Total Syntheses of Daldiniapyrone, Annularin B, and (±)-Annularin F

Aleksey V. Kurdyumov,[a] R. Lizeth P. Muñoz,[a] Richard P. Hsung*[b]

[a] Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

[b] Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, WI 53705, USA
Fax +1(608)2625345; E-mail: rphsung@pharmacy.wisc.edu

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Abstract: The first concise total syntheses of daldiniapyrone, annularin B, and (±)-annularin F are described.

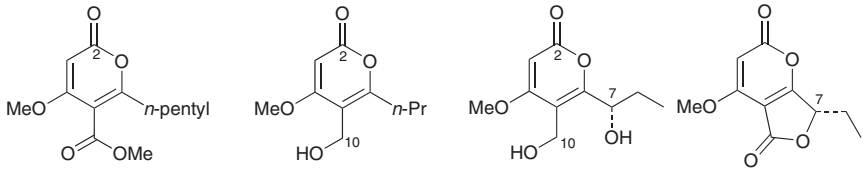
Key words: pyrones, malonic chloride condensation, selenium oxidation, daldiniapyrone, annularins

Pyrones are among the most important heterocyclic structures in medicinal and natural product chemistry, and specifically, 4-hydroxy-2-pyrones (or α-pyrones) can be found in a wide range of medicinally significant natural products.[1–3] Daldiniapyrone[4] (**1**) was isolated from organic extracts of fruit bodies of *Daldinia concentria* collected in Europe. Annularins[5] B (**2**), C (**3**) and F (**4**) were isolated from a fresh water fungus *Annulatascus triseptatus*, and were reported to possess antibacterial properties. Herein, we report the first total syntheses of daldiniapyrone, annularin B, and (±)-annularin F.

Despite numerous known pathways,[6,7] condensation of malonyl dichloride with β-keto esters[8] **5a–c** still remains to be the more straightforward and economical method for the preparation of 4-hydroxy-2-pyrones **6a–c** (Scheme 1). Our own attempts to modify the outcome of this reaction by using higher temperatures produced mainly the self-condensation product of **5a–c**. Use of Lewis acid, such as $ZnBr_2$, did not notably improve the yield. Other attempts such as deprotonation-alkylation at the C-7 position[9] of **6a** or **7a** also failed to give **6b**,**6c** or **7b** and **1**. The synthesis of daldiniapyrone (**1**) was ultimately completed through treating 2-pyrone **6c** with methyl sulfate and K_2CO_3 in refluxing acetone. The spectroscopic data of synthetic daldiniapyrone are identical to the reported values.[4]

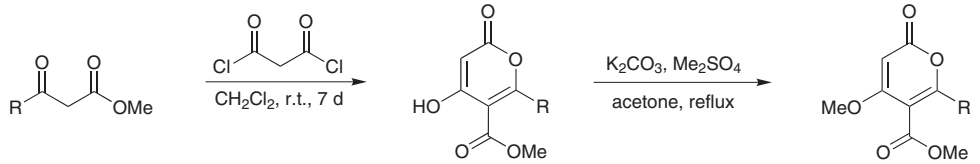
The ester group in 4-hydroxy-2-pyrone **6b** was subsequently reduced by using $BH_3{\cdot}Me_2S$ at room temperature for two hours[8] and the resulting alcohol **8** was selectively O-methylated to afford annularin B (**2**) (Scheme 2). Synthetic annularin B also gave spectroscopic data that are identical to the reported data.[5]

We then investigated the application of this methodology to the synthesis of annularins (i.e., C and F). Allylic oxidation[10] at C-7 of **7a** was best accomplished using 5.0 equivalents of SeO_2 in dioxane at 150 °C in a sealed tube for two days. Under these conditions, 4-methoxy-2-pyrone **7a** was completely consumed at the end of the reaction and the only isolatable product was aldehyde **9**.



1: daldiniapyrone **2**: annularin B **3**: annularin C **4**: annularin F

Figure 1 Daldiniapyrone and annularins B, C and F



5a: R = Me
5b: R = *n*-Pr
5c: R = *n*-pentyl

6a: 40%
6b: 51%
6c: 47%

7a: 93%
7b: 95%
daldiniapyrone ⇨ **1:** 95%

Scheme 1

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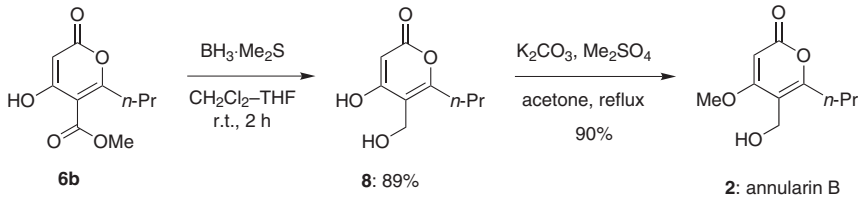


Scheme 2

Higher temperatures than 150 °C or longer reaction times than two days did not improve the yield of the reaction. Addition of EtMgBr Grignard reagent to aldehyde **9** fortuitously led to a spontaneous formation of the lactone ring, thereby completing the total synthesis of (±)-annularin F (**4**) (Scheme 3). Synthetic annularin F also gave spectroscopic data that are identical to the reported data.[5]

To explore the possible biosynthetic connection, we attempted to convert (±)-annularin F to (±)-annularin C. To our big disappointment, reduction of annularin F proved to be very challenging. Our attempts to finish the total synthesis of (±)-annularin C via allylic oxidation of C-7 position of 2-pyrone **6b**, annularin B, or TBS-protected annularin B all failed resulting in either no reaction or decomposition of the starting material.

In conclusion, we have described here the first concise total syntheses of new pyrone-based natural products daldiniapyrone, annularin B, and (±)-annularin F. However, the synthesis of annularin C remains to be further studied.

Column chromatography was performed on Bodman silica gel (60 Å, 230–400 mesh). Solvents were dried before use. Flasks were flame dried under vacuum and purged with N_2 before use. TLC plates (Whatman, polyester backed) were visualized with UV (254 nm) and either anisaldehyde or permanganate stains. IR spectra were recorded on NaCl plates using a Midac M2000 FTIR spectrometer. 500 MHz ^{1}H NMR spectra were recorded on a Varian Inova spectrometer; 300 MHz spectra were recorded on a Varian Unity or Varian Inova instruments and are referenced to TMS at δ = 0.00. ^{13}C NMR spectra were recorded on a Varian Inova spectrometers at 125 MHz and 75 MHz and are referenced to the center of $CHCl_3$ peak at δ = 77.23. Electrospray mass spectra were recorded on a Bruker Biotof II ESI-TOF/MS using PEG standards as high resolution calibrants. Unless noted, all reagents (Acros, TCI, Aldrich) were used as received.

4-Hydroxy-5-methoxycarbonyl-6-methyl-2-pyrone (6a); Typical Procedure

A solution of methyl acetoacetate (**5a**; 18.9 mL, 0.175 mol) and malonyl dichloride (17.0 mL, 0.175 mol) in anhyd CH_2Cl_2 (750 mL) was stirred at r.t. for 7 d. After which, the mixture was then washed with aq sat. $NaHCO_3$. The aqueous layer was acidified with 1% aq HCl and the crude product extracted with equal volume of CH_2Cl_2. The combined organic extracts were washed with brine and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and the resulting crude residue was subjected to silica gel column flash chromatography (50% EtOAc in hexanes) to give 2-pyrone **6a**; yield: 12.9 g (40%); R_f = 0.11 (50% EtOAc in hexanes); mp 105–108 °C.

IR (film): 2988m, 1745s, 1693s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 3.95 (s, 3 H), 5.47 (s, 1 H), 11.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 53.3, 88.8, 101.8, 161.7, 169.1, 169.3, 173.8.

MS (APCI): *m*/*z* (%) = 185 (100, [M$^+$ + H]), 101 (5).

HRMS: *m*/*z* calcd for $C_8H_8O_5$: 184.0372; found: 184.0452.

4-Hydroxy-5-methoxycarbonyl-6-propyl-2-pyrone (6b)

R_f = 0.20 (50% EtOAc in hexanes); mp 98–101 °C.

IR (film): 2964m, 1700s, 1652s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.5 Hz, 3 H), 1.77 (tq, *J* = 7.5, 7.5 Hz, 2 H), 2.95 (t, *J* = 7.5 Hz, 2 H), 4.00 (s, 3 H), 5.55 (s, 1 H), 11.50 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.3, 36.6, 53.3, 90.1, 101.5, 162.0, 169.0, 169.3, 176.9.

MS (APCI): *m*/*z* (%) = 211 (50, [M$^+$ – H]), 167 (5), 111 (100).

HRMS: *m*/*z* calcd for $C_{10}H_{12}O_5$: 212.0685; found: 212.0732.

4-Hydroxy-5-methoxycarbonyl-6-pentyl-2-pyrone (6c)

R_f = 0.50 (50% EtOAc in hexanes); mp 86–89 °C.

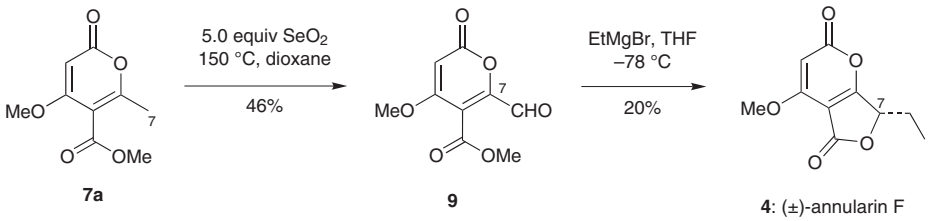
IR (film): 2958m, 2872m, 1739s, 1652m cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.3 Hz, 3 H), 1.26–1.41 (m, 4 H), 1.65–1.79 (m, 2 H), 2.95 (t, *J* = 7.8 Hz, 2 H), 3.99 (s, 3 H), 5.55 (s, 1 H), 11.51 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.3, 27.9, 32.1, 35.6, 53.1, 90.7, 101.3, 161.9, 169.2, 169.4, 177.5.

MS (APCI): *m*/*z* (%) = 241 (80, [M$^+$ + H]), 209 (100), 123 (5).

HRMS: *m*/*z* calcd for $C_{12}H_{16}O_5$: 240.0998; found: 240.1016.



Scheme 3

4-Methoxy-5-methoxycarbonyl-6-methyl-2-pyrone (7a); Typical Procedure

To a solution of 2-pyrone **6a** (8.50 g, 46.2 mmol) in acetone (300 mL) were added anhyd K_2CO_3 (19.0 g, 0.14 mol) and dimethyl sulfate (8.90 mL, 94.1 mmol). The mixture was refluxed for 5 h and then allowed to stir at r.t. for an additional 16 h. The mixture was filtered through Celite and concentrated under reduced pressure. Recrystallization of the crude product from acetone–hexane gave **7a**; 8.50 g (93%); R_f = 0.20 (50% EtOAc in hexanes); mp 91–94 °C.

IR (film): 2996w, 2957w, 1748s, 1713s cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 5.46 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 52.8, 56.6, 87.7, 108.9, 162.7, 164.0, 164.3, 168.3.

MS (APCI): *m*/*z* (%) = 199 (100, $[M^+ + H]$), 141 (5), 115 (5).

HRMS: *m*/*z* calcd for $C_9H_{10}O_5$: 198.0528; found: 198.0548.

4-Methoxy-5-methoxycarbonyl-6-propyl-2-pyrone (7b)

R_f = 0.25 (40% EtOAc in hexanes); mp 67–70 °C.

IR (film): 2964m, 1739s, 1559s cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.73 (tq, *J* = 7.5, 7.5 Hz, 2 H), 2.53 (t, *J* = 7.5 Hz, 2 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 5.50 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 20.6, 34.0, 52.6, 56.5, 87.6, 108.7, 162.7, 164.2, 166.3, 168.0.

MS (APCI): *m*/*z* (%) = 227 (60, $[M^+ + H]$), 209 (40), 195 (50), 177 (100), 149 (80).

HRMS: *m*/*z* calcd for $C_{11}H_{14}O_5$: 226.0841; found: 226.0892.

Daldiniapyrone (1)

R_f = 0.29 (40% EtOAc in hexanes); mp 54–56 °C (Lit.[4] mp 56–58 °C).

IR (film): 1733s, 1652m, 1558m cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.26–1.36 (m, 4 H), 1.60–1.75 (m, 2 H), 2.54 (t, *J* = 7.8 Hz, 2 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 5.47 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 23.4, 28.1, 32.3, 33.1, 53.4, 57.7, 88.6, 110.5, 165.2, 165.7, 167.7, 170.3.

MS (APCI): *m*/*z* (%) = 255 (100, $[M^+ + H]$), 197 (10), 171 (5).

HRMS: *m*/*z* calcd for $C_{13}H_{18}O_5$: 254.1154; found: 254.1168.

4-Hydroxy-5-hydroxymethyl-6-propyl-2-pyrone (8)

To a solution of **6b** (4.53 g, 21.3 mmol) in anhyd THF was added a solution of $BH_3{\cdot}Me_2S$ (1.0 M in CH_2Cl_2, 32.0 mL, 32.0 mmol) carefully dropwise at 0 °C. The mixture was allowed to warm up to r.t. and stirred for an additional 2 h. Anhyd MeOH was added and the resulting mixture was stirred for 1 h before being concentrated under reduced pressure. The crude residue was subjected to silica gel column flash chromatography (EtOAc) to afford diol **8**; yield: 3.46 g (89%); R_f = 0.37 (EtOAc); mp 135–137 °C.

IR (film): 3436br, 1700m, 1683w, 1652m cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.70 (tq, *J* = 7.5, 7.5 Hz, 2 H), 2.57 (t, *J* = 7.5 Hz, 2 H), 3.81 (br s, 1 H), 4.47 (s, 2 H), 5.52 (s, 1 H), 11.23 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ = 12.5, 19.8, 31.2, 52.4, 88.1, 110.5, 163.4, 164.0, 169.3.

MS (APCI): *m*/*z* (%) = 183 (100) $[M^+ - H]$, 139 (30), 121 (20), 113 (10).

HRMS: *m*/*z* calcd for $C_9H_{12}O_4$: 184.0736; found: 184.0812.

Annularin B (2)

Diol **8** was converted to the methoxy derivative **2** following the typical procedure given above for the preparation of **7a**; R_f = 0.42 (EtOAc); mp 88–92 °C (Lit.[5] mp 92–95 °C).

IR (film): 3412br, 1751w, 1655m cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.70 (tq, *J* = 7.5, 7.5 Hz, 2 H), 2.37 (br s, 1 H), 2.55 (t, *J* = 7.5 Hz, 2 H), 3.85 (s, 3 H), 4.45 (s, 2 H), 5.46 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ = 13.8, 21.3, 32.8, 55.5, 56.4, 88.4, 110.9, 164.1, 164.6, 170.2.

MS (APCI): *m*/*z* (%) = 199 (100) $[M^+ + H]$.

HRMS: *m*/*z* calcd for $C_{10}H_{14}O_4$: 198.0892; found: 198.0904.

4-Methoxy-5-methoxycarbonyl-6-carbaldehyde-2-pyrone (9)

A solution of 4-methoxy-2-pyrone (**7a**; 2.20 g, 11.1 mmol) and SeO_2 (6.60 g, 59.5 mmol) in anhyd dioxane (30 mL) was heated for 2 d at 150 °C in a sealed reaction flask. After cooling, the precipitate was filtered through Celite and the filtrate was evaporated under reduced pressure. The crude residue was subjected to silica gel column flash chromatography (20% EtOAc in hexanes) to afford aldehyde **9**; yield: 1.08 g (46%); R_f = 0.18 (50% EtOAc in hexanes); mp 96–99 °C.

IR (film): 2955w, 1751brs, 1640m cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 3.95 (s, 3 H), 5.81 (s, 1 H), 9.64 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.7, 57.3, 94.4, 114.2, 150.6, 160.1, 162.0, 166.2, 182.7.

MS (APCI): *m*/*z* (%) = 213 (100) $[M^+ + H]$, 185 (10), 137 (5).

HRMS: *m*/*z* calcd for $C_9H_8O_6$: 212.0321; found: 212.0506.

(±)-Annularin F (4)

Aldehyde **9** (75.0 mg, 0.36 mmol) was taken up in anhyd THF (5 mL) and cooled to –78 °C. To this solution was added dropwise EtMgBr (3.0 M solution in Et_2O, 0.13 mL, 0.39 mmol). After stirring for 2 h at –78 °C, the mixture was allowed to warm up to r.t. and stirred for an additional 14 h. The reaction was quenched with ice-cold 3% aq HCl. The crude mixture was then extracted several times with equal volume of CH_2Cl_2, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column flash chromatography (20% EtOAc in hexanes) of crude residues afforded (±)-annularin F (**4**); yield: 14.9 mg (20%); R_f = 0.47 (90% EtOAc in hexanes); mp 140–144 °C (Lit.[5] mp 143–145 °C).

IR (film): 2963w, 1740brs, 1662m, 1575m, 1486m, 1457m cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.2 Hz, 3 H), 1.84–1.96 (m, 1 H), 2.09–2.19 (m, 1 H), 3.99 (s, 3 H), 5.11 (dd, *J* = 4.5, 6.9 Hz, 1 H), 5.49 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.4, 25.0, 57.0, 78.5, 87.6, 101.1, 161.8, 164.1, 166.3, 179.5.

MS (GC): *m*/*z* (%) = 210 (50, $[M^+]$), 185 (100), 153 (20), 124 (100).

HRMS: *m*/*z* calcd for $C_{10}H_{10}O_5$: 210.0528; found: 210.0534.

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References

(1) For a review, see: Romines, K. R.; Chrusciel, R. A. *Curr. Med. Chem.* **1995**, *2*, 825.

(2) For recent reports, see: (a) Fors, K. S.; Gage, J. R.; Heier, R. F.; Kelly, R. C.; Perrault, W. R.; Wicnienski, N. *J. Am. Chem. Soc.* **1998**, *63*, 7348. (b) Vara Prasad, J. V. N.; Tummino, P. J.; Ferguson, D.; Saunders, J.; Vander Roest, S.; McQuade, T. J.; Heldsinger, A.; Reyner, E. L.; Stewart, B. H.; Guttendorf, R. J.; Para, K. S.; Lunney, E. A.; Gracheck, S. J.; Domagala, J. M. *Biochem. Biophys. Res. Commun.* **1996**, *221*, 815.

(3) (a) Schwartz, T. M.; Bundy, G. L.; Strohbach, J. W.; Thaisrivongs, S.; Johnson, P. D.; Skulnick, H. I.; Tomich, P. K.; Lynn, J. C.; Chong, K.-T.; Hinshaw, R. R.; Raub, T. J.; Padbury, G. E.; Toth, L. N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 399. (b) Thaisrivongs, S.; Janakiraman, M. N.; Chong, K.-T.; Tomich, P. K.; Dolak, L. A.; Turner, S. R.; Strohbach, J. W.; Lynn, J. C.; Horng, M.-M.; Hinshaw, R. R.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 2400. (c) Thaisrivongs, S.; Watenpaugh, K. D.; Howe, W. J.; Tomich, P. K.; Dolak, L. A.; Chong, K.-T.; Tomich, C. S. C.; Tomasselli, A. G.; Turner, S. R.; Strohbach, J. W.; Mulichak, A. M.; Janakiraman, M. N.; Moon, J. B.; Lynn, J. C.; Horng, M.-M.; Hinshaw, R. R.; Curry, K. A.; Rothrock, D. J. *J. Med. Chem.* **1995**, *38*, 3624.

(4) Quang, D. N.; Hashimoto, T.; Tanaka, M.; Baumgartner, M.; Stadler, M.; Asakawa, Y. *J. Nat. Prod.* **2002**, *65*, 1869.

(5) Li, C.; Nitka, M. V.; Gloer, J. B. *J. Nat. Prod.* **2003**, *66*, 1302.

(6) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854.

(7) For an account of our work in this area, see: Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Golding, G. M.; Mathias, D. S.; Degen, S. J.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683.

(8) Shimizu, T.; Hiranuma, S.; Watanabe, T. *Heterocycles* **1993**, *36*, 2445.

(9) (a) Shimo, T.; Matsuzaki, S.; Somekawa, K. *J. Heterocycl. Chem.* **1994**, *31*, 387. (b) Groutas, W. C.; Stanga, M. A.; Brubaker, M. J.; Huang, T. L.; Moi, M. K.; Carroll, R. T. *J. Med. Chem.* **1985**, *28*, 1106. (c) Poulton, G. A.; Cyr, T. D. *Can. J. Chem.* **1982**, *60*, 2821.

(10) Suzuki, E.; Hamajima, R.; Inoue, S. *Synthesis* **1975**, 192.