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Synthesis of the seed germination stimulant 3-methyl-2*H*-furo[2,3-*c*]pyran-2-ones utilizing direct and regioselective Ti-crossed aldol addition

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ABSTRACT

3-Methyl-2*H*-furo[2,3-*c*]pyran-2-ones **1** and **2**, a unique and remarkable seed germination stimulant, and its analogue were synthesized using direct and regioselective Ti-crossed aldol addition between dihydro-2*H*-pyran-3(4*H*)-ones and methyl pyruvate as the key step, followed by furanone formation.

1. Introduction

In 2004, Flematti's group disclosed the unique and remarkable seed germination stimulatory activity of 3-methyl-2*H*-furo[2,3-*c*]-pyran-2-one **1** in a wide range of plant species.[1] This lead generation finding is considered to be a promising candidate tool for the plant production industry. Since this discovery, three syntheses have appeared: the first synthesis by Flematti's group themselves,[2] the second by Goddard-Borger's group,[3] and the third by Xu's group.[4] Recently, a patent by one of the author (N.M.) groups was released.[5]

The first method, starting from pyromeconic acid, is short and straightforward but results in low overall yield (ca. <10%). The second method produces a significantly greater total yield to 30%, but requires 9 steps from 1,2-*O*-isopropylidene-D-xylofuranose as the starting compound. The third method is performed in 8 steps from diethyl isopropylidenemalonate in 8% overall yield. Our longstanding interest in Ti-Claisen condensations,[6] relevant Ti-direct aldol-type,[7] and Mannich-type additions[8] led us to investigate the synthesis of **1** and its dihydro analogue **2** (Fig. 1). We present herein an efficient short synthesis of **1** and **2** utilizing a direct and regioselective Ti-crossed aldol addition between dihydro-2*H*-pyran-3(4*H*)-ones and methyl pyruvate as the key step, followed by furanone formation.

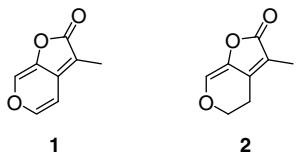
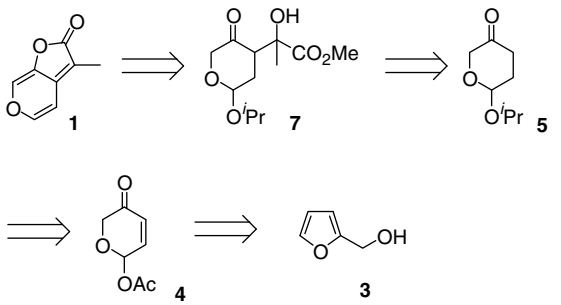


Figure 1. 3-Methyl-2*H*-furo[2,3-*c*]pyran-2-one **1** and the dihydro analogue **2**.

2. Results and discussion

Scheme 1 outlines the retrosynthetic route of **1** starting from 2-furfurylmethanol (**3**). The reported oxidative ring expansion of **3** using *m*CPBA,[9] followed by treatment with AcCl–Et_3N–cat. DMAP, gave 5,6-dihydro-5-oxo-2*H*-pyran-2-yl acetate (**4**) in 82% yield



Scheme 1. Retrosynthesis of 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one **1**.

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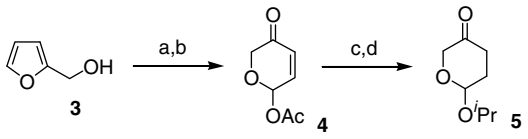
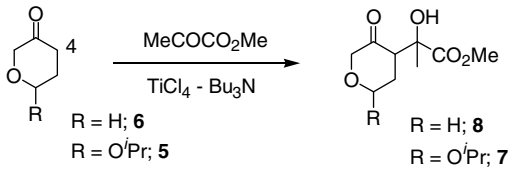


Scheme 2. Reagents and conditions: (a) *m*CPBA/CH_2Cl_2, 0–5 °C; (b) AcCl–Et_3N–cat. DMAP/CH_2Cl_2, 0–5 °C; (c) ^{i}PrOH–cat. $SnCl_4$/$ClCH_2CH_2Cl$, 20–25 °C; (d) H_2–cat. Pd–C/AcOEt, 20–25 °C.



Scheme 3. Regioselective direct Ti-aldol reaction of dihydro-2*H*-pyran-3(4*H*)-ones **5** and **7**.

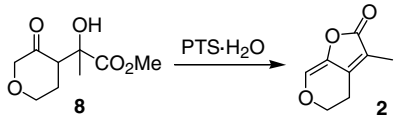
(Scheme 2).[10] An $SnCl_4$-catalyzed acetal exchange with ^{i}PrOH and subsequent catalytic hydrogenation gave 6-isopropoxy-2*H*-pyran-3(6*H*)-one (**5**) in 68% yield (2 steps).[11]

The initial model study of the Ti-crossed direct aldol addition was guided using commercially available dihydro-2*H*-pyran-3(4*H*)-one **6** and methyl pyruvate (Scheme 3). Regioselectivity of the enolate formation of dihydro-2*H*-pyran-3(4*H*)-ones **5** and **6** was speculated to be of primary importance in this synthetic plan. Extensively reported studies on this issue revealed that the desired enolate formation was kinetically as well as thermodynamically predominant.[12] Indeed, Ti-direct aldol addition using $TiCl_4$–Bu_3N reagent between **6** and methyl pyruvate proceeded smoothly at the C4 position, presumably under kinetic conditions (−55 to −78 °C), to give the aldol adduct **8** as a desired sole regioisomer in 71% yield. A similar result was observed in our previous synthetic study of (*R*)-mintlactone.[7b] The presence of a TMSCl co-reagent did not affect the present reaction.[7a]

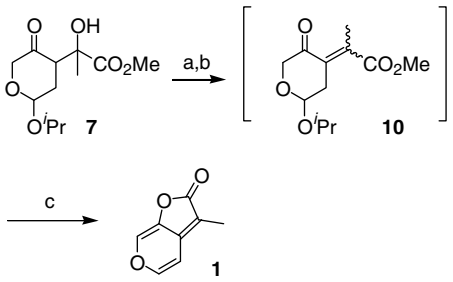
With this result in hand, the reaction using **5** also successfully afforded the key aldol-adduct **7** in 47% yield. Although the yield was decreased, probably due to the labile acetal moiety in **5**, the regiochemistry was similar to that when **6** was used.

Subsequent furanone transformation was investigated. The direct transformation of **8** using *p*-toluenesulfonic acid (PTS)·H_2O catalyst gave the desired furanone **2** in 48% yield (Scheme 4). The identical reaction using **6**, however, gave disappointing results: only a trace amount of the desired product **1** was detected due to decomposition of the acetal moiety in **7**. To overcome this problem, the stepwise dehydration and lactonization procedures were examined: Successive treatment of **6** with $(CF_3CO)_2O$–Et_3N–cat. DMAP and DBU gave the conjugated ene-dicarbonyl intermediate **10**, which was treated with a PTS·H_2O catalyst to successfully afford the desired furanone **1** in 45% yield (Scheme 5).

In conclusion, we have achieved a new synthesis of 3-methyl-2*H*-furo[2,3-*c*]pyran-2-ones **1** (7 steps; 12% overall yield) and **2** (2 steps; 34% overall yield) through a direct and regioselective Ti-aldol addition. Further studies of the analogue synthesis and the structure–activity relationship are in progress.



Scheme 4. Direct furanone transformation of **8**–**2** using PTS·H_2O.



Scheme 5. Reagents and conditions: (a) $(CF_3CO)_2O$–Et_3N–cat. DMAP/ CH_3CN, 0–5 °C; (b) DBU/CH_3CN, 0–5 °C; (c) PTS·H_2O/ toluene, reflux.

3. Experimental

3.1. General

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a SHIMADZU FT/IR-8100A spectrophotometer.

3.1.1. 5,6-Dihydro-5-oxo-2*H*-pyran-2-yl acetate (4)[8,10]

*m*CPBA (18.1 g, 105 mmol) was added to a stirred solution of 2-furfurylmethanol (**3**; 6.87 g, 70.0 mmol) in CH_2Cl_2 (210 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred for 6 h at the same temperature. The resultant white precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was diluted with CH_2Cl_2 (190 mL) and cooled to 0–5 °C. Et_3N (12.0 g, 119 mmol) and DMAP (420 mg, 3.5 mmol) in CH_2Cl_2 (10 mL), and AcCl (9.34 g, 119 mmol) in CH_2Cl_2 (10 mL) were successively added to the stirred solution at 0–5 °C under an Ar atmosphere, and the mixture was stirred for 2 h at the same temperature. The mixture was poured into $NaHCO_3$ aqueous solution and extracted twice with CH_2Cl_2. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (neutral) (hexane–AcOEt = 4:1) to give the desired product **4** (8.96 g, 82%).

Yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.15 (3H, s), 4.22 (1H, d, J_{gem} = 16.9 Hz), 4.52 (1H, d, J_{gem} = 16.9 Hz), 6.28 (1H, d, J = 10.3 Hz), 6.50 (1H, d, J = 3.9 Hz), 6.94 (1H, dd, J = 3.9, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 20.8, 67.3, 86.5, 128.6, 142.2, 169.4, 193.3; IR (neat) 3485, 2988, 1751, 1373, 1221, 1006, 933 cm^{-1}.

3.1.2. Dihydro-6-isopropoxy-2*H*-pyran-3(4*H*)-one (5)

$SnCl_4$ (1.0 M in CH_2Cl_2, 750 μL, 0.75 mmol) was added to a stirred solution of **4** (2.34 g, 15.0 mmol) and ^{i}PrOH (1.80 g, 30.0 mmol) in CH_2Cl_2 (45 mL) at 20–25 °C under an Ar atmosphere, followed by being stirred for 2 h. Satd $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (neutral) (hexane–AcOEt = 10:1) to give 6-isopropoxy-2*H*-pyran-3(6*H*)-one (1.97 g, 84%).

Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, d, J = 6.2 Hz), 1.27 (3H, d, J = 6.2 Hz), 4.05 (1H, sept, J = 6.2 Hz), 4.09 (1H, d, J_{gem} = 16.9 Hz), 4.49 (1H, d, J_{gem} = 16.9 Hz), 5.31 (1H, d, J = 3.4 Hz), 6.13 (1H, d, J = 10.3 Hz) 6.86 (1H, dd, J = 3.4, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.2, 66.2, 71.0, 91.3, 127.6, 145.0, 195.0; IR (neat) 2975, 1709, 1383, 1262, 1181, 1159, 1121, 1102, 1080, 1042 cm^{-1}.

10% Pd–C (670 mg, 0.63 mmol) was added to a stirred solution of 6-isopropoxy-2*H*-pyran-3(6*H*)-one (1.97 g, 12.6 mmol) in AcOEt (25 mL), and the mixture was stirred equipped with a H_2 balloon for 1.5 h at 20–25 °C. The mixture was filtered through the Celite using glass filter, and the filtrate was concentrated under reduced pressure. The obtained crude oil was purified with SiO_2-column chromatography (hexane–AcOEt = 10:1) to give the desired product **5** (1.62 g, 81%).

Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, d, J = 6.2 Hz), 1.23 (3H, d, J = 6.2 Hz), 1.96 (1H, dddd, J = 4.1, 6.2, 7.2 Hz, J_{gem} = 14.1 Hz), 2.25 (1H, dddd, J = 4.1, 5.9, 8.3 Hz, J_{gem} = 14.1 Hz), 2.45 (1H, ddd, J = 6.2, 7.2 Hz, J_{gem} = *16.5 Hz), 2.59 (1H, ddd,* J = 5.9, 8.3 Hz, J_{gem} = 16.5 Hz), 3.90 (1H, d, J_{gem} = 16.9 Hz), 3.98 (1H, sept, J = 6.2 Hz), 4.20 (1H, d, J_{gem} = 16.9 Hz), 5.10 (1H, t, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 23.3, 28.6, 33.8, 67.2, 68.9, 93.8, 209.1; IR (neat) 2975, 1736, 1381, 1248, 1200, 1171, 1125, 1076, 1046, 1009 cm^{-1}. HRMS (ESI) calcd for $C_8H_{14}O_3$ (M^+) 158.0943, found 158.0938.

3.1.3. Methyl 2-(tetrahydro-5-oxo-2*H*-pyran-4-yl)-2-hydroxypropanoate (8)

$TiCl_4$ (162 μL, 1.5 mmol) and a solution of Bu_3N (371 mg, 2.0 mmol) in CH_2Cl_2 (0.5 mL) were successively added to a stirred solution of dihydro-2*H*-pyran-3(4*H*)-one (**6**; 100 mg, 1.0 mmol) in CH_2Cl_2 (4.0 mL) at −78 °C under an Ar atmosphere. After 15 min, methyl pyruvate (204 mg, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added to the mixture at −78 °C, followed by being stirred for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (neutral) (hexane–AcOEt = 10:1) to give the desired product **8** (144 mg, 71%).

Diastereomixtures; Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.33 (3H × 3/5, s), 1.46 (3H × 2/5, s), 2.12–2.30 (2H, m), 2.83 (1H × 2/5, dd, J = 7.6, 10.7 Hz), 3.12 (1H × 3/5, dd, J = 8.3, 10.7 Hz), 3.73–3.88 (1H, m), 3.78 (3 H × 2/5, s), 3.79 (3H × 3/5, s), 3.88–4.13 (3H, m); ^{13}C NMR ($CDCl_3$) δ 23.0, 24.9, 47.5, 53.1, 66.6, 73.0, 175.7, 176.0, 207.3; IR (neat) 3489, 2974, 1748, 1452, 1379, 1184, 1122, 1026, 979 cm^{-1}. HRMS (ESI) calcd for $C_9H_{14}O_5$ (M^+) 202.0841, found 202.0939.

3.1.4. Methyl 2-(tetrahydro-2-isopropoxy-5-oxo-2*H*-pyran-4-yl)-2-hydroxypropanoate (7)

$TiCl_4$ (484 μL, 4.4 mmol) was added to a stirred solution of dihydro-6-isopropoxy-2*H*-pyran-3(4*H*)-one (**5**; 316 mg, 2.0 mmol), Bu_3N (1.11 g, 6.0 mmol), and methyl pyruvate (408 mg, 4.0 mmol) in CH_2Cl_2 (6.0 mL) at −60–−55 °C under an Ar atmosphere, and the mixture was stirred for 1.5 h at the same temperature. A similar work-up in the case of **8** gave the desired product **7** (245 mg, 47%).

Diastereomixtures; Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.15–1.27 (6H, m), 1.29 (3H × 3/10, s), 1.34 (3H × 2/10, s), 1.42 (3H × 4/10, s), 1.48 (3H × 1/10, s), 1.92 (1H × 2/10, dt, J = 6.5 Hz, J_{gem} = 14.1 Hz), 1.99 (1H × 1/10, ddd, J = 6.2, 12.0 Hz, J_{gem} = 14.5 Hz), 2.11 (1 H × 4/10, ddd, J = 2.4, 7.2 Hz, J_{gem} = 13.1 Hz), 2.19–2.34 (1H × 4/10 + 2H × 3/10, m), 2.38 (1H × 1/10, dt, J = 6.2 Hz, J_{gem} = 14.5 Hz), 2.52 (1H × 2/10, dt, J = 6.5 Hz, J_{gem} = 14.5 Hz), 2.92 (1H × 1/10, dd, J = 5.9, 12.4 Hz), 3.09 (1H × 4/10, dd, J = 7.2, 12.4 Hz), 3.14 (1H × 2/10, dd, J = 6.2, 13.8 Hz), 3.38 (1H × 3/10, dd, J = 7.2, 12.0 Hz), 3.762 (3H × 3/10, s), 3.763 (3 H × 2/10, s), 3.79 (3H × 1/10, s), 3.81 (3H × 4/10, s), 3.83–4.04 (2H, m), 4.10–4.27 (1H, m), 5.11 (1H × 4/10, t, J = 2.4 Hz), 5.17 (1H × 3/10, t, J = 2.4 Hz), 5.18 (1H × 1/10, t, J = 6.2 Hz), 5.25 (1H × 2/10, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.3, 21.5, 23.0, 23.2, 23.3, 23.36, 23.40, 23.6, 23.9, 27.6, 29.9, 30.6, 32.3, 49.9, 50.1, 50.6, 51.2, 52.6, 52.8, 52.9, 66.3, 66.7, 67.4, 67.9, 68.7, 68.9, 69.2, 69.4, 72.2, 72.8, 74.8, 75.9, 93.5, 93.8, 95.1, 95.5, 175.0, 175.1, 176.8, 177.0, 206.8, 209.3, 210.7, 210.8; IR (neat) 2974, 1736, 1458, 1372, 1333, 1250, 1190, 1127, 1044, 980 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{20}O_6$ (M^+) 260.1260, found 260.1258.

3.1.5. 3-Methyl-2*H*-furo[2,3-c]pyran-2-one (1)[1]

$(CF_3CO)_2O$ (71 μL, 0.51 mmol) was added to a stirred solution of **7** (78 mg, 0.30 mmol), Et_3N (46 mg, 0.45 mmol), and DMAP (1.8 mg, 0.015 mmol) in CH_3CN (1.0 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred for 30 min. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to the product, to which DBU (64 mg, 0.42 mmol) in CH_3CN (1.0 mL) was added at 0–5 °C under an Ar atmosphere, followed by being stirred for 1 h. Satd $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. A solution of the obtained crude product and $PTSH_2O$ (68 mg, 0.36 mmol) in toluene (2 mL) was refluxed for 2 h under an Ar atmosphere, followed by being cooled down to room temperature. Satd $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, and dried (Na_2SO_4), and concentrated. The obtained crude oil was purified with SiO_2-column chromatography (hexane–AcOEt = 4:1) to give the desired product **1** (20 mg, 45%).

Yellow crystals; mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (*Me*; 3H, s), 6.52 (4-*H*; 1H, d, J = 5.5 Hz), 7.32 (5-*H*; 1H, d, J = 5.5 Hz), 7.44 (7-*H*; 1H, s); ^{13}C NMR ($CDCl_3$) δ 7.6, 100.2, 103.4, 126.8, 139.7, 142.2, 148.0, 171.2; IR (KBr) 1734 cm^{-1}. These spectroscopic parameters agreed with those reported.

3.1.6. 4,5-Dihydro-3-methyl-2*H*-furo[2,3-c]pyran-2-one (2)

A solution of **8** (61 mg, 0.3 mmol) and PTS (*p*-toluenesulfonic acid)·H_2O (114 mg, 0.6 mmol) in toluene (9 mL) was refluxed for 1 h, under an Ar atmosphere, followed by being cooled down to room temperature. Satd $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, and dried (Na_2SO_4), and concentrated. The obtained crude oil was purified with SiO_2-column chromatography (hexane:AcOEt = 5:1) to give the desired product **2** (22 mg, 48%).

Yellow crystals; mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 1.89 (3H, s), 2.84 (2H, t, J = 6.5 Hz), 4.19 (2H, t, J = 6.5 Hz), 6.92 (1H, s); ^{13}C NMR ($CDCl_3$) δ 8.3, 23.0, 66.8, 115.9, 131.6, 138.7, 142.4, 170.8; IR (KBr) 3011, 1779, 1294, 1148, 1067, 878 cm^{-1}. HRMS (ESI) calcd for $C_8H_8O_3$ (M^+) 152.0473, found 152.0471.

Acknowledgements

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