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Short Synthesis of the Seed Germination Inhibitor 3,4,5-Trimethyl-2(5*H*)-furanone†

Riccardo Surmont,‡ Guido Verniest,§ and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Gent, Belgium. ‡*Aspirant of the Research Foundation - Flanders (FWO - Vlaanderen, Belgium).* §*Postdoctoral Fellow of the Research Foundation - Flanders (FWO - Vlaanderen, Belgium).*

norbert.dekimpe@ugent.be

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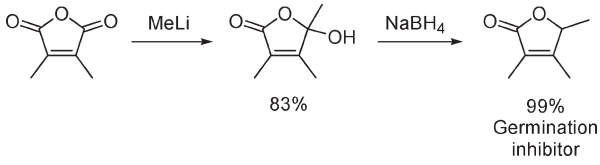

3,4,5-Trimethyl-2(5*H*)-furanone, a new seed germination inhibitor with very promising agrochemical applications, was efficiently synthesized from 2,3-dimethylmaleic anhydride via nucleophilic addition of methyllithium followed by reduction using sodium borohydride. This two-step synthesis is straightforward and high-yielding and permits the large-scale preparation of the seed germination inhibitor.

The ability of smoke to promote seed germination after a forest fire was noted 20 years ago, and the concept was proved by experimental setup with smoke−water on a wide range of plant species.[1] In 2004, Flematti et al. identified and isolated the bioactive signaling molecule 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one **1** from plant- and cellulose-derived smoke. This compound (**1**, KAR_1, Figure 1) is part of a new class of natural plant growth regulators, named karrikins, which are responsible for promoting seed germination at extremely low concentrations (1 nM).[2] The mechanism of the formation of these karrikins in smoke is still under discussion, but they are believed to be products of the Maillard reaction.[3] Also the mode of action of smoke and karrikins is unknown. It has been suggested that the bicyclic butenolides activate the light sensing system of seeds and seedlings.[4] A major breakthrough in the understanding of the mechanism is the recent discovery of the existence of the germination inhibitor 3,4,5-trimethyl-2(5*H*)-furanone **2**.[5] This small butenolide was isolated from plant-derived smoke by van Staden et al. and proved to reduce significantly the promotive effect of the bicyclic karrikins at concentrations of 10 μM. It is speculated that this water-soluble monocyclic inhibitor **2** blocks the possible receptor related to the action of the bicyclic karrikin **1**, preventing seed germination until sufficient water is available.[5] Compound **2** was also identified in tobacco flavor and cigarette smoke,[6] dried fish flavor[7] and roasted coffee (Maillard reaction).[8]

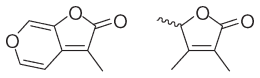

FIGURE 1. Karrikin **1** and the seed germination inhibitor **2**.

It is clear that karrikins and their inhibitor have an enormous potential as powerful agrochemicals that can be used to regulate the moment of the germination of seeds, depending on the environmental conditions, and to stimulate the growth of crops. Unfortunately, the widespread application of these compounds remains limited because of their often low-yielding and expensive synthesis.[9] Since the discovery of the germination-stimulating karrikin **1**, various methods for its preparation have appeared in the literature.[10] The germination inhibitor 3,4,5-trimethyl-2(5*H*)-furanone **2**, which was discovered by van Staden et al.,[5] was prepared using a classical synthetic protocol[11] starting from the reaction of the dianion of (phenylthio)acetic acid with propylene oxide giving γ-methyl-α-phenylthio-γ-butyrolactone. This lactone was oxidized using sulfuryl chloride to the corresponding 5-methyl-3-phenylthio-2(5*H*)-furanone, followed by Michael addition of Me_2CuLi across the 2(5*H*)-furanone. A subsequent α-methylation using MeI, oxidation of the α-thiophenyl moiety to the corresponding sulfoxide, and

† Dedicated to Prof. Dr. Heinz Heimgartner on the occasion of his 70th birthday.

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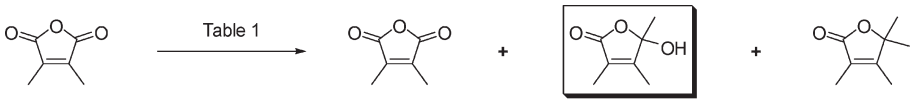
TABLE 1. Optimization of the Nucleophilic Addition of Methyl Organometallic Reagents to 2,3-Dimethylmaleic Anhydride 4



entry	reaction conditions	4	3	5	ratio 3:5
1	1.2 equiv of MeMgBr (3 M in Et_2O, comm.), Et_2O, 0 °C, 30 min	44	36	20	64:36
2	1.1 equiv of MeMgI[a] (0.3 M in Et_2O), Et_2O, −78 °C, 2 h	72	26	2	93:7
3	1.1 equiv of MeMgI[a] (0.15 M in Et_2O), THF/Et_2O 1:1, −20 to 0 °C, 2 h[b]	35	47	18	72:28
4	1.1 equiv of MeMgI[a] (0.15 M in Et_2O), hexane/Et_2O 1:1, −20 to 0 °C, 2 h[b]	35	61	4	94:6
5	1.1 equiv of MeMgI[a] (0.3 M in Et_2O), Et_2O, −20 to 0 °C, 2 h	8	84 (79)[d]	8 (5)[d]	91:9
6	1.1 equiv of MeMgI[a] (0.15 M in Et_2O), Et_2O, −20 to 0 °C, 2.5 h[c]	10	84	6	93:7
7	1.1 equiv of MeMgI[a] (0.25 M in Et_2O), Et_2O/HMPA (10:1), −20 to 0 °C, 2 h	8	73	19	79:21
8	1.1 equiv of MeMgI[a] (0.25 M in Et_2O), THF, −78 °C, 2 h	11	76	13	85:15
9	1.1 equiv of MeMgI[a] (0.3 M in Et_2O), 2 equiv LiCl, Et_2O, −20 to 0 °C, 2 h	8	87	5	94:6
10	1.1 equiv of Me_2Cd (0.06 M in THF), THF, 0 °C, 2 h	100	0	0	n.a.[e]
11	**1.0 equiv of MeLi (1.6 M in Et_2O), THF, −78 °C, 15 min**	**1**	**91 (83)**[d]	**8 (3)**[d]	**92:8**

[a]Freshly prepared from 1.1 equiv of MeI and 5.5 equiv of Mg in Et_2O; addition of MeI to Mg over 20 min at 0 °C, further stirring for 30 min at 0 °C. [b]Slow addition of MeMgI over 1 h. [c]Slow addition of MeMgI over 1.5 h. [d]Isolated yield in parentheses. [e]Not applicable.

subsequent dehydrosulfenylation by heating to 70 °C in pyridine yielded 3,4,5-trimethyl-2(5*H*)-furanone **2**. The reported overall yield of this long reaction sequence (7 steps) is 42%. 3,4,5-Trimethyl-2(5*H*)-furanone **2** was also prepared via a $TiCl_4$-catalyzed photoreaction of 3-methylpentane-2,4-dione and methanol in undisclosed yields.[12] In a more recent strategy, lithium propynolate, prepared in situ from ethyl 2,2-dibromopropanoate, is reacted with a 3-silyloxy-2-butanone and MeI affording methyl 4-silyloxy-2,3-dimethyl-2-pentenoate, which is further hydrolyzed to 3,4,5-trimethyl-2(5*H*)-furanone **2**.[13] It is clear that a short, straightforward, and efficient synthesis of 3,4,5-trimethyl-2(5*H*)-furanone **2**, allowing a multigram scale preparation, has not been described before despite the great interest for potential agro-industrial applications and for the further study of its mode of action in seed germination inhibition. Therefore, a strategy for the synthesis of 3,4,5-trimethyl-2(5*H*)-furanone **2** was put forward, starting from the commercially available 2,3-dimethylmaleic anhydride **4**. 1,2-Addition of MeLi or a Grignard reagent to the anhydride followed by reduction of the resulting hemiacetal **3** gives rise to compound **2** in a very straightforward manner (Figure 2).

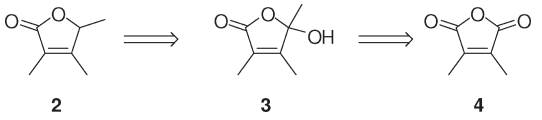


FIGURE 2. Retrosynthetic analysis for butenolide **2**.

In a first attempt to introduce the methyl group at C-5 of 3,4,5-trimethyl-2(5*H*)-furanone **2**, a commercially available solution of methylmagnesium bromide (1.2 equiv, 3 M in diethyl ether) was slowly added to the symmetrically substituted anhydride **4** in diethyl ether at 0 °C (Table 1, entry 1).[14] After reaction for 30 min, the obtained reaction mixture contained 44% of starting material **4**, 36% of the desired hemiacetal **3**, and 20% of the tetramethyl-substituted 2(5*H*)-furanone **5** (ratio determined by ^{1}H NMR analysis).

This result indicates that the anion derived from hemiacetal **3**, which can be in equilibrium with the ring-opened reactive 4-ketocarboxylate, was formed as an intermediate and participated in a second nucleophilic attack of methylmagnesium bromide to yield 3,4,5,5-tetramethyl-2(5*H*)-furanone **5**. Interestingly, only traces of compounds resulting from 1,4-addition reactions were observed. This demonstrates the favored 1,2-addition of the Grignard reagent to the α,β-unsaturated anhydride. In order to avoid the formation of 3,4,5,5-tetramethyl-2(5*H*)-furanone **5**, the reaction was performed at lower temperature. Furthermore, to permit a better control of the stoichiometry of the reaction, a freshly prepared 0.3 M solution of methylmagesium iodide in diethyl ether was used.[15] Despite the incomplete conversion of 2,3-dimethylmaleic anhydride **4** by reaction with methylmagnesium iodide in diethyl ether at −78 °C, partly due to the poor solubility of the starting material, a much better ratio of hemiacetal **3** and side product **5** (ratio 93:7) was obtained at this low temperature (entry 2), as compared to the reaction at 0 °C. When the reaction was performed at −20 °C in a solvent mixture of THF/Et_2O (1:1) at −20 °C, to improve the solubility of the starting material, the amount of tetramethyl-substituted compound **5** increased (ratio **3**:**5** 72:28) and unidentified side products appeared (entry 3). On the other hand, the reaction in the more apolar solvent mixture hexane/Et_2O (1:1) at −20 °C resulted in an excellent ratio of compounds **3** and **5** (ratio 94:6) but in an incomplete conversion (entry 4). By reacting **4** with 1.1 equiv of freshly prepared methylmagnesium iodide in diethyl ether at −20 °C, a mixture containing 84% of the desired hemiacetal **3** (entry 5) was obtained. Despite the very slow addition of the Grignard reagent to a more diluted solution of anhydride **4** in Et_2O (entry 6), the formation of small amounts of 3,4,5,5-tetramethyl-2(5*H*)-furanone **5** (8%) could not be avoided. Changing the solvent to THF or adding HMPA or LiCl did

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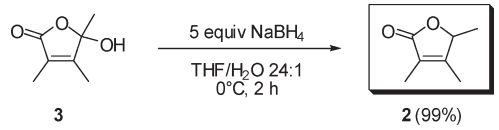
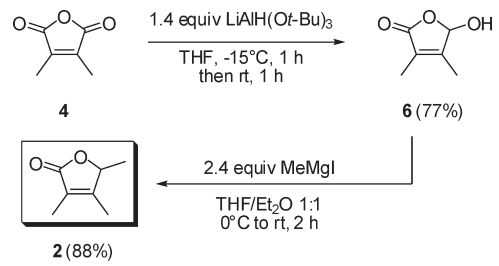
SCHEME 1. Reduction of 5-Hydroxy-3,4,5-trimethyl-2(5*H*)-furanone 3



SCHEME 2. Reduction of Anhydride 4 Followed by Methylation



not improve the yields of hemiacetal **3** (entries 7−9). Therefore, it was decided to evaluate other methyl organometallic reagents. While the use of dimethylcadmium at 0 °C resulted in the recovery of the starting material accompanied by small amounts of unidentified side products, the reaction of anhydride **4** with MeLi in dry THF at −78 °C for 15 min gave rise to a clean mixture of mainly 5-hydroxy-3,4,5-trimethyl-2(5*H*)-furanone **3** (entry 11). Because of its higher polarity, hemiacetal **3** was very easily separated from the unreacted anhydride **4** and the tetramethylated compound **5** by flash silica gel chromatography and was isolated in 83% yield.

In a final step, the reduction of hemiacetal **3** was performed by reaction with sodium borohydride in wet THF (4% water) during 2 h at 0 °C, affording the seed germination inhibitor 3,4,5-trimethyl-2(5*H*)-furanone **2** in 99% yield.[14] The butenolide **2** was separated from residual traces of borane salts by filtration of the compound over silica gel without loss of product.

In a subsequent step, an alternative strategy for the functionalization of lactones at the γ-position, starting from the corresponding maleic anhydrides, was applied for the preparation of the germination inhibitor **2**. This known strategy consists of the reduction of anhydride **4** to the corresponding 5-hydroxylactone, followed by introduction of the methyl substituent at C-5,[16] which is the reverse order of the reaction sequence described above. Therefore, 2,3-dimethylmaleic anhydride **4** was first reduced using LiAlH(O-*t*-Bu)$_3$ toward 5-hydroxy-3,4-dimethyl-2(5*H*)-furanone **6** in 77% yield after crystallization according to literature procedures[17] and was next treated with methyl nucleophiles. Although various Grignard reagents have been used previously to further functionalize 5-hydroxyfuranones such as **6**,[16] the synthesis of furanone **2** from **6** has not been evaluated before. The reaction of 5-hydroxy-3,4-dimethyl-2(5*H*)-furanone **6** with 2.4 equiv of MeLi (1.6 M in Et_2O) in THF at room temperature during 2 h gave the desired 3,4,5-trimethyl-2(5*H*)-furanone **2** in 74% yield after silica gel chromatography. The yield was further improved to 88% by using freshly prepared MeMgI, affording the germination inhibitor **2** in 68% overall yield.

When both strategies toward 3,4,5-trimethyl-2(5*H*)-furanone **2** are compared (Schemes 1 and 2), i.e., the reduction of the anhydride **4** followed by nucleophilic attack of MeMgI versus the nucleophilic addition of MeLi to anhydride **4** followed by reduction, it can be stated that both approaches give rise to the target compound **2** in comparable high yields (68% and 82%, respectively), although the required use of LiAlH(O-*t*-Bu)$_3$ at −15 °C is less economical as compared to the $NaBH_4$ reduction at 0 °C.

In conclusion, a very short and efficient synthetic route toward 3,4,5-trimethyl-2(5*H*)-furanone **2**, a recently discovered seed germination inhibitor with very promising agrochemical applications, was developed. The two-step synthesis involves the nucleophilic addition of methyllithium to commercially available 2,3-dimethylmaleic anhydride followed by reduction using sodium borohydride. The two steps are straightforward, and the intermediate is easily purified, finally leading to 3,4,5-trimethyl-2(5*H*)-furanone **2** in 82% overall yield. This method is a huge improvement compared to earlier synthetic routes, which are not appropriate for synthesis on large scale and which hindered the development of the agrochemical potential of the seed germination inhibitor 3,4,5-trimethyl-2(5*H*)-furanone **2**.

Experimental Section

Synthesis of 5-Hydroxy-3,4,5-trimethyl-2(5*H*)-furanone 3 and 3,4,5,5-Tetramethyl-2(5*H*)-furanone 5. A 1.6 M solution of methyllithium in Et_2O (2.5 mL, 4 mmol) was added dropwise over 15 min to a solution of 0.504 g (4 mmol, 1 equiv) of 2,3-dimethylmaleic anhydride **4** in 25 mL of dry THF under nitrogen atmosphere at −78 °C. The mixture was further stirred at −78 °C for 15 min. The reaction was quenched by the addition of 20 mL of satd aq NH_4Cl, and 30 mL of ethyl acetate was added to the mixture. The organic layer was separated, and the aqueous phase was extracted twice with 30 mL of ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was purified via flash silica gel chromatography to give 0.470 g of 5-hydroxy-3,4,5-trimethyl-2(5*H*)-furanone **3** (3.31 mmol; 83% yield) and 0.03 g of 3,4,5,5-tetramethyl-2(5*H*)-furanone **5** (0.23 mmol; 3% yield).

5-Hydroxy-3,4,5-trimethyl-2(5*H*)-furanone 3. Flash chromatography (hexane/EtOAc 7:3): R_f = 0.12. Mp = 62.9 °C (hexane/Et_2O 1:1). White crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63 (3H, s, Me); 1.80 (3H, q, J = 1.1 Hz, Me); 1.98 (3H, q, J = 1.1 Hz, Me); 3.82 (1H, s, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.2 (Me); 10.5 (Me); 23.2 (Me); 105.9 (OC_qO); 123.9 ($=C_q$); 159.4 ($=C_q$); 173.0 (C=O). IR (ATR, cm^{-1}): ν = 3284 (OH); 2988; 2929; 1719 (C=O); 1692; 1419; 1374; 1330; 1278; 1208; 1152; 1048; 952; 884; 839; 769; 628. GC−MS (EI) m/z: 142 (M^+, 2); 127 (M^+ − Me, 100); 114 (6); 99 (74); 83 (17); 69 (2); 67 (2); 61 (3); 54 (28); 43 (35). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.01; H, 7.31.

3,4,5,5-Tetramethyl-2(5*H*)-furanone 5. Spectral data of compound **5** were identical to those reported in the literature.[13] Flash chromatography (hexane/EtOAc 7:3): R_f = 0.14. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (6H, s, 2 × Me); 1.79 (3H, s, Me); 1.94 (3H, s, Me). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.4 (Me); 10.9 (Me); 24.5 (2 × Me); 85.7 (OC_q); 121.8 ($=C_q$); 163.7 ($=C_q$); 173.5 (C=O). IR (ATR, cm^{-1}): ν = 2980; 2931; 1742 (C=O); 1684; 1439; 1382; 1325; 1291; 1206; 1130; 1109;

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1066; 970; 899; 766; 622. GC−MS (EI) *m*/*z*: 140 (M^+, 28); 125 ($M^+ - Me$, 100); 110 (1); 97 (83); 81 (7); 69 (18); 59 (5); 54 (14); 43 (70).

Synthesis of 5-Hydroxy-3,4-dimethyl-2(5*H*)-furanone 6. The spectral data of compound **6** were identical with those reported in the literature.[17] A solution of 2.77 g (10.91 mmol, 1.38 equiv) of LiAlH(O-*t*-Bu)$_3$ in 15 mL of dry THF was added dropwise over 10 min to a solution of 1.00 g (7.94 mmol, 1 equiv) of 2,3-dimethylmaleic anhydride **4** in 25 mL of dry THF at −15 °C. The mixture was stirred at −15 °C for 1 h and then at room temperature for 1 h. The reaction mixture was quenched with 40 mL of 2 M HCl and extracted three times with 40 mL of EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were evaporated in vacuo. The obtained solid was recrystallized to give 0.78 g of 5-hydroxy-3,4-dimethyl-2(5*H*)-furanone **6** (6.09 mmol, 77% yield). Mp = 78.6 °C (hexane/Et_2O 1:1). White crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.73 (3H, s, Me); 1.93 (3H, s, Me); 5.80 (1H, d, J = 7.7 Hz, OCHO); 5.86 (1H, d, J = 7.7 Hz, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.2 (Me); 11.3 (Me); 98.7 (OCHO); 125.5 (=C_q); 156.8 (=C_q); 173.8 (C=O). IR (ATR, cm^{-1}): ν = 3372 (OH); 2928; 1723 (C=O); 1687; 1465; 1383; 1330; 1294; 1195; 1152; 1079; 965; 925; 758. GC−MS (EI) *m*/*z*: 128 (M^+, 1); 127 ($M^+ - H$, 4); 111 ($M^+ -$ OH, 3); 100 ($M^+ - CO$, 100); 83 (34); 55 (74); 41 (13).

Synthesis of 3,4,5-Trimethyl-2(5*H*)-furanone 2. Method A. To a solution of 0.73 g (5.14 mmol; 1 equiv) of 5-hydroxy-3,4,5-trimethyl-2(5*H*)-furanone **3** in 72 mL of tetrahydrofuran and 3 mL of water (THF/H_2O 24:1) was added 0.98 g (25.70 mmol; 5 equiv) of sodium borohydride in portions at 0 °C. The solution was stirred for 2 h at 0 °C, and then the reaction mixture was quenched by addition of 30 mL of 1 M HCl. The mixture was extracted three times with 40 mL of ethyl acetate. The combined organic phases were dried over $MgSO_4$, and the solvents were evaporated in vacuo to yield virtually pure 3,4,5-trimethyl-2(5*H*)-furanone **2**. To obtain an analytically pure sample, the product was purified via flash chromatography (hexane/EtOAc 4:1, R_f = 0.09) affording 0.64 g of pure 3,4,5-trimethyl-2(5*H*)-furanone **2** (5.09 mmol, 99% yield) as a colorless oil.

Method B. To a solution of 5.53 mmol (2.4 equiv) of MeMgI, prepared from 147 mg (6.14 mmol, 2.6 equiv) of Mg and 785 mg (5.53 mmol, 2.4 equiv) of MeI in 10 mL of dry Et_2O by stirring 1 h at 0 °C under N_2 atmosphere, was added dropwise a solution of 300 mg (2.34 mmol, 1 equiv) of 5-hydroxy-3,4-dimethyl-2(5*H*)-furanone **6** in 10 mL of dry THF. The reaction mixture was stirred for 2 h at room temperature, quenched with 3 M HCl, extracted with diethyl ether, dried over $MgSO_4$, concentrated, and purified by flash chromatography to yield 261 mg of compound **2** (2.06 mmol, 88% yield). Spectral data of compound **2** were identical to those reported in the literature.[11] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.40 (3H, d, J = 6.8 Hz, Me); 1.81 (3H, s, Me); 1.96 (3H, s, Me); 4.80 (1H, q, J = 6.8 Hz, OCH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 8.1 (Me); 11.5 (Me); 17.9 (Me); 79.3 (OCH); 122.4 (=C_q); 160.4 (=C_q); 174.3 (C=O). IR (ATR, cm^{-1}): ν = 2981; 2929; 1741 (C=O); 1684; 1439; 1387; 1314; 1106; 1047; 964; 766. GC−MS (EI) *m*/*z*: 126 (M^+, 67); 111 ($M^+ -$ Me, 21); 97 (2); 83 (100); 79 (2); 67 (4); 55 (97); 51 (7); 43 (17).

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Supporting Information Available: General experimental methods; ^{1}H NMR, ^{13}C NMR, and GC−MS spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.