Regioselective Addition of \( n \)-Alkyllithiums to \( \alpha, \alpha' \)-Disubstituted-1,8-Naphthyridines: Synthesis of 6-Amino-3-Pyridinol Analogs of \( \alpha \)-Tocopherol

Tae-gyu Nam, Maikel Wijtmans, Derek A. Pratt, Ned A. Porter

Abstract: \( n \)-Alkyllithiums were added to \( \alpha, \alpha' \)-disubstituted-1,8-naphthyridines in non-polar solvents such as \( \text{Et}_2\text{O-hexane} \) 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 pentamethyl-chromanol (PMC), an \( \alpha \)-tocopherol derivative with its isoprenoid side chain truncated to a methyl group.

Key words: 1,8-naphthyridine, alkyllithium, chelation, solvent effects, \( \alpha \)-tocopherol

1,8-Naphthyridines (1, Figure 1) are important scaffolds in many compounds with pharmacological applications. They are also known to be good bidentate ligands in organometallic complexes. The dihydro- and tetrahydro forms have also shown pharmacological application as high affinity ligands of the \( \beta_1 \)-adreno and \( \alpha_1, \beta_1 \)-vitronectin 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 tetrahydrornaphthyridine 2 is almost 30 times more effective at inhibiting lipid peroxidation than \( \alpha \)-tocopherol, the most potent form of vitamin E and nature’s most powerful lipophilic antioxidant.

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 \( \alpha \)-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. Since it has been reported that the isoprenoid side chain of \( \alpha \)-tocopherol also plays an important role in its biological activity, 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. 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.

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, PhLi and KCN 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
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(1H)-pyrimidinone] (entry 2). Decreasing the polarity of the solvent afforded a significant increase in the yield; 62% when Et₂O was used (entry 3). Addition of hexanes to the solution afforded a maximum yield of 87% for a 2:1 ratio of hexanes–Et₂O (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 D₂O gave di-deuterated starting material (d₂-4) almost quantitatively by ¹H NMR (Scheme 3A). The preference for lithiation of 2,4-dimethylpyridine is consistent with this kinetically favored deprotonation (Scheme 3B). 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. 1,8-Naphthyridines are known as good bidentate ligands (Figure 2, A) 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).

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, N₈. In order to induce this complexation, the C(7)-CH₃ group of 4 was modified to (CH₂)ₙ-X (Figure 2, C) such that the alkyllithium could form a cyclic chelate with N₈ and another coordinating moiety, X.

Naphthyridines with X = OH, O MOM 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 dimethylaminopyridine 6, which was synthesized by the Skraup reaction of 2,4-dimethyl-6-aminopyridine and acrolein.

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**Scheme 2** Nucleophilic addition to 1,8-naphthyridines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>5a:5b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>0</td>
<td>12 (25)</td>
<td>1:0.9</td>
</tr>
<tr>
<td>2</td>
<td>DMPU</td>
<td>0</td>
<td>&lt; 3</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>0</td>
<td>62 (71)</td>
<td>1:0.9</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O–hexanes(1:2)</td>
<td>0</td>
<td>87</td>
<td>1:0.9</td>
</tr>
<tr>
<td>5</td>
<td>Et₂O–hexanes(1:2)</td>
<td>−78</td>
<td>26</td>
<td>1:0.9</td>
</tr>
<tr>
<td>6</td>
<td>Et₂O</td>
<td>−43</td>
<td>50</td>
<td>1:0.9</td>
</tr>
<tr>
<td>7</td>
<td>Et₂O–hexanes(1:2)</td>
<td>−43</td>
<td>74</td>
<td>1:0.9</td>
</tr>
</tbody>
</table>

*a*-BuLi (4.5 equiv) was used.

*b*- Determined by ¹H NMR on crude reaction mixtures. Values in parentheses are the yields in presence of LiBr (1 equiv).
Alkyllithium Addition to 1,8-Naphthyridine

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 regiosomer 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, 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 X containing a quaternary center at C(7) (Scheme 5). Thus, MeLi was added to 12 and the desired regiosomer 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 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\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chelation</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>Ratio (A:B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Five-membered</td>
<td>9</td>
<td>50</td>
<td>1:5</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10</td>
<td>72</td>
<td>1:1.5</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>12</td>
<td>80</td>
<td>1:5.2</td>
</tr>
<tr>
<td>4(^d)</td>
<td></td>
<td>12</td>
<td>95</td>
<td>1:5.2</td>
</tr>
<tr>
<td>5(^e)</td>
<td>Six-membered</td>
<td>14</td>
<td>&lt;5</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>15</td>
<td>93</td>
<td>1:0.9</td>
</tr>
</tbody>
</table>

\(^a\) X = co-chelation group. MeLi (4 equiv) [except for entry 1 (12 equiv)].
\(^b\) Et\(_2\)O–hexanes = 1:1.5–2.
\(^c\) Determined by \(^1\)H NMR on crude reaction mixtures.
\(^d\) MeLi–LiBr complex (4 equiv) was added.
\(^e\) Performed in Et\(_2\)O because of its low solubility in Et\(_2\)O–hexanes system.

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CH2Cl2, –78 °C, 40 min, 75%; (f) HCHO (aq), NaBH3CN, AcOH, °C, 1 h, 78% for two steps; (e) 1,3-dibromo-5,5-dimethylhydantoin,

Procedure

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<tbody>
<tr>
<td>21a</td>
<td>MeLi, Et2O–hexanes (1:2), 0 °C, 1 h, 65%; (b) Pd/C, MeOH, r.t., overnight, 86%; (c) TBAF, THF, r.t., 1 h, 98%; (d) (i) Ph3P, imidazole, I2, CH2Cl2, r.t., 1.5 h; (ii) Zn, AcOH, 70 °C, 1 h, 78% for two steps; (e) 1,3-dibromo-5,5-dimethylhydantoin, CH2Cl2, –78 °C, 30 min, DMPU followed by –BuLi (for 21b), THF, –78 °C, 30 min, DMFU followed by o-nitro-m-xylene, –78 °C, 2.5 h, 37% for 21a, 48% for 21b.</td>
<td>1H NMR (300 MHz, CDCl3): δ = 8.01 (t, 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).</td>
<td>1H NMR (300 MHz, CDCl3): δ = 14.5, 18.0, 23.4, 24.2, 26.9, 31.8, 45.0, 56.8, 110.1, 114.8, 119.8, 123.9, 142.4, 154.9, 155.4.</td>
</tr>
<tr>
<td>21b</td>
<td>-</td>
<td>13C NMR (75 MHz, CDCl3): δ = 123.0, 133.2, 145.4, 156.0, 162.4, 162.6.</td>
<td>13C NMR (75 MHz, CDCl3): δ = 18.3, 25.9, 114.9, 121.3, 123.9, 133.4, 145.7, 153.2, 156.3, 163.0.</td>
</tr>
</tbody>
</table>

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 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, Et2O and CH2Cl2 were dried using a Solvent Purification System from Spectrum. 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 Et3N. 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

$$\text{[M + H]+ calcd for C12H12N2Na: 207.0893; found: 207.0920.}$$

$$\text{[M + Na]+ calcd for C15H22N2: 231.1856; found: 231.1834.}$$

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

To a solution of naphthyridine 6 (1.22 g, 7.7 mmol) in Et2O (75 mL) was added vinylvinylmagnesium 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 NH4Cl, neutralized with 1 M 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 MgSO4 and concentrated in vacuo. The residue was dissolved in CH2Cl2 (70 mL) and MnO2 (activated, 0.95 g) was added. After stirring overnight, MnO2 was filtered off and the filtrate was concentrated under reduced pressure. The resulting brown oil was purified by column chromatography on silica gel (CHCl3 then MeOH–CH2Cl2, 1:40) to yield the product as a light brown oil (1.02 g, 72% from 6).

$$\text{[M + H]+ calcd for C12H12N2Na: 207.0893; found: 207.0920.}$$

$$\text{[M + Na]+ calcd for C15H22N2: 231.1856; found: 231.1834.}$$

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

To a solution of naphthyridine 7 (4.08 g, 22.2 mmol), potassium ferricyanide [K3[Fe(CN)6], 21.9 g, 66.6 mmol], K2CO3 (9.19 g, 66.6 mmol) and 1,4-diacycloclo[2.2.2]octane (DABCDO, 622 mg, 5.55 mmol) in t-BuOH (150 mL) and water (150 mL) was added os-
mixture tetroxide (OsO₄, 4% in water, 2.82 g, 0.44 mmol). The brown slurry was stirred for 40 min at r.t. NaHSO₃ (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 CHCl₃ (3 × 40 mL). The combined organic layer was washed with brine, dried over anhyd MgSO₄ and concentrated to give crude diol (4.37 g, ca 90%).

To a mixture of alcohol (4.34 g, 93%).


1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 13.5, 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 C₁₁H₁₂N₂ONa: 211.0842; found: 211.0842.

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

A mixture of alcohol (640 mg, 3.44 mmol), tert-butyldimethylsilyl chloride (1.03 g, 6.88 mmol), Et₂N (1.18 mL, 8.6 mmol) and 4-dimethylaminopyridine (83 mg, 0.69 mmol) in CH₂Cl₂ (33 mL) was stirred overnight at r.t. The reaction mixture was diluted with CHCl₃ (20 mL), washed with water (3 × 10 mL) and brine, dried over anhyd MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 2:1) to give 8 (256 mg, 40%).

1H NMR (300 MHz, CDCl₃): δ = 0.28 (t, J = 8.7 Hz, 1 H), 1.70–1.77 (m, 2 H), 2.65 (s, 3 H), 4.87 (s, 2 H), 7.16 (s, 1 H), 7.32 (d, J = 8.4 Hz, 1 H), 8.3 (d, J = 8.4 Hz, 1 H).

13C NMR (75 MHz, CDCl₃): δ = 21.5, 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.


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

A mixture of alcohol (746 mg, 4.05 mmol) in a THF–H₂O mixture (4.1:20 mL) was added mercuric(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, NaBH₄ (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 CHCl₃ (3 × 15 mL). The combined organic layer was washed with brine, dried over anhyd MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 2:1) to give 10 (165 mg, 31%).

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 14.4, 18.4, 23.0, 25.9, 29.5, 32.1, 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 (250 mg, 1.34 mmol) in MeOH (10 mL), was added NaBH₄ (25 mg, 0.67 mmol) at r.t. After stirring for 1 h, water was added and the mixture was extracted with CHCl₃ (3 × 15 mL). The combined organic layer was washed with water (10 mL) and the aq layer was back-extracted with CHCl₃ (8 mL). The combined organic layer was washed with brine, dried over anhyd MgSO₄ and concentrated in vacuo to give alcohol (256 mg, 100%), which was sufficiently pure to be used directly without purification.

1H NMR (300 MHz, CDCl₃): 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 (d, J = 8.4 Hz, 1 H), 8.21 (d, J = 8.4 Hz, 1 H).

13C NMR (75 MHz, CDCl₃): 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 C₁₁H₁₂N₂ONa: 211.0842; found: 211.0843.

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HRMS: \[ m/z \ (M + Na)^+ \text{ calcd for C}_{12}H_{18}N_{2}ONa: 225.0998; \text{ found: 225.0991}. \]

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$_2$Cl$_2$ (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$_2$CO$_3$ 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 evaporation of solvent, the residue (which still contained triphenylphosphine oxide) was dissolved in glacial AcOEt (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 0 °C, the mixture was neutralized with sat. aq NaHCO$_3$ and extracted with CHCl$_3$. 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 was purified by column chromatography on silica gel (EtOAc–hexanes, 3:2) to give the product (70 mg, 100%).

HRMS: \[ m/z \ (M + H)^+ \text{ calcd for C}_{18}H_{32}N_{2}O: 271.2149; \text{ found: 271.2143}. \]
tion, the residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:5) to give the product (425 mg, 75%).

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): δ = 19.5, 22.4, 25.8, 29.3, 34.4, 49.5, 111.8, 112.5, 143.6, 152.2, 154.4.

HRMS: m/z [M + H]+ calcd for C₁₂H₁₈N₂O: 207.1492; found: 207.1495.

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 mixture was neutralized with sat. aq NH₄Cl. The residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:3) to give orange solid (126 mg, 48%).

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): 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 C₁₂H₁₈N₂O: 207.1495; found: 207.1492.

6,7,8-Tetramethyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-ol (21a)
At –78 °C, n- BuLi (1.5 M in pentane, 4.10 mmol) was added to a solution of 20a (344 mg, 1.28 mmol) in anhyd THF (8 mL). After 30 min, the formation of the metalated adduct was monitored by TLC. After 2 h, n- BuLi (1.5 M in pentane, 2.73 mL, 4.10 mmol) was added at the same temperature. After 3 h of stirring, the reaction mixture was quenched and neutralized with sat. aq NH₄Cl. The mixture was extracted with CHCl₃ (4 × 15 mL) and brine and dried over anhyd MgSO₄. After concentration, the residue was purified by column chromatography on silica gel (EtOAc–hexanes, 1:5) to give the product (425 mg, 75%).

1H NMR (300 MHz, DMSO-d₆): 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).

13C NMR (75 MHz, DMSO-d₆): 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 C₁₂H₁₈N₂O: 221.1648; found: 221.1660.

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References
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(17) We speculate that a cyclopropane intermediate is formed by radical cyclization upon treatment of the initial Markovnikov adduct with NaBH₄. Then, the cyclopropane ring opens in such a way that anti-Markovnikov alcohol is produced. Similar cyclopropane intermediates have been proposed in a conjugated diene system: Brown, H. C.; Geoghegan, P. J.; Lynch, G. J.; Kurek, J. T. J. Org. Chem. 1972, 37, 1941.

(18) Deprotection of TBS group in 16 resulted in unidentified by-product up to 50%.