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CONCISE AND EFFICIENT SYNTHESIS OF 4-HYDROXY-2-PYRONES FROM PENTANE-2,4-DIONES‡

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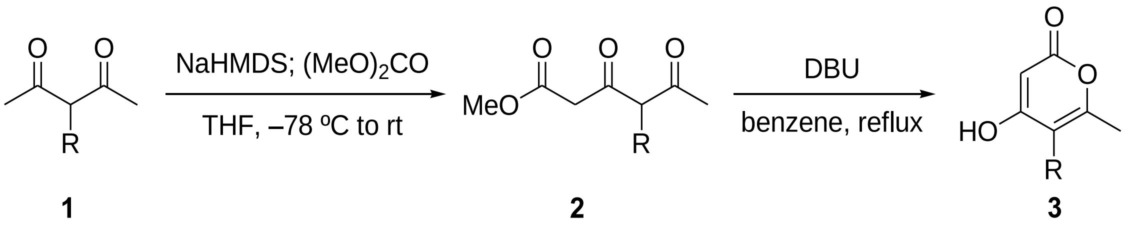
Abstract – A concise method for the synthesis of 4-hydroxy-2-pyrones has been developed. Various 5-substituted 4-hydroxy-2-pyrones were efficiently prepared in two steps from 3-substituted pentane-2,4-diones.

2-Pyrones are an important class of heteroaromatic molecules which are components in a variety of biologically active compounds.[1] They are also extensively utilized in organic synthesis as dienes in Diels–Alder reactions[2] and as precursors to other carbo- and heterocyclic systems.[3] For these reasons, considerable effort has been devoted toward finding an efficient synthesis of substituted 2-pyrones.[4] For example, 4-hydroxy-2-pyrones were prepared via the intramolecular cyclization of β,δ-diketo esters under basic conditions.[5] Although this method is useful for the synthesis of various 4-hydroxy-2-pyrones, there are problems with the low yields of the products and the lack of reproducibility. We report herein an improved method for the synthesis of 4-hydroxy-2-pyrones, in which various 5-substituted derivatives were efficiently prepared in two steps from 3-substituted pentane-2,4-diones.[6]

Scheme 1. Procedure for 5-substituted 4-hydroxy-2-pyrones **3**



Our procedure for the synthesis of 4-hydroxy-2-pyrones is described in Scheme 1. Thus, methoxycarbonylation of the pentane-2,4-diones **1** in the presence of sodium bis(trimethylsilyl)amide

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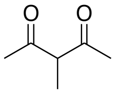
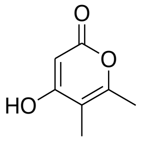
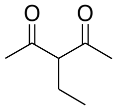
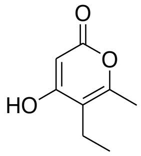
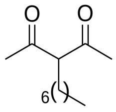
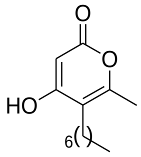
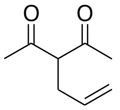
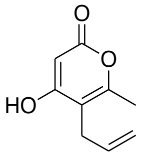
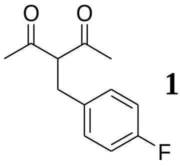
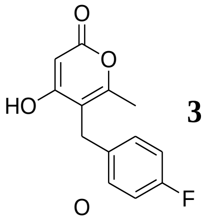
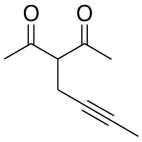
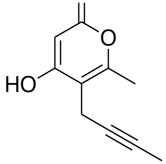
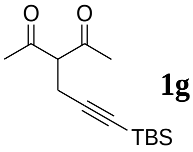
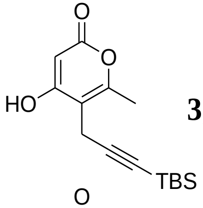
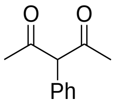
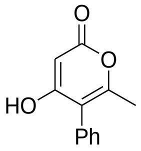
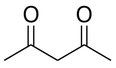
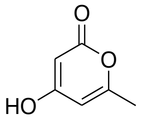
‡ This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

(NaHMDS) gives β,δ-diketo esters **2**. Subsequent cyclization of **2** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene produces 4-hydroxy-2-pyrones **3**.

Table 1. Synthesis of various 4-hydroxy-2-pyrones **3a**–**3i** from pentane-2,4-diones **1a**–**1i**

Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **3a**	68
2	 **1b**	 **3b**	62
3	 **1c**	 **3c**	89
4	 **1d**	 **3d**	56
5	 **1e**	 **3e**	40
6	 **1f**	 **3f**	68
7	 **1g**	 **3g**	79
8	 **1h**	 **3h**	43
9	 **1i**	 **3i**	62

[a] All the reactions were carried out as shown in Scheme 1.

[b] The yields were determined in two steps from **1**.

The results of the reactions using various pentane-2,4-diones **1a–1i** are summarized in Table 1. When 3-methylpentane-2,4-dione (**1a**) was subjected to the reaction, the 4-hydroxy-5,6-dimethyl-2-pyrone (**3a**) was obtained in two steps in 68% overall yield (entry 1). The reactions of the 3-ethyl- and 3-heptylpentane-2,4-diones (**1b** and **1c**) uneventfully afforded the corresponding products **3b** and **3c** in 62% and 89% overall yields, respectively (entries 2 and 3). The allyl- and *p*-fluorobenzyl-substituted substrates **1d** and **1e** also reacted to deliver the 4-hydroxy-2-pyrones **3d** and **3e** in moderate yields, respectively (entries 4 and 5). The pentane-2,4-diones **1f** and **1g** having a propargylic substituent at the 3-position were successfully transformed to the 4-hydroxy-2-pyrones **3f** and **3g**, respectively, in good yields (entries 6 and 7). When 3-phenylpentane-2,4-dione (**1h**) was subjected to the reaction, the phenyl-substituted product (**3h**) was produced in 43% overall yield (entry 8). The reactions of the parent pentane-2,4-dione (**1i**) also afforded the corresponding non-substituted product **3i** in 62% overall yield (entry 9).

Thus, we have developed a practical methodology for the synthesis of 5-substituted 4-hydroxy-2-pyrones. The reaction afforded a variety of substituted 4-hydroxy-2-pyrones, and the process provided an efficient and convenient protocol for the preparation of these derivatives.[7]

EXPERIMENTAL

Solvents were dried and distilled according to standard protocols. The phrase ‘residue upon workup’ refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure.

General procedure for the synthesis of 4-hydroxy-2-pyrones 3

Synthesis of **3c** (Table 1, entry 3): To a stirred solution of 1.06 M solution of NaHMDS in THF (14.3 mL, 15.1 mmol) was added dropwise 3-heptylpentane-2,4-dione (**1c**) (1.00 g, 5.04 mmol) in THF (30 mL) at −78 ºC. Stirring was continued for 2 h at rt, and dimethyl carbonate (0.42 mL, 5.04 mmol) was added dropwise to the reaction mixture at −78 ºC; stirring continued for another 10 h at rt. The reaction mixture was quenched with 10% HCl and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on a small amount of silica gel with hexane-AcOEt (30:70 v/v) as eluent to give the corresponding β,δ-diketo ester as a yellow oil. To a stirred solution of this β,δ-diketo ester in benzene (25 mL) was added DBU (1.51 mL, 10.08 mmol) at rt, and stirring was continued for 2.5 h under refluxing conditions. The reaction mixture was quenched with 10% HCl and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (60:40 v/v) as eluent to give the 4-hydroxy-2-pyrone **3c** (1.00 g, 89%, 2 steps) as a colorless solid.

5-Methyl-4-hydroxy-6-methylpyran-2-one (3a)[7]

Colorless powder; mp 204.5−206.8 °C (recrystallized from MeOH); IR (KBr) 3355, 2938, 1680, 1625 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.94 (3H, s), 2.26 (3H, s), 5.62 (1H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 9.2 (CH_3), 17.1 (CH_3), 88.3 (CH), 106.4 (Cq), 158.5 (Cq), 163.2 (Cq), 170.2 (Cq); HRMS (ESI) *m/z* calcd for $C_7H_8O_3$ $[M+Na]^+$ 163.0371, found 163.0373.

5-Ethyl-4-hydroxy-6-methylpyran-2-one (3b)

Colorless powder; mp 140.0−141.6 °C (recrystallized from MeOH-H_2O); IR (KBr) 3370, 2976, 2606, 1683, 1605 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, *J* = 7.6 Hz), 2.26 (3H, s), 2.41 (2H, q, *J* = 7.6 Hz), 5.62 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 17.0 (CH_3), 17.7 (CH_2), 90.1 (CH), 114.9 (Cq), 159.3 (Cq), 167.5 (Cq), 172.5 (Cq),; HRMS (ESI) *m/z* calcd for $C_8H_{10}O_3$ $[M+Na]^+$ 177.0528, found 177.0532.

5-Heptyl-4-hydroxy-6-methylpyran-2-one (3c)[8]

Colorless plates; mp 88.8−90.0 °C (recrystallized from MeOH-H_2O); IR (KBr) 3394, 2924, 2360, 1732, 1654 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.6 Hz), 1.28−1.46 (10H, m), 2.26 (3H, s), 2.36 (2H, t, *J* = 7.6 Hz), 5.63 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 17.2 (CH_3), 22.6 (CH_2), 24.3 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 90.0 (CH), 113.7 (Cq), 159.4 (Cq), 167.5 (Cq), 172.6 (Cq); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_3$ $[M+Na]^+$ 247.1310, found 247.1306.

5-Allyl-4-hydroxy-6-methylpyran-2-one (3d)[9]

Colorless plates; mp 128.0−129.1 °C (recrystallized from MeOH-H_2O); IR (KBr) 3446, 2928, 2742, 1714, 1698, 1645, 1620 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 3.16 (2H, d, *J* = 6.0 Hz), 5.01−5.07 (2H, m), 5.65(1H, s), 5.79−5.89 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.2 (CH_3), 28.0 (CH_2), 90.0 (CH), 111.0 (Cq), 115.6 (CH_2), 134.1 (CH), 160.6 (Cq), 167.3 (Cq), 172.1 (Cq); HRMS (ESI) *m/z* calcd for $C_9H_{10}O_3$ $[M+Na]^+$ 189.0528, found 189.0531.

5-(4-Fluorobenzyl)-4-hydroxy-6-methylpyran-2-one (3e)

Colorless powder; mp 195.9−197.4 °C (recrystallized from MeOH-H_2O); IR (KBr) 3447, 2946, 2577, 2531, 1689, 1643, 1613 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 3.73 (2H, s), 5.58 (1H, s), 6.98 (2H, d, *J* = 8.8 Hz), 7.29 (2H, d, *J* = 8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.2 (CH_3), 28.2 (CH_2), 88.7 (CH), 110.0 (Cq×2), 115.0 (CH, d, *J* = 11.5 Hz), 129.5 (CH, d, *J* = 7.4 Hz), 135.6 (Cq), 160.3 (Cq), 163.0 (Cq), 169.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{13}H_{11}FO_3$ $[M+Na]^+$ 257.0590, found 257.0588.

5-But-2-ynyl-4-hydroxy-6-methylpyran-2-one (3f)

Colorless needles; mp 196.8−199.1 °C (recrystallized from MeOH-H_2O); IR (KBr) 3385, 3107, 2926, 2738, 2672, 2615, 1700, 1652, 1622 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 1.70 (3H, s), 2.20 (3H, s), 3.16 (2H, s), 3.33 (2H, s), 5.29 (1H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 3.0 (CH_3), 13.2 (CH_2), 17.0 (CH_3), 75.4 (Cq), 76.1 (Cq), 88.4 (CH), 107.9 (Cq), 160.1 (Cq), 162.8 (Cq), 169.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{10}H_{10}O_3$ $[M+Na]^+$ 201.0528, found 201.0527.

5-[3-(*tert*-Butyldimethylsilanyl)prop-2-ynyl]-4-hydroxy-6-methylpyran-2-one (3g)

Colorless powder; mp 173.0−174.9 °C (recrystallized from MeOH-H_2O); IR (KBr) 3393, 2930, 2858, 2177, 1715, 1644 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.94 (9H, s), 2.37 (3H, s), 3.39 (2H, s), 5.70 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ −4.6 (CH_3), 14.8 (CH_2), 16.5 (Cq), 17.7 (CH_3), 26.0 (CH_3), 83.9 (Cq), 90.2 (CH), 102.5 (Cq), 109.2 (Cq), 161.4 (Cq), 166.9 (Cq), 170.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_3Si$ $[M+H]^+$ 279.1416, found 279.1417.

5-Phenyl-4-hydroxy-6-methylpyran-2-one (3h)[10]

Colorless powder; mp 189.1–191.4 °C (recrystallized from MeOH-H_2O); IR (KBr) 3363, 2927, 2683, 2625, 2595, 1658 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, s), 5.68 (1H, s), 7.26−7.29 (2H, m), 7.45−7.53 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 88.4 (CH), 113.8 (Cq), 127.6 (CH), 128.1 (CH), 130.5 (CH), 132.2 (Cq), 160.2 (Cq), 162.8 (Cq), 169.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{12}H_{10}O_3$ $[M+Na]^+$ 225.0528, found 225.0524.

4-Hydroxy-6-methylpyran-2-one (3i)[11]

Colorless needles; mp 187.3−188.9 °C (recrystallized from MeOH-H_2O); IR (kBr) 3382, 2926, 2735, 2622, 1715, 1660, 1625 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 5.48 (1H, s), 5.88 (1H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 19.4 (CH_3), 88.1 (CH), 100.2 (CH), 163.3 (Cq), 163.9 (Cq), 170.5 (Cq); HRMS (ESI) *m/z* calcd for $C_6H_6O_3$ $[M+H]^+$ 127.0395, found 127.0395.

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REFERENCES AND NOTES

1. (a) J. M. Dickinson, *Nat. Prod. Rep.*, 1993, **10**, 71; (b) P. S. Steyn and F. R. van Heerden, *Nat. Prod. Rep.*, 1998, **15**, 397; (c) G. P. McGlacken and I. J. Fairlamb, *Nat. Prod. Rep.*, 2005, **22**, 369; (d) C. E.

Salomon, N. A. Magarvey, and D. H. Sherman, *Nat. Prod. Rep.*, 2004, **21**, 105; (e) M. J. van Raaij, J. P. Abrahams, A. G. W. Leslie, and J. E. Walker, *Proc. Natl. Acad. Sci. USA.*, 1996, **93**, 6913; (f) P.-L. Wu, Y.-L. Hsu, T.-S. Wu, K. F. Bastow, and K.-H. Lee, *Org. Lett.*, 2006, **8**, 5207; (g) B. R. Clark, R. J. Capon, E. Lacey, S. Tennant, and J. H. Gill, *Org. Lett.*, 2006, **8**, 701; (h) J. C. Lee, E. Lobkovsky, N. B. Pliam, G. Strobel, and J. Clardy, *J. Org. Chem.*, 1995, **60**, 7076; (i) S. Thaisrivongs, M. N. Janakiraman, K.-T. Chong, P. K. Tomich, L. A. Dolak, S. R. Turner, J. W. Strohbach, J. C. Lynn, M.-M. Horng, R. R. Hinshaw, and K. D. Watenpaugh, *J. Med. Chem.*, 1996, **39**, 2400.

2. (a) T. F. Tam and P. Coles, *Synthesis*, 1988, 383; (b) C. J. Moody and K. F. Rahimtoola, *J. Chem. Soc., Perkin Trans. 1*, 1990, 681.
3. (a) G. H. Posner, T. D. Nelson, Ch. M. Kinter, and K. Afarinkia, *Tetrahedron Lett.*, 1991, 32, 5295; (b) K. Afarinkia and G. H. Posner, *Tetrahedron Lett.*, 1992, 33, 7839; (c) V. J. Ram and A. Goel, *J. Chem. Res. (S)*, 1997, 460; (d) B. Danieli, G. Lesma, M. Martinelli, D. Pasarella, I. Peretto, and A. Silvani, *Tetrahedron*, 1998, 54, 14081; (e) R. P. Hsung, H. C. Shen, C. J. Douglas, C. D. Morgan, S. J. Degen, and L. J. Yao, *J. Org. Chem.*, 1999, **64**, 609; (f) C.-H. Chen and C.-C. Liao, *Org. Lett.*, 2000, 2, 2049.
4. Recent examples of the synthesis of 2-pyrones, see: (a) C. J. Douglas, H. M. Sklenicka, H. C. Shen, D. S. Mathias, S. J. Degen, G. M. Golding, C. D. Morgan, R. A. Shih, K. L. Mueller, L. M. Scurer, E. W. Johnson, and R. P. Hsung, *Tetrahedron*, 1999, **55**, 13683; (b) R. C. Larock, M. J. Doty, and X. Han, *J. Org. Chem.*, 1999, **64**, 8770; (c) Y. Kishimoto and I. Mitani, *Synlett*, 2005, 2141; (d) R. Hua and M. Tanaka, *New J. Chem.*, 2001, **25**, 179; (e) S. Ma, S. Yu, and S. Yin, *J. Org. Chem.*, 2003, **68**, 8996; (f) I. Hachiya, H. Shibuya, and M. Shimizu, *Tetrahedron Lett.*, 2003, **44**, 2061; (g) T. Fukuyama, Y. Higashibeppu, R. Yamaura, and I. Ryu, *Org. Lett.*, 2007, **9**, 587.
5. (a) A. G. M. Barrett, T. M. Morris, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2272; (b) H. Hagiwara, N. Fujimoto, T. Suzuki, and M. Ando, *Heterocycles*, 2000, **53**, 549.
6. One of the results of our preliminary studies has been presented in the *47th Symposium on the Chemistry of Natural Products*, 2005, Tokushima, Japan (abstract pp. 595–600).
7. Very recently, Katoh utilized our methodology in the total syntheses of natural products: (a) T. Oguchi, K. Watanabe, K. Ohkubo, H. Abe, and T. Katoh, *Chem. Eur. J.*, 2009, **15**, 2826; (b) T. Oguchi, K. Watanabe, H. Abe, and T. Katoh, *Heterocycles*, 2010, **80**, 229.
8. I. P. Lolot, F. S. Fashkovsky, and F. A. Lakhvich, *Tetrahedron*, 1999, **55**, 4783.
9. J. Cervelló, J. Marquet, and M. Moreno-mañas, *Synth. Commun.*, 1990, **20**, 1931.
10. W. I. O'sullivan and C. R. Hauser, *J. Org. Chem.*, 1960, **25**, 1110.
11. R. R. Nagawade, V. V. Khanna, S. S. Bhagwat, and D. B. Shinde, *Eur. J. Med. Chem.*, 2005, **40**, 1325.