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Synthesis of butenolides as seed germination stimulants

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Abstract

Syntheses of a series of novel butenolides as seed germination stimulants are described. The key steps include the cyclization reaction of enamine **4** to form a pyran ring, the efficient halogenating reaction and the selective lithiation reaction of butenolides.

1. Introduction

The butenolide, 3-methyl-2H-furo[2,3-*c*]pyran-2-one (**1**), has recently been identified as a constituent of smoke. It has been shown to possess unique germination properties at extraordinarily low concentrations, as low as 10^{-9} M, and has therefore been postulated to play a role in field and forest restoration following fires.[1] The synthesis of **1** has recently been reported, however, we sought an alternate synthesis for our analog program directed at structure–activity studies.[2] Here we report a new synthesis to the plant-derived butenolide **1** as well as the synthesis of analogs of formula **2** (Fig. 1).

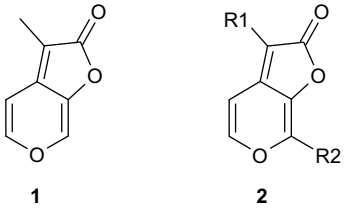

Fig. 1.

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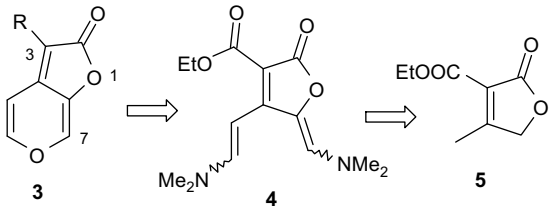
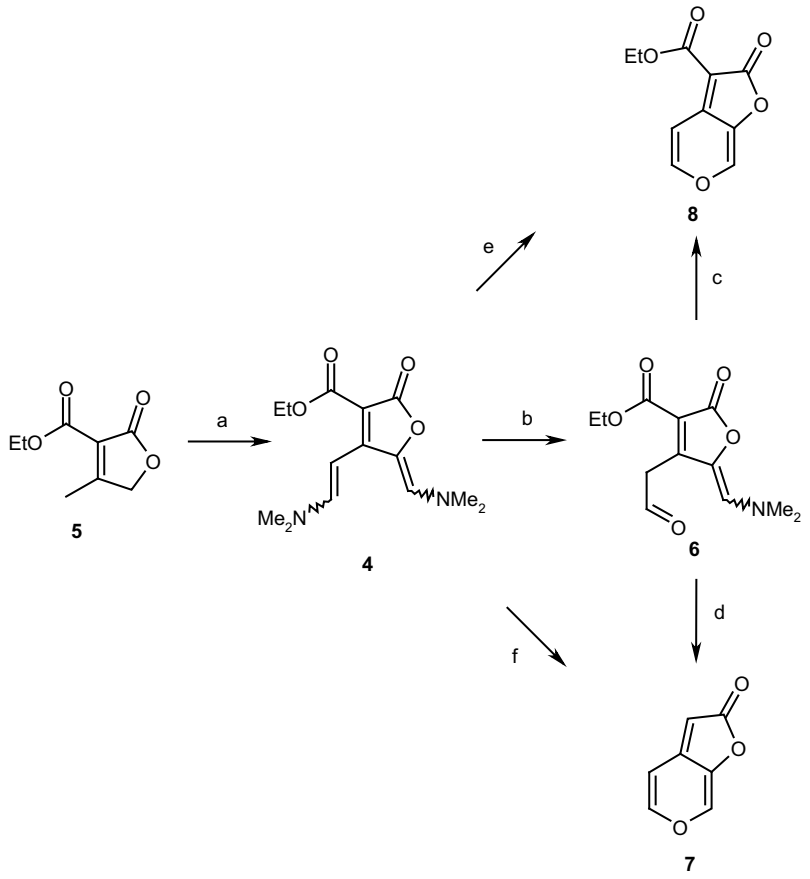


Fig. 2.

To accomplish this we envisioned a strategy that utilized a ring closure of compound **4**, or its equivalent aldehyde, to form the pyran ring of butenolide **3** (Fig. 2). Enamine **4** is readily available from the known butenolide **5**.[3]

2. Results and discussion

Enamine **4** was readily prepared by simply heating butenolide **5** with excess *N*,*N*-dimethylformamide dimethyl acetal and removing the methanol generated by distillation (Scheme 1). Without further purification, **4** was converted to aldehyde **6** by treatment with 1.0 M aqueous HCl affording compound **6** in 60% yield over two steps.[4] Cyclization of aldehyde **6** in the mixed solvents THF/CF_3COOH/H_2O (20:2:1) resulted in butenolide **8** in 29% yield. In contrast cyclization of aldehyde **6** in the solvent mixture CF_3COOH/dioxane (3.75:1) provided the decarboxylated



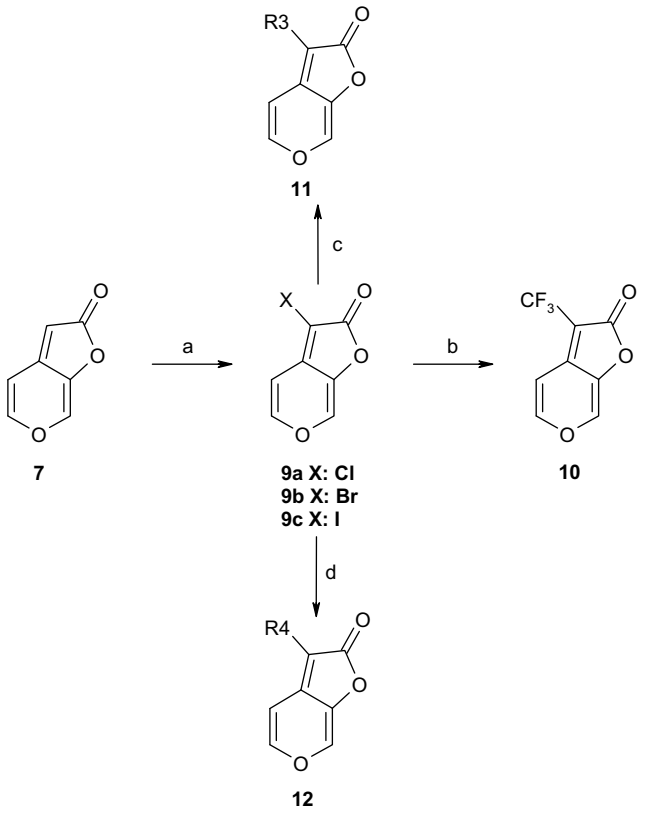
Scheme 1. Reagents and conditions: (a) $Me_2NCH(OMe)_2$; (b) HCl, THF, 60% for two steps; (c) THF/CF_3COOH/H_2O; 29%; (d) dioxane/CF_3COOH, 32%; (e) THF/CF_3COOH/H_2O; 15% for two steps; (f) CF_3COOH/H_2O, 15% for two steps.

butenolide **7** in 32% yield.[5] Butenolides **7** and **8** could also be prepared directly from the freshly prepared enamine **4** although in the significantly lower yield of 15%.[6]

Introduction of substituents at the 3-position of compound **7** was accomplished as shown in Scheme 2. Treatment of **7** with NBS in ethanol at room temperature[7] provided the corresponding bromide **9b** in excellent yield. Chloride **9a** and iodide **9c** were obtained via the same procedure using NCS or NIS in good yield. With the halogenated compounds **9** in hand, various functional groups could be introduced. For example, the trifluoromethyl analog **10** was obtained by treatment of **9c** with trifluromethyltriethylsilane in the presence of copper iodide and potassium fluoride in NMP according to the literature procedure.[8] Introduction of electrophilic groups was accomplished by reaction of bromide **9b** or iodide **9c** with an alkyllithium or alkylmagnesium halide to form an organometallic intermediate, followed by quenching with an electrophile R_3X.[9] Alternatively, the palladium catalyzed coupling reaction of **9b** or **9c** with boronic acids or tin reagents provided analogs **12** in moderate to good yield.[10] The natural butenolide **1** could be prepared by either method (Table 1, entries 2 and 5).

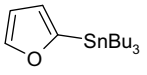
In order to introduce substituents at the 7-position of compound **13** or **1** an interesting method was developed via direct metalation as shown in Scheme 3. Treament of **13a** with LHMDS in THF at −78 °C followed by quenching with trimethylsilyl chloride, afforded **14b** (R = H, $R_2 = SiMe_3$) in 50% yield. The structure of **14b** was unambiguously confirmed by X-ray structural analysis.[11] Application of this procedure with different substrates of compounds **13** or **1** (R = H, Br or Me) provided the corresponding analogs of **14**. These results are summarized in Table 2. In addition, the chemical yield was improved from 50% to 90% by mixing substrate **13a** with the TMSCl prior to the addition of LHMDS as can be seen in Table 2 by comparison of entries 2 and 6. A similar result was obtained with substrate **1** ($R = CH_3$, Table 2, entry 5). Alternatively, the palladium catalyzed coupling of iodide **14a** with a variety of boronic acids or organotin reagents also allowed for preparation of derivatives at the 7-position.

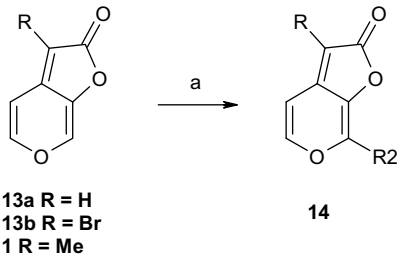
In conclusion, we have demonstrated a very efficient route to butenolides **7** and **8**. The halogenation of **7** opens the door to various butenolide analogs for SAR exploration, including the preparation of the natural seed germination stimulant **1**. The selective lithiation of **13** or **1** allows for the preparation of a variety of derivatives. Some of these analogs have shown germination activity equivalent to butenolide **1**.



Scheme 2. Reagents and conditions: (a) (i) NCS, EtOH, **8a**, 70%; (ii) NBS, EtOH, **8b**, 90%; (iii) NIS, EtOH, **8c**, 60%; (b) CF_3SiEt_3, KF, CuI, 1-methyl-2-pyrrolidinone, 50%; (c) *n*-BuLi, THF, −78 °C, R_3X; (d) $Pd(OAc)_2$, S-Phos, K_3PO_4, $R_4B(OH)_2$, toluene; or $Pd(PPh_3)_4$, LiCl, R_4SnBu_3, toluene. S-Phos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Table 1
Electrophilic substitution of compounds **9**

Entry	Substrate	Reactant (R_3X or R_4X)	Product	Yield (%)
1	**9c**	CF_3SiEt_3	**10**	45
2	**9b**	MeI	**1** (R_3 = Me)	20
3	**9b**	TMSCl	**11b** (R_3 = $SiMe_3$)	20
4	**9c**	PhCHO	**11c** (R_3 = CHOHPh)	10
5	**9b**	$MeB(OH)_2$	**1** (R_4 = Me)	90
6	**9b**	$EtB(OH)_2$	**12b** (R_4 = Et)	55
7	**9b**	CH_2=$CHSnBu_3$	**12c** (R_4 = $CHCH_2$)	60
8	**9b**	$PhB(OH)_2$	**12d** (R_4 = Ph)	85
9	**9c**		**12e** (R_4 = 2-furan)	80



Scheme 3. Reagents and conditions: (a) LHMDS, THF, −78 °C, R_2X. LHMDS: lithium bis(trimethylsilyl)amide.

Table 2
Electrophilic substitution of compounds **13**

Entry	Substrate	R_2X	Product	Yield (%)
1	**13a** (R = H)	I_2	**14a** (R_2 = I)	35
2	**13a** (R = H)	TMSCl	**14b** (R_2 = $SiMe_3$)	50
3	**13a** (R = H)	ClCOOMe	**14c** (R_2 = COOMe)	30
4	**13b** (R = Br)	TMSCl	**14d** (R_2 = $SiMe_3$)	10
5	**1** ($R = CH_3$)	TMSCl	**14e** (R_2 = $SiMe_3$)	90
6	**13a** (R = H)	TMSCl	**14b** (R_2 = $SiMe_3$)	90

Acknowledgments

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4. Procedure to prepare enamine **4** and aldehyde **6**: Ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate (1.5 g, 8.82 mole) and dimethylformamide dimethylacetal (30 mL) were combined and heated under stirring in a round bottom flask with a distillation apparatus equipped with a vacuum jacketed vigreux column. The temperature at the distillation head gradually rose to 105 °C over the course of about 2 h. The reaction mixture in the round bottom flask was cooled to room temperature, and concentrated under reduced pressure with a Rotovap at room temperature to give compound **4** (2.7 g, containing small amounts of dimethylformamide and DMF-dimethylacetal. This material was used fresh for the subsequent reaction without further purification.). ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 2.98 (s, 6H), 3.23 (s, 6H), 4.31 (q, J = 7.2 Hz, 2H), 5.77 (d, J = 13 Hz, 1H), 6.22 (s, 1H), 7.15 (d, J = 13 Hz, 1H). To ethyl 5-dimethylamino-methylene-4-(2-dimethylamino-vinyl)-2-oxo-2,5-dihydro- furan-3-carboxylate (7.5 g, crude product freshly prepared from 4.25 g (25 mmol) of ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate as described above) in tetrahydrofuran (50 mL) under stirring, hydrochloric acid (1 N, 30 mL) was added. The reaction mixture was further stirred at room temperature for 2 h and concentrated under reduced pressure with the use of a room temperature bath. The residue thus obtained was purified with a silica gel column eluted with dichloromethane and methanol mixtures (from dichloromethane to methanol/dichloromethane: 10/90) to give compound **6** as a foam (3.8 g, 60% from ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate). TLC R_f = 0.28 ($MeOH/CH_2Cl_2$, 1:9). This material was kept in a refrigerator to avoid decomposition. A sample of this material was recrystallized from benzene and showed no decomposition at room temperature over a week. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 3.25 (bs, 3H), 3.43 (bs, 3H), 3.94 (d, J = 1.2 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 6.36 (s, 1H), 9.66 (t, J = 1.2 Hz, 1H).
5. Procedure for butenolides **7** and **8** from aldehyde **6**: Dioxane (400 ml) and trifluoroacetic acid (1500 ml) were combined and stirred. When

the exotherm subsided, the mixture was warmed to 90 °C. Ethyl 5-dimethylaminomethylene-2-oxo-4-(2-oxo-ethyl)-2,5-dihydro-furan-3-carboxylate (20 g, solid) was added in one portion with good mechanical stirring. The temperature of the reaction was controlled between 92 and 95 °C. The reaction was stopped at 13 minutes by quickly cooling in a dry-ice/acetone bath to below room temperature. The reaction mixture was concentrated on a rotovap with a high vacuum oil pump at 25 °C. The residue was directly applied to a silica gel column and eluted with hexanes then with hexanes/ethyl acetate mixtures to give butenolide **7** (3.46 g, 32%). TLC $R_f = 0.26$ (EtOAc/hexanes, 1:1); mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 5.42 (d, $J = 1.2$ Hz, 1H), 6.66 (d, $J = 5.4$ Hz, 1H), 7.43 (d, $J = 5.4$ Hz, 1H), 7.55 (d, $J = 1.2$ Hz, 1H). Ethyl 5-dimethylaminomethylene-2-oxo-4-(2-oxo-ethyl)-2,5-dihydro-furan-3-carboxylate (1.5 g, 5.93 mmol) was dissolved in a mixture of tetrahydrofuran (37 mL), trifluoroacetic acid (3.7 mL) and water (1.9 mL) and warmed to reflux with stirring. The reaction was closely monitored with NMR and TLC (methanol/dichloromethylene: 1/19). After 2 h of heating, the reaction mixture was cooled to room temperature and concentrated under reduced pressure with the use of a bath at room temperature. The residue thus obtained was dissolved in a small amount of dichloromethane and purified with a silica gel column eluted with ethyl acetate and hexanes (ethyl acetate/hexanes from 1/5 to 2/1) to give butenolide **8** (0.36 g, 29.2%). TLC $R_f = 0.13$ (EtOAc/hexanes, 1:1); mp 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, $J = 6.8$ Hz, 3H), 4.38 (q, $J = 6.8$ Hz, 2H), 7.53 (d, $J = 5.2$ Hz, 1H), 7.83 (d, $J = 5.2$ Hz, 1H), 7.91 (s, 1H).

6. Procedure for butenolides **7** and **8** from enamine **4**: To a mixture of ethyl 5-dimethylaminomethylene-4-(2-dimethylamino-vinyl)-2-oxo-2,5-dihydro-furan-3-carboxylate (2.9 g, crude product freshly prepared from 1.5 g (8.82 mmol) of ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate as described above) and ice (10 g) cooled in an external ice/water bath under stirring, trifluoroacetic acid (50 mL) was added slowly maintaining the temperature of the reaction mixture below 25 °C. After the addition, the reaction mixture was further stirred at room temperature for one hour and then refluxed for 30 minutes. The reaction mixture was concentrated under reduced pressure at room temperature. The residue thus obtained was dissolved in a small amount of dichloromethane and applied to the top of a silica gel column, eluted with ethyl acetate and hexane mixtures (ethyl acetate/hexane from 1/1 to 2/1) to give butenolide **7** (0.175 g, 14.6% from ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate). Ethyl 5-dimethylaminomethylene-4-(2-dimethylamino-vinyl)-2-oxo-2,5-dihydro- furan-3-carboxylate (5 g, crude product freshly prepared from 2.78 g (16.3 mmol) of ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate as described above) in a mixture of trifluoroacetic acid (25 mL), water (12.5 mL), and tetrahydrofuran (125 mL) was stirred at room temperature for 2 h and then warmed to reflux. The reaction was closely monitored with NMR and TLC (methanol (5%) to dichloromethylene (95%)). After 3 h of heating, the reaction mixture was cooled and concentrated under reduced pressure at room temperature to a thick residue. This residue was dissolved in a small amount of dichloromethane and purified with a silica gel column eluted with ethyl acetate and hexane mixtures (ethyl acetate/hexane from 1/5 to 2/1) to give butenolide **8** (0.51 g, 15% from ethyl 4-methyl-2-oxo-2,5-dihydro-furan-3-carboxylate).
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11. Crystallographic data for **14b**: $C_{10}H_{12}O_3Si$, from Et_2O/hexane, colorless, irregular block, $\sim 0.540 \times 0.480 \times 0.080$ mm, monoclinic, *Cc*, $a = 7.676(6)$ Å, $b = 22.260(19)$ Å, $c = 6.979(6)$ Å, $\beta = 112.329(8)°$, Vol = 1103.0(16) Å^3, $Z = 4$, $T = -100$ °C, formula weight = 208.29, density = 1.254 g/cm^3, μ(Mo) = 0.19 mm^{-1}. The details of the crystal data have been deposited with Cambridge Crystal Data Centre as supplementary publication No. CCDC 676590.