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The Dianion of Dehydroacetic Acid: A Direct Synthesis of Pogopyrone A

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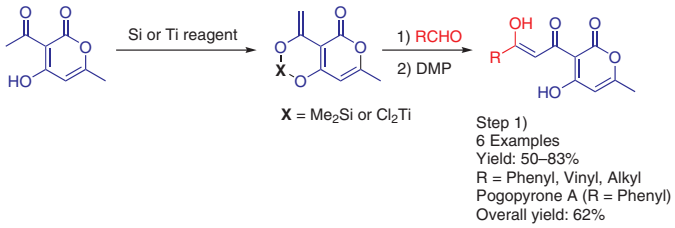

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Abstract Dehydroacetic acid was converted into a silyl enol ether and titanium enolate. These reacted effectively with aldehydes and *N*-bromosuccinimide. Oxidation of the adduct with benzaldehyde afforded pogopyrone A in excellent overall yield.

Key words dianion, dehydroacetic acid, silyl enol ether, titanium enolate, pogopyrone A

Dehydroacetic acid (**1**) is a readily available, biobased pyrone. It has been employed in a number of condensations including acylations, Mannich condensations and aldol condensation–dehydrations mediated by secondary amines. Its chemistry has been summarized in a recent review.[1] Metal complexes of **1** are also well documented.[2] Harris and co-workers reported the preparation and use of the trianion of **1**, generated in ammonia using sodium amide.[3] Despite the extensive carbanion chemistry of **1**, alkylation or aldol formation via the dianion of **1** does not appear to have been reported.[4] When we attempted to deprotonate **1** using 2 equivalents of lithium diisopropylamide followed by the addition of benzaldehyde, we obtained the expected aldol product in only 27% yield. The majority of the material was starting material. Reasoning that the corresponding silyl enol ether **2** might be more reactive, we reacted **1** with dichlorodimethylsilane and triethylamine in dichloromethane at room temperature. This process afforded the silane **2** in 99% yield (Figure 1).

Compound **2**, which could be generated in situ, reacted readily with a number of aldehydes and *N*-bromosuccinimide.[5] Boron trifluoride etherate was an effective Lewis acid catalyst for the aldol reaction. The products and yields are listed in Scheme 1.

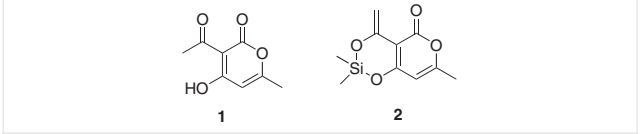
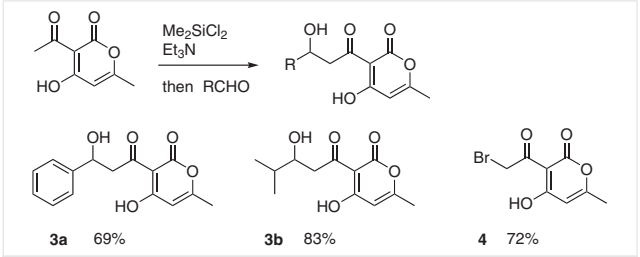


Figure 1 Structures of dehydroacetic acid and silyl enol ether **2**



Scheme 1 Addition reactions via silyl enol ether **2**

Although **2** made possible the synthesis of compounds on millimole scales, its tendency to decompose during storage prompted us to evaluate other dianion equivalents. Although the boron or tin enolate was unreactive, the titanium enolate, generated via titanium tetrachloride and *N*,*N*-diisopropylethylamine in dichloromethane at –78 °C, afforded an 80% yield of the aldol product **3a** with benzaldehyde. Workup conditions at low temperature were essential to minimize dehydration. The products and yields are shown in Scheme 2. This chemistry was scalable and **3b** was synthesized on a 50 mmol scale.

Pogopyrone A (**5**) is a compound isolated from *Pogostemon heynianus* Benth Syn.[6] Although the acylation of either silyl enol ether **2** or the titanium enolate of **1** with benzoyl chloride gave no product, oxidation of **3a** with Dess–Martin periodinane (DMP) afforded a 78% yield of pogopyrone A (enol/keto = 4:1) (Scheme 3).

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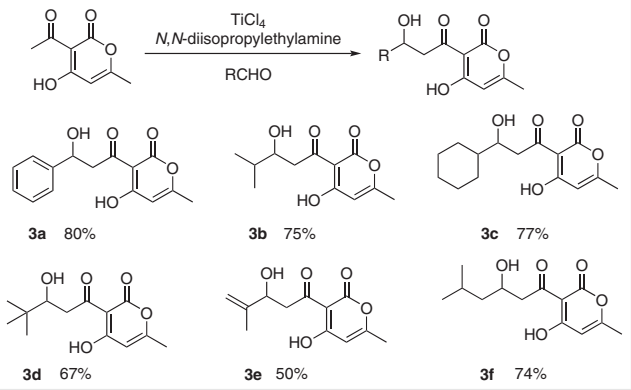
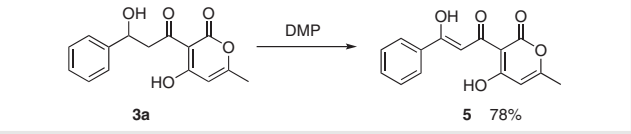


Scheme 2 Addition reactions via the titanium enolate



Scheme 3 Synthesis of pogopyrone A

Selective reactions at the acetyl group of **1** have been achieved via either silyl enol ether **2** or the titanium enolate of **1**. The titanium chemistry can be scaled to make **3b** on a 50 mmol scale. A direct synthesis of pogopyrone A was achieved.

^{1}H and ^{13}C NMR spectra were recorded on Varian MR-400 M and Bruker AV III 600 M spectrometers. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet). High-resolution mass spectrometry (HRMS) data were obtained on an Agilent QTOF 6540 instrument.

Addition Reactions via Silyl Enol Ether 2; General Procedure

To a stirred solution of dehydroacetic acid (168 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added dichlorodimethylsilane (129 mg, 1.0 mmol) followed by triethylamine (202 mg, 2.0 mmol) at 0 °C. The mixture was stirred for 90 min at room temperature. Then, boron trifluoride etherate (284 mg, 2.0 mmol) and aldehyde (2.0 mmol) were added to the flask at 0 °C, and the mixture was stirred at 0 °C for 2 h. Sat. ammonium chloride solution (10 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate, 10:1 (v/v)) gave the product.

Addition Reactions via the Titanium Enolate; General Procedure

To a stirred solution of dehydroacetic acid (168 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added titanium tetrachloride (209 mg, 1.1 mmol) followed by *N*,*N*-diisopropylethylamine (284 mg, 2.2 mmol) at –78 °C. The mixture was stirred for 30 min at that temperature. Then, aldehyde (1.2 mmol) was added to the flask, and the mixture was stirred at –78 °C for 2 h. Sat. ammonium chloride solution (10 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate, 10:1 (v/v)) gave the product.

4-Hydroxy-3-(3-hydroxy-3-phenylpropanoyl)-6-methyl-2*H*-pyran-2-one (3a)

Yellow oil; yield (Si method): 189 mg (69%); yield (Ti method): 219 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 2 H), 7.38–7.34 (m, 2 H), 7.30–7.26 (m, 1 H), 5.97 (s, 1 H), 5.26 (dd, *J* = 8.1, 3.9 Hz, 1 H), 3.59–3.44 (m, 2 H), 3.12 (d, *J* = 3.9 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 181.0, 169.6, 161.3, 142.9, 128.5, 127.7, 125.8, 101.5, 100.0, 70.3, 50.5, 20.8.

HRMS (ESI-TOF): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{13}O_5$: 273.0768; found: 273.0771.

4-Hydroxy-3-(3-hydroxy-4-methylpentanoyl)-6-methyl-2*H*-pyran-2-one (3b)

Colorless oil; yield (Si method): 199 mg (83%); yield (Ti method): 180 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (s, 1 H), 3.90 (ddd, *J* = 8.8, 5.5, 2.9 Hz, 1 H), 3.28–3.22 (m, 1 H), 3.17 (dd, *J* = 16.7, 9.3 Hz, 1 H), 2.70 (s, 1 H), 2.27 (s, 3 H), 1.78 (pd, *J* = 6.8, 5.6 Hz, 1 H), 0.98 (d, *J* = 4.5 Hz, 3 H), 0.97 (d, *J* = 4.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 181.0, 169.3, 161.4, 101.5, 100.1, 72.9, 45.8, 33.6, 20.7, 18.5, 17.6.

HRMS (ESI-TOF): *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{15}O_5$: 239.0925; found: 239.0925.

3-(3-Cyclohexyl-3-hydroxypropanoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3c)

White solid; mp 70–72 °C; yield (Ti method): 215 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (s, 1 H), 3.91 (ddd, *J* = 8.9, 5.8, 2.8 Hz, 1 H), 3.27 (dd, *J* = 16.7, 2.9 Hz, 1 H), 3.19 (dd, *J* = 16.7, 9.3 Hz, 1 H), 2.28 (s, 3 H), 1.91 (d, *J* = 12.8 Hz, 1 H), 1.82–1.62 (m, 4 H), 1.45 (dddt, *J* = 11.6, 8.8, 6.0, 2.9 Hz, 1 H), 1.31–0.98 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.6, 181.0, 169.3, 161.4, 101.5, 100.1, 72.4, 46.0, 43.5, 28.9, 28.1, 26.4, 26.2, 26.1, 20.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}O_5$: 281.1384; found: 281.1385.

4-Hydroxy-3-(3-hydroxy-4,4-dimethylpentanoyl)-6-methyl-2*H*-pyran-2-one (3d)

Colorless oil; yield (Ti method): 170 mg (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (s, 1 H), 3.79 (d, *J* = 10.2 Hz, 1 H), 3.47 (s, 1 H), 3.31–3.20 (m, 1 H), 3.15 (m, 1 H), 2.27 (s, 3 H), 0.97 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 181.0, 169.3, 161.5, 101.5, 100.2, 75.9, 43.8, 34.9, 25.6, 20.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}O_5$: 255.1227; found: 255.1228.

4-Hydroxy-3-(3-hydroxy-4-methylpent-4-enoyl)-6-methyl-2*H*-pyran-2-one (3e)

Yellow oil; yield (Ti method): 119 mg (50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (s, 1 H), 5.08–5.02 (m, 1 H), 4.89 (d, *J* = 1.7 Hz, 1 H), 4.64–4.56 (m, 1 H), 3.32 (d, *J* = 6.5 Hz, 2 H), 2.81 (d, *J* = 4.0 Hz, 1 H), 2.28 (s, 3 H), 1.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 181.0, 169.5, 161.4, 146.0, 111.2, 101.5, 100.0, 71.5, 47.2, 20.7, 18.4.

HRMS (ESI-TOF): *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{13}O_5$: 237.0757; found: 237.0764.

4-Hydroxy-3-(3-hydroxy-5-methylhexanoyl)-6-methyl-2*H*-pyran-2-one (3f)

Colorless oil; yield (Ti method): 188 mg (74%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.97 (s, 1 H), 4.24 (ddt, *J* = 6.3, 4.4, 2.0 Hz, 1 H), 3.30–3.25 (m, 1 H), 3.21–3.14 (m, 1 H), 2.73 (s, 1 H), 2.29 (s, 3 H), 1.97–1.78 (m, 1 H), 1.62–1.53 (m, 1 H), 1.31 (ddd, *J* = 13.8, 6.7, 3.5 Hz, 1 H), 0.94 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.0, 181.0, 169.4, 161.3, 101.5, 100.0, 66.3, 49.2, 46.1, 24.5, 23.3, 22.1, 20.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}O_5$: 255.1227; found: 255.1225.

3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (4)

White solid; mp 114–116 °C; yield (Si method with NBS, boron trifluoride etherate not needed): 178 mg (72%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.01 (s, 1 H), 4.70 (s, 2 H), 2.31 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.3, 181.0, 170.1, 160.6, 101.3, 98.4, 35.2, 20.8.

HRMS (ESI-TOF): *m*/*z* [M – H]$^-$ calcd for $C_8H_6BrO_4$: 244.9450; found: 244.9445.

4-Hydroxy-3-[(*Z*)-3-hydroxy-3-phenylacryloyl]-6-methyl-2*H*-pyran-2-one (Pogopyrone A, 5)

To a stirred solution of **3a** (137 mg, 0.5 mmol, 1.0 equiv) in dichloromethane (13 mL) was added Dess–Martin periodinane (318 mg, 0.75 mmol, 1.5 equiv), and the mixture was stirred at room temperature overnight. After reaction completion, dichloromethane was removed by rotary evaporation. Purification by column chromatography on silica gel (hexane/ethyl acetate, 10:1 (v/v)) gave **5**.

Yellow solid; mp 138–140 °C; yield: 106 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–7.91 (m, 2 H), 7.73 (s, 1 H), 7.54–7.46 (m, 1 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 5.93 (s, 1 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 180.0, 177.6, 167.8, 160.9, 133.5, 132.5, 128.7, 127.2, 101.8, 97.6, 95.6, 20.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}O_5$: 273.0757; found: 273.0757.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610752.

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