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Improved synthesis of 2,4,6-trialkylpyridines from 1,5-diketoalkanes: the total synthesis of Anibamine†

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Many pyridine syntheses have been developed to date. In this study, we focused on pyridine synthesis with 1,5-diketone derivatives and hydroxylamine. Treatment of simple 1,5-diketoalkanes and hydroxylamine in basic or acidic conditions gave aldol adducts without any pyridine compounds. However, by screening the reaction conditions, we found that acidic conditions produced *via* the formation of oxime intermediates derived from 1,5-diketoalkanes allowed the formation of the corresponding pyridine derivatives. This is the first example of 2,4,6-trialkylpyridine synthesis from quite simple 1,5-diketoalkanes. In order to demonstrate the utility of the reaction, we demonstrated the synthesis of pyridine derivatives and the total synthesis of a 6-substituted pyridyl-natural product, anibamine. This was achieved by following the above methodology using a reported compound as the starting material to give the product in 12% yield.

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Introduction

Pyridine is a crucial heterocyclic framework that features in natural products and has been incorporated into organic materials and pharmaceuticals.[1–3] It is obvious that this structure is a useful scaffold that can be used to create attractive molecules. Hence, the development of methods for pyridine synthesis has been an important and attractive target in organic chemistry. Plenty of methods for pyridine synthesis have been reported to date, for example, metal-catalyzed pyridine syntheses using Fe, Cu, Rh, *etc.*[4a–f] For instance, in 2017, Guan *et al.* reported pyridine synthesis based on a combination of the N–O bond reductive cleavage of ketoxime acetates with the C(sp^3)–N bond oxidative cleavage of *N*,*N*-dimethylaniline *via* a Fe(II)/Fe(III) catalytic cycle.[4a] In the same year, Yoshikai *et al.* developed a copper-catalyzed condensation reaction of oxime acetates and α,β-unsaturated ketimines.[4b] In 2015, Wan *et al.* reported pyridine synthesis *via* the cationic rhodium(I)/MeOBiphep complex-catalyzed [2 + 2 + 2] cycloaddition of oximes with diynes using ethanol.[4c] In contrast, metal-free reactions have also been achieved. One of the most popular methods is the Hantzsch approach. The corresponding symmetrical heterocycles are obtained *via* a cyclodehydration reaction between *in situ*-formed enamino ester and alkylidene malonate intermediates. Subsequent oxidation affords the corresponding aromatized products.[1,5a] In 1906, Chichibabin developed a pseudo-four-component pyridine synthesis based on three equivalents of an enolizable aldehyde and one equivalent of ammonia.[1,5b] In 1957, the Bohlmann–Rahtz reaction was discovered, based on the conjugate addition of an enaminoester to an alkynone followed by thermal cyclodehydration leading to a pyridine core.[1,5c] Recently, in 2016, Deng *et al.* developed a metal-free protocol for the synthesis of substituted pyridines from *O*-acetyl ketoximes and α,β-unsaturated aldehydes.[6a] Rychnovsky *et al.* reported a synthesis combining 1,4-addition, ozonolysis and condensation processes.[6b] Maulide *et al.* reported the metal-free formal [2 + 2 + 2] intermolecular cycloaddition of heteroalkynes and nitriles.[6c] Many substituted pyridine synthesis methods have been developed to date, however, even in these recent reports, it was found that almost all of the synthesized pyridine derivatives have rigid and bulky functionalities including phenyl, naphthyl, furanyl, pyrroyl, pyridyl, thiophenyl and other such groups, or no functionalities, with nothing at the 2,6-positions to prevent side reactions. That is, pyridine derivative synthesis with, for example, alkyl substitution at the 2,6-positions derived from 1,5-diketoalkanes, has not yet been reported. Herein, we demonstrate the synthesis of 2,4,6-trialkylpyridine derivatives from 1,5-diketoalkanes under acidic conditions and apply this methodology to synthesize anibamine (**1**) (Fig. 1).

Anibamine (**1**), isolated from *Aniba* sp. by Jayasuriya *et al.* in 2004, is a novel pyridine quaternary alkaloid that effectively

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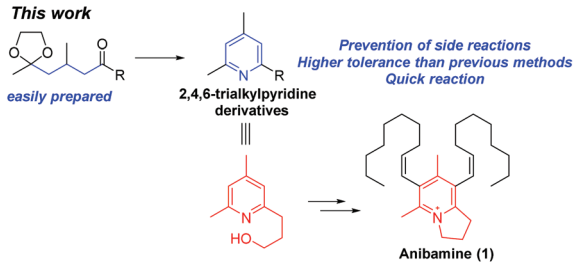
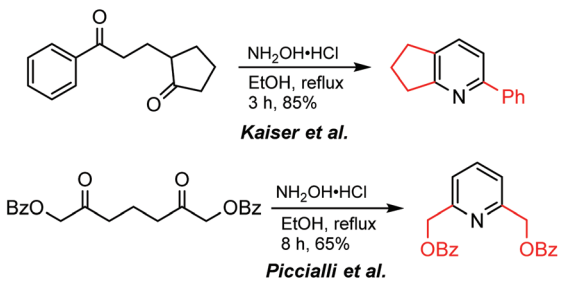


Fig. 1 An overview of the preparation of 2,4,6-trialkylpyridine derivatives and **1**.

competes with ^{125}I-gp120 to bind with the human CCR5 receptor with an IC_{50} value of 1 μM.[7] Li *et al.* reported that **1**, the first and only pyridyl natural product CCR5 antagonist, shares many common binding features with the other known CCR5 ligands in each model of a docking study.[8] Therefore, **1** is an attractive target for novel drug discovery. Previously, the total synthesis of **1** was reported by Zhang's group.[9] The key reaction is the base-mediated pyridine formation involving acetylacetone and cyanoacetamide. However, CuCN, a very toxic reagent, was used and this did not seem to be a suitable strategy for a structure–activity relationship (SAR) study.

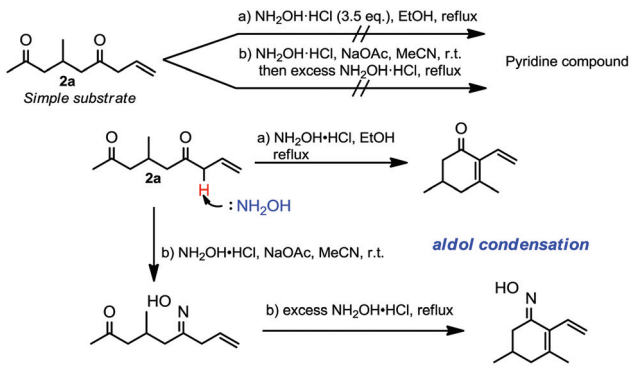
Results and discussion

Metal-free pyridine synthesis tends to require substrates that have bulky and rigid functionalities at the 2,6-positions, as detailed in previous reports.[6a–h] From a reference investigation, we focused on metal-free pyridine cyclization with hydroxylamine, as employed by Kaiser *et al.* and Piccialli *et al.*, and shown in Scheme 1.[10a–k] The method resulting from the classical Knoevenagel route first requires the construction of 1,5-diketones followed by reaction with hydroxylamine and cyclization. The driving force is the elimination of water with the generation of an aromatic system.[10c,d,j] In these cases, the corresponding substrates have rigid and bulky functionalities that prevent side reactions. For this reason, we firstly attempted pyridine synthesis using a simple substrate under the same conditions. However, as a result, an aldol type reaction occurred to give the side adducts shown in Scheme 2.[10a–k] This suggests that substrates with non-bulky and non-rigid functionalities rarely transform the corresponding pyridines *via* the previously reported methods (Schemes 1 and 2).[10a–k]



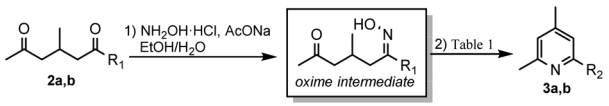
Scheme 1 Metal-free pyridine synthesis using hydroxylamine.

In order to prevent side reactions, the screening of acidic conditions was conducted and acidic conditions were found that gave smooth cyclization after the formation of oxime intermediates. The optimizations of the acidic conditions for pyridine synthesis are shown in Table 1. The 1,5-diketone derivatives **2a–b** reacted with hydroxylamine to produce oxime intermediates, which were exposed to acidic reagents. Several sets of acidic conditions were attempted. The reaction proceeded in HCl and EtOH at reflux, albeit with low yields (Table 1, entries 1 and 2).[11] The alkene isomerized product **3a** was synthesized from **2a** in yields of up to 20%. These conditions were used by Shibuya *et al.*[11] to synthesize 2,6-diphenylpyridines for their research on photochemical reactions. Consequently, we found that the use of acetic acid resulted in conditions that yielded **3a** in 28% yield (Table 1, entry 3), even though the alkene portion was also isomerized when using HCl, which made us consider that thermodynamic stability is relevant. In addition, **3b** was synthesized from **2b** in 38% yield. These conditions were used in the following pyridine synthesis (Table 1).



Scheme 2 The cyclization of simple substrates using hydroxylamine.

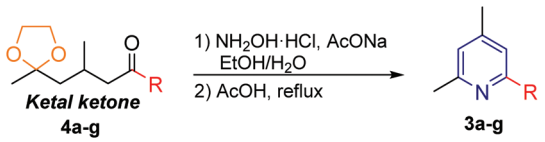
Table 1 Attempted pyridine cyclization under acidic conditions

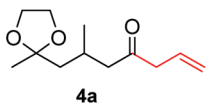
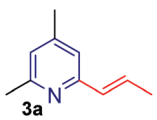
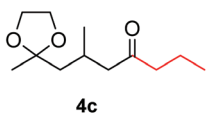
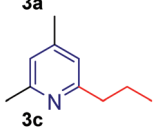
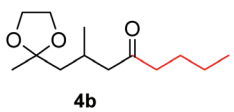
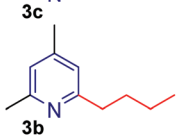
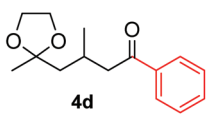
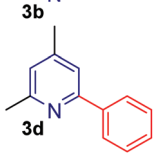
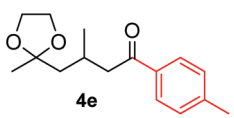
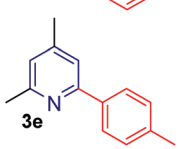
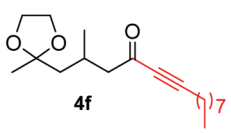
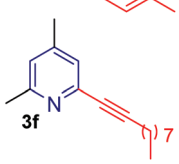
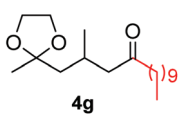
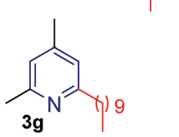
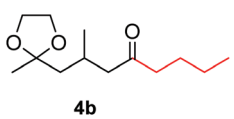
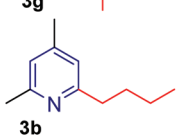


Entry	2a,b/R_1	Condition	3a,b/R_2	Yield (2 steps)
1	2a	2 N HCl/EtOH, ref lux	3a	6%
2	2a	0.5 N HCl/EtOH, ref lux	3a	20%
3	2a	AcOH, ref lux	3a	28%
4	2b	AcOH, ref lux	3b	38%

It was also proposed that 1,5-diketone derivatives may be converted to multiple intermediates using hydroxylamine in reduced chemical yields. Accordingly, one of the two ketones in 1,5-diketone starting materials was protected as a ketal, followed by oxime formation, and pyridine formation proceeded under the acidic conditions shown in Table 2. Using this methodology, we demonstrated the synthesis of 3-substituted pyridine derivatives with a variety of functionalities at the 2-position. A medium length alkyl chain (C3–C4) gave better yields than unblocked substrates (Table 2, entries 1, 2, and 3). Mesylation of the oxime **4b** led to a lower yield (entry 8). The phenyl group was found to barely influence the pyridine synthesis (Table 2, entries 4 and 5), as reported for other metal-free methods.[6,12] Even the very bulky substrates **4f–g** gave the corresponding pyridines (Table 2, entries 6 and 7), albeit in a low yield in the case of **4f**. The reason for this is that Michael addition occurred due to the presence of an oxime hydroxyl group to give a five membered heterocyclic compound, that is, an isoxazole product. To the best of our knowledge, to date, there have been only a few reports on 2,6-dialkyl-pyridine synthesis without rigid and bulky functionalities at the 2,6-positions.[6,12] Therefore, it can be said that this method is useful and has a higher tolerance than previously reported metal-free methods (Table 2). Further screening of acidic reagents to find more suitable acidic conditions is currently underway.

Table 2 Synthesis of substituted pyridines *via* oxime-pyridine cyclization

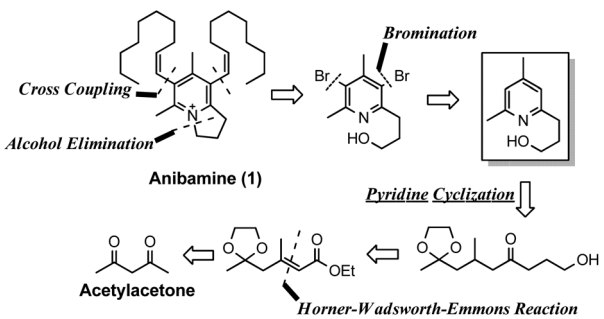


Entry	Starting material	Product	Yield[a,b] (%)
1			37
2			61[c]
3			86
4			88
5			78
6			35[d]
7			65
8			31[e,f]

[a] Isolated yield. [b] 2 steps yield. [c] Reaction was conducted at 110 °C. [d] Methoxyamine was used. [e] Oxime's hydroxy group was mesylated. [f] 3 steps yield.

To demonstrate the higher tolerance of this reaction than that of previously reported metal-free pyridine syntheses, we next decided to apply this method to synthesize **1**, which is a 6-substituted pyridyl-natural product with IC_{50} = 1 μM against CCR5.[7] A structural feature of **1** is that it is a multi-substituted pyridine framework and features two characteristic ten-carbon alkyl chains with *cis* double bonds. A pyridine quaternary ion is embodied by a fused five-membered ring.[9] It is a challenging task to construct a multi-substituted pyridine framework, a well-known target in organic chemistry. For our synthetic approach, we planned to employ our new metal-free pyridine synthesis using 1,5-diketone derivatives. The retrosynthetic analysis is shown in Scheme 3. The pyridine framework of **1** is made up of a pyridine precursor with a terminal hydroxyl group that can be derived from acetylacetone. Bromination, followed by cross coupling, enables the formation of **1** (Scheme 3).

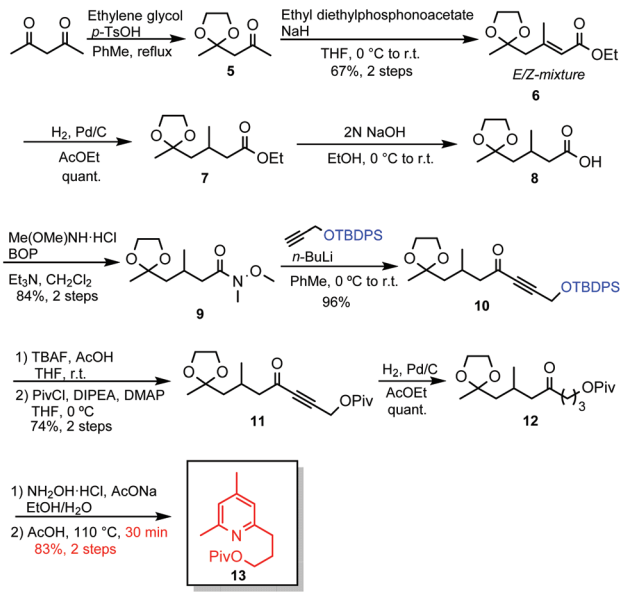
Acetylacetone was used as a starting material to synthesize precursor **12** in the pyridine formation. Firstly, the Horner–Wadsworth–Emmons reaction of ketone **5**, derived from acetylacetone, gave unsaturated ethylester **6** in 67% yield as an *E*/*Z*-mixture.[13,14] After the hydrogenolysis of **6** to obtain saturated ethyl ester **7**, saponification, followed by amidation afforded Weinreb amide **9** in 84% yield over 2 steps. Weinreb amide **9** was a reasonable substrate to produce **10**. A *tert*-butyldiphenylsilyl (TBDPS)-protected propargyl alcohol was used to intro-



Scheme 3 Retrosynthetic analysis of **1**.

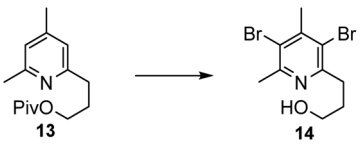
duce a terminal alcohol group, which was then eliminated to close a fused five-membered ring.[15] It is noteworthy that toluene was preferred over tetrahydrofuran (THF) in this nucleophilic substitutional reaction. The hydrogenolysis of **10** afforded a cyclization precursor. The pyridine cyclization method was attempted here, but the desired product was not observed, instead giving a complex mixture, since a nucleophilic attack on oxime by a deprotected hydroxyl group was thought to have occurred. In order to prevent the deprotection of TBDPS in the cyclization step, TBDPS was converted into a pivaloyl group in 74% yield over 2 steps from **10**, followed by the hydrogenolysis of **11**. Finally, the pyridine synthesis of **12** produced the desired pyridine framework **13** in 83% yield. Surprisingly, this cyclization reaction occurred within 30 minutes (Scheme 4).

Next, the bromination conditions of **13** were investigated in order to achieve cross coupling (Table 3). Firstly, we tried the bromination of **13** with NBS/conc. H_2SO_4 at 50 °C, as reported by Rajesh *et al.*[16] However, the desired compound **14** was produced in only 7% yield (Table 3, entry 1). This result indicated that **13** was unreactive because of the existence of alkyl groups at the 2,4,6-positions, that is, resulting in a steric effect. In order to activate the pyridine framework **13**, increased temperature and microwave conditions were applied to produce 22% and 21% yields, respectively (Table 3 entries 2 and 3). The amount of NBS was increased to 100 eq. to give 39% yield (Table 3, entry 4). As a result, bromination with NBS (100 eq.) in conc. H_2SO_4/H_2O, (2 : 1) at 60 °C afforded **14** in 55% yield. It is noteworthy that the bromination of pyridine with no active functionalities was achieved by adding H_2O, since in the reported conditions, a brominated product was produced in a lower yield (Table 3).



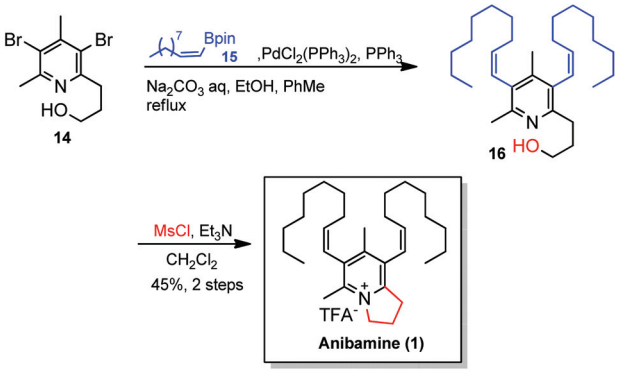
Scheme 4 Synthesis of the pyridine framework **13**.

Table 3 Screening of conditions for the bromination of **13**



Entry	Condition	Yield[a] (%)
1	NBS, conc. H_2SO_4, 50 °C[b]	7.1
2	NBS, conc. H_2SO_4, 60 °C[b]	22
3	NBS, conc. H_2SO_4, 60 °C,MW[c]	21
4	NBS, conc. H_2SO_4, 60 °C[c]	39
5	NBS, conc. H_2SO_4/H_2O = 2 : 1, 60 °C[c]	55

[a] Isolated yield. [b] NBS (12 eq.). [c] NBS (100 eq.).



Scheme 5 The synthesis of **1**.

At the beginning of the cross coupling, we attempted a Sonogashira cross coupling with 1-decyne and **14**, which did not give any coupling products due to steric hindrance. Next, Suzuki–Miyaura cross coupling was employed. Boron reagent **15** was prepared *Z*-selectively *via* conditions described by Brown *et al.* and Takagi *et al.*[17a–d] By Suzuki coupling dibromopyridine **14** and organo boron **15** in the presence of $PdCl_2(PPh_3)_2$, two alkenyl chains **15** were successfully introduced to the pyridine framework **14** to give **16**.[18] Finally, elimination of the hydroxyl group of **16** with MsCl allowed the formation of the desired five-membered ring.[9,18] The crude product was purified by preparative HPLC to afford **1** as a trifluoroacetic acid salt in 45% yield over two steps and a mixture of its isomers (*E*,*Z* and *Z*,*E*) as trifluoroacetic acid salts in 29% yield over two steps.[9] We observed that the NMR spectrum of the synthesized **1** matched that of the natural compound (Scheme 5).[7]

Experimental

General

All solvents used were reagent grade. CH_2Cl_2 was distilled over CaH_2 and THF over Na. All commercial reagents were of the highest purity available. An oil bath was used for heating. ^1H (400, 500 or 600 MHz) and ^{13}C NMR (100, 125 or 150 MHz)

spectra were recorded on JNM-ECX400, JNM-ECX500 or JNM-ECA600 spectrometers. Chemical shifts are expressed in ppm relative to $CHCl_3$ (7.26 ppm for ^1H and 77.16 ppm for ^{13}C) and CD_3CN (1.94 ppm for ^1H and 1.32 and 118.26 ppm for ^{13}C). Analytical TLC was performed on Merck Silica gel $60F_{254}$. Crude products were purified by column chromatography on Silica Gel 60 N [Kanto, particle size, (spherical, neutral) 63–210 μm or 100–200 μm]. Analytical HPLC was carried out using a COSMOSIL 5C18-AR-II column (4.6 ID × 150 mm) with a gradient of MeCN (0.1% TFA) in H_2O (0.1% TFA) at a run time of 35 min (flow rate of 1 mL min^{-1}), with a SHIMADZU SPD-10A used as a UV-Vis detector, HITACHI L-6000 Pump and HITACHI L-6200 Intelligent Pump. Preparative HPLC was performed using a COSMOSIL 5C18-AR-II column (10 ID × 250 mm) with a linear gradient of MeCN (0.1% TFA) in H_2O (0.1% TFA) at a run time of 35 min (flow rate of 2 mL min^{-1}), with a SHIMADZU SPD-10Ai used as a UV-Vis detector and HITACHI L-6200 Intelligent Pump. UV measurements were recorded at a wavelength of 254 nm. High-resolution mass spectra (HRMS) were obtained using a JEOL AccuTOF JMS-T100LC (ESIMS).

***t*-Butyldiphenylsilyloxy-2-propyne.** Imidazole (817 mg, 12.0 mmol) and TBDPSCl (1.84 mL, 7.20 mmol) were added to a solution of propargyl alcohol (355 μL, 6.00 mmol) in DMF (20 mL) at 0 °C. The solution was allowed to warm to room temperature and was then stirred overnight. The reaction mixture was added to a saturated aqueous solution of NH_4Cl and the aqueous layer was extracted using Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give *t*-butyldiphenylsilyloxy-2-propyne (1.40 g, 79% yield). This product was used without further purification.[15]

Bromodecyne. NBS (5.0 g, 3.40 mmol) and $AgNO_3$ (1.0 g, 6.0 mmol) were added to a solution of 1-decyne (3.62 mL, 20 mmol) in acetone (500 mL) at room temperature and stirred under a shading mask overnight. The reaction mixture was filtered carefully and concentrated *in vacuo*. The residue was purified by column chromatography (hexane) to give 1-bromo-1-decyne (3.95 g, 90%) as a colorless oil.[17a]

[*Z*]-1-Bomo-1-decene. 1-Bromodecyne (508 mg, 2.30 mmol) in THF (0.4 mL) was added to a solution of 9-BBN (1.0 M in THF, 5.52 mL, 2.76 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and was then stirred for 30 h. After the evaporation of the solvent *in vacuo*, the residue was added to hexane (2.3 mL) and AcOH (158 μL, 2.76 mmol). After stirring for 30 h, ethanolamine (333 μL, 5.52 mmol), H_2O and hexane were added to the reaction mixture. After the separation of the organic layers, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane) to give (*Z*)-1-bromo-1-decene (259 mg, 51% over 2 steps, $E:Z = 4:96$) as a yellow oil.[17b,c]

(*Z*)-2-(Dec-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15). $PdCl_2(PPh_3)$ (47 mg, 0.067 mmol), Ph_3P (35 mg, 0.134 mmol), bis(pinacolato)diboron (623 mg, 2.45 mmol), PhOH (315 mg, 3.35 mmol) and *t*-BuOK (375 mg, 3.35 mmol) were added to a flask. The flask was flushed with nitrogen and then charged with toluene (15 mL) and 1-bromooctyne (488 mg, 2.23 mmol). The mixture was stirred at 50 °C for 9 h. The reaction mixture was then added to H_2O and extracted with toluene. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane 1 : 20 v/v) to give **15** (364 mg, 61%, $E:Z = 4:96$) as a yellow oil.[17d]

(2*E*,*Z*)-Ethyl 3-methyl-5-(2,2-dimethyldioxolane)-hex-2-enoate (6). A stirring solution of 2,4-pentanedione (40.1 g, 400 mmol), 1,2-ethanediol (24.8 g, 400 mmol) and *p*-TsOH (catalytic amount) in toluene (130 mL) was refluxed for 24 h in Dean–Stark apparatus. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. To the residue was added a saturated aqueous solution of $NaHCO_3$ and AcOEt. The organic layer was dried over $MgSO_4$, filtered and removed under reduced pressure. The resulting residue, **5**, was used in the following reaction without further purification (39.1 g, 68% crude yield). Ethyl diethylphosphonoacetate (15.7 g, 70.0 mmol) in THF (5 mL) was added to a solution of THF (20 mL) and NaH (2.80 g, 70.0 mmol) at 0 °C. After the mixture was stirred for 30 min, residue **5** (2.90 g, 20.0 mmol) in THF (5 mL) was added to the reaction mixture at 0 °C, and the solution was then allowed to gradually warm to room temperature with stirring overnight. The reaction was quenched by the addition of a saturated solution of aqueous NH_4Cl at 0 °C. After the separation of the organic layers, the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 5 v/v) to give **6** (*E*/*Z*-mixture, 4.23 g, 67% yield over 2 steps) as a pale yellow oil.[13,14] ^1H NMR (600 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 0.9H), 1.26 (t, J = 7.2 Hz, 2.1H), 1.31 (s, 2.1H), 1.32 (s, 0.9H), 1.96 (s, 0.9H), 2.23 (s, 2.1H), 2.44 (s, 1.5H), 3.07 (s, 0.5H), 3.91–3.94 (m, 4H), 4.13 (q, J = 7.2 Hz, 2H), 5.74 (s, 0.75H), 5.77 (s, 0.25H) as an *E*,*Z*-mixture. ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.4, 20.2, 24.2, 24.4, 26.6, 41.2, 49.7, 59.68, 59.70, 64.6, 64.8, 109.5, 110.0, 119.4, 119.8, 154.5, 155.3, 166.5, 166.7 as an *E*,*Z*-mixture. IR (film) ν max cm^{-1}: 2983, 1714, 1645, 1446, 1379, 1149, 1042. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{18}O_4Na$ $[M + Na]^+$ 237.1103, found 237.1114.

Ethyl 3-methyl-5-(2,2-dimethyldioxolane)-hexanoate (7). Pd/C (catalytic amount) was added to a solution of **6** (645 mg, 3.01 mmol) in AcOEt (12 mL) and the reaction mixture was stirred for 2 h under a hydrogen atmosphere. The reaction mixture was filtered and the solvent was removed under reduced pressure. The desired product **7** was obtained as a colorless oil (650 mg, 100% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.8 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.33 (s, 3H), 1.57 (dd, J = 13.6, 5.2 Hz, 1H), 1.68 (dd, J = 14.4, 6.0 Hz, 1H), 2.11 (dd, J = 14.8, 8.4 Hz, 1H), 2.15–2.24 (m, 1H), 2.51 (dd, J = 15.2, 5.6 Hz, 1H), 3.92–3.94 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.2, 24.1, 26.5, 42.2, 44.9, 60.1, 64.4 (C2), 110.1, 173.2. IR (film) ν max cm^{-1}: 2982, 1734,

1374, 1189, 1074, 1035. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{21}O_4$ $[M + H]^+$ 217.1440, found 217.1477.

***N*-Methyl-*N*,3-dimethyl-5-(2,2-dimethyldioxolane)-hexamide (9).** To a solution of **7** (650 mg, 6.24 mmol) in EtOH (10 mL), 2 N NaOH (3.0 mL, 12.5 mmol) was added at 0 °C and the resulting mixture was stirred at room temperature overnight. The organic solvent was carefully removed under reduced pressure. A saturated aqueous solution of NH_4Cl, 1 M HCl (6 mL) and Et_2O was added to the mixture to achieve separation. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **8** (524 mg, 93% crude yield) as a colorless oil. To a solution of crude **8** in dry CH_2Cl_2 (10 mL), Et_3N (1.55 mL, 11.1 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.543 g, 5.56 mmol), and BOP reagent (2.46 g, 5.56 mmol) were added at 0 °C, and the reaction mixture was then stirred at room temperature overnight. After stirring, the mixture was added to H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (MeOH–$CHCl_3$, 3 : 97 v/v) to give **9** (0.582 g, 84% yield over 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 1.00 (d, J = 6.4 Hz, 3H), 1.33 (s, 3H), 1.57 (dd, J = 14.8, 6.4 Hz, 1H), 1.70 (dd, J = 13.6, 5.2 Hz, 1H), 2.23–2.30 (m, 2H), 2.58 (dd, J = 18.4, 8.0 Hz, 1H), 3.17 (s, 3H), 3.66 (s, 3H), 3.92 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 24.2, 26.1, 32.2, 39.7, 45.3, 61.3, 64.46, 64.49, 110.3, 174.2. IR (film) ν max cm^{-1}: 2960, 1713, 1660, 1379, 1166, 1067, 1004. HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{21}NO_4Na$ $[M + Na]^+$ 254.1368, found 254.1389.

Synthetic procedure for the pyridine precursor (see the ESI† for the other procedures):

4-Methyl-2-(2,2-dimethyldioxolane)-decan-6-one (4b). *n*-BuLi (2.5 M in hexane, 0.5 mL, 0.938 mmol) was added in a dropwise manner to a solution of **9** (107 mg, 0.469 mmol) in Et_2O (10 mL) at −78 °C under a nitrogen atmosphere and the reaction was stirred for 3 h, maintaining the temperature at −78 °C. The reaction mixture was quenched by adding a saturated aqueous solution of NH_4Cl at −78 °C and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 4 v/v) to give **4b** (84.7 mg, 80% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.6 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.26 (qt, J = 7.6, 7.5 Hz, 2H), 1.28 (s, 3H), 1.46–1.53 (m, 3H), 1.57 (dd, J = 14.0, 6.4 Hz, 1H), 2.17–2.26 (m, 2H), 2.33 (t, J = 7.2 Hz, 2H), 2.56 (dd, J = 19.2, 7.6 Hz, 1H), 3.91–3.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.6, 22.4, 24.1, 25.3, 26.0, 43.1, 45.2, 50.6, 64.37, 64.41, 110.2, 211.2. IR (film) ν max cm^{-1}: 2957, 2875, 1713, 1373. HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$ 251.1623, found 251.1603.

6-Methyl-8-(2,2-dimethyldioxolane)-nonen-4-one (4a). 237 mg, 85% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 6.4 Hz, 3H), 1.31 (s, 3H), 1.56 (dd, J = 14.4, 5.6 Hz, 1H), 1.63 (dd, J = 14.0, 6.8 Hz, 1H), 2.22–2.31 (m, 2H), 2.64 (dd, J = 19.6, 8.4 Hz, 1H), 3.15 (d, J = 6.8 Hz, 2H), 3.87–3.95 (m, 4H), 5.12 (dd, J = 17.6, 1.2 Hz, 1H), 5.17 (dd, J = 10.8, 1.6 Hz, 1H), 5.86–5.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.2, 25.2, 45.2, 48.4, 50.2, 64.4, 64.5, 110.2, 118.8, 130.9, 208.6. IR (film) ν max cm^{-1}: 3080, 2981, 2956, 2880, 1714, 1638, 1377. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ 235.1310, found 235.1302.

3-Methyl-5-(2,2-dimethyldioxolane)-1-phenylhexanone (4d). 60.2 mg, 53% yield, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H), 1.65 (dd, J = 14.4, 6.6 Hz, 1H), 1.76 (dd, J = 14.4, 7.2 Hz, 1H), 2.40–2.45 (m, 1H), 2.77 (dd, J = 16.2, 8.4 Hz, 1H), 3.21 (dd, J = 16.8, 4.8 Hz, 1H), 3.89–3.93 (m, 4H), 7.45 (t, J = 7.2 Hz, 2H), 7.55 (tt, J = 7.2, 1.2 Hz, 1H), 7.96 (dt, J = 7.8, 1.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 24.3, 25.9, 45.5, 46.5, 64.46, 64.51, 110.3, 128.2, 128.7, 132.9, 137.6, 200.4. IR (film) ν max cm^{-1}: 3060, 2957, 2879, 1685, 1598. HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{20}O_3Na$ $[M + Na]^+$ 271.1310, found 271.1324.

***p*-Methylphenyl-3-methyl-5-(2,2-dimethyldioxolane)-hexanone (4e).** 32.6 mg, 79% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 7.2 Hz, 3H), 1.35 (s, 3H), 1.64 (dd, J = 14.8, 6.4 Hz, 1H), 1.76 (dd, J = 14.8, 6.8 Hz, 1H), 2.41 (s, 3H), 2.45–2.37 (m, 1H), 2.73 (dd, J = 16.0, 8.4 Hz, 1H), 3.18 (dd, J = 16.0, 4.8 Hz, 1H), 3.89–3.94 (m, 4H), 7.25 (d, J = 9.2 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.6, 21.8, 24.3, 26.0, 45.5, 46.4, 64.48, 64.50, 110.3, 128.4, 129.3, 135.2, 143.7, 200.1. IR (film) ν max cm^{-1}: 2956, 2878, 1681, 1606, 1455. HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467, found 285.1466.

4-Methyl-2-(2,2-dimethyldioxolane)-7-hexadecyn-6-one (4f). 125 mg, 93% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 1.20–1.31 (brs, 10H), 1.33 (s, 3H), 1.37–1.40 (m, 2H), 1.65 (dd, J = 14.8, 6.4 Hz, 1H), 1.57 (dd, J = 14.4, 6.0 Hz, 1H), 2.35 (t, J = 7.2 Hz, 2H), 2.30–2.40 (m, 2H), 2.78 (dd, J = 19.6, 8.4 Hz, 1H), 3.89–3.96 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.1, 21.4, 22.8, 24.2, 26.0, 27.9, 29.0, 29.1, 29.2, 31.9, 45.1, 53.4, 64.48, 64.52, 81.3, 94.2, 110.1, 188.3. IR (film) ν max cm^{-1}: 2928, 2857, 2211, 1672. HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{32}O_3Na$ $[M + Na]^+$ 331.2249, found 331.2259.

6-Methyl-8-(2,2-dimethyldioxolane)-nonan-4-one (4c). Pd/C (catalytic amount) was added to a solution of **4a** (159 mg, 0.749 mmol) in AcOEt (1.4 mL) and the reaction mixture was stirred overnight under a hydrogen atmosphere. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The desired product **4c** (161 mg, 101%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 8.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.32 (s, 3H), 1.54–1.64 (m, 2H), 1.54 (dd, J = 16.0, 7.2 Hz, 1H), 1.62 (dd, J = 14.4, 6.4 Hz, 1H), 2.19–2.30 (m, 2H), 2.35 (dt, J = 7.2, 0.8 Hz, 2H), 2.54–2.63 (m, 1H), 3.87–3.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 17.3, 21.7, 24.2, 25.4, 45.3, 45.4, 50.7, 64.44, 64.48, 110.3, 211.1. IR (film) ν max cm^{-1}: 2960, 2876, 1711, 1376. HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{22}O_3Na$ $[M + Na]^+$ 237.1467, found 237.1444.

4-Methyl-2-(2,2-dimethyldioxolane)-7-hexadecan-6-one (4g). Pd/C (catalytic amount) was added to a solution of **4f** (125 mg,

0.405 mmol) in AcOEt (1.4 mL) and the reaction mixture was stirred overnight under a hydrogen atmosphere. The reaction mixture was then filtered and the solvent was removed under reduced pressure to give the desired product **4g** (123 mg, 97% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 1.25 (brs, 14H), 1.32 (s, 3H), 1.50–1.65 (m, 2H), 1.55 (dd, J = 14.5, 5.5 Hz, 1H), 1.62 (dd, J = 15.0, 6.5 Hz, 1H), 2.20–2.29 (m, 2H), 2.36 (dt, J = 7.0, 2.0 Hz, 2H), 2.59 (m, 1H), 3.88–3.94 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 21.7, 22.8, 24.0, 24.2, 25.4, 29.43, 29.46, 29.59, 29.64, 29.7, 32.0, 43.5, 45.3, 50.7, 64.45, 64.49, 110.3, 211.3. IR (film) ν max cm^{-1}: 2925, 2854, 1713, 1465, 1375. HRMS (ESI) m/z: calcd for $C_{19}H_{36}O_3Na$ $[M + Na]^+$ 335.2562, found 335.2580.

Synthetic procedure for the pyridine (see the ESI† for the other procedures):

2-Butyl-4,6-dimethylpyridine (3b). AcONa (33 mg, 0.402 mmol) and hydroxylamine hydrochloride (18.6 mg, 0.268 mmol) were added to a solution of **4b** (30.9 mg, 0.134 mmol) in EtOH (0.5 mL) and H_2O (0.5 mL) and the reaction mixture was stirred for 5 h. After stirring, the reaction mixture was added to H_2O and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (1.68 mL) was refluxed for 12 h. The reaction mixture was then cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 2 v/v) to give **3b** (19.1 mg, 86% yield over 2 steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.6 Hz, 3H), 1.37 (tq, J = 7.6, 7.6 Hz, 2H), 1.65 (tt, J = 8.0, 7.6 Hz, 2H), 2.25 (s, 3H), 2.46 (s, 3H), 2.69 (t, J = 8.0 Hz, 2H), 6.75 (s, 1H), 6.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 21.0, 22.8, 24.5, 32.5, 38.3, 120.5, 121.5, 147.4, 157.5, 161.8. IR (film) ν max cm^{-1}: 2956, 2928, 2860, 1608, 1570, 1460, 1375, 1220, 1037. HRMS (EI) m/z: calcd for $C_{11}H_{17}N$ $[M]^+$ 163.1361, found 163.1384.

4,6-Dimethyl-2-(propen-1-ny)-pyridine (3a). 28.3 mg, 37% yield over 2 steps, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (dd, J = 7.0, 2.0 Hz, 2.82H), 2.04 (dd, J = 7.5, 3.5 Hz, 0.18H), 2.27 (s, 2.82H), 2.30 (s, 0.18H), 2.48 (s, 2.82H), 2.50 (s, 0.18H), 5.95 (dq, J = 15.0, 9.0 Hz, 0.06H), 6.45 (dq, J = 19.5, 2.0 Hz, 1H), 6.67 (dq, J = 19.5, 8.5 Hz, 0.94H), 6.79 (s, 0.94H), 6.81 (s, 0.06H) 6.88 (s, 0.94H) 6.90 (s, 0.06H) as *E*,*Z*-mixture (*E* : *Z* = 94 : 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 21.0, 24.5, 118.8, 122.3, 130.2, 131.7, 147.6, 155.6, 157.8. IR (film) ν max cm^{-1}: 2925, 1603, 1449, 968, 848, 665. HRMS (EI) m/z: calcd for $C_{10}H_{13}N$ $[M]^+$ 147.1048, found 147.1050.

4,6-Dimethyl-2-(propanyl)-pyridine (3c). 38.9 mg, 61% yield over 2 steps, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.953 (t, J = 7.8 Hz, 3H), 1.70 (dq, J = 7.8, 7.8 Hz, 2H), 2.26 (s, 3H), 2.47 (s, 3H), 2.67 (t, J = 7.8 Hz, 2H), 6.76 (s, 1H), 6.78 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 21.0, 23.6, 24.5, 40.5, 120.7, 121.5, 147.5, 157.5, 161.6. IR (film) ν max cm^{-1}: 2955, 2925, 2863, 1716, 1608, 1456, 1381, 1265. HRMS (EI) m/z: calcd for $C_{10}H_{15}N$ $[M]^+$ 149.1205, found 149.1197.

4,6-Dimethyl-2-phenylpyridine (3d). 8.0 mg, 88% yield over 2 steps, pale orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.59 (s, 3H), 6.94 (s, 1H), 7.34 (s, 1H), 7.39 (tt, J = 7.3, 1.5 Hz, 1H), 7.46 (t, J = 7.3 Hz, 2H), 7.97 (dt, J = 6.5, 2.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 24.7, 118.9, 122.7, 127.2, 128.67, 128.73, 140.1, 147.9, 157.1, 158.2. IR (film) ν max cm^{-1}: 3060, 3029, 2955, 2925, 2854, 2359, 2338, 1741, 1607, 1456, 1230, 1029. HRMS (ESI) m/z: calcd for $C_{13}H_{14}N$ $[M + H]^+$ 184.1126, found 184.1100.

2-*p*-Methylphenyl-4,6-dimethylpyridine (3e). 16.4 mg, 78% yield over 2 steps, pink oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.40 (s, 3H), 2.57 (s, 3H), 6.91 (s, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.31(s, 1H), 7.86 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.4, 24.5, 118.7, 122.6, 127.1 129.5, 137.0, 138.7, 148.1, 157.0, 158.0. IR (film) ν max cm^{-1}: 3032, 2923, 2855, 1605, 1566, 1515, 1454, 1231, 1036. HRMS (ESI) m/z: calcd for $C_{14}H_{16}N$ $[M + H]^+$ 198.1283, found 198.1266.

2-Decynyl-4,6-dimethylpyridine (3f). 14.4 mg, 36% yield over 2 steps, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.872 (t, J = 6.9 Hz, 3H), 1.24–1.30 (brs, 10H), 1.41–1.44 (m, 2H), 1.61 (tt, J = 7.5, 7.2 Hz, 2H), 2.26 (s, 3H), 2.40 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 6.87 (s, 1H), 7.03 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 19.5, 20.8, 22.8, 24.5, 28.6, 29.16, 29.26, 29.31, 32.0, 80.6, 90.4, 123.2, 125.0, 143.1, 147.4, 158.5. IR (film) ν max cm^{-1}: 2926, 2855, 2229, 1601. HRMS (ESI) m/z: calcd for $C_{17}H_{26}N$ $[M + H]^+$ 244.2065 found, 244.2063.

2-Decanyl-4,6-dimethylpyridine (3g). 37.3 mg, 65% yield over 2 steps, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.865 (t, J = 6.8 Hz, 3H), 1.24 (brs, 14H), 1.66 (tt, J = 7.6, 7.6 Hz, 2H), 2.25 (s, 3H), 2.47 (s, 3H), 2.68 (t, J = 8.0 Hz, 2H), 6.76 (s, 1H), 6.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.0, 22.8, 24.4, 29.5, 29.68 (C2), 29.70, 29.73, 30.5, 32.0, 38.6, 120.6, 121.5, 147.5, 157.5, 161.9. IR (film) ν max cm^{-1}: 2925, 2853, 1608, 1571, 1458, 1374, 1218, 1036. HRMS (ESI) m/z: calcd for $C_{17}H_{30}N$ $[M + H]^+$ 248.2378, found 248.2397.

5-Methylnonen-4,8-dione (2a). To a solution of **4a** (28.7 mg, 0.135 mmol) in acetone (1.4 mL) and H_2O (1.4 mL), *p*-TsOH (catalytic amount) was added and the reaction mixture was stirred at 40 °C for 4 h. A saturated aqueous solution of $NaHCO_3$ was added to the mixture at room temperature and the aqueous phase was extracted with AcOEt. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 5 v/v) to give **2a** (21.8 mg, 96% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 7.0 Hz, 3H), 2.11 (s, 3H), 2.30 (dd, J = 16.5, 6.5 Hz, 1H), 2.33 (dd, J = 16.5, 7.0 Hz, 1H), 2.42–2.53 (m, 3H), 3.14 (d, J = 7.5 Hz, 2H), 5.12 (ddt, J = 18.0, 2.0, 1.5 Hz, 1H), 5.17 (dd, J = 10.0, 1.0 Hz, 1H), 5.84–5.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 24.9, 30.0, 47.7, 48.3, 49.7, 118.5, 130.3, 207.6, 207.8. IR (film) ν max cm^{-1}: 2960, 2879, 2360, 1714, 1638, 1406, 1368, 1168, 1043, 994, 922. HRMS (EI) m/z: calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1150.

4-Methyldecan-2,6-dione (2b). From **4b** (29.1 mg, 0.175 mmol), the same conditions as **2a** were used to afford **2b** (35.1 mg, quant.) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.29 (qt, J = 7.6, 7.2 Hz, 2H), 1.53 (tt, J = 7.8, 7.8 Hz, 2H), 2.12 (s, 3H), 2.28 (dd, J = 7.8, 3.0 Hz, 1H), 2.31 (dd, J = 7.2, 3.0 Hz, 1H), 2.36–2.47 (m, 4H), 2.50 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 20.3, 22.5, 25.5, 26.0, 30.4, 43.1, 49.3, 50.4, 208.5, 210.7. IR (film) ν max cm^{-1}: 2959, 2933, 2874, 1714. HRMS (EI) m/z: calcd for $C_{11}H_{20}O_2$ $[M]^+$ 184.1463, found 184.1442.

***t*-Butyldiphenylsiloxy-6-methyl-8-(2,2-dimethyldioxolane)-2-nonyn-4-one (10).** *n*-BuLi (2.5 M in hexane, 1.73 mL, 4.32 mmol) was added to a solution of *t*-butyldiphenylsilyloxy-2-propyne (1.27 g, 4.32 mmol) in toluene (5 mL) at −78 °C under a nitrogen atmosphere. After 30 min at 0 °C, **9** (500 mg, 2.16 mmol) in toluene (5 mL) was added at −78 °C and the reaction mixture was allowed to warm to room temperature. After stirring for 12 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl at 0 °C. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 6 v/v) to give **10** (0.972 g, 96% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$,) δ 0.98 (d, J = 6.4 Hz, 3H), 1.06 (s, 9H), 1.32 (s, 3H), 1.58 (dd, J = 14.8, 6.0 Hz, 1H), 1.64 (dd, J = 14.0, 6.4 Hz, 1H), 2.29 (dd, J = 15.6, 8.0 Hz, 1H), 2.31–2.36 (m, 1H), 2.76 (dd, J = 15.2, 4.0 Hz, 1H), 3.91 (m, 4H), 4.45 (s, 2H), 7.38–7.47 (m, 6H), 7.68–7.71 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.5, 24.2, 25.7, 26.7, 45.0, 52.6, 53.0, 64.46, 64.53, 84.5, 89.7, 110.1, 128.0, 130.2, 132.6, 135.7, 187.5. IR (film) ν max cm^{-1}: 3071, 3049, 2957, 2932, 2858, 2213, 1676, 1428, 1112. HRMS (ESI) m/z: calcd for $C_{28}H_{36}O_4SiNa$ $[M + Na]^+$ 487.2281, found 487.2253.

6-Methyl-8-(2,2-dimethyldioxolane)-1-pivaloyloxy-2-nonyn-4-one (11). To a solution of AcOH (11.5 μL, 0.165 mmol) and TBAF (0.2 mL, 0.165 mmol) in THF (0.4 mL), a solution of **10** (56.3 mg, 0.11 mmol) in THF (0.4 mL) was added at room temperature. After stirring for 5 min, the reaction mixture was added to a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the alcohol product. To a solution of the obtained alcoholic product in THF (0.4 mL), DIPEA (371 μL, 2.2 mmol), DMAP (catalytic amount) and PivCl (54.3 mL, 0.44 mmol) were added at 0 °C and the mixture was stirred overnight. The reaction mixture was added to a saturated aqueous solution of NH_4Cl at 0 °C and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt–hexane, 1 : 5 v/v) gave **11** (27.9 mg, 74% yield over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, J = 6.0 Hz, 3H), 1.23 (s, 9H), 1.32 (s, 3H), 1.60 (dd, J = 14.5, 5.5 Hz, 1H), 1.65 (dd, J = 14.0, 6.5 Hz, 1H), 2.32–2.37 (m, 1H), 2.34 (dd, J = 17.5, 8.5 Hz, 1H), 2.84 (dd, J = 15.5, 4.0 Hz, 1H), 3.91–3.94 (m, 4H), 4.81 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 24.3, 25.7, 27.2, 38.9, 45.1, 51.7, 53.1, 64.5, 64.6, 85.2, 110.1, 177.6, 187.1. IR (film) ν max cm^{-1}: 2978, 2877, 1740, 1679, 1137. HRMS (ESI) m/z: calcd for $C_{17}H_{26}O_5Na$ $[M + Na]^+$ 333.1678, found 333.1653.

6-Methyl-8-(2,2-dimethyldioxolane)-1-pivaloyloxy-2-nonan-4-one (12). Pd/C (catalytic amount) was added to a solution of **11** (74.1 mg, 0.239 mmol) in AcOEt (10 mL), which was then stirred overnight under a hydrogen atmosphere. The reaction mixture was then filtered and the solvent was removed under reduced pressure to give the desired product **12** (76.1 mg, 101% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.4 Hz, 3H), 1.17 (s, 9H), 1.30 (s, 3H), 1.55 (dd, J = 14.8, 5.2 Hz, 1H), 1.60 (dd, J = 14.8, 6.4 Hz, 1H), 1.89 (quintet, J = 6.8 Hz, 2H), 2.23 (dd, J = 14.8, 5.6 Hz, 1H), 2.27–2.23 (m, 1H), 2.41 (dt, J = 18.0, 6.8 Hz, 1H), 2.47 (dt, J = 17.6, 7.2 Hz, 1H), 2.60 (dd, J = 19.6, 8.4 Hz, 1H), 3.88–3.92 (m, 4H), 4.03 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.8, 24.1, 25.4, 27.3, 38.9, 39.5, 45.2, 50.7, 63.7, 64.4, 64.5, 110.2, 178.6, 209.7. IR (film) ν max cm^{-1}: 2960, 2876, 1727, 1285, 1158. HRMS (ESI) m/z: calcd for $C_{17}H_{30}O_5Na$ $[M + Na]^+$ 337.1991, found 337.2003.

4,6-Dimethyl-2-(3-pivaloyloxy)-propylpyridine (13). AcONa (563 mg, 6.86 mmol) and hydroxylamine hydrochloride (191 mg, 2.74 mmol) were added to a solution of **12** (216 mg, 0.686 mmol) in EtOH (0.3 mL) and H_2O (0.3 mL) and the reaction mixture was stirred for 4 h. After completion of the reaction, H_2O was added to the mixture and the aqueous layer was then extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the oxime intermediate. A stirring solution of the oxime intermediate in AcOH (8.6 mL) was heated to 110 °C for 30 min. The reaction mixture was then cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was added to a saturated aqueous solution of $NaHCO_3$ and then extracted with CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 4 v/v) to give **13** (142 mg, 83% yield over 2 steps) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (s, 9H), 2.08–2.02 (m, 2H), 2.26 (s, 3H), 2.47 (s, 3H), 2.77 (t, J = 7.8 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 6.76 (s, 1H), 6.80 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0, 24.4, 27.3, 28.9, 34.7, 38.9, 64.1, 120.8, 121.9, 147.7, 157.8, 160.3, 178.7. IR (film) ν max cm^{-1}: 2961, 2872, 1727, 1609, 1284, 1157, 1038. HRMS (ESI) m/z: calcd for $C_{15}H_{24}NO_2$ $[M + H]^+$ 250.1807, found 250.1808.

3,5-Dibromo-4,6-dimethyl-2-propanolpyridine (14). NBS (2.3 g, 13 mmol) was added to a solution of **13** (32.3 mg, 0.130 mmol) in conc. H_2SO_4 (2 mL) and H_2O (1 mL) at 60 °C and the reaction mixture was stirred for 4 d at 60 °C. The mixture was then poured into crushed ice and 4 M NaOH and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 1 v/v) to give **14** (23.0 mg, 55%) as a white solid. Mp 64–66 °C. ^{1}H NMR

(600 MHz, $CDCl_3$) δ 2.00 (quintet, J = 6.0 Hz, 2H), 2.62 (s, 6H), 3.10 (t, J = 7.2 Hz, 2H), 3.26 (brs, 1H), 3.69 (t, J = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 25.7, 30.3, 35.0, 62.4, 121.2, 121.7, 147.4, 155.1, 157.5. IR (film) ν max cm^{-1}: 3347, 2927, 2870, 1548, 1439, 1388, 1042, 756. HRMS (ESI) m/z: calcd for $C_{10}H_{14}NOBr_2$ $[M + H]^+$ 321.9442, found 321.9467.

Anibamine (1) . $PdCl_2(PPh_3)_2$ (1.6 mg, 2.20 μmol), PPh_3 (1.2 mg, 4.40 μmol), and 3,5-dibromo-4,6-dimethyl-2-propanol-pyridine (17.8 mg, 55.1 μmol) were stirred in toluene (0.36 mL) and Na_2CO_3 aq. (2 M, 0.2 mL) under nitrogen for 0.5 h. A solution of diisopropyl (*Z*)-1-decenylboronate (59 mg, 220 μmol) in EtOH (0.2 mL) was added to the mixture, which was then refluxed for 10 h before being diluted with AcOEt. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (AcOEt–hexane, 1 : 1 v/v) to give the coupling product. This compound was reacted on without further purification. To a solution of the product in CH_2Cl_2 (0.15 mL), Et_3N (60 μL, 496 μmol) and MsCl (30 μL, 331 μmol) were added at 0 °C and then the reaction mixture was allowed to warm to room temperature. After stirring overnight, the reaction mixture was then added to H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by RP-HPLC to give anibamine (**1**) (13.4 mg, 45% over 2 steps) as a yellow oil.[9,18] ^{1}H NMR (600 MHz, CD_3CN) δ 0.87 (t, J = 7.2 Hz, 6H), 1.20 (m, 7H), 1.23 (m, 7H), 1.27 (m, 6H), 1.35 (m, 4H), 1.80 (m, 4H), 2.27 (s, 3H), 2.38 (tt, J = 8.1, 7.8 Hz, 2H), 2.54 (s, 3H), 3.23 (m, 2H), 4.61 (t, J = 7.5 Hz, 2H), 6.04 (dt, J = 10.8, 7.5 Hz, 1H), 6.07 (dt, J = 12.0, 7.2 Hz, 1H), 6.27 (d, J = 11.4 Hz, 1H), 6.28 (d, J = 11.4 Hz, 1H). ^{13}C NMR (150 MHz, CD_3CN) δ 14.4, 18.3, 19.1, 21.2, 23.4, 29.3, 29.4, 29.5, 29.7, 29.97, 30.00, 30.04, 30.07, 32.6, 33.0, 58.6, 122.1, 123.1, 132.2, 135.9, 139.4, 139.5, 148.8, 155.2, 155.6. IR (film) ν max cm^{-1}: 2926, 2855, 1739, 1690, 1198. HRMS (ESI) m/z: calcd for $C_{30}H_{50}N$ $[M]^+$ 424.3943, found 424.3972.

Conclusions

In summary, we have developed a method for the acid-promoted synthesis of pyridines *via* oxime intermediates avoiding any aldol-type reactions. To the best of our knowledge, this is the first reported method that uses simple non-bulky, non-rigid, 1,5-diketone substrates to synthesize the corresponding pyridine derivatives. Therefore, we think this method has a higher tolerance than previously reported metal-free methods. In this study, we applied the methodology to construct the pyridine framework of **1** as a demonstration and achieved the total synthesis of **1** in 12% yield from reported compound **6**, which was about twice the yield of the previous total synthesis. We assume that the alkyl functionalities of **1** can be easily changed while using this method, for the purposes of a SAR study. The further optimization of the reaction conditions for the preparation of a variety of pyridine derivatives and their application to analogue syntheses are currently underway.

Conflicts of interest

There are no conflicts to declare.

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