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The synthesis and investigation of impurities found in clandestine laboratories: Baeyer-Villiger route part II; synthesis of Phenyl-2-propanone (P2P) analogues from substituted benzaldehydes

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ABSTRACT

We have previously reported phenylpropan-2-one (most commonly known as phenyl-2-propanone, P2P) and methamphetamine derived by-products formed in the Baeyer-Villiger route starting from benzaldehyde. This route is a three step synthesis to P2P; an aldol condensation of benzaldehyde and methyl ethyl ketone (MEK), a Baeyer-Villiger reaction and a subsequent ester hydrolysis. We now report on our investigations into the synthesis of P2P analogues from substituted benzaldehydes via the Baeyer-Villiger route. When strong electron donating substituents are present in the three position of a substituted benzaldehyde (e.g. 3-methoxy and 3,4-methylenedioxy), the resulting aldol reaction is very sensitive to the amount of hydrogen chloride present due to the occurrence of a competing cyclization side reaction yielding various indenes by-products. In contrast, substrates bearing electron-withdrawing substituents react poorly under the Baeyer-Villiger reaction conditions described in this paper. Several new compounds were identified, namely esters **4c**, **f** and **g**, amongst the known P2P precursors and derivatives. In addition, this work identifies several new by-products in the Baeyer-Villiger route namely **6**, **10**, **13**, **14**, **15** and **21**; we also report the analytical data for various analogues prepared by this method and this is of value to forensic analysts.

1. Introduction

Phenylpropan-2-one (most commonly known as phenyl-2-propanone, P2P) **5a** is a key intermediate molecule synthesized *en route* in the clandestine production of amphetamine type stimulants (ATS) [1–3]. P2P **5a** may be manufactured using: hydrolysis of α-phenylacetoacetonitrile (APAAN) with sulfuric acid [4] (commonly seen in Europe), reaction of α-methylstyrene (AMS) with NH_4I and Oxone [4,5], or more classically from phenylacetic acid and acetic anhydride using the Dakin-West reaction (Fig. 1) [3,6,7].

In 2015 13% of the methamphetamine detected at Australian borders was determined to be produced via P2P, yet only 4.6% of methamphetamine detected within Australia was from P2P [8]. Clandestine laboratories in Australia overwhelmingly used pseudoephedrine/ephedrine based methods for the manufacture of methylamphetamine [1,8]. Whilst the authors are aware of methods being utilised to manufacture P2P in Australia (which is typically either from the hydrolysis of the phenyl-2-nitropropene manufactured from benzaldehyde or the manufacture of P2P from phenylacetic acid) the utilisation of the method which is the subject of this article is not routinely encountered [8]. The determination of the methodology used for methamphetamine production is carried out by profiling of the impurities and enantiomeric purity of the material. Indeed it is the various methodologies used to generate P2P that sets the different approaches apart. One of the more recently reported synthetic routes to P2P discussed in open [9], closed [10] and underground [11] literature is known as the Baeyer-Villiger route reflecting that named reaction used in the second step of the reaction sequence. This reaction, which bears their names, was discovered by Adolf von Baeyer and Victor Villiger in 1899 [12] and is used widely in organic chemistry to transform ketones into esters by the use of peracids or hydrogen peroxide. In the clandestine setting the Baeyer-Villiger route is a three step sequence; an aldol condensation of benzaldehyde and methyl ethyl ketone (MEK), a Baeyer-Villiger reaction and a subsequent ester hydrolysis.

Previous investigations have reported on the identification and targeted synthesis of impurities formed in the Baeyer-Villiger route (Fig. 2) to P2P **5a** using benzaldehyde and methyl ethyl ketone (MEK) [9]. Several of the key impurity by-products are shown in Fig. 2.

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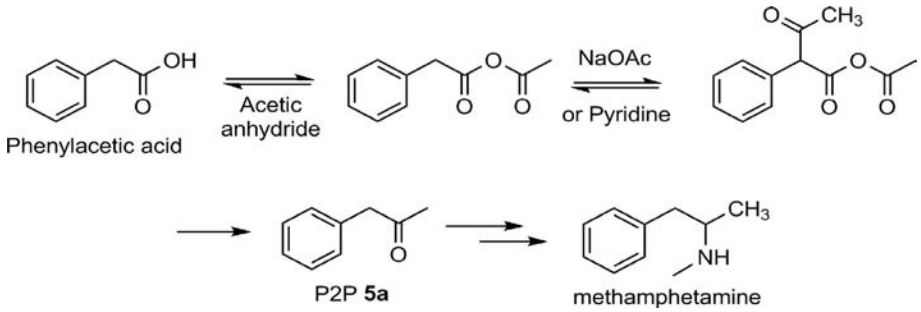


Fig. 1. Classical clandestine chemistry of the Dakin-West reaction to produce P2P and hence methamphetamine from phenyl acetic acid.

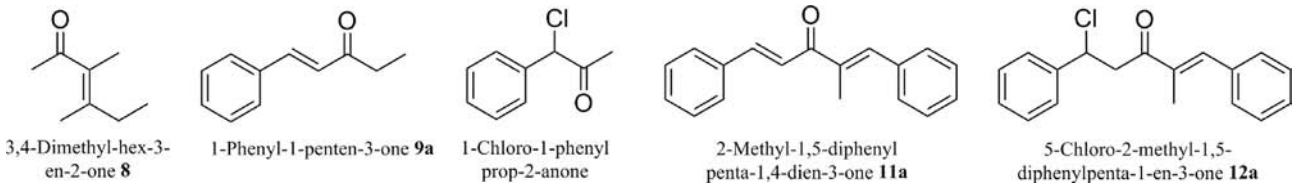


Fig. 2. By-product impurities previously identified in the Baeyer-Villiger route to P2P.

This paper reports our results from the examination of substituted benzaldehydes in the Baeyer-Villiger route to form P2P analogues and the significant effect that the substituent has on substrate reactivity. The Baeyer-Villiger pathway was used to synthesize analogues of P2P in three steps starting from substituted benzaldehydes and MEK as shown in Fig. 3. The first step is an acid catalyzed aldol condensation between substituted benzaldehydes **1** (**a** H, **b** 4-OMe, **c** 3-OMe, **d** 2-OMe, **e** 4-Me, **f** 3-Me, **g** 3,4-O_2CH_2, **h** 4-NO_2, **i** 3-NO_2, **j** 4-F, **k** 4-Cl, **l** 4-OH, **m** C_6H_{11}) and MEK **2** which forms the aldol products **3a–m**. The second step is the Baeyer-Villiger reaction which forms the esters **4a–m** from the reaction between aldol products **3a–m** and peracetic acid formed *in situ* from sodium perborate and glacial acetic acid. The last step is the hydrolysis of the resulting esters **4a–m** from the Baeyer-Villiger reaction with sodium hydroxide to form the P2P analogues **5a–m**. The majority of compounds discussed in the Baeyer-Villiger pathway are known in the literature but not necessarily associated with the pathway.

Aldol adduct **3** was reported in the clandestine context in 2008 [10]. Furthermore, **4** is reported in the literature as a by-product formed from the manufacture of P2P from phenylacetic acid using acetic anhydride. It is commonly referred to as the 'acetate of P2P' or the 'acetate enol of P2P' [2,3]. As a by-product it was reported as a mixture of *cis*- and *trans*- isomers yet in the Baeyer-Villiger route there is significant selectivity towards the *trans*- isomer [9]. Finally, P2P **5** is a classical clandestine impurity commonly observed in methamphetamine samples [13–15].

2. Experimental

All reagents were purchased from Sigma–Aldrich (Australia) and used without purification. HCl and H_2SO_4 acids were purchased from ACI Labscan (Australia). Solvents were purchased from Sigma–Aldrich and Chemsupply (Australia) and used as received.

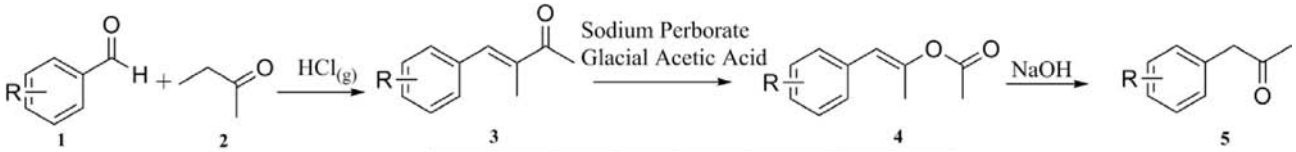
3. Computer modeling details

All calculations were performed using Gaussian09 program with all structures optimized by Density Functional Theory (DFT) B3LYP and 6-31G(d) as the basis set. Frequency calculations were performed on all stationary points located to determine the nature of the stationary point and to correct the relative energies for zero point energy (ZPE) or Gibbs Free energy. All calculations were performed in a vacuum at 298.15 K.

4. Instrumentation

NMR spectra were recorded on either a Bruker Avance III 400 or 600 MHz NMR spectrometers using $CDCl_3$ as the solvent and internal lock for ^1H and ^{13}C spectra. Chemical shifts are recorded in ppm for all spectra. Coupling constants (J values) are recorded in Hz.

GC-MS analysis was performed on a Varian Saturn 2200 using a sample dissolved in chloroform. Helium was used as the carrier gas at a constant flow of 1.2 mL/min. with a solvent delay of 3 min; the column was Varian DB-5(5% phenyl methyl polysiloxane) 30 m × 0.25 mm × 0.25 mm film thickness. The spilt ratio was 50:1. The



Series	R	Series	R	Series	R	Series	R
a	H	d	2-OMe	g	3,4-O_2CH_2	j	4-F
b	4-OMe	e	4-Me	h	4-NO_2	k	4-Cl
c	3-OMe	f	3-Me	i	3-NO_2	l	4-OH
						m	C_6H_{11}

Fig. 3. Three-step reaction sequence of the Baeyer-Villiger route used to convert substituted benzaldehydes and MEK into P2P analogues.

injector temperature was 280 °C, with the initial column temperature at 60 °C for 2.5 min and then ramped at 45 °C per min to 280 °C and held at 280 °C for 12 min. The mass spectrometer operated from 40 to 400 amu electron impact ionization (EI) with an ionization energy of 70 eV.

High resolution MS was performed by Flinders Analytical on a Perkin Elmer, AxION, DSA-ToF in APCI ionization mode in the mass range of 105–1000.

Melting points were determined using Sanyo Gallenkamp melting point apparatus using visual observation.

4.1. Synthetic procedures

4.1.1. General procedure for the aldol reaction **3**

Hydrogen chloride (generated from the reaction between conc. HCl (37%) and conc. H_2SO_4 (98%)) was bubbled slowly through a mixture of the aldehyde (2 g, 0.019 mol) and MEK (20 mL, 0.22 mol) for 1.5 h at 0 °C. The solution was stirred for 1.5 h at room temperature. Water was added and the solution extracted with chloroform then washed with sodium bicarbonate solution and dried (Na_2SO_4). Solvent was removed under high vacuum and product was distilled under vacuum **3a**–**f**, **g**, **j**, **m** or recrystallized from ethanol **3i**, **k**, **h**. In contrast, **3l** was used without purification.

*4.1.1.1. 3-Methyl-4-phenyl-3-buten-2-one **3a**.* 61% (0.7 g, 4.4 mmol), bp: 76–78 °C (0.1 mmHg), mp: 38–42 °C. GC-MS: GC: 6.26 min MS: 43 (15%), 63 (5%) 91 (7.5%), 115 (55%), 145 (10%), 159 (base peak). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52 (s, 1H, C=C*H*) 7.42–7.33 (m, 5H, Ar-*H*), 2.417 (s, 3H, CH_3C=O), 2.07 (s, 3H, C=C-CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.4, 139.8, 137.6, 135.8, 129.7, 128.5, 128.4, 25.8, 12.9. HR-MS: expected $C_{11}H_{13}O$ $[M+H]^+$ 161.0966, observed 161.0965. Data compares well to literature GC-MS [10] and NMR (^{1}H and ^{13}C) [4].

*4.1.1.2. 3-Methyl-4-(4′-methoxyphenyl)-3-buten-2-one **3b**.* 45% (3.1 g, 16.3 mmol), bp: 114–118 °C (0.1 mmHg). GC-MS: GC: 7.05 min, MS: 43 (15%), 91 (10%), 115 (10%), 131 (5%), 147 (25%), 175 (35%), 191 (base peak). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.41 (s, 1H, C=C*H*), 7.37 (d, 2H, J = 8.7 Hz, Ar-*H*), 6.90, (d, 2H, J = 8.7 Hz, Ar-*H*), 3.78 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3C=O), 2.01 (s, 3H, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.3, 159.9, 139.6, 135.8, 131.6, 128.4, 114.0, 55.3, 25.8, 12.9. ^{1}H NMR compares with literature [16].

*4.1.1.3. 3-Methyl-4-(3′-methoxyphenyl)-3-buten-2-one **3c**.* 55% (4.4 g, 23.2 mmol), bp: 90–104 °C (0.1 mmHg). GC-MS: GC: 6.91 min, MS: 43 (40%), 51 (10%), 63 (15%), 77 (15%), 91 (55%), 103 (20%), 115 (30%), 131 (15%), 147 (35%), 159 (95%), 175 (50%), 189 (base peak). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (s, 1H, C = C*H*), 7.31 (t, 1H J = 8 Hz, Ar-*H*), 7.00 (d, 1H J = 7.68 Hz, Ar-*H*), 6.94 (s, 1H, Ar-*H*), 6.88 (d, 1H, J = 8.2 Hz, Ar-*H*), 3.81 (s, 3H, OCH_3), 2.44 (s, 3H, CH_3-C=O), 2.04, (s, 3H, C=CCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.1, 159.5, 139.5, 137.9, 137.2, 129.4, 122.1, 115.2, 114.1, 55.2, 25.8, 13.0. ^{1}H NMR compares with literature [16].

*4.1.1.4. 3-Methyl-4-(2′-methoxyphenyl)-3-buten-2-one **3d**.* 72% (4.5 g, 23.7 mmol), bp: 110 °C–112 °C (0.1 mmHg). GC-MS: GC: 6.73 min, MS: 43.2 (10%), 131.0 (9.0%), 160.0 (10%), 174.9 (15%), 190.8 (15%), 159.0 (base peak). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.66 (s, 1H, C=C*H*), 7.26–6.84 (m, 4H, Ar-*H*), 3.77 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3C=O), 1.92 (d, 3H, J = 1.38 Hz, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.5, 157.4, 137.6, 135.7, 130.3, 130.1, 124.8, 120.2, 110.5, 55.5, 25.9, 13.0. Data compares well to literature GC-MS and NMR (^{1}H and ^{13}C) [17].

*4.1.1.5. 3-Methyl-4-(4′-methylphenyl)-3-buten-2-one **3e**.* 56% (1.62 g, 9.3 mmol), bp: 100 °C (0.1 mmHg). GC-MS: GC: 6.58 min, MS: 43 (15%), 91 (10%), 115 (20%), 131 (25%), 159 (base peak), 175 (90%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.48 (s, 1H, C=C*H*), 7.33 (d, 2H, J = 7.98 Hz, Ar-*H*), 7.2 (d, 2H, J = 7.98 Hz, Ar-*H*), 2.43 (s, 3H, CH_3-C=O), 2.36 (s, 3H, Ar-CH_3) 2.05 (s, 3H, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.2, 139.9, 138.7, 136.9, 133.0, 129.8, 129.2, 25.7, 21.3, 12.9. ^{1}H NMR compares with literature [16].

*4.1.1.6. 3-Methyl-4-(3′-methylphenyl)-3-buten-2-one **3f**.* 55% (2.1 g, 12.1 mmol), bp: 124–128 °C (0.1 mmHg). GC-MS: GC: 6.46 min, MS; 43 (15%), 91 (10%), 115 (25%), 131 (25%), 159 (base peak), 175 (75%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49 (s, 1H, C=C*H*), 7.31–7.15 (m, 4H, Ar-*H*), 2.45 (s, 3H, CH_3C=O), 2.38 (s, 3H, Ar-CH_3), 2.05 (d, 3H, J = 1.38 Hz, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.3, 139.9, 138.1, 137.6, 130.4, 129.4, 128.4, 126.8, 25.8, 21.4, 13.0. **3f** is a known compound [18].

*4.1.1.7. 3-Methyl-4-(3′,4′-methylenedioxyphenyl)-3-buten-2-one **3g**.* 64% (1.4 g, 6.9 mmol), bp: 115–118 °C (0.1 mmHg), mp: 97–98.5 °C. GC-MS: GC: 7.29 min, MS: 43 (25%), 77 (25%), 103 (75%), 131 (45%), 159 (45%), 204 (base peak). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.42 (s, 1H, C = C*H*), 6.98 (d, 1H, J = 1.5 Hz, Ar-*H*), 6.94 (dd, 1H, J = 1.5 Hz, 6.6 Hz, Ar-*H*), 6.86 (d, 1H, J = 6 Hz, Ar-*H*) 6.01 (s, 2H), 2.44 (s, 3H, CH_3C=O), 2.05 (s, 3H, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.2, 148.0, 139.6, 136.3, 130.0, 125.0, 109.6, 108.4, 101.4, 25.8, 13.0. Data compares well to literature GC-MS and NMR (^{1}H and ^{13}C) [17].

*4.1.1.8. 3-Methyl-4-(4′-nitrophenyl)-3-buten-2-one **3h**.* 85% (2.6 g, 12.9 mmol), mp: 93–95 °C. GC-MS: GC: 7.31 min, MS: 43 (50%), 63 (5%), 89 (5%), 115 (70%), 188 (base peak), 205 (20%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.28 (d, 2H, J = 8.8 Hz, Ar-*H*), 7.55 (d, 2H, J = 8.6 Hz, Ar-*H*), 7.51 (s, 1H, C=C*H*), 2.49 (s, 3H, CH_3C=O), 2.05 (d, 3H, J = 1.38 Hz, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 199.6, 147.3, 142.5, 140.7, 136.4, 130.2, 124.1, 123.7, 26.0, 13.2. ^{1}H NMR compares with literature [16].

*4.1.1.9. 3-Methyl-4-(3′-nitrophenyl)-3-buten-2-one **3i**.* 90% (1.5 g, 7.3 mmol), GC-MS: GC: 7.31 min, MS: 43 (50%), 115 (70%), 158 (20%), 188 (base peak), 205 (25%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.20 (s, 1H, Ar-*H*) 8.13 (d, 1H, J = 10.1 Hz, Ar-*H*), 7.65 (d, 1H, J = 7.74 Hz, Ar-*H*), 7.40 (t, 1H, J = 8.00 Hz, Ar-*H*), 7.45 (s, 1H, C=C*H*), 2.42 (s, 3H, CH_3C=O), 2.00 (d, 3H, J = 1.26 Hz, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 199.6, 148.3, 141.2, 137.6, 136.4, 135.2, 124.2, 123.6, 26.0, 13.0. ^{1}H and ^{13}C NMR data compare with literature [4].

*4.1.1.10. 3-Methyl-4-(4′-fluorophenyl)-3-buten-2-one **3j**.* 55% (2.7 g, 15.2 mmol), bp: 91 °C (0.1 mmHg). GC-MS: GC: 6.23 min, MS: 43 (30%), 109 (15%), 115 (40%), 135 (45%), 163 (35%), 179 (base peak). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (s, 1H, C=C*H*), 7.40 (dd, 2H, J = 8.5, 5.4 Hz, Ar-*H*), 7.10 (t, 2H, J = 8.64 Hz, Ar-*H*), 2.45 (s, 3H, CH_3-C=O), 2.03 (d, 3H, J = 1.26 Hz, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.1, 163.4, 138.4, 137.5, 132.0, 131.9, 130, 25.8, 12.9. ^{1}H NMR compares with literature [19].

*4.1.1.11. 3-Methyl-4-(4′-chlorophenyl)-3-buten-2-one **3k**.* 70% (4.9 g, 25.2 mmol), mp: 56–59 °C. GC-MS: GC: 6.76 min, MS: 43 (50%), 63 (10%), 89 (10%), 115 (base peak), 151 (30%), 159 (90%), 179 (60%), 181 (20%), 193 (50%), 194 (50%), 195 (55%) 197 (15%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.45 (s, 1H, C=C*H*), 7.4–7.26 (m, 4H, Ar-*H*), 2.45 (s, 3H, CH_3C=O), 2.05 (d, 3H, J = 1.38 Hz, C=CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.0, 138.2, 138.2, 134.5, 134.4, 131.0, 128.7, 25.9, 13.0. ^{1}H and ^{13}C NMR compare with literature [5].

4.1.1.12. 3-Methyl-4-(4′-hydroxyphenyl)-3-buten-2-one ***3l***. 68% (2.0 g, 11.4 mmol), GC-MS: GC: 7.17 min, MS: 43 (45%), 51(25%), 77 (30%), 106 (90%), 134 (90%), 162 (95%), 177 (base peak) ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (s, 1H, C = C*H*), 7.36 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 6.90 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 2.46 (s, 3H, CH_3C=O), 2.07 (d, 3H, *J* = 1.3 Hz, C = CCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 200.8, 156.4, 139.9, 135.8, 131.8, 131.1, 127.8, 115.6, 25.8, 13.0. ^{1}H NMR compares with that reported in literature [19].

4.1.1.13. 3-Methyl-4-cyclohexyl-3-buten-2-one ***3m***. 83% (2.1 g, 12.7 mmol), bp: 84 °C (0.1 mmHg). GC-MS: GC: 5.0 min, MS: 41 (30%), 43 (50%), 67 (40%), 81 (40%), 95 (30%), 109 (70%), 123 (60%), 137 (10%), 151 (20%), 166 (base peak), 167 (70%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.34 (d, 1H, *J* = 8.34 Hz, C=C*H*), 2.31 (m, 1H), 2.22 (s, 3H, CH_3C=O), 1.70 (s, 3H, C=CCH_3), 1.67 (m, 2H), 1.62 (m, 2H), 1.25 (m, 2H), 1.14 (m, 2H), 1.09 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 199.4, 147.7, 134.7, 37.1, 31.0, 24.9, 24.6, 24.4, 10.2. ^{1}H NMR compares with literature [19].

4.1.2. General procedure for the Baeyer-Villiger reaction ***4***

Sodium perborate (1.5 g, 9.7 mmol) was added in portions over 6 h to a mixture of aldol product **3** (0.5 g, 3.1 mmol), glacial acetic acid (1.75 mL, 30 mmol), and acetone (1 mL) at 55 °C, followed by heating under reflux at 55 °C for 24 h. Water was added (20 mL) and the solution extracted with chloroform, dried (Na_2SO_4) and the solvent removed under vacuum. Compound(s) **4** were not purified further but checked for identity using GC-MS and NMR (^{1}H and ^{13}C). Esters **4a–m** are known compounds, except for **4c**, **4f**, **4g**, with limited GC-MS and NMR data available [10,20–25].

4.1.3. 2-Acetoxy-1-phenyl-1-propene ***4a***

80%, GC-MS: GC: 6.05 min, MS: 43 (15%), 91 (20%), 133 (base peak), 176 (10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5H, Ar-*H*), 6.24 (s, 1H, C=C*H*), 2.16 (s, 3H, CH_3C=O), 2.10 (s, 3H, C=CCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 147.9, 134.9, 128.8, 128.3, 126.96, 118.8, 21.1, 17.1. HR-MS: $C_{11}H_{13}O_2$ $[M+H]^+$ expected 177.0916, observed 177.0911. GC-MS compares to literature [10].

4.1.4. 2-Acetoxy-1-(4′-methoxyphenyl)-1-propene ***4b***

Characterized without purification GC-MS: GC: 6.81 min, MS: 43 (15%), 121 (60%), 164 (base peak), 206 (5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 6.87 (d, 2H *J* = 8.76 Hz, Ar-*H*), 6.19 (s, 1H, C=C*H*) 3.8 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3-C=O), 2.08 (s, 3H, C=CCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.6, 158.5, 146.6, 129.9, 127.36, 118.2, 113.8, 55.2, 21.1, 17.1. ^{1}H NMR compares to literature [20].

4.1.4.1. 2-Acetoxy-1-(3′-methoxyphenyl)-1-propene ***4c***. Characterized without purification GC-MS: 6.74 min, MS: 43 (15%), 91 (5%) 121 (20%), 164 (base peak), 206 (5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (t, 1H, *J* = 7.5 Hz, Ar-*H*) 6.87 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 6.8 (d, 1H, *J* = 7.5 Hz, Ar-*H*) 6.25 (s, 1H, C=C*H*), 3.81 (s, 3H, OCH_3) 2.20 (s, 3H, CH_3C=O), 2.13 (s, 3H, C=CCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.5, 159.5, 148.1, 136.2, 129.3, 121.3, 120.4, 115.1, 112.6, 55.4, 21.1, 17.2.

4.1.4.2. 2-Acetoxy-1-(2′-methoxyphenyl)-1-propene ***4d***. GC-MS: GC 6.56 min, MS: 43 (20%), 107 (45%), 137 (95%), 164 (base peak).

4.1.4.3. 2-Acetoxy-1-(4′-methylphenyl)-1-propene ***4e***. GC-MS: GC 6.39 min, MS: 43 (10%), 105 (40%), 148 (base peak), 191 (5%).

4.1.4.4. 2-Acetoxy-1-(3′-methylphenyl)-1-propene ***4f***. Characterized without purification, GC-MS: GC: 6.26 min, MS: 43 (15%), 105 (30%), 148 (base peak).

4.1.4.5. 2-Acetoxy-1-(3′,4′-methylenedioxyphenyl)-1-propene ***4g***. Crude yield 82%, characterized without purification. GC-MS: GC: 7.07 min, MS: 43 (10%), 135 (55%), 178 (base peak), 222 (5%) ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.8–6.7 (m, 3H, Ar*H*), 6.16 (s, 1H, C=C*H*), 5.9 (s, 2H, OCH_2O), 2.17 (s, 3H, CH_3C=O), 2.08 (s, 3H, C=CCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.5, 147.6, 147.1 146.5, 129.6, 122.5, 118.5, 109.1, 108.2, 101.2, 20.7, 17.2.

4.1.4.6. 2-Acetoxy-1-(4′-nitrophenyl)-1-propene ***4h***. BV reaction failed under general procedure.

4.1.4.7. 2-Acetoxy-1-(3′-nitrophenyl)-1-propene ***4i***. GC-MS: GC: 7.16 min, MS: 43 (75%), 63 (10%), 103 (10%), 133 (40%), 162 (base peak), 179 (50%).

4.1.4.8. 2-Acetoxy-1-(4′-fluorophenyl)-1-propene ***4j***. GC-MS: GC: 6.02 min, MS: 43 (35%), 109 (35%), 151 (base peak).

4.1.4.9. 2-Acetoxy-1-(4′-chlorophenyl)-1-propene ***4k***. GC-MS: GC: 6.68 min, MS: 43 (30%), 63 (5%), 89 (5%), 10595%), 125 (25%), 168 (base peak), 180 (30%).

4.1.4.10. 2-Acetoxy-1-(4′-hydroxyphenyl)-1-propene ***4l***. BV reaction fails under general procedure.

4.1.4.11. 2-Acetoxy-1-(cyclohexyl)-1-propene ***4m***. GC-MS: GC: 5.76 min, MS: 43 (base peak), 59 (50%), 73 (30%), 79 (25%), 82 (25%), 97 (95%), 107 (10%), 122 (50%), 139 (10%).

4.1.5. Baeyer-Villiger reaction with hydrogen peroxide and 2-acetoxy-1-(4′-nitrophenyl)-1-propene ***4h***

A mixture of aldol product **3h** (0.38 g, 1.8 mmol), glacial acetic acid (5 mL, 83 mmol), and H_2O_2 (50%, 0.5 g, 7.4 mmol) was heated at 55 °C for 24 h. Water was added and the solution extracted with chloroform, dried (Na_2SO_4) and the solvent removed under vacuum. Yield 45%. GC: 7.23 min, MS: 43 (70%), 77 (10%), 107 (5%), 132 (5%), 149 (5%).

4.1.5. General procedure for the hydrolysis of esters to 1-phenyl-2-propanones ***5***

A mixture of ester (0.55 g, 3.1 mmol) and aqueous sodium hydroxide (5 mL, 2 M), was stirred at 50 °C overnight. Solution extracted with chloroform, dried (Na_2SO_4) and the solvent removed under vacuum. Compound(s) **5** were not purified further but checked for identity using GC-MS only.

4.1.6. 1-(3′,4′-Methylenedioxphenyl)propan-2-one ***5g*** *(MDP2P)*

A mixture of 2-acetoxy-1-(1,3-benzodioxolyl)-1-propene (0.5 g, 2.7 mmol), aqueous sodium hydroxide (5 mL, 2 M) and ethanol (5 mL) was stirred at room temperature overnight. Solution was extracted with chloroform, dried (Na_2SO_4) and the solvent removed under vacuum. Yield over two steps 65%.

Yields over two steps shown along with confirmatory GC-MS data. **5a–m** are known compounds in the literature [10,26–32].

4.1.7.1. 1-Phenyl-2-propanone ***5a***. 80% (1.0 g, 7.5 mmol), GC-MS: GC: 5.26 min, MS: 43 (25%), 65 (15%), 91 (30%), 135 (base peak).

4.1.7.2. 1-(4′-Methoxyphenyl)-2-propanone ***5b***. 82% (1.4 g, 8.5 mmol), GC-MS: GC: 6.17 min, MS: 43 (5%), 77 (10%), 91 (5%), 121 (base peak), 163 (10%).

4.1.7.3. 1-(3′-Methoxyphenyl)-2-propanone ***5c***. 74% (0.32 g, 2.0 mmol), GC-MS: GC: 6.11 min, MS: 43 (55%), 63 (5%). 77 (10%), 91 (30%), 107 (5%), 121 (75%), 164 (base peak).

4.1.7.4. 1-(2′-Methoxyphenyl)-2-propanone ***5d***. 77% (0.34 g, 2.1 mmol), GC-MS: GC: 5.95 min, MS: 43 (10%), 65 (5%), 91 (25%), 121 (base peak), 163 (45%).

4.1.7.5. 1-(4′-Methylphenyl)-2-propanone ***5e***. 60% (0.27 g, 1.8 mmol), GC-MS: GC: 5.95 min, MS: 43 (15%), 105 (base peak), 149 (20%).

4.1.7.6. 1-(3′-Methylphenyl)-2-propanone ***5f***. 53% (0.4 g, 2.7 mmol), GC-MS: GC: 5.54 min, MS: 43 (55%), 51 (10%), 77 (20%), 105 (base peak) 133 (10%), 148 (15%).

4.1.7.7. 1-(3′,4′-Methylenedioxyphenyl)-2-propanone ***5g***. 65% (0.26 g, 1.5 mmol), GC-MS: GC 6.49 min, MS: 51 (10%), 77(10%), 135 (base peak), 178 (30%).

4.1.7.8. 1-(3′-Nitrophenyl)-2-propanone ***5i***. <10%, GC-MS: GC 6.67 min, MS: 43 (base peak), 54 (15%), 89 (40%), 120 (10%), 136 (10%), 149 (5%), 179 (5%).

4.1.7.9. 1-(4′-Fluorophenyl)-2-propanone ***5j***. 30% (0.13 g, 0.8 mmol), GC-MS: GC: 5.28 min, MS: 43 (90%), 57 (10%), 83 (30%), 109, (base peak), 152 (5%).

4.1.7.10. 1-(4′-Chlorophenyl)-2-propanone ***5k***. 30% (0.11 g, 0.7 mmol), GC-MS: GC: 5.93 min, MS: 43 (base peak), 63 (15%), 89 (25%), 125 (55%), 167 (10%).

4.1.7.11. 1-Cyclohexyl-2-propanone ***5m***. 40% (0.15 g, 1.1 mmol), GC-MS: GC: 5.07 min, MS: 43 (base peak), 55 (50%), 59 (95%), 67 (75%), 81 (20%), 122 (5%), 141 (5%).

5. Results and discussion

The first step in the Baeyer-Villiger pathway is an aldol condensation between substituted benzaldehydes **1a–m** and MEK **2** to form the aldol products **3a–m** as shown in Fig. 3. In this case the reaction is initiated by bubbling dry hydrogen chloride gas through the solution. The dry gas is needed due to the equilibrium involved in the initial step of the aldol reaction prior to elimination to the alkene product.

This aldol reaction was carried out with a variety of different substituted benzaldehydes. After reaction workup, the organic material was subjected to analysis by GC-MS. Fig. 4 shows a typical partial GC-MS trace of a reaction mixture, in this instance 4-methylbenzaldehyde **1e** and MEK, and shows the dominance of the aldol product **3e** as well as by-products that are formed in the aldol condensation reaction. Table 1 shows the structure of the by-products and some of the major fragments observed in the mass spectrum. In particular, various compounds were tentatively identified; namely **6e**, which is a chlorinated derivative of **3e**, **7e** being the *cis*- isomer of **3e**, **8** which comes from the self-aldol reaction of MEK, **9e** is a regioisomer of adduct **3e**, **10e** a chloroderivative of **9e**, **11e** from a second aldol reaction of adduct **3e** and **12e** a chloroderivative of **11e.** These by-products are similar to those previously investigated [9] except for the chloroderivatives **6e** and **10e**. Previously the chloroderivative of **11a** has been seen to form **12a** so the observation of **6e** and **10e** is not surprising. Of interest were compounds **11a–m**, which were expected to be minimized by the use of a large excess of MEK as previously observed [9]. However, when 4-methoxybenzaldehyde **1b** was used in the aldol reaction with two equivalents of MEK, the aldol product **3b** precipitated from solution before any subsequent

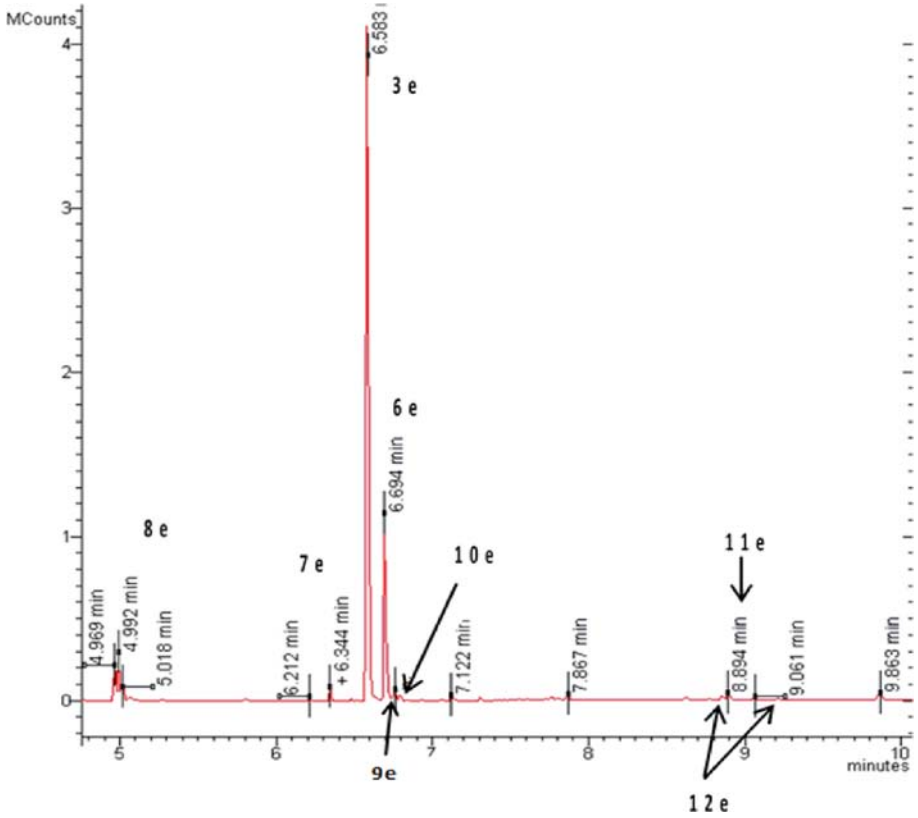


Fig. 4. Partial GC-MS trace of reaction mixture of 4-methylbenzaldehyde **1e** and MEK (six equivalents) which shows the dominance of aldol adduct **3e** as well as the types of by-products formed in the aldol condensation reaction.

Table 1
Numbers and structures for compounds shown in Fig. 4 and the MS data with major fragmentations identified.

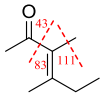
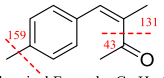
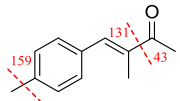
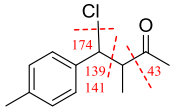
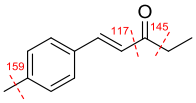
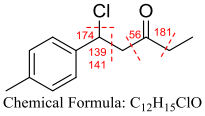
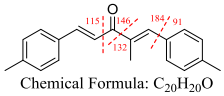
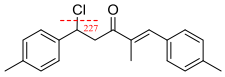
Compound Number	Compound	Mass Spectrum data
8	 Chemical Formula: $C_8H_{14}O$ Monoisotopic Mass: 126.10	43 (base peak), 55 (30%), 69 (40%), 83 (30%), 111 (45%), 126 (45%)
7e	 Chemical Formula: $C_{12}H_{14}O$ Monoisotopic Mass: 174.10	43 (15%), 91 (20%), 115 (15%), 131 (10%), 159 (base peak), 174 (5%)
3e	 Chemical Formula: $C_{12}H_{14}O$ Monoisotopic Mass:174.10	43 (20%), 91 (10%), 115 (15%), 131 (20%), 159 (base peak), 174 (75%)
6e	 Chemical Formula: $C_{12}H_{15}ClO$ Monoisotopic Mass: 210.08	43 (45%), 117 (35%), 139 (60%), 141 (25%), 174 (base peak)
9e	 Chemical Formula: $C_{12}H_{14}O$ Monoisotopic Mass: 174.10	65 (5%), 91 (10%), 115 (20%), 117 (20%), 145 (base peak), 159 (15%), 174 (5%)
10e	 Chemical Formula: $C_{12}H_{15}ClO$ Monoisotopic Mass: 210.08	51 (10%), 56 (95%), 65 (15%), 77 (15%), 91 (30%), 103 (15%), 115 (15%), 117 (base peak), 139 (70%), 141 (25%), 174 (40%), 181 (40%), 210 (20%), 212 (5%)
11e	 Chemical Formula: $C_{20}H_{20}O$ Monoisotopic Mass: 276.15	65 (5%), 91 (15%), 115 (30%), 116 (70%), 132 (95%), 146 (40%), 184 (10%) 276 (base peak)
12e	 Chemical Formula: $C_{20}H_{21}ClO$ Monoisotopic Mass:312.13	65 (10%), 91 (25%), 115 (35%), 117 (35%), 132 (15%), 143 (5%), 166 (65%), 207 (15%), 233 (5%), 261 (10%), 277 (base peak), 312 (15%), 314 (5%)

Table 2
Different aldehydes used in the aldol condensation reaction and the yield of the aldol product **3**.

No.	R Group	Yield of aldol product **3** (%)
1a	H	61
1b	4-OMe	45
1c	3-OMe	55
1d	2-OMe	72
1e	4-Me	56
1f	3-Me	55
1g	3,4-O_2CH_2	64
1h	4-NO_2	85
1i	3-NO_2	90
1j	4-F	55
1k	4-Cl	70
1l	4-OH	68
1m	C_6H_{11}	83

reaction to form **11b** (which is the *p*-methoxy analogue of **11e** (Table 1)).

As shown in a typical GC-MS trace of these reaction mixtures, the aldol product **3** is the major material present in most of the reactions with only very minor levels of other impurities present. The isolated yield of the various aldol adducts **3a–m** is reported in Table 2 and range from 45% (4-OMe) to 90% (3-NO_2).

When an aldehyde that has a strong electron-donating group in the 3- position is used in the aldol reaction (e.g. **1c**, **g**), the reaction becomes very sensitive to the amount of hydrogen chloride present, due to a competing cyclization reaction. This cyclization is only observed when an electron-donating group is in the 3-position as the para carbon to the donating group needs to be activated to attack the carbonyl of the side chain. Fig. 5 shows a suggested mechanism for the cyclization. This cyclization reaction has been investigated by monitoring the reaction over time with ^{1}H NMR and FTIR spectroscopy which allowed the progress and product distribution of the reaction to be monitored. This indicated aldol product **3g** to be formed initially then subsequently converted to the cyclized by-product **13g**. An analysis of the changes in concentration of the various species with time allowed the determination of orders of reaction of the various species. The orders of reaction as determined by NMR and IR experiments are consistent and are aligned with the suggested mechanism (Fig. 5). The experimental results are supported by theoretical molecular modeling calculations which show aldol product **3g** as the thermodynamic and kinetically favored product and the cyclized by-product **13g** forms as the result of extended reaction time or excess HCl concentration. More details of this cyclization reaction will be reported in due course.

A gas chromatogram of the reaction products from the initial attempt of using piperonal **1g** in the aldol reaction can be seen in Fig. 6. No aldol product **3g** was detected by GC-MS and the major material present was identified as 1-chloro-2,3-dimethyl-6,7-(methylendioxy)indene **13g** (82%) by NMR and GC-MS. 2-Methyl-1-methylene-6,7-(methylendioxy)indene **14g** and 1-chloro-1,2-dimethyl-6,7-(methylendioxy)indene **15g** were also tentatively identified by GC-MS and were only detected in very minor levels. As detailed in Table 2, piperonal **1g** can be used in the aldol reaction to yield **3g**, (64%). However, this reaction is very sensitive to the amount of hydrogen chloride used. Our initial attempt using 9.5 equivalents of $HCl_{(g)}$ yielded **13g** whilst 8 equivalents produced **3g**. Further decreasing the equivalents to 6.5 lead to piperonal **1g** being isolated. Whilst the exact amount of HCl used in these reactions is difficult to estimate, the $HCl_{(g)}$ is generated by addition of $HCl_{(aq)}$ to sulfuric acid, and the amount of $HCl_{(aq)}$ added is used in an approximate calculation of the amount of $HCl_{(g)}$ generated. This gives an estimation of how many equivalents were used in the reaction. Whilst the value of the equivalents added may not be accurate, it does demonstrate how sensitive the reaction is to HCl. In addition, observational evidence suggests that when $HCl_{(g)}$ is added into the mixture through a pipette producing smaller bubbles (2 mm diameter) more cyclization material is detected by GCMS. Conversely, when larger diameter glass tubing is employed large bubbles (5 mm diameter) yield less cyclization products. This presumably results from the higher surface area of small bubbles aiding $HCl_{(g)}$ diffusion into the reaction solution. In addition, piperonal **1g** was also used in the aldol reaction with only two equivalents of MEK to determine if the aldol product **3g** would precipitate out of solution before cyclization; in a similar manner to that seen with the 4-methoxy derivative above. However, in this case the precipitation was slow and cyclized product **13g** was isolated from the reaction. The exacted amount of $HCl_{(g)}$ used in the reaction is difficult to control using the $HCl_{(g)}$ system found in clandestine laboratories so **13g** is an important byproduct in 3,4-methylenedioxy phenyl-2-propanone (MDP2P) and hence 3,4-methylenedioxy-N-methylamphetamine (MDMA). Fig. 7 shows the proposed fragmentation in the mass spectrum for this important by-product.

The second step in the reaction pathway is the Baeyer-Villiger reaction, well known in traditional organic chemistry for the trans-

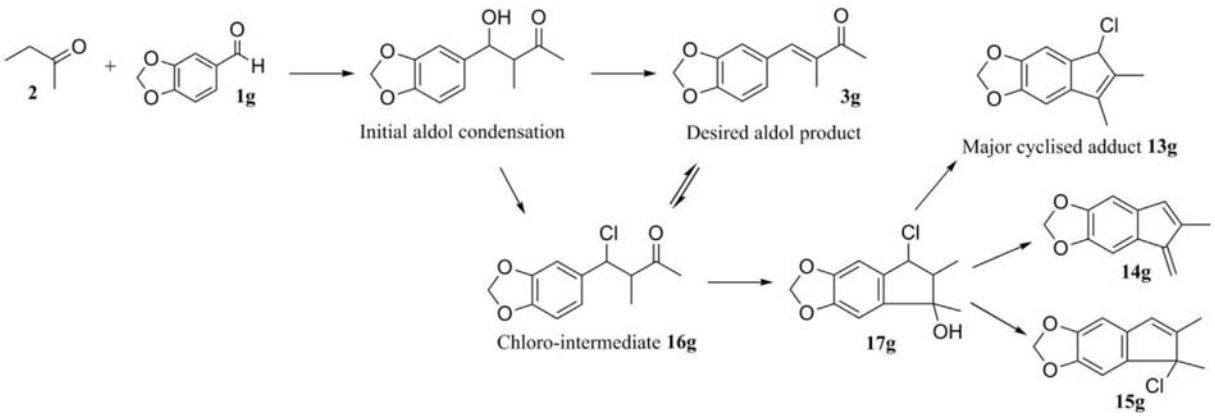


Fig. 5. Suggested pathways for the formation of the various cyclized by-products.

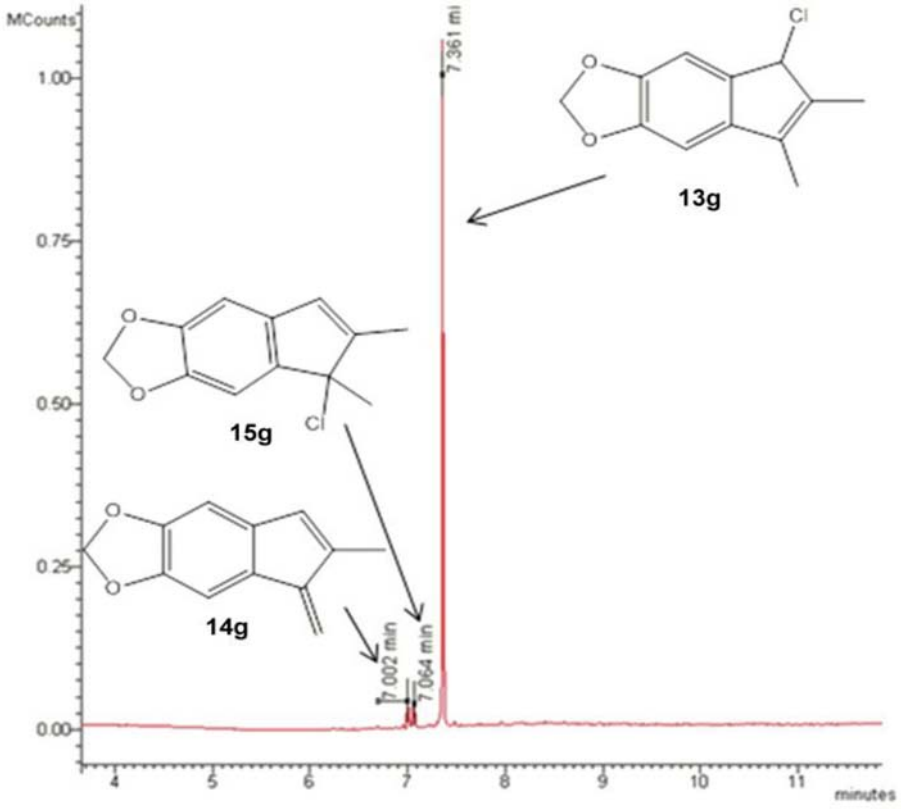


Fig. 6. Partial GC-MS trace of aldol reaction showing 1-chloro-2,3-dimethyl-6,7-(methylendioxy)indene **13g** formed during the reaction of piperonal **1g** and MEK under previously reported conditions.

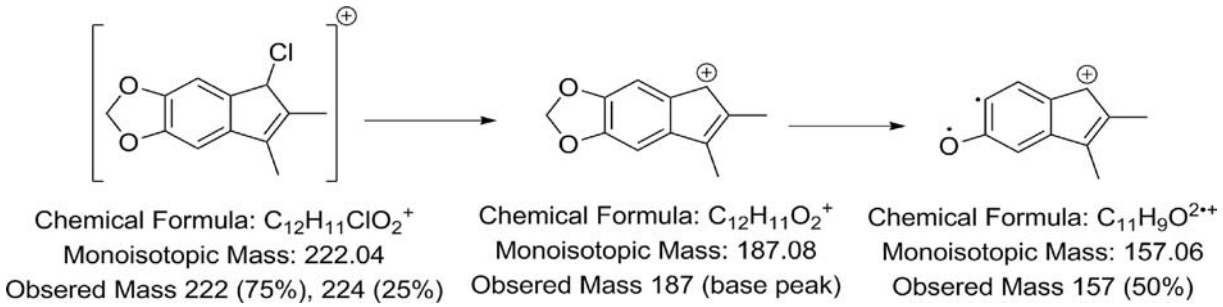
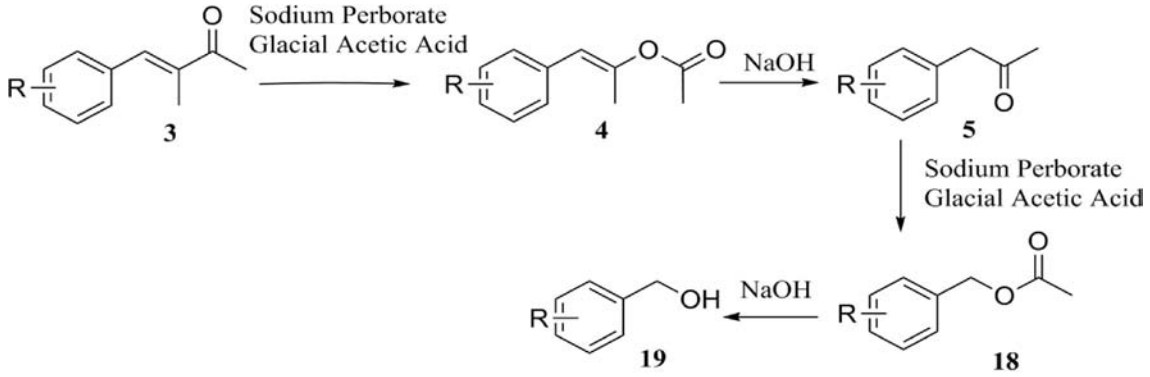


Fig. 7. Proposed fragmentations in the mass spectrum of **13g**.

formation of ketones into ester and cyclic ketones into lactones [12]. In our case the Baeyer-Villiger reaction is used to convert aldol products **3a–m** into esters **4a–m** as can be seen in Fig. 8. The aldol products **3a–m** were allowed to react with peracetic acid, formed *in situ* when glacial acetic acid is treated with sodium perborate. Whilst sodium perborate could be considered an unusual reagent for a Baeyer-Villiger reaction, its use has previously been reported [33,34]. Mostly the esters **4a–m** were not isolated and purified since our interest lay in the overall conversion of **3a–m** into the known P2P derivatives **5a–m**.

After workup of the Baeyer-Villiger reaction, the organic material was subjected to analysis by GC-MS to determine the distribution of products formed. By way of example, shown in Fig. 9 is a partial GC-MS trace of reaction mixture from a Baeyer-Villiger reaction on **3g** with 3,4-methylendioxy substituent, revealing that the major product from this reaction is the desired ester **4g** along with smaller amounts of by-products. The by-products are substituted forms of the previously reported by-products arising from ester hydrolysis during the Baeyer-Villiger reaction [9,10]. In addition, epoxidation products are common by-products when conjugated ketones are used in the Baeyer–Villiger reaction [35]. In this case an epoxidised derivative was tentatively identified as **21g** formed from ester **4g**. Previously epoxidised **21a** formed from ester **4a,** was indicated in the GC-MS but not reported (See Table 3).



Series	R	Series	R	Series	R	Series	R
a	H	d	2-OMe	g	3,4-O_2CH_2	j	4-F
b	4-OMe	e	4-Me	h	4-NO_2	k	4-Cl
c	3-OMe	f	3-Me	i	3-NO_2	l	4-OH
						m	C_6H_{11}

Fig. 8. Baeyer-Villiger reaction of ketone **3a–m** to yield ester **4a–m** along with several of the by-products formed in the reaction 5, 18, and 19.

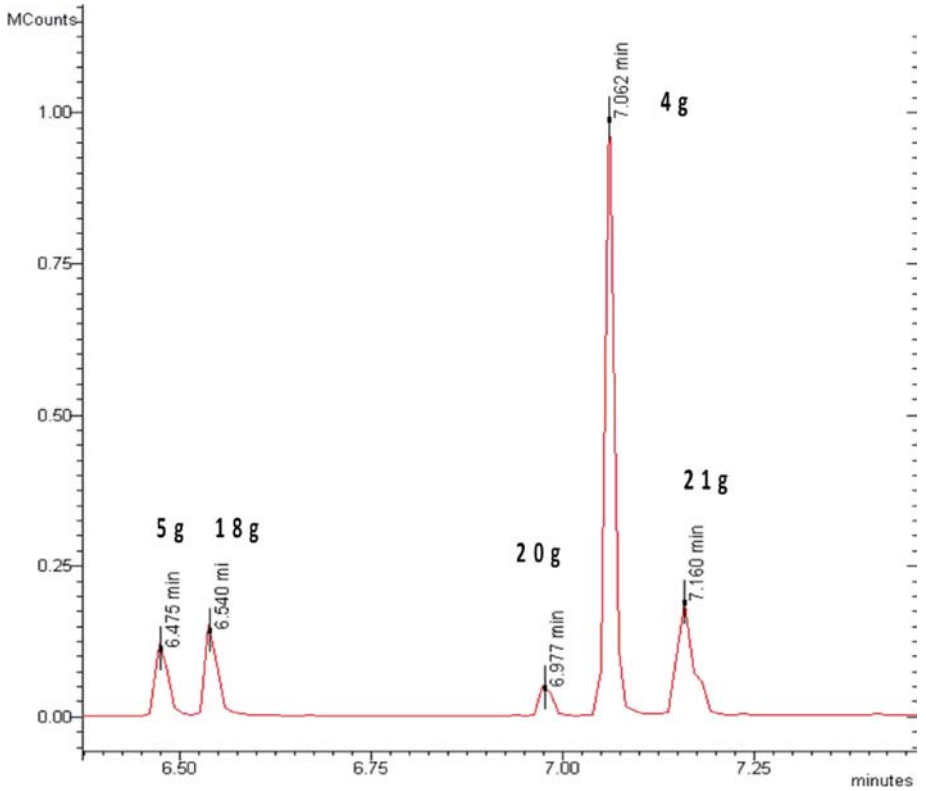
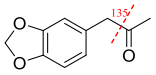
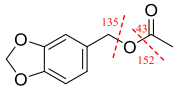
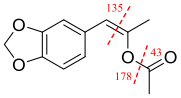
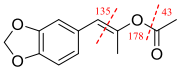
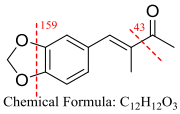
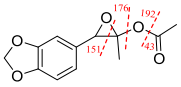


Fig. 9. Partial GC-MS trace of Baeyer-Villiger reaction on **3g**, forming **4g**. Compound structures and MS data are collected in Table 3.

Table 3
Chemical structure and compound numbers used in Fig. 9 and the MS data with major fragmentations identified.

Compound Number	Compound	Mass Spectrum data
5g	 Chemical Formula: $C_{10}H_{10}O_3$ Monoisotopic Mass:178.06	51 (10%), 77(10%), 135 (base peak), 178 (30%)
18g	 Chemical Formula: $C_{10}H_{10}O_4$ Monoisotopic Mass:194.06	43 (20%), 61 (20%), 65 (15%), 77 (25%), 105 (10%), 135 (base peak), 152 (90%), 194 (95%)
20g	 Chemical Formula: $C_{12}H_{12}O_4$ Monoisotopic Mass: 220.07	43 (20%), 91 (10%), 135 (85%), 178 (base peak), 220 (5%)
4g	 Chemical Formula: $C_{12}H_{12}O_4$ Monoisotopic Mass: 220.07	43 (20%), 135 (70%), 178 (base peak), 220 (10%)
3g	 Chemical Formula: $C_{12}H_{12}O_3$ Monoisotopic Mass: 204.08	MS: 43 (35%), 77 (25%), 103 (75%), 131 (45%), 159 (45%), 204 (base peak)
21g	 Chemical Formula: $C_{12}H_{12}O_5$ Monoisotopic Mass: 236.07	MS: 43 (25%), 65 (15%), 91 (20%), 123 (25%), 151 (base peak), 176 (30%), 192 (10%)

The Baeyer-Villiger reaction was unsuccessful when the aldol adduct **3** was substituted by electron withdrawing groups (ie **3h**, **i**, **l**) when using sodium perborate or the commercially available SARD-Oxy Plus® (sodium percarbonate) under the conditions previously reported [9]. A Baeyer-Villiger reaction on **3h** was, however, successful when hydrogen peroxide was used in place of sodium perborate with a yield of **4h** (45%) observed. This poor reactivity can be rationalized by examining the mechanism of the reaction in more detail. The generally accepted mechanism of Baeyer-Villiger oxidation is a two-step process with the first step being attack of the peracid onto the carbonyl to form the so called Criegee intermediate **22**. This is then followed by concerted migration of the substituent to produce an ester as shown in Fig. 10. The fundamentals of this mechanism were reported by Criegee in 1948 [36].

Table 4
Yields of P2P analogues over two steps of Baeyer-Villiger reaction.

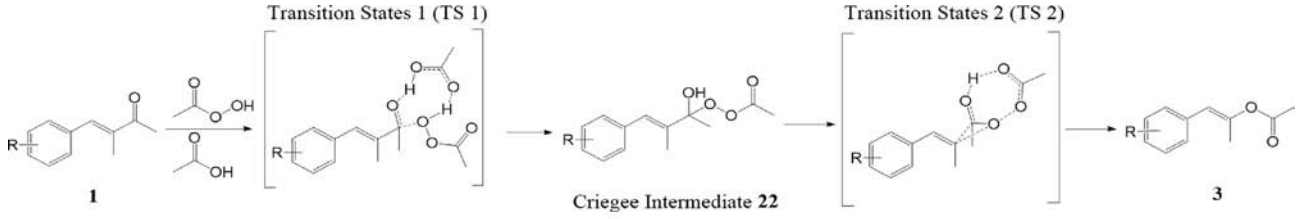
No.	R group	Yield of P2P analogues **5** (%)
3a	H	80
3b	4-OMe	82
3c	3-OMe	74
3d	2-OMe	77
3e	4-Me	60
3f	3-Me	53
3g	3,4-O_2CH_2	65
3h	4-NO_2	0[a]
3i	3-NO_2	Minor amount of **5i** detected by GCMS
3j	4-F	30
3k	4-Cl	30
3l	4-OH	0[a]
3m	C_6H_{11}	40

[a] Only starting materials **3** were identified from reaction mixture implying that the initial Baeyer-Villiger reaction was not successful.

Given the unsuccessful reaction of aldol adducts substituted by electron withdrawing groups, the lack of reactivity of **3l** is surprising in the Baeyer-Villiger reaction and subsequent hydrolysis to produce **5l**. This has been attributed to electron delocalization from the phenolic oxygen through to the carbonyl. This makes the carbonyl carbon atom more electron rich than seen in the other substrates and hence less susceptible to the first step in the Baeyer-Villiger reaction, namely peracid attack. So the failed reaction of **3l** is due to the first step of the Baeyer-Villiger reaction, where the poor reactivity of the electron withdrawing groups observed in Table 4 is due to second step of the Baeyer-Villiger reaction.

Examination of the two steps in the process using molecular modeling gave insights into the effect of the substituents. The electronic properties of the substituent have no effect on the first step, which is reflected in the activation energy for the step and the charge of the carbonyl carbon atom, with no significant change between the various substituted ketones being determined. In contrast, the electronic properties of the substituent have a large effect on the second, migration step. In particular, the activation energy of the migration step increases as the substituent becomes more electron withdrawing, as shown in the energy profiles (Fig. 11) between **22** and **4**. So the electron withdrawing substituents react to form Criegee intermediate **22** but the activation energy for the back reaction is smaller by a 2 kJmol^{-1} (in comparison to step 2) which is significant for a reaction to have some selectivity. This selectivity for the back reaction explains the poor reactivity of electron withdrawing substituents.

Conjugated systems are also less reactive under Baeyer-Villiger oxidation conditions [35]. In our case this means that the by-product **11a** (Table 1) from the aldol reaction does not undergo



Series	R	Series	R	Series	R	Series	R
a	H	d	2-OMe	g	3,4-O_2CH_2	j	4-F
b	4-OMe	e	4-Me	h	4-NO_2	k	4-Cl
c	3-OMe	f	3-Me	i	3-NO_2	l	4-OH
						m	C_6H_{11}

Fig. 10. The generally accepted mechanism of Baeyer-Villiger oxidation; a two-step process involving peracid attack on the carbonyl to form the Criegee intermediate, followed by substituent migration.

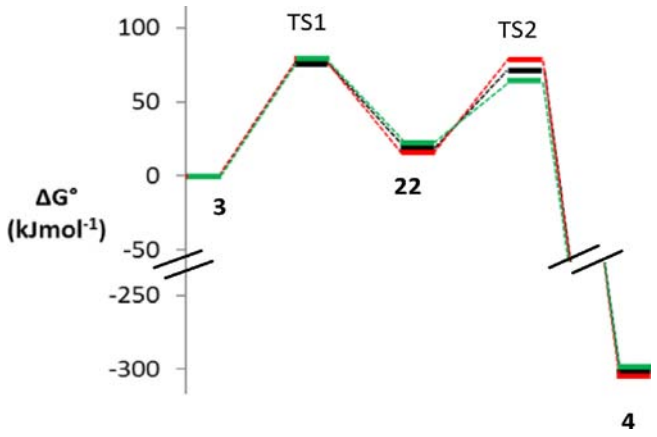


Fig. 11. Energy profiles of the Baeyer-Villiger reactions with **3a** R = H (black), **3b** R = 4-OMe (green), and **3h** R = 4-NO_2 (red).

the Baeyer-Villiger reaction under the conditions examined. This may be due to conjugated ketones having more electron density around the carbonyl group, making the compound less electrophilic therefore less reactive towards nucleophilic peracids. The effect of conjugation on the Baeyer-Villiger reaction is more complicated than this and investigations are currently underway using molecular modeling to examine the effect of conjugation on the Baeyer-Villiger reaction. The results of this investigation will be reported in due course.

The final step in the Baeyer-Villiger pathway is hydrolysis of esters **4a–m** to form P2P analogues **5a–m**. All of the P2P derivatives **5a–m** are known in the literature and in this case GC-MS was used to verify their formation in the ester hydrolysis step. Many different aldol products **3a–m** were used in the Baeyer-Villiger reaction and subsequent ester hydrolysis and, as shown in Table 4, occurred with yields over two steps of 60–80%. The exceptions were those substrates with electron withdrawing substituents which reacted poorly under Baeyer-Villiger reaction conditions and hence yielded little P2P product.

In several examples, some of the product ester is hydrolyzed during the Baeyer-Villiger reaction to form P2P which is then able to undergo a second Baeyer-Villiger reaction to form **18a–m** (Fig. 8). Thus in the formal ester hydrolysis step **18a–m** are hydrolyzed to **19a–m**. The by-products **18a–m**, **19a–m** are identical to those previously investigated [9], but were only tentatively identified by GC-MS in the current work.

6. Conclusions

A new clandestine ATS synthetic sequence, known as the Baeyer-Villiger pathway, describes the synthesis of P2P analogues in 30–50% yield from substituted benzaldehydes over three steps; an aldol condensation of substituted benzaldehyde and MEK; a Baeyer-Villiger reaction and subsequent hydrolysis of the ester. Investigations have revealed the significant role that the substituent plays in the reactivity of the substrate. Most benzaldehydes containing electron donating substituents **1b**, **c**, **e**, **f** behaved in a similar manner to benzaldehyde **1a**. However, when strong electron donating substituents are present in the three position of a substituted benzaldehyde (e.g. **1c**, **g**), the resulting aldol reaction is very sensitive to the amount of hydrogen chloride present due to the occurrence of a cyclization side reaction. Compounds substituted with electron withdrawing groups, namely **3h**, **i**, **j**, **k**, and **n**, react poorly under the Baeyer-Villiger reaction conditions used in this paper. This result was investigated and explained with aid of molecular modeling. Several new by-products in the Baeyer-Villiger route, namely compounds **6**, **10**, **13**, **14**, **15** and **21**, have also been identified.

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