Supporting Information

Improved synthesis of 2,4,6-trialkylpyridines from 1,5-diketoalkanes: total synthesis of Anibamine
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Synthetic procedures for 4a, b, d, e, f and 3a-g

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\begin{align*}
\text{9} & \xrightarrow{\text{Nu}^-} \text{4a, b, d, e, f} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>condition</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allylmagnesiumbromide, THF, -78 °C, 3h</td>
<td>4a</td>
<td>85</td>
</tr>
<tr>
<td>n-BuLi, ether, -78 °C, 3h</td>
<td>4b</td>
<td>80</td>
</tr>
<tr>
<td>Phenylmagnesiumbromide, THF, r.t., 1h</td>
<td>4d</td>
<td>53</td>
</tr>
<tr>
<td>p-Tolylmagnesiumbromide, THF, 0 °C to r.t., 3h</td>
<td>4e</td>
<td>79</td>
</tr>
<tr>
<td>1-Decyne, n-BuLi, THF, -78 °C to r.t., 12h</td>
<td>4f</td>
<td>93</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{4a-g} & \xrightarrow{\text{Table}} \text{3a-g} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>substrate</th>
<th>condition</th>
<th>product</th>
<th>yield (%)^a,b</th>
</tr>
</thead>
</table>
| 4a | 1) NH\(_2\)OH\(\cdot\)HCl, AcONa, EtOH, H\(_2\)O 
2) AcOH, reflux | 3a | 37 |
| 4c | | 3c | 61^c |
| 4b | | 3b | 86 |
| 4d | | 3d | 88 |
| 4e | | 3e | 78 |
| 4f | | 3f | 35^d |
| 4g | | 3g | 65 |
| 4b | | 3b | 31^e,f |

^aIsolated yield. ^b2 steps yield. ^cReaction was conducted at 110 °C. ^dMethoxyamine was employed.
^eOxime's hydroxy group was mesylated. ^f3 steps yield.
6-Methyl-8-(2,2-dimethylidioxolane)-nonen-4-one (4a) To a solution of 9 (303 mg, 1.31 mmol) in THF (4.5 mL) at -78 °C under nitrogen atmosphere was added allylmagnesiumbromide (0.7 M in Et₂O, 2.70 mL, 1.89 mmol) with dropwise manner and stirred at -78 °C for 3 h. The reaction mixture was quenched by sat. NH₄Cl aq. at 0 °C and the aqueous phase was extracted by AcOEt, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:5 v/v) to give 4a (237 mg, 85% yield) as a colorless oil.

4,6-Dimethyl-2-(propen-1-nyl)-pyridine (3a) To a solution of 4a (109 mg, 5.14 mmol) in EtOH (1.6 mL) and H₂O (1.6 mL) were added NaOAc (77.3 mg, 10.3 mmol) and hydroxylamine hydrochloride (65.5 mg, 10.3 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was added to H₂O. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (5.8 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to sat. NaHCO₃ aq. and the aqueous layer was extracted with CH₂Cl₂. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:4 v/v) to give 3a (28.3 mg, 37% yield over 2 steps) as a yellow oil.

4,6-Dimethyl-2-(propanyl)-pyridine (3c) To a solution of 4c (91.9 mg, 0.439 mmol) in EtOH (1.4 mL) and H₂O (1.4 mL) was added AcONa (360 mg, 4.39 mmol), hydroxylamine hydrochloride (153 mg, 2.20 mmol). The reaction mixture was stirred overnight. The reaction mixture was added to H₂O and separated. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (5.5 mL) was heated at 110 °C for 1 h. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to sat. NaHCO₃ aq. and the aqueous layer was extracted with CH₂Cl₂. The organic layers were washed with brine, dried over MgSO₄,
filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:5 v/v) to give 3c (38.9 mg, 61% yield over 2 steps) as a yellow oil.

3-Methyl-5-(2,2-dimethyldioxolane)-1-phenylhexanone (4d) To a solution of THF (4.3 mL) was added Mg (110 mg, mmol), iodide (catalytic amount) and bromobenzene (0.20 mL) under nitrogen atmosphere. After color of the reaction mixture changed into colorless, the reaction mixture was added bromobenzene (0.25 mL) dropwise. To this solution was added 9 (105 mg, 0.454 mmol) in THF (1.5 mL) dropwise at room temperature and stirred for 1 h. The reaction mixture was quenched with sat. NH₄Cl aq. at 0 °C. The aqueous phase was extracted by Et₂O, washed with 1M NaOH, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:6 v/v) to give 4d (60.2 mg, 53% yield) as a colorless oil.

4,6-Dimethyl-2-phenylpyridine (3d) To a solution of 4d (14.4 mg, 0.05 mmol) in EtOH (0.2 mL) and H₂O (0.2 mL) were added AcONa (41 mg, 0.5 mmol) and hydroxylamine hydrochloride (18 mg, 0.25 mmol). The reaction mixture was stirred at 45 °C overnight. The reaction mixture was added to H₂O and separated. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (1.2 mL) was refluxed for 16 h. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to sat. NaHCO₃ aq. and extracted with CH₂Cl₂. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification of column chromatography (AcOEt-hexane, 1:6 v/v) gave 3d (8.0 mg, 88% yield over 2 steps) as a pale orange oil.

p-Methylphenyl-3-methyl-5-(2,2-dimethyldioxolane)-hexanone (4e) To a solution of 9 (31.6 mg, 0.137 mmol) in THF (0.4 mL) was added p-tolylmagnesium bromide (0.1 M in THF, 4 mL, 0.39 mmol) at 0 °C, then warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with sat. NH₄Cl aq. at 0 °C. The aqueous phase was extracted by Et₂O, washed with 1M NaOH, dried over MgSO₄, filtered and
concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:4 v/v) to give 4e (32.6 mg, 79% yield) as a colorless oil.

2-p-Methylphenyl-4,6-dimethylpyridine (3e) To a solution of 4e (32.6 mg, 0.11 mmol) in EtOH (0.4 mL) and H₂O (0.4 mL) were added AcONa (90.2 mg, 1.1 mmol) and hydroxylamine hydrochloride (38.2 mg, 0.55 mmol). The reaction mixture was stirred at 45 °C overnight. The reaction mixture was added to H₂O and separated. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (2.5 mL) was refluxed for 23 h. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to sat. NaHCO₃ aq. and extracted with CH₂Cl₂. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:6 v/v) to give 3e (16.4 mg, 78% yield over 2 steps) as a pink oil.

4-Methyl-2-(2,2-dimethyldioxolane)-7-hexadecyn-6-one (4f) To a solution of 1-Decyne (295 µL, 1.43 mmol) in THF (1.4 mL) at -78 °C under nitrogen atmosphere was added n-BuLi (2.5 M in hexane, 0.6 mL, 1.30 mmol) at -78 °C. After the stirring for 30 min at 0 °C, 9 (101 mg, 0.437 mmol) was added to the mixture at -78 °C and the reaction mixture was allowed to warm to room temperature. After the stirring for 12 h, the reaction was quenched with sat. NH₄Cl aq. at 0 °C. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:8 v/v) to give 4f (125 mg, 93% yield) as a colorless oil.

2-Decynyl-4,6-dimethylpyridine (3f) To a solution of 4f (51.1 mg, 0.166 mmol) in EtOH (0.5 mL) and H₂O (0.5 mL) was added AcONa (136 mg, 1.66 mmol), methoxyamine hydrochloride (0.15 mL, 0.83 mmol) and stirred at room temperature overnight. The reaction mixture was added to H₂O. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the methoxyamine intermediate. A stirring solution of the methoxyamine intermediate in AcOH (2.1 mL) was refluxed for 6 h. The reaction
mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to sat. NaHCO₃ aq. and extracted with CH₂Cl₂. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:8 v/v) to give 3f (14.4 mg, 36% yield over 2 steps) as a yellow oil.

2-Decanyl-4,6-dimethylpyridine (3g) To a solution of 4g (72.3 mg, 0.231 mmol) in EtOH (0.8 mL) and H₂O (0.8 mL) were added AcONa (189 mg, 2.31 mmol) and hydroxylamine hydrochloride (80.3 mg, 1.16 mmol). After the stirring overnight, the reaction mixture was added to H₂O. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (2.9 mL) was refluxed for 1 h. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to sat. NaHCO₃ aq. and extracted with CH₂Cl₂. The organic fractions were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified with column chromatography (AcOEt-hexane, 1:10 v/v) gave 3g (37.3 mg, 65% yield over 2 steps) as a yellow oil.
$^1$H NMR of 2a
$^{13}$C NMR of 2a
$^1$H NMR of 2b

X : parts per Million : Proton

Y : Parts per Million : Proton

Quadrupole

6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5
$^{13}$C NMR of 2b
$^1$H NMR of 3a
$^{13}$C NMR of 3a
$^1$H NMR of 3b
$^{13}$C NMR of 3b
$^1$H NMR of 4a
$^{13}$C NMR of 4a
$^1$H NMR of 4c
13C NMR of 4c
$^1$H NMR of 3c
$^{13}$C NMR of 3c
$^{13}$C NMR of 4b
$^1$H NMR of 4d
$^{13}$C NMR of 4d
$^1$H NMR of 3d
$^{13}$C NMR of 3d
$^1$H NMR of 4e
$^{13}$C NMR of 4e
$^1\text{H NMR of 3e}$
$^{13}$C NMR of 3e
$^1$H NMR of 4f
$^{13}$C NMR of 4f
$^1$H NMR of 3f
$^{13}$C NMR of 3f
$^1$H NMR of 4g
$^{13}$C NMR of $4g$
$^1$H NMR of 3g
$^{13}$C NMR of 3g
$^1$H NMR of 6

![NMR Spectrogram]

X: parts per Million :: Proton

Y: ppm
$^{13}$C NMR of 6
$^1$H NMR of 7

[Graph showing NMR spectrum with peaks at various chemical shift values]
$^{13}$C NMR of 7
$^{13}$C NMR of 9

[Graph showing NMR spectrum with chemical shifts and integration areas marked]
$^1$H NMR of 10
$^{1}H$ NMR of 11
$^{13}$C NMR of 11
$^1$H NMR of 12
\[ ^{13}\text{C} \text{NMR of 12} \]
$^1$H NMR of 13
$^{13}$C NMR of 13
$^1$H NMR of 14
$^{13}$C NMR of 14
$^1$H NMR of Anibamine (1)
\(^{13}\)C NMR of Anibamine (1)
Spectral comparison with natural anibamine (1) and synthetic one

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\begin{align*}
\text{Natural Anibamine} & \quad \text{(}^{1}H: 400MHz, ^{13}C: 100MHz \text{)} & \quad \text{Synthetic Anibamine} & \quad \text{(}^{1}H: 600MHz, ^{13}C: 150MHz \text{)} \\
\text{position} & \delta_c & \delta_h & \delta_c & \delta_h & \Delta \delta_c & \Delta \delta_h \\
2 & 149.0 & & 148.8 & & 0.2 & \\
3 & 135.9 & & 135.9 & & 0.0 & \\
4 & 155.6 & & 155.6 & & 0.0 & \\
5 & 132.2 & & 132.2 & & 0.0 & \\
6 & 155.2 & & 155.2 & & 0.0 & \\
7 & 33.0 & 3.24 & 33.0 & 3.23 & 0.0 & 0.01 \\
8 & 21.3 & 2.30 & 21.2 & 2.38 & 0.1 & 0.08 \\
9 & 58.6 & 4.6 & 58.6 & 4.61 & 0.0 & 0.01 \\
10 & 18.3 & 2.50 & 18.3 & 2.54 & 0.0 & 0.04 \\
11, 22 & 123.0, 122.1 & 6.3 & 123.1, 122.1 & 6.28, 6.27 & 0.1, 0 & 0.02, 0.03 \\
12, 23 & 139.5, 139.4 & 6.0 & 139.5, 139.4 & 6.07, 6.04 & 0.0, 0 & 0.07, 0.04 \\
13, 24 & 29.7, 29.5 & 1.78 & 29.7, 29.5 & 1.80 & 0.0, 0 & 0.02 \\
14, 25 & 29.3, 29.2 & 1.40 & 29.4, 29.3 & 1.35 & 0.1, 0.1 & 0.05 \\
15, 26 & 29.95, 29.95 & 1.21 & 29.97, 29.97 & 1.27, 1.23, 1.20 & 0.02, 0.02 & 0.06, 0.02, 0.01 \\
16, 27 & 30.03, 29.99 & 1.21 & 30.04, 30.00 & 1.27, 1.23, 1.20 & 0.01, 0.01 & 0.06, 0.02, 0.01 \\
17, 28 & 30.06, 30.06 & 1.21 & 30.07, 30.07 & 1.27, 1.23, 1.20 & 0.01, 0.01 & 0.06, 0.02, 0.01 \\
18, 29 & 32.6 & 1.21 & 32.6 & 1.27, 1.23, 1.20 & 0.0, 0.06, 0.02, 0.01 \\
19, 30 & 23.3 & 1.25 & 23.4 & 1.27 & 0.1 & 0.02 \\
20, 31 & 14.4 & 0.83 & 14.4 & 0.87 & 0.0 & 0.04 \\
21 & 19.1 & 2.26 & 19.1 & 2.27 & 0.0 & 0.01
\end{align*}
\]