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Abstract

Antileukemic pyrone 1 was synthesized by way of a five-step procedure from *4*-Hydroxy-5-methoxycarbonyl-6-methyl-2-pyrone (8). This is the first synthesis of 4-methoxy-6-methyl-5-(3-oxobutyl)-2H-pyran-2-one (1).

Keywords

Antileukemic, Pyrone, First synthesis, Selective reduction

Disciplines

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Synthesis of an Antileukemic Pyrone from *Alternaria phragmospora*

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Antileukemic pyrone **1** was synthesized by way of a five-step procedure from *4*-Hydroxy-5-methoxycarbonyl-6-methyl-2-pyrone (**8**). This is the first synthesis of 4-methoxy-6-methyl-5-(3-oxobutyl)-2H-pyran-2-one (**1**).

Keywords: Antileukemic, Pyrone, First synthesis, Selective reduction.

In 2014 Ross and coworkers isolated the novel alpha-pyrones **1**–**3** from *Alternaria phragmospora*, an endophytic fungus from *Vinca rosea* leaves. Structures **1**–**3** are shown in Figure 1. Compound **1** showed promising antileukemic activities against HL60 cells with IC_{50} values of 0.9 μM and against K562 cells with IC_{50} values of 1.5 μM [1]. Pyrone **1** bears a substituent at the C-5 position and no substituent at C-3. This is rare among pyrone natural products. Compound **4** was recently isolated from the endophytic fungus *Embellisia* sp [2].

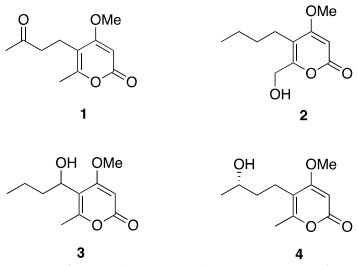
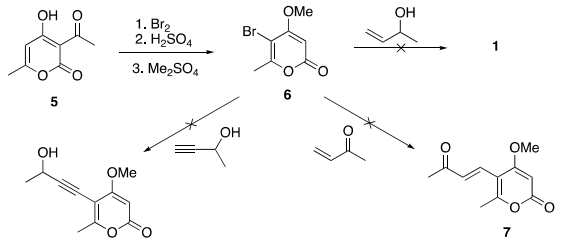


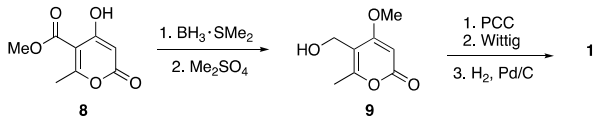
Figure 1: Pyrones from *Alternaria phragmospora* and *Embellisia* sp.

Initially, our strategy was to transform commercially available keto pyrone **5** into bromopyrone **6** by way of the three-step pathway shown in Scheme 1 [3]. We then expected to utilize palladium mediated coupling reactions to produce either **1** or **7**. Unfortunately, neither the Heck reaction with methyl vinyl ketone or 1-buten-3-ol nor the Sonogashira reaction with 3-butyn-2-ol afforded the desired products [4-5]. Either returned starting material or debrominated products were recovered. Presumably, the substituents at C-4 and C-6 were responsible, since 4-bromo-pyrone undergoes straightforward couplings [6].



Scheme 1: Attempted synthesis.

In view of the unexpected recalcitrance of **6**, we devised a new strategy shown in Scheme 2 focusing on pyrone **8**, readily available in one step from ethyl acetoacetate and malonyl chloride [7]. Selective reduction of the ester in pyrone **8** was difficult. Fortunately, a report from Shimizu that borane-dimethyl sulfide complex selectively reduces esters in the presence of pyrones enabled the selective reduction of **8** in 96% yield [8]. Methylation using dimethyl sulfate provided pyrone **9** in 84% yield.



Scheme 2: Synthesis of compound **1**.

Oxidation of **9** using pyridinium chlorochromate (PCC) followed by Wittig reaction using $AcCH{=}PPh_3$ afforded enone **7**. This enone could be reduced to **1** using hydrogen gas with Pd/C catalyst in 70% overall yield from **9**.

Pyrone **1** is prepared in five steps from pyrone **8**. This represents the first synthesis of **1**, a promising antileukemic natural product.

Experimental

4-Hydroxy-5-methoxycarbonyl-6-methyl-2-pyrone (8): A solution of methyl acetoacetate (11.0 mL, 102 mmol) and malonyl chloride (9.92 mL, 102 mmol) in anhydrous CH_2Cl_2 (300 mL) was stirred at r.t. for 7 days. After which, the mixture was then washed with aqueous sat. $NaHCO_3$. The aqueous layer was acidified with 1% aqueous HCl and the crude product extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine and dried over anhydrous 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 **8** (7.7 g, 41%).
R_f: 0.3 (50% EtOAc in hexanes).
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.51 (s, 1H), 5.55 (s, 1H), 3.99 (s, 3H), 2.65 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 169.2, 169.1, 161.5, 101.5, 90.1, 53.2, 22.6;
HRMS (ESI-QTOF) calcd for $C_8H_8O_5$ $[M+H]^+$ 185.0444, found 185.0441.

5-Hydroxymethyl-4-methoxy-6-methyl-2-pyrone (9): To a solution of **8** (1.08 g, 5.86 mmol) in anhydrous THF (20 mL) was added a solution of $BH_3{\cdot}Me_2S$ (2.0M in toluene, 4.4 mL, 8.8 mmol)

dropwise at 0 °C. The mixture was allowed to warm up to r.t. and stirred for an additional 2 hours. Anhydrous MeOH was added and the resulting mixture was stirred for 1 hour before being concentrated under reduced pressure. The crude residue was used for the next step without further purification.

To a solution of the crude product above (910 mg, 5.83 mmol) in acetone (20 mL) was added anhydrous K_2CO_3 (2.4 g, 17.37 mmol) and dimethyl sulfate (1.1 mL, 11.6 mmol). The mixture was refluxed overnight. The mixture was filtered through Celite and concentrated under reduced pressure. Recrystallization of the crude product from EtOAc-hexane gave **9** (992 mg, 84%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (s, 1H), 4.47 (s, 2H), 3.87 (s, 3H), 2.33 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 163.9, 161.1, 110.7, 88.1, 56.3, 55.4, 17.1.
HRMS (ESI-QTOF) calcd for $C_8H_{10}O_4$ $[M+H]^+$ 171.0652, found 171.0651.

4-methoxy-6-methyl-5-(3-oxobut-1-en-1-yl)-2H-pyran-2-one (7)
R_f: 0.28 (5% MeOH in CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 16.3 Hz, 1H), 6.64 (d, *J* = 16.2 Hz, 1H), 5.50 (s, 1H), 3.87 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 169.6, 163.7, 162.5, 132.5, 130.9, 108.6, 88.2, 56.4, 28.2, 18.9.
HRMS (ESI-QTOF) calcd. for $C_{11}H_{12}O_4$ $[M+H]^+$ 209.0808, found 209.0804.

4-methoxy-6-methyl-5-(3-oxobutyl)-2H-pyran-2-one (1): A solution of **7** (123.7 mg, 0.59 mmol) in ethanol under H_2 atmosphere (1 atm) was stirred overnight in the presence of 10 mol % Pd/C (10% wt.). After which, the catalyst was removed by Celite and the filtrate was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc : hexanes 2:1) to afford **1** in 89% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (s, 1H), 3.79 (s, 3H), 2.56 (s, 4H), 2.22 (s, 3H), 2.12 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 170.4, 164.3, 158.5, 110.0, 87.9, 56.1, 42.5, 29.9, 18.6, 17.2.
HRMS (ESI-QTOF) calcd. for $C_{11}H_{14}O_4$ $[M+H]^+$ 211.0865, found 211.0963.

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