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Optimization of Manganese Coupling Reaction for Kilogram-scale Preparation of two Aryl-1,3-dione Building Blocks

Tomas Smejkal,[1]‡ Vijayagopal Gopalsamuthiram,[2]‡ Sujit K. Ghorai,[2] Anup M. Jawalekar,[2] Dinesh Pagar,[2] Krishna Sawant,[2] Srinivas Subramanian,[2] Jonathan Dallimore,[3] Nigel Willetts,[3] James N. Scutt,[3] Louisa Whalley,[3] Matthew Hotson,[3] Anne-Marie Hogan,[3]† George Hodges,[3]*

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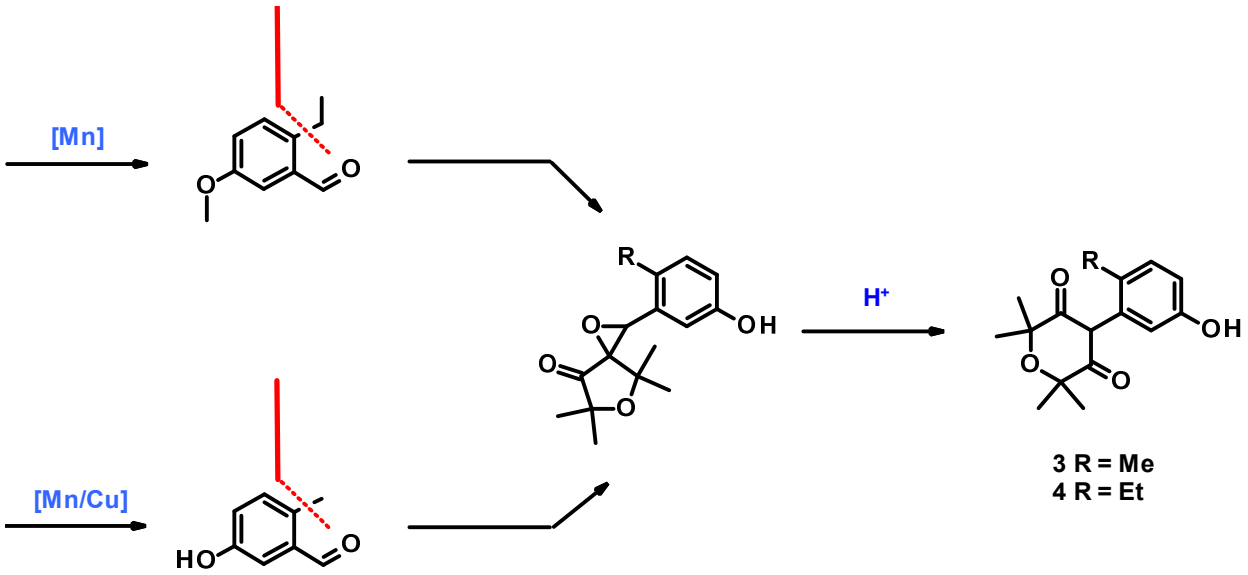


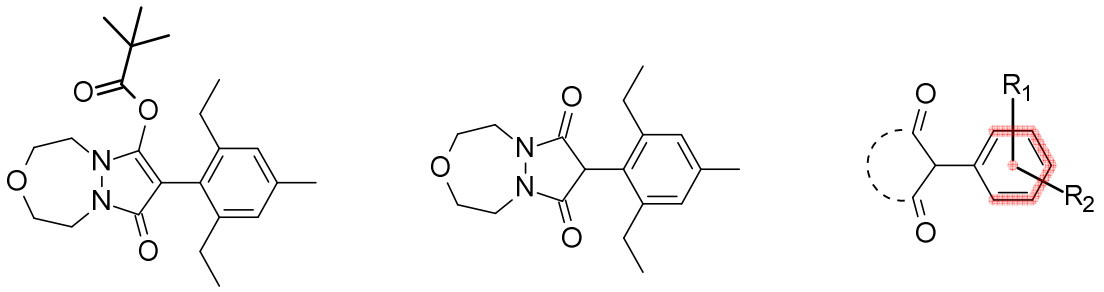
Abstract: Aryl-1,3-diones represent a promising new class of herbicidal acetyl-CoA carboxylase (ACCase) inhibitors. The original synthesis of this structural motif employed in the Research phase, involved a selenium oxide mediated oxidation, the use of diazoacetate and aryl lead reagents, and a low temperature oxidation of an aryl lithium intermediate so was not well suited to large scale synthesis. For kilogram scale synthesis of the two aryl-1,3-dione building blocks (**3** and **4**), we developed an alternative route which employs a manganese or manganese-copper catalyzed alkyl Grignard coupling and a semi-pinacol rearrangement of an epoxide as the key steps. The optimized conditions could be of general interest as scalable methods for the synthesis of 2-alkyl substituted benzaldehydes and of 2-aryl-1,3-diones.

Keywords: Manganese, Copper, Grignard coupling, Semi-pinacol, Aryl-1,3-dione, ACCase

INTRODUCTION

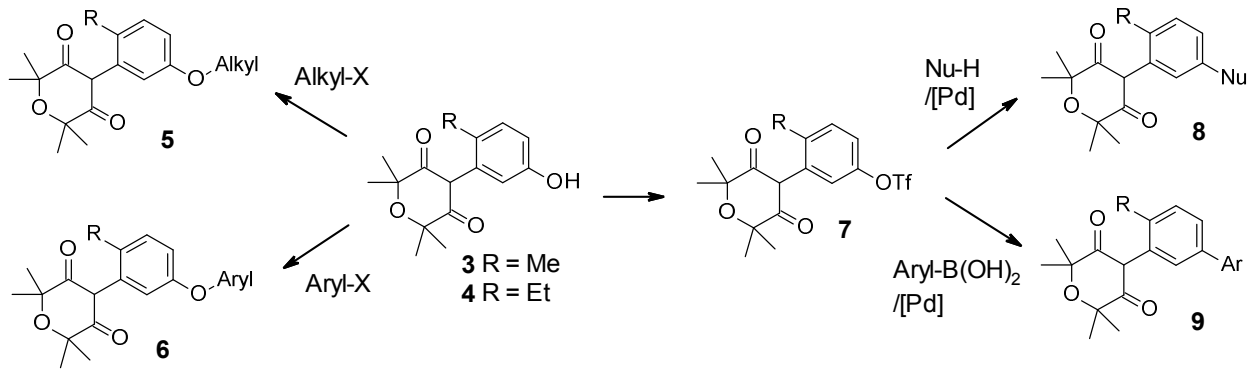
Inhibitors acting on acetyl-CoA carboxylase (ACCase) are among the most important herbicidal modes of action for the control of grass weeds. Pinoxaden (**1**, Figure 1), the active ingredient of AXIAL™ an herbicide that was introduced by Syngenta in 2006. Pinoxaden is a procidal form of Pinoxaden acid (the active principle) which contains the unique 2 aryl-1,3-dione moiety (Figure 1).[1, 2]

Figure 1. Structure of Pinoxadene 1, Pinoxadene acid 2 and 2-aryl-1,3-dione design principle.



As a part of our Herbicide Research program exploring novel 2-aryl-1,3-dione structures, kilogram scale synthesis of two building blocks (**3**, R = ethyl and **4**, R = methyl, Scheme 1) was required. These phenolic building blocks were designed to enable broad exploration of the structure activity relationship around the aromatic core by further modifications (including alkylation, arylation and triflation followed by various metal couplings).[3]

Scheme 1. Aryl-1,3-diones building blocks 3 and 4, some derivatization possibilities.

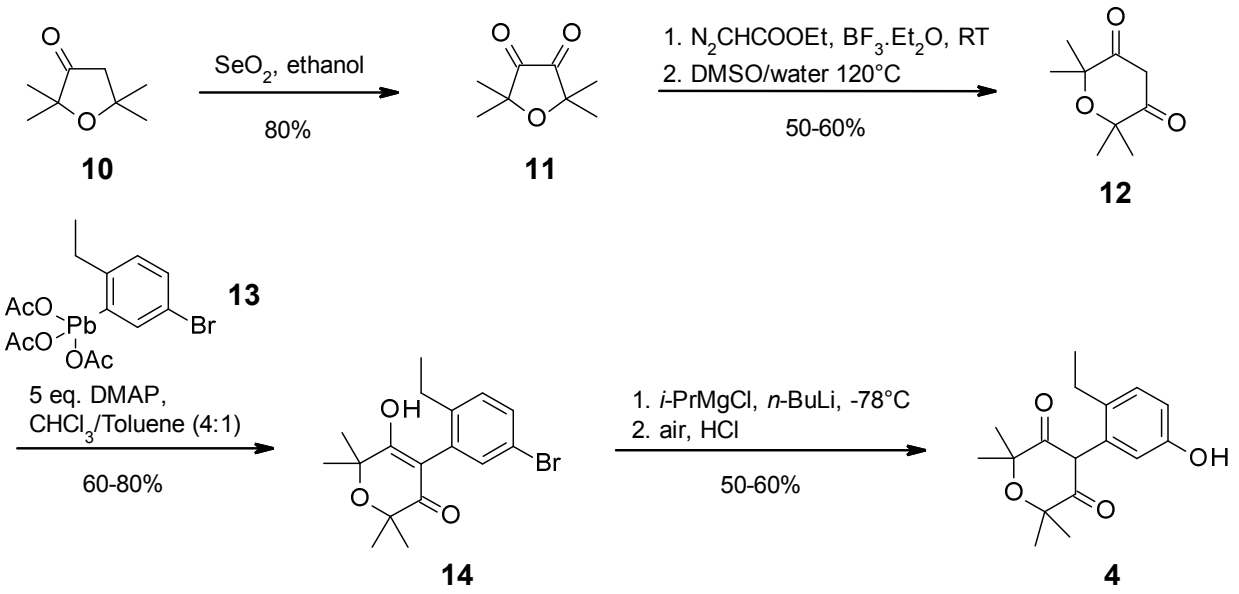


FIRST-GENERATION SYNTHESIS

The discovery synthesis of building blocks **3** and **4** started from commercially available 2,2,5,5-teramethyltetrahydrofuran-3-one (**10**). It was oxidized using selenium oxide in ethanol to give the corresponding dione **11**.[4] Ring expansion using diazonium acetate, followed by decarboxylation gave 2,2,6,6- tetramethyltetrahydropyrane-3,5-dione (**12**) in 50-60% yield.[5] Unfortunately, direct arylation of building block **12** using palladium catalyzed conditions[6] proved only moderately successful, probably due to high steric hindrance of both dione and aryl bromide coupling partners. The most robust method for the direct coupling of ortho-substituted aryls was found to be an unusual aryl lead cross coupling reaction using conditions reported by Morgan and Pinhey.[7, 8] Aryl lead reagents had to be prepared from the corresponding aryl boronic acid using lead tetraacetate and catalytic mercury(II) acetate in chloroform.[7] The arylation itself was performed using a large excess of N,N-dimethyl-4-aminopyridine in a 4:1 chloroform / toluene mixture. Finally, after deprotonation of the dione moiety, low temperature bromine-lithium exchange followed by air oxidation provided the required building blocks **3** and **4** (Scheme 2, only **4** shown).

Although the aryl lead coupling route was relatively high yielding and short, scale up issues throughout the synthesis precluded any work beyond gram scale. We therefore focused on designing a novel synthetic approach.

Scheme 2. Discovery Chemistry Synthesis of Aryldione Building Block 4

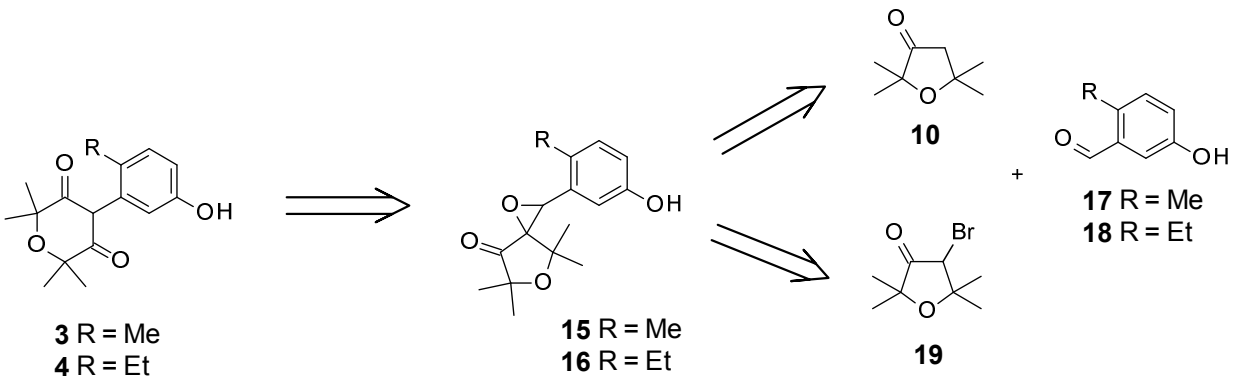


SECOND-GENERATION SYNTHESIS

It was envisioned that the aryl-1,3-diones **3** and **4** could be obtained by semi-pinacol rearrangement of the corresponding epoxy-ketone **15** and **16**.[9, 10] Our previous experience of this rearrangement showed that is relatively general method favoring aryl-1,3-diones, over the isomeric 1,2-diones, through a preferential acyl transfer mechanism under protic or Lewis acid catalysis.[8] The required epoxide starting materials (compounds **15** and **16**, Scheme 2) could in turn be synthesized by condensation of furanone **10** with aldehydes **17** or **18** followed by epoxidation or alternatively by Darzens reaction of bromo-furanone **19** and the corresponding aldehyde (Scheme 3).[8] Accordingly, our first goal was to find an efficient synthesis of aldehyde

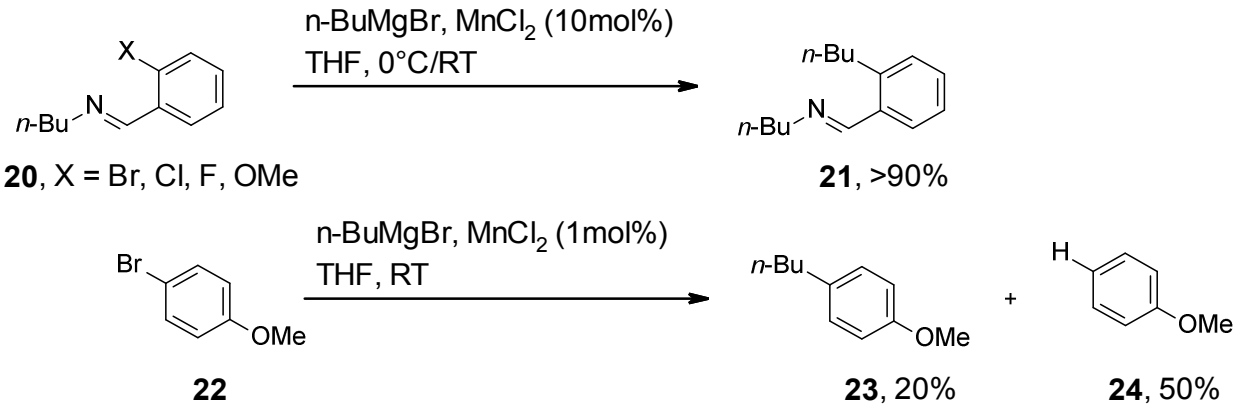
building blocks **17** and **18**. To this end we focused on an interesting manganese coupling reaction which was supported by literature precedent.[11]

Scheme 3. Retrosynthesis of Aryl-tetramethylpyrandione via Semi-pinacol Rearrangement, Condensation/Epoxidation and Darzens approaches



Manganese catalyzed coupling of Grignard reagents with various ortho- and para-substituted benzaldehyde imines has been described by Cahiez as a very efficient route to substituted benzaldehydes (compound **20** to **21**, Scheme 4).[11] Furthermore, electron rich substrates such as 4-bromo-anisole were also shown to undergo the same transformation albeit with reduction predominating in reactions performed with Grignard reagents possessing β-hydrogens (compound **22** to **23** and **24**, Scheme 4).[12]

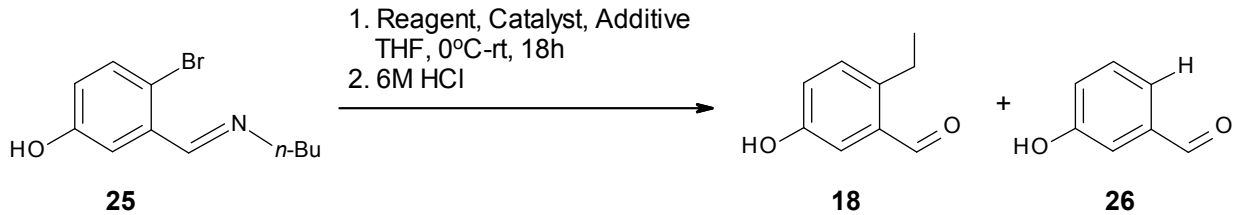
Scheme 4. Manganese catalyzed coupling and reduction of aromatic substrates using *n*-butyl Grignard reagent.[12]



In an initial test reaction, addition of an excess of ethyl magnesium bromide to **25** without manganese catalyst gave only a trace amount of the desired product **18** (Table 1, Entry 1). The same reaction in the presence of anhydrous $MnCl_2$ (10mol %) gave clean reaction providing a 4:1 – 5:1 mixture of the desired coupling product **18** and by-product **26** (Table 1, Entry 2). Best results regarding the **18** vs. **26** selectivity were obtained adding ethyl magnesium bromide slowly (over 45min) and vigorous stirring to limit localised concentration of the Grignard reagent. Reaction in less polar solvent systems (Toluene/THF or MeTHF/THF) led to lower selectivity (Table 1, Entry 3). Reaction under atmosphere of ethylene gave improved selectivity (Table 1, Entry 4). And finally, addition of methyl Grignard (1.5 eq.) followed by the addition of ethyl Grignard (1.5 eq.) gave improved selectivity of the ethyl Grignard coupling (8:1 = coupling: reduction) and no coupling of methyl Grignard at all (Table 1, Entry 5). Therefore, $MnCl_2$ is involved both in the formation of the desired product and reduction by-product. Reduction by-product **26** may be formed via β-hydrogen elimination of ethyl-manganese species and aryl bromide **25** reduction according the mechanism described by Cahiez.[12] A vacant coordination site on manganese next to the ethyl substituent is needed for β-hydrogen elimination, and so the addition of coordinating reagents (such as ethylene, solvent molecule or methyl Grignard) is presumably improving the reaction selectivity by blocking this site. Despite, significantly

improving the reaction selectivity we could not improve it further and challenges in separating compounds **18** and **26** led us to consider an alternative approach.

Table 1. Optimization of Ethyl Grignard Cross-Coupling Reaction – Substrate 25



25 **18** **26**

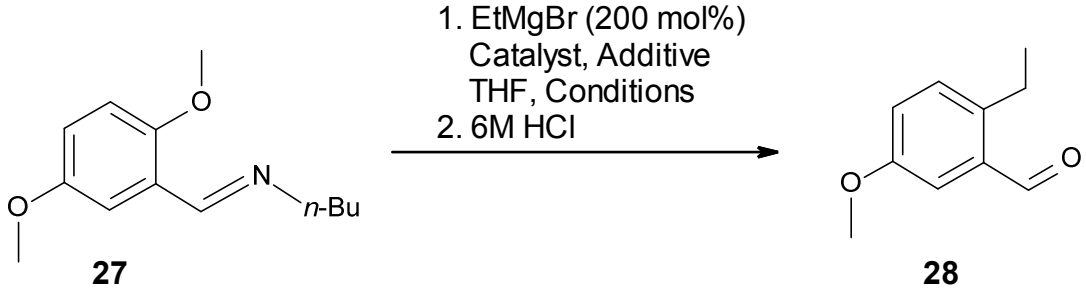
Entry	Reagent	Catalyst	Additive	Conv. **25**[a]	Ratio of **18**/**26**[b]
1	EtMgBr (300 mol%)	-	-	<20%	nd
2	EtMgBr (300 mol%)	$MnCl_2$ (10mol%)	-	100%	4:1-5:1
3[c]	EtMgBr (300 mol%)	$MnCl_2$ (10 mol%)	-	100%	~2.5:1
4	EtMgBr (300 mol%)	$MnCl_2$ (10 mol%)	Ethylene (1 bar)	100%	8:1
5[d]	EtMgCl (150 mol%)	$MnCl_2$ (10 mol%)	MeMgCl (150mol%)	100%	8:1

[a] HPLC area (%), nd = not determined (<5% yield of **18**/**26**) [b] ^{1}H NMR ratio in crude product, [c] Alternative reaction solvents: Toluene/THF (2:1) or MeTHF/THF (3:1), [d] Addition of methyl Grignard followed by ethyl Grignard reagent, no coupling product of methyl Grignard observed.

We turned our attention to an alternative substrate **27**, which could be easily accessed form 1,4-dimethoxybenzene. Coupling of **27** with ethyl Grignard provided **28**. As before there was no

conversion to the desired product in the absence of the catalyst (Table 2, Entry 1). In the presence of anhydrous $MnCl_2$ (10%) clean conversion to the desired product was observed with no reduction by-product, but the reaction was unfeasibly slow (Table 2, Entry 2). Pleasingly, addition of lithium chloride (2 eq.) significantly increased the reaction rate and provided the desired coupling product in excellent yield (Table 2, Entry 3).[13]

Table 2. Optimization of Ethyl Grignard Cross-Coupling Reaction – Substrate 27



27 **28**

Entry	Catalyst	Additive	Conditions	Conv.**27**[a]	Yield **28**[a]
1	-	-	0°C 30min, RT 15h	<10%	0%
2	$MnCl_2$ (10 mol%)	-	0°C 30min, RT 15h	25%	21%
3	$MnCl_2$ (10 mol%)	LiCl (200 mol%)	0°C 30min, RT 15h	100%	>90%

[a] HPLC area (%)

For our second target, aldehyde building block **17**, selective introduction of a methyl group was required. Cross-coupling of a methyl group on an aromatic core is a well-established transformation with numerous coupling protocols having been developed.[14] Approaches utilising methyl boron derivatives have the major drawback of high cost and poor availability on large scale. Alternatively, dimethyl zinc and trimethyl aluminium are highly pyrophoric making the

large scale handling of the reagent troublesome. From the scale up and cost point of view the most preferable would be the direct use of methyl Grignard reagent (Table 3).

Table 3. Organometallic methyl equivalents

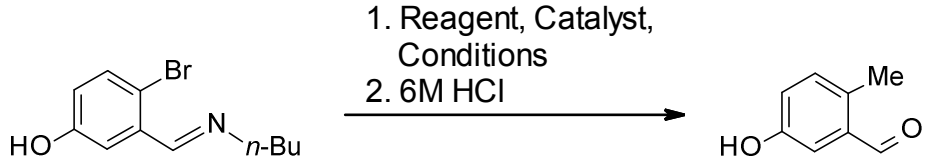
Reagent	Cost[a] (scale)
methylboronic acid	1'820$/mol (5g)
trimethylboroxine	954$/mol (250g)
potassium methyltrifluoroborate	4'475$/mol (5g)
trimethylaluminum (neat)	168$/mol (100g)
trimethylaluminum (2M in toluene)	86$/mol (18L)
dimethylzinc (2M in toluene)	2'225$/mol (500mL)
methylmagnesium bromide (3M in diethyl ether)	29$/mol (18L)

[a] Cost $/mol and the largest scale available in Aldrich catalogue http://www.sigmaaldrich.com on 13.03.2017.

We started our investigation by adding an excess of methyl magnesium bromide to a stirred mixture of substrate **25** and anhydrous $MnCl_2$ catalyst (10 mol%). After increasing the reaction temperature to reflux only a trace of the desired product **17** was formed (Table 4, Entry 1). Using an alternative catalyst, copper chloride (10 mol%), no formation of the desired product **17** was observed and mostly unreacted starting material was recovered (Table 4, Entry 2). Interestingly, combining both metals gave 41% of the desired coupling product **17** after 20 hours at room temperature (Table 4, Entry 3). The yield was further improved by running the reaction at reflux for 1.5 hours (Table 4, Entry 4). Manganese-copper catalysis is known, but to the best of our knowledge has previously been employed only in sp^3-sp^3 couplings.[15] Reaction employing

methyl magnesium bromide solution in MeTHF was slightly less clean, giving up to 20% of dehalogenation by-product (Table 4, Entry 5).

Table 4 Optimization of Methyl Grignard Cross-Coupling Reaction – Substrate 25



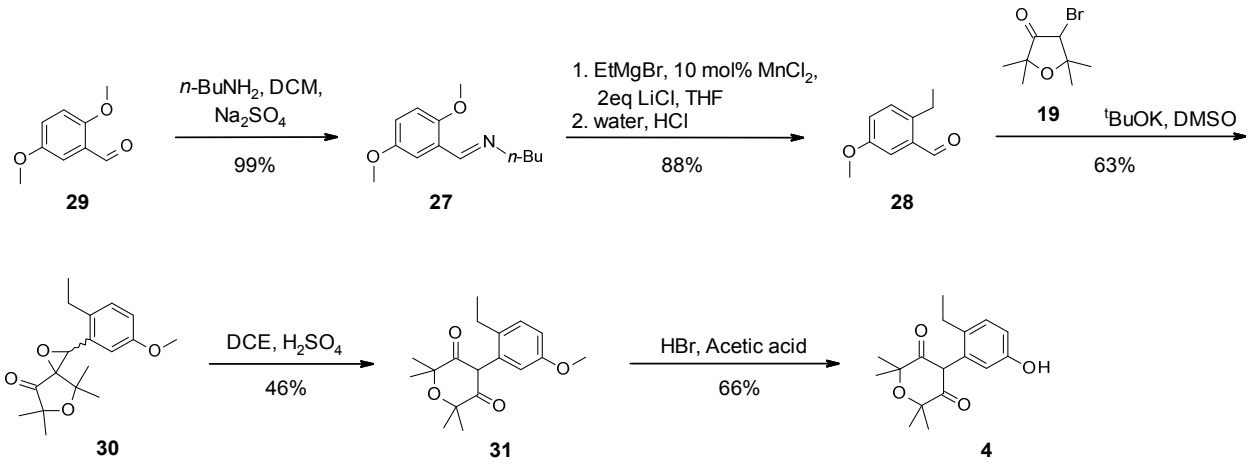
25 **17**

Entry	Reagent	Catalyst	Conditons	Conv. 25[a]	17[a]
1	MeMgBr in Et_2O (300 mol%)	$MnCl_2$ (10 mol%)	0°C, 1h Reflux, 1.5h	<10%	Trace
2	MeMgBr in Et_2O (300 mol%)	CuCl (20 mol%)	0°C, 1h RT/20h	<10%	0
3	MeMgBr in Et_2O (300 mol%)	$MnCl_2$ (10 mol%) CuCl (10 mol%)	0°C, 1h RT/20h	80%	41%
4	MeMgBr in Et_2O (300 mol%)	$MnCl_2$ (20 mol%) CuCl (10 mol%)	0°C, 1h Reflux, 1.5 h	100%	95%
5	MeMgBr in MeTHF (300 mol%)	$MnCl_2$ (20 mol%) CuCl (10 mol%)	0°C, 1h Reflux, 1.5 h	100%	80%

[a] HPLC area (%)

With the required aldehyde building block in hand we turned our attention to the optimization and scale up of the remaining reaction sequence (Scheme 5). Dimethoxy benzaldehyde was condensed with *n*-butyl amine using sodium sulfate as dehydrating agent to provide imine **27** in quantitative yield. The crude product was concentrated, re-dissolved in THF and added directly over a period of 30min to a stirred mixture of anhydrous $MnCl_2$ (10 mol%), lithium chloride (2 eq.) and ethyl magnesium chloride (2eq.) in THF at 0-5°C. After 15 hours at room temperature, the reaction was quenched and hydrolyzed providing aldehyde intermediate **28** in 88% yield. Darzens reaction of **28** and bromo-furanone **19** gave us 63% of epoxyaldehyde **30**. Rearrangement to dione **31** was realized using concentrated sulphuric acid – toluene in 46% yield. Final, deprotection using aq. hydrobromic acid / acetic acid mixture provided dione building block **4** in 66% yield.

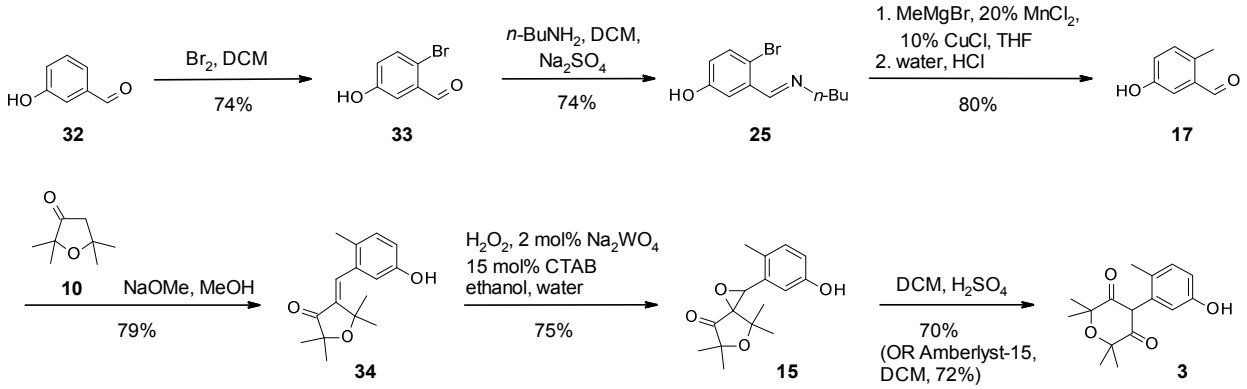
Scheme 5. Optimized Second Generation Route to 4



In the second sequence 3-hydroxybenzaldehyde (**32**) was brominated using bromine in dichloromethane. Condensation with *n*-butyl amine gave imine **25**, which was successfully isolated in this case. The coupling reaction was performed by adding methyl magnesium bromide (2.2M in diethylether) to a stirred suspension of **25**, anhydrous $MnCl_2$ 20 mol% and copper (I)

chloride (10 mol%) in THF at -10 to 0°C. After the addition, the reaction mixture was brought to reflux over 1h and maintained at reflux for additional 2 hours. After quench and acidic hydrolysis the aldehyde building block **17** was isolated in 80% yield. The Darzens reaction was problematic with the unprotected phenol group and so we opted for an alternative sequence consisting of a condensation reaction followed by epoxidation. Condensation with 2,2,5,5-tetramethyltetrahydrofuran-3-one (**10**) using sodium methoxide in methanol yielded chalcone **34** in 79% yield. Epoxidation was realized by slow addition of hydrogen peroxide to a mixture of **34**, sodium tungstate catalyst, sodium hydroxide and phase transfer catalyst in a water-ethanol mixture. Spiroepoxide **15** was rearranged to the dione **3** using dichloromethane / sulphuric acid in 70% yield. On a smaller scale, the rearrangement of **15** to **3** was also found to be successful with Amberlyst-15 ion exchange resin in comparable yields.

Scheme 6. Optimized Second Generation Route to 3



In conclusion a straightforward synthesis of two aryl-1,3-dione building blocks was realized on kilogram scale employing manganese and manganese-copper catalyzed alkyl Grignard couplings and a semi-pinacol rearrangement of an epoxide as the key steps. Our optimized ethyl and methyl Grignard coupling protocols could find applications in the synthesis of other 2-alkyl substituted benzaldehydes and related transformations.

EXPERIMENTAL SECTION

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Commercial grade anhydrous $MnCl_2$ was used as received unless otherwise stated. All reactions were carried out under a nitrogen atmosphere unless otherwise stated. All glassware was dried and purged with nitrogen before use. Reactions were monitored by Agilent 1200 Series HPLC and Agilent ESI LCMS systems, detection was by UV at 220 nm unless otherwise specified.

All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. Agilent Q-TOF instrument. 4-bromo-2,2,5,5-tetramethyl-tetrahydrofuran-3-one (**19**) was prepared according to literature precedent.[16]

(*E*)-N-butyl-1-(2,5-dimethoxyphenyl)methanimine (27). At 25°C anhydrous sodium sulphate (8.60 kg) was added to a suspension of 2,5-methoxy benzaldehyde (5.00 kg, 30.08 mol) in dichloromethane (50.0 L) followed by addition *n*-butyl amine (2.30 kg, 31.45 mol) over a period of 1 hr. The reaction mixture was stirred at 25°C and monitored by ^{1}H NMR. After complete consumption of starting material (12h), the reaction mass was filtered to remove sodium sulphate and the filter cake was washed with dichloromethane (25.0 L). The combined organic extract was concentrated to afford (*E*)-N-butyl-1-(2,5-dimethoxyphenyl)methanimine (6.60 kg, 99% NMR purity, 99% yield) as a yellow semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, J = 7.2 Hz), 1.35-1.41 (m, 2 H), 1.63-1.67 (m, 2 H), 3.60-3.63 (m, 2 H), 3.80 (2s, 6 H), 6.85 (d, J = 8.8 Hz, 1 H), 6.92 (dd, J = 8.8 Hz & 3.2 Hz, 1 H) 7.48 (d, J = 3.2 Hz, 1 H), 8.60 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.8, 20.4, 33.1, 55.7, 56.0, 61.6, 110.4, 112.6, 118.3, 125.3, 153.1, 153.7, 156.4 **Note: Product skin and eye irritant, moisture sensitive.** The crude product was directly used in the following step.

2-ethyl-5-methoxy-benzaldehyde (28). Anhydrous $MnCl_2$ (188 g, 1.49 mol) and lithium chloride (1.25 kg, 29.49mol) were suspended in in anhydrous tetrahydrofuran (50.0 L), stirred at 25°C for 30 min and cooled to -10°C. Then ethyl magnesium bromide solution in tetrahydrofuran (15.2 L, 2.0 M solution, 30.4 mol) was added over a period of 30 min. (internal temperature -10°C to 0°C). The reaction mass was stirred for 30 min and to the Grignard reaction mass, a solution of imine **27** (3.30 kg in 5.0 liters of tetrahydrofuran, 14.91 mol) was added at 0-5°C over a period of 30 min. The reaction mixture was bought to 25°C during 30 minutes and stirred at this temperature for additional 15h. The reaction was monitored by HPLC. The reaction mass was then eventually cooled to 0°C and excess of Grignard was quenched with 2.2 L of acetone. To the above reaction mass was further added saturated ammonium chloride solution (10.0 L) followed by 6M aqueous hydrochloric acid (10.0 L). The reaction mixture was stirred for 30 min at 25°C. The reaction mass was extracted with ethyl acetate (3 x 5.0 L) and the combined organic extract was washed with saturated brine (2 X 10 L). Concentration of the organic layer afforded 2-ethyl-5-methoxy-benzaldehyde (**28**) (2.15 kg, 95% NMR purity, 83% yield) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 1.25 (t, 3H, J = 7.7 Hz), 3.00 (q, 2H, J = 7.7 Hz), 3.85 (s, 3 H), 7.09 (dd, 1H, J = 8.4, 2.9 Hz), 7.21 (d, 1H, J = 8.4 Hz), 7.36 (d, 1H, J = 2.9 Hz), 10.30 (s, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 16.9, 24.6, 55.5, 113.5, 121.2, 131.4, 134.1, 139.7, 158.1, 191.7; HRMS m/e 165.0911 [$(M+H)^+$, calcd for $C_{10}H_{12}O_2$ 165.0910] The crude product was directly used in the following step.

2-(2-ethyl-5-methoxy-phenyl)-5,5,7,7-tetramethyl-1,6-dioxaspiro[2.4]heptan-4-one (30). To a solution of potassium *t*-butoxide (1.20 kg, 10.69 mol) in dimethyl sulfoxide (4.4 L), 2,2,5,5-tetramethyl-4-bromo tetrahydrofuran-3-one (**19**) (1.78 kg, 8.05 mol) was added dropwise maintaining the reaction mass below 20°C. The reaction mass was stirred for 1 hr and after that

time a solution of 2-ethyl-5-methoxy-benzaldehyde (**28**) (885g, 5.12 mol) in DMSO (4.5 L) was added slowly during 30 minutes. The reaction mass was warmed to 25°C and stirred for 15 hr. The reaction was monitored by HPLC. The reaction was diluted with water (50.0 L) and extracted with t-butyl methyl ether (3 x 10.0 L). The combined organic layer was washed with brine (5 L) and concentrated to afford crude product (1.9 Kg). The crude mass was adsorbed on silica and chromatographed over silica using ethyl acetate-cyclohexane as solvent to afford diastereomeric mixture of expected product (2-(2-ethyl-5-methoxy-phenyl)-5,5,7,7-tetramethyl-1,6-dioxaspiro[2.4]heptan-4-one, 1.03 Kg, 63% yield). Major isomer ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 1.08 (s, 3H), 1.25 (t, 2H, J = 8 Hz), 1.34 (s, 3H), 1.40 (s, 3H), 1.51 (s, 3H), 2.57-2.69 (m, 2H), 3.65 (s, 3H), 4.50 (s, 1H), 6.83 (dd, 2H, J = 8 Hz, 4 Hz), 7.06 (d, 1H, J = 8 Hz), 7.17 (d, 1H, J = 4Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.9, 24.7, 25.9, 25.9, 26.1, 26.1, 55.4, 64.0, 70.5, 75.1, 78.5, 111.6, 115.2, 128.7, 130.7, 132.9, 157.3, 211.2; HRMS m/e 305.1764 [$(M+H)^+$, calcd for $C_{10}H_{12}O_2$ 305.1764] **4-(2-ethyl-5-methoxy-phenyl)-2,2,6,6-tetramethyl-tetrahydropyran-3,5-dione (31).** Concentrated sulphuric acid (10.0 L) was added to a solution of spiroepoxide **30** (10.0 kg, 32.85 mol) in toluene (80.0 L) at 0-5°C. The reaction mixture was warmed to 25°C and stirred at this temperature for 16 hr. The conversion monitored by LC-MS. The reaction mass was quenched by pouring into ice-water (50.0 L). The organic layer was separated. The aqueous layer was neutralized with sodium bicarbonate to a pH of ~6-7 and extracted with ethyl acetate (3 x 20.0 L). The combined organic extract (toluene & ethyl acetate) was washed with brine (20.0 L) and concentrated under vacuum. The crude product was purified by chromatography using silica as stationery phase and cyclohexane-ethyl acetate as mobile phase to afford pure 4-(2-ethyl-5-methoxy-phenyl)-2,2,6,6-tetramethyl-tetrahydropyran-3,5-dione (4.60 Kg, 46% yield). ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 1.09 (t, 3H, J = 7.5 Hz), 1.48 (s, 3

H), 1.49 (s, 3 H), 1.60 (s, 6 H) 2.33-2.41 (m, 2 H), 3.79 (s, 3 H), 5.71 (s, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 6.88-6.95 (m, 1 H) 7.23-7.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 15.3, 25.4, 27.5, 27.8, 28.5, 28.8, 55.4, 72.5, 78.4, 110.9, 115.1, 116.6, 129.0, 130.5, 136.9, 158.3, 171.7, 196.9; HRMS m/e 305.1752 [$(M+H)^+$, calcd for $C_{18}H_{24}O_4$ 305.1747].

4-(2-ethyl-5-hydroxy-phenyl)-2,2,6,6-tetramethyl-tetrahydropyran-3,5-dione (4). Acetic acid (27.3 L) and aq. hydrobromic acid (48%, 27.3 L) was added sequentially to a stirred solution of 4-(2-ethyl-5-methoxy-phenyl)-2,2,6,6-tetramethyl-tetrahydropyran-3,5-dione (**31**) (1.90 kg, 6.24 mol) at 25-30˚C. The reaction mixture was warmed to 100°C and stirred at this temperature for 7 hr. The reaction progress was monitored by LC-MS. At the end of the reaction, the reaction mass was cooled to 25°C, diluted with water (150.0 L) and extracted with ethyl acetate (3 x 20.0 L). The combined organic extract was washed with brine (10.0 L) and concentrated. The crude product was purified by chromatography using silica as stationery phase and cyclohexane-ethyl acetate as mobile phase to afford pure 4-(2-ethyl-5-hydroxy-phenyl)-2,2,6,6-tetramethyl-tetrahydropyran-3,5-dione (1.20 kg, 66% yield). ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 1.06 (t, 3H, *J* = 7.5 Hz), 1.41 - 1.53 (m, 6H), 1.53 - 1.70 (m, 6H), 2.25-2.45 (m, 2H), 6.11 (bs, 1H), 6.31 (d, 1H, *J* = 2.6 Hz), 6.55-6.75 (bm, 2H) 7.10 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 15.3, 25.4 , 27.8 (m, 2C) 28.6 (m, 2C), 72.7, 78.3, 110.8, 117.0, 118.6, 128.0, 130.4, 135.9, 154.9, 173.2, 198.6; HRMS m/e 291.1583 [$(M+H)^+$, calcd for $C_{17}H_{22}O_4$ 291.1591].

2-bromo-5-hydroxy-benzaldehyde (33). Bromine (1.468 L, 28.66 mol, 1 eq.) was added to a suspension of 3-hydroxy benzaldehyde (3.5 kg, 17.4 mol) in dichloromethane (26.5 L) over a period of 3 hr at -5 to 0°C. The reaction mass was brought to 25°C and stirred at this temperature for 12 hr. The reaction was monitored by HPLC and TLC. The reaction mass was

purged with nitrogen at room temperature to remove dissolved hydrobromic acid. The reaction mass was cooled to 0°C and was filtered and suck dried on a glass Neutche filter. The filter cake was re-suspended in saturated sodium bicarbonate (50.0 L) and stirred at room temperature for 3 hr. The product suspension was filtered over a Neutche filter and washed with water (10.0 L). The filtered product was air dried to moisture content less than 2% giving 2-bromo-5-hydroxy-benzaldehyde **(**4.3 Kg, 97% purity by HPLC 258 nm, 74% yield). **Note: Product is skin and eye irritant.** The analytical data correspond to those reported in literature.[17]

4-bromo-3-[(*E*)-butyliminomethyl]phenol (25). 2-Bromo-5-hydroxy benzaldehyde (4.3 Kg, 21.39 mol, considered to be 100% pure) was suspended in dichloromethane (64.5 L) and stirred at 5°C. Anhydrous sodium sulphate (6.07 Kg, 42.78 mol, 2 eq.) was added to the reaction mixture followed by slow addition of n-butyl amine (3.20 L, 2.37 Kg, 32.08 mol, 1.56 eq.) at 0 - 5°C over a period of 1 h. The reaction mass was brought to 25°C and stirred at this temperature for 12 hr. The reaction progress was monitored by GC. The reaction mass was filtered off to remove sodium sulphate and the filter cake was washed with ethyl acetate (25.0 L). The combined filtrate was concentrated to afford a semi-solid. The crude product was suspended in toluene (50.0 L) and ~50% of toluene was distilled off under reduced pressure to remove unreacted amine and any residual moisture. The reaction mixture was cooled to 25°C and the product was filtered on a glass Neutche filter. The solid was washed with fresh toluene (5.0 L) and then with cyclohexane (2 x 5.0 L). The solid mass was dried under vacuum to provide 4-bromo-3-[(*E*)-butyliminomethyl] phenol (3.90 kg, 97% NMR purity, 74% yield). **Note: Product skin and eye irritant, moisture sensitive upon prolong exposure.** ^{1}H NMR (DMSO-d6, 400 MHz,): δ 9.78 (brs, 1H), 8.46 (s, 1H), 7.42-7.39 (m, 2H), 6.82-6.79 (m, 1H), 3.57 (t, 2H, J = 8 Hz), 1.61-1.54 (m, 2H), 1.32-1.27 (m, 2H), 0.89 (t, 3H, J = 8 Hz); ^{13}C NMR

(DMSO-d6, 101 MHz): δ 158.8, 156.9, 134.7, 133.6, 119.9, 114.5, 112.7, 60.3, 32.5, 19.9, 13.7 HRMS m/e 198.94 [(M-nBu+H)$^+$, calcd for C_7H_6BrNO 198.96].

5-hydroxy-2-methyl-benzaldehyde (17). Anhydrous THF (25.0 L) was added to imine 25 (2.55 kg, 9.66 mol) and the suspension was stirred at 25°C. Then anhydrous $MnCl_2$ (250 g, 1.98 mol, freshly dried at 80°C under vacuum for 2 hr) and copper (I) chloride (98.5g, 0.995mol) were added. The reaction mass was cooled to -10°C, and then 2.2 M methyl magnesium bromide solution in diethyl ether (13.57 L, 29.85mol) was added over a period of 1 hr (temperature between -10°C and 0°C). The reaction mass was slowly bought to reflux temperature over a period of 1 hr and maintained at reflux temperature for 2 hr. The reaction progress was monitored by HPLC. The reaction mass was cooled to 0°C and excess of methyl magnesium bromide reagent was quenched with acetone (2.2 L). The reaction mass was further quenched with 1M hydrochloric acid (~40 L) till the reaction mass was acidic (pH ~1). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20.0 L). The combined organic extract was washed with saturated brine (2 x 10.0 L) and concentrated to give brown solid (1.7 Kg). The crude product was purified by column chromatography using cyclohexane : ethyl acetate (0-30%) to provide 1.29 Kg of solid which was further slurried in 2.6 L of DCM - Petrolether (1:1), filtrated and dried to give 5-hydroxy-2-methyl-benzaldehyde (1.08 kg, 98% NMR purity, 80% yield). ^{1}H NMR (DMSO-d6, 400 MHz): δ 10.15 (s, 1H), 9.65 (s, 1H), 7.19 (s, 1H), 7.12 (d, 1H, J = 8.0 Hz), 6.96 (d, 1H, J = 8 Hz), 2.48 (s, 3H); ^{13}C NMR (DMSO-d6, 101 MHz): δ 193.2, 156.0, 134.8, 133.0, 130.7, 17.9, two carbon signals not observed; HRMS m/e 136.045 [(M)$^+$, calcd for $C_8H_8O_2$ 136.052].

(4)-4-[(5-hydroxy-2-methyl-phenyl)methylene]-2,2,5,5-tetramethyl-tetrahydrofuran-3-one (34). To a solution of 2,2,5,5-tetramethyltetrahydrofuran-3-one (**10**) (2.48 kg, 17.4 mol,

1.93 eq.) in methanol (3.7 L) was added sodium methoxide in methanol (25 mass %, 7.35 L, 32.13 mol) at 0°C over a period of 35 min and stirred at 0°C for additional 5 min. A solution of 5-hydroxy-2-methyl-benzaldehyde (1.25 kg, 9.00 mol) in methanol (8.8 L) was added to the reaction mass at 0°C over a period of 1 hr. The reaction mass was slowly bought to reflux temperature ~65°C and refluxed for 4 hr. The reaction progress was monitored by HPLC. The reaction was cooled to 20°C, acidified with 2M hydrochloric acid (4.4 L) and stirred at room temperature for 12h. The suspension formed was suction filtered and the filter cake was washed with water (~5.0 L, until neutral pH). The crude product was dissolved in TBME (10.0 L), water phase was separated and TBME layer was evaporated to yield 1880 g of pure product 34 (1880 g, 79% yield). ^{1}H NMR (DMSO-d6, 400 MHz): δ 9.39 (s, 1H), 7.44 (s, 1H), 7.03 (d, 1H, J = 8 Hz), 6.69 (d, 1H, J = 8 Hz), 6.68 (s, 1H), 2.08 (s, 3H), 1.30 (s, 6H), 1.23 (s, 6H); ^{13}C NMR (DMSO-d6, 101 MHz): δ 206.9, 155.1, 140.7, 134.9, 134.3, 131.1, 126.4, 116.0, 114.9, 79.2, 78.8, 29.8, 26.1, 18.9, one carbon signal not observed; HRMS m/e 260.13 [$(M)^{+}$, calcd for $C_{16}H_{20}O_3$ 260.14].

2-(5-hydroxy-2-methyl-phenyl)-5,5,7,7-tetramethyl-1,6-dioxaspiro[2.4]heptan-4-one (15). To a solution of (4*E*)-4-[(5-hydroxy-2-methyl-phenyl)methylene]-2,2,5,5-tetramethyl-tetrahydro-furan-3-one (1.00 kg, 3.84 mol) in ethanol (5.7 liter) and water (5.7 liter) at 25°C, was added 1M NaOH solution (3.96 L, 3.96 mol) over a period of 15 min. To this alkali solution, sodium tungstate dehydrate (2.28 g, 0.0076 mol, 0.002 eq.) and cetyl trimethyl ammonium bromide (212 g, 0.576 mol, 0.15 eq.) were added and the reaction mass was heated to 50°C. Hydrogen peroxide (342 ml, 40% in water, 0.576 mol, 0.15 eq.) was added slowly over a period of 15 min at 50°C using a dosing pump (**exothermic**) and the reaction mixture was stirred at 50°C for additional 15min. The reaction conversion was monitored by HPLC. The reaction mixture was

quenched with aqueous sodium meta-bisulphite solution (10.0 L, 1 g / ml), cooled to 5°C and stirred for at 5°C for 3 h. The reaction was filtered and the filter cake (product) was washed with water (5.0 L) and dried under coarse vacuum. The dried product was dissolved in of ethyl acetate (20.0 L), filtered through a plug of Celite®, washed with brine (5.0 L) and concentrated to yield 800 g of pure product **15** (75 % yield). ^{1}H NMR (DMSO-d6, 400 MHz): δ 9.34 (s, 1H), 6.99 (d, 1H, *J* = 8.0 Hz), 6.67 (s, 1H), 6.66 (d, 1H, *J* = 8.0 Hz), 4.37 (s, 1H), 2.13 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (DMSO-d6, 101 MHz): δ 214.6, 155.6, 131.2, 126.0, 115.4, 112.1, 77.8, 75.0, 67.6, 62.5, 27.7, 26.0, 25.1, 17.6, one carbon signal not observed; HRMS m/e 276.13 [$(M)^+$, calcd for $C_{16}H_{20}O_4$ 276.14].

4-(5-hydroxy-2-methyl-phenyl)-2,2,6,6-tetramethyl-tetrahydropyran-3,5-dione (3).

Procedure A

A solution of 1-(5-hydroxy-2-methyl-phenyl)-5,5,7,7-tetramethyl-2,6-dioxaspiro[2.4]heptan-4-one (1.5 kg, 5.43 mol) in DCM (15.0 L) was cooled to 0°C. Conc. sulphuric acid (1.3 L, 24.48 mol, 4.5 eq.) was added over a period of 1.5 hr maintaining the reaction temperature below 5°C. Thereafter the reaction mixture was stirred at 0-5°C for 15 min. The reaction progress was monitored by HPLC. The reaction mixture was added to 13.0 L of ice cold water, stirred for 3 hr and the solid was filtered. The filter cake was washed with water until neutral pH (~3 L) and then dried at 50°C under high vacuum (water content below 1%) to yield pure product **3** (1050 g, 70% yield). ^{1}H NMR (DMSO-d6, 400 MHz): δ 6.98 (d, 1H, *J* = 8.0 Hz), 6.60 (d, 1H, *J* = 8.0 Hz), 6.37 (s, 1H), 1.91 (s, 3H), 1.42 (s, 12H); ^{13}C NMR (DMSO-d6, 101 MHz): δ 154.7, 132.6, 130.0, 127.4, 118.0, 114.1, 109.7, 74.9, 27.9, 18.0, four carbons not observed, HRMS m/e 276.13 [$(M)^+$, calcd for $C_{16}H_{20}O_4$ 276.14].

Procedure B

Amberlyst 15 Ion exchange resin (1 g) was added to a solution of 1-(5-hydroxy-2-methyl-phenyl)-5,5,7,7-tetramethyl-2,6-dioxaspiro[2.4]heptan-4-one **15** (1 g, 3.6 mmol) in DCM (20 mL) at 25-30°C. The reaction mixture was stirred at this temperature for 22 hr. The conversion monitored by HPLC. The reaction mass was filtered and the Amberlyst residue washed with ethyl acetate (20 mL). The combined organic layer was concentrated under vacuum to afford the desired product 3. (0.72 g, 72% yield). The analytical data of the product thus obtained was identical in all respects to the one mentioned above in Procedure A.

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Notes

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ABBREVIATIONS

$CDCl_3$, chloroform-d; $CHCl_3$, chloroform; CTAB, cetyl trimethyl ammonium bromide; DMAP, N,N-dimethyl-4-aminopyridine; DMSO, dimethylsulfoxide; eq, equivalents; EtMgBr, ethyl magnesium bromide; EtMgCl, ethyl magnesium chloride; HCl, hydrochloric acid; HPLC, high performance liquid chromatography; hr, hour; *i*-PrMgCl, *iso*-propyl magnesium chloride; *i*-PrOH, isopropanol; MeMgBr, methyl magnesium bromide; MeMgCl, methyl magnesium chloride; MeTHF, 2-methyl tetrahydrofurane; min, minute; $MnCl_2$, manganese dichloride; *n*-BuLi, *n*-butyl lithium; *n*-BuMgBr, *n*-butyl magnesium bromide; NMR, nuclear magnetic resonance; THF, tetrahydrofurane; TBME *tert*-butyl methyl ether.

REFERENCES

(1) Muehlebach, M.; Boeger, M.; Cederbaum, F.; Cornes, D.; Friedmann, A. A.; Glock, J.; Niderman, T.; Stoller, A.; Wagner, T. *Bioorg. & Med. Chem.* **2009**, *17*, 4241-4256.

(2) Muehlebach, M.; Cederbaum, F.; Cornes, D.; Friedmann, A. A.; Glock, J.; Hall, G.; Indolese, A. F.; Kloer, D. P.; Le Goupil, G.; Maetzke, T.; Meier, H.; Schneider, R.; Stoller, A.; Szczepanski, H.; Wendeborn, S.; Widmer, H. *Pest Manag Sci* **2011**, *67*, 1499–1521.

(3) Muehlebach, M.; Mathews, C. J.; Scutt, J. N.; Mangala, G.; PCT Patent WO 2008071405 June 19, 2008; Mathews, C. J.; Scutt, J. N.; Mangala, G.; Muehlebach, M. PCT Int. Appl. WO 2009150095 December 17, 2009; Scutt, J. N.; Mathews, C. J. PCT Int. Appl. WO 2009150094 December 17, 2009; Scutt, J. N.; Mathews, C. J.; Muehlebach, M. PCT Int. Appl. WO

2009150093 December 17, 2009; Mathews, C. J.; Finney, J.; Scutt, J. N.; Robinson, L.; Delaney, J. S. PCT Int. Appl. WO 2010081755 July 22, 2010.

(4) Kuronen, P.; Laitalainen, T.; Orama, O. *Journal of Heterocyclic Chemistry*, **1993**, *30*, 961-965.

(5) Anderson, R. J.; Lee, S. F.; Luehr, G. W., Scott, C. R. Patent GB 2205316 December 7, 1988.

(6) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.*, **1997**, *119*, 11108-11109; Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2000**, *122*, 1360-1370.

(7) Morgan, J.; Pinhey, J. T., *J. Chem. Soc., Perkin Trans. 1* **1990**, 715-720.

(8) Scutt, J. N.; Jeanmart, Stephane A. M.; Mathews, C. J.; Muehlebach, M.; Smejkal, T.; Smith, S. C.; Smits, H.; Wailes, J. S.; Whittingham, W. G.; Willetts, N. J. *ACS Symposium Series* **2015**, *1204*, 291-304.

(9) House, H. O.; Wasson, R. L. *J. Am. Chem. Soc.* **1956**, *78,* 4394-4400.

(10) Scutt, J. N. PCT Patent. WO 2010136431 December 2, 2010.

(11) Cahiez, G. *Synthesis* **1999**, 2138–2144.; Cahiez, G.; Duplais, C.; Buendia J. *Chem. Rev.*, **2009**, *109*, 1434–1476; for $MnCl_2$ catalysed Grignard couplings on other substrates see for example Rueping, M.; Ieawsuwan, W. *Synlett.* **2007**, 247-250.

(12) Cahiez, G.; Bernard, D.; Normant, J. F. J. *Organomet. Chem.* **1976**, *113*, 107-113.; Cahiez, G.; Gager, O. *Preparation and Reactivity of Organomanganese Compounds*, Patai's Chemistry of Functional Groups 2010.

(13) LiCl may help break EtMgBr aggregates: Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336; LiCl also significantly increases solubility of $MnCl_2$ in THF; for an example of using LiCl to facilitate a manganese coupling see Fugami, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, *16*, 2203-2206.

(14) Suzuki: Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. *Tetrahedron Letters* **2000**, *41*, 6237-6240.; Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534–5539; Trimethylaluminium: Morioka, T.; Nishizawa, A.; Nakamura, K.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1729; Cooper, T., Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward S. *Adv. Synth. Catal.* **2006**, *348*, 686-690; Dimethylzinc: Herbert, J. M. *Tet. Lett.* **2014**, *45*, 817-819; Methyl Grignard: Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P. ; Wang, B.-Q.; Zhao, K.-Q.; Shi Z.-J. *Chem. Comm.*, **2008**, 1437-1439; Agrawal, T.; Cook S. P. *Org. Lett.* **2014**, *16*, 5080-5083; review: Yan, G.; Jyoti Borah, A.; Wang, L.; Yang, M. *Adv. Synth. Catal.* **2015**, *357*, 1333-1350.

(15) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, H. T. B. H.; Gossage, R. A.; Cahiez, G.; Van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61-69.; Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, H. T. B. H.; Cahiez, G.; Van Koten, G. *Recueil des Travaux Chimiques des Pays-Bas* **1996**, 115, 547-548.; Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53-60.; Cahiez, G.; Marquais, S. *Synlett* **1993**, 45-47.

(16) Carroll, W. A.; Dart, M. J.; Perez-Medrano, A.; Frost, J. M.; Peddi, S. Patent US 20080287510 November 20, 2008.

(17) Kaiser, F. *J. Org. Chem.* **2002**, *67*, 9248-9256.