Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1749

www.rsc.org/obc

PAPER

New synthetic route to N-tocopherol derivatives: synthesis of pyrrolopyridinol analogue of α-tocopherol from pyridoxine†

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Received 8th November 2010, Accepted 2nd December 2010
DOI: 10.1039/c0ob00991a

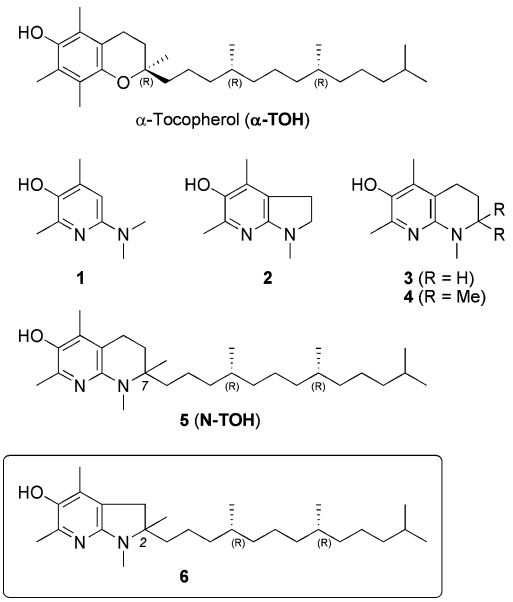
A new synthetic route to pyrrolopyridinol antioxidants from easily accessible pyridoxine was developed which includes phase-transfer catalytic alkylation and intramolecular Cu(I)-catalyzed amination as key steps.

Introduction

Since the seminal report by Pratt *et al.* in 2001 that the incorporation of nitrogen atom at a *meta*-position to the –OH in the phenol ring significantly increases the IP (ionization potential) but increases the O–H BDE (bond dissociation enthalpy) to a smaller extent,[1,2] a series of 6-aminopyridin-3-ols (**1–5**), electron-rich phenolic antioxidants with air-stability, have been rationally designed as lipid peroxyl radical-trapping chain-breaking antioxidants by Porter and coworkers.[3–7] The pyridinols indeed showed higher antioxidant activity than α-tocopherol (α-TOH), a nature's best lipophilic antioxidant.[3,6,7].

Among the series, tetrahydronaphthyridinol **3** showed ~30-fold better antioxidant activity, expressed as rate constant (k_{inh}) to inhibit propagation of radical chain reaction, than α-TOH in benzene.[3] Certain lipophilic derivatives of **3** (*e.g.* N–$C_{16}H_{33}$) further added beneficial properties such that they inhibit the oxidation of cholesteryl linoleate in human LDL and spared consumption of endogenous α-TOH *in vitro*.[6] N-TOH (**5**), an α-TOH isostere, has strongly suggested that it can act as an excellent antioxidant both in membranes and in lipoproteins *in vivo*. Its lateral diffusional movement in model membranes was about 1.5-fold faster than α-TOH. Its binding affinity to the human α-tocopherol transfer protein (hTTP)[8] was exceptionally high compared to α-TOH.[7]

On the other hand, the pyrrolidine-fused aminopyridinol **2** showed 3-fold higher radical-trapping ability than that of the piperidine-fused aminopyridinol **3**, which is equivalent to ~90-fold higher antioxidant activity than α-TOH.[3,4] This information prompted us to design a five-membered analogue **6**, expecting enhanced antioxidant activity over N-TOH (**5**) with similar advantageous behaviors that **5** showed in lipid membranes and LDLs retained.



Results and discussion

I. Investigation of electrophilic aromatic hydroxylation

Electrophilic aromatic hydroxylation of 3-bromopyridines with n-butyllithium and 2-nitro-*m*-xylene was the key step in the preparation of the aminopyridinols **1–4**.[3–6] Albeit successful as the earliest strategy for the discovery of novel antioxidants, this approach has been challenged by the low yields and delicate reaction conditions.

We isolated and identified by-products (**8a** and **8b**) of this electrophilic aromatic hydroxylation, and confirmed that the formation of **8a** and **8b** was the cause of the troublesome low

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† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c0ob00991a

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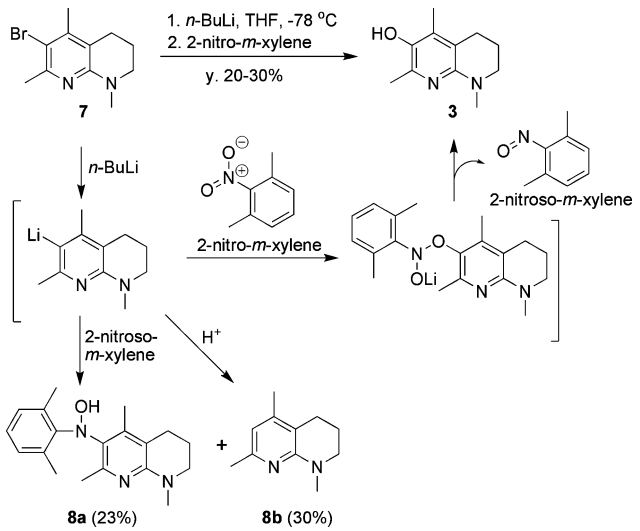
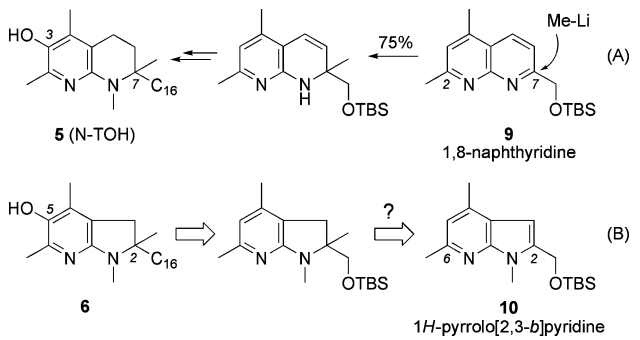
yields (Scheme 1). As judged from the comparable yields of **3** and **8a**, 2-nitroso-*m*-xylene appears to be at least as reactive as 2-nitro-*m*-xylene, so it is able to react with the aryllithium as soon as it is generated during the reaction. The nitroso adduct was assigned as **8a**, a hydroxyamination product, formed through *N*-attack by alkyllithium. Presumably, oxophilic lithium species, enriched in the reaction mixture, coordinate the oxygen atom of 2-nitroso-*m*-xylene to make nitrogen atom electrophilic. In this circumstance, 2-nitroso-*m*-xylene dimer (azodioxide) can be formed and also serve as an electrophile in such a manner that the partially negative charged oxygen atom(s) in azodioxide is preferentially coordinated with lithium species and promotes *N*-attack. Significant improvement in the hydroxylation step was reported by us through a CuI-mediated benzyloxylation-catalytic hydrogenolysis sequence,[7] but it is still not ideal for large scale synthesis.



Scheme 1 By-products from the electrophilic aromatic hydroxylation with 2-nitro-*m*-xylene.

In our previous report,[7] the preparation of N-TOH (**5**), as a C(7)-racemate, featured chelation-controlled regioselective MeLi addition to C(7)-position of **6** over C(2)-position (path A in Scheme 2). Unlike a 1,8-naphthyridine **9**, a pyrrolopyridine **10** is not a suitable electrophile toward MeLi addition to generate a quaternary center at C(2)-position (path B in Scheme 2). In addition, this approach requires a highly efficient hydroxylation step

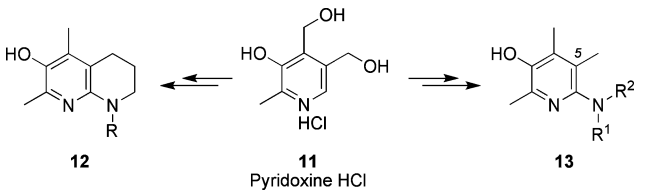


Scheme 2

in the end, which is not readily available at this point. We needed a new synthetic route for the preparation of pyrrolopyridinol **6**.

II. Synthesis of pyrrolopyridinol analogue of α-tocopherol

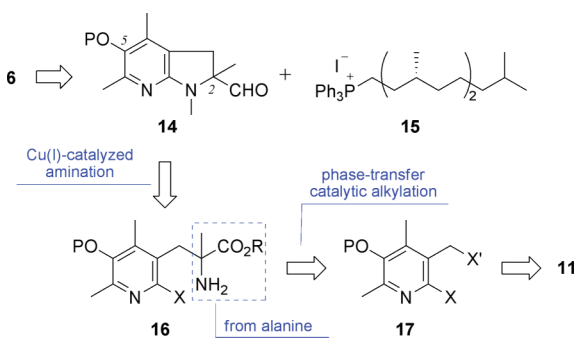
We have recently demonstrated that pyridoxine (**11**, HCl salt), one of the constituents of vitamin B_6, is an excellent starting material for the efficient synthesis of several bicyclic aminopyridinols such as **12** (Scheme 3).[9]



Scheme 3 Pyridoxine, a highly effective natural resource for aminopyridinols (R, R^1, R^2 = H or alkyl group).

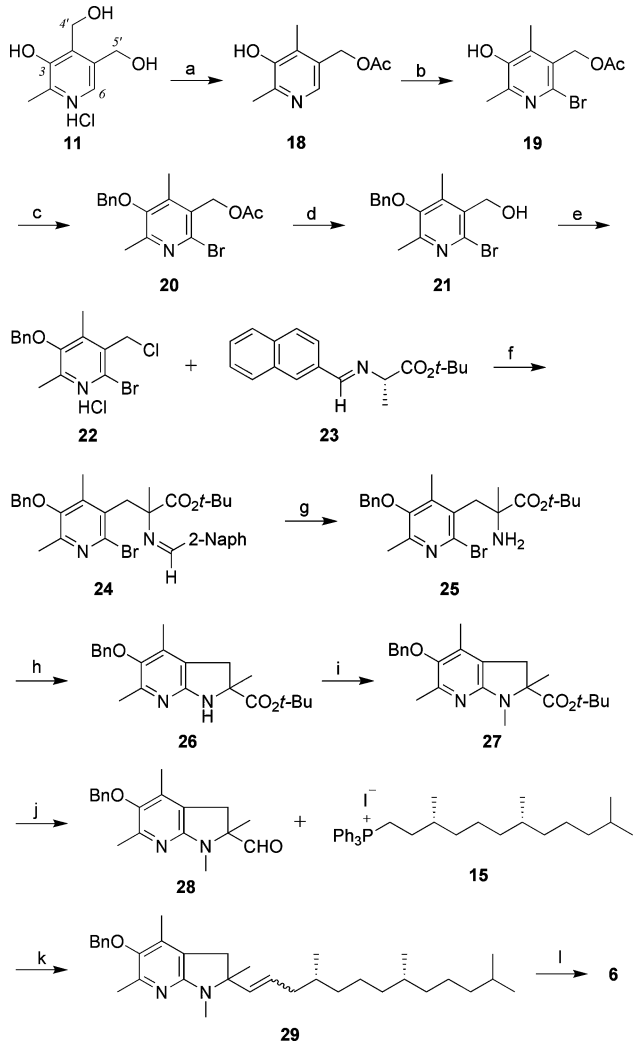
Furthermore, a novel class of monocyclic aminopyridinols **13** with additional methyl group at C(5)-position compared to **1** can be also synthesized from pyridoxine.[9] This new class of aminopyridinols is also equipped with good antioxidant properties, including an excellent co-antioxidant activity and potential toxicological benefits.[9,10]

A new synthetic route to the pyrrolopyridinol **6**, a five membered ring version of N-TOH (**5**) also starts from pyridoxine·HCl (**11**). We designed a convergent synthetic strategy depicted in Scheme 4 in which two main parts (*i.e.*, pyrrolopyridine carbaldehyde **14** and chiral C_{16}-isoprenoidal phosphonium salt **15**) are coupled together under Wittig reaction conditions as in the previous report for **5**.[7] As we have already established the efficient synthetic method for **15** from the natural product phytol,[7] this report will mainly focus on our exploration for a new and efficient way toward **14**. The key intermediate **14** was expected to be synthesized by a transition metal-mediated intramolecular amination of 3-alkoxy-5-aminoalkyl-6-halopyridine **16**. Manipulation of pyridoxine·HCl (**11**) can afford a halide **17**, which in turn is able to give an alanine moiety-incorporated **16** under the phase-transfer catalytic alkylation conditions.



Scheme 4 Retrosynthesis of the pyrrolopyridinol **6** (P = protective group; R = alkyl group; X, X' = halogen).

Scheme 5 shows the synthesis of **6** from pyridoxine·HCl (**11**) starting with the treatment of **11** with zinc dust in refluxing acetic acid. This condition provided selective cleavage of the *C*(4′)–*O* bond over the *C*(5′)–*O* bond, which was accompanied by



Scheme 5 *Reagents and conditions*: (a) Zn, AcOH, reflux, 6 h, 95%; (b) DBDMH, CH_2Cl_2, rt, 30 min, 98%; (c) NaH, $PhCH_2Br$, THF, reflux, 2 h; (d) NaOMe, MeOH, rt, 30 min, 92% (for 2 steps); (e) $SOCl_2$, CH_2Cl_2, rt, 10 min, 99%; (f) KOH, *n*-Bu_4NBr, CH_2Cl_2, rt, 2 h; (g) 1 M HCl, THF, rt, 1 h, 81% (for 2 steps); (h) CuOAc, K_3PO_4, diethylsalicylamide, DMF, 80 °C, 10 h, 90%; (i) HCHO, $NaBH_3CN$, AcOH, MeOH, rt, 6 h, 96%; (j) DIBAL-H, CH_2Cl_2, –78 °C, 30 min, 93%; (k) *n*-BuLi, THF, 0 °C, 1 h, then rt, 1 h, 90%; (l) H_2, Pd/C, EtOH, rt, 30 h, 99%.

O-acetylation to afford **18** in 95% yield. Electrophilic aromatic bromination at the *C*(6)-position of **18** was accomplished with DBDMH (1,3-dibromo-5,5-dimethylhydantoin) in almost quantitative yield. It should be noted that *C*(6)-bromination must precede the protection of *C*(3)-OH. Once the *C*(3)-OH is protected with benzyl group, no useful synthetic conditions for ring halogenation were found (data not shown).[11] After the ring bromination, benzyl-protection of the *C*(3)-OH and the following deacetylation gave **21** in 92% yield for two steps. *C*(5′)-*O*-acetyl group in **19** turned out to be a prerequisite for the successful benzylation; a pyridinol that has free OH at *C*(5′)-position resulted in unwanted extra benzylation either at the *C*(5′)-OH or at the ring nitrogen along with the wanted *C*(3)-*O*-benzylation. Chlorination of the *C*(5′)-OH in **21** with thionyl chloride quantitatively afforded **22** as HCl salt. Alanine moiety was then introduced to **22** in 92% yield by the two-step sequence developed by some of us.[12] Briefly, an alkylation of 2-naphthalene aldimine of alanine *tert*-butyl ester (**23**) with **22** under phase-transfer conditions (KOH base and *n*-Bu_4NBr in CH_2Cl_2) and the subsequent hydrolysis of the imine under acidic condition gave **25**. Intramolecular Cu(I)-catalyzed amination was accomplished in 90% yield using Buchwald's protocol,[13] and then the NH in **26** was reductively methylated in 96% yield. Finally, the *tert*-butyl ester was partially reduced with DIBAL-H to afford aldehyde **28** in 93% yield. Assembly of the aldehyde **28** and the chiral C_{16}-isoprenoid side chain **15** was achieved by the Wittig coupling (88% yield). The phosphonium iodide **15** was prepared from phytol, a natural acyclic diterpene alcohol, by the six-step sequence we have developed.[7] Both benzyl protection group and the isolated olefin of **29** were removed at the same time by catalytic hydrogenation condition to afford **6** in almost quantitative yield.

III. Preliminary trial for asymmetric synthesis

We then turned our attention toward asymmetric synthesis of **6**. Since the streochemistry of the two chiral centers in the C_{16} side chain is already established in the optically active C_{16}-isoprenoid starting material,[7] we mainly focused on the enantioselective synthesis of **25**. For the identical stereochemistry to that of α-TOH, the absolute configuration of the chiral center in the aldehyde **28** should be *S*. It can be accomplished during the formation of **25** from **22** by enantioselective alkylation using a chiral phase-transfer catalyst (PTC). Preliminary results of our efforts to synthesize optically pure **25** are summarized in Table 1. The representative cinchonidine-derived quaternary ammonium salts, **30**[12,14] and **31**,[15] developed by some of us were used as chiral PTCs in this asymmetric transformation, and tuning of reaction conditions including the change of electrophile from **21** to **32** were performed. In summary, the best result (91% chemical yield and 87% ee) was obtained with the chiral PTC **31** and the electrophile **32** at –20 °C under the given conditions (entry 6) from this initial screening. Full investigations on enantioselective alkylation with various chiral PTCs as well as fine tuning of reaction conditions are currently underway.

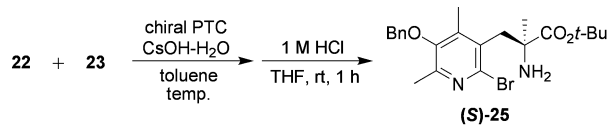
Conclusions

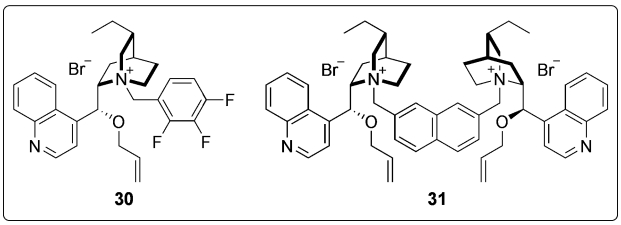
We elucidated the detailed mechanism of the electrophilic aromatic hydroxylation and suggested that 2-nitroso-*m*-xylene generated during the reaction is the main cause of low yield. A new synthetic route from pyridoxine·HCl to the pyrrolopyridinol **6** which cannot be prepared by the known strategy for N-TOH (**5**) was developed in which phase-transfer catalytic alkylation and Cu(I)-catalyzed intramolecular amination were used as the key steps. A preliminary screening on the conditions of the enantioselective phase-transfer catalytic alkylation was carried out with the cinchona PTCs.

Experimental details

General. Unless noted otherwise, materials were purchased from commercial suppliers and used without further purification. Air- or moisture-sensitive reactions were carried out under an inert gas atmosphere. THF and CH_2Cl_2 were dried using a Solvent Purification System from Solvtek. Progress of reaction was monitored by thin-layer chromatography (TLC) using silica gel F_{254} plates. Purification of the products was performed by

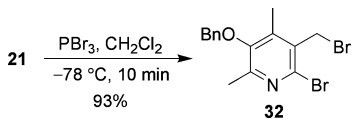
Table 1 Preliminary results for enantioselective formation of **(*S*)-25** under phase-transfer conditions in the presence of chiral catalyst (**30** or **31**)[a]





Entry	PTC	*T*/°C	Time (h)[b]	Yield (%)[c]	ee (%)[d]
1	**30**	0	2	72	67
2	**30**	–20	1	85	74
3	**30**	–40	3	70	65
4	**31**	0	1	81	74
5	**31**	–20	1	86	79
6[e]	**30**	–20	2	91	87
7[e]	**31**	–20	1	86	81

[a] Reaction was carried out with **22** (1.0 equiv), **23** (1.0 equiv), and $CsOH{\cdot}H_2O$ (7.0 equiv) in the presence of either **30** (10 mol%) or **31** (5 mol%) in toluene at the given conditions to afford the alkylated aldimine which was then subjected to hydrolysis in acidic conditions to give the optically enriched **(*S*)-25**. [b] Reaction time for consumption of the aldimine **23** to transform the corresponding alkylated aldimine. [c] Isolated yield of **(*S*)-25** for the two steps from **22**. [d] Enantiopurity was determined by HPLC analysis of **(*S*)-25**, using a chiral column [Chiralpak AD-H column, hexanes:2-propanol = 90 : 10, flow rate = 1 mL min^{-1}, detection = 280 nm], and absolute configuration was tentatively assigned as *S* according to the trend shown in the reports on the enantioselective alkylation of **23**.[12] [e] **32** was used instead of **22**.



flash column chromatography using silica gel 60 (230–400 mesh) or a Biotage SP-1 system with indicated solvents. Infrared (IR) spectra were recorded on a JASCO FT/IR-300E and Perkin-Elmer 1710 FT spectrometer.NMR spectra were taken with a 300, 400, 500 MHz Bruker NMR spectrometer, or 300, 400 MHz JEOL NMR spectrometer. Chemical shifts (δ) were expressed in ppm using solvent as an internal standard and coupling constant (*J*) in hertz. Low-resolution mass spectra (MS) were recorded on a VG Trio-2 GC-MS spectrometer, and high-resolution mass spectra (HRMS) were measured on a JEOL JMS-AX 505wA, JEOL JMS-HX/HX 110A spectrometer or performed at Ohio State University. Melting points were measured on a Buchi B-540 melting point apparatus and were not corrected.

2,4-Dimethyl-5-acetoxymethylpyridin-3-ol (18). [*Activation of Zn*:10~20 g of zinc dust was washed with 1 M HCl in a 1 : 11 ratio. This solution was stirred for 10 min at room temperature. The solution was then filtered and the filter cake of zinc was washed with H_2O, MeOH, and Et_2O. The zinc was then dried under vacuum for approximately 2 h. Pyridoxine hydrochloride (**1**, 50.0 g, 0.243 mol) was dissolved in acetic acid (200 mL). Activated zinc dust (63.6 g, 0.972 mol) was added to this solution in small portions. The solution was refluxed for 2 h (if it seemed that the reaction was not proceeding, a small amount of zinc dust was added to make the reaction be completed). After completion of the reaction,the excess zinc andthe inorganic salt of zinc formed were filtered off through a Celite pad and the filter cake was washed with CH_3CN. After concentration of the filtrate, water (250 mL) was added to the residue and the pH of the solution was adjusted to 5~6 with $NaHCO_3$. CH_2Cl_2 was added to the mixture and the pH was finally adjusted to about 7 in that time white solid precipitated. The solid was filtered and the filtrate was concentrated. The residue was purified by flash silica gel column chromatography ($CHCl_3$–MeOH = 20 : 1) to afford **18** (45.0 g, 95%) as a colorless oil. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.89 (s, 1H), 5.04 (s, 2H), 2.35 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 170.5, 149.6, 146.9, 140.9, 132.5, 128.9, 62.3, 20.9, 20.2, 11.6 ppm; IR (KBr) ν 3463, 3012, 1746, 1565, 1500, 1451, 1420, 1357, 1245, 1214, 1033, 895, 765 cm^{-1}; MS (FAB+): *m*/*z* 196 $[M+H]^+$; HRMS calculated for $C_{10}H_{14}NO_3$: 196.074; Found: 196.0968 $[M+H]^+$.

6-Bromo-2,4-dimethyl-5-acetoxymethyl-3-hydroxypyridine (19). To a suspension of **18** (6.50 g, 33.3 mmol) in CH_2Cl_2 (180 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (4.76 g, 16.7 mmol) and the resulting mixture was stirred for 30 min at room temperature. Water (100 mL) was added to the mixture and then extracted with dichloromethane (200 mL × 3). The organic layer was washed with brine and dried over $MgSO_4$, concentrated to afford **19** (8.95 g, 98%) as a light yellow solid, m.p. 100–103 °C; ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 5.03 (s, 2H), 2.27 (s, 3H), 2.11 (s, 3H), 1.88 (s, 3H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 171.3, 149.3,

146.5, 137.1, 134.6, 129.2, 63.8, 21.1, 19.2, 13.1;IR (KBr) ν 3366, 1739, 1590, 1412,,1378, 1241, 1109, 1029, 970, 917, 791 cm^{-1}; MS (FAB+): *m/z* 274 $[M+H]^+$; HRMS calculated for $C_{10}H_{13}BrNO_3$: 274.0079; Found: 274.0082 $[M+H]^+$.

6-Bromo-2,4-dimethyl-5-acetoxymethyl-3-benzyloxypyridine-(20), 6-Bromo-2,4-dimethyl-5-hydroxymethyl-3-benzyloxypyridine (21). To a suspension of 60% sodium hydride (160 mg, 4.0 mmol) in dry THF (1 mL) was slowly added a solution of **19** (910 mg, 3.32 mmol) in dry THF (10 mL). After addition of benzyl bromide (0.42 mL, 3.5 mmol), the mixture was refluxed for 2 h. The mixture containing **20** was cooled to room temperature. Purification of **20** for analysis: The mixture was concentrated and the residue was diluted with chloroform and water. The aqueous layer was extracted with chloroform. The combined organic solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexanes : EtOAc = 5 : 1) to give **20** as a colorless oil, m.p. 97 °C; ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 7.41–7.45 (m, 5H), 5.25 (s, 2H), 4.82 (s, 2H), 2.51 (s, 3H), 2.33 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 171.1, 154.3, 152.1, 144.1, 139.1, 136.6, 129.5, 129.1, 128.9, 128.4, 75.5, 63.8, 21.1, 19.9, 13.5;IR (KBr) ν 3788, 2924, 1727, 1591, 1355, 1208, 1104, 964, 841 cm^{-1}; MS (FAB+): *m/z* 364 $[M+H]^+$; HRMS calculated for $C_{17}H_{19}BrNO_3$: 364.0548; Found: 364.0554 $[M+H]^+$.

Methanol was added until the mixture became a clear solution and then 30% sodium methoxide solution in methanol (0.63 mL) was added to this solution. After concentration of the mixture, the residue was diluted with chloroform (50 mL) and water (10 mL). The aqueous layer was extracted with chloroform (10 mL × 2) and the combined organic solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexanes : EtOAc = 2 : 1) to yield **21** (984 mg, 92%) as a white solid, m.p. 109 °C; ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 7.39–7.44 (m, 5H), 4.79–4.81 (m, 4H), 2.59 (t, 1H), 2.47 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 153.6, 152.3, 143.7, 138.1, 136.6, 133.8, 129.1, 128.9, 128.4, 75.4, 62.3, 19.7, 13.4; IR (KBr) ν 3369, 2919, 1575, 1407, 1365, 1216, 1097, 1010, 746, 700 cm^{-1}; MS (FAB+): *m/z* 322 $[M+H]^+$; HRMS calculated for $C_{15}H_{17}BrNO_2$: 322.0443; Found: 322.0448 $[M+H]^+$.

3-Benzyloxy-6-bromo-5-chloromethyl-2,4-dimethylpyridine hydrochloride (22). To a solution of **21** (5.25 g, 16.29 mmol) in CH_2Cl_2 (30 mL) was added thionyl chloride (1.25 mL, 17.10 mmol). The mixture was stirred for 10 min at room temperature and concentrated to afford **22** (6.08 g, 99%) as a white solid, m.p. 131.8 °C; ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 7.31–7.37 (m, 5H), 4.80 (s, 2H), 4.66 (s, 2H), 2.57 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 153.7, 152.8, 146.7, 135.8, 135.3, 133.1, 129.3, 129.2, 128.6, 76.2, 42.6, 18.2, 13.8; IR (KBr) ν 2923, 1571, 1405, 1365, 1216, 1155, 1091, 919, 740 cm^{-1}; MS (FAB+): *m/z* 342 $[M+H]^+$.

***tert*-Butyl 2-amino-3-(6-bromo-2,4-dimethyl-3-benzyloxypyridin-5-yl)-2-methyl-2-(naphthalen-2-ylmethyleneamino)propanoate (24), *tert*-Butyl 2-amino-3-(6-bromo-2,4-dimethyl-3-benzyloxypyridin-5-yl)-2-methylpropanoate (25).** To a suspension of potassium hydroxide (240 mg, 3.52 mmol) in CH_2Cl_2 (4 mL) were added **23** (200 mg, 0.70 mmol) and *n*-tetrabutylammonium bromide (23 mg, 0.07 mmol). **22** (265 mg, 0.70 mmol) was added to the mixture and the resulting suspension was stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and water (5 mL) and the aqueous layer was extracted with dichloromethane (10 mL × 2). The organic solution was dried over $MgSO_4$ and concentrated to give the crude **24**. Purification of **24** for analysis: The residue was purified by silica gel column chromatography (hexanes : EtOAc = 20 : 1) to give **24** as a colorless oil. ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 8.15 (s, 1H), 7.97–8.02 (m, 2H), 7.83–7.90 (m, 4H), 7.51–7.55 (m, 2H), 7.26–7.30 (m, 2H), 7.07–7.12 (m, 2H), 4.50 (d, 1H, *J* = 11.1 Hz), 4.28 (d, 1H, *J* = 11.1 Hz), 3.66 (dd, 2H, *J* = 34.5, 16.5 Hz), 2.45 (s, 3H), 2.34 (s, 3H), 1.61 (s, 3H), 1.55 (s, 9H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 173.3, 158.6, 152.2, 151.4, 145.2, 140.4, 136.8, 135.2, 134.4, 133.4, 132.4, 131.0, 128.9, 128.8, 128.5, 128.2, 127.8, 127.7, 127.5, 127.0, 124.0, 82.0, 74.8, 71.2, 40.8, 28.4, 22.8, 19.6, 15.7.

The crude **24** was dissolved in THF (4 mL) followed by addition of 1 M HCl in water (1 mL). The resulting mixture was stirred for 1 h at room temperature. After concentration of the reaction mixture, the residue was diluted with water (10 mL) and washed with ether (10 mL × 3). The aqueous layer was then basified with sat. Na_2CO_3 solution and extracted with EtOAc (30 mL × 2). The combined organic solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 2 : 1) under 280 nm to give **25** (255 mg, 81%) as a colorless oil. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.38–7.49 (m, 5H), 4.82 (s, 2H), 3.11 (s, 2H), 2.35 (s, 6H), 1.78 (s, 2H), 1.40 (s, 9H), 1.17 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 176.3, 151.5, 150.4, 144.4, 139.8, 137.0, 132.3, 128.8, 128.6, 128.5, 80.4, 74.3, 59.8, 41.0, 27.8, 25.9, 19.1, 15.5; IR (KBr) ν 2975, 1724, 1573, 1452, 1369, 1249, 1214, 1159, 1114, 848, 748, 700 cm^{-1}; MS (FAB+): *m/z* 449 $[M+H]^+$; HRMS calculated for $C_{22}H_{30}BrN_2O_3$: 449.1440; Found: 449.1445 $[M+H]^+$.

***tert*-Butyl 5-benzyloxy-2,4,6-trimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine-2-carboxylate (26).** To a mixture of copper(I) acetate (3 mg, 0.022 mmol), N,N-diethylsalicylamide (17 mg, 0.089 mmol) and potassium phosphate tribasic (189 mg, 0.89 mmol) was added a solution of **25** (200 mg, 0.445 mmol) in dry DMF (1 mL). After the reaction mixture was stirred for 10 h at 80 °C, 1 M NaOH (2 mL) was added to the mixture. The mixture was diluted with EtOAc (100 mL) and water (10 mL) and the organic layer was washed with water (10 mL × 4). After drying the organic layer with $MgSO_4$ and filtration, the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexanes : EtOAc = 2 : 1) to afford **26** (148 mg, 90%) as a white solid, m.p. 127 °C; ^{1}H-NMR (400 MHz, $CHCl_3$-*d*) δ 7.35–7.47 (m, 5H), 4.94 (s, 1H), 4.73 (s, 2H), 3.50 (d, 1H, *J* = 16.4 Hz), 2.79 (d, 1H, *J* = 16.4 Hz), 2.39 (s, 3H), 2.12 (s, 3H), 1.57 (s, 3H), 1.47 (s, 9H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 174.0, 157.1, 146.9, 144.9, 136.7, 136.5, 127.9, 127.4, 127.3, 116.9, 81.2, 74.4, 64.7, 37.2, 26.4, 18.4, 12.3; IR (KBr) ν 3856, 3218, 2975, 2925, 1727, 1606, 1452, 1369, 1257, 1157, 846, 750 cm^{-1}; MS (FAB+): *m/z* 369 $[M+H]^+$; HRMS calculated for $C_{22}H_{28}N_2O_3$: 369.2178; Found: 369.2173 $[M+H]^+$.

***tert*-Butyl 5-benzyloxy-1,2,4,6-tetramethyl-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine-2-carboxylate (27).** To a solution of **26** (80 mg, 0.217 mmol) in methanol (3 mL) were added 37% formaldehyde (0.9 mL, 10.85 mmol) and acetic acid (0.6 mL, 10.85 mmol). After addition of sodium cyanoborohydride

(136 mg, 2.17 mmol), the reaction mixture was stirred for 6 h at room temperature. Methanol was evaporated and the residue was basified with sat. Na_2CO_3 solution. Extraction of the mixture with EtOAc (50 mL × 2) was performed. The combined organic solution was washed with brine and dried over $MgSO_4$, concentrated. The residue was purified by silica gel column chromatography (hexanes : EtOAc = 6 : 1) to give **27** (80 mg, 96%) as a colorless oil. ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 7.28–7.48 (m, 5H), 4.71 (s, 2H), 3.24 (d, 1H, J = 16.2 Hz), 2,93 (s, 3H), 2.76 (d, 1H, J = 16.2 Hz), 2.40 (s, 3H), 2.09 (s, 3H), 1.50 (s, 3H), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 173.4, 158.3, 147.2, 144.6, 137.9, 136.1, 128.9, 128.4, 128.3, 117.7, 81.8, 75.4, 69.3, 38.4, 28.3, 28.2, 22.1, 19.5, 13.0; IR (KBr) ν 2976, 1726, 1585, 1455, 1397, 1367, 1213, 1155, 1112, 1016, 846, 733 cm^{-1}; MS (FAB+): *m/z* 383 [M+H]$^+$; HRMS calculated for $C_{23}H_{31}N_2O_3$: 383.2335; Found: 383.2339 [M+H]$^+$.

5-Benzyloxy-1,2,4,6-tetramethyl-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine-2-carbaldehyde (28)

To a cooled (–78 °C) solution of **27** (70 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (1 mL) was added 1 M DIBAL-H in CH_2Cl_2 (0.18 mL, 0.18 mmol). After the mixture was stirred for 30 min at –78 °C, the mixture was quenched with a few drops of methanol and warmed up to room temperature. sat. Sodium potassium tartrate solution (2 mL) was added and the mixture was stirred for 1 h at room temperature. Extraction with CH_2Cl_2 (20 mL × 2) was carried out and the combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexanes : EtOAc = 2 : 1) to yield **28** (52 mg, 93%) as a colorless oil. ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 9.64 (s, 1H), 7.36–7.49 (m, 5H), 4.73 (s, 2H), 3.11 (d, 1H, J = 16.5 Hz), 2.90 (s, 3H), 2.73 (d, 1H, J = 16.5 Hz), 2.42 (s, 3H), 2.11 (s, 3H), 1.39 (s, 3H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 201.0, 158.2, 148.1, 145.2, 137.7, 137.1, 128.9, 128.5, 128.3, 117.2, 75.4, 71.7, 34.9, 28.1, 19.6, 17.4, 13.2; IR (KBr) ν 3363, 2925, 2859, 2705, 1731, 1585, 1477, 1400, 1213, 1089, 1016, 738 cm^{-1}; MS (FAB+): *m/z* 311 [M+H]$^+$.

5-Benzyloxy-1,2,4,6-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridec-1-enyl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine (29). To acooled (0 °C) solution of **15** (217 mg, 0.362 mmol) in anhydrous THF (1.5 mL) was added 1.6 M n-butyllithium in hexane solution (226 μL, 0.362 mmol), and the mixture was stirred at 0 °C for 1 h. A solution of **28** (45 mg, 0.145 mmol) in anydrous THF (2.9 mL) was added to the mixture using cannular at 0 °C and then the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with sat NH_4Cl solution (2 mL) and was diluted with EtOAc and water. Extraction with EtOAc (20 mL × 2) was carried out and the combined extracts were dried over Na_2SO4 and concentrated. The residue was purified by silica gel column chromatography (hexanes : EtOAc = 20 : 1) to afford **29** (66 mg, 90%) as a colorless oil. ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 7.46–7.29 (m, 5H), 5.55 (d, 1H, J = 11.7 Hz), 5.50–5.41 (m, 1H), 4.69 (s, 3H), 2.97–2.77 (m, 2H), 2.81 (s, 3H), 2.38 (s, 3H), 2.06 (s, 3H), 2.17–2.03 (m, 1H), 1.95–1.84 (m, 1H), 1.56–0.99 (m, 18H), 0.85–0.79 (m. 12H); ^{13}C-NMR (75 MHz, $CHCl_3$-*d*) δ 157.1, 143.8, 137.6, 136.2, 134.5, 132.3, 132.2, 128., 128.0, 127.8, 118.5, 77.2, 75.0, 65.5, 65.4, 41.2, 39.3, 37.3, 37.1, 37.0, 35.3, 33.6, 32.7, 28.0, 26.8, 25.5, 25.4, 24.8, 24.6, 24.5, 22.7, 22.6, 19.7, 18.9, 12.7; IR (KBr) ν 2925, 1586, 1465, 1394, 1216, 1095, 1016, 734 cm^{-1}; MS (FAB+): *m/z* 505 [M+H]$^+$; HRMS calculated for $C_{34}H_{53}N_2O$: 505.4158; Found: 505.4156 [M+H]$^+$.

1,2,4,6-Tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)-2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridin-5-ol (6). To a solution of **29** (27 mg, 0.0535 mmol) in ethanol (1 mL) was added palladium (10% on activated carbon, 5 mg). The mixture was stirred with hydrogen balloon at room temperature for 30 h. The solid in the reaction mixture was filterd through Celite pad and the filtrated was filtered again with syringe filter (Advantec® JP050AN). The filtrate was concentrated to give **6** (22 mg, 99%) as a pale yellow oil. ^{1}H-NMR (300 MHz, DMSO-*d*) δ 7.33 (bs, 1H), 2.71 (d, 1H, J = 16.1 Hz), 2.60 (s, 3H), 2.50 (d, 1H, J = 15.57 Hz), 2.16 (s, 3H), 1.97 (s, 3H), 1.56–1.45(m, 3H), 1.34–1.06 (m, 21H), 0.85–0.79 (m, 12H); ^{13}C-NMR (75 MHz, DMSO-*d*) δ 155.4, 140.7, 139.9, 131.8, 117.6, 64.9, 64.2, 38.7, 38.2, 36.9, 36.8, 36.8, 36.7, 36.5, 32.0, 31.9, 27.3, 25.9, 24.1, 23.7, 23.5, 22.5, 22.4, 21.2, 21.1, 19.6, 19.2, 15.1, 12.6; IR (KBr) ν 3608, 2927, 1461, 1396, 1218, 1093 cm^{-1}; MS (FAB+): *m/z* 417 [M+H]$^+$; HRMS calculated for $C_{27}H_{49}N_2O$: 417.3845; Found: 417.3856 [M+H]$^+$.

3-Benzyloxy-6-bromo-5-bromomethyl-2,4-dimethylpyridine (32). To a cooled (–78 °C) solution of **21** (210 mg, 0.652 mmol) in anhydrous CH_2Cl_2 (3.2 mL) was added 1 M phosphorus tribromide (652 μL, 0.652 mmol). After stirring for 10 min at –78 °C, the mixture was allowed to warm up to room temperature. The reaction mixture was concentrated to give solid. Benzene (20 mL) was added to this crude solid, and the suspension was stirred for 1 h followed by decantation. EtOAc (100 mL) was added to the residual solid and the resulting solution was washed with sat $NaHCO_3$ solution. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated. The residue was purified with flash silica gel column chromatography (hexanes : EtOAc = 6 : 1) to afford **32** (234 mg, 93%) as a white solid, m.p. 83.5 °C; ^{1}H-NMR (300 MHz, $CHCl_3$-*d*) δ 7.39 (s, 5H), 4.79 (s, 2H), 4.58 (s, 2H), 2.47 (s, 3H), 2.33 (s, 3H); ^{13}C-NMR (125 MHz, $CHCl_3$-*d*) 153.6, 151.7, 142.6, 137.6, 136.0, 131.2, 128.7, 128.5, 128.0, 75.1, 30.2, 19.4, 12.9; IR (KBr) ν 2923, 1574, 1497, 1434, 1401, 1366, 1227, 1207, 1132, 958, 905, 776, 751, 696 cm^{-1}; MS (FAB+): *m/z* 384 [M+]$^+$; HRMS calculated for $C_{15}H_{16}Br_2NO$: 383.9599; Found: 383.9606 [M+H]$^+$.

Acknowledgements

This work was supported by the National Science Foundation, and by a Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2008-331-E00460).

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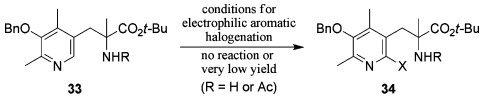

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