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A TOTAL SYNTHESIS OF (17S)-HEXAHYDRO-TMC-69

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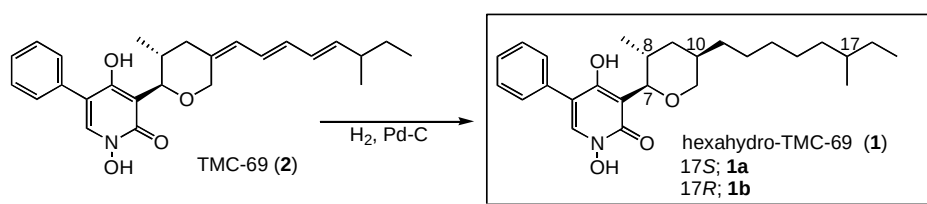
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Abstract – The cdc25A protein phosphatase inhibitor (7*R*,8*R*,10*R*, 17*S*)-hexahydro-TMC-69 (**1a**) has been synthesized in a stereoselective manner, starting from an enantiomerically pure pyranone (**3**) using Knoevenagel condensation as a key step.

INTRODUCTION

The TMC-69(6H) (hexahydro-TMC-69) (**1**) is a stabilized saturated analogue of novel antitumor natural antibiotic TMC-69 (**2**), which was isolated from a fermentation broth of *Chrysosporium* sp. TC1068 as a labile amorphous by Kohno and co-workers.^{1a,1b} The semi-synthetic compound showed cytotoxic activities *in vitro* against various tumor cell lines (cf. HCT-116, IC₅₀ = 0.70 μM). It has also been found that **1** has a potent inhibitory activity against protein phosphatase cdc25A (IC₅₀ = 3.1 μM),² a novel class of a dual specificity phosphatase. Recently, phosphatase inhibitors have received considerable attention due to the crucial role they play in human cell cycle progression.³ Inappropriate over-expression of cdc25A has been also reported in certain types of cancer.

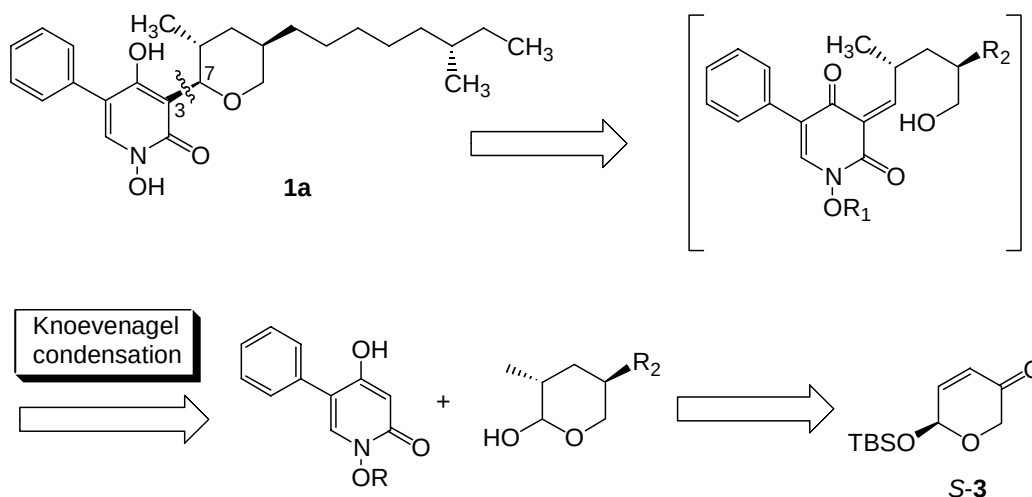
Structurally **2** accommodates a tetrahydropyran-substituted 1,4-dihydroxy-2-pyridone skeleton. Recent representatives of this family, sumbutoxin,^{4a,4b} funiculosin,⁵ and oxysporidinone,⁶ possess a range of biological activities. The absolute stereochemistry of **1**, except for the C-17 carbon, was estimated to be 7*R*, 8*R*, and 10*R* by the N. O. E. experiment of 400MHz-¹H-NMR analysis and a degradation study of TMC-69 (**2**) followed by application of the modified Mosher's method.^{1a} The unique structure and interesting biological activities of TMC-69 derivatives prompted us to investigate a total synthesis of this class of compounds to clarify the structure-bioactivity relationship (Scheme 1).



Scheme 1. Chemical structures of TMC-69 and TMC-69(6H)

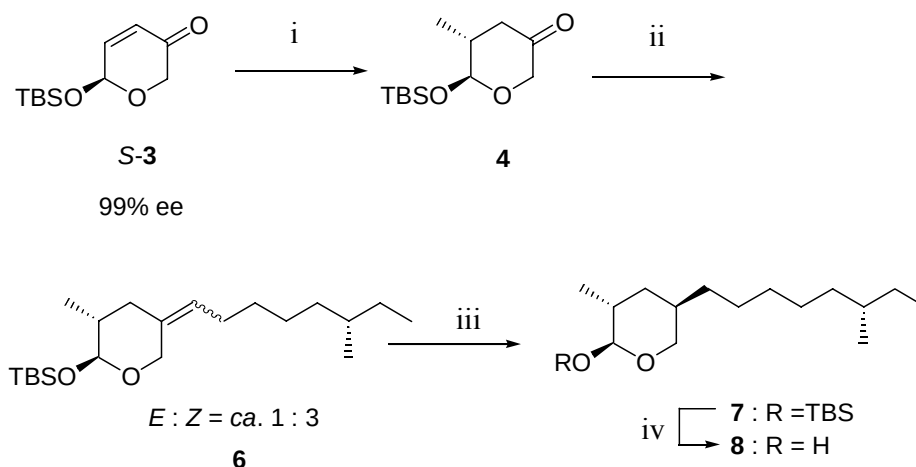
RESULTS AND DISCUSSION

During our synthetic studies of **1**,^{7a} the total synthesis of (17*S*)-TMC-69(6H) (**1a**) and (17*R*)-TMC-69(6H) (**1b**) was reported by Fürstner and coworkers using a Pd-catalyzed allyl-coupling method as a key step.^{7b,7c} However, the absolute configuration of C-17 carbon was not clarified because of the almost similar spectral characteristics of the two molecules. Therefore, we envisaged another approach to the (17*S*)-TMC-69(6H) (**1a**) as a tentative synthetic target. Our synthetic strategy is outlined in Scheme 2. Thus, C₃–C₇ bonds of **1a** could be constructed by the Knoevenagel condensation of 4-hydroxy-5-phenyl-2-pyridone with pyranol derivatives via a pyridinone methide intermediate followed by intramolecular conjugate addition.⁸ At this stage, the thermodynamic conditions should lead the relative stereochemistry of C-7 and C-8 substituents into a more thermodynamically favored *trans* configuration. Concerning the pyranol unit, we have recently developed an efficient preparation of both enantiomers of 6-*tert*-butyldimethylsilyloxy-3-pyranones, ((*R*)-**3**, and (*S*)-**3**), in high e.e. via the lipase AK-catalyzed kinetic resolution,⁹ and planned to use the (*S*) enantiomer as a precursor.

Scheme 2. Retrosynthetic analysis of 17*S*-(+) hexahydro-TMC-69

Starting from the pyranone ((*S*)-**3**), the *trans*-selective 1,4-addition of methyl-cuprate gave the ketone (**4**). Subsequent Wittig olefination with known triphenylphosphonium salt **5**¹⁰ gave **6** as a mixture of isomers (*E*:*Z* = *ca.* 1:2). Stereoselective hydrogenation of the olefinic moiety was accomplished with Ir-black as a catalyst to give **7**.¹¹ Removal of the TBS group with tetra-*n*-butylammonium fluoride provided the pyranol

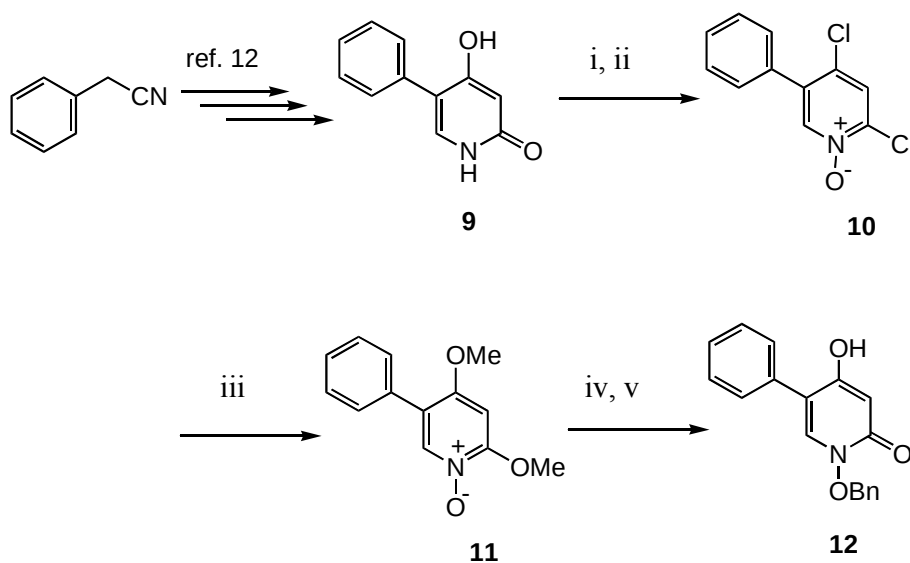
pyranol (**8**), the key intermediate for the subsequent condensation reaction (Scheme 3).



Reagents and conditions: (i) MeLi, CuCN, TMSCl, THF (90%); (ii) *n*-BuLi, (*S*)-CH₃CH₂(CH₃)CH(CH₂)₄CH₂PPh₃⁺Br[−] (**5**) (95%); (iii) Ir-black, H₂, dioxane (85%); (iv) TBAF, THF (quant.).

Scheme 3

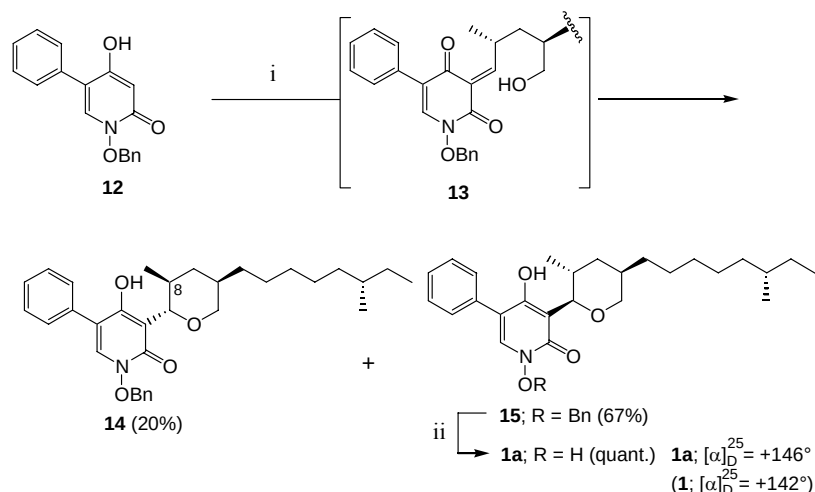
The pyridone unit was synthesized as follows. According to Snider's procedure, pyridone (**9**) was synthesized from phenylacetonitrile in three steps.¹² Treatment with PhPOCl₂, then oxidation with *m*-CPBA, gave 2,4-dichloropyridine-*N*-oxide (**10**), which was treated with NaOMe to give **11**. Demethylation under acidic conditions, followed by monobenzoylation, furnished the desired pyridone (**12**)¹⁴ (Scheme 4).



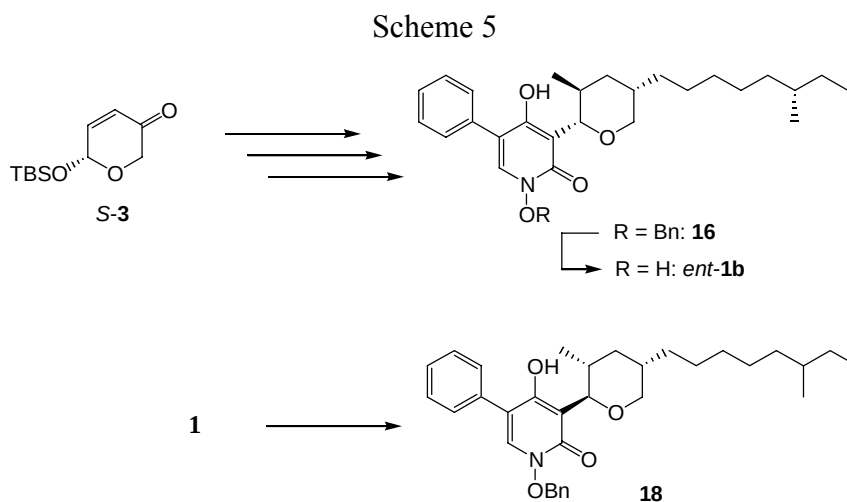
Reagents and conditions: (i) PhPOCl₂; (ii) *m*-CPBA, CH₂Cl₂ (80% 2 steps); (iii) NaOMe, MeOH (75%); (iv) 47% HBr; (v) BnBr, K₂CO₃, DMF (54% 2 steps).

Scheme 4

With both required units in hand, we then examined the crucial condensation step using various catalysts and solvents. The best result was obtained when **12** was treated with two equivalents of **8** in the presence of ethylenediammonium diacetate in methylene chloride at room temperature. Thus, condensation took place cleanly, and the cyclized product (**15**) was obtained at a yield of 67% along with the stereoisomer (**14**)¹³ (20%) via C-8 epimerization (Scheme 5). After separation of the undesired diastereomer (**14**), **15** was deprotected under hydrogenolytic conditions to give the desired (17*S*)-TMC-69(6H) (**1a**), which showed good accordance with the analytical data of **1** derived from natural product (**2**) including optical rotation.¹⁴ However, enantiomer of C17-epimer (*ent*-**1b**), synthesized by the same procedure starting from (*R*)-**3**, showed almost same chemical shifts in the 300 MHz ¹H-NMR analysis and similar optical rotation with its mirror image.¹⁵ Next, we envisaged the comparison of **15** and **16** with semi-synthetic product (**18**), which is derived via benzylation of authentic sample (**1**) (Scheme 6).¹⁶ However, again, neither the comparison in the 400MHz ¹H nor ¹³C-NMR analysis could find distinct differences between them. As a result, determination of the absolute configuration of C-17 still remains a task for the future.



Reagents and conditions: (i) **8**, H₂N(CH₂)₂NH₂·2AcOH, CH₂Cl₂, **15** (67%), **14** (20%); (ii) Pd/C, H₂ (quant.).



Scheme 6

In conclusion, we have established a convergent and efficient route to TMC-69 derivatives in a stereo-controlled manner. Structure–activity relationship studies of TMC-69 derivatives using the route described here and determination of the absolute stereochemistry of C-17 are under investigation and will be reported elsewhere.

EXPERIMENTAL

General

Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a Horiba SEPA-200 high sensitive polarimeter. IR spectra were obtained with a PerkinElmer Paragon 1000 FT-IR spectrophotometer. ^1H -NMR spectra were measured with a Varian Gemini-300 or a JEOL-LA400 spectrometer. Mass spectra were taken using a Finnigan MAT SSQ7000C (APCI) or a JEOL JMS-HX 100 (FAB) mass spectrometer. Elemental analysis was performed on a Perkin-Elmer 2400 or a Dionex-IC 320 elemental analyzer. All reactions were monitored by TLC on silica gel 60 GF₂₅₄ (Merck). Column chromatography was performed on Silica Gel 60N (spherical, neutral) (100–210 μm , KANTO). Flash chromatography was performed on Silica Gel 60N (spherical, neutral) (40–100 μm , KANTO). Recycling preparative HPLC was performed on LC-908 (Japan analytical industry Co., Ltd. JAIGEL-2H, CHCl_3). In general, reactions were carried out in dry solvents under argon atmosphere.

(5R,6S)-6-[(*tert*-Butyl(dimethyl)silyl]oxy}-5-methyldihydro-2H-pyran-3(4H)-one (**4**)

To a cooled ($-78\text{ }^\circ\text{C}$) suspension of CuCN (1.08g, 12.1 mmol) in THF (10 mL) was added MeLi (1.14 M in Et_2O , 19.0 mL, 21.8 mmol), then the mixture was warmed up to $0\text{ }^\circ\text{C}$ over 10 min. After stirring at $0\text{ }^\circ\text{C}$ for 10 min, the reaction mixture was recooled to $-78\text{ }^\circ\text{C}$ and was added TMSCl (3.07 mL, 24.2 mmol) then a solution of (*S*)-(+)-6-*tert*-butyldimethylsilyloxy-2H-pyran-3(6H)-one (1.79 g, 7.84 mmol) in THF (5 mL). After stirring at $-78\text{ }^\circ\text{C}$ for 10 min, the mixture was warmed up to $0\text{ }^\circ\text{C}$ over 15 min and stirred at $0\text{ }^\circ\text{C}$ for 15 min. The reaction mixture was quenched with 2 N HCl (20 mL), diluted with Et_2O , and then filtered through a pad of Celite. The organic layer was separated and washed with H_2O and sat. aqueous NaHCO_3 , dried (MgSO_4), and concentrated *in vacuo*. Purification of the residue by column chromatography (10% AcOEt-hexane) gave 1.72 g (90%) of **4** as a colorless oil: $[\alpha]_{\text{D}}^{20} = -131.8^\circ$ ($c = 0.710$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ : 0.14 (s, 6H), 0.92 (s, 9H), 1.06 (d, 3H, $J = 6.8\text{ Hz}$), 2.14 (m, 1H), 2.23 (dd, 1H, $J = 15.6, 7.5\text{ Hz}$), 2.66 (dd, 1H, $J = 15.7, 4.9\text{ Hz}$), 3.87 (dd, 1H, $J = 16.7, 0.7\text{ Hz}$), 4.22 (dd, 1H, $J = 16.7, 0.6\text{ Hz}$), 4.93 (d, 1H, $J = 4.2\text{ Hz}$); IR (neat) 1732, 1472, 1463, 1253 cm^{-1} ; MS (APCI, +AcONH₄) m/z 294 ($\text{M} + \text{MeOH} + \text{NH}_4$)⁺; Anal. Calcd for $\text{C}_{12}\text{H}_{24}\text{O}_3\text{Si}$: C 58.97; H 9.90. Found: C 58.75; H 9.81.

***tert*-Butyl(dimethyl)((*(2S,3R)*-3-methyl-5-[(*(6S)*-6-methyloctylidene)]tetrahydro-2*H*-pyran-2-yl}oxy)-silane (6)**

To a cooled (0 °C) suspension of ((*(S)*-6-methyloctyl)triphenylphosphonium bromide¹⁰ (1.63 g, 3.47 mmol) in THF (20 mL) was added *n*-BuLi (1.6 M in hexane, 2.12 mL, 3.4 mmol). The reaction mixture was stirred at 0 °C. After 30 min, resulting red suspension was cooled to –78 °C. To above mixture was added a solution of (*(5R,6S)*-6-[[*tert*-butyl(dimethyl)silyl]oxy]-5-methyldihydro-2*H*-pyran-3(*4H*)-one (4) (565 mg, 2.31 mmol) in THF (3 mL), and then allowed to warmed up to 0 °C over 30 min before stirring at this temperature for 30 min. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with H₂O and sat. aqueous NaCl, dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by column chromatography (50% CHCl₃-hexane) gave 778 mg (95%) of **6** as a colorless oil (*E* : *Z* = *ca.* 3:1 mixuture). ¹H NMR (300 MHz, CDCl₃) δ: 0.12 (d, 6H, 5.7 Hz), 0.80-0.95 (m, 18H), 1.05-1.35 (m, 9H), 1.60-1.74 (m 1H), 1.78-1.89 (m 1H), 1.92-2.20 (m, 2H), 2.47 (dd, 3/4H, *J* = 13.7, 4.4 Hz), 2.56 (dd, 1/4H, *J* = 14.3, 4.4 Hz), 3.83 (d, 1/4H, *J* = 12.8 Hz), 3.96 (d, 3/4H, *J* = 13.0 Hz), 4.22 (d, 1/4H, *J* = 11.9 Hz), 4.41 (d, 3/4H, *J* = 12.8 Hz), 4.55-4.58 (m, 1H), 5.15 (t, 3/4H, *J* = 7.5 Hz), 5.27 (t, 1/4H, *J* = 7.5 Hz).

***tert*-Butyl(dimethyl)((*(2S,3R,5R)*-3-methyl-5-[(*(6S)*-6-methyloctyl)]tetrahydro-2*H*-pyran-2-yl}oxy)-silane (7)**

To a mixture of *tert*-butyl(dimethyl)((*(2S,3R)*-3-methyl-5-[(*(6S)*-6-methyloctylidene)]-tetrahydro-2*H*-pyran-2-yl}oxy)silane (**6**) (354 mg, 1.00 mmol) in dioxane (10 mL) was added Iridium-black (96 mg) and hydrogenated under H₂ atmosphere in an ordinary pressure and temperature. After 24 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (9%-28% CH₂Cl₂-hexane) gave 302 mg (85%) of **7** as a colorless oil. [α]_D²⁰ = –37.05° (*c* = 0.448, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ: 0.08 (s, 3H), 0.10 (s, 3H), 0.83 (d, 3H, *J* = 7.5 Hz), 0.85 (t, 3H, *J* = 8.4 Hz), 0.91 (s, 9H), 0.97 (d, 3H, *J* = 6.8 Hz), 1.00-1.38 (m, 14H), 1.58-1.74 (m, 3H), 3.46 (dd, 1H, *J* = 11.2, 2.9 Hz), 3.58 (dd, 1H, *J* = 11.0, 8.4 Hz), 4.57 (d, 1H, *J* = 3.5 Hz); IR (neat) 3425, 1361, 1331, 1252 cm^{–1}; MS (APCI, +AcONH₄) *m/z* 374 (M+NH₄)⁺; Anal. Calcd for C₂₁H₄₄O₂Si: C 70.72; H 12.43. Found: C 70.61; H 12.37.

(*3R,5R*)-3-Methyl-5-[(*(6S)*-6-methyloctyl)]tetrahydro-2*H*-pyran-2-ol (8)

To a cooled (0 °C) solution of *tert*-butyl(dimethyl)((*(2S,3R,5R)*-3-methyl-5-[(*(6S)*-6-methyloctyl)]-tetrahydro-2*H*-pyran-2-yl}oxy)silane (**7**) (187 mg, 0.52 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 0.63 mL, 0.63 mmol), and the reaction mixture was allowed to warmed up to rt. After stirring at rt for 2 h, the reaction mixture diluted with AcOEt, washed with H₂O

and sat. aqueous NaCl. The organic layer was dried (MgSO₄) and concentrated *in vacuo*. Obtained crude material (126 mg) was used for the next conversion without further purification.

2,4-Dichloro-5-phenylpyridine 1-oxide (10)

Mixture of 4-hydroxy-5-phenylpyridin-2(1*H*)-one¹² (**9**) (1.88 g, 10.0 mmol) and phenylphosphoric dichloride (25 mL) was heated at 170 °C for 2 h. After cooled to rt, the reaction mixture was poured into crashed-ice and afforded crystal was collected by filtration. Filtered solid was dissolved into AcOEt, washed with sat. aqueous NaHCO₃ and sat. aqueous NaCl. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give crude dichloride 2.22 g as a colorless solid and used for the next conversion without further purification. To a cooled (0 °C) solution of above dichloride (2.20 g, 9.82 mmol) in CH₂Cl₂ (30 mL) was added *m*-chloroperbenzoic acid (72% purity, 4.84 g, 19.6 mmol). After 2 days, additional *m*-chloroperbenzoic acid (72% purity, 4.84 g, 19.6 mmol) was added. After 20 h, to the reaction mixture was added 10% Na₂S₂O₃ and stirred at rt for 15 min. The reaction mixture was diluted with CH₂Cl₂, washed with sat. aqueous NaHCO₃ and sat. aqueous NaCl, dried (Na₂SO₄) and concentrated *in vacuo*. The residual solid was recrystallized from CH₂Cl₂-Et₂O to give 1.90 g, (80%, 2 steps) of **10** as a colorless crystal.

mp 133-135 °C; ¹H NMR (300 MHz, CDCl₃) δ: 7.39-7.52 (m, 5H), 7.62 (s, 1H), 8.34 (s, 1H); IR (Nujol) 1351, 1313, 1279, 1251, 1220 cm⁻¹; MS (APCI) *m/z* 240 (M+H)⁺; Anal. Calcd for C₁₁H₇NOCl₂: C 55.03; H 2.94; Cl 29.53; N 5.83. Found: C 54.85; H 2.88; Cl 29.55; N 5.93.

2,4-Dimethoxy-5-phenylpyridine 1-oxide (11)

To a 0.71 M NaOMe solution in MeOH (800 mL) [prepared from Na (13.2 g, 570 mmol) and MeOH (800 mL)], 2,4-dichloro-5-phenylpyridine 1-oxide (**10**) (19.2 g, 80 mmol) was added at 0 °C then stirred at rt. After stirring at rt for 2 days, to above mixture was added 2 M HCl-MeOH (235 mL). Precipitated NaCl was removed by filtration through a pad of Celite. The filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10-20% MeOH-CHCl₃) then recrystallization from AcOEt gave 13.9 g (75%) of **11** as colorless crystals. mp 111-113 °C; ¹H NMR (300 MHz, CDCl₃) δ: 3.93 (s, 3H), 4.16 (s, 3H), 6.48 (s, 1H), 7.38-7.46 (m, 5H), 8.23 (s, 1H); IR (Nujol) 1669, 1621 cm⁻¹; MS (APCI) *m/z* 232 (M+H)⁺; Anal. Calcd for C₁₃H₁₃NO₃ 2H₂O: C 58.42; H 6.41; N 5.24. Found: C 58.32; H 6.27; N 5.37.

1-(Benzyloxy)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (12)

The mixture of 2,4-dimethoxy-5-phenylpyridine 1-oxide (**11**) (12.0 g, 51.9 mmol) and 47% HBr (360 mL) was heated at reflux for 4 days. After cooled to rt, the reaction mixture was concentrated *in vacuo*

and the residual semisolid was triturated with H₂O to give crude 1-(hydroxy)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (8.95 g) as a colorless solid. To a solution of above solid (4.0 g) in DMF (80 mL), was added K₂CO₃ (4.08 g, 29.6 mmol) and BnBr (2.30 mL, 19.7 mmol) at rt. After stirring at rt for 12 h, the reaction mixture was quenched with H₂O and extracted with AcOEt. The organic layer was washed with H₂O and sat. aqueous NaCl, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% MeOH-CHCl₃) gave 3.1 g (54%, 2 steps) of **12** as a colorless crystal. mp 252-255 °C; ¹H NMR (300 MHz, DMSO-d₆) δ: 5.18 (s, 2H), 5.88 (s, 1H), 7.27-7.53 (m, 5H), 7.69 (s, 1H), 11.03 (s, 1H); IR (Nujol) 3855, 3059, 1654, 1623, 1601, 1537 cm⁻¹; MS (APCI) *m/z* 294 (M+H)⁺; Anal. Calcd for C₁₈H₁₅NO₃: C 73.71; H 5.15; N 4.78. Found: C 73.25; H 5.22; N 4.75.

1-(Benzyloxy)-4-hydroxy-3-[(2*R*,3*R*,5*R*)-3-methyl-5-[(6*S*)-6-methyloctyl]tetrahydro-2*H*-pyran-2-yl]-5-phenylpyridin-2(1*H*)-one (15) and 1-(benzyloxy)-4-hydroxy-3-[(2*S*,3*S*,5*R*)-3-methyl-5-[(6*S*)-6-methyloctyl]tetrahydro-2*H*-pyran-2-yl]-5-phenylpyridin-2(1*H*)-one (14)

To a solution of 1-(benzyloxy)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (**12**) (73.0 mg, 0.25 mmol) and (3*R*,5*R*)-3-methyl-5-[(6*S*)-6-methyloctyl]tetrahydro-2*H*-pyran-2-ol (**8**) (121 mg, 0.50 mmol) in CH₂Cl₂ (5.0 mL) was added MS4A (powdered, 220 mg) and ethylenediammonium diacetate (45.0 mg, 0.25 mmol) at rt. After stirring at rt for 7 days, the reaction mixture was diluted with CH₂Cl₂ and filtered through a pad of Celite. The filtrate was washed with H₂O and sat. aqueous NaCl, dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by column chromatography (20-40% AcOEt-hexane) gave **14** 26.0 mg (20%; less polar) and **15** 86.7 mg (67%; more polar) as a both colorless oil.

14: ¹H NMR (300 MHz, CDCl₃) δ: 0.83 (d, 3H, *J* = 7.2 Hz), 0.84-0.88 (m, 3H), 0.95 (d, 3H, *J* = 6.6 Hz), 1.00-1.38 (m, 14H), 1.60-1.78 (m, 1H), 1.85-1.99 (m, 2H), 3.21 (t, 1H, *J* = 11.4 Hz), 4.09 (m, 1H), 4.74 (d, 1H, *J* = 10.3 Hz), 5.21 (d, 1H, *J* = 10.8 Hz), 5.30 (d, 1H, *J* = 10.8 Hz), 7.04 (s, 1H), 7.18-7.45 (m, 10H), 9.52 (s, 1H); IR (Nujol) 3061, 1651, 1599 cm⁻¹; MS (APCI) *m/z* 518 (M+H)⁺.

15: [*α*]_D²⁵ = +148.12° (*c* = 0.960, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ: 0.83 (d, 3H, *J* = 7.3 Hz), 0.84 (t, 3H, *J* = 8.1 Hz), 0.91 (d, 3H, *J* = 6.8 Hz), 1.07-1.17 (m, 2H), 1.20-1.38 (m, 9H), 1.46-1.68 (m, 4H), 1.78 (d, 1H, *J* = 12.1 Hz), 2.08 (m, 1H), 3.76 (dd, 1H, *J* = 11.7, 2.6 Hz), 3.98 (d, 1H, *J* = 11.4 Hz), 4.77 (d, 1H, *J* = 10.4 Hz), 5.21 (d, 1H, *J* = 10.8 Hz), 5.30 (d, 1H, *J* = 10.8 Hz), 7.02 (s, 1H), 7.18-7.45 (m, 10H), 9.54 (s, 1H); ¹³C-NMR (400MHz, CDCl₃) δ: 11.4, 18.1, 19.2, 27.1, 27.8, 29.5, 30.0, 30.9, 31.0, 34.0, 34.4, 36.2, 36.6, 72.5, 78.6, 81.7, 111.5, 113.1, 127.5, 128.3, 128.8, 129.1, 129.4, 130.3, 133.1, 133.9, 134.5, 158.1, 161.6; IR (Nujol) 3209, 1651, 1599 cm⁻¹; MS (APCI) *m/z* 518 (M+H)⁺.

1,4-Dihydroxy-3-((2*R*,3*R*,5*R*)-3-methyl-5-[(6*S*)-6-methyloctyl]tetrahydro-2*H*-pyran-2-yl)-5-phenylpyridin-2(1*H*)-one (1a)

To a mixture of 1-(benzyloxy)-4-hydroxy-3-((2*R*,3*R*,5*R*)-3-methyl-5-[(6*S*)-6-methyloctyl]tetrahydro-2*H*-pyran-2-yl)-5-phenylpyridin-2(1*H*)-one (**15**) (50.0 mg, 0.097 mmol) in dioxane (2 mL) was added 10% Pd/C (20 mg) and hydrogenated in H₂ atmosphere in an ordinary pressure and temperature. After 1 h, the catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated *in vacuo*. Purification of the residue by recycling preparative HPLC gave 41.0 mg (quant.) of desired compound as a colorless foam. $[\alpha]_D^{25} = +146.12^\circ$ ($c = 0.516$, MeOH); ¹H NMR (300 MHz, CDCl₃) δ : 0.77 (d, 3H, $J = 6.6$ Hz), 0.82-0.87 (m, 6H), 1.00-1.16 (m, 2H), 1.18-1.38 (m, 9H), 1.40-1.64 (m, 4H), 1.76 (d, 1H, $J = 11.9$ Hz), 2.06 (m, 1H), 3.72 (dd, 1H, $J = 11.5, 2.6$ Hz), 3.96 (d, 1H, $J = 11.4$ Hz), 4.68 (d, 1H, $J = 10.4$ Hz), 7.32-7.49 (m, 5H), 7.67 (s, 1H), 9.55 (s, 1H); IR (Nujol) 3178, 3109, 2599, 1641 cm⁻¹; MS (APCI) m/z 428 (M+H)⁺.

1,4-Dihydroxy-3-((2*S*,3*S*,5*S*)-3-methyl-5-[(6*S*)-6-methyloctyl]tetrahydro-2*H*-pyran-2-yl)-5-phenylpyridin-2(1*H*)-one (ent-1b)

ent-1b was prepared by the same procedure as above described manners starting from (*R*)-3

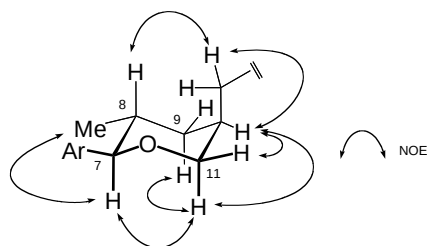
$[\alpha]_D^{25} = -139.62^\circ$ ($c = 0.265$, MeOH); ¹H NMR (300 MHz, CDCl₃) δ : 0.79 (d, 3H, $J = 6.6$ Hz), 0.82-0.87 (m, 6H), 1.00-1.16 (m, 2H), 1.18-1.38 (m, 9H), 1.40-1.64 (m, 4H), 1.76 (d, 1H, $J = 12.1$ Hz), 2.06 (m, 1H), 3.72 (dd, 1H, $J = 11.5, 2.6$ Hz), 3.96 (d, 1H, $J = 11.4$ Hz), 4.68 (d, 1H, $J = 10.6$ Hz), 7.32-7.49 (m, 5H), 7.67 (s, 1H), 9.52 (s, 1H); IR (Nujol) 3182, 1641, 1580, 1554, 1498 cm⁻¹; MS (APCI) m/z 428 (M+H)⁺.

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Representative observed NOE of **15**

14. The optical rotation of **1a**, $[\alpha]_{\text{D}}^{25} = +146.12^\circ$ ($c = 0.516$, MeOH), showed higher value compared with the reported data in the reference **7c**, $[\alpha]_{\text{D}}^{20} = +88.6^\circ$ ($c = 0.95$, MeOH). The reason for this discrepancy is not clear, but purity of **1a** may differ. According to the experimental section in the literature, it apparently does not include purification step after final *N*-hydroxylation reaction.
15. According to ref. 7b) **1a** and its C-17 epimer, (**1b**) had almost the same analytical properties in 600 MHz ^1H and ^{13}C -NMR analysis
16. **18** was synthesized as follows: To a cooled (0°C) solution of **1** (ref. 1a, 100 mg, 0.234 mmol) in

DMF (2 mL), NaH was added (60% in oil, 9.0 mg, 0.225 mmol) and then allowed to warm up to rt, before adding benzyl bromide (0.028 mL, 0.235 mmol). The solution was then stirred at rt for 15 h. The reaction mixture was poured into crushed-ice and extracted with AcOEt. The organic layer was separated and washed with H₂O, sat. aqueous NaCl, dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by column chromatography (33–66% AcOEt-hexane) gave 114 mg of **18** (94%) as colorless oil.