Regioselective Addition of *n*-Alkyllithiums to α,α′-Disubstituted-1,8-Naphthyridines: Synthesis of 6-Amino-3-Pyridinol Analogs of α-Tocopherol

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This manuscript is dedicated to Bernd and Anne Giese for their many contributions to the organic and bioorganic communities.

Abstract: *n*-Alkyllithiums were added to α,α′-disubstituted-1,8-naphthyridines in non-polar solvents such as Et_2O–hexane mixtures. In polar solvents such as THF, alkyllithium acts as a base rather than a nucleophile. Regioselective addition was achieved for substrates capable of five-membered cyclic chelation of the (alkyl)lithium reagent. Substrates with a TBS-protected alcohol as the co-chelating moiety afforded the best combination of yield and regioselectivity. This methodology was successfully employed in the preparation of two 6-amino-3-pyridinol analogs of pentamethylchromanol (PMC), an α-tocopherol derivative with its isoprenoid side chain truncated to a methyl group.

Key words: 1,8-naphthyridine, alkyllithium, chelation, solvent effects, α-tocopherol

1,8-Naphthyridines (**1**, Figure 1) are important scaffolds in many compounds with pharmacological applications.[3] They are also known to be good bidentate ligands in organometallic complexes.[4] The dihydro- and tetrahydro forms have also shown pharmacological application as high affinity ligands of the β_3-adreno[5] and $\alpha_V\beta_3$-vitronectin[6] receptors, respectively. Recently we demonstrated that this moiety can also serve as the key skeleton in novel radical-trapping 3-pyridinol antioxidants, such as **2** (Figure 1). For example, in model studies, we found that the tetrahydronaphthyridine **2** is almost 30 times more effective at inhibiting lipid peroxidation than α-tocopherol, the most potent form of vitamin E and nature's most powerful lipophilic antioxidant.[7]

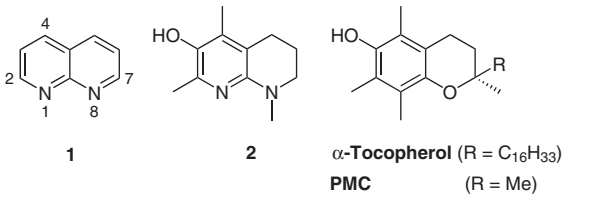
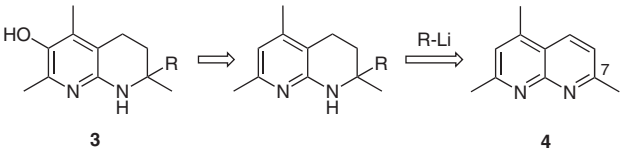


Figure 1

Inspired by this finding, we have endeavored to synthesize new 3-pyridinols such as **3**, which exhibit both the key structure of **2** (2,4-dimethyl-3-hydroxy-tetrahydro naphthyridine moiety) and similar side chain substitution as α-tocopherol or its structural analog 2,2,5,7,8-pentamethyl-6-chromanol (PMC) wherein the isoprenoid side chain has been truncated to a methyl group.[8] Since it has been reported that the isoprenoid side chain of α-tocopherol also plays an important role in its biological activity,[9] this protocol could lead to novel antioxidants with therapeutic potential.

Alkyllithium addition to the C(7)-position of **4** was envisioned as a promising route to **3** (Scheme 1). The trimethylated 1,8-naphthyridine **4** is readily obtained by the Skraup reaction of 2,4-dimethyl-6-aminopyridine and crotonaldehyde.[10] In addition to installing the desired 2,4-dimethyl substitution on the left ring, the asymmetry of **4** may provide some preference for addition at the more electron-poor C(7)- over the undesired C(2)-position.



Scheme 1 Retrosynthesis of desired 3-pyridinols with a quaternary center adjacent the 6-amino group from a substituted 1,8-naphthyridine

Some precedent can be found in the literature regarding nucleophilic addition to the C(7)-position of 1,8-naphthyridines when no alkyl substituents are present. For example, MeLi,[11] PhLi[12] and KCN[13] are readily added to the unsubstituted C(7)-position of 1,8-naphthyridines (Scheme 2). However, additions generating a quaternary center at C(2)/C(7), such as that which we desire at the C(7)-position in Scheme 1, have yet to be described. Herein we report on the addition of *n*-alkyllithiums to 1,8-naphthyridines such as **4** that hold alkyl substitution at the C(7)-position, thereby generating a quaternary center in high yield and good regioselectivity. We also present the synthesis of two 3-pyridinol analogs of PMC.

The results of our initial explorations utilizing *n*-BuLi as model alkyllithium reagent in additions to the 2,7-disubstituted naphthyridine **4** are presented in Table 1. The data reveal that both solvent polarity and reaction temperature play important roles in the yield of the two regioisomeric addition products **5a** and **5b**. In THF (entry 1), only a

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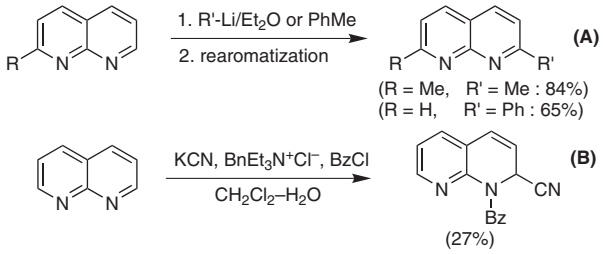


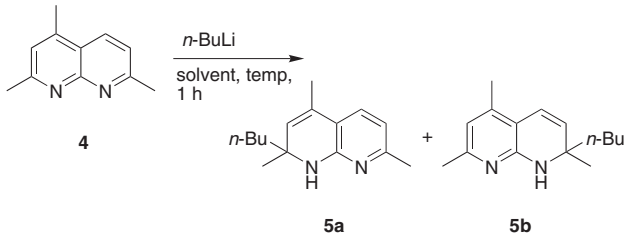
Scheme 2 Nucleophilic addition to 1,8-naphthyridines

small amount of the products (**5a** + **5b** = 12%) was obtained. The yield was even lower in more polar solvents, such as DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone] (entry 2). Decreasing the polarity of the solvent afforded a significant increase in the yield; 62% when Et_2O was used (entry 3). Addition of hexanes to the solution afforded a maximum yield of 87% for a 2:1 ratio of hexanes–Et_2O (entry 4). Higher amounts of hexanes caused solubility problems with **4** leading to lower yields. Solubility also becomes an issue at lower reaction temperatures. At –78 °C, **4** precipitated, leading to a poor yield (26%, entry 5). Although the starting material was soluble at –43 °C, the yields obtained at 0 °C could not be matched (entries 6 and 7).

The poor yields (and recovered starting material) that were obtained when THF and DMPU were employed as solvents prompted us to investigate whether preferential deprotonation could account for our observations. Indeed, treatment of **4** with *n*-BuLi followed by D_2O gave di-deuterated starting material (d_2-**4**) almost quantitatively by ^{1}H NMR (Scheme 3**A**). The preference for lithiation of 2,4-dimethylpyridine is consistent with this kinetically favored deprotonation (Scheme 3**B**).[14] Thus, it appears that two competing reaction pathways which depend heavily on solvent polarity exist. This solvent dependence can be rationalized on the basis of a chelation effect.[15] 1,8-Naphthyridines are known as good bidentate ligands (Figure 2, **A**)[11] and alkyllithium coordination to the bidentate naphthyridine moiety would be expected to dramatically increase the electrophilicity of the C(2) and C(7) positions, activating them towards *n*-BuLi addition (Figure 2, **B**). In more polar solvents, this chelation is interrupted, reducing the rate of nucleophilic addition and allowing deprotonation to compete. This explanation is supported by the observation that addition of LiBr to the reaction mixtures leads to an increase in yield (entries 1 and 3).

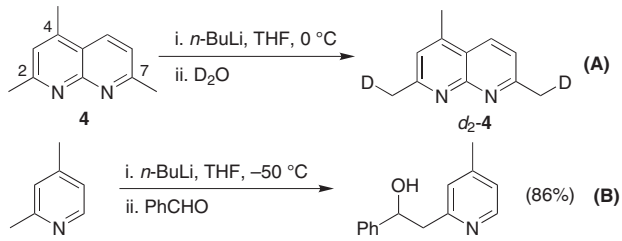
The marginal observed regioselectivity of the additions can also be rationalized on the basis of this coordination chemistry. By virtue of the electron-donating effect of the C(4′)-methyl group, the slightly more electron-rich left ring should more strongly coordinate *n*-BuLi, leading to a preference for left ring attack (**5a** > **5b**, Table 1).

Table 1 Effect of Solvent Polarity and Reaction Temperature on *n*-BuLi Addition to **4**[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]	**5a**:**5b**[b]
1	THF	0	12 (25)	1:0.9
2	DMPU	0	< 3	n/a
3	Et_2O	0	62 (71)	1:0.9
4	Et_2O–hexanes(1:2)	0	87	1:0.9
5	Et_2O–hexanes(1:2)	–78	26	1:0.9
6	Et_2O	–43	50	1:0.9
7	Et_2O–hexanes(1:2)	–43	74	1:0.9

[a] *n*-BuLi (4.5 equiv) was used.
[b] Determined by ^{1}H NMR on crude reaction mixtures. Values in parentheses are the yields in presence of LiBr (1 equiv).



Scheme 3 Kinetically favored deprotonation by *n*-BuLi

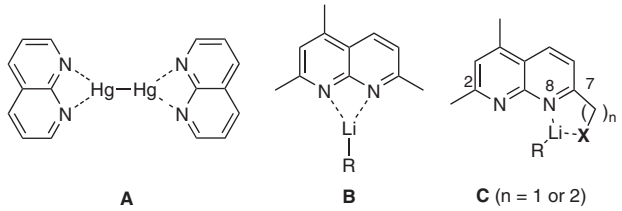


Figure 2 Chelation in naphthyridine chemistry

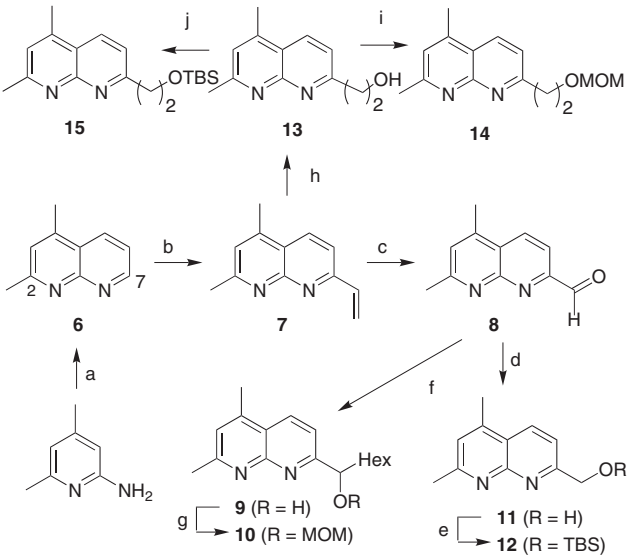
These initial studies led us to the hypothesis that alkyllithiums may be added regioselectively to the C(7) position if the interaction between the reagent and the naphthyridine ring system could be biased to the right ring nitrogen, N_8. In order to induce this complexation, the C(7)-CH_3 group of **4** was modified to $(CH_2)_n$-X (Figure 2, **C**) such that the alkyllithium could form a cyclic chelate with N_8 and another coordinating moiety, X.

Naphthyridines with X = OH, OMOM and OTBS as part of either five-membered (**9**–**12**) or six-membered (**13**–**15**) cyclic chelates were investigated (Scheme 4). The preparation of each of these compounds began from the dimethylnaphthyridine **6**, which was synthesized by the Skraup reaction of 2,4-dimethyl-6-aminopyridine and acrolein

(generated in situ from glycerol).[10] A vinyl group was added regioselectively to the unsubstituted C(7)-position of **6**, which was followed by re-aromatization with the mild oxidant MnO_2 to give **7** in 72% yield. Carrying on to obtain the five-membered cyclic chelating agents, treatment of **7** with OsO_4 followed by $NaIO_4$ gave aldehyde **8** in 84% yield. There were two pathways for generating the alcohol function. First, **8** was treated with hexylmagnesium bromide to give secondary alcohol **9**. This alcohol was further modified to give MOM-protected **10** by a LiBr-mediated alkoxy-exchange reaction.[16] Secondly, **8** was simply reduced by $NaBH_4$ to alcohol **11**, which was subsequently protected with a TBS group to give **12**. Substrates for six-membered chelation were obtained by oxymercuration–demercuration of **7** to yield the anti-Markovnikov alcohol **13**,[17] which was subsequently converted into the MOM- and TBS-protected compounds **14** and **15** under the same conditions as for **10** and **12**, respectively.

Table 2 summarizes the results of MeLi addition to the 1,8-naphthyridines where either five-membered (**9, 10** and **12**) or six-membered (**14** and **15**) cyclic chelation is possible. In general, five-membered chelation gave higher regioselectivity than six-membered chelation. The hexyl side chain in **9** provided adequate solubility for the alcohol to be useful (entry 1), but it required 12 equivalents of MeLi instead of the 4 equivalents used for all other substrates. Nevertheless, the desired regioisomer was obtained in five-fold excess. In contrast, the five- and six-membered chelates derived from alcohols **11** and **13**, respectively, yielded only trace product (not shown). MOM-protected **10** provided a higher yield (72%, entry 2), but lower regioselectivity (1:1.5). The low solubility of the MOM-protected **14** lead to a very poor yield from this substrate. The TBS-protected compounds **12** and **15** afforded the highest yields (entries 3 and 5), presumably due to their improved solubility. However, regioselectivity was significantly different between them. While **12** gave good regioselectivity (5.2:1, entry 3) through five-membered cyclic chelation, **15** (entry 6) showed practically no regioselectivity. The six-membered chelate would appear to be too large and flexible to afford a preference for MeLi addition to the proximal ring nitrogen. Again, addition of LiBr to the reaction mixture was found to improve the yield of addition product (entry 4).

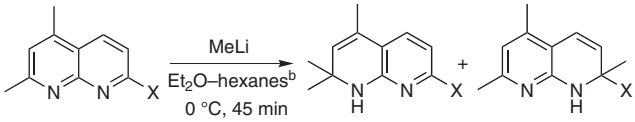
We demonstrate here the synthetic potential of our methodology by preparing **21a** and **21b**, the simplest examples of **3** containing a quaternary center at C(7) (Scheme 5). Thus, MeLi was added to **12** and the desired regioisomer **16** was isolated in 63% yield following column chromatography. The dihydronaphthyridine was subsequently hydrogenated to afford the tetrahydro derivative **17**, from which the TBS group was removed with TBAF to give **18** in 98% yield.[18] The alcohol function of **18** was reductively cleaved in 78% yield via the corresponding iodide. The 2,2-dimethyl derivative **19** was subsequently brominated to give **20a**, which could be used to reductively aminate formaldehyde to afford the *N*-methyl analog **20b** thereby



Scheme 4 Synthesis of substrates for five- and six-membered cyclic chelation. *Reagents and conditions*: (a) H_2SO_4, H_3BO_3, glycerol, NO_2PhSO_3Na, H_2O, $FeSO_4$, 150 °C, 4 h, 75%; (b) (i) CH_2=CHMgBr, Et_2O, 0 °C, 1 h; (ii) MnO_2, CH_2Cl_2, r.t., overnight, 72% for two steps; (c) (i) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, DABCO, *t*-BuOH–H_2O, r.t., 40 min, 90%; (ii) $NaIO_4$, 1,4-dioxane–H_2O, r.t., 45 min, 93%; (d) $NaBH_4$, MeOH, r.t., 1 h, quant.; (e) TBSCl, 4-DMAP, Et_3N, CH_2Cl_2, r.t., overnight, 93%; (f) $C_6H_{13}MgBr$, THF, –78 °C, 1 h, 42%; (g) $(MeO)_2CH_2$, LiBr, CH_3SO_3H, r.t., 2 h, 31% (h) $Hg(O_2CCF_3)_2$, NaOH, $NaBH_4$, THF–H_2O, r.t., 3 h, 70%; (i) $(MeO)_2CH_2$, LiBr, CH_3SO_3H, r.t., 2 h, 43%; (j) TBSCl, 4-DMAP, imidazole, CH_2Cl_2, r.t., 8 h, 100%

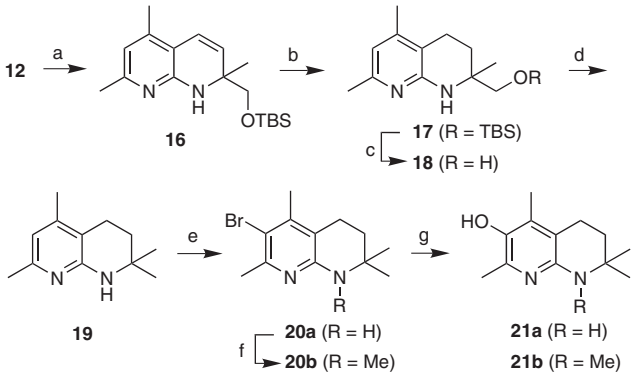
increasing structural similarity to **2**. Finally, **21a** and **21b** were obtained using a lithiation/oxidation sequence recently reported by us.[7]

Table 2 Chelation-Directed MeLi Addition[a]



Entry	Chelation	Substrate	Yield (%)[c]	Ratio (A:B)[c]
1	Five-membered	**9**	50	1:5
2		**10**	72	1:1.5
3		**12**	80	1:5.2
4[d]		**12**	95	1:5.2
5[e]	Six-membered	**14**	< 5	n/a
6		**15**	93	1:0.9

[a] X = co-chelation group. MeLi (4 equiv) [except for entry 1 (12 equiv)].
[b] Et_2O–hexanes = 1:1.5–2.
[c] Determined by ^1H NMR on crude reaction mixtures.
[d] MeLi–LiBr complex (4 equiv) was added.
[e] Performed in Et_2O because of its low solubility in Et_2O–hexanes system.



Scheme 5 Synthesis of 6-amino-3-pyridinol analogs of PMC. *Reagents and conditions*: (a) MeLi, Et_2O–hexanes (1:2), 0 °C, 1 h, 63%; (b) Pd/C, MeOH, r.t., overnight, 86%; (c) TBAF, THF, r.t., 1 h, 98%; (d) (i) Ph_3P, imidazole, I_2, CH_2Cl_2, r.t., 1.5 h; (ii) Zn, AcOH, 70 °C, 1 h, 78% for two steps; (e) 1,3-dibromo-5,5-dimethylhydantoin, CH_2Cl_2, –78 °C, 40 min, 75%; (f) HCHO (aq), $NaBH_3CN$, AcOH, MeOH, r.t., 3 h, 95%; (g) *n*-BuLi (for **21a**) or *t*-BuLi (for **21b**), THF, –78 °C, 30 min, DMPU followed by *o*-nitro-*m*-xylene, –78 °C, 2.5 h, 37% for **21a**, 48% for **21b**

The two 3-pyridinols **21a** and **21b** are the most complex in the series of antioxidants that we have prepared to date. These compounds are expected to be upwards of 30-fold more reactive towards peroxidation chain-carrying peroxyl radicals than PMC, the structural analog on which their design was based. Studies of their radical-trapping activities are underway and will be reported in due course. We are currently working towards a 3-pyridinol analog of α-tocopherol with its C16 isoprenoid side chain intact using the regioselective alkylation strategy described here.

Unless noted otherwise, materials were purchased from commercial suppliers and used as received. Air- and/or moisture-sensitive reactions were carried out under an inert gas atmosphere. THF, Et_2O and CH_2Cl_2 were dried using a Solvent Purification System from Solvtek. Reaction progress was monitored by TLC using silica gel F_{254} plates. Flash column chromatography was performed using silica gel 60 (230–400 mesh) with the indicated solvents. For **21a**, the silica gel was pre-treated with Et_3N. NMR spectra were taken on either a 300 MHz or 400 MHz Bruker DRX spectrometer. Chemical shifts (δ) are expressed in ppm using the indicated deuterated solvent as internal standard and coupling constants (*J*) are given in Hz. GC–MS spectra were obtained with a Hewlett-Packard 5890 series II gas chromatograph and 5971 mass selective detector. HRMS spectra were recorded in the positive ion mode using the electrospray technique and were obtained at the Ohio State University.

2,4,7-Trimethyl-1,8-naphthyridine (4)

Compound **4** was prepared according to the literature procedure.[10]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63 (d, *J* = 0.9 Hz, 3 H), 2.72 (s, 3 H), 2.77 (s, 3 H), 7.13 (d, *J* = 0.9 Hz, 1 H), 7.30 (d, *J* = 8.7 Hz, 1 H), 8.18 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 25.8, 25.8, 119.0, 121.9, 123.0, 133.2, 145.4, 156.0, 162.4, 162.6.

n-BuLi Addition to Compound 4 (Table 1, Entry 4); Typical Procedure

To a solution of naphthyridine **4** (70 mg, 0.4 mmol) in Et_2O (4 mL) was added hexanes (8 mL) followed by slow addition of *n*-BuLi (2.5 M in hexane, 720 μL, 1.8 mmol) at 0 °C and the reaction mixture turned deep brown instantly. After stirring for 1 h at 0 °C, the reaction mixture was quenched with water, neutralized with sat. aq NH_4Cl (pH 6) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with water (3 × 5 mL) and brine, dried over anhyd $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (MeOH–$CHCl_3$, 5:95) to give **5a** (41 mg, 44%) and **5b** (36 mg, 38%).

Compound 5a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t-like, 3 H), 1.42–1.20 (m, 6 H), 1.22 (s, 3 H), 2.07 (s, 3 H), 2.18 (s, 3 H), 4.46 (br s, 1 H), 5.26 (dd, *J* = 10.1, 2.1 Hz, 1 H), 6.09 (s, 1 H), 6.34 (d, *J* = 10.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 18.0, 23.4, 24.2, 26.9, 31.8, 45.0, 56.8, 110.1, 114.8, 119.8, 129.3, 142.4, 154.9, 155.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{22}N_2$: 231.1856; found: 231.1848.

Compound 5b

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t-like, 3 H), 1.18–1.44 (m, 6 H), 1.20 (s, 3 H), 1.86 (d, *J* = 1.5 Hz, 3 H), 2.23 (s, 3 H), 4.48 (br s, 1 H), 5.07 (s, 1 H), 6.25 (dd, *J* = 7.4, 0.3 Hz, 1 H), 6.99 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 18.3, 23.4, 24.4, 26.8, 31.9, 45.3, 56.5, 112.0, 113.4, 127.0, 128.2, 130.8, 155.1, 155.9.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{22}N_2$: 231.1856; found: 231.1834.

2,4-Dimethyl-1,8-naphthyridine (6)

Compound **6** was prepared according to the literature procedure.[10]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (d, *J* = 0.7 Hz, 3 H), 2.75 (s, 3 H), 7.28 (s, 1 H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1 H), 8.31 (dd, *J* = 8.3, 1.9 Hz, 1 H), 9.05 (dd, *J* = 4.2, 1.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 25.9, 114.9, 121.3, 123.9, 133.4, 145.7, 153.2, 156.3, 163.0.

2,4-Dimethyl-7-vinyl-1,8-naphthyridine (7)

To a solution of naphthyridine **6** (1.22 g, 7.7 mmol) in Et_2O (75 mL) was added vinylmagnesium bromide (1.0 M in THF, 23.1 mL, 23.1 mmol) at 0 °C. The reaction mixture was stirred for 1 h, quenched with sat. aq NH_4Cl, neutralized with 1 N HCl (pH 6) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with water (3 × 15 mL) and brine, dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (70 mL) and MnO_2 (activated, <5 μ, 85% assay, 6.7 g, 77 mmol) was added slowly and the reaction mixture stirred overnight. MnO_2 was filtered over Celite and the filtrate was concentrated under reduced pressure. The resulting brown oil was purified by column chromatography on silica gel ($CHCl_3$ then MeOH–$CHCl_3$, 1:40) to yield the product as a light brown oil (1.02 g, 72% from **6**).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (d, *J* = 0.9 Hz. 3 H), 2.76 (s, 3 H), 5.70 (dd, *J* = 10.8, 0.9 Hz, 1 H), 6.51 (dd, *J* = 17.6, 0.9 Hz, 1 H), 7.07 (dd, *J* = 17.4, 10.8 Hz, 1 H), 7.18 (d, *J* = 0.6 Hz, 1 H), 7.59 (d, *J* = 8.7 Hz, 1 H), 8.29 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 25.9, 119.1, 120.4, 121.4, 123.5, 133.7, 137.8, 145.4, 156.2, 158.7, 163.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2Na$: 207.0893; found: 207.0900.

5,7-Dimethyl-1,8-naphthyridine-2-carbaldehyde (8)

To a solution of vinyl naphthyridine **7** (4.08 g, 22.2 mmol), potassium ferricyanide [$K_3Fe(CN)_6$, 21.9 g, 66.6 mmol], K_2CO_3 (9.19 g, 66.6 mmol) and 1,4-diazacyclo[2.2.2]octane (DABCO, 622 mg, 5.55 mmol) in *t*-BuOH (150 mL) and water (150 mL) was added os-

mium tetroxide (OsO_4, 4% in water, 2.82 g, 0.44 mmol). The brown slurry was stirred for 40 min at r.t. $NaHSO_3$ (60% assay, 17.7 g) in water (70 mL) was added and the mixture was stirred for 10 min. The reaction mixture was diluted with water (50 mL) and extracted with $CHCl_3$ (3 × 40 mL). The combined organic layer was washed with brine, dried over anhyd $MgSO_4$ and concentrated to give crude diol (4.37 g, ca 90%).

^{1}H NMR (300 MHz, CD_3OD): δ = 2.72 (s, 3 H), 2.73 (d, *J* = 0.9 Hz, 3 H), 3.86 (dd, *J* = 11.3, 6.3 Hz, 1 H), 4.0 (dd, *J* = 11.3, 4.2 Hz, 1 H), 4.96 (dd, *J* = 6.2, 4.2 Hz, 1 H), 7.37 (d, *J* = 0.6 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 8.55 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 18.4, 25.3, 68.0, 76.7, 120.8, 121.8, 125.0, 135.9, 148.9, 155.9, 164.3, 166.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_2Na$: 241.0947; found: 241.0932.

The crude diol (3.77 g, 17.2 mmol) was dissolved in 1,4-dioxane (130 mL) and water (130 mL). Sodium periodate ($NaIO_4$, 3.80 g, 17.7 mmol) was added at r.t. The reaction mixture was stirred at the same temperature for 45 min. Water (150 mL) was added and the mixture was extracted with $CHCl_3$ (5 × 40 mL). The combined organic layer was washed with brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH–$CHCl_3$, 1:20) to give **8** (3.44 g, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (s, 3 H), 2.74 (s, 3 H), 7.27 (d, *J* = 0.9 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.43 (dd, *J* = 8.4, 0.6 Hz, 1 H), 10.2 (d, *J* = 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 26.0, 117.4, 124.0, 125.8, 135.2, 145.9, 154.5, 155.9, 164.7, 194.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{10}N_2ONa$: 209.0690; found: 209.0680.

1-(5,7-Dimethyl-1,8-naphthyridin-2-yl)heptan-1-ol (9)

To a solution of aldehyde **8** (755 mg, 4.1 mmol) in THF (80 mL) was added *n*-hexylmagnesium bromide (2.0 M in Et_2O, 2.2 mL, 4.3 mmol) at –78 °C. The reaction mixture was stirred at the same temperature for 1 h. After quenching with sat. aq NH_4Cl, THF was removed under reduced pressure. Water was added and the mixture was extracted with EtOAc (4 × 15 mL). The combined organic layer was washed with water (2 × 20 mL) and brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH–$CHCl_3$, 1:9) to give a yellow oil (457 mg, 42%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t-like, 3 H), 1.17–1.47 (m, 8 H), 1.81–1.92 (m, 1 H), 1.63–1.75 (m, 1 H), 2.62 (d, *J* = 0.6 Hz, 3 H), 2.65 (s, 3 H), 4.87 (m, 1 H), 5.57 (s, 1 H), 7.16 (s, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 8.3 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 18.5, 23.0, 25.6, 25.9, 29.7, 32.1, 38.9, 73.3, 118.8, 120.4, 123.8, 134.2, 146.0, 155.0, 163.2, 166.1.

GC–MS (EI): *m*/*z* = 172 [M]$^+$.

7-[1-(Methoxymethoxy)heptyl]-2,4-dimethyl-1,8-naphthyridine (10)

To a mixture of alcohol **9** (457 mg, 1.68 mmol), LiBr (73 mg, 1.68 mmol) and 2,2-dimethoxymethane (30 mL) was added methanesulfonic acid (110 μL, 1.68 mmol). After stirring for 2 h at r.t., the reaction mixture was quenched with sat. aq Na_2CO_3 and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with water (2 × 10 mL) and brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 3:1) to give **10** (165 mg, 31%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 6.6 Hz, 3 H), 1.13–1.48 (m, 8 H), 1.83 (q, *J* = 7.5 Hz, 2 H), 2.60 (d, *J* = 0.3 Hz, 3 H), 2.68 (s, 3 H), 3.30 (s, 3 H), 4.33 (dd, *J* = 7.5, 6.3 Hz, 2 H), 4.85 (t, *J* = 6.3 Hz, 1 H), 7.13 (d, *J* = 0.9 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 8.26 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 18.4, 23.0, 25.9, 29.5, 32.1, 37.1, 39.6, 56.2, 81.3, 96.1, 118.5, 120.2, 123.6, 134.0, 145.5, 155.6, 163.0, 166.5.

GC–MS (EI): *m*/*z* = 316 [M]$^+$.

(5,7-Dimethyl-1,8-naphthyridin-2-yl)methanol (11)

To a solution of aldehyde **8** (250 mg, 1.34 mmol) in MeOH (10 mL), was added $NaBH_4$ (25 mg, 0.67 mmol) at r.t. After stirring for 1 h, water was added and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layer was washed with water (10 mL) and the aq layer was back-extracted with $CHCl_3$ (8 mL). The combined organic layer was washed with brine, dried over anhyd $MgSO_4$ and concentrated in vacuo to give alcohol **11** (256 mg, 100%), which was sufficiently pure to be used directly without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59 (d, *J* = 0.6 Hz, 3 H), 2.67 (s, 3 H), 4.51 (br s, 1 H), 4.88 (s, 2 H), 7.13 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 25.8, 64.6, 118.5, 120.4, 123.8, 134.2, 146.1, 155.1, 162.9, 163.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}N_2ONa$: 211.0842; found: 211.0843.

7-[(*tert*-Butyldimethylsilyloxy)methyl]-2,4-dimethyl-1,8-naphthyridine (12)

A mixture of alcohol **11** (640 mg, 3.44 mmol), *tert*-butyldimethylsilyl chloride (1.03 g, 6.88 mmol), Et_3N (1.18 mL, 8.6 mmol) and 4-dimethylaminopyridine (83 mg, 0.69 mmol) in CH_2Cl_2 (33 mL) was stirred overnight at r.t. The reaction mixture was diluted with $CHCl_3$ (20 mL), washed with water (3 × 10 mL) and brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 2:1) to give **12** (970 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.84 (s, 9 H), 2.52 (s, 3 H), 2.59 (s, 3 H), 4.90 (s, 2 H), 7.02 (s, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 8.20 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.94, 18.4, 18.7, 25.9, 26.3, 67.0, 118.4, 120.0, 123.3, 133.9, 145.6, 155.4, 162.9, 165.3.

HRMS: *m*/z [M + Na]$^+$ calcd for $C_{17}H_{26}N_2OSi$: 325.1687; found: 325.1698.

2-(5,7-Dimethyl-1,8-naphthyridin-2-yl)ethanol (13)

To a solution of vinyl naphthyridine **7** (746 mg, 4.05 mmol) in a THF–H_2O mixture (4:1, 20 mL) was added mercury(II) trifluoroacetate (1.73 g, 4.05 mmol). After stirring at r.t. for 1.5 h, 3 M NaOH (4.1 mL) was added. After 3 min, $NaBH_4$ (0.5 M in 3 M NaOH, 4.1 mL) was added. The resulting dark green slurry was stirred at r.t. for 1 h. Extraction was performed with water (50 mL) and $CHCl_3$ (3 × 15 mL). The combined organic layer was washed with brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH–$CHCl_3$, 1:9) to give a pale yellow solid (576 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (d, *J* = 0.9 Hz, 3 H), 2.68 (s, 3 H), 3.23 (t, *J* = 5.7 Hz, 2 H), 4.22 (t, *J* = 5.4 Hz, 2 H), 4.54 (s, 1 H), 7.09 (d, *J* = 0.6 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 25.8, 41.1, 61.5, 119.5, 122.3, 123.3, 133.4, 145.7, 155.5, 162.7, 164.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_2ONa$: 225.0998; found: 225.0991.

7-[2-(Methoxymethoxy)ethyl]-2,4-dimethyl-1,8-naphthyridine (14)

The same procedure was applied as for compound **10** (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.51 (s, 3 H), 3.08 (s, 3 H), 3.06–3.10 (overlapped, 2 H), 3.87 (t, *J* = 6.8 Hz, 2 H), 4.40 (s, 2 H), 6.94 (s, 1 H), 7.17 (d, *J* = 8.4 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 25.9, 39.7, 55.6, 67.3, 96.9, 119.6, 122.1, 123.3, 133.4, 145.5, 156.1, 162.8, 163.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}N_2O_2Na$: 269.1260; found: 269.1271.

7-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-2,4-dimethyl-1,8-naphthyridine (15)

A solution of alcohol **13** (45 mg, 0.22 mmol), imidazole (24 mg, 0.35 mmol), DMAP (5.4 mg, 0.04 mmol) and TBSCl (50 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) was stirred overnight at r.t. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (3 × 8 mL) and brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 3:2) to give the product (70 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.0 (s, 6 H), 0.88 (s, 9 H), 2.68 (d, *J* = 0.3 Hz, 3 H), 2.76 (s, 3 H), 3.25 (t, *J* = 6.6 Hz, 2 H), 4.15 (t, *J* = 6.6 Hz, 2 H), 7.19 (s, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.98, 18.4, 18.6, 25.9, 26.3, 42.9, 63.2, 119.5, 122.7, 123.2, 132.9, 145.5, 156.2, 162.7, 163.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_2ONa$: 225.0998; found: 225.1001.

MeLi Additions to Compounds 9–15 (Table 2, entry 3); Typical Procedure

2-[(*tert*-Butyldimethylsilyloxy)methyl]-2,5,7-trimethyl-1,2-dihydro-1,8-naphthyridine (16)

To a solution of **12** (1.85 g, 6.12 mmol) in a mixture of Et_2O (50 mL) and hexanes (80 mL), was added MeLi (1.6 M in Et_2O, 15.3 mL, 24.5 mmol) at 0 °C. The reaction mixture was stirred for 45 min after which it was quenched with sat. aq NH_4Cl and neutralized with 1 N HCl. The mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with water (3 × 10 mL) and brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:3) to give a yellow oil (1.23 g, 63%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (d, *J* = 3.0 Hz, 6 H), 0.85 (s, 9 H), 1.23 (s, 3 H), 2.11 (s, 3 H), 2.23 (s, 3 H), 3.48 (dd, *J* = 60.5, 9.6 Hz, 2 H), 4.82 (s, 1 H), 5.31 (dd, *J* = 10.1, 2.1 Hz, 1 H), 6.15 (s, 1 H), 6.44 (d, *J* = 9.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.03, 18.0, 18.7, 24.3, 26.3, 26.9, 57.5, 71.4, 110.5, 115.1, 121.3, 126.5, 142.4, 154.9, 155.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}N_2OSi$: 319.2200; found: 319.2208.

2-[(*tert*-Butyldimethylsilyloxy)methyl]-2,5,7-trimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (17)

To a solution of **16** (1.21 g, 3.80 mmol) in MeOH (150 mL) was added palladium (10 wt% on charcoal, dry type, 182 mg). The reaction mixture was stirred overnight at r.t. under a H_2 atmosphere. The catalyst was removed over Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:3) to give a colorless oil (1.05 g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (d, *J* = 0.9 Hz, 6 H), 0.86 (s, 9 H), 1.15 (s, 3 H), 1.48–1.58 (m, 1 H), 1.70–1.79 (m, 1 H), 2.07 (s, 3 H), 2.24 (s, 3 H), 2.55 (d, *J* = 6.9 Hz, 2 H), 3.39 (dd, *J* = 34.8, 9.3 Hz, 2 H), 4.79 (s, 1 H), 6.23 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.03, 18.7, 19.0, 20.3, 24.1, 24.4, 26.3, 29.4, 53.2, 70.6, 110.7, 114.6, 146.0, 154.3, 155.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{32}N_2OSi$: 321.2357; found: 321.2346.

(2,5,7-Trimethyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-yl)methanol (18)

To a solution of **17** (1.05 g, 3.27 mmol) in THF (20 mL) was added *n*-tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 3.43 mL, 3.43 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at the same temperature. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to give the product (664 mg, 98%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.09 (s, 3 H), 1.42–1.51(m, 1 H), 1.68–1.76 (m, 1 H), 2.04 (s, 3 H), 2.14 (s, 3 H), 2.50 (t, *J* = 6.3 Hz, 2 H), 3.23 (dd, *J* = 27.6, 10.5 Hz, 2 H), 4.78 (s, 1 H), 5.79 (s, 1 H), 6.19 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.5, 19.7, 23.6, 24.3, 29.0, 52.7, 68.1, 110.1, 113.4, 145.0, 153.0, 155.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}N_2O$: 207.1492; found: 207.1493

2,2,5,7-Tetramethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (19)

To a solution of triphenylphosphine (1.04 g, 3.98 mmol), imidazole (483 mg, 7.1 mmol) and alcohol **18** (586 mg, 2.84 mmol) in CH_2Cl_2 (20 mL) was added I_2 (1.01 g, 3.98 mmol) at 0 °C. After 10 min, the ice bath was removed and the reaction mixture was stirred for 1.5 h at r.t. Na_2SO_3 (4.5 g, 35.7 mmol) in water (20 mL) was added and the mixture was stirred for 30 min. The mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water (3 × 15 mL) and brine and dried over anhyd $MgSO_4$. After evaporation of solvent, the residue (which still contained triphenylphosphine oxide) was dissolved in glacial AcOH (2 mL). Zinc dust (activated, 428 mg, 3.93 mmol) was added at r.t. in one portion and the mixture was stirred at 70 °C for 1 h. After cooling down to r.t., the zinc metal was filtered through a pad of Celite. The filtrate was neutralized with sat. aq $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried over anhyd $MgSO_4$ and purified by column chromatography on silica gel (EtOAc–$CHCl_3$, 1:1 then MeOH–$CHCl_3$, 1:20). A pale yellow solid (424 mg, 78%) was obtained.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 6 H), 1.62 (t, *J* = 6.6 Hz, 2 H), 2.05 (s, 3 H), 2.21 (s, 3 H), 2.53 (t, *J* = 6.6 Hz, 2 H), 4.52 (s, 1 H), 6.20 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 20.9, 24.1, 29.5, 34.4, 49.6, 110.4, 114.6, 146.2, 154.1, 155.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}N_2$: 191.1543; found: 191.1540.

6-Bromo-2,2,5,7-tetramethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (20a)

To a solution of **19** (400 mg, 2.10 mmol) in CH_2Cl_2 (10 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (330 mg, 1.16 mmol) at –78 °C. After stirring for 40 min, the reaction mixture was quenched with sat. aq Na_2CO_3 and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with water (3 × 15 mL) and brine and dried over anhyd $MgSO_4$. After concentra-

tion, the residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:5) to give the product (425 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 6 H), 1.63 (t, *J* = 6.6 Hz, 2 H), 2.21 (s, 3 H), 2.39 (s, 3 H), 2.60 (t, *J* = 6.6 Hz, 2 H), 4.49 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 22.4, 25.8, 29.3, 34.4, 49.5, 111.8, 112.5, 145.4, 153.1, 153.7.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{12}H_{17}BrN_2$: 269.0648; found: 269.0643.

6-Bromo-1,2,2,5,7-pentamethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (20b)

To a solution of **20a** (349 mg, 1.30 mmol) in MeOH (15 mL) was added formaldehyde (37% in water, 5.3 g, 65 mmol) and AcOH (3.72 mL, 65 mmol). At r.t., sodium cyanoborohydride (817 mg, 13 mmol) was added portionwise. After stirring for 3 h, the reaction mixture was neutralized with sat. aq Na_2CO_3 and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (3 × 15 mL) and brine and dried over anhyd $MgSO_4$. After concentration, the residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:6) to give **20b** (351 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 6 H), 1.69 (t, *J* = 6.6 Hz, 2 H), 2.18 (s, 3 H), 2.42 (s, 3 H), 2.57 (t, *J* = 6.6 Hz, 2 H), 2.97 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 22.4, 26.2, 26.3, 29.2, 36.2, 53.5, 111.1, 114.5, 143.6, 152.2, 154.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{13}H_{19}BrN_2$: 283.0804; found: 283.0814.

2,4,7,8-Tetramethyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-ol (21a)

At –78 °C, *t*-BuLi (1.5 M in pentane, 2.73 mL, 4.10 mmol) was added to a solution of **20a** (344 mg, 1.28 mmol) in anhyd THF (8 mL). The formation of the metalated adduct was monitored by TLC. After 45 min, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 304 μL, 2.56 mmol) was added at the same temperature. After 10 min, anhyd 2-nitro-*m*-xylene (1.22 mL, 8.96 mmol) was added in one portion. The color changed immediately from yellow to dark brown. After stirring for 3 h at –78 °C, the reaction mixture was quenched and neutralized with sat. aq NH_4Cl. The mixture was extracted with $CHCl_3$ (4 × 15 mL). The combined organic layer was dried over anhyd $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$ then MeOH–$CHCl_3$, 1:20) to give orange solid (126 mg, 48%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.09 (s, 6 H), 1.55 (t, *J* = 6.9 Hz, 2 H), 2.00 (s, 3 H), 2.24 (s, 3 H), 2.51 (overlapped t, *J* = 6.9 Hz, 2 H), 5.34 (s, 1 H), 7.39 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.0, 19.4, 21.3, 28.6, 34.4, 48.4, 110.9, 134.3, 140.8, 141.5, 149.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{12}H_{18}N_2O$: 207.1492; found: 207.1495.

2,4,7,7,8-Pentamethyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-ol (21b)

At –78 °C, *n*-BuLi (2.5 M in hexane, 1.1 mL, 2.73 mmol) was added to a solution of **20b** (350 mg, 1.24 mmol) in anhyd THF (6 mL). The formation of the metalated adduct was monitored by TLC. After 30 min, DMPU (648 μL, 5.46 mmol) was added at the same temperature. After 10 min, anhyd 2-nitro-*m*-xylene (844 μL, 6.20 mmol) was added in one portion. The color changed immediately from yellow to brown. After 3 h of stirring, the reaction mixture was quenched and neutralized with sat. aq NH_4Cl. The mixture was extracted with $CHCl_3$ (4 × 15 mL). The combined organic layers were dried over anhyd $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:3) to give a brown thick oil (102 mg, 37%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (s, 6 H), 1.70 (t, *J* = 6.9 Hz, 2 H), 2.00 (s, 3 H), 2.20 (s, 3 H), 2.53 (t, *J* = 6.9 Hz, 2 H), 2.87 (s, 3 H), 7.44 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.1, 20.0, 21.1, 25.4, 28.9, 35.9, 52.5,, 113.3, 133.6, 140.4, 140.5, 149.5.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}N_2O$: 221.1648; found: 221.1660.

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