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Graphical Abstract

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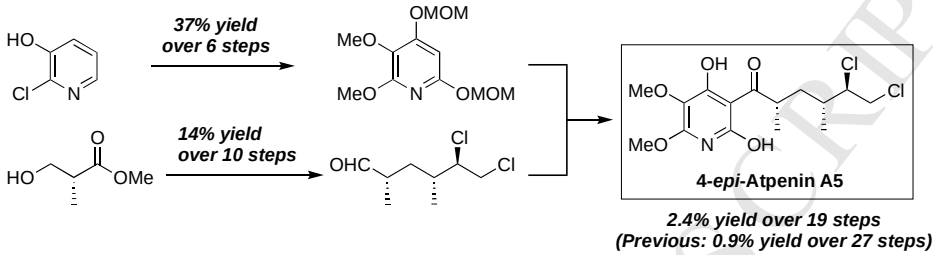

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Total synthesis of 4-*epi*-atpenin A5 as a potent nematode complex II inhibitor.

Daiki Lee[a], Hiroki Kondo[a], Yui Kuwayama[a], Kento Takahashi[a], Shiho Arima[a], Satoshi Omura[b], Masaki Ohtawa[a]*, and Tohru Nagamitsu[a]*

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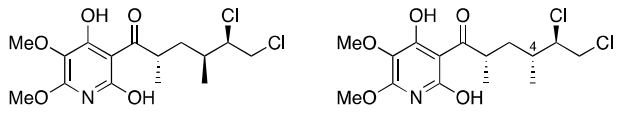
ABSTRACT

It is clear that atpenins and their analogs are useful chemical tools for elucidation of complex II functionality and that they could act as lead compounds for the development of novel helminth complex II-specific inhibitors. Recently, we discovered 4-*epi*-atpenin A5 as a potent nematode complex II inhibitor during our SAR studies of atpenin A5. This result led us to embark on a concise total synthesis of 4-*epi*-atpenin A5. In this study, we describe the total synthesis of 4-*epi*-atpenin A5. Importantly, this was more concise and practical synthesis than our previous total synthesis of atpenin A5.

1. Introduction

Atpenin A5 (**1**) and its analogs, which possess a highly functionalized pyridine unit, were first isolated in 1988 from a fermentation broth of the atpenin-producing strain *Penicillium* sp. FO-125. They were isolated as growth inhibitors of both fatty acid synthase deficient (A-1) and acyl-CoA synthase I deficient (L-7) mutants of *Candida lipolytica* (Figure 1).[1,2] The absolute configuration of atpenin A5 (**1**) has been confirmed by X-ray crystallographic analysis.[3,4] The total synthesis of (±)-atpenin B (5',6'-dedichloroatpenin A5) was reported by the Quéguiner group in 1994.[5] In 2003, new interest in atpenin A5 (**1**) developed when a microbial screening assay showed that the compound provided high levels of inhibition against mitochondrial complex II (succinate-ubiquinone oxidoreductase), which is an attractive target for the treatment of helminthiasis.[6] In particular, atpenin A5 (**1**) proved to be much more potent against bovine heart complex II than any known complex II inhibitor, although the inhibition of **1** was non-selective across helminthes and mammals. Crystal structure analysis of *Escherichia coli* complex II co-crystallized with atpenin A5 (**1**) has also been achieved.[3] It is clear that atpenins and their analogs are useful chemical tools for elucidation of complex II functionality and that they could act as lead compounds for the development of novel helminth complex II-specific inhibitors. In 2009, we achieved a stereoselective total synthesis of atpenin A5 (**1**)[7] by improving the Quéguiner procedure (Scheme 1). We have also reported the total synthesis of other natural atpenin A5 analogs (A4 and B etc.) using this synthetic strategy.[8] Moreover, we reported on the structure–activity relationship of atpenin A5 analogs with chemical modification of the side chain moiety, including atpenin A5 stereoisomers,[9,10] in which 4-*epi*-atpenin A5 (**2**) was shown to be a more potent nematode complex II inhibitor than **1** (Figure 1). Therefore, a large scale synthesis of 4-*epi*-atpenin A5 (**2**) was suggested for future animal tests and use as a chemical tool. Unfortunately, our total synthesis of **1** was suitable only for small scale synthesis of a variety of atpenin A5 analogs; it was inadequate for large scale synthesis of **2**. Herein, we report a concise total synthesis of 4-*epi*-atpenin A5.



Atpenin A5 (**1**) **4-*epi*-Atpenin A5** (**2**)

Figure 1 Structures of atpenin A5 (**1**) and 4-*epi*-atpenin A5 (**2**).

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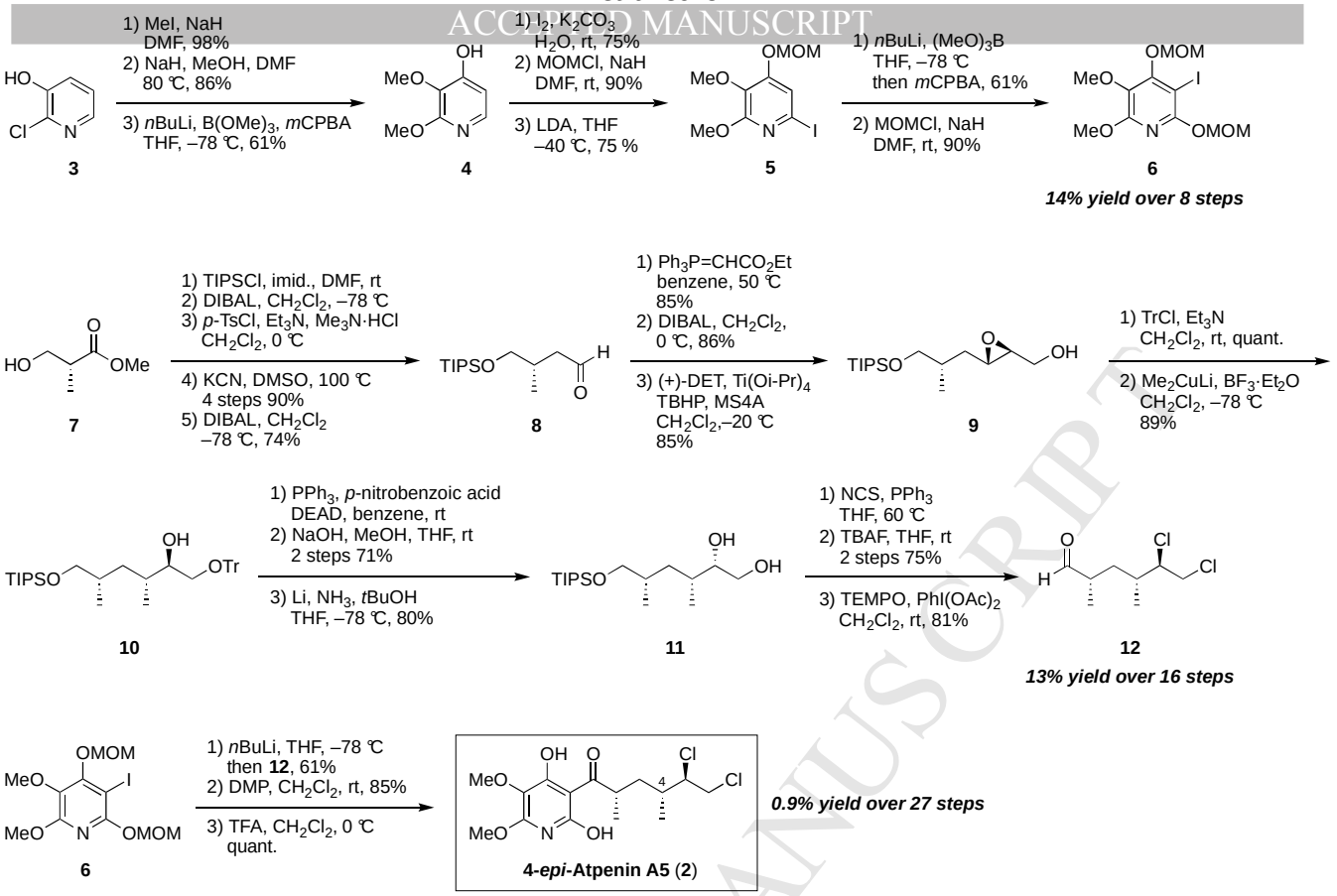
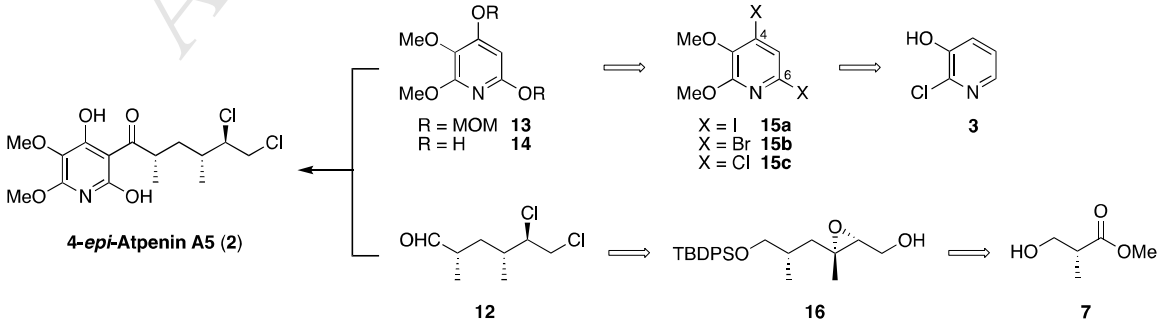


Scheme 1 Total synthesis of 4-*epi*-atpenin A5 (**2**), reported previously by our group.

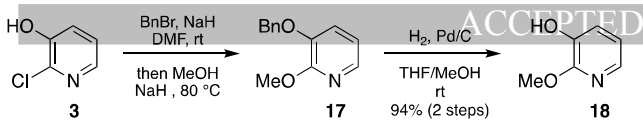
2. Results and discussion

Our previous total synthesis of **2**, in which **2** was synthesized by a coupling reaction between pyridine unit **6** and aldehyde **12**, corresponding to the side chain moiety, is shown in Scheme 1.[7-9] The pyridine unit **6** was constructed by a clockwise introduction of oxygen functionalities on the pyridine ring from a commercially available pyridinol **3** (14% yield over eight steps). The aldehyde **12** was prepared from a commercially available (–)-Roche ester (**7**) via Sharpless asymmetric epoxidation, regio- and stereoselective epoxide-opening reaction, and Mitsunobu reaction as the key reactions (13% yield over 16 steps). Our previous synthetic procedure was developed to synthesize a variety of atpenin A5 analogs with chemical transformation of each functional group and its stereoisomers; however, this required the frequent use of strong bases during synthesis of the pyridine unit **6**, as well as time-consuming steps to obtain each final product, including **2**. Therefore, a new synthetic strategy only for 4-*epi*-atpenin A5 (**2**) was formulated, as shown in Scheme 2. It is clear that the coupling reaction between the highly oxygen-functionalized pyridine unit **13** and the aldehyde **12** followed by chemical transformations afford 4-*epi*-atpenin A5 (**2**), according to our previous synthetic procedure. The key pyridine unit **13**, derived easily from 4,6-dihydroxypyridine **14**, could be synthesized from a commercially available pyridinol **3** via 4,6-dihalogenation and substitution reaction of C–X to C-OR (R = alkyl or H). This synthetic strategy would lead to a concise synthesis of the key intermediate **13**. The aldehyde **12** could be synthesized via construction of epoxy alcohol **16** from a commercially available (–)-Roche ester **7** using Sharpless asymmetric epoxidation, regio- and stereoselective reduction, and dichlorination.

We undertook a concise synthesis of the key intermediate **13**, which was commenced with dihalogenation of 3-pyridinol **18**.[11,12] 3-Pyridinol **18** was readily synthesized from a commercially available 2-chloro-3-pyridinol (**3**) via *O*-benzylation, one-pot S_NAr reaction with sodium methoxide, and debenzylation by hydrogenolysis (Scheme 3).

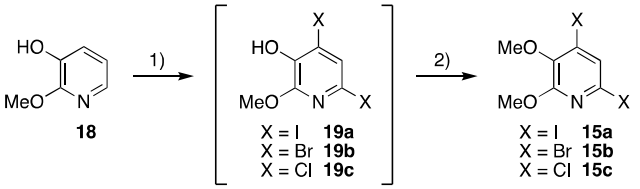


Scheme 2 Retrosynthesis of 4-*epi*-atpenin A5 (**2**).



Scheme 3 Synthesis of the 3-pyridinol **18**.

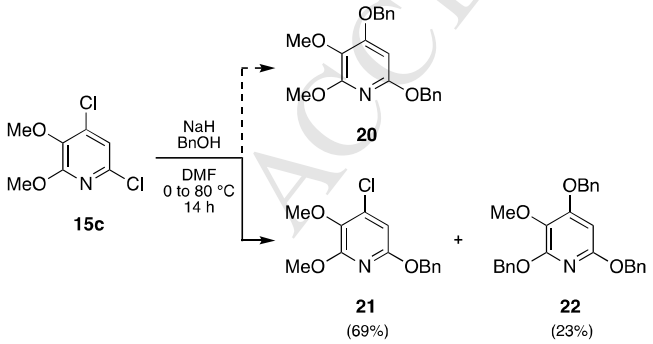
Table 1 Dihalogenation of **18**.



Run	Conditions	Yield (%)
1	1) I_2, K_2CO_3, H_2O, rt, 3 h	decomposed
2	1) NIS, K_2CO_3, THF-H_2O (1:1), rt, 1 h	decomposed
3	1) NBS, K_2CO_3, THF-H_2O (1:1), rt, 3 h	decomposed
4	1) Bis(*sym*-collidine)bromide(I) hexafluorophosphate, CH_2Cl_2, rt, 3 h	decomposed
5	1) NCS, K_2CO_3, THF-H_2O (1:1), rt, 1 h 2) NaH, MeI, DMF, rt, 1 h	**15c** (55)

First, we attempted the dihalogenation of 3-pyridinol **18** under the same conditions as those used in our previous synthesis (*o*-iodination of **4** in Scheme 1)[7] (Table 1). However, the desired diiodide **19a** was not obtained at all; the reaction led to decomposition of the substrates (Run 1). Diiodination with NIS instead of iodine gave the same result (Run 2). Next, dibromination was investigated under similar conditions using NBS and Rousseau's conditions with bis(*sym*-collidine)bromide(I);[11d] however, the desired dibromide **19b** was not observed (Runs 3 and 4). Dichlorination with NCS proceeded smoothly to afford the corresponding dichloride **19c**, which was subjected to methylation without purification to afford the desired dichloride **15c** in 55% yield over two steps (Run 5).

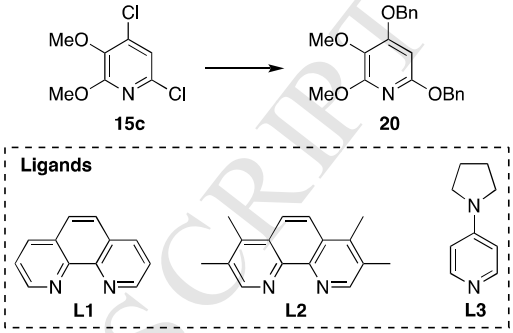
With this dichloride **15c**, we next explored conversion to 4,6-dihydroxypyridine **14**. First, S_NAr reaction of **15c** by treatment with BnONa was attempted, as shown in Scheme 4. Unfortunately, the desired **20** was not obtained at all; instead, the undesired S_NAr products **21** and **22** was obtained in 69% and 23% yields, respectively.



Scheme 4 S_NAr reaction of **15c**.

Second, we investigated the conversion of **15c** to **20** via an Ullmann-type reaction (Table 2). Although the copper-promoted C–O coupling reaction has been widely used in synthetic organic chemistry, the coupling reactions between halopyridines and aliphatic alcohols have been hardly reported and no coupling reaction with dichloropyridine has been reported. The coupling reaction was attempted according to the first catalytic reaction of aliphatic alcohols with aryl halides, as reported by Buchwald et al.[13] Treatment of **15c** with benzyl alcohol in the presence of Cs_2CO_3 as a base, **L1** or **L2** as a ligand, and CuI led to no reaction (Runs 1 and 2). Other reaction conditions using **L3** as a ligand[14] and without a ligand[15] were also tested; however, the results were not improved (Runs 3 and 4). This is attributable to the low reactivity of our substrate dichloropyridine in the Ullmann-type reaction.

Table 2 Unsuccessful conversion of **15c** to **20** via Ullmann-type reaction.

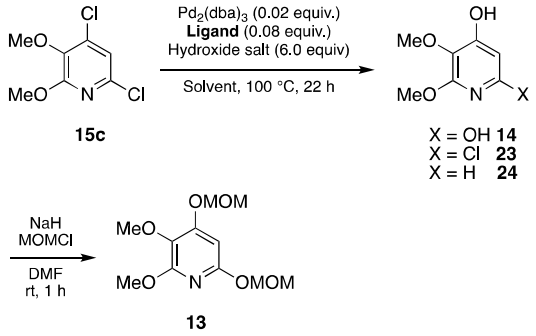


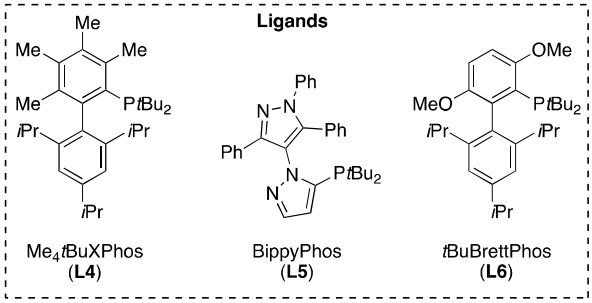
Run	Conditions (equiv.)[a]	Solvent	Results
1	BnOH (4), Cs_2CO_3 (4), CuI (0.1), **L1** (0.2)	toluene	No reaction
2	BnOH (4), Cs_2CO_3 (4), CuI (0.1), **L2** (0.2)	toluene	No reaction
3	BnOH (4), K_3PO_4 (4), CuI (0.1), **L3** (1.2)	toluene	No reaction
4	BnOH (3), K_2CO_3 (6), CuI (0.1), Cu (0.3)	DMF	No reaction

a) All reactions were carried out under reflux for 18 h.

Third, a palladium-catalyzed C–Cl hydroxylation was explored (Table 3). The first set of reaction conditions used followed the first report of Buchwald et al.[16] Although the low reactivity of dichloropyridine was a continual concern, the C–Cl hydroxylation of **15c** in 1,4-dioxane-H_2O (1:1) at 100 °C in the presence of $Pd_2(dba)_3$ as a palladium catalyst, Me_4*t*BuXPhos (**L4**) as a ligand, and KOH as a hydroxide salt proceeded smoothly to afford the desired dihydroxypyridine **14**, including an inseparable by-product and pure mono-hydroxypyridine **24**, in 3% yield after purification by a silica-gel column chromatography. The former was subjected to MOM protection to give the pure desired product **13** in 40% yield over two steps (Run 1). Next, the reaction conditions reported by Stradiotto et al.[17] were used, in which $Pd_2(dba)_3$ as a palladium catalyst, Singer's BippyPhos (**L5**)[18] as a ligand, and CsOH·H_2O as a hydroxide salt were used in 1,4-dioxane at 100 °C (Run 2). This reaction also provided the desired product **13** in 45% yield over two steps, accompanied by **24** in 7% yield. To improve the yield of the desired product **13**, optimization of the reaction conditions was conducted. In Runs 3 and 4, **L4** as a ligand was used and only the solvent or solvent and hydroxide salt were changed (unlike Run 1). Consequently, the yields of **13** in these reactions greatly decreased. In addition, **L5** as a ligand was fixed (like Run 2) and only the hydroxide salt or hydroxide salt and solvent were changed (Runs 5 and 6). Fortunately, the reaction using KOH instead of CsOH·H_2O (Run 5) in 1,4-dioxane afforded the desired product **13** in 71% yield

Table 3 Conversion of **15c** to **13** via a palladium-catalyzed C–Cl hydroxylation.

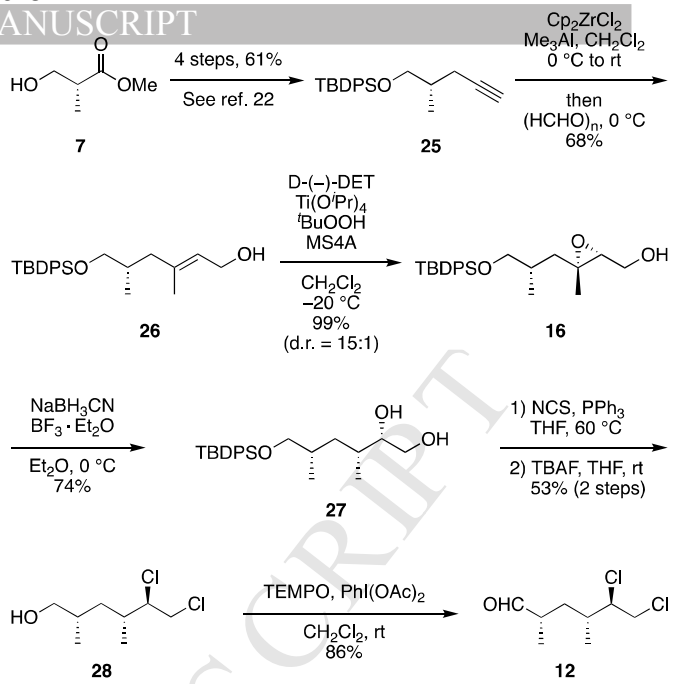




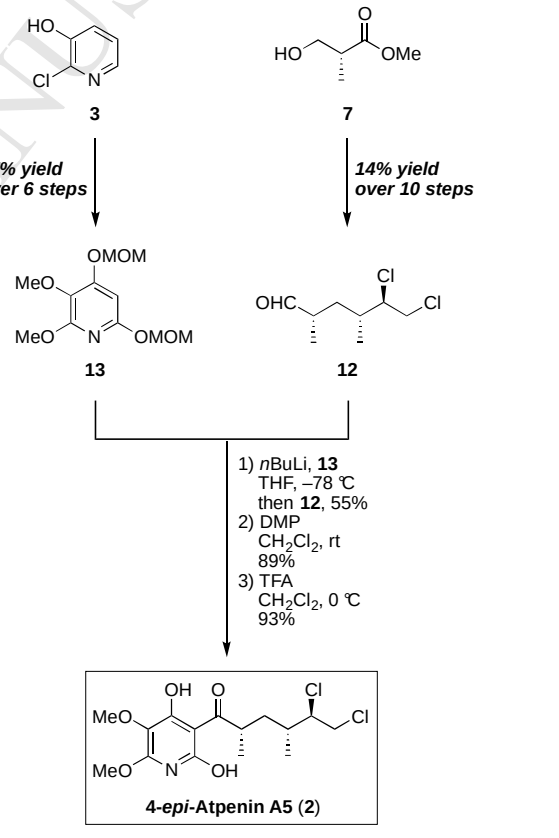
Run	Ligand	Hydroxide salt	Solvent	Yield (%)		
				13[a]	**23**	**24**
1	**L4**	KOH[b]	1,4-dioxane -H_2O (1:1)	40	-	3
2	**L5**	CsOH·H_2O	1,4-dioxane	45	-	7
3	**L4**	KOH[b]	1,4-dioxane	9	-	31
4	**L4**	CsOH·H_2O	1,4-dioxane	18	-	-
5	**L5**	KOH[b]	1,4-dioxane	71	8	14
6	**L5**	KOH[b]	1,4-dioxane -H_2O (1:1)	45	-	6
7	**L6**	KOH[b]	1,4-dioxane	27	-	5
8	**L6**	KOH[b]	1,4-dioxane -H_2O (1:1)	32	-	-
9	**L6**	CsOH·H_2O	1,4-dioxane	54	-	4

a) Over two steps from **15c** b) Used as powder by grinding pellets

over two steps, accompanied by small amounts of **23**[19] (8%) and **24** (14%). The change of solvent (Run 6) gave similar results to those of Run 2. The reaction conditions using a new ligand **L6**[20] were also screened. As such, the use of KOH as a hydroxide salt, regardless of solvent, led to a small decrease in the yield of the desired product **13** and the reaction yield using CsOH·H_2O increased as compared with the reaction using **L4**. In all reactions with KOH, the use of powdered KOH was very important. The formation of diaryl ethers was not observed in Runs 1–9. Another synthetic procedure using a catalytic amount of RockPhos Pd G3, Cs_2CO_3, and benzaldehyde oxime as a hydroxide surrogate for the palladium-catalyzed C–Cl hydroxylation, as reported by Fier and Maloney et al.,[21] was also attempted; however, the desired **14** was not obtained (not shown in Table 3). We thus determined the effective reaction conditions for the palladium-catalyzed C–Cl hydroxylation of dichloropyridine **15c** (Table 3, Run 5) and succeeded to develop a concise synthesis of the key intermediate **13** without using any strong bases (37% yield over six steps).



Scheme 5 Synthesis of **12**.



Scheme 6 Completion of the total synthesis of 4-*epi*-atpenin A5 (**2**).

We then turned to the synthesis of another key intermediate **12** (Scheme 5). Acetylene **25** was prepared from a commercially available (–)-Roche ester (**7**) according to a known procedure.[22] Subsequent Negishi carboalumination and treatment with a paraformaldehyde[23] afforded *trans*-allyl alcohol **26** in 68% yield stereoselectively, which was subjected to Sharpless epoxidation[24] using (–)-DET to give the epoxide **16** in 99% yield stereoselectively (d.r. = 15:1). Regio- and stereoselective reduction of the epoxide **16** with $NaBH_3CN$ in the presence of

$BF_3 \cdot Et_2O$[25] proceeded to furnish diol **27** in 74% yield. Other reactions leading to the desired aldehyde **12** were followed according to our previous synthesis. Finally, concise synthesis of the key intermediate aldehyde **12** was achieved in 14% yield over 10 steps. The coupling reaction between **12** and **13** (55% yield), Dess-Martin oxidation (89% yield), and MOM deprotection under acidic conditions (93% yield) according to our previous synthesis afforded 4-*epi*-atpenin A5 (**2**) (Scheme 6). All analytical data of the synthetic **2** were identical to those reported by us previously.[9]

In conclusion, we have achieved a concise total synthesis of 4-*epi*-atpenin A5 (**2**). Key features of the synthetic strategy included dihalogenation of pyridinol **18** and the palladium-catalyzed C–Cl hydroxylation for the synthesis of the key pyridine unit **13** and Sharpless epoxidation and regio- and stereoselective reductive epoxide-opening reaction for the synthesis of the key aldehyde **12**. Our new total synthesis of **2** was provided in 2.4% overall yield over 19 steps (0.9% overall yield over 27 steps for our previous total synthesis). Future structure–activity relationship studies of atpenin A5 (**1**) and 4-*epi*-atpenin A5 (**2**) analogs in our laboratory will allow substantial progress in this field because the synthesis of the key pyridine unit **13** was both efficient and practical. Such research is currently under way and will be reported in due course.

3. Experimental section

3.1. General

The reactions were carried out in flame-dried glassware under a nitrogen or argon atmosphere employing standard techniques for handling air-sensitive materials. Commercial reagents were used without further purification, unless otherwise indicated. Organic solvents were distilled and dried over 3 or 4Å molecular sieves. Cold baths were prepared as follows: 0 °C, wet ice/water, −78 °C, dry ice/acetone. Purifications by flash column chromatography were performed over silica gel 60N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 nm Merck silica gel 60 F254 plates and the effluents were visualized by UV (254 nm) as well as by phosphomolybdic acid and *p*-anisaldehyde TLC stains. Yields refer to chromotographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H- and ^{13}C-NMR spectra were recorded using an internal deuterium lock on 400-MR, VNMRS-400, and UNITY-400 spectrometers (Agilent Technologies, Waldbormn, Germany). All NMR signals were reported in ppm relative to the internal reference standard provided by chloroform (that is, 7.26 and 77.0 ppm for the ^{1}H and ^{13}C spectra, respectively). Multiplicity data were presented as follows: s = singlet, d = doublet, t = triplet, q = quarted, m = multiplet, br = broad, dd = double doublet, and dt = double triplet. Coupling constants (*J*) were reported in Hz. IR spectra were recorded on a FT/IR460-plus IR spectrometer (JASCO, Tokyo, Japan). Absorption data were given as wavenumber (cm^{-1}). Optical rotations were recorded on a JASCO DIP-1000 polarimeter (JASCO, Tokyo, Japan) and reported as follows: $[\alpha]^T_D$, concentration (g per 100 mL), and solvent. High-resolution mass spectra were obtained on JEOL JMS-700 Mstation, JEOL JMS-AX505HA, and JEOL JMS-T100LP systems (JEOL, Tokyo, Japan) equipped with FAB, EI, and ESI high-resolution mass spectrometers.

*3.2. 2-Methoxypyridin-3-ol (**18**)*

To a solution of **3** (10.0 g, 77.2 mmol) in DMF (175 mL) was added NaH (55 %, 5.05 g, 116 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was treated with BnBr (11.1 mL, 92.6 mmol) and stirred at 0 °C for 15 min. To the mixture were carefully added MeOH (110 mL) and NaH (55 %, 16.8 g, 386 mmol). The resulting mixture was stirred for 17 h at 80 °C, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude **17**.

Next, a suspension of the crude **17** and 10% Pd/C (1.7 mg) in THF/MeOH (1:1, 300 mL) was vigorously stirred under an H_2 atmosphere overnight at room temperature. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (8:1 hexanes/EtOAc) to afford **18** (9.10 g, 94%, two steps) as a yellow oil.

18: IR (KBr): 3403, 3068, 2952, 1609, 1477, 1247, 1107, 789, 754 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, 1H, *J* = 1.6, 5.1 Hz), 7.11 (dd, 1H, *J* = 1.6, 7.6 Hz,), 6.81 (dd, 1H, *J* = 5.1, 7.6 Hz), 5.53 (s, 1H), 4.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.8, 140.5, 137.1, 120.7, 117.7, 53.6; HRMS (EI) $[M]^+$ calcd for $C_6H_7NO_2$ 428.1862, found 428.1855.

*3.3. 4,6-Dichloro-2,3-dimethoxypyridine (**15c**)*

To a solution of **18** (2.08 g, 16.6 mmol) in H_2O/THF (1:1, 84 mL) were added K_2CO_3 (11.5 g, 83.0 mmol) and NCS (11.1 g, 83.0 mmol) at 0 °C. After stirring for 1 h at 0 °C, 2N HCl was added and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude **19c**. Next, the crude **19c** was dissolved in DMF (166 mL) and treated with NaH (55%, 1.09 g, 33.2 mmol) and MeI (2.07 mL, 33.2 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (hexanes) to afford **15c** (1.90 g, 55%, two steps) as a white solid.

15c: IR (KBr): 2941, 1567, 1474, 1413, 1378, 1293, 1246, 1173, 1113, 1037, 996, 912, 838, 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 4.01 (s, 3H), 3.87 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.8, 141.4, 139.4, 138.1, 117.5, 60.6, 54.6; HRMS (EI) $[M]^+$ calcd for $C_7H_7Cl_2NO_2$ 206.9854, found 206.9855.

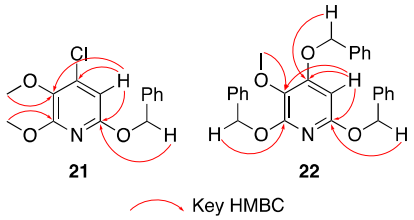
*3.4. 6-(Benzyloxy)-4-chloro-2,3-dimethoxypyridine (**21**) and 2,4,6-tris(benzyloxy)-3-methoxypyridine (**22**)*

To a solution of **15c** (41.4 mg, 0.200 mmol) in DMF (800 μL) were added NaH (55%, 34.9 mg, 0.800 mmol) and a solution of BnOH (83.1 μL, 0.800 mmol) in DMF (1.2 mL) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was stirred for 14 h at 80 °C. The resulting mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (30:1 hexanes/EtOAc) to afford **21** (38.8 mg, 69%) as a colorless oil and **22** (19.9 mg, 23%) as a colorless oil.

21: IR (KBr): 2931, 2831, 1583, 1484, 1446, 1371, 1235, 1114, 998, 894, 744 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 6.60 (s, 1H), 5.14 (s, 2H), 3.97 (s, 3H), 3.83 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.3, 157.7, 142.1, 135.4, 131.3, 128.8 (2C), 128.4 (2C), 127.2, 103.9, 71.0, 60.8, 54.4; HRMS (ESI+) $[M+H]^+$ calcd for $C_{14}H_{15}ClNO_3$, 280.0740, found 280.0731.

22: IR (KBr): 3031, 2930, 1600, 1485, 1348, 1111, 1062, 1028, 906, 801 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42-7.23

(m, 15H), 6.01 (s, 1H), 5.42 (s, 2H), 5.23 (s, 2H), 5.11 (s, 2H), 3.80 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9, 157.4, 138.0, 137.6, 136.1, 128.6(2C), 128.4(2C), 128.3(2C), 128.1(2C), 127.8(3C), 127.5(2C), 127.1(2C), 126.8(2C), 88.4, 70.5, 67.7, 67.6, 60.9; HRMS (ESI) $[M+H]^+$ calcd for $C_{27}H_{26}NO_4$, 428.1862, found 428.1855.



*3.5. 2,3-Dimethoxy-4,6-bis(methoxymethoxy)pyridine (**13**), 6-chloro-2,3-dimethoxypyridin-4-ol (**23**), and 2,3-dimethoxypyridin-4-ol (**24**) (Table 3, Run 5)*

To a solution of **15c** (100 mg, 0.481 mmol) in 1,4-dioxane (1.0 mL) were added $Pd_2(dba)_3$ (8.8 mg, 9.58 μmol), Bippyphos (19.4 mg, 38.3 μmol), and KOH (161 mg, 2.87 mmol) at room temperature. The mixture was stirred for 22 h at 100℃. After cooling to room temperature, 2N HCl was added and the mixture was extracted with EtOAc/MeOH (10:1). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was semipurified by flash silica-gel column chromatography (8:1 to 0:1 hexane/EtOAc) to afford **23**[19] (7.1 mg, 8%) as a yellow solid, **24** (10.1 mg, 14%) as a yellow oil, and the crude **14**.

Next, to a solution of the crude **14** (80.1 mg) in DMF (4.8 mL) were added NaH (55 %, 83.6 mg, 1.92 mmol) and MOMCl (144 μL, 1.92 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (5:1 hexanes/EtOAc) to afford **13** (88.1 mg, 71%, two steps) as a colorless oil.

23: IR (KBr): 3358, 2992, 2942, 1587, 1473, 1390, 1254, 1098, 1050, 994, 753 cm^{-1}; HRMS (EI+) $[M]^+$ calcd for $C_7H_8ClNO_3$, 189.0193, found 189.0199; Major regioisomer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 3.92 (s, 3H), 3.80 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ156.4, 155.8, 140.1, 134.5, 100.8, 60.8, 54.3; Minor regioisomer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 3.98 (s, 3H), 3.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ156.9, 156.0, 142.0, 129.2, 105.8, 60.8, 54.2.

24: IR (KBr): 3423, 2928, 1599, 1465, 1403, 1102, 709 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 1H, *J* = 5.4 Hz), 6.57 (d, 1H, *J* = 5.4 Hz), 6.16 (s, 1H), 3.99 (s, 3H), 3.90 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.2, 155.5, 141.5, 130.2, 106.5, 60.7, 53.6; HRMS (ESI+) $[M+H]^+$ calcd for $C_7H_{10}NO_3$, 156.0662, found 156.0661.

13: IR (KBr): 2951, 2829, 1603, 1487, 1422, 1381, 1351, 1239, 1154, 1118, 1075, 1025, 999, 924, 904, 814, 794 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.43 (s, 2H), 5.24 (s, 2H), 3.94 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 3.79 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.1, 156.4, 156.0, 127.4, 94.5, 91.9, 89.9, 60.8, 56.9, 56.4, 53.6; HRMS (EI) $[M]^+$ calcd for $C_{11}H_{17}NO_6$ 259.1056, found 259.1052.

*3.6. (S,E)-6-((tert-Butyldiphenylsilyl)oxy)-3,5-dimethylhex-2-en-1-ol (**26**)*

To a solution of Cp_2ZrCl_2 (128 mg, 0.440 mmol) in CH_2Cl_2 (2.4 mL) was added dropwise Me_3Al (1.07 M in *n*-hexane, 1.23 mL, 1.32 mmol) at 0 °C under argon. After stirring for 0.5 h at 0 °C, a solution of **25** (148 mg, 0.440 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added. The mixture was allowed to warm to room temperature and was then stirred for 11 h. The resulting mixture was cooled to 0 °C and treated with $(HCHO)_n$ (198 mg). After stirring for 0.5 h at 0 °C, the mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (10:1 hexanes/EtOAc) to afford **26** (116 mg, 68%) as a colorless oil.

26: $[\alpha]^{24}_D$ −8.41 (*c* 1.0, $CHCl_3$); IR (KBr): 3313, 2929, 1427, 1108, 869, 701, 504 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.43-7.35 (m, 6H), 5.39-5.36 (m, 1H), 4.12-4.09 (m, 2H), 3.47 (dd, 2H, *J* = 2.0, 6.0 Hz), 2.25-2.21 (m, 1H), 1.84-1.73 (m, 2H), 1.61 (s, 3H), 1.05 (s, 9H), 0.89 (d, 3H, *J* = 6.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.3, 135.6, 134.0, 129.5, 127.6, 125.0, 68.5, 59.3, 43.6, 33.7, 26.9, 19.3, 16.6, 16.1; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{34}NaO_2Si$, 405.2226, found 405.2220.

*3.7. ((2R,3R)-3-((S)-3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-3-methyloxiran-2-yl)methanol (**16**)*

To a suspension of 4Å molecular sieves (80 mg) and Ti(O*i*-Pr)$_4$ (182 μL, 0.620 mmol) in CH_2Cl_2 (1.0 mL) were added dropwise (–)-DET (126 μL, 0.740 mmol) and a solution of **26** (158 mg, 0.410 mmol) in CH_2Cl_2 (3.0 mL) at −20 °C. After stirring for 20 min, TBHP (5.0 M in decane, 224 μL, 1.23 mmol) was added dropwise to the suspension at −20 °C and the resulting mixture was stirred for 2 h. The reaction was quenched with 10% aqueous tartaric acid solution (4.0 mL) and 10% aqueous Na_2SO_3 solution (1.0 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (5:1 hexanes/EtOAc) to afford **16** (162 mg, 99%, d.r. = 15:1) as a colorless oil.

16: $[\alpha]^{24}_D$ −4.01 (*c* 1.0, $CHCl_3$); IR (KBr): 3446, 2958, 2857, 1470, 1387, 1109, 862, 797, 702, 650 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67-7.62 (m, 4H), 7.46-7.35 (m, 6H), 3.63-3.57 (m, 2H), 3.52-3.43 (m, 2H), 2.95-2.80 (m, 1H), 2.07-2.03 (m, 1H), 1.89-1.84 (m, 2H), 1.25 (s, 3H), 1.06 (s, 9H), 0.97 (d, 3H, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6, 133.8, 133.7, 129.7, 129.6, 127.7, 127.6, 68.0, 62.6, 61.2, 60.3, 42.1, 33.0, 26.9, 19.3, 17.6, 16.6; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{34}NaO_3Si$, 421.2175, found 421.2595.

*3.8. (2S,3R,5S)-6-((tert-Butyldiphenylsilyl)oxy)-3,5-dimethylhexane-1,2-diol (**27**)*

To a solution of **16** (77.1 mg, 0.190 mmol) in Et_2O (1.9 mL) was added $NaBH_3CN$ (53.5 mg, 0.890 mmol) at 0 °C. The resulting mixture was vigorously stirred at 0 °C and treated with $BF_3 \cdot Et_2O$ (122 μL, 0.970 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with 2 N HCl and extracted with EtOAc. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (3:1 hexanes/EtOAc) to afford **27** (57.4 mg, 74%) as a colorless oil.

27: $[\alpha]^{24}_D$ +3.44 (*c* 1.0, $CHCl_3$); IR (KBr) 3432, 2957, 2857, 1629, 1469, 1388, 1109, 1079 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.45-7.35 (m, 6H), 3.60-3.43 (m, 5H), 1.74-

1.52 (m, 4H), 1.05 (s, 9H), 0.94 (d, 3H, *J* = 8.0 Hz), 0.86 (d, 3H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6, 133.9, 129.6, 127.7, 127.6, 77.3, 77.0, 76.7, 75.3, 68.4, 65.2, 37.1, 33.0, 26.9, 19.3, 18.0, 14.9; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{36}NaO_3Si$, 423.2331, found 423.2321.

*3.9. (2S,4R,5R) -5,6-Dichloro-2,4-dimethylhexan-1-ol (**28**)*

To a solution of **27** (898 mg, 2.24 mmol) in THF (11.2 mL) were added NCS (898 mg, 6.73 mmol) and PPh_3 (1.76 g, 6.73 mmol) at room temperature. The mixture was stirred for 3 h at 60 °C, quenched with H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was semipurified by flash silica-gel column chromatography (hexanes) to afford the crude dichloride.

A solution of the crude dichloride in THF (22.4 mL) was treated with TBAF (1.0 M in THF, 4.48 mL, 4.48 mmol) at room temperature. After stirring for 1.5 h at room temperature, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (15:1 hexanes/EtOAc) to afford **28** (237 mg, 53%, two steps) as a white solid.

28: $[\alpha]^{27}_D$ +18.3 (*c* 0.1, $CHCl_3$); IR (KBr) 3020, 1215, 930, 794, 754, 667, 534, 438, 409 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.03 (ddd, 1H, *J* = 2.7, 5.3, 5.3 Hz), 3.76 (dd, 1H, *J* = 5.3 Hz), 3.76 (dd, 1H, *J* = 5.3 Hz), 3.57 (dd, 1H, *J* = 3.3, 7.8 Hz), 3.46 (dd, 1H, *J* = 4.5, 7.8 Hz), 2.29-2.20 (m, 1H), 1.75-1.70 (m, 1H), 1.53 (ddd, 1H, *J* = 4.5, 6.6, 9.6 Hz), 1.08 (d, 3H, *J* = 5.4 Hz), 1.00 (d, 3H, *J* = 5.1 Hz), 0.95-0.89 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 67.4, 67.2, 46.0, 34.3, 33.5, 33.1, 18.3, 17.7; HRMS (EI) $[M–CH_2OH]^+$ calcd for $C_7H_{13}Cl_2$ 167.0394, found 167.0392.

*3.10. 4-epi-Atpenin A5 (**2**)*

To a solution of **28** (56.0 mg, 0.281 mmol) in CH_2Cl_2 (2.8 mL) were added TEMPO (4.4 mg, 0.0281 mmol) and $PhI(OAc)_2$ (136 mg, 0.422 mmol) at room temperature. The mixture was stirred for 3.3 h at room temperature, quenched with a saturated aqueous $Na_2S_2O_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (20:1 hexanes/EtOAc) to afford **12** (47.7 mg, 86%) as a colorless oil. All analytical data of the synthetic **12** were identical to those reported by us previously.[9]

A solution of **13** (75.3 mg, 0.290 mmol) in THF (2.4 mL) was added to a solution of *n*BuLi (1.55 M in hexanes, 225 µL, 0.248 mmol) in THF (1.2 mL) at –78 °C. After stirring for 1.5 h at –78 °C, a solution of **12** (47.7 mg, 0.242 mmol) in THF (1.2 mL) was added dropwise to the resulting mixture. The reaction mixture was stirred for 1.5 h at –78 °C, quenched with MeOH, diluted with H_2O, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was semipurified by flash silica-gel column chromatography (3:1 hexanes/EtOAc) to afford the corresponding coupling product (60.2 mg, 55%) as a diastereomixture.

Next, a solution of the coupling product (54.4 mg, 0.119 mmol) in CH_2Cl_2 (1.2 mL) was treated with DMP (101 mg, 0.238 mmol). The reaction mixture was stirred for 1.5 h at room temperature, quenched with a saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (10:1 hexanes/EtOAc) to afford the MOM-protected 4-*epi*-atpenin A5 (48.4 mg, 89%) as a colorless oil.

MOM-protected 4-*epi*-atpenin A5: $[\alpha]^{27}_D$ +19.7 (*c* 0.1, $CHCl_3$); IR (KBr) 3401, 3020, 1636, 1589, 1471, 1389, 1213, 787, 754, 671 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.60 (d, 1H, *J* = 5.6, Hz), 5.39 (d, 1H, *J* = 5.6 Hz), 5.33 (d, 1H, *J* = 5.2, Hz), 5.26 (d, 1H, *J* = 5.2 Hz), 4.03 (ddd, 1H, *J* = 2.4, 6.6, 7.0 Hz), 3.96 (s, 3H), 3.87 (dd, 1H, *J* = 6.6, 11.6 Hz), 3.76 (dd, 1H, *J* = 7.0, 11.6 Hz), 3.76 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 3.27-3.19 (m, 1H), 2.25-2.17 (m, 1H), 2.07 (ddd, 1H, *J* = 3.2, 10.0, 13.5 Hz), 1.28-1.19 (m, 1H), 1.17 (d, 3H, *J* = 7.2 Hz), 1.10 (d, 3H, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.5, 157.2, 156.1, 152.8, 129.8, 110.6, 99.0, 91.9, 68.1, 60.8, 57.8, 57.4, 54.0, 46.6, 44.8, 34.6, 33.8, 18.0, 17.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{29}Cl_2NNaO_7$ 476.1219, found 476.1223.

A solution of MOM-protected 4-*epi*-atpenin A5 (27.8 mg, 0.0612 mmol) in CH_2Cl_2 (600 µL) was treated with TFA (600 µL) at 0 °C. After stirring for 0.5 h at 0 °C, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash silica-gel column chromatography (1:1 hexanes/EtOAc) to afford 4-*epi*-atpenin A5 (**2**) (20.9 mg, 93%) as a white solid.

4-*epi*-Atpenin A5 (2): $[\alpha]^{27}_D$ +38.7 (*c* 1.0, $CHCl_3$); IR (KBr) 2934, 1646, 1593, 1457, 1325, 1289, 1195, 1163, 994, 956, 592 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 4.22-4.12 (m, 1H), 4.00 (ddd, 1H, *J* = 2.8, 6.6, 7.2 Hz) 3.85 (dd, 1H, *J* = 7.2, 11.4 Hz), 3.80 (s, 3H), 3.75 (dd, 1H, *J* = 6.6, 11.4 Hz), 2.10 (ddd, 1H, *J* = 3.2, 10.2, 12.3 Hz), 2.07-1.98 (m, 1H), 1.27-1.20 (m, 1H), 1.18 (d, 3H, *J* = 6.8 Hz), 1.03 (d, 3H, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.4, 172.1, 161.6, 155.5, 121.4, 100.8, 67.7, 61.6, 57.9, 46.3, 40.2, 34.1, 33.8, 19.1, 17.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{21}Cl_2NNaO_5$ 388.0695, found 388.0707.

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Supplementary Material

Supplementary data to this article can be found online at .