Graphical Abstract

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ABSTRACT

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The one-pot reaction of aldehydes, triacetic acid lactone, and Hantzsch 1,4-dihydropyridine affords 3-alkyl pyrones via a reductive alkylation strategy.

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Triacetic acid lactone (TAL) (**1**) and dehydroacetic acid (**2**) are readily available building blocks. Comprehensive reviews by Pleixats¹ and by Goel² nicely collate the chemistry of **1** and **2**. A number of natural products bearing the TAL subunit have been discovered and two representative compounds are illustrated below in Figure 1. Pyrone **3** was isolated from *Streptomyces violascens* obtained from *Hylobates hoolock* feces and showed moderate antibacterial activities against *Bacillus subtilis* and *Staphylococcus aureus* with MIC values of 4–32 $\mu\text{g/mL}$.³ Compound **4** is involved in signaling at nanomolar concentrations in certain bacteria.⁴

Fig 1. Representative structures of naturally occurring triacetic acid lactone derivatives

Although many synthetic analogues of **1** have been prepared by acylation/cyclization protocols, the direct alkylation of **1** at C-3 is rare. Majumdar and coworkers reported the direct allylation of **1**,⁵ but to the best of our knowledge, the reaction of the anion of **1** with other alkyl halides affords mainly *O*-alkylation products.⁶ The palladium-mediated reaction of **1** at C-3 with allylic acetates has

also been reported.⁷ Recently, Moreno-Manas and Pleixats reported a two-step procedure that involved the reaction of benzenethiol with intermediate **5** to produce the phenylthioalkyl pyrone **6**, as shown in Scheme 1.⁸

Scheme 1. Synthetic approaches to 3-alkyl triacetic acid lactones

Desulfurization of **6** using deactivated Raney nickel afforded **7**. Their two-step route is applicable to both aromatic and aliphatic aldehydes. We reasoned that if the alkylidene intermediate **5** could be intercepted in situ with a hydride, it would constitute a convenient one-pot route to 3-alkyl triacetic acid lactones.

Initially, we examined a three-component reaction using benzaldehyde, TAL and various hydride equivalents. Reactions using sodium cyanoborohydride or sodium borohydride as the hydride equivalent afforded complex mixtures with products derived from reduction of compounds **1**, **5** and the aldehyde. The use of a hydrogen atmosphere and Pd/C catalyst led to recovered starting material. Fortunately, the use of readily available dihydropyridine **8** as the hydride equivalent afforded a clean reaction with **9** as the only isolated pyrone product in good yield. This reagent had been used to produce 2-alkyl-1,3-diketones and tetrahydro-isobenzofuran-1,5-diones.⁹

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Table 1. 3-Alkyl triacetic acid lactones generated through the reductive alkylation strategy.¹⁰

Entry	R	Product	% yield
1	Isopropyl	9a	94
2	Ethyl	9b	58
3	Methyl	9c	60
4	2-Furyl	9d	66
5	Phenyl	9e	73
6	<i>p</i> -Cl-phenyl	9f	76
7	Hexyl	9g	52
8	Pentyl	9h	62
9	2-Pyridinyl	9i	14

Several aryl and aliphatic aldehydes were studied. Table 1 collates the results with a variety of aldehydes. Notably, no byproduct derived from reduction of the aldehyde was observed. Although the methodology is fairly generalizable with aldehyde substrates, this reaction does not proceed with ketones.

The reaction of TAL, **8**, and *S*-perillaldehyde (**10**) afforded a product containing the TAL substructure, but the proton and carbon NMR were not consistent with the expected adduct. Moreover, the product was significantly less polar than the other products previously obtained. After a review of the literature, we concluded that the structure was actually compound **12** instead of product **11**. Hua and others had reported the reaction of TAL with **9** in the absence of nucleophiles and had observed that a facile electrocyclic reaction occurred after condensation to generate **12** as shown in Scheme 2.¹¹ Our proton NMR spectrum matched their reported spectrum.

Scheme 2. Reaction of TAL (**1**) and *S*-perillaldehyde (**10**).

We applied the results of our reductive alkylation studies to quorum-sensing molecule **4**. Generation of the dianion of TAL with *n*-BuLi in THF/HMPA/TMEDA at 0 °C, followed by treatment with isopropyl bromide afforded **13** in 58% yield.¹² Reductive alkylation produced **4** in 30% yield as shown in Scheme 3.¹³

Scheme 3. Synthesis of 2-pyrone **4**

The reductive alkylation of triacetic acid lactone affords good to excellent yields of 3-alkyl pyrones in a one-pot procedure. This procedure produces a product whose purification is not complicated by separation from alcohols produced by competitive reduction of the aldehyde. Although α,β -unsaturated aldehydes undergo a different reaction pathway, the reductive alkylation reaction proceeds with aliphatic, aromatic and heteroaromatic aldehydes. Its use in synthesis is shown by the direct synthesis of **4**.

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- A representative experimental procedure and spectroscopic data of compounds: To a round bottom flask in open air was added isobutylaldehyde (0.27 mL, 3 mmol), 4-hydroxy-6-methyl-2-pyrone (**1**) (0.13 g, 1 mmol), diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (0.31 g, 1.2 mmol), and dichloromethane (15 mL). *L*-Proline (25 mg, 0.2 mmol) was then added and the sides of the flask were rinsed with dichloromethane again. The reaction mixture was then stirred vigorously overnight. The solvent was then removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:9 to 1:1) to afford **9a** (0.17 g, 94% yield) as a tan powder. **9a**: m.p. 143 – 148 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.61 (s, 1H), 6.18 (s, 1H), 2.34 (d, *J* = 7.3 Hz, 2H), 2.21 (s, 3H), 1.97 – 19.1 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 168.0, 159.8, 102.3, 101.7, 31.7, 27.4, 22.3, 19.6 ppm. HRMS (ESI-QTOF) calcd for C₁₀H₁₅O₃ [*M* + H]⁺ 183.1016, found 183.1013. **9b**: Tan crystalline solid (0.0945 g, 58% yield) m.p. 148-151 °C, *R*_f = 0.24 (silica gel, EtOAc:hexanes 1:1); ¹H NMR (300 MHz, CDCl₃) δ 10.05 (s, 1H), 6.20 (s, 1H), 2.42 (t, *J* = 6.9, 2H), 2.21 (s, 3H), 1.64 – 1.41 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 168.9, 167.9, 160.4, 103.7, 102.2, 25.5, 21.8, 20.2, 14.5 ppm. HRMS (ESI-QTOF) calcd for C₉H₁₃O₃ [*M* + H]⁺ 169.0859, found 169.0859. **9c**: Brown crystalline solid (0.0837 g, 60% yield). m.p. 146-152 °C, *R*_f = 0.23 (silica gel, EtOAc:hexanes 1:1); ¹H NMR (300 MHz, (CD₃)₂CO) δ 5.98 (s, 1H), 2.39 (q, *J* = 7.4 Hz, 2H), 2.14 (s, 3H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm. ¹³C NMR (75 MHz, (CD₃)₂SO) δ

- 165.0, 159.8, 102.8, 102.8, 100.2, 19.64 16.2, 12.7 ppm. HRMS (ESI-QTOF) calcd for $C_8H_{11}O_3$ $[M + H]^+$ 155.0703, found 155.0702. **9d**: Brown crystalline solid (0.139 g, 66% yield), R_f = 0.36 (silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, CD_3OD) δ 7.27 (s, 1H), 6.22 (s, 1H), 6.00 (s, 1H), 5.91 (s, 1H), 3.67 (s, 2H), 2.20 (s, 3H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 166.6, 165.1, 161.4, 153.9, 141.6, 111.0, 105.7, 100.5, 97.8, 22.4, 20.0 ppm. HRMS (ESI-QTOF) calcd for $C_{11}H_{11}O_4$ $[M + H]^+$ 207.0652, found 207.0654. **9e**: White powder (0.1592 g, 73% yield). m.p. 156-158 °C, R_f = 0.13 (silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, $(CD_3)_2SO$) δ 11.35 (s, 1H), 7.26 – 7.03 (m, 5H), 6.01 (s, 1H), 3.56 (s, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 167.1, 166.7, 161.8, 141.1, 129.1, 128.9, 126.8, 101.6, 100.9, 29.1, 20.0 ppm. HRMS (ESI-QTOF) calcd for $C_8H_{11}O_3$ $[M + H]^+$ 155.0703, found 155.0702. **9f**: White crystalline solid (0.1882 g, 76% yield) m.p. 211-213 °C, R_f = 0.34 (silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, $(CD_3)_2CO$) δ 7.32 – 7.23 (m, 4H), 6.05 – 6.02 (s, 1H), 3.68 (s, 2H), 2.15 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO) δ 165.6, 164.8, 160.7, 139.6, 130.3, 129.9, 128.0, 100.1, 99.8, 27.8, 19.4 ppm. HRMS (ESI-QTOF) calcd for $C_{13}H_{12}ClO_3$ $[M + H]^+$ 251.0469, found 251.0471. **9g**: Orange crystalline solid (0.0584 g, 48% yield), R_f = 0.16 (silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, $CDCl_3$) δ 6.21 (s, 1H), 2.47 – 2.39 (m, 2H), 2.20 (s, 3H), 1.54 – 1.41 (m, 2H), 1.31 – 1.22 (m, 8H), 0.85 (t, J = 6.9, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 167.8, 159.9, 103.6, 102.0, 32.1, 29.8, 29.5, 28.3, 23.26, 22.9, 19.9, 14.3 ppm. HRMS (ESI-QTOF) calcd for $C_{13}H_{21}O_3$ $[M + H]^+$ 225.1485, found 225.1489. **9h**: Orange crystalline solid (0.3926 g, 62% yield), m.p. 120-121 °C, R_f = 0.18 (silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 6.27 (s, 1H), 2.48 – 2.40 (m, 2H), 2.21 (s, 3H), 1.49 – 1.29 (m, 8H), 0.84 (t, J = 6.6, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 166.6, 160.0, 103.6, 101.9, 32.0, 29.5, 28.3, 23.3, 22.9, 19.9, 14.3 ppm. HRMS (ESI-QTOF) calcd for $C_{12}H_{19}O_3$ $[M + H]^+$ 211.1329, found 211.1331. **9i**: Brown crystalline solid (0.0314 g, 14% yield), R_f = 0.26 (silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.63 (d, J = 4.9 Hz, 1H), 8.05 – 7.97 (m, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.53 – 7.46 (m, 1H), 6.07 (s, 1H), 4.12 (s, 2H), 2.28 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 165.9, 160.5, 159.8, 146.1, 139.3, 123.9, 122.3, 102.5, 98.6, 32.1, 19.93 ppm. HRMS (ESI-QTOF) calcd for $C_{12}H_{12}O_3N$ $[M + H]^+$ 218.0812, found 218.0810.
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12. To a stirred suspension of 4-hydroxy-6-methyl-2-pyrone (**1**) (1.0 g, 7.93 mmol) in THF (22 mL) at room temperature was added *N,N,N',N'*-tetramethylethylenediamine (1.19 mL, 7.93 mmol) and HMPA (4.4 mL). The resulting pale yellow reaction mixture was cooled to 0 °C and *n*-BuLi (7.60 mL, 2.5 M in hexane, 19.0 mmol) was added dropwise, during which the solution became dark red in color. The reaction mixture was stirred for an additional hour at 0 °C, followed by dropwise addition of 2-iodopropane (2.43 g, 14.3 mmol). The reaction mixture was then warmed to room temperature and stirred for 16 hours. The reaction was acidified by the addition of 3.0 M HCl until the pH reached 2-3 then extracted with diethyl ether (3 x 40 mL). The organic layer was washed with water (3 x 20 mL), brine (20 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:9 to 1:1) to afford **13** (0.78 g, 58% yield) as a pale yellow crystalline solid. **13**: m.p. 98-100 °C; R_f = 0.40 (silica gel, EtOAc:hexanes 1:1); 1H NMR (400 MHz, $CDCl_3$) δ 6.00 (d, J = 2.0 Hz, 1H), 5.63 (d, J = 2.1 Hz, 1H), 2.35 (d, J = 7.2 Hz, 2H), 2.06 (hept, J = 13.7, 6.9 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.5, 166.4, 102.4, 89.8, 42.7, 26.9, 22.2 ppm. HRMS (ESI-QTOF) calcd for $C_9H_{13}O_3$ $[M + H]^+$ 169.0857, found 169.0857.
13. To a round bottom flask in open air was added hexaldehyde (0.18 mL, 1.5 mmol), 4-hydroxy-6-(2-methylpropyl)-2-pyrone (**13**) (91.2 mg, 0.5 mmol), diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (0.20 g, 0.6 mmol), and dichloromethane (10 mL). *L*-Proline (12.3 mg, 0.1 mmol) was then added and the sides of the flask were rinsed with dichloromethane again. The reaction mixture was then stirred vigorously overnight. The solvent was then removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:9 to 1:1) to afford **4** (41 mg, 30% yield) as a white powder. **4**: R_f = 0.38 (silica gel, silica gel, EtOAc:hexanes 1:1); 1H NMR (300 MHz, CD_3OD) δ 5.97 (s, 1H), 2.43 – 2.28 (m, 5H), 2.02 (hept, J = 13.7, 6.9 Hz, 1H), 1.51 – 1.21 (m, 9H), 1.00 – 0.84 (m, 8H) ppm. HRMS (ESI-QTOF) calcd for $C_{15}H_{25}O_3$ $[M + H]^+$ 253.1798, found 253.1797.