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PREPARATION OF PYRIDINE DERIVATIVES FROM THE CORRESPONDING 5-ACETAL-1-CARBONYL COMPOUNDS BY ACID PROMOTED CYCLIZATION

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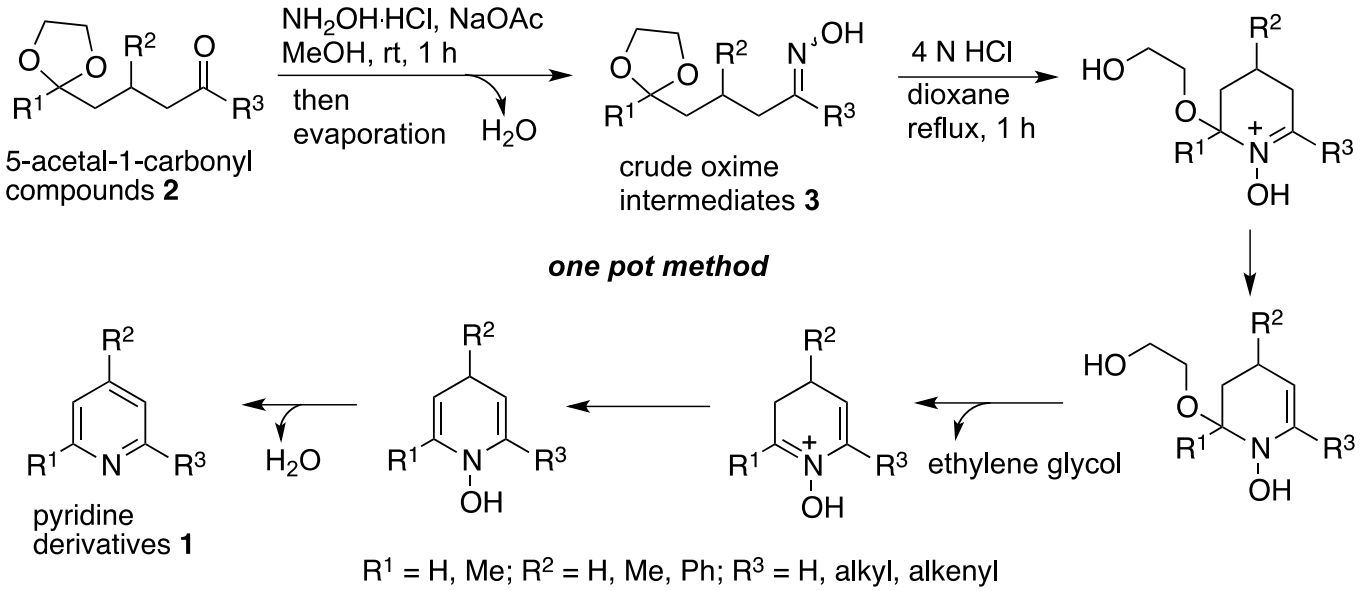
Abstract – The synthesis of four alkylpyridine derivatives from 5-acetal-1-carbonyl compounds via the one-pot, acid-promoted cyclization of oxime intermediates is described. In addition, a dihydroxypyridine and pyridinium salt were also synthesized. The pyridine formation step was not affected by the stereochemistry of the precursors used.

INTRODUCTION

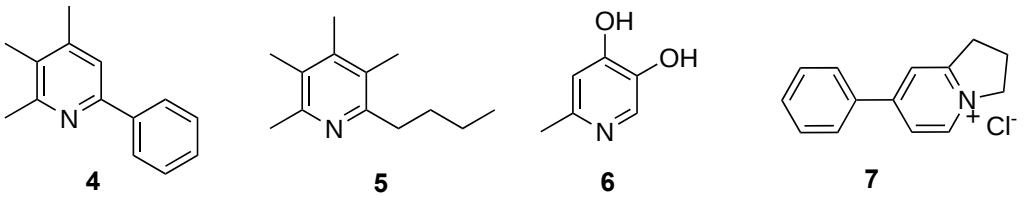
The pyridine ring is a simple structural moiety found in numerous natural products, organic materials and pharmaceuticals;[1-3] and pyridine itself is used as a solvent, base, additive and starting material in organic synthesis. Substituted pyridine derivatives are usually prepared from commercially available pyridines and/or simple derivatives thereof, but the electron-deficient pyridine ring is poorly reactive and its alkylation and functionalization is often difficult. For this reason, although many methods to effect pyridine ring formation from aliphatic starting materials have been reported to date, most entail use of metal-catalysts such as Fe, Cu, Rh, etc.[4] For example, in 2017, Guan *et al.* reported a pyridine synthesis based on the combination of the reductive cleavage of the N-O bond of ketoxime acetates and the oxidative cleavage of *N*,*N*-dimethylaniline using catalytic Fe(II)/Fe(III);[4a] Yoshikai *et al.* developed a copper-catalyzed condensation reaction of oxime acetates and α,β-unsaturated ketimines;[4b] and in 2015, Wan *et al.* reported a rhodium(I)/MeOBiphep complex-catalyzed [2+2+2] cycloaddition of oximes with diynes using EtOH.[4c] A few metal-free pyridine syntheses have been achieved, however Deng *et al.* developed a metal-free protocol for the synthesis of substituted pyridines from *O*-acetyl ketoximes and α,β-unsaturated aldehydes;[5a] Rychnovsky *et al.* reported a synthesis by combining 1,4-addition, ozonolysis and condensation;[5b] and Maulide *et al.* reported the metal-free formal [2+2+2] intermolecular cycloaddition of heteroalkynes and nitriles.[5c] Despite these advances, substituted pyridines bearing bulky

and rigid functionalities at the 2,6-positions[6,7] are still prepared by aliphatic materials because of the propensity of the substrates to under aldol reaction.[8,9] Inspired by the pioneering work of Kaiser,[10] Piccialli,[11] and Knoevenagel,[12] we developed methodology for the construction of pyridine frameworks **1** from 5-acetal-1-carbonyl substrates **2** via the corresponding oximes **3** without observable aldol-type side reactions.[13] Scheme 1 depicts our approach. Condensation of hydroxylamine with the carbonyl group of **2** gives oxime **3**, which undergoes cyclization by attack of the nitrogen atom on the acetal carbon (upon its activation by AcOH to give the corresponding oxonium). Aromatization of the pyridine ring by removal of ethylene glycol and dehydration give the desired pyridine derivatives **1**. We also report the execution of this process in one pot, using 4 N HCl/dioxane instead of AcOH (Scheme 1).[13]



Scheme 1. Acid-promoted synthesis of pyridine derivatives **1** from the corresponding simple-5-acetal-1-carbonyl compounds **2** by one-pot process

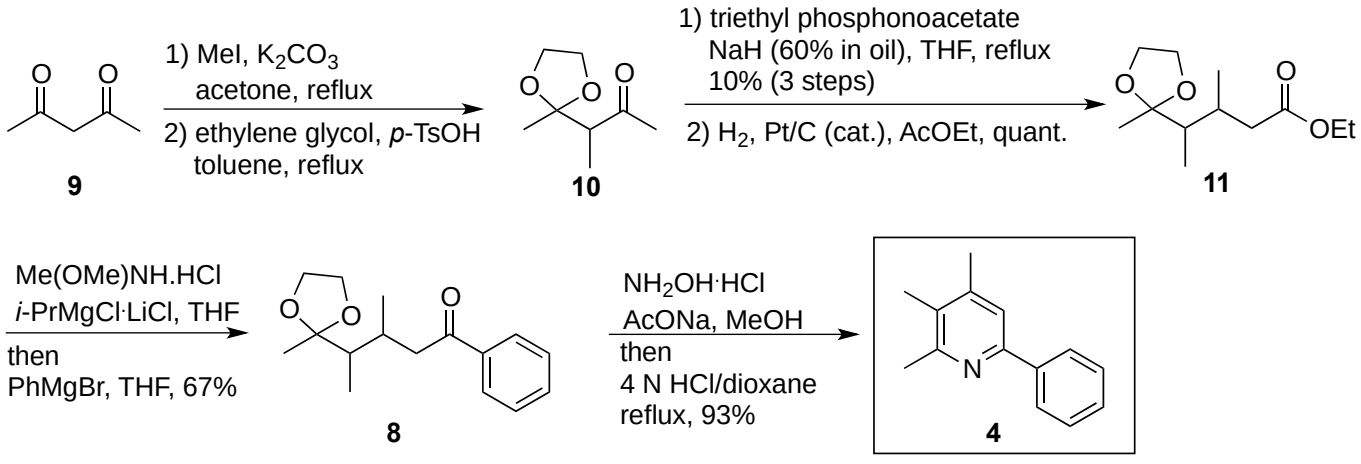
Using this process as a key step, we achieved the total synthesis of anibamine,[13] a pyridinyl alkaloid isolated from *Aniba* sp.[14,15] In the present study, we further exemplify the utility of our method through the synthesis of four alkylpyridines (Scheme 2).



Scheme 2. Target compounds **4**, **5**, **6**, and **7** in the present study

RESULTS AND DISCUSSION

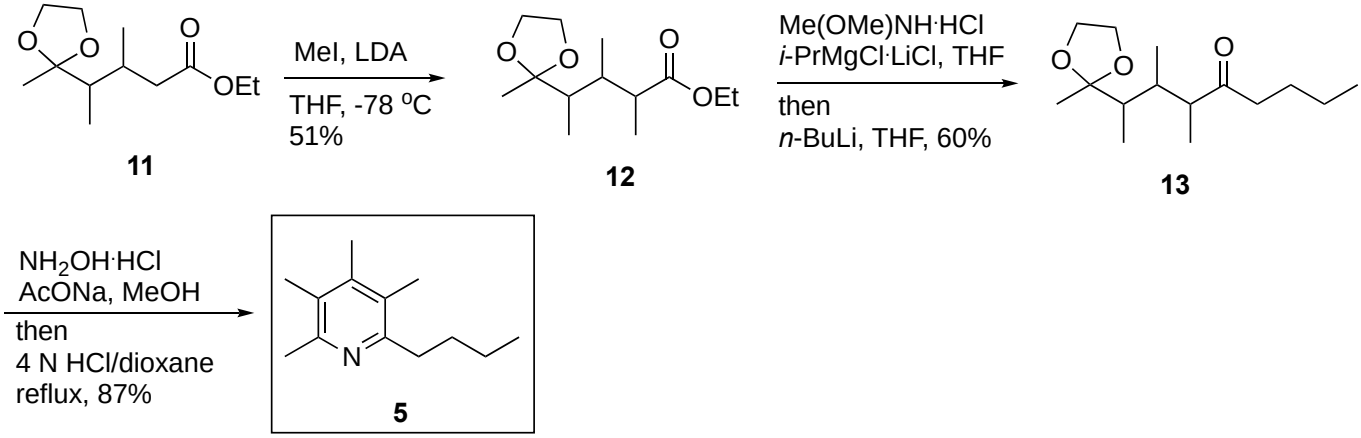
In our previous study, 2,4,6-trialkylpyridines were synthesized from alkyl-1,5-diketone derivatives by the refluxing them in AcOH[13] or HCl.[16] For this study, we did not attempt the synthesis of 4-, and 5-substituted alkylpyridine using that method. Dzhemilev reported the synthesis of tetra-alkylpyridines by treating eneyne compounds with AcCl and NH_3 in the presence of $ZnCl_2$.[17] McCormick synthesized a variety of pyridines using a nickel-catalyst.[18] However, despite the brevity of these sequences, the chemical yields of the products are relatively low. Accordingly, we studied the applicability of our method to targets incorporating a 4- and 5-substituted alkylpyridine motif. 2,3,4-Trimethyl-6-phenylpyridine (**4**) was selected as the initial target. Substrate **8** was obtained starting 2,4-pentanedione (**9**). Methylation of **9** followed by mono-ketal protection with ethylene glycol afforded ketone **10**. Horner-Emmons reaction of ketone **10** and then hydrogenation in the presence of catalytic Pt/C under a hydrogen atmosphere gave saturated ester **11** in 10% yield over 4 steps and as 3:1 mixture of diastereomers, which advanced to the next stage without separation. Weinreb amidation of ester **11** with Me(OMe)NH·HCl/*i*-PrMgCl·LiCl followed by Grignard reaction of PhMgBr afforded pyridine cyclization precursor **8** in 67% yield. Treatment of the precursor **8** with NH_2OH·HCl/AcONa/MeOH yielded the corresponding oxime intermediate which was refluxed in a solution of 4 N HCl in dioxane for 1 h to give the desired 2,3,4-trimethyl-6-phenylpyridine (**4**) in 93% yield. The stereochemistry of **8** did not seem to affect the pyridine formation (Scheme 3).



Scheme 3. Synthesis of tetrasubstituted pyridine derivative **4**

Next, we attempted the synthesis of 2,3,4,5-tetramethyl-6-butylpyridine (**5**). Methylation of α-carbon of ethyl ester **11** gave a diastereomeric mixture (16:2:1:1) of product **12** in 51% yield. Conversion of the ethyl ester functionality of **12** to the corresponding butanone was achieved by Weinreb amidation and Grignard reaction to give pyridine formation precursor **13** in 60% yield. Pyridine formation of precursor

13 under our optimized conditions proceeded smoothly to give 2,3,4,5-tetramethyl-6-butylpyridine (**5**) in 87% yield (Scheme 4).

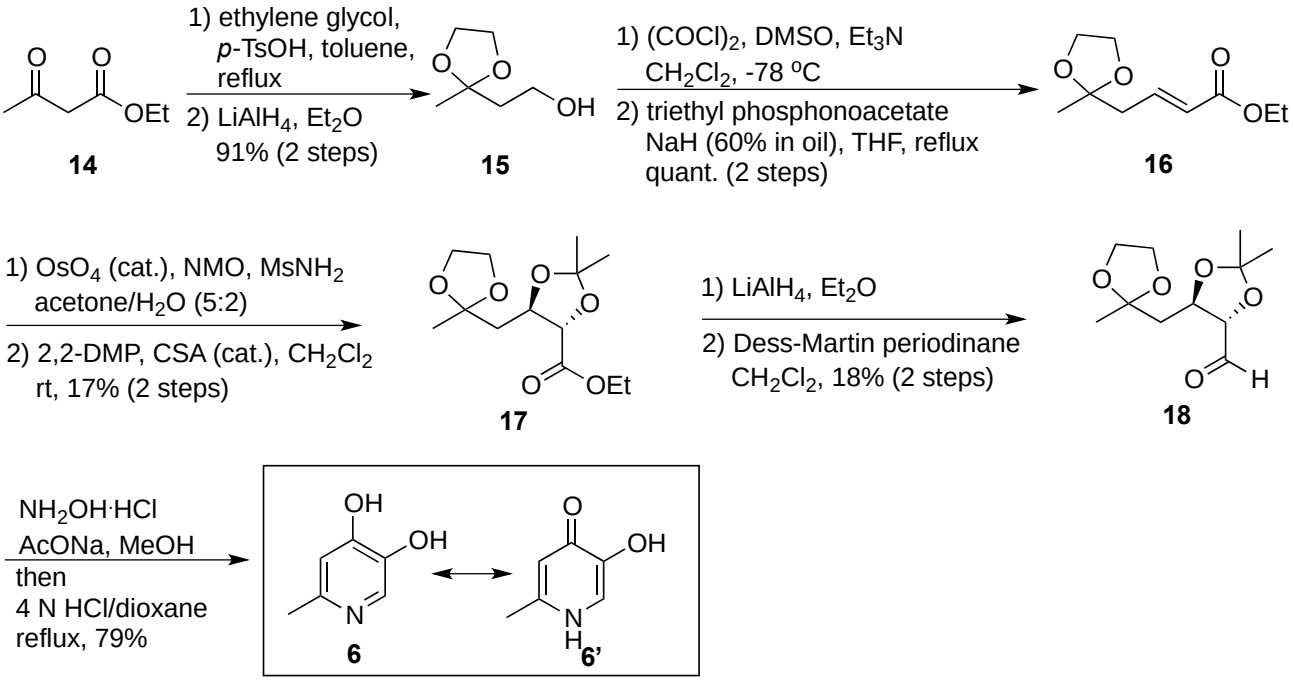


Scheme 4. Synthesis of pentasubstituted pyridine derivative **5**

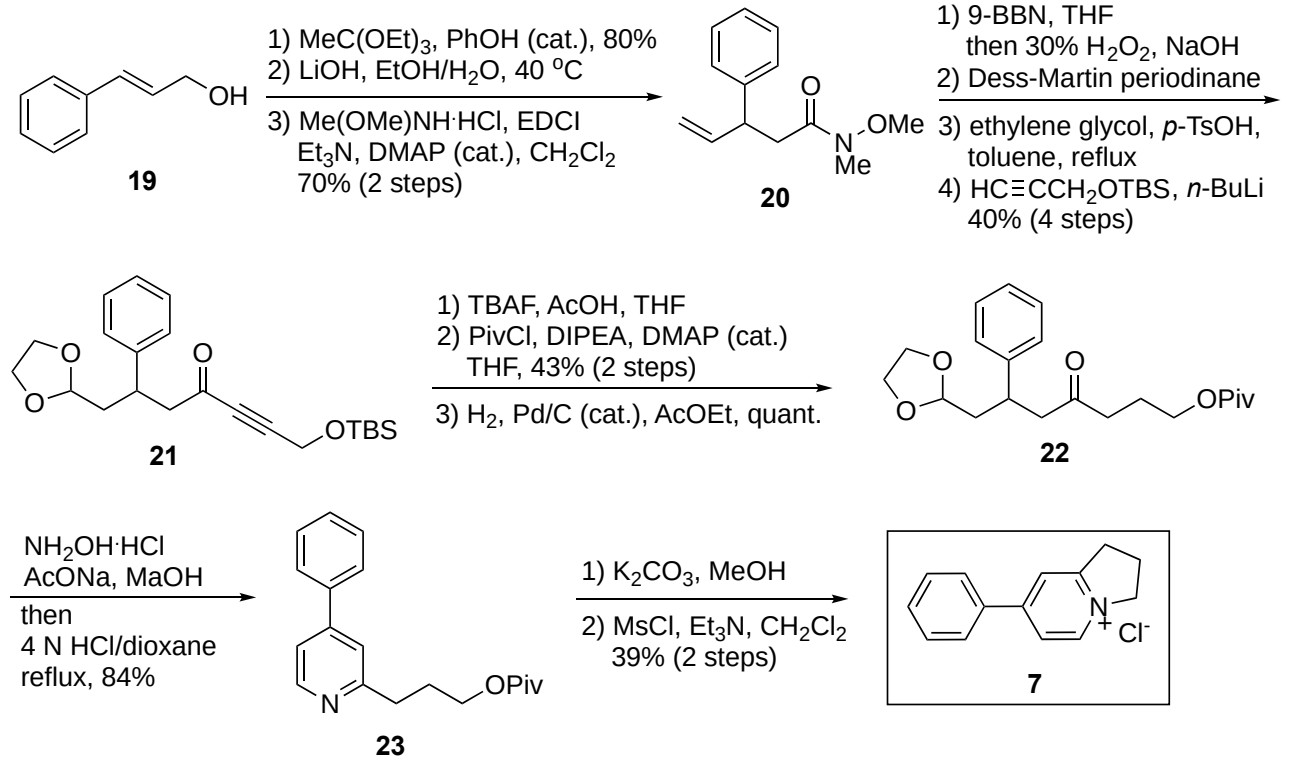
We also attempted the synthesis of 6-methylpyridine-3,4-diol (**6**)[19] from ethyl acetoacetate (**14**) (Scheme 5). Xie synthesized the target compound **6** starting from the pyrone derivative kojic acid[20] but did not disclose extension of this method to other synthetic targets incorporating the pyridine moiety. Ketal protection of **14** followed by reduction of the ester group gave alcohol **15** in 91% yield over 2 steps, which was converted to unsaturated ester **16** in quantitative yield by Swern oxidation and Horner-Emmons olefination. Dihydroxylation of **16** under osmium-catalysis followed by protection of the resulting diol as an acetonide gave **17**. Aldehyde **18** was obtained by hydride reduction and Dess-Martin oxidation of **17**. Submission of aldehyde **18** to our pyridine formation conditions afforded 6-methylpyridine-3,4-diol (**6**) and its tautomer 5-hydroxy-2-methyl-4(1*H*)-pyridone (**6'**) in 79% yield. We observed that the NMR spectra of the synthesized **6** and **6'** matched those of the reported compounds;[19] Xie reported that pyridine derivative **6** existed as a mixture of two mesomeric forms **6** and **6'** in a solvent-dependent ratio.[19] We determined the ratio of 6-methylpyridine-3,4-diol (**6**) and 5-hydroxy-2-methyl-4(1*H*)-pyridone (**6'**) to be 1:1 in $CDCl_3$ using ^1H NMR. In contrast, the reverse phase HPLC profile of the mixture of **6** and **6'** using 0.1% TFA MeCN-H_2O was 2:1 (see supporting information). This result was consistent with the DFT simulation reported by Xie.[19] These conditions led to concomitant deprotection of the acetonide (Scheme 5).

Finally, we attempted the synthesis of pyridinium salt **7**. The 4-phenylpyridine and/or quaternary nitrogen motifs are valuable for the synthesis of natural products, ligands, pharmaceuticals and organic materials. Johnson-Claisen rearrangement of cinnamyl alcohol (**19**) followed by saponification and Weinreb amidation gave *N*-methoxy-*N*-methylamide **20** in 70% over 3 steps. Then, a 4 step sequence was carried out, to yield ynone **21** in 80% yield. Exchange of TBS group of **21** to with a pivaloyl group followed by

reduction of the triple bond afforded pyridine formation precursor **22**. Submission of **22** to our pyridine formation conditions gave phenylpyridine **23** in 84% yield. After the deprotection of pivaloyl group with K_2CO_3, and treatment of the corresponding alcohol with MsCl/Et_3N, **7** was obtained in 39% yield (Scheme 6).



Scheme 5. Synthesis of dihydroxypyridine derivative **6**



Scheme 6. Synthesis of pyridinium salt derivative **7**

In conclusion, the synthesis of four alkylpyridine derivatives, a dihydroxypyridine, and a pyridinium salt from 5-acetal-1-carbonyl compounds via the one-pot, acid-promoted cyclization of oxime intermediates has been accomplished. This method is operationally easy, highly scalable, uses only inexpensive reagents, and is not affected by the stereochemistry of the intermediates. Further studies to understand the scope of this method and use it to synthesize pyridine-containing natural products are now underway.

EXPERIMENTAL

General General All solvents were reagent grade. CH_2Cl_2 was distilled from CaH_2 and THF from Na. All commercial reagents were of the highest purity available. ^1H (400, 500 or 600 MHz) and ^{13}C NMR (100, 125 or 150 MHz) spectra were recorded on 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). 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) 60-210 mm or 100-200 mm]. High-resolution mass spectra (HRMS) were obtained using a JEOL AccuTOF JMS-T100LC (ESIMS). IR spectra were recorded at FT/IR-460 plus (JASCO, Tokyo, Japan) and Spectrum Two (PerkinElmer, Waltham, MA, USA).

Ethyl (*2E,Z*)-3-methyl-4-(2-methyl-1,3-dioxolan-2-yl)pent-2-enoate A solution of acetylacetone (**9**) (2.0 mL, 20 mmol), potassium carbonate (4.1 g, 30 mmol) and iodomethane (1.9 mL, 30 mmol) in acetone (70 mL) was refluxed overnight with stirring. The reaction mixture was cooled to room temperature, then filtered and the filtrate concentrated *in vacuo* to give a residue which was used for following reaction without further purification. A stirring solution of the residue, ethylene glycol (1.1 mL, 20 mmol) and *p*-TsOH (catalytic amount) in toluene (70 mL) was refluxed for 5 h with 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 sat. $NaHCO_3$ aq. and Et_2O. The organic layer was dried over $MgSO_4$, filtered and removed under reduced pressure. The residue (**10**) was used for following reaction without further purification. To a solution of THF (30 mL) and NaH (60% in oil, 2.80 g, 70 mmol) was added triethyl phosphonoacetate (14 mL, 70 mmol) in THF (30 mL) at 0 ^oC. After the mixture was stirred for 1 h, the residue **10** in THF (10 mL) was added to the reaction mixture at 0 ^oC, gradually warmed to room temperature and refluxed for overnight. The reaction was quenched by addition of sat. NH_4Cl aq. After the separation of 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 with column chromatography (AcOEt-hexane, 1:5 v/v) to give the unsaturated ester (*E/Z*-mixture, 428 mg, 10% yield over 3 steps). ^1H NMR (600 MHz, $CDCl_3$) δ 5.77 (s, 0.67H), 5.69

(s, 0.33H), 4.07-4.16 (m, 2H), 3.81-3.99 (m, 4H), 2.52 (q, *J* = 7.2 Hz, 1H), 2.17 (d, *J* = 1.2 Hz, 2H), 1.86 (d, *J* = 1.2 Hz, 1H), 1.24 (t, *J* = 6.9 Hz, 3H), 1.22 (s, 1H), 1.21 (s, 2H), 1.08 (d, *J* = 6.6 Hz, 2H), 1.03 (d, *J* = 6.6 Hz, 1H). as *E,Z*-mixture (2.7:1) ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 166.3, 160.9, 118.7, 118.1, 110.8, 65.5, 65.4, 64.5, 64.3, 59.6, 52.1, 42.0, 23.1, 23.0, 21.2, 17.5, 14.4, 13.8, 12.7. as *E,Z*-mixture IR (film) ν max cm^{-1}: 2982, 2938, 2883, 1715, 1641. HRMS (ESI) *m/z*: calcd. for $C_{12}H_{20}O_4Na$ $[M+Na]^+$ 251.1259, found 251.1286.

Ethyl 3-methyl-4-(2-methyl-1,3-dioxolan-2-yl)pentanoate (11) Pt/C (2 mg) was added to a solution of unsaturated ethyl ester (364 mg, 1.7 mmol) in AcOEt (6 mL). The reaction was stirred for 3 h under a hydrogen atmosphere, then filtered. The solvent was removed under reduced pressure to give the desired product **11** was obtained (quant.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.01-4.16 (m, 2H), 3.81-3.96 (m, 4H), 2.67 (dd, *J* = 15.0, 3.0 Hz, 0.75H), 2.25-2.46 (m, 1.25H), 2.07-2.18 (m, 0.25H), 1.92 (dd, *J* = 15.0, 12.0 Hz, 0.75H), 1.62-1.77 (m, 1H), 1.14-1.28 (m, 6H), 0.78-1.02 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 173.3, 112.3, 77.3, 77.1, 76.9, 65.1, 64.2, 60.2, 60.1, 46.0, 44.3, 41.6, 37.1, 30.0, 29.6, 22.7, 22.1, 20.0, 15.4, 14.3, 9.0, 8.9. IR (film) ν max cm^{-1}: 2980, 2883, 1733. HRMS (ESI) *m/z*: calcd. for $C_{12}H_{22}O_4Na$ $[M+Na]^+$ 253.1416, found 253.1435.

3-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1-phenylpentan-1-one (8) *N,O*-Dimethylhydroxylamine hydrochloride (136 mg, 1.4 mmol) and Turbo Grignard reagent (1.3 M in THF, 1.6 mL, 2.1 mmol) were added to a solution of **11** (136 mg, 1.4 mmol) in THF (5 mL) under nitrogen atmosphere at 0 ºC. After stirring for 30 min at 0 ºC, phenylmagnesium bromide (1.8 g, 7.0 mmol) in THF (4 mL) was added and the reaction mixture was allowed to warm to room temperature. After the stirring for 5 h, the reaction was quenched with sat. NH_4Cl aq. 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 with column chromatography (AcOEt-hexane, 1:5 v/v) to give **8** (123 mg, 67% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92-8.02 (m, 2H), 7.50-7.60 (m, 1H), 7.43-7.49 (m, 2H), 3.80-4.02 (m, 4H), 3.29-3.37 (m, 0.75H), 2.53-3.03 (m, 2.25H), 1.78-1.83 (m, 1H), 1.30 (s, 2H), 1.29 (s, 1H), 0.90-1.03 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.1, 200.5, 137.7, 132.8, 129.7, 128.6, 128.5, 128.2, 112.5, 120.7, 115.4, 112.5, 65.1, 64.2, 46.2, 45.7, 44.1, 41.0, 29.5, 28.5, 22.9, 21.1, 20.4, 9.3, 9.1. IR (film) ν max cm^{-1}: 2973, 2932, 2876, 1684. HRMS (ESI) *m/z*: calcd. for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1467 , found 285.1483.

2,3,4-Trimethyl-6-phenylpyridine (4) AcONa (12.3 mg, 0.15 mmol) and hydroxylamine hydrochloride (8.3 mg, 0.12 mmol) were added to a solution of **8** (26.2 mg, 0.1 mmol) in MeOH (0.4 mL). The reaction mixture was stirred for 30 min at 50 ºC, concentrated *in vacuo*, then redissolved in dioxane (1.3 mL). A

solution of 4 N HCl/dioxane (0.1 mL, 0.4 mmol) was added, and the mixture refluxed for 1 h. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. The residue was diluted to sat. $NaHCO_3$ aq. 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 with column chromatography (AcOEt-hexane, 1:5 v/v) to give **4** (18.3 mg, 93% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32-7.36 (m, 2H), 2.58 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 153.7, 145.8, 139.9, 128.8, 128.6, 128.3, 126.8, 120.0, 23.5, 20.3, 14.7. IR (film) ν max cm^{-1}: 3060, 2927, 2857. HRMS (ESI) *m/z*: calcd. for $C_{14}H_{16}N$ $[M+H]^+$ 198.1283, found 198.1289.

Ethyl 2,3-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)pentanoate (12) LDA (1.0 M in THF/hexane, 15.0 mL, 15.0 mmol) at -78 °C was added to a solution of **11** (1.2 g, 5.0 mmol) in THF (16 mL) under a nitrogen atmosphere. After the stirring for 1 h at -78 °C, MeI (1.6 mL, 25.0 mmol) was added to the mixture at -78 °C and the reaction mixture was allowed to warm to room temperature. After the stirring for 5 h, the reaction was quenched with sat. NH_4Cl aq. 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 with column chromatography (AcOEt-hexane, 1:8 v/v) to give **12** (626 mg, 51% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.01-4.13 (m, 2H), 3.81-3.95 (m, 4H), 2.59-2.78 (m, 1H), 2.03-2.45 (m, 1H), 1.58-1.85 (m, 1H), 0.82-1.24 (m, 15H). IR (film) ν max cm^{-1}: 2980, 2940, 2882, 1730. HRMS (ESI) *m/z*: calcd. for $C_{13}H_{24}O_4Na$ $[M+Na]^+$ 267.1572, found 267.1581.

3,4-Dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)nonan-5-one (13) *N*,*O*-Dimethylhydroxylamine hydrochloride (365 mg, 3.75 mmol) and Turbo Grignard reagent (1.3 M in THF, 5.7 mL, 7.5 mmol) were added to a solution of **12** (610 mg, 2.5 mmol) in THF (8 mL) under a nitrogen atmosphere at 0 °C. After stirring for 30 min at room temperature, *n*-BuLi (2.5 M in hexane, 3.0 mL, 7.5 mmol) was added at -78 °C and the reaction mixture was allowed to warm to room temperature. After the stirring for 4 h, the reaction was quenched with sat. NH_4Cl aq. 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 with column chromatography (AcOEt-hexane, 1:6 v/v) to give **13** (384 mg, 60% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.84-3.94 (m, 4H), 2.00-2.80 (m, 4H), 1.46-1.66 (m, 3H), 1.15-1.39 (m, 5H), 0.80-1.00 (m, 12H). IR (film) ν max cm^{-1}: 2960, 2937, 2877, 1708. HRMS (ESI) *m/z*: calcd. for $C_{15}H_{28}O_3Na$ $[M+Na]^+$ 279.1936, found 279.1939.

2-Butyl-3,4,5,6-tetramethylpyridine (5) AcONa (123 mg, 1.5 mmol) and hydroxylamine hydrochloride

(83 mg, 1.2 mmol) were added to a solution of **13** (256 mg, 1.0 mmol) in MeOH (4 mL). The reaction mixture was stirred for 30 min at 50 °C and then concentrated *in vacuo*. The residue was redissolved in dioxane (13 mL), then a solution of 4 N HCl/dioxane (1.0 mL, 4 mmol) was added and the mixture 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. $NaHCO_3$ aq. 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 with column chromatography (AcOEt-hexane, 1:4 v/v) to give **5** (166 mg, 87% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.73 (t, *J* = 8.4 Hz, 2H), 2.44 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 1.54-1.59 (m, 2H), 1.37-1.43 (m, 2H), 0.92 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 152.5, 144.1, 127.1, 126.5, 36.3, 32.1, 23.3, 23.1, 15.9, 15.4, 15.1, 14.1 IR (film) ν max cm^{-1}: 2955, 2929, 2870. HRMS (ESI) *m/z*: calcd. for $C_{13}H_{22}N$ $[M+H]^+$ 192.1752, found 192.1775.

2-(2-Methyl-1,3-dioxolan-2-yl)ethan-1-ol (15) A stirring solution of ethyl acetoacetate (**14**) (6.3 mL, 50 mmol), ethylene glycol (8.4 mL, 150 mmol) and *p*-TsOH (catalytic amount) in toluene (170 mL) was refluxed for 2 h with 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 sat. $NaHCO_3$ aq. and ether. The organic layer was dried over $MgSO_4$, filtered and removed under reduced pressure. The residue was used for following reaction without further purification. To a suspension of $LiAlH_4$ (3.8 g, 100 mmol) in Et_2O (50 mL) under nitrogen atmosphere was added the residue in Et_2O (20 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After the stirring for 1 h, the reaction was quenched by adding H_2O (3.8 mL), 1M NaOH (3.8 mL), and H_2O (11.4 mL) in that order at 0 °C. The reaction mixture was filtered and the solvent was removed under reduced pressure. The desired product **15** was obtained (6.0 g, 91% yield over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.89 (s, 4H), 3.65 (t, *J* = 5.4 Hz, 2H), 2.94 (s, 1H), 1.85 (t, *J* = 5.4 Hz, 2H), 1.26 (s, 3H).

Ethyl (2*E*)-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate (16) DMSO (5.7 mL, 80 mmol) in CH_2Cl_2 (30 mL) was added to a solution of CH_2Cl_2 (20 mL) and $(COCl)_2$ (5.2 mL, 60 mmol) at -78 °C with stirring. After 15 min, **15** (20 mmol) in THF (20 mL) was added and the mixture stirred for another 15 min. Then, the reaction mixture was added Et_3N (17 mL, 120 mmol) and the mixture was stirred until it reached room temperature. The reaction was quenched by addition of sat. NH_4Cl aq. After the separation of organic layers, 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* to give a residue which was advanced to the next reaction without further purification. Triethyl phosphonoacetate (14 mL, 70 mmol) was added to a suspension of NaH (60% in oil, 2.80 g, 70 mmol) in THF (30 mL) at 0 °C. After the mixture was stirred

for 1 h, a solution of the residue from the previous step in THF (10 mL) was added to this reaction mixture at 0 °C, gradually warmed to room temperature and stirred for overnight. The reaction was quenched by addition of sat. NH_4Cl aq. After the separation of 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 with column chromatography (AcOEt-hexane, 1:4 v/v) to give **16** (only *E* isomer, quant., over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81-6.88 (m, 1H), 5.79 (d, *J* = 15.0 Hz, 1H), 4.08 (q, *J* = 7.5 Hz, 2H), 3.83-3.88 (m, 4H), 2.44 (d, *J* = 7.2 Hz, 2H), 1.24 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H).

Ethyl *anti*-2,2-dimethyl-5-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,3-dioxolane-4-carboxylate (17) OsO_4 (catalytic amount) in *t*-BuOH (5 mL) and **16** (1.96 g, 9.8 mmol) were added to a solution of NMO (4.8 M in water, 4.1 mL, 20 mmol) and $MeSO_2NH_2$ (1.86 g, 20 mmol) in acetone/H_2O (20 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for overnight. The reaction was quenched by addition of sat. $NaHSO_3$ aq. After the separation of 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 used for following reaction without further purification. 2,2-DMP (12 mL, 98 mmol) and D-CSA (45 mg, 0.20 mmol) were added to a solution of the residue in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 6 h. The reaction was quenched by addition of sat. $NaHCO_3$ aq. After the separation of organic layers, 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 with column chromatography (AcOEt-hexane, 1:2 v/v) to give **17** (468 mg, 17% yield over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24-4.32 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.04 (d, *J* = 7.2 Hz, 1H), 3.79-3.90 (m, 4H), 1.94-2.07 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 110.6, 108.4, 79.7, 75.4, 64.6, 64.5, 61.2, 42.3, 27.2, 25.7, 24.4, 14.2. IR (film) ν max cm^{-1}: 2986, 2938, 2889, 1744. HRMS (ESI) *m/z*: calcd. for $C_{13}H_{22}O_6Na$ $[M+Na]^+$ 297.1314, found 297.1288.

***anti*-2,2-Dimethyl-5-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,3-dioxolane-4-carbaldehyde (18)** **17** (274 mg, 1.0 mmol) in Et_2O (10 mL) was added to a suspension of $LiAlH_4$ (115 mg, 3.0 mmol) in Et_2O (6.0 mL) under nitrogen a atmosphere at 0 °C with stirring. The reaction was allowed to warm to room temperature and, stirring for 1 h, and quenched by the sequential addition of H_2O (115 μL), 1 M NaOH (115 μL), and H_2O (345 μL) in that order at 0 °C. The reaction mixture was filtered and the solvent was removed under reduced pressure to give a residue which was advanced to the next step without further

purification. Dess-Martin periodinane (1.27 g, 3.0 mmol) was added to a solution of the residue in CH_2Cl_2 (5.0 mL) at room temperature. The reaction mixture was stirred for 30 min, then quenched by addition of sat. $NaHCO_3$ aq. and sat. $Na_2S_2O_3$ aq. After the separation of organic layers, 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 with column chromatography (AcOEt-hexane, 2:1 v/v) to give **18** (41 mg, 18% yield over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.67 (d, *J* = 2.4 Hz, 1H), 4.27 (q, *J* = 6.4 Hz, 1H), 4.04 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.86-3.94 (m, 4H), 2.11 (dd, *J* = 14.4, 5.4 Hz 1H), 2.02 (dd, *J* = 14.4, 6.0 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.2, 110.8, 108.4, 84.9, 73.3, 64.6, 64.4, 42.1, 27.2, 26.3, 24.5. IR (film) ν max cm^{-1}: 2985, 2935, 2887, 1732.

6-Methylpyridine-3,4-diol (6 and 6') AcONa (22 mg, 0.27 mmol) and hydroxylamine hydrochloride (15 mg, 0.22 mmol) were added to a solution of **18** (41 mg, 0.18 mmol) in MeOH (0.6 mL). The reaction mixture was stirred for 30 min at room temperature, concentrated *in vacuo*, and then redissolved in dioxane (2.3 mL). A solution of 4 N HCl/dioxane (0.18 mL, 0.72 mmol) was added, and the mixture 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. $NaHCO_3$ aq. 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, 3:1 v/v) to give **6/6'** mixture (18 mg, 79% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (s, 0.5H), 7.42 (brs, 1H), 7.17 (d, *J* = 3.6 Hz, 0.5H), 6.49 (d, *J* = 2.4 Hz, 0.5H), 6.13 (d, *J* = 3.6 Hz, 0.5H), 6.05 (d, *J* = 2.4 Hz, 0.5H), 2.34 (s, 1.5H), 2.33 (s, 1.5H). The above-mentioned ^{1}H NMR spectral data was almost identified to those of the synthesized compound by us along the reference of Xie group.[19]

***N*-Methoxy-*N*-methyl-3-phenylpent-4-enoate (20)** A stirring solution of (*E*)-cinnamyl alcohol (**19**) (2.7 g, 20 mmol), triethyl orthoacetate (11 mL, 60 mmol) and phenol (catalytic amount) was refluxed overnight. The reaction mixture was cooled to room temperature and the reaction was quenched by adding sat. $NaHCO_3$ aq. After the separation of 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 with column chromatography (AcOEt-hexane, 1:5 v/v) to give ethyl 3-phenylpent-4-enoate (1.8 g, 45% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.34 (m, 2H), 7.15-7.21 (m, 3H), 5.95-6.00 (m, 1H), 5.05-5.08 (m, 2H), 4.03-4.09 (m, 2H), 3.86 (q, *J* = 7.6 Hz, 1H), 2.65-2.76 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). LiOH (630 mg, 15 mmol) was added to a solution of ethyl 3-phenylpent-4-enoate (2.04 g, 10 mmol) in H_2O/EtOH (40 mL) at 0 ^{o}C. The reaction mixture was

warmed to 40 °C and stirred for 1 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to give a residue to which was added a mixture of 1 M HCl and Et_2O. After the separation of organic layers, the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, filtered and removed under reduced pressure. The residue was used for following reaction without further purification. EDC (2.5 g, 13 mmol) and DMAP (catalytic amount) were added to a solution of the residue in CH_2Cl_2 (30 mL) at 0 °C with stirring. After 10 min, *N*,*O*-dimethylhydroxylamine hydrochlorid**e** (1.27 g, 13 mmol) and Et_3N (2.1 mL 15 mmol) were added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by adding sat. NH_4Cl aq. After separation of organic layers, 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 with column chromatography (AcOEt-hexane, 1:2 v/v) to give **20** (1.53 g, 70% yield over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11-7.39 (m, 5H), 5.92-6.12 (m, 1H), 4.96-5.14 (m, 2H), 3.98 (m, 1H), 3.58 (s, 3H), 3.12 (s, 3H), 2.79-2.97 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 143.3, 140.8, 128.6, 127.8, 126.6, 114.7, 61.3, 44.9, 37.5, 32.2. IR (film) ν max cm^{-1}: 3027, 3000, 2972, 2937, 1663. HRMS (ESI) *m/z*: calcd. for $C_{13}H_{17}NO_2Na$ $[M+Na]^+$ 242.1157, found 242.1186.

***t*-Butyldimethylsiloxy-6-phenyl-8-(1,3-dioxolane)-2-nonyn-4-one (21)** 9-BBN (0.5 M in THF, 19 mL, 9.6 mmol) was added to a solution of **20** (1.05 g, 4.8 mmol) in THF (16 mL) at 0 °C. The reaction mixture was warmed to room temperature, with stirring. After 12 h, the reaction mixture was cooled to 0 °C and then diluted with 3 M NaOH (6 mL) and 30% H_2O_2 (6 mL). The mixture was warmed to room temperature with stirring. After 1 h, the reaction was quenched by adding sat. NH_4Cl aq. After the separation of 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 used for following reaction without further purification. DMP (5.1 g, 12.8 mmol) was added to a solution of the crude compound in CH_2Cl_2 (16 mL). The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched by addition of sat. $NaHCO_3$ aq and sat. $Na_2S_2O_3$ aq. After the separation of organic layers, 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 used for following reaction without further purification. A stirring solution of the residue, ethylene glycol (0.8 mL, 14.4 mmol) and *p*-TsOH (catalytic amount) in toluene (30 mL) was refluxed for 4 h with Dean-Stark apparatus. The reaction mixture was cooled to room temperature and the solvent was carefully removed under reduced pressure. Sat. $NaHCO_3$ aq. and Et_2O were added. The organic layer was dried over $MgSO_4$, filtered, and removed under reduced pressure. The residue was used for following reaction without further

purification. *n*-BuLi (2.5 M in hexane, 3.84 mL, 9.60 mmol) was added to a solution of *t*-butyldmethylsilyloxy-2-propyne (1.63 g, 9.60 mmol) in THF (11 mL) at -78 °C under a nitrogen atmosphere with stirring. The reaction was allowed to warm to 0 °C with stirring. After 30 min, the mixture was cooled to -78 °C and diluted with THF (12 mL). The mixture was stirred overnight at room temperature, then quenched with sat. NH_4Cl aq. 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 with column chromatography (AcOEt-hexane, 1:5 v/v) to give **21** (746 mg, 40% yield over 4 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11-7.36 (m, 5H), 4.61 (dd, *J* = 7.2 Hz, 3.0 Hz, 1H), 4.41 (s, 2H), 3.84-3.94 (m, 2H), 3.67-3.84 (m, 2H), 3.45-3.55 (m, 1H), 2.98 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.88 (dd, *J* = 16.2, 8.4 Hz, 1H), 1.83-2.06 (m, 2H), 0.90 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6, 143.1, 128.7, 127.6, 126.8, 102.8, 90.7, 84.0, 64.8, 64.7, 52.0, 51.6, 40.2, 37.1, 25.8, 18.3, -5.1. IR (film) ν max cm^{-1}: 2954, 2929, 2885, 2857, 2213, 1676. HRMS (ESI) *m/z*: calcd. for $C_{22}H_{32}O_4SiNa$ $[M+Na]^+$ 411.1968, found 411.1939.

6-Phenyl-8-(1,3-dioxolane)-1-pivaloyloxy-2-nonyn-4-one A solution of **21** (330 mg, 0.85 mmol) in THF (2.8 mL) was added to a solution of AcOH (73 µL, 1.28 mmol) and TBAF (1.0 M in THF, 1.28 mL, 1.28 mmol) in THF (4 mL) at room temperature. After the stirring for 5 min, the reaction mixture was added to sat. $NaHCO_3$ aq. 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 used for following reaction without further purification. DIPEA (3.0 mL, 17 mmol), DMAP (catalytic amount) and PivCl (414 µL, 6.2 mmol) were added to a solution of the residue in THF (2.8 mL) at 0 °C. The mixture was stirred for 1 h, then added to sat. NH_4Cl aq. at 0 °C. 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 with column chromatography (AcOEt-hexane, 1:5 v/v) to give 6-phenyl-8-(1,3-dioxolane)-1-pivaloyloxy-2-nonyn-4-one (131 mg, 43% yield over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02-7.39 (m, 5H), 4.76 (s, 2H), 4.61 (dd, *J* = 6.6 Hz, 3.0 Hz, 1H), 3.85-3.94 (m, 2H), 3.70-3.84 (m, 2H), 3.45-3.54 (m, 1H), 2.98 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.89 (dd, *J* = 16.2, 7.8 Hz, 1H), 1.98-2.06 (m, 1H), 1.88-1.93 (m, 1H), 1.22 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.3, 177.5, 143.0, 128.7, 127.6, 126.8, 102.8, 86.0, 84.9, 64.8, 64.7, 52.1, 51.6, 40.2, 38.9, 37.1, 27.1. IR (film) ν max cm^{-1}: 2973, 2880, 2222, 1736, 1677. HRMS (ESI) *m/z*: calcd. for $C_{21}H_{26}O_5Na$ $[M+Na]^+$ 381.1678, found 381.1689.

6-Phenyl-8-(1,3-dioxolane)-1-pivaloyloxy-2-nonan-4-one (22) Pd/C (2 mg) was added to a solution of 6-phenyl-8-(1,3-dioxolane)-1-pivaloyloxy-2-nonyn-4-one (132 mg, 0.37 mmol) in AcOEt (1.5 mL) and

the mixture stirred for overnight at the hydrogen atmosphere. The reaction mixture was filtered and the solvent was removed under reduced pressure to give the desired product **22** (126 mg, 95% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10-7.32 (m, 5H), 4.60 (dd, *J* = 7.2 Hz, 3.0 Hz, 1H), 3.83-4.04 (m, 4H), 3.66-3.81 (m, 2H), 3.38-3.45 (m, 1H), 2.80 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.72 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.67-2.75 (m, 1H), 2.31-2.46 (m, 1H), 2.20-2.30 (m, 1H), 1.95-2.08 (m, 1H), 1.85-1.90 (m, 1H), 1.71-1.82 (m, 1H), 1.14 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 178.5, 143.8, 128.7, 127.5, 126.7, 102.9, 64.8, 64.7, 63.5, 49.8, 40.3, 39.6, 38.8, 37.1, 27.2, 22.6. IR (film) ν max cm^{-1}: 2961, 2885, 1720. HRMS (ESI) *m/z*: calcd. for $C_{21}H_{30}O_5Na$ $[M+Na]^+$ 385.1991, found 385.2006.

4-Phenyl-2-(3-pivaloyloxy)propylpyridine (23) AcONa (43 mg, 0.53 mmol) and hydroxylamine hydrochloride (29 mg, 0.42 mmol) were added to a solution of **22** (126 mg, 0.35 mmol) in MeOH (1.1 mL). The reaction mixture was stirred for 30 min at room temperature and then concentrated *in vacuo* to give residue which was redissolved in dioxane (4.3 mL). A solution of 4 N HCl/dioxane (347 µL, 1.4 mmol) was added and the mixture 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. $NaHCO_3$ aq. 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 with column chromatography (AcOEt-hexane, 1:2 v/v) to give **23** (87 mg, 84% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.58-7.65 (m, 2H), 7.38-7.50 (m, 3H), 7.30-7.37 (m, 2H), 4.13 (t, *J* = 6.6 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.04-2.24 (m, 2H), 1.19 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 161.5, 149.8, 149.0, 138.4, 129.1, 129.0, 127.1, 120.9, 119.5, 63.9, 38.8, 34.8, 28.6, 27.3. IR (film) ν max cm^{-1}: 2969, 2871, 1725. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{24}NO_2$ $[M+H]^+$ 298.1807, found 298.1808.

Ammonium salt derivative (7) K_2CO_3 (469 mg, 3.4 mmol) was added to a solution of **23** (61.6 mg, 0.17 mmol) in MeOH (2.0 mL) at room temperature. The mixture was stirred for 1 d, then diluted with water. 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* to give a residue which was used for following reaction without further purification. Et_3N (190 µL, 1.36 mmol) and MsCl (79 µL, 1.02 mmol) were added to a solution of the residue in CH_2Cl_2 (2 mL) at 0 ºC. The mixture was allowed to warm to room temperature with stirring. After 12 h, the solution was concentrated *in vacuo* to give a residue which was purified by preparative TLC and a RP-HPLC to give the ammonium salt derivative (**7**) (13.0 mg, 39% over 2 steps). mp 113-115 ºC (dec.). ^{1}H NMR (600 MHz, CD_3OD) δ 9.22 (d, *J* = 5.5 Hz, 1H), 8.70 (t, *J* = 7.2 Hz, 1H), 8.05 (t, *J* = 6.9 Hz, 1H), 7.75-7.78 (m, 2H), 7.43-7.57 (m, 3H), 4.91 (t, *J* = 7.2 Hz, 2H), 3.55 (t, *J* = 7.2 Hz, 2H), 2.52-2.57 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 142.8, 140.0, 139.6, 133.0,

130.3, 129.8, 127.4, 124.5, 59.5, 32.1, 21.7. IR (film) ν max cm^{-1}: 3042, 3025, 3008, 2966, 2991. HRMS (ESI) *m/z*: calcd. for $C_{14}H_{14}N$ $[M]^+$ 196.1126, found 196.1155.

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