Syntheses of 2-Pyrones via Electrophilic Substitutions at C7 of 4-Hydroxy-6-methyl-2-pyrone through Mono- or Dianion Formation

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Abstract: Electrophilic substitution protocols useful for functionalizations at C7 of 4-hydroxy-6-methyl-2-pyrone, or triacetic acid, are described here. This method was applied to the synthesis of annularin E.

Key words: dianion, 2-pyrones, 4-hydroxy-6-methyl-2-pyrone, triacetic acid, electrophilic substitution

Pyrones are among the most important heterocyclic structures in medicinal chemistry, and specifically, 2-pyrones or α-pyrones can be found in a wide range of medicinally significant natural products.[1–3] These natural products range from complex natural products such as orevactaene (anti-HIV, see Figure 1)[4,5] and arisugacins (AChE inhibitors),[6–8] to simple ones such as rosellisin (antibacterial).[9,10]

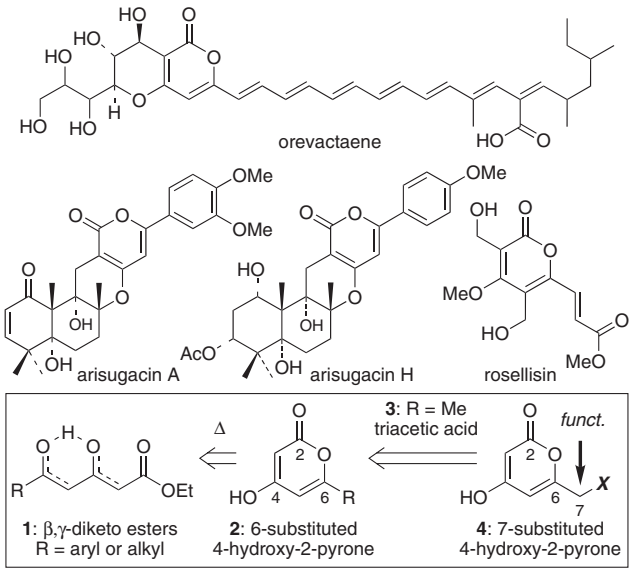
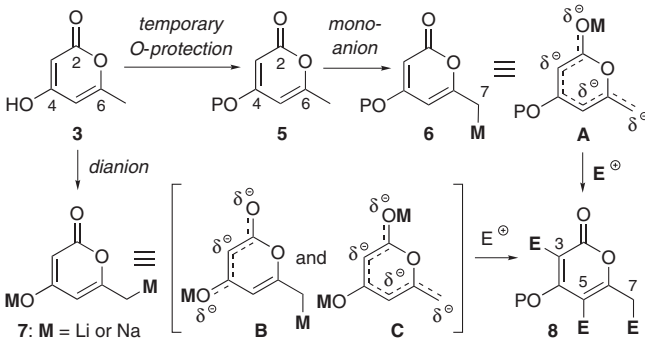


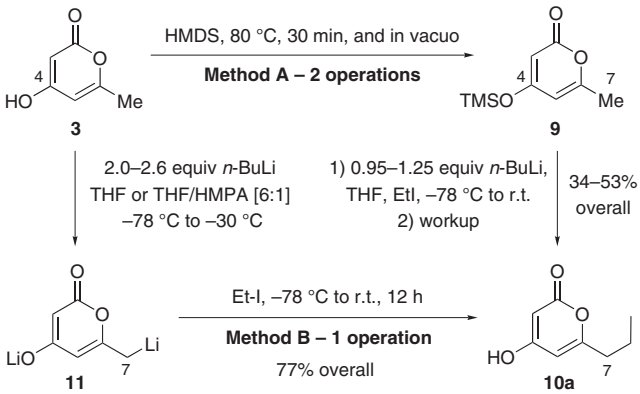
Figure 1 C7 Functionalization of 4-hydroxy-6-methyl-2-pyrones

Cyclizations of various β,δ-diketo esters **1** represent a common and practical synthetic entry to 6-substituted 4-hydroxy-2-pyrones **2** (Figure 1).[11–13] A subset of these 6-substituted 4-hydroxy-2-pyrones such as **4** can also be accessed directly from readily available 4-hydroxy-6-methyl-2-pyrone (triacetic acid, **3** ≡ **2**, R = Me) via functionalization at the C7 position. This method could provide a facile entry for constructing the C9–C10 bond to connect the side chain with the AB ring of orevactaene.[4,5] Despite various reports for the functionalization at C7 of 4-hydroxy-6-methyl-2-pyrone,[3,14] there are no general approaches. We report here electrophilic substitutions at the C7 position of 4-hydroxy-6-methyl-2-pyrones.

We examined two protocols for functionalizing C7 of 4-hydroxy-6-methyl-2-pyrone (**3**), the first involved temporary monoprotection of the C4-OH group as shown in **5**, and the second involved dianion formation as shown in **7** (Scheme 1). An obvious concern would be the regioselectivity of the ensuing electrophilic substitution of these anions (C3 vs C5 vs C7 as shown in **8**). The extent of delocalization in these anions as shown in their respective resonance structures **A** and **B/C** reveals potentially serious competing electrophilic substitutions.



Scheme 1 Dianion versus mono-O-protection protocol



Scheme 2 Method A versus Method B

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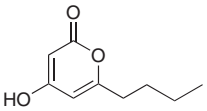
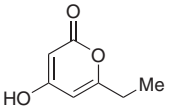
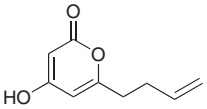
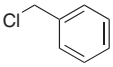
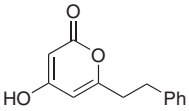
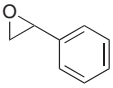
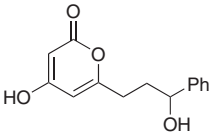
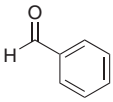
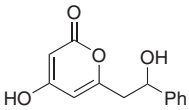
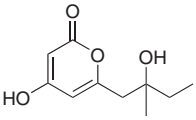
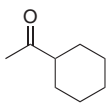
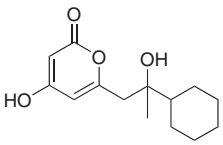
Firstly, for the monoanion approach (Method A, Scheme 2), we quickly found that we could cap the C4-OH group of **3** with a trimethylsilyl group employing hexamethyldisilazane. Subsequently, in a one-pot/two operation manner, we could evaporate the excess hexamethyldisilazane in vacuo and deprotonate at C7 using butyllithium (0.95 to 1.25 equiv) at –78 °C after recharging the reaction flask with anhydrous tetrahydrofuran. Ensuing addition of iodoethane led to pyrone **10a**[15] in 34–53% overall yield with the trimethylsilyl protection being hydrolytically cleaved during workup.

On the other hand, the dianion approach (Method B) appeared to be more effective. In a one-pot/one-operation manner, pyrone **10a** was obtained with an improved 77% overall yield by deprotonation of **3** with 2.0–2.6 equivalents of butyllithium followed by addition of iodoethane.

The generality of this C7 functionalization protocol is illustrated in Table 1. Except in the case of benzaldehyde (entries 8 and 9), the dianion protocol (Method B) is overall more effective than Method A when comparisons were explicitly made (entry 1 vs 2 and 4 vs 5). A range of electrophiles was feasible, including an epoxide (entry 7) and aldehyde (entries 8 and 9), although ketones were rather sluggish (entries 10 and 11). It is noteworthy that for some of the lower yielding reaction, the starting pyrone was found the to be the major remaining component in the crude reaction mixture, although minor amount of products with substitutions at C3 and C5 were seen sometimes in the crude mass spectrum.

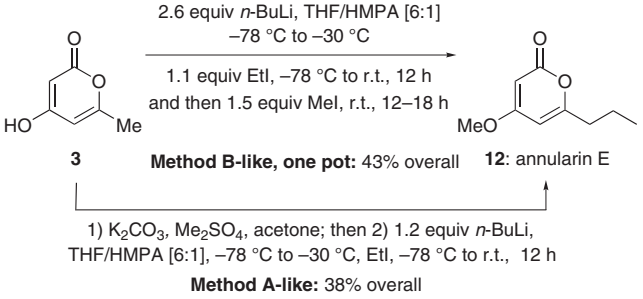
Finally, to illustrate an application of this protocol, we synthesized a simple 2-pyrone containing natural product annularin E (**12**) (Scheme 3).[16,17] Although related family

Table 1 Scope of Alkylations and Aldol Reactions

Entry	Electrophiles	C7 Addition products		Method	Yield (%)[a]
1			**10b**	A	35–42%
2				B	55–87%
3	MeI		**10c**	B	71
4			**10d**	A	25
5				B	64
6			**10e**	B	80
7			**10f**	B	80
8			**10g**	A	50
9				B	54
10			**10h**	B	20
11			**10i**	B	27

[a] Isolated yields.

members have shown promising activity against *Staphylococcus aureus* (ATCC 29213), annularin E itself has not been tested because of its scarcity.[16] As shown in Schemes 3, 4-hydroxy-6-methyl-2-pyrone (**3**) could be readily transformed into annularin E (**12**) by either Method B-like or Method A-like (since an O-methylation is in place of O-silylation) routes in good overall yields. We believe that Method A is overall less consistent because it depends on the extent of the silylation and the fate and/or stability of the trimethylsilylated intermediate. However, in the case of the annularin E synthesis, Method A appeared to be comparably effective as Method B, as it entailed a permanent capping of the C4-OH group.



Scheme 3 Application in the synthesis of annularin E

We have described here a useful protocol for functionalizing C7 of 4-hydroxy-6-methyl-2-pyrone en route to various substituted 2-pyrone building blocks that can be useful for natural product synthesis.

Commercially available 4-hydroxy-6-methyl-2-pyrone was used. NMR data were collected on Varian Unity-Inova 400 MHz or 500 MHz spectrometers. MS and HRMS spectra were obtained on a Bruker BioTOF II mass spectrometer or an Agilent 1100 LC/MSD. IR spectra were collected on a Bruker Equinox 55/5 FT-IR spectrophotometer.

4-Hydroxy-6-propyl-2-pyrone (10a); Typical Procedure for Method A

A suspension of 4-hydroxy-6-methyl-2-pyrone (**3**, 6.31 g, 50.0 mmol) in hexamethyldisilazane (100 mL), which was used both as the solvent and silylating agent, was heated at 80 °C and stirred under N_2 for 30 min. After cooling to r.t., the solvent was removed under reduced pressure. The residue was dissolved in THF and cooled to –78 °C. To this soln was added 2.6 M *n*-BuLi in hexanes (24.0 mL, 62.5 mmol). After stirring for 1 h, EtI (20.0 g, 10.4 mL, 130.0 mmol) was added dropwise via syringe and the soln was warmed to r.t. and stirred for 20 h.

The reaction was quenched with aq 6 M HCl (50 mL), and the organic layer was concentrated under reduced pressure. The crude residue was dissolved in EtOAc (0.5 L) and washed with sat. aq NaCl (2 × equal volume). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, gradient: 0–40% EtOAc–hexanes) to give the desired pyrone **10a** as a yellow oil; yield: 4.07 g (53%); R_f = 0.15 (50% EtOAc–hexanes).

IR (film): 2906 (m), 2596 (br s), 1562 (s), 1498 (s), 1421 (m), 1239 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H), 1.62–1.74 (m, 2 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 5.61 (d, *J* = 1.8 Hz, 1 H), 6.04 (d, *J* = 1.8 Hz, 1 H), 11.37 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 20.3, 35.7, 90.3, 101.7, 167.3, 168.7, 172.9.

MS (ESI): *m*/*z* = 177.0 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_8H_{10}NaO_3$: 177.0528; found: 177.0523.

6-Butyl-4-hydroxy-2-pyrone (10b); Typical Procedure for Method B

4-Hydroxy-6-methyl-2-pyrone (**3**, 5.90 g, 46.8 mmol) was dried via concentrating its soln in benzene (3 ×) under reduced pressure. To the residue solid was added anhyd THF (150 mL) and the resulting slurry was cooled to –78 °C; 2.5 M *n*-BuLi in hexanes (43.0 mL, 107.6 mmol) was added slowly dropwise via a syringe. HMPA was not always used, but when used, the ratio of THF to HMPA was ~ 6:1.

After stirring at –78 °C for 1 h, PrI (9.20 mL, 94.2 mmol) was added dropwise via a syringe. The resulting mixture was warmed to r.t. and stirred for 15 h. The soln was carefully quenched with 3 M HCl with the final pH being ~ 2. After partitioning, the aqueous layer was extracted with Et_2O (3 × equal volume), washed with sat. aq NaCl, and dried (Na_2SO_4). After filtration and concentration under reduced pressure, the crude dark oil was purified via flash column chromatography (silica gel, gradient: 0–40% EtOAc–hexanes) to give the desired pyrone **10b** as a yellow oil;[18] yield: 6.85 g (87%); R_f = 0.16 (50% EtOAc–hexanes).

IR (film): 2961 (br s), 1693 (s), 1660 (s), 1566 (s), 1445 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 1.37 (sextet, *J* = 7.4 Hz, 2 H), 1.63 (quintet, *J* = 7.5 Hz, 2 H), 2.50 (t, *J* = 7.5 Hz, 2 H), 5.62 (d, *J* = 2.1 Hz, 1 H), 6.05 (d, *J* = 1.8 Hz, 1 H), 11.39 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 21.8, 28.5, 33.1, 89.6, 101.3, 167.2, 168.5, 172.7.

MS (ESI): *m*/*z* = 191.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_9H_{12}NaO_3$: 191.0679; found: 191.0671.

6-Ethyl-4-hydroxy-2-pyrone (10c)

Yellow oil; R_f = 0.13 (50% EtOAc–hexanes).

IR (film): 2979 (br s), 1696 (s), 1566 (s), 1445 (m), 1243 cm^{-1} (s).

^{1}H NMR (75 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.5 Hz, 3 H), 2.55 (q, *J* = 7.5 Hz, 2 H), 5.62 (d, *J* = 2.1 Hz, 1 H), 6.05 (m, 1 H), 11.37 (br s, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 10.9, 26.9, 89.8, 100.7, 168.5, 168.6, 173.0.

MS (ESI): *m*/*z* = 163.0 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_7H_8NaO_3$: 163.0366; found: 163.0368.

6-But-3-enyl-4-hydroxy-2-pyrone (10d)

Yellow oil; R_f = 0.11 (50% EtOAc–hexanes).

IR (film): 3081 (br s), 1694 (s), 1665 (s), 1566 (s), 1445 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (q, *J* = 7.5 Hz, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 5.01–5.10 (m, 2 H), 5.60 (d, *J* = 2.0 Hz, 1 H), 5.78 (dddd, *J* = 6.5, 6.5, 10.5, 17.0 Hz, 1 H), 6.03 (d, *J* = 2.0 Hz, 1 H), 11.30 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.6, 33.0, 90.0, 101.9, 116.5, 135.9, 166.3, 168.6, 172.8.

MS (ESI): *m*/*z* = 189.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_9H_{10}NaO_3$: 189.0522; found: 189.0519.

4-Hydroxy-6-(2-phenylethyl)-2-pyrone (10e)
Yellow oil; R_f = 0.45 (60% acetone–hexanes).

IR (film): 3064 (m), 3029 (m), 2929 (m), 2352 (m), 1664 (s), 1568 (s), 1496 (m), 1448 (m), 1410 (w), 1252 (m), 1141 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 (m, 2 H), 2.97 (m, 2 H), 5.64 (d, *J* = 2.1 Hz, 1 H), 6.00 (d, *J* = 2.1 Hz, 1 H), 7.08–7.32 (m, 5 H), 11.37 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9, 35.5, 90.1, 102.1, 126.6, 128.3, 128.7, 139.7, 166.1, 168.5, 172.8.

MS (ESI): *m*/*z* = 239.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_{13}H_{12}NaO_3$: 239.0679; found: 239.0684.

4-Hydroxy-6-(3-hydroxy-3-phenylpropyl)-2-pyrone (10f)
Yellow oil; R_f = 0.30 (60% acetone–hexanes).

IR (film): 3064 (m), 3029 (m), 2926 (m), 2360 (m), 2340 (m), 1696 (s), 1669 (s), 1566 (s), 1505 (w), 1495 (m), 1255 (m), 1141 cm^{-1} (m).

^1H NMR (300 MHz, acetone-d_6): δ = 2.02 (m, 2 H), 2.61 (m, 2 H), 4.77 (t, *J* = 6.4 Hz, 1 H), 4.90–5.12 (br s, 1 H), 5.32 (d, *J* = 2.1 Hz, 1 H), 5.98 (td, *J* = 0.9, 2.1 Hz, 1 H), 7.23–7.44 (m, 5 H), 11.39 (br s, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 30.0, 36.5, 72.2, 89.0, 99.4, 125.8, 127.0, 128.2, 145.6, 164.2, 166.9, 170.2.

MS (ESI): *m*/*z* = 269.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{14}NaO_4$: 269.0784; found: 269.0777.

4-Hydroxy-6-(2-hydroxy-2-phenylethyl)-2-pyrone (10g)
Yellow oil; R_f = 0.33 (50% EtOAc–hexanes).

IR (film): 3088 (br s), 2623 (w), 2361 (m), 2342 (w), 1678 (s), 1626 (m), 1567 (s), 1446 (w), 1254 (m), 1053 cm^{-1} (w).

^1H NMR (500 MHz, acetone-d_6): δ = 2.81–2.86 (m, 2 H), 4.62–4.78 (br, 1 H), 5.09 (t, *J* = 6.3 Hz, 1 H), 5.28–5.33 (m, 1 H), 5.95–6.01 (m, 1 H), 7.22–7.48 (m, 5 H), 11.40 (br s, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 44.0, 70.8, 89.3, 101.2, 125.8, 127.3, 128.3, 144.7, 163.8, 164.0, 169.9.

MS (ESI): *m*/*z* = 255.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_{13}H_{12}NaO_4$: 255.0628; found: 255.0637.

4-Hydroxy-6-(2-hydroxy-2-methylbutyl)-2-pyrone (10h)
Yellow oil; R_f = 0.20 (60% acetone–hexanes).

IR (film): 3362 (br s), 2974 (w), 2934 (w), 2630 (w), 1694 (s), 1567 (s), 1448 (m), 1292 (w), 1259 (m), 1144 cm^{-1} (w).

^1H NMR (500 MHz, acetone-d_6): δ = 0.95 (t, *J* = 7.0 Hz, 3 H), 1.20 (q, *J* = 4.0 Hz, 3 H), 1.53–1.59 (m, 2 H), 2.61 (s, 2 H), 3.50–3.80 (br, 1 H), 5.32–5.36 (m, 1 H), 6.02–6.06 (m, 1 H), 11.39 (br s, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 44.0, 70.8, 89.3, 101.2, 125.8, 127.3, 128.3, 163.8, 164.0, 169.9.

MS (ESI): *m*/*z* = 221.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_{10}H_{14}NaO_4$: 221.0784; found: 221.0790.

6-(2-Cyclohexyl-2-hydroxypropyl)-4-hydroxy-2-pyrone (10i)
Yellow oil; R_f = 0.35 (60% acetone–hexanes).

IR (film): 3082 (br s), 2961 (w), 1696 (s), 1553 (m), 1446 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90–1.43 (m, 10 H), 1.60–1.85 (m, 5 H), 2.60 (d, *J* = 14.1 Hz, 1 H), 2.68 (d, *J* = 14.1 Hz, 1 H), 5.58 (d, *J* = 2.1 Hz, 1 H), 6.08 (d, *J* = 2.1 Hz, 1 H), 11.40 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2, 23.5, 26.6, 26.7, 26.8, 27.2, 28.1, 48.6, 75.5, 90.0, 102.1, 164.4, 168.0, 172.5.

MS (ESI): *m*/*z* = 275.4 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_{14}H_{20}NaO_4$: 275.1253; found: 275.1251.

Annularin E (12)
Yellow oil; R_f = 0.53 (50% EtOAc–hexanes).

IR (film): 2964 (m), 2874 (w), 1703 (s), 1647 (m), 1566 (s), 1455 (m), 1409 (m), 1245 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H), 1.68 (qt, *J* = 7.4, 7.4 Hz, 2 H), 2.42 (t, *J* = 7.4 Hz, 2 H), 3.80 (s, 3 H), 5.41 (d, *J* = 2.4 Hz, 1 H), 5.77 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.1, 35.6, 56.0, 87.6, 100.0, 165.2, 165.7, 171.5.

MS (ESI): *m*/*z* = 191.1 $(M + Na)^+$.

HRMS: *m*/*z* calcd for $C_9H_{12}NaO_3$: 191.0684; found: 191.0686.

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