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Research Article

Short Hydroacylation-Based Synthesis of Four Aryl-3-hydroxypropanones, Predictable Biomass-Derived C9 Platform Molecules

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Abstract

A two-step protocol for the synthesis of aryl-3-hydroxypropanones, which were regarded as lignin degradation products, was proposed herein. This protocol provided a more rapid and easier access to aryl-3-hydroxypropanones, and aryl-3-hydroxypropanones were expected to be ideal platform molecules for the synthesis of more complex value-added targets.

Keywords

Lignin; aryl-3-hydroxypropanone; hydroacylation; rhodium catalysis; Fleming-Tamao oxidation

1. Introduction

As the earth's petroleum resources are becoming scarcer and scarcer, the production of bulk chemicals from renewable resources is of utmost importance for the development of new sustainable industrial processes. The most abundant carbon-based raw material is lignocellulosic biomass, which is composed of the polysaccharides cellulose and hemicellulose, as well as the aromatic-rich polymer lignin. For these three lignocellulose components, the generation and subsequent exploitation of the corresponding monomers are of high industrial relevance [1-3]. The isolation of cellulose and the monomerization of the two carbohydrate-based polymers into the constituent monosaccharides (or their derivatives) has been well established. However, the separation of lignin from hemicellulose and its subsequent depolymerization are much more challenging tasks [4]. This hurdle is mainly caused by the robust and irregular structure of lignin and the presence of different types of lignin with varying ratios of guaiacyl and syringyl units, as well as linkage types present depending on the biomass source [5]. As a result, lignin isolation and its subsequent depolymerization are hot and rapidly evolving topics [6]. In particular, the old protocols for lignocellulosic biomass separation focused primarily on cellulose production, giving rather degraded lignins as secondary products, and vanillin as the main final monomer, which is by far the most abundant product available on the industrial scale [7, 8]. Newer lignin isolation and depolymerization approaches are milder, provide more native-like lignins, and generate less degraded monomers relative to simple vanillin [9]. Although such second-generation monomeric structures have been presently obtained only on a small scale, they may soon become potential new platform molecules for bulk or fine chemistry targets. To quickly enable follow-up synthetic studies starting from potential lignin-derived platform molecules [10-12] in parallel to the improvement of the efficiency and scalability of respective lignin depolymerizations, protocols for the rapid synthesis of preconized monomers and analogs are needed.

Based on the current framework for biomass valorization through C–H activation protocols [13-17], lignin depolymerization products as a source of renewable carbon have attracted our attention. Furthermore, several research demonstrated that biocatalytic depolymerization of lignin allowed to obtain guaiacyl-3-hydroxypropanone (GHP) and syringyl-3-hydroxypropanone (SHP) as major degradation products [18, 19]. These aryl-3-hydroxypropanones appear to be ideal starting platform molecules for the synthesis of more complex value-added targets. So far, however, biocatalytic depolymerization has allowed to access only small amounts of these molecules, and the reported chemical syntheses have been very inefficient. Therefore, studies currently are underway on how to upscale the above biocatalytic depolymerizations, and obtain GHP and SHP in higher quantities. In particular, these monomers are seen as precursors for high value-added scaffolds like indanones, coumarins, flavones, xanthanes or dihydrochalcones. Thus, in the prospect that more efficient large-scale depolymerization protocols will be available in the future, it is desirable to develop modern, rapid, and efficient chemical syntheses of these aryl 3-hydroxypropanones, to enable in advance their valorization studies. Other aryl-3-hydroxypropanones are also highly desirable since they can be very interesting model substrates for those studies.

We proposed here a new, short and efficient protocol for synthesis of anisyl-3-hydroxypropanone (AHP), GHP, SHP and veratryl-3-hydroxypropanone (VHP) based on alkene hydroacylation (Figure 1).

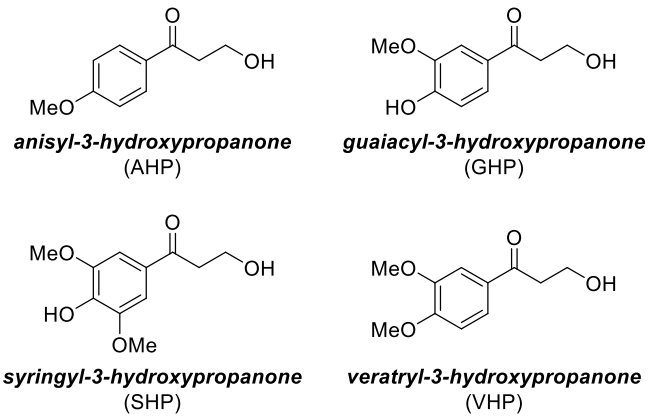


Figure 1 The lignin depolymerization monomers synthesized in this study

2. Materials and Methods

2.1 General Information

Reactions: All reactions were carried out under an argon atmosphere by standard syringe and septa techniques. Glassware was flame-dried under vacuum or taken directly from the oven at 100°C and cooled under vacuum before use. Purifications were performed by flash column chromatography using silica gel Merck Geduran® SI 60 (40-63 µm). Yields referred to chromatographically and spectroscopically pure compounds.

Reagents and solvents: Commercial reagents were purchased from Alfa Aesar, Acros Organics, Sigma Aldrich, TCI Chemicals, Fluorochem and ABCR suppliers. Commercial solvents were purchased at Carlo Erba or VWR. Dichloromethane was dried on a Mbraun purification system MB SPS-800. THF was dried and then distilled over Na/benzophenone. Anhydrous methanol was dried appropriately and kept under inert atmosphere.

TLC: Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kieselgel 60F_{254} plates and analyzed with an ultra-violet lamp (λ = 254 nm) using potassium permanganate or *p*-anisaldehyde as a stain.

NMR: NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AM 300 MHz or a Bruker AVANCE 400 MHz spectrophotometer. NMR experiments were carried out at room temperature in $CDCl_3$, acetone-d_6 and CD_3OD. Chemical shifts were given in parts per million (ppm) using the solvent's residual non-deuterated signals as reference (δ ^{1}H = 7.26 ppm; δ ^{13}C = 77.16 ppm for $CDCl_3$, δ ^{1}H = 2.05 ppm; δ ^{13}C = 29.84 ppm and 206.26 ppm for acetone-d_6, δ ^{1}H = 3.31 ppm; δ ^{13}C = 49.00 ppm for CD_3OD). The terms m, s, d, t and q correspond to multiplet, singulet, doublet, triplet and quartet, respectively. The term br. and app. were respectively used in the case of the peak being broad or apparent, and in the latter case the correct real multiplicity cannot be surely assigned. Coupling constants (J) were given in Hertz (Hz). For previously unknown compounds, a combination of ^{13}C DEPT, JMOD and 2D experiments (COSY, HSQC, HMBC) were used to complete the assignment of ^{1}H and ^{13}C signals.

IR: IR spectra were recorded with a Tensor 27 (ATR Diamond) Bruker spectrophotometer. IR spectra were reported as characteristic bands (cm^{-1}).

HRMS: High-resolution mass spectra (HRMS) were obtained using a mass spectrometer MicroTOF from Bruker with an electron spray source (ESI) and a TOF detector at Institut Parisien de Chimie Moléculaire (FR 2769).

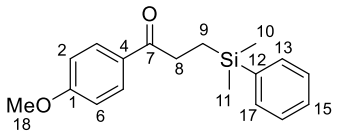
Melting points: Melting points were measured in capillary tubes on a Stuart Scientific SMP3 apparatus and are uncorrected.

2.2 Synthesis of Aryl-3-silylpropanones 1a-1d

2.2.1 General Procedure

A round bottom flask was charged with tris(triphenylphosphine)rhodium (I) chloride (Wilkinson's catalyst, 5 mol%), benzoic acid (10 mol%), 2-amino-3-methylpyridine (40 mol%) and aromatic aldehyde (1.0 equiv.). The flask was sealed with a septum and placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and a 1:2 v/v mixture of dry toluene and THF (C = 1.5 M) was introduced. Dimethylphenylvinylsilane (4.0 equiv.) was added to this solution and the flask was equipped with a reflux condenser. The mixture was heated at 160°C until complete conversion was reached as checked by TLC (overnight). The crude solution was directly purified by flash column chromatography on silica gel to give the desired aryl-3-silylpropanones **1a-1d**.

2.2.2 Characterization of Aryl-3-silylpropanones **1a-1d**



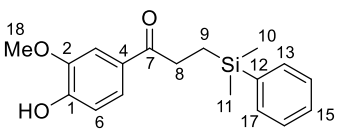
3-(dimethyl(phenyl)silyl)-1-(4-methoxyphenyl)propan-1-one (1a). Obtained using the general procedure from 0.61 mL (5.0 mmol, 1.0 equiv.) of *p*-anisaldehyde. Purification by flash column chromatography on silica gel (Cyclohexane/AcOEt 9:1) gave *3-(dimethyl(phenyl)silyl)-1-(4-methoxyphenyl)propan-1-one* **1a** (716 mg, 48% yield) as a yellow oil.

IR (Diamond-ATR, neat, cm^{-1}): 3033, 2857, 1734, 1636, 1583, 1514, 1255, 1139.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.97-7.79 (m, 2H, H-3 and H-5), 7.64-7.50 (m, 2H, H-13 and H-17), 7.44-7.31 (m, 3H, H-14, H-15 and H-16), 6.91 (d, *J* = 8.9 Hz, 2H, H-2 and H-6), 3.86 (s, 3H, H-18), 2.95-2.83 (m, 2H, H-8), 1.24-1.11 (m, 2H, H-9), 0.35 (s, 6H, H-10 and H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 199.7 (C-7), 163.4 (C-1), 138.6 (C-12), 133.7 (2C, C-13 and C-17), 130.4 (2C, C-3 and C-5), 129.9 (C-4), 129.2 (C-15), 128.0 (2C, C-14 and C-16), 113.8 (2C, C-2 and C-6), 55.5 (C-18), 32.8 (C-9), 10.3 (C-8), -3.0 (2C, C-10 and C-11).

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}O_2SiNa$: 321.1281; found: 321.1275.



3-(dimethyl(phenyl)silyl)-1-(4-hydroxy-3-methoxyphenyl)propan-1-one (1b). Obtained using the general procedure from 456 mg (3.0 mmol, 1.0 equiv.) of vanillin. Purification by flash column

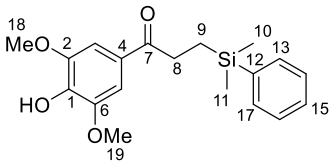
chromatography on silica gel (Cyclohexane/AcOEt 9:1) gave *3-(dimethyl(phenyl)silyl)-1-(4-hydroxy-3-methoxyphenyl)propan-1-one* **1b** (677 mg, 72% yield) as a brown oil.

IR (Diamond-ATR, neat, cm^{-1}): 3387, 3069, 2955, 2896, 2837, 1671, 1590, 1514, 1480, 1426, 1269.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64-7.62 (m, 2H, H-13 and H-17), 7.52 (d, *J* = 1.9 Hz, 1H, H-3), 7.46 (dd, *J* = 8.3, 2.0 Hz, 1H, H-5), 7.43-7.35 (m, 3H, H-14, H-15 and H-16), 6.93 (d, *J* = 8.3 Hz, 1H, H-6), 6.62 (br s, 1H, OH), 3.88 (s, 3H, H-18), 2.98-2.83 (m, 2H, H-8), 1.27-1.10 (m, 2H, H-9), 0.37 (s, 6H, H-10 and H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.0 (C-7), 150.4 (C-4), 146.8 (C-2), 138.5 (C-12), 133.6 (2C, C-14 and C-16), 129.5 (C-1), 129.1 (C-15), 127.9 (2C, C-13 and C-17), 123.3 (C-5), 113.9 (C-6), 110.1 (C-3), 56.0 (C-18), 32.6 (C-8), 10.6 (C-9), -3.1 (2C, C-10 and C-11).

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}SiO_3Na$: 337.1230; found: 337.1241.



3-(dimethyl(phenyl)silyl)-1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one (1c). Obtained using the general procedure from 981 mg (5.0 mmol, 1.0 equiv.) of syringaldehyde. Purification by flash column chromatography on silica gel (Cyclohexane/AcOEt 1:1) gave *3-(dimethyl(phenyl)silyl)-1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one* **1c** (1.43 g, 83% yield) as a brown solid.

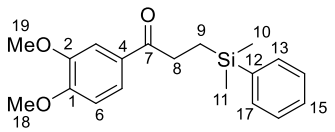
m.p.: 98-99°C.

IR (Diamond-ATR, neat, cm^{-1}): 3328, 2974, 2902, 1658, 1578, 1518, 1465, 1454, 1334, 1223, 1107.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.58-7.51 (m, 2H, H-13 and H-17), 7.41-7.33 (m, 3H, H-14, H-15 and H-16), 7.15 (s, 2H, H-3 and H-5), 3.88 (s, 6H, H-18 and H-19), 2.92-2.80 (m, 2H, H-8), 1.21-1.11 (m, 2H, H-9), 0.34 (s, 6H, H-10 and H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 199.8 (C-7), 146.8 (2C, C-2 and C-6), 139.6 (C-1), 138.6 (C-12), 133.7 (2C, C-13 and C-17), 129.2 (C-15), 128.2 (C-4), 128.0 (2C, C-14 and C-16), 105.6 (2C, C-3 and C-5), 56.5 (2C, C-18 and C-19), 32.7 (C-8), 10.9 (C-9), -3.0 (2C, C-10 and C-11).

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{24}O_4SiNa$: 367.1336; found: 367.1351.



1-(3,4-dimethoxyphenyl)-3-(dimethyl(phenyl)silyl)propan-1-one (1d). Obtained using the general procedure from 830.9 mg (5.0 mmol, 1.0 equiv.) of veratraldehyde and 2.0 mL (11.0 mmol, 2.2 equiv.) of dimethylphenylvinylsilane. Purification by flash column chromatography on silica gel (Cyclohexane/AcOEt 8:2) afforded *1-(3,4-dimethoxyphenyl)-3-(dimethyl(phenyl)silyl)propan-1-one* **1d** (1.52 g, 92% yield) as a colorless-yellow solid.

m.p.: 63-64°C.

IR (Diamond-ATR, neat, cm^{-1}): 3071, 3004, 1678, 1597, 1586, 1513, 1418, 1263.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.57-7.52 (m, 2H, H-13 and H-17), 7.50-7.45 (m, 2H, H-5 and H-3), 7.40-7.34 (3, 3H, H-14, H-15 and H-16), 6.84 (d, *J* = 8.8 Hz, 1H, H-6), 3.92 (s, 3H, H-18), 3.90 (s, 3H, H-19), 2.95-2.83 (m, 2H, H-8), 1.22-1.13 (m, 2H, H-9), 0.34 (s, 6H, H-10 and H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 198.3 (C-7), 152.5 (C-1), 148.4 (C-2), 137.9 (C-12), 132.9 (2C, C-13 and C-17), 129.2 (C-4), 128.4 (C-15), 127.3 (2C, C-14 and C-16), 121.8 (C-5), 109.7 (C-3), 109.5 (C-6), 55.1 (C-18), 55.0 (C-19), 31.8 (C-8), 9.7 (C-9), -3.7 (2C, C-10 and C-11).

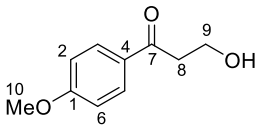
HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{24}O_3SiNa$: 351.1387; found: 351.1390.

2.3 Synthesis of Aryl-3-hydroxypropanones 2a-2d

2.3.1 General Procedure

A round bottom flask was charged with the aryl-3-silylpropanone 1a-1d (1.0 equiv.). The flask was sealed with a septum and placed under vacuum before being backfilled with argon. The vacuum/argon cycles were repeated twice and dry dichloromethane (C = 0.16 M) was introduced. The solution was cooled to 0°C (ice/water bath) and tetrafluoroboric acid diethylether complex (2.5 equiv.) was introduced. The mixture was stirred at 0°C for 1 h and the solvent was concentrated under reduced pressure. Potassium fluoride (2.1 equiv.) and potassium bicarbonate (5.7 equiv.) were added to the residue. The mixture was placed under vacuum and backfilled with argon. It was then suspended in a 1:1 v/v mixture of THF and methanol (C = 0.08 M) and stirred at 0°C for 15 min. An aliquot of the mixture was taken to evaluate the conversion of the intermediate into the alcohol by TLC. To this suspension was introduced hydrogen peroxide (15.0 equiv., 30 wt% aqueous solution) at 0°C and the mixture was stirred until complete conversion of the intermediate was observed by TLC. The mixture was then quenched with an aqueous saturated solution of sodium sulfite followed by an aqueous solution of 1 M hydrochloric acid. The organoaqueous mixture was then poured into a separatory funnel and the mixture was extracted three times with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was then purified by flash column chromatography to give the desired aryl-3-hydroxypropanones **2a-2d**.

2.3.2 Characterization of Aryl-3-hydroxypropanones **2a-2d**



3-hydroxy-1-(4-methoxyphenyl)propan-1-one (AHP, 2a). Obtained using the general procedure from 200 mg (0.67 mmol, 1.0 equiv.) of 3-(dimethyl(phenyl)silyl)-1-(4-methoxyphenyl)propan-1-one **1a**. Purification by flash column chromatography on silica gel (Cyclohexane/AcOEt 7:3 to 1:1) gave *3-hydroxy-1-(4-methoxyphenyl)propan-1-one* **2a** (88.8 mg, 59% yield) as colorless crystals.

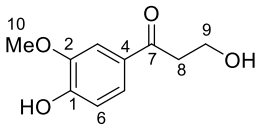
m.p.: 87-89°C.

IR (Diamond-ATR, neat, cm^{-1}): 3735, 2906, 2865, 2846, 1667, 1636, 1584, 1236, 1142.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.91 (d, *J* = 8.9 Hz, 2H, H-3 and H-5), 6.90 (d, *J* = 8.9 Hz, 2H, H-2 and H-6), 3.89 (t app., *J* = 6.6 Hz, 2H, H-9), 3.85 (s, 3H, H-10), 3.17 (t app., *J* = 6.6 Hz, 2H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 197.0 (C-7), 163.6 (C-1), 130.5 (2C, C-3 and C-5), 130.3 (C-4), 113.8 (2C, C-2 and C-6), 66.7 (C-9), 55.6 (C-10), 38.5 (C-8).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}O_3$: 181.0859; found: 181.0855.



3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)propan-1-one (GHP, 2b). Obtained using the general procedure from 200 mg (0.64 mmol, 1.0 equiv.) of 3-(dimethyl(phenyl)silyl)-1-(4-hydroxy-3-methoxyphenyl)propan-1-one **1b**. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH 99:1) afforded *3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)propan-1-one* **2b** (67 mg, 54% yield) as a colorless solid.

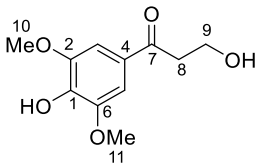
m.p.: 96-98°C.

IR (Diamond-ATR, neat, cm^{-1}): 3360, 3280, 3009, 2920, 1671, 1591, 1518, 1484, 1464, 1451, 1424.

^{1}H NMR (acetone-d_6, 300 MHz): δ = 8.47 (br. s, 1H, OH phenol), 7.59 (dd, *J* = 8.2, 2.0 Hz, 1H, H-5), 7.55 (d, *J* = 2.0 Hz, 1H, H-3), 6.91 (d, *J* = 8.2 Hz, H-6), 3.96-3.88 (m, 2H, H-9), 3.90 (s, 3H, H-10), 3.65 (t, *J* = 5.6 Hz, 1H, OH alcohol), 3.15 (t app., *J* = 6.1 Hz, 2H, H-8).

^{13}C NMR (acetone-d_6, 75 MHz): δ = 198.2 (C-7), 152.4 (C-1), 148.3 (C-2), 130.7 (C-4), 124.0 (C-5), 115.4 (C-6), 111.5 (C-3), 58.7 (C-9), 56.3 (C-10), 41.5 (C-8).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{13}O_4$: 197.0808; found: 197.0809.



3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one (SHP, 2c). Obtained using the general procedure from 775 mg (2.25 mmol, 1.0 equiv.) of 3-(dimethyl(phenyl)silyl)-1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one **1c**. A portion of the product was collected by filtration after crystallization during the extraction. Purification of the concentrated and dry organic layer by flash column chromatography on silica gel (CH_2Cl_2/MeOH 99:1) gave *3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one* **2c** (379.7 mg in total, 75% yield) as a brown solid.

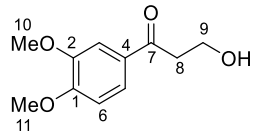
m.p.: 90-91°C.

IR (Diamond-ATR, neat, cm^{-1}): 3536, 3399, 2929, 1658, 1518, 1459, 1115.

^{1}H NMR (CD_3OD, 300 MHz): δ = 7.31 (s 2H, H-3 and H-5), 3.95 (t app., 2H, H-9), 3.90 (s, 6H, H-10 and H-11), 3.18 (t app., 2H, H-8).

^{13}C NMR (CD_3OD, 75 MHz): δ = 199.7 (C-7), 149.0 (2C, C-2 and C-6), 142.5 (C-1), 129.3 (C-4), 107.3 (2C, C-3 and C-5), 58.9 (C-9), 56.9 (2C, C-10 and C-11), 41.7 (C-8).

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{11}H_{14}O_5Na$: 249.0733; found: 249.0735.



1-(3,4-dimethoxyphenyl)-3-hydroxypropan-1-one (VHP, 2d). Obtained using the general procedure from 1.50 g (4.57 mmol, 1.0 equiv.) of 1-(3,4-dimethoxyphenyl)-3-(dimethyl(phenyl)silyl)propan-1-one **1d**. Purification by flash column chromatography on silica gel (Cyclohexane/AcOEt 1:1) gave *1-(3,4-dimethoxyphenyl)-3-hydroxypropan-1-one* **2d** (732.0 mg, 76% yield) as a colorless solid.

m.p.: 86-87°C.

IR (Diamond-ATR, neat, cm^{-1}): 3275, 3014, 2953, 2901, 1663, 1585, 1518, 1461, 1420, 1262, 1179, 1159.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (dd, *J* = 8.4, 2.0 Hz, 1H, H-5), 7.53 (d, *J* = 2.0 Hz, 1H, H-3), 6.90 (d, *J* = 8.4 Hz, 1H, H-6), 4.02 (q, *J* = 5.6 Hz, 2H, H-9), 3.95 (s, 3H, H-11), 3.94 (s, 3H, H-10), 3.20 (t app., *J* = 5.3 Hz, 2H, H-8), 2.71 (t, *J* = 6.6 Hz, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 199.3 (C-7), 153.8 (C-1), 149.3 (C-2), 130.2 (C-4), 123.1 (C-5), 110.2 (C-6), 110.1 (C-3), 58.5 (C-9), 56.3 (C-11), 56.2 (C-10), 40.0 (C-8).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{15}O_4$: 211.0965; found: 211.0973.

3. Results and Discussion

We started our study by reproducing the reported GHP syntheses, which involved aldol condensations between acetovanillone – or its derivative – and formaldehyde (Figure 2) [20, 21].

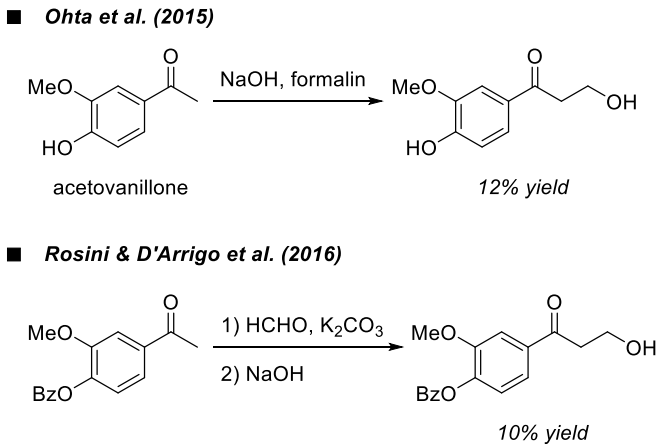


Figure 2 Reported aldolisation reactions for the synthesis of GHP.

Unfortunately, but not unexpectedly [22], following the reaction conditions described by Ohta *et al.* (*i.e.* by deprotonating acetovanillone in the α-position of the ketone and reacting the enolate formed with formaldehyde) [20], we obtained the adduct from the double condensation of formaldehyde, **3**, with a low 13% yield together with a trace amount of the desired GHP **2b** (Figure 3). Furthermore, we tested an analogous aldol reaction starting from *O*-benzoyl vanillin using potassium carbonate as the base and an aqueous solution of formaldehyde, according to the protocol reported by Rosini, D'Arrigo *et al.* The in situ generated benzoyl-GHP was then hydrolyzed in the same pot with an aqueous solution of sodium hydroxide. Unfortunately, this protocol proved to be unsuccessful in our hands since the yield of GHP was less than 5% together with compound **3** with 7% yield, and acetovanillone was produced from the hydrolysis of the unreacted starting material (80%) [21].

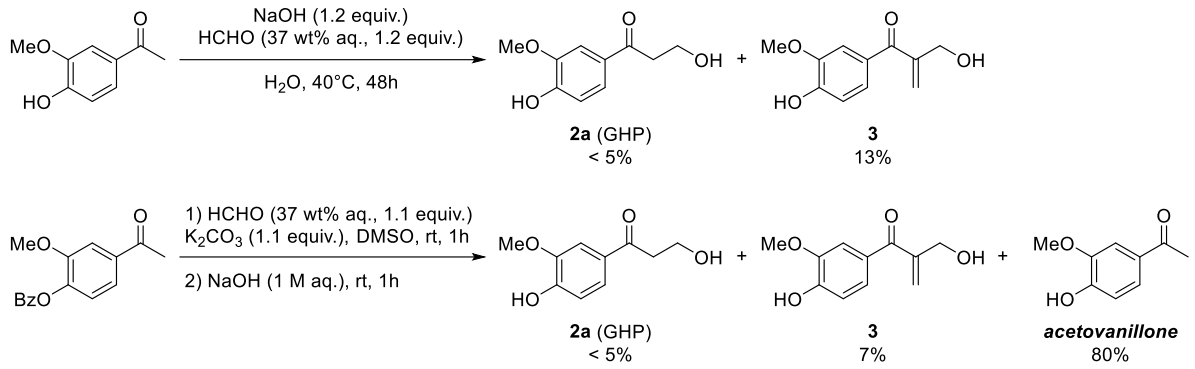
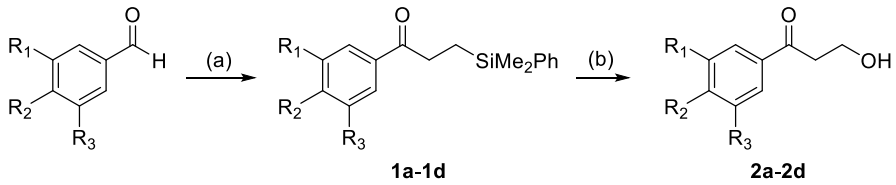


Figure 3 Steps of GHP synthesis by reported aldolisation protocols.

In light of these unsatisfactory results, we decided to develop an original, possibly scalable, and more efficient strategy to access different aryl-3-hydroxypropanones based on a modern C–H to C–C coupling [23-26]. Inspired by previous reports of chelation-assisted alkene hydroacylation [27-30] of phenolic aldehydes, we tried to prepare the carbon skeleton of the molecules. Therefore, we developed a two-step strategy to access the desired aryl-3-hydroxypropanones. The first step consists in a Rh-catalyzed hydroacylation of aldehydes to produce aryl-3-silylpropanones, followed by a Fleming-Tamao oxidation to convert the silyl group into alcohol.

Thus, according to the protocol of C.-H. Jun *et al.* [27, 28], treating *p*-anisaldehyde, vanillin, syringaldehyde, or veratraldehyde with dimethylphenylvinylsilane (4.0 equiv.) in the presence of the catalytic system [$RhCl(PPh_3)_3$ (5 mol%)/benzoic acid (10 mol%)/2-amino-3-methylpyridine (40 mol%)] at 160°C in a mixture of toluene and THF, gave the corresponding aryl-3-silyl-propanones **1a-d** in moderate to excellent (**1a**, 48%; **1b**, 72%; **1c**, 83%; and **1d**, 92%) yields (Table 1, entries 1-4). Besides, in the case of veratraldehyde, the amount of dimethylphenylvinylsilane could be reduced to 2.2 equivalents.

Table 1 Synthesis of AHP, GHP, SHP and VHP.



Entry [a]	substrate	R_1	R_2	R_3		Yield (%) [b]		Yield (%) [b]
1	*p*-anisaldehyde	H	OMe	H	**1a**	48	**2a**	59
2	vanillin	OMe	OH	H	**1b**	72	**2b**	54
3	syringaldehyde	OMe	OH	OMe	**1c**	83	**2c**	75
4	vertraldehyde	OMe	OMe	H	**1d**	92	**2d**	76

[a] Conditions: (a) $RhCl(PPh_3)_3$ (5 mol%), 2-amino-3-methylpyridine (40 mol%), $PhCO_2H$ (10 mol%), dimethylphenylvinylsilane (4.0 equiv.), Toluene/THF 1:2 v/v, 160°C, overnight; (b) 1) $HBF_4.Et_2O$ (2.5 equiv.), CH_2Cl_2, 0°C, 1h *then* concentration and 2) KF (2.1 equiv.), $KHCO_3$ (5.7 equiv.), MeOH/THF 1:1 v/v, 0°C, 15 min *then* 3) H_2O_2 (30 wt% aqueous, 15.0 equiv.), 0°C. [b] isolated yield.

The resulting adducts were then converted into the corresponding alcohols by the Fleming-Tamao oxidation protocol (Figure 3) [31-34]. The obtained aryl-3-silylpropanones **1a**-**1d** were then treated with: 1) tetrafluoroboric acid diethylether complex in dry dichloromethane, followed by 2) potassium fluoride and potassium bicarbonate in a 1:1 v/v mixture of THF and methanol to activate the silane, and 3) 30 wt% aqueous hydrogen peroxide solution to oxidize the activated silane intermediate. Starting from silane **1a**, we obtained AHP **2a** in 59% yield (Table 1, entry 1). Submission of the remaining three aryl-3-silylpropanones to the same oxidation conditions gave the desired aryl-3-hydroxypropanones **2b**, **2c** and **2d** in moderate to good yields of 54%, 75% and 59%, respectively (Table 1, entries 2-4). Furthermore, we noted that the phenolic substrates **1b** and **1c** were compatible with acidic as well as oxidative conditions and did not suffer aromatic ring oxidation or degradation. In all cases, this two-step procedure provided the corresponding aryl-3-hydroxypropanones with moderate to good yields. Especially in the particular case of the synthesis of GHP (**2b**), this strategy was more efficient than the aldolisation method.

4. Conclusions

In summary, we reported an operationally simple and scalable two-step protocol to prepare aryl-3-hydroxypropanones, which can be regarded as second-generation lignin degradation products. Both steps rely on reported robust conditions starting from naturally occurring aromatic aldehydes. The first step consisted in the Rh-catalyzed directed C-H activation of aldehydes with dimethylphenylvinylsilane to build the entire carbon skeleton of the desired aryl-3-hydroxypropanones. This demonstrated that metal-catalyzed C-H activation protocols could be particularly powerful for the preparation of specific target molecules. The second step dealed with the oxidation of the alkylsilane formed by a Fleming oxidation procedure. Taken together, these aryl 3-hydroxypropanones are expected to be ideal starting platform molecules for the synthesis of more complex value-added targets. Future work will be dedicated to exploiting these substrates for the synthesis of different molecular scaffolds such as indanones, coumarins and flavones.

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Author Contributions

Preliminary experiments have been performed by AP. All the experimental work was carried out by SB. Mentoring and writing/correcting the article was performed by AS, JO, GP and AP.

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Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Figure S1: ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) for compound **1a**.
2. Figure S2: ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) for compound **1a**.
3. Figure S3: IR spectrum (Diamond-ATR) for compound **1a**.
4. Figure S4: HRMS (ESI) for compound **1a**.
5. Figure S5: ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) for compound **1b**.
6. Figure S6: ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) for compound **1b**.
7. Figure S7: IR spectrum (Diamond-ATR) for compound **1b**.
8. Figure S8: HRMS (ESI) for compound **1b**.
9. Figure S9: ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) for compound **1c**.
10. Figure S10: ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) for compound **1c**.
11. Figure S11: IR spectrum (Diamond-ATR) for compound **1c**.
12. Figure S12: HRMS (ESI) for compound **1c**.
13. Figure S13: ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) for compound **1d**.
14. Figure S14: ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) for compound **1d**.
15. Figure S15: IR spectrum (Diamond-ATR) for compound **1d**.
16. Figure S16: HRMS (ESI) for compound **1d**.
17. Figure S17: ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) for compound **2a**.
18. Figure S18: ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) for compound **2a**.
19. Figure S19: IR spectrum (Diamond-ATR) for compound **2a**.
20. Figure S20: HRMS (ESI) for compound **2a**.
21. Figure S21: ^{1}H NMR spectrum (acetone-d_6, 300 MHz) for compound **2b**.
22. Figure S22: ^{13}C NMR spectrum (acetone-d_6, 75 MHz) for compound **2b**.
23. Figure S23: IR spectrum (Diamond-ATR) for compound **2b**.
24. Figure S24: HRMS (ESI) for compound **2b**.
25. Figure S25: ^{1}H NMR spectrum (CD_3OD, 300 MHz) for compound **2c**.
26. Figure S26: ^{13}C NMR spectrum (CD_3OD, 75 MHz) for compound **2c**.
27. Figure S27: IR spectrum (Diamond-ATR) for compound **2c**.
28. Figure S28: HRMS (ESI) for compound **2c**.
29. Figure S29: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for compound **2d**.
30. Figure S30: ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for compound **2d**.
31. Figure S31: IR spectrum (Diamond-ATR) for compound **2d**.
32. Figure S32: HRMS (ESI) for compound **2d**.

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