

# Ethylenation of aldehydes to 3-propanal, propanol and propanoic acid derivatives

Payne, Daniel T.; Zhao, Yiming; Fossey, John S.

DOI:

[10.1038/s41598-017-01950-7](https://doi.org/10.1038/s41598-017-01950-7)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Payne, DT, Zhao, Y & Fossey, JS 2017, 'Ethylenation of aldehydes to 3-propanal, propanol and propanoic acid derivatives', *Scientific Reports*, vol. 7, 1720. <https://doi.org/10.1038/s41598-017-01950-7>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

# SCIENTIFIC REPORTS

OPEN

## Ethylenation of aldehydes to 3-propanal, propanol and propanoic acid derivatives

Daniel T. Payne , Yiming Zhao  & John S. Fossey 

**Methodology** has been developed for the synthesis of 3-propanaldehydes through a five-step process in 11–67% yield from aldehydes. Aldehydes were reacted with Meldrum's acid through a Knoevenagel condensation to give materials that upon reduction with sodium borohydride and subsequent hydrolysis decarboxylation generated the corresponding 3-propanoic acid derivatives. The -propanoic acid derivatives were reduced to give 3-propanol derivatives, which were readily oxidised to target 3-propanal derivatives.

Aryl-3-propanaldehydes have demonstrated themselves as synthetically useful in the synthesis of natural products<sup>1</sup>, chiral tetrahydroquinolines<sup>2,3</sup>, chemosensors<sup>4,5</sup> and in the perfume industry<sup>6</sup>. As such, facile synthesis of a range of these derivatives would be advantageous.

The chemoselective reduction of cinnamaldehydes to hydrocinnamaldehydes has been reported by Hashizume *et al.* and List *et al.* via either a palladium catalysed reduction<sup>7</sup> or the organocatalysed Hantzsch's ester reduction<sup>8</sup>, respectively. The synthesis of cinnamaldehydes has been reported utilising a range of conditions including the Wittig reaction<sup>7</sup> from aryl aldehydes and the Heck cross-coupling of aryl halides<sup>7,9–13</sup>. Alternatively, the products from the Knoevenagel condensation of aldehydes with Meldrum's acid can be converted to hydrocinnamaldehydes. Frost *et al.* reported the hydrosilylation of Meldrum's acid derivatives (**3**) either through a one-step<sup>14</sup> or two-step<sup>15</sup> process, using palladium or molybdenum catalysts and reagents.

A study by Andrews *et al.* (Glaxo-Smith-Kline (GSK)) reported a four-step synthesis of 3-(anthracen-9-yl)propan-1-ol (**6d**) on a 20-gram scale. Upon oxidation, this material would give the corresponding aldehyde (**7d**)<sup>16</sup>. However, this route was reported to have been carried out on a single substrate, starting with 9-anthraldehyde (**1d**) affording 3-(anthracen-9-yl)propan-1-ol (**6d**) in an overall yield of 84% over four steps.

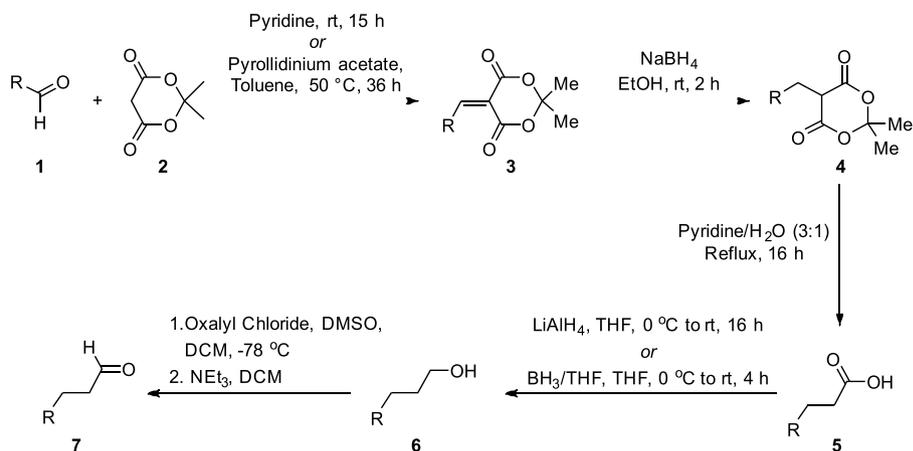
Herein we provide alternative methodology to the established literature and build on previous studies<sup>16</sup> for the synthesis of 3-propanal derivatives (Fig. 1) utilising a Knoevenagel condensation, olefin reduction, decarboxylation, carboxylic acid reduction and an alcohol oxidation. Substrate scope is expanded and a range of versatile hydrocinnamaldehyde derivatives are synthesised.

### Results and Discussion

The synthesis of condensation products *para*-nitro (**3a**), *para*-dimethylamino (**3b**) and *para*-methoxy (**3c**) could be achieved via the literature reported Knoevenagel condensation of aldehydes **1a–c** with Meldrum's acid (**2**) in 74–87% yields<sup>14</sup>. Whilst this method successfully delivered **3a–c** in our hands, the use of an aqueous solvent system prevented us from successfully applying the same conditions to substrates with low water solubility such as 9-anthryl (**3d**, Fig. 2, entry 7). The issue was overcome utilising the method reported by Andrews *et al.* (GSK) for the synthesis of **3d**, where pyridine is used as the reaction solvent<sup>16</sup>. Pleasingly, in contrast to the aqueous solvent system the reaction proceeded smoothly with the 9-anthryl derivative **3d** in 93% yield. We expanded the substrate scope of these conditions to include electron rich (**3b,c,h,i**, Fig. 2, entry 4,6,12,13), electron poor (**3a**, Fig. 2, entry 2), heterocyclic (**3e,l**, Fig. 2, entry 9,16), alkyl (**3g**, Fig. 2, entry 11) and hindered (**3f,j,k,m**, Fig. 2, entry 10,14,15,17) groups yielding the desired products in good to moderate yields (34–93%). On the other hand, extremely electron-deficient substrates such as *para*-trifluoromethyl (**3n**, Fig. 2, entry 18) were amenable to this procedure, e.g., decomposition of the starting material was observed.

A literature reported method for the synthesis of **3n** was used<sup>17</sup>, for which we carried out minor solvent modifications to avoid the use of benzene (Fig. 2, entry 19) giving the desired Knoevenagel condensation

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK. Correspondence and requests for materials should be addressed to D.T.P. (email: [dxp854@bham.ac.uk](mailto:dxp854@bham.ac.uk)) or J.S.F. (email: [j.s.fossey@bham.ac.uk](mailto:j.s.fossey@bham.ac.uk))

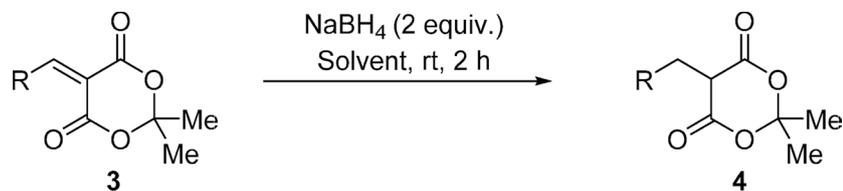


**Figure 1.** General route for the synthesis of hydrocinnamaldehydes.

Entry	Substituent (R)	Conditions	Yield
1	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - (3a)	H <sub>2</sub> O, 75 °C, 2 h <sup>18</sup>	79%
2	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - (3a)	Pyridine, rt, 15 h	74%
3	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - (3b)	H <sub>2</sub> O, 75 °C, 2 h <sup>14</sup>	87%
4	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - (3b)	Pyridine, rt, 15 h	93%
5	4-OMe-C <sub>6</sub> H <sub>4</sub> - (3c)	H <sub>2</sub> O, 75 °C, 2 h <sup>18</sup>	75%
6	4-OMe-C <sub>6</sub> H <sub>4</sub> - (3c)	Pyridine, rt, 15 h	91%
7	9-Anthryl (3d)	H <sub>2</sub> O, 75 °C, 2 h	0%
8	9-Anthryl (3d)	Pyridine, rt, 15 h <sup>16</sup>	93%
9	2-Furyl (3e)	Pyridine, rt, 15 h	91%
10	1-Pyrenyl (3f)	Pyridine, rt, 15 h	88%
11	C <sub>6</sub> H <sub>11</sub> - (3g)	Pyridine, rt, 15 h	74%
12	4-Me-C <sub>6</sub> H <sub>4</sub> - (3h)	Pyridine, rt, 15 h	73%
13	4-OH-C <sub>6</sub> H <sub>4</sub> - (3i)	Pyridine, rt, 15 h	67%
14	2-HCC-C <sub>6</sub> H <sub>4</sub> - (3j)	Pyridine, rt, 15 h	56%
15	2-Br-C <sub>6</sub> H <sub>4</sub> - (3k)	Pyridine, rt, 15 h	55%
16	3-Indole (3l)	Pyridine, rt, 15 h	48%
17	2-Naphthyl (3m)	Pyridine, rt, 15 h	34%
18	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> - (3n)	Pyridine, rt, 15 h	0% <sup>a</sup>
19	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> - (3n)	Pyrollidinium acetate (10 mol%), Toluene, 50 °C, 36 h <sup>17</sup>	N.D. <sup>b</sup>
20	C <sub>6</sub> F <sub>5</sub> - (3o)	Pyrollidinium acetate (10 mol%), Toluene, 50 °C, 36 h	N.D. <sup>b</sup>

<sup>a</sup> The crude material thus obtained contained more than 20 signals in the <sup>19</sup>F NMR spectrum and no aldehyde remaining judged by <sup>1</sup>H NMR spectroscopy; <sup>b</sup> Compounds were taken to the next step without purification.

**Figure 2.** Substrate scope for the Knoevenagel condensation of aldehydes with Meldrum's acid.



Entry	Substituent (R)	Solvent	Yield
1	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>4a</b> )	EtOH	99%
2	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>4b</b> )	MeOH	75%
3	4-OMe-C <sub>6</sub> H <sub>4</sub> - ( <b>4c</b> )	EtOH	91%
4	9-Anthryl ( <b>4d</b> )	MeOH	N.D.
5	2-Furyl ( <b>4e</b> )	EtOH	87%
6	1-Pyrenyl ( <b>4f</b> )	MeOH	95%
7	C <sub>6</sub> H <sub>11</sub> - ( <b>4g</b> )	EtOH	99%
8	4-Me-C <sub>6</sub> H <sub>4</sub> - ( <b>4h</b> )	EtOH	94%
9	2-HCC-C <sub>6</sub> H <sub>4</sub> - ( <b>4j</b> )	EtOH	88%
10	2-Br-C <sub>6</sub> H <sub>4</sub> - ( <b>4k</b> )	EtOH	88%
11	3-Indole ( <b>4l</b> )	EtOH	91%
12	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>4n</b> )	EtOH	98% (2 steps)
13	C <sub>6</sub> F <sub>5</sub> - ( <b>4o</b> )	EtOH	99% (2 Steps)

N.D. – Not determined, compound was taken to the next step containing residual water.

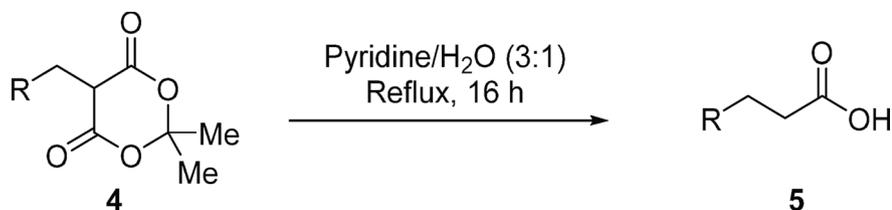
**Figure 3.** Reduction of Knoevenagel products to afford saturated Meldrum's derivatives.

products. The same procedure also yielded the novel pentafluorophenyl derivative (**3o**, Fig. 2, entry 20), Both the *para*-trifluoromethyl (**3n**) and pentafluoro (**3o**) derivatives were not purified at this stage due to instability of the substrates during attempted purification protocol, which included recrystallisation and flash column chromatography. Instead, when full conversion was determined to have been reached by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixtures for these reactions, they were taken forward to the next step<sup>18</sup>.

With alkene containing compounds **3a–o** in hand, the next step was reduction of the conjugated double bonds introduced through the Knoevenagel condensation. This was successfully carried out according to the method reported for the synthesis of **4d** by Andrews *et al.*<sup>16</sup> giving high yields (87–99%) for **4a,c–h,j–l,n–o**. The 4-dimethylamino derivative (**4b**) gave a lower than expected yield of 75%, minor decomposition was observed. In the case of compounds **4c** (Fig. 3, entry 3) and **4h** (Fig. 3, entry 8) methanol led to ring opening of the Meldrum's moiety to the dimethyl malonate, whereas under otherwise identical conditions the use of ethanol furnished the desired compounds. Therefore, ethanol was selected as the preferable solvent for manipulation of **3** to **4** from this point.

The hydrolysis and decarboxylation of derivatives **4** was required in order to synthesise **5**, this was achieved with the method reported for the synthesis of **5d** by Andrews *et al.*<sup>16</sup> in acceptable to good yields (48–98%, Fig. 4) for **5a–h,j–l,n–o**.

For the synthesis of the *para*-methyl (**5h**) and *para*-methoxy (**5c**) derivatives from **4h** and **4c**, respectively, undesired side-products were detected. In order to minimise the formation of the side-products, the reaction was run initially at room temperature for one hour, followed by heating to reflux for a further 4 hours. The desired compounds were obtained after work-up without requiring further purification. Furthermore, under the standard reaction conditions the synthesis of 2-furyl derivative **5e** from **4e** led to the formation of the desired compound alongside a minor undesired side-product, the desired compound was poorly soluble in common laboratory solvents and therefore this impurity was taken through to the LiAlH<sub>4</sub> reduction. The low yield for the synthesis



Entry	Substituent (Ar)	Yield
1	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>5a</b> )	65%
2	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>5b</b> )	91%
3	4-OMe-C <sub>6</sub> H <sub>4</sub> - ( <b>5c</b> )	93% <sup>b</sup>
4	9-Anthryl ( <b>5d</b> )	80% (2 steps)
5	2-Furyl ( <b>5e</b> )	≤ 94% <sup>a</sup>
6	1-Pyrenyl ( <b>5f</b> )	98%
7	C <sub>6</sub> H <sub>11</sub> - ( <b>5g</b> )	57% <sup>b</sup>
8	4-Me-C <sub>6</sub> H <sub>4</sub> - ( <b>5h</b> )	81% <sup>b</sup>
9	2-HCC-C <sub>6</sub> H <sub>4</sub> - ( <b>5j</b> )	86% <sup>a</sup>
10	2-Br-C <sub>6</sub> H <sub>4</sub> - ( <b>5k</b> )	81% <sup>b</sup>
11	3-Indole ( <b>5l</b> )	48%
12	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>5n</b> )	63%
13	C <sub>6</sub> F <sub>5</sub> - ( <b>5o</b> )	91%

<sup>a</sup>Compound taken forward containing impurities; <sup>b</sup>Modified conditions: Pyridine/H<sub>2</sub>O (3:1), 1 h at rt followed by 4 h reflux.

**Figure 4.** Decarboxylation to synthesise hydrocinnamic acid derivatives.

of 3-indole derivative **5l** was most likely due to product loss during reaction work-up because of the probable zwitterionic nature of **5l** having some water solubility.

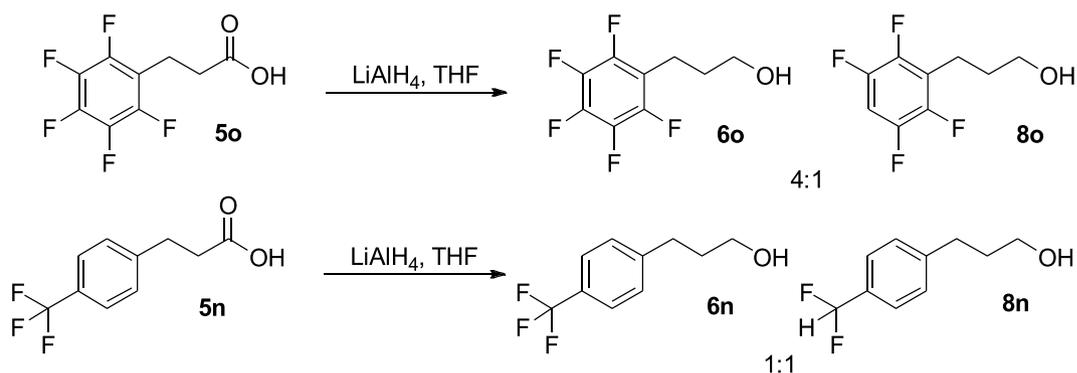
In order to synthesis **7**, isolated **5a-h,j-l,n-o** should first be converted to the corresponding primary alcohols **6a-h,j-l,n-o** before oxidation to aldehydes **7a-h,j-l,n-o**. The reduction of **5b-d, f-h,j-l** to **6b-d, f-h,j-l** was carried out with lithium aluminium hydride (LiAlH<sub>4</sub>) in THF to give the primary alcohols in 83% to 99% yields (Fig. 5). The reduction of **5e** to **6e** was attempted with lithium aluminium hydride (LiAlH<sub>4</sub>) in THF led to the formation of a number of unidentified decomposition products.

The reduction of **5n** and **5o** to **6n** and **6o** was attempted with lithium aluminium hydride (LiAlH<sub>4</sub>) however partial fluorine displacement was observed. Pentafluoro derivative **5o** underwent a nucleophilic aromatic substitution (S<sub>N</sub>Ar) displacing one of the fluorine substituents to give **8o** in an approximate 4:1 ratio **6o:8o** (Fig. 6), similar observations are reported in the literature with related substrates<sup>19</sup>. When *para*-trifluoromethyl derivative **6n** was exposed to LiAlH<sub>4</sub> it underwent a hydride-fluorine exchange to give the *para*-difluoromethyl compound **8n** (Fig. 6) in an approximate 1:1 ratio **6n:8n** by <sup>1</sup>H NMR spectroscopic analysis. Fluorine substitution by hydride within trifluoromethyl groups has been previously reported with related substrates<sup>20</sup>.

Entry	Substituent (R)	Yield
1	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>6b</b> )	93%
2	4-OMe-C <sub>6</sub> H <sub>4</sub> - ( <b>6c</b> )	95%
3	9-Anthryl ( <b>6d</b> )	99%
4	2-Furyl ( <b>6e</b> )	0%
5	1-Pyrenyl ( <b>6f</b> )	99%
6	C <sub>6</sub> H <sub>11</sub> - ( <b>6g</b> )	57%
7	4-Me-C <sub>6</sub> H <sub>4</sub> - ( <b>6h</b> )	83%
8	2-HCC-C <sub>6</sub> H <sub>4</sub> - ( <b>6j</b> )	53%
9	3-Indole ( <b>6l</b> )	66%
10	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>6n</b> )	≤96% <sup>a</sup>
11	C <sub>6</sub> F <sub>5</sub> - ( <b>6o</b> )	≤57% <sup>a</sup>

<sup>a</sup>Reaction conditions led to partial fluorine substitution.

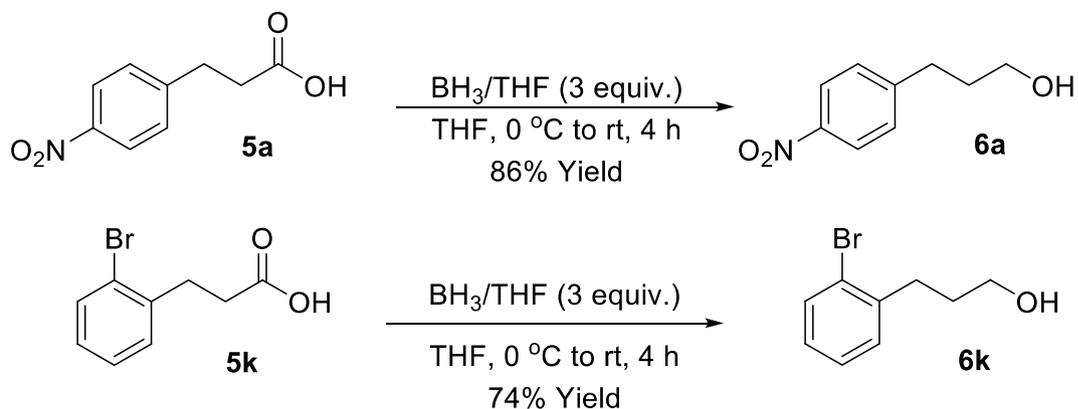
**Figure 5.** Reduction of carboxylic acids to afford hydrocinnamyl alcohol.



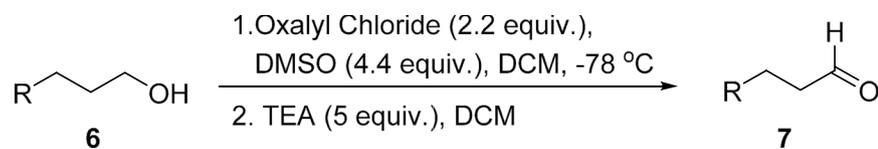
**Figure 6.** By-products formed during the lithium aluminium hydride reduction of fluorinated hydrocinnamic acids.

Reduction of **5a** and **5k** to **6a** and **6k** was carried out using borane to give the desired compounds in 86% and 74%, respectively (Fig. 7). This procedure provides an alternative, milder, method to reduce carboxylic acids when incompatible with LiAlH<sub>4</sub>. Thus, this procedure should also be applicable to fluorinated derivatives **5n** and **5o** and has previously been demonstrated in the literature<sup>21, 22</sup>.

Hydrocinnamyl alcohol derivatives **6 a,c,d,f-h,j,k,o** were converted to aldehydes **7a,c,d,f-h,j,k,o** using a Swern oxidation in 29–89% yield (Fig. 8). The oxidation of 4-dimethylamino derivative **6b** to **7b** and 3-indole derivative **6l** to **7l** was unsuccessful, a complex mixture of unidentifiable by-products alongside the desired compound precluded satisfactory synthesis and isolation. Oxidation of a mixture of **6o** and **8o** led to the formation of the desired aldehyde **7o** in acceptable yield (29%) and the by-product from the oxidation of **8o** could be separated with column chromatography.



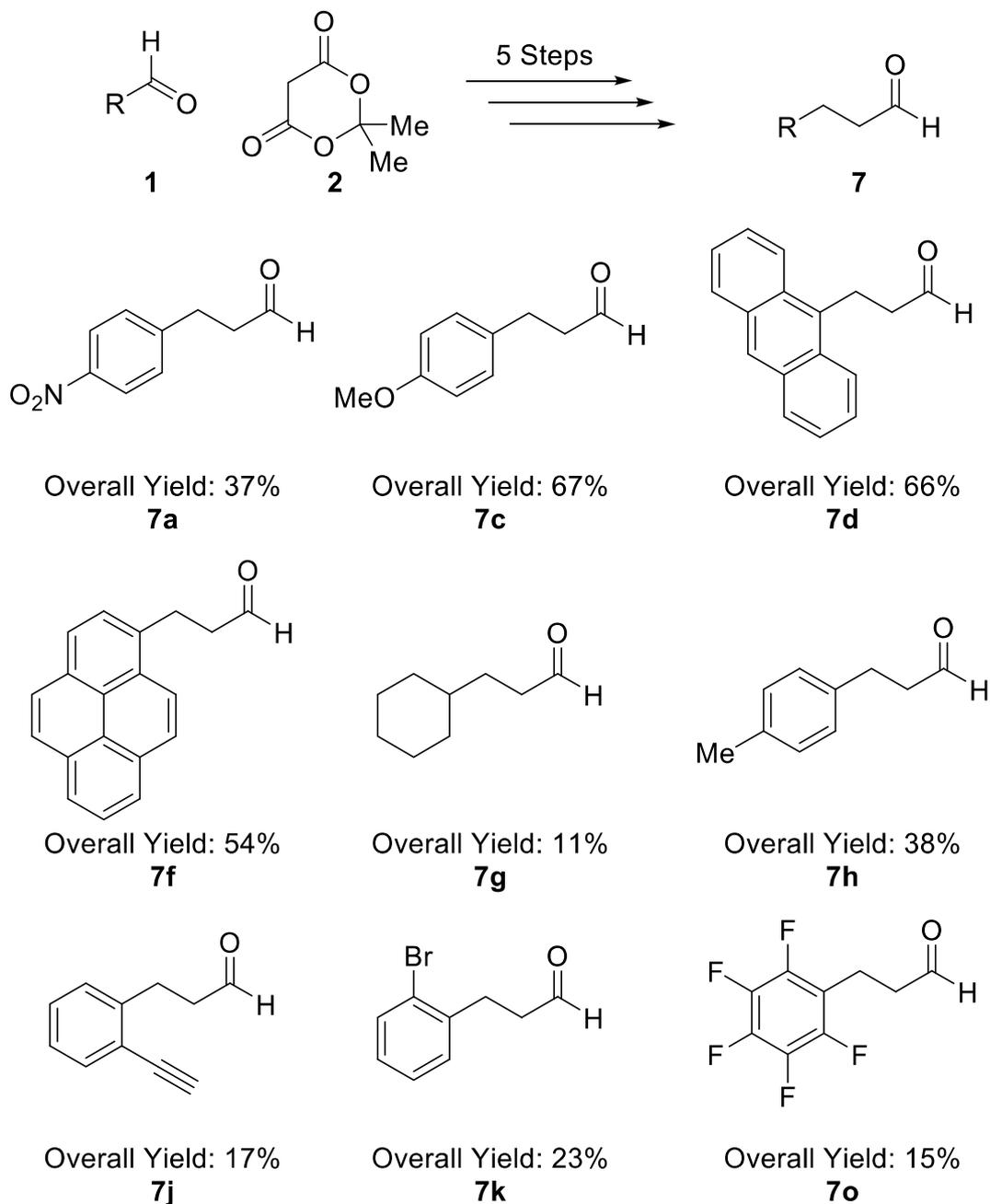
**Figure 7.** Borane reduction of 4-nitro **5b** and 2-bromo **5k** derivatives.



Entry	Substituent (R)	Yield
1	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>7a</b> )	84%
2	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> - ( <b>7b</b> )	N.D. <sup>a</sup>
3	4-OMe-C <sub>6</sub> H <sub>4</sub> - ( <b>7c</b> )	84%
4	9-Anthryl ( <b>7d</b> )	89%
5	1-Pyrenyl ( <b>7f</b> )	66%
6	C <sub>6</sub> H <sub>11</sub> - ( <b>7g</b> )	46%
7	4-Me-C <sub>6</sub> H <sub>4</sub> - ( <b>7h</b> )	83%
8	2-HCC-C <sub>6</sub> H <sub>4</sub> - ( <b>7j</b> )	77%
9	2-Br-C <sub>6</sub> H <sub>4</sub> - ( <b>7k</b> )	75%
10	3-Indole ( <b>7l</b> )	N.D. <sup>a</sup>
11	C <sub>6</sub> F <sub>5</sub> - ( <b>7o</b> )	29%

<sup>a</sup> Reaction conditions led to formation of an inseparable by-product

**Figure 8.** Swern oxidation of cinnamoyl alcohols to give corresponding hydrocinnamaldehyde derivatives.



**Figure 9.** Summary of five step synthesis of hydrocinnamaldehyde derivatives with overall yields.

The outlined five-step synthesis of aldehydes **7** was successful in providing a range of derivatives in acceptable yields (11–67%, Fig. 9). Our studies found that a single set of conditions were not applicable to all substrates but tailoring of reaction conditions can give a diverse range of derivatives. By-products were observed in the  $\text{LiAlH}_4$  reduction of **6n** and **6o**, the decarboxylation of **4d** and **4h** but modifications to the synthetic procedure can minimise their formation<sup>23</sup>. Experimental procedures are detailed in the Supplementary Information.

## References

1. Yadav, J. S. *et al.* Stereoselective total synthesis of 4-((3S,5R)-3,5-dihydroxynonadecyl)phenol. *Tetrahedron Letters* **55**(8), 1395–1397, doi:10.1016/j.tetlet.2013.12.056 (2014).
2. Rawat, V., Kumar, B. S. & Sudalai, A. Proline catalyzed sequential [small alpha]-aminoxylation or -amination/reductive cyclization of o-nitrohydrocinnamaldehydes: a high yield synthesis of chiral 3-substituted tetrahydroquinolines. *Organic & Biomolecular Chemistry* **11**(22), 3608–3611, doi:10.1039/c3ob40320c (2013).
3. Kang, Y. K. & Kim, D. Y. Enantioselective organocatalytic oxidative enamine catalysis-1,5-hydride transfer-cyclization sequences: asymmetric synthesis of tetrahydroquinolines. *Chemical Communications* **50**(2), 222–224, doi:10.1039/c3cc46710d (2014).
4. Richter, I. *et al.* Intramolecular cation- $\pi$  interactions control the conformation of nonrestricted (phenylalkyl)pyridines. *Chem. Commun.* **9**, 1082–1084, doi:10.1039/b716937j (2008).

- Chen, W. *et al.* A pyridinium cation- $\pi$  interaction sensor for the fluorescent detection of alkyl halides. *Chem. Commun.* **47**(1), 253–255, doi:10.1039/c0cc01420f (2010).
- Pybus, D. H.; Sell, C. S. *The Chemistry of Fragrances*. Royal Society of Chemistry: (1999).
- Hashizume, H. *et al.* Synthesis and Biological Activity of New 3-Hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) Synthase Inhibitors: 2-Oxetanones with a Side Chain Mimicking the Folded Structure of 1233A. *CHEMICAL & PHARMACEUTICAL BULLETIN* **42**(3), 512–520 (1994).
- Yang, J. W., Hechavarria Fonseca, M. T. & List, B. A Metal-Free Transfer Hydrogenation: Organocatalytic Conjugate Reduction of  $\alpha,\beta$ -Unsaturated Aldehydes. *Angewandte Chemie International Edition* **43**(48), 6660–6662, doi:10.1002/anie.200461816 (2004).
- Battistuzzi, G., Cacchi, S. & Fabrizi, G. An Efficient Palladium-Catalyzed Synthesis of Cinnamaldehydes from Acrolein Diethyl Acetal and Aryl Iodides and Bromides. *Organic Letters* **5**(5), 777–780, doi:10.1021/ol034071p (2003).
- Noël, S., Djakovitch, L. & Pinel, C. Influence of the catalytic conditions on the selectivity of the Pd-catalyzed Heck arylation of acrolein derivatives. *Tetrahedron Letters* **47**(23), 3839–3842, doi:10.1016/j.tetlet.2006.03.186 (2006).
- Noël, S., Luo, C., Pinel, C. & Djakovitch, L. Efficient Heterogeneously Palladium-Catalysed Heck Arylation of Acrolein Diethyl Acetal. Selective Synthesis of Cinnamaldehydes or 3-Arylpropionic Esters. *Advanced Synthesis & Catalysis* **349**(7), 1128–1140, doi:10.1021/jo062453d (2007).
- Alacid, E. & Nájera, C. Acrolein Diethyl Acetal: A Three-Carbon Homologating Reagent for the Synthesis of  $\beta$ -Arylpropanoates and Cinnamaldehydes by Heck Reaction Catalyzed by a Kaiser Oxime Resin Derived Palladacycle. *European Journal of Organic Chemistry* **2008**(18), 3102–3106, doi:10.1002/(ISSN)1099-0690 (2008).
- Pan, K., Noël, S., Pinel, C. & Djakovitch, L. Heck arylation of acrolein acetals using the 9-bromoanthracene: A case of study. *Journal of Organometallic Chemistry* **693**(17), 2863–2868, doi:10.1016/j.jorganchem.2008.05.042 (2008).
- Frost, C. G. & Hartley, B. C. Tandem Molybdenum Catalyzed Hydrosilylations: An Expedient Synthesis of  $\beta$ -Aryl Aldehydes. *Organic Letters* **9**(21), 4259–4261, doi:10.1021/ol701812w (2007).
- Frost, C. G. & Hartley, B. C. Lewis Base-Promoted Hydrosilylation of Cyclic Malonates: Synthesis of  $\beta$ -Substituted Aldehydes and  $\gamma$ -Substituted Amines. *The Journal of Organic Chemistry* **74**(9), 3599–3602, doi:10.1021/jo900390d (2009).
- Andrews, S. P. & Ladlow, M. Convenient Preparation and Use of a New Analytical Construct for the Analysis and Development of Solid-Phase Chemistries. *The Journal of Organic Chemistry* **68**(14), 5525–5533, doi:10.1021/jo034340p (2003).
- Dumas, A. M., Seed, A., Zorzitto, A. K. & Fillion, E. A general and practical preparation of alkylidene Meldrum's acids. *Tetrahedron Letters* **48**(40), 7072–7074, doi:10.1016/j.tetlet.2007.08.012 (2007).
- Bigi, F. *et al.* Clean synthesis in water. Part 2: Uncatalysed condensation reaction of Meldrum's acid and aldehydes. *Tetrahedron Letters* **42**(31), 5203–5205, doi:10.1016/S0040-4039(01)00978-9 (2001).
- Zhang, D., Chen, Z., Cai, H. & Zou, X. A new synthetic route to polyfluorobenzyl alcohol. *Journal of Fluorine Chemistry* **130**(10), 938–941, doi:10.1016/j.jflchem.2009.07.008 (2009).
- Fuchibe, K., Ohshima, Y., Mitomi, K. & Akiyama, T. Low-Valent Niobium-Catalyzed Reduction of  $\alpha,\alpha,\alpha$ -Trifluorotoluenes. *Organic Letters* **9**(8), 1497–1499, doi:10.1021/ol070249m (2007).
- Brooke, G. M.; Wallis, D. I., Partially fluorinated heterocyclic compounds. Part 14. Syntheses of 4,5,6,7-tetrafluoro-2,3-dihydro-2-methyl-1-benzothiophen and 5,6,7,8-tetrafluorothiochroman from pentafluorophenyl prop-2-enyl sulphide via the Claisen rearrangement intermediate and the related reaction of prop-2-enyl 2,3,5,6-tetrafluorophenyl sulphide. Reactions which appear to proceed via homolytic fission of an aliphatic carbon-fluorine bond. *Journal of the Chemical Society, Perkin Transactions 1* **1981** (0), 1659–1664.
- Nguyen, J., Duncan, N. & Lalic, G. Direct  $\beta$ -Selective Cross-Coupling of Alkenyl Gold Complexes with Alkyl Electrophiles. *European Journal of Organic Chemistry* **2016**(35), 5803–5806, doi:10.1002/ejoc.v2016.35 (2016).
- Payne, D. T., Fossey, J. S. & Elmes, R. B. P. Catalysis and Sensing for our Environment (CASE2015) and the Supramolecular Chemistry Ireland Meeting (SCI 2015): Dublin and Maynooth, Ireland. 8th–11th July. *Supramolecular Chemistry* **28**(11–12), 921–931, doi:10.1080/10610278.2016.1150595 (2016).

## Acknowledgements

The authors would like to thank Louise Male, Chi Tsang, Allen Bowden, Peter Ashton and Cécile S. Le Duff for analytical support. J.S.F. would like to thank the Royal Society for an Industrial Fellowship and the EPSRC for funding (EP/J003220/1). J.S.F., Y.Z. and D.T.P. thank the University of Birmingham for support. D.T.P. thanks the Royal Society of Chemistry and the Society for Chemical Industry for travel support. The Catalysis and Sensing for our Environment (CASE) group is thanked for providing essential networking opportunities.

## Author Contributions

All authors contributed to designing experiments, preparing the manuscript, suggested modifications and analysed the data. J.S.F. led the project, D.T.P. and Y.Z. conducted the experiments.

## Additional Information

**Supplementary information** accompanies this paper at doi:10.1038/s41598-017-01950-7

**Competing Interests:** The authors declare that they have no competing interests.

**Publisher's note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2017