stirring at 100 °C for 1.5 h, the resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **16** (850 mg, quant.) as a colorless oil. $[\alpha]_D^{27}$ −18.0 (*c* 1.0, $CHCl_3$); IR (KBr) 2952, 2867, 2246, 1463, 1108, 883, 788, 680 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.71 (dd, 1H, *J*=8.4, 4.3 Hz), 3.51 (dd, 1H, *J*=8.4, 4.3 Hz), 2.53 (dd, 1H, *J*=16.5, 6.5 Hz), 3.49 (dd, 1H, *J*=16.5, 6.5 Hz), 2.10−2.02 (m, 1H), 1.11−1.00 (m, 3H), 1.06 (bs, 18H), 0.98 (d, 3H, *J*=3.3 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 118.9, 66.4, 33.5, 20.8, 17.9, 15.8, 11.8; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{14}H_{30}NOSi$ 256.2100, found 256.2096.

(*S*)-3-Methyl-4-(triisopropylsilyloxy)butanal (17)

A solution of **16** (850 mg, 3.33 mmol) in CH_2Cl_2 (16 ml) was treated with DIBAL (1.02 M in hexane, 7.5 ml, 7.65 mmol) at −78 °C. After stirring for 1 h at −78 °C, 3 N aqueous HCl solution was added to the mixture. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **17** (630 mg, 73%) as a colorless oil. The physical properties of **17** were completely identical to those reported in the literature.[11]

(*S*,*E*)-Ethyl 5-methyl-6-(triisopropylsilyloxy)hex-2-enoate (18)

A solution of **17** (630 mg, 2.44 mmol) in benzene (24 ml) was treated with (carbethoxymethylene)triphenylphosphorane (1.70 g, 4.88 mmol). After stirring at 50 °C for 24 h, the resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **18** (680 mg, 85%) as a colorless oil. $[\alpha]_D^{28}$ −1.80 (*c* 1.0, $CHCl_3$); IR (KBr) 2950, 2867, 2350, 2337, 1724, 1654, 1463, 1263, 1174, 1108, 1049, 883, 790, 678 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.02−6.92 (m, 1H), 5.83 (d, 1H, *J*=15.6, 1.4 Hz), 4.18 (q, 2H, *J*=7.1 Hz), 3.56 (dd, 1H, *J*=9.7, 6.0 Hz), 3.48 (dd, 1H, *J*=9.7, 6.0 Hz), 2.47−2.37 (m, 1H), 2.07−1.97 (m, 1H), 1.85−1.78 (m, 1H), 1.28 (t, 3H, *J*=7.1 Hz), 1.09−1.02 (m, 3H), 1.06 (bs, 18H), 0.90 (d, 3H, *J*=6.8 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.5, 148.0, 122.4, 67.8, 60.0, 36.0, 35.7, 18.0, 16.4, 14.2, 11.9; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{18}H_{37}O_3Si$ 329.2512, found 329.2511.

(*S*,*E*)-5-Methyl-6-(triisopropylsilyloxy)hex-2-en-1-ol (19)

A solution of **18** (650 mg, 1.98 mmol) in CH_2Cl_2 (20 ml) was treated with DIBAL (1.02 M in hexane, 4.85 ml, 4.95 mmol) at −78 °C. After stirring for 1 h at 0 °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 (1.50 g) and Na_2SO_4•$10H_2O$ (1.60 g) and then stirred for 12 h at room temperature. The resulting solution was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **19** (510 mg, 91%) as a colorless oil. $[\alpha]_D^{28}$ −4.27 (*c* 1.0, $CHCl_3$); IR (KBr) 3334, 2950, 2865, 1463, 1105, 1006, 883, 794, 678, 595 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.75−5.60 (m, 2H), 4.09 (d, 2H, *J*=4.0 Hz), 3.50 (d, 2H, *J*=3.2 Hz), 2.27−2.20 (m, 1H), 1.91−1.81 (m, 1H), 1.75−1.65 (m, 1H), 1.12−1.02 (m, 3H), 1.06 (bs, 18H), 0.88 (d, 3H, *J*=6.6 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 131.7, 130.3, 68.0, 63.7, 36.1, 35.9, 18.0, 16.4, 12.0; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{16}H_{35}O_3Si$ 287.2403, found 287.2408.

{(2*R*,3*R*)-3-[(*S*)-2-Methyl-3-(triisopropylsilyloxy)propyl] oxiran-2-yl}methanol (20)

A mixture of Ti(O*i*Pr)$_4$ (3.2 ml, 10.8 mmol) and 4 Å MS (1.24 g) in CH_2Cl_2 (50 ml) was treated with (−)-DET (1.9 ml, 10.8 mmol), and the solution was vigorously stirred at −5 °C for 0.5 h. TBHP (5.0–6.0 M in decane, 4.4 ml, 21.6 mmol) was slowly added to the above mixture, and the solution was stirred at −20 °C for 20 min. A solution of **19** (3.10 g, 10.8 mmol) in CH_2Cl_2 (58 ml) was added to the above mixture, and the solution was stirred at −20 °C for 10.5 h. After Me_2S (1.19 ml, 16.2 mmol) was added, the mixture was further stirred at −20 °C for 1 h. The resulting mixture was diluted with Et_2O, treated with celite (6.50 g) and Na_2SO_4•$10H_2O$ (6.50 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 silica gel flash column chromatography (5 : 1 hexanes/EtOAc) to afford **20** (3.27 g, quant.) as a colorless oil. $[\alpha]_D^{28}$ +16.1 (*c* 1.0, $CHCl_3$); IR (KBr) 3432, 2944, 2865, 1463, 1382, 1103, 887, 792, 678, 653 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.56 (m, 4H), 3.09−3.02 (m, 1H), 2.90−2.88 (m, 1H), 1.85−1.75 (m, 3H), 1.11−1.02 (m, 3H), 1.06 (bs, 18H), 0.99 (d, 3H, *J*=6.6 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 68.0, 61.7, 58.4, 55.1, 35.4, 34.5, 18.0, 17.0, 11.9; HRMS (ESI) $[M+Na]^+$ calcd for $C_{16}H_{34}O_3SiNa$ 325.2175, found 325.2212.

Triisopropyl{[(*S*)-2-methyl-3-(2*R*,3*R*)-3-(triphenylmethyloxymethyl) oxiran-2-yl]propoxy}silane (21)

A solution of **20** (496 mg, 1.46 mmol) in CH_2Cl_2 (16 ml) was treated with TrCl (914 mg, 3.28 mmol) and Et_3N (680 µl, 4.92 mmol), and the mixture was stirred at room temperature for 8.5 h. The resulting solution was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (150 : 1 hexanes/EtOAc) to afford **21** (869 mg, 97%) as a colorless oil. $[\alpha]_D^{28}$ +4.76 (*c* 1.0, $CHCl_3$); IR (KBr) 2942, 2865, 1596, 1490, 1448, 1091, 1070, 883, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48−7.12(m, 15H), 3.57 (dd, 1H, *J*=9.6, 5.7 Hz), 3.51 (dd, 1H, *J*=9.6, 6.0 Hz), 3.26 (dd, 1H, *J*=10.6, 3.2 Hz), 3.12 (dd, 1H, *J*=10.6, 5.4 Hz) 2.92−2.84 (m, 2H), 1.88−1.78 (m, 1H), 1.77−1.69 (m, 1H), 1.41−1.31 (m, 1H), 1.10−0.95 (m, 3H), 1.03 (bs, 18H), 0.99 (d, 3H, *J*=6.7 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 143.8, 128.6, 127.8, 127.0, 86.6, 68.0, 64.6, 57.1, 55.4, 35.6, 34.5, 18.0, 17.1, 11.9; HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_{35}H_{48}O_3SiNa$ 567.3271, found 567.3248.

(2*S*,3*S*,5*S*)-3,5-Dimethyl-6-(triisopropylsilyloxy)-1-(trityloxy) hexan-2-ol (22)

A mixture of CuI (1.57 g, 8.25 mmol) in CH_2Cl_2 (8.0 ml) was treated with MeLi (1.04 M in Et_2O, 15.8 ml, 16.5 mmol), and the solution was stirred at −78 °C for 5 min. BF_3•OEt_2 (314 µl, 2.48 mmol) was added to the above mixture, and the solution was stirred at −78 °C for 5 min. A solution of **21** (900 mg, 1.65 mmol) in CH_2Cl_2 (8.5 ml) was added to the above mixture, and the solution was stirred at −78 °C for 2 h. The reaction mixture was warmed to room temperature and treated with saturated aqueous NH_4Cl. The resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (50 : 1 hexanes/EtOAc) to afford **22** (720 mg, 97%) as a colorless oil. $[\alpha]_D^{26}$ –4.09 (*c* 1.0, $CHCl_3$); IR (KBr) 3478, 2950, 2865, 1712, 1596, 1455, 1378, 1097, 1074, 887, 773, 698 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.47−7.20 (m, 15H), 3.58−3.53 (m, 1H), 3.43 (d, 2H, *J*=6.3 Hz), 3.26 (dd, 1H, *J*=9.4, 3.2 Hz), 3.08 (dd, 1H, *J*=9.4, 7.9 Hz), 2.38 (d, 1H, *J*=3.3 Hz), 1.72−1.56 (m, 2H), 1.26−1.13 (m, 2H), 1.07−1.01 (m, 3H), 1.04 (bs, 18H), 0.81 (d, 3H, *J*=6.6 Hz), 0.72 (d, 3H, *J*=6.8 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 143.9, 128.6, 127.8, 127.0, 86.7, 75.2, 69.4, 65.6, 35.5, 33.4, 33.3, 18.0, 16.1, 15.0, 12.0; HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_{36}H_{52}O_3SiNa$ 583.3583, found 583.3607.

(2*S*,3*S*,5*S*)-3,5-Dimethyl-6-(triisopropylsilyloxy)hexan-1,2-diol (23)

To a mixture of Li (57.7 mg, 8.89 mmol) in liquid ammonia (9.0 ml, 0.1 M) was added a solution of **22** (498 mg, 0.890 mmol) in THF (5.0 ml) and *t*BuOH (0.21 ml, 2.22 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 30 min. MeOH was added at −78 °C until the color of the solution changed, and after complete volatilization of ammonia, the resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (5 : 1 hexanes/EtOAc) to afford **23** (241 mg, 85%) as a colorless oil. $[\alpha]_D^{27}$ –17.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3419, 2948, 2867, 1625, 1461, 1382, 1105, 1068, 881, 790, 678 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.75−3.68 (m, 1H), 3.54−3.44 (m, 4H), 1.76−1.65 (m, 2H), 1.42−1.23 (m, 2H), 1.13−1.02 (m, 3H), 1.07 (bs, 18H), 0.88 (d, 3H, *J*=6.6 Hz), 0.85 (d, 3H, *J*=6.6 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 78.8, 71.9, 67.9, 36.3, 34.7, 32.4, 17.9, 17.3, 15.1, 12.1; HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_{17}H_{38}O_3SiNa$ 341.2488, found 341.2490.

(2*S*,4*S*,5*R*)-5,6-Dichloro-2,4-dimethylhexan-1-ol (24)

A solution of **23** (211 mg, 0.660 mmol) in THF (3.3 ml) was treated with NCS (266 mg, 1.99 mmol) and PPh_3 (552 mg, 1.99 mmol), and the mixture was stirred at 60 °C for 3 h. The resulting solution was partitioned between CH_2Cl_2 and H_2O. 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 semi-purified by flash silica gel column chromatography (5 : 1 hexanes/EtOAc) to afford the crude dichloride as a colorless oil. A solution of the crude dichloride in THF (6.6 ml) was treated with TBAF (1.0 M THF, 1.32 ml, 1.32 mmol), and the reaction mixture was stirred at room temperature for 1 h and quenched with saturated aqueous NH_4Cl. The resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (5 : 1 hexanes/EtOAc) to afford **24** (86.0 mg, 65% for 2 steps) as a colorless oil. $[\alpha]_D^{27}$ –11.3 (*c* 1.0, $CHCl_3$); IR (KBr) 3365, 2964, 2925, 1457, 1380, 1037, 738, 686 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.12−4.06 (m, 1H), 3.81−3.66 (m, 2H), 3.56−3.41 (m, 2H), 2.32−2.25 (m, 1H), 1.78−1.69 (m, 1H), 1.55–1.45 (m, 2H), 0.94 (d, 3H, *J*=6.6 Hz), 0.93 (d, 3H, *J*=6.6 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 73.1, 61.6, 46.0, 35.0, 33.8, 31.8, 18.0, 17.6, 15.4, 12.0; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_8H_{17}Cl_2O$ 199.0656, found 199.0647.

(2*S*,4*S*,5*R*)-5,6-Dichloro-2,4-dimethylhexanal (5)

A solution of **24** (54.0 mg, 0.270 mmol) in CH_2Cl_2 (2.7 ml) was treated with TEMPO (4.3 mg, 27.1 µmol) and PhI(OAc)$_2$ (131 mg, 0.410 mmol). The reaction mixture was then stirred at room temperature for 2.5 h and quenched with saturated aqueous $Na_2S_2O_3$. The resulting solution was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20 : 1 hexanes/EtOAc) to afford **5** (43.0 mg, 81%) as a colorless oil. $[\alpha]_D^{27}$ +1.13 (*c* 1.0, $CHCl_3$); IR (KBr) 2971, 2715, 1725, 1457, 1382, 1257, 925, 815, 740, 688 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.64 (d, 1H, *J*=8.6 Hz), 4.13−4.07 (m, 1H), 3.78 (dd, 1H, *J*=11.3, 5.7 Hz), 3.70 (dd, 1H,

J=11.3, 8.8 Hz), 2.48–2.39 (dq, 1H, *J*=7.0, 1.8 Hz), 2.33–2.25 (m, 1H), 1.89–1.79 (m, 1H), 1.48–1.38 (m, 1H), 1.14 (d, 3H, *J*=7.0 Hz), 0.95 (d, 3H, *J*=6.6 Hz); HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_8H_{14}Cl_2O$ 196.0422, found 199.0431.

(2*S*,4*S*,5*R*)-5,6-Dichloro-1-(5,6-dimethoxy-2,4-bis(methoxymethoxy) pyridin-3-yl)-2,4-dimethylhexan-1-ol (25)

To a solution of *n*-BuLi (1.59 M in hexane, 672 µl, 1.07 mmol) in THF (3.6 ml) was added a solution of **4b** (138 mg, 359 µmol) in THF (1.8 ml) at −78 °C. A solution of **5** (58.0 mg, 299 µmol) in THF (1.8 ml) was then added and the mixture was stirred for 15 min at −78 °C. MeOH was added, and the resulting solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (3 : 1 hexanes/EtOAc) to afford a diastereomixture of **25** (101 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ −11.8 (*c* 1.0, $CHCl_3$); IR (KBr) 3561, 2962, 1590, 1469, 1392, 1160, 1116, 1060, 1025, 904 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.60–5.47 (m, 2H), 5.38–5.27 (m, 2H), 4.16–4.05 (m, 1H), 3.93 (s, 3H), 3.83–3.65 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.58–3.50 (m, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 3.52 (s, 6H), 2.37–2.25 (m, 1H), 2.21–2.10 (m, 1H), 2.08–2.00 (m, 1H), 1.64–1.51 (m, 1H), 1.07 (d, 3H, *J*=6.6 Hz), 0.96 (d, 3H, *J*=6.5 Hz), 0.82 (d, 3H, *J*=6.9 Hz), 0.73 (d, 3H, *J*=6.7 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 157.3, 157.2, 155.2×2, 153.2, 153.1, 130.0×2, 110.0×2, 99.4×2, 92.1×2, 72.4, 71.9, 67.7, 66.9, 60.8×2, 58.1×2, 57.7×2, 53.9, 53.8, 46.5, 45.4, 38.7, 38.3, 36.7, 36.6, 33.2, 32.6, 16.6, 16.2, 13.0, 12.6; HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_{19}H_{31}Cl_2NO_7$ 478.1373, found 478.1378.

(2*S*,4*S*,5*R*)-5,6-Dichloro-1-(5,6-dimethoxy-2,4-bis(methoxymethoxy) pyridin-3-yl)-2,4-dimethylhexan-1-one (26)

A solution of **25** (93.3 mg, 205 µmol) in CH_2Cl_2 (2.0 ml) was treated with Dess–Martin periodinane (130 mg, 307 µmol). The mixture was then stirred at room temperature for 15 min and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The resulting solution was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (10 : 1 hexanes/EtOAc) to afford **26** (79.5 mg, 86%) as a colorless oil. $[\alpha]_D^{27}$ −2.91 (*c* 1.0, $CHCl_3$); IR (KBr) 2971, 2715, 1725, 1457, 1382, 1257, 925, 815, 740, 688 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.50 (s, 2H), 5.30 (s, 2H), 4.19 (ddd, 1H, *J*=7.6, 6.3, 2.9 Hz), 3.97 (s, 3H), 3.77 (s, 3H), 3.78–3.63 (m, 2H), 3.49 (s, 6H), 3.24–3.12 (m, 1H), 2.37–2.26 (m, 1H), 1.94–1.84 (m, 1H), 1.51–1.46 (m, 1H), 1.17 (d, 3H, *J*=7.0 Hz), 0.93 (d, 3H, *J*=6.6 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 204.8, 157.3, 156.3, 152.9, 130.1, 110.7, 99.1, 92.0, 66.2, 60.9, 57.9, 57.6, 54.2, 46.5, 44.2, 37.3, 32.7, 16.8, 13.0; HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_{19}H_{29}Cl_2N$ Na O_7 476.1219, found 476.1210.

Atpenin A5 (3)

A solution of **26** (76.7 mg, 169 µmol) in CH_2Cl_2 (1.7 ml) was treated with TFA (1.7 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 silica gel flash column chromatography (5 : 1 hexanes/EtOAc) to afford atpenin A5 (**3**) (57.4 mg, 93%) as a white solid.

Synthetic atpenin A5 (3). mp 83–85 °C; $[\alpha]_D^{25}$ −0.82 (*c* 1.0, EtOH); IR (KBr) 1648, 1602, 1454, 1324, 1199, 1160, 993 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 4.14–4.10 (m, 2H), 3.82 (s, 3H), 3.74 (dd, 1H, *J*=11.1, 6.1 Hz), 3.65 (dd, 1H, *J*=11.3, 8.5 Hz), 2.21 (dq, 1H, *J*=7.1, 2.4 Hz), 1.91 (ddd, 1H, *J*=14.2, 6.9, 6.9 Hz), 1.55–1.47 (m, 1H), 1.18 (d, 3H, *J*=6.7 Hz), 0.95 (d, 3H, *J*=6.6 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 210.0, 172.8, 162.2, 155.6, 121.2, 101.1, 65.7, 61.8, 58.6, 46.1, 39.6, 37.7, 32.8, 18.3, 13.2; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{15}H_{22}NO_5Cl_2$ 366.0875, found 366.0876; Anal. calcd for $C_{15}H_{22}NO_5Cl_2$: C, 5.78; H, 49.19; O, 3.82, found: C, 5.64; H, 49.37; O, 3.92; UVλ_{max}^{EtOH} nm (ε (cm^2 $mmol^{-1}$)) 239 (3160), 277 (2220), 333 (1450).

Revised data of natural atpenin A5 (3). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.13 (s, H), 4.14–4.10 (m, 2H), 3.82 (s, 3H), 3.73 (dd, 1H, *J*=11.2, 5.9 Hz), 3.65 (dd, 1H, *J*=11.3, 8.9 Hz), 2.20 (dq, 1H, *J*=7.0, 2.7 Hz), 1.91 (ddd, 1H, *J*=14.3, 7.0, 7.0 Hz), 1.55–1.47 (m, 1H), 1.18 (d, 3H, *J*=6.7 Hz), 0.95 (d, 3H, *J*=6.5 Hz).

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