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Sustainable Syntheses of Paracetamol and Ibuprofen from Biorenewable β-pinene

Joshua D. Tibbetts,[a] Marc Hutchby,[a] William B. Cunningham,[a] Robert S. L. Chapman,[a] Gabriele Kociok-Köhn,[c] Matthew G. Davidson,[a] and Steven D. Bull*[a, b]

Scalable processes have been developed to convert β-pinene into 4-isopropenylcyclohexanone, which is then used as a feedstock for the divergent synthesis of sustainable versions of the common painkillers, paracetamol and ibuprofen. Both synthetic routes use Pd^0 catalysed reactions to aromatize the cyclohexenyl rings of key intermediates to produce the benzenoid ring systems of both drugs. The potential of using bioderived 4-hydroxyacetophenone as a drop-in feedstock replacement to produce sustainable aromatic products is also discussed within a terpene biorefinery context.

Introduction

Global concerns surrounding the effect of fossil fuel use on the environment means that much effort is currently being focussed on developing sustainable routes to transform biorenewable feedstocks into biofuels and biopolymers.[1] In contrast, less attention has been directed towards developing methods to transform biomass into the many chemical products that are currently sourced from non-renewable petrochemicals.[2] The availability of industrial processes to transform biorenewables into sustainable chemicals will become increasingly important, because reductions in fossil fuel usage will inevitably lead to increased costs and decreased availability of petrochemicals.

Benzenoid petrochemicals that are produced from crude oil refining processes are widely used as non-renewable feedstocks for the industrial production of many aromatic products, including polymers, drugs, pesticides, flavours, stabilisers and lubricants.[3] However, relatively few processes have been developed to convert biomass sources into aromatic feedstocks on an industrial scale. Several processes based on the large-scale depolymerisation/processing of lignocellulosic biomass for the generation of benzenoid feedstocks have been proposed.[4] However, most of these processes are costly, resource intensive and low-yielding, often producing highly oxygenated aromatics (e.g., vanillin, syringic acid)[5] that are poorly suited as feedstocks for manufacturing aromatic products in existing chemical plants.[6]

Monoterpenes are an alternative class of biorenewable whose unsaturated hydrocarbon structures are ideally suited as feedstocks for the industrial syntheses of many sustainable chemical products. Multi-tonne quantities of turpentine (mixtures of α-pinene, β-pinene and 3-carene) and limonene feedstocks are available as waste products of the forestry and citrus juice industries.[7] The ready availability of these cheap monoterpene feedstocks means that numerous industrial processes have been developed to convert monoterpene feedstocks into value-added chemical products, including fragrances, flavourings, vitamins, and polymers (See Figure SI1 for selected examples).[8] However, their use as biorenewable feedstocks to produce the wide range of benzenoid aromatics (e.g. drugs, pesticides, lubricants, polymers, etc.) that are currently sourced from petrochemical feedstocks is less well explored. As part of a research program directed towards expanding the range of sustainable chemicals available from terpene biorefineries, we recognised that the *p*-menthadiene skeleton of monocyclic monoterpenes (e.g., limonene) could be aromatised to give valuable benzenoid products (e.g., *p*-cymene). This led us to develop tandem catalytic ring-opening-aromatisation-oxidation protocols to transform cheap turpentine mixtures (360 000 tonnes available pa at ~£0.20 per litre) into sustainable versions of four common platform aromatics-*p*-cymene, *p*-methyl-acetophenone, *p*-toluic acid and terephthalic acid (see Scheme 1).[9] These terpene derived aromatics may then be used as 'drop-in' replacement feedstocks for the large scale production of sustainable versions of many commercial aromatic products (see Scheme 1).

Many commonly prescribed aromatic drugs contain benzenoid rings, however there are only a few cases where these drugs have been prepared from sustainable feedstocks.[10] Consequently, we decided to develop synthetic routes that would allow β-pinene (~100 000 tonnes available pa) to be converted into two widely consumed analgesics, paracetamol

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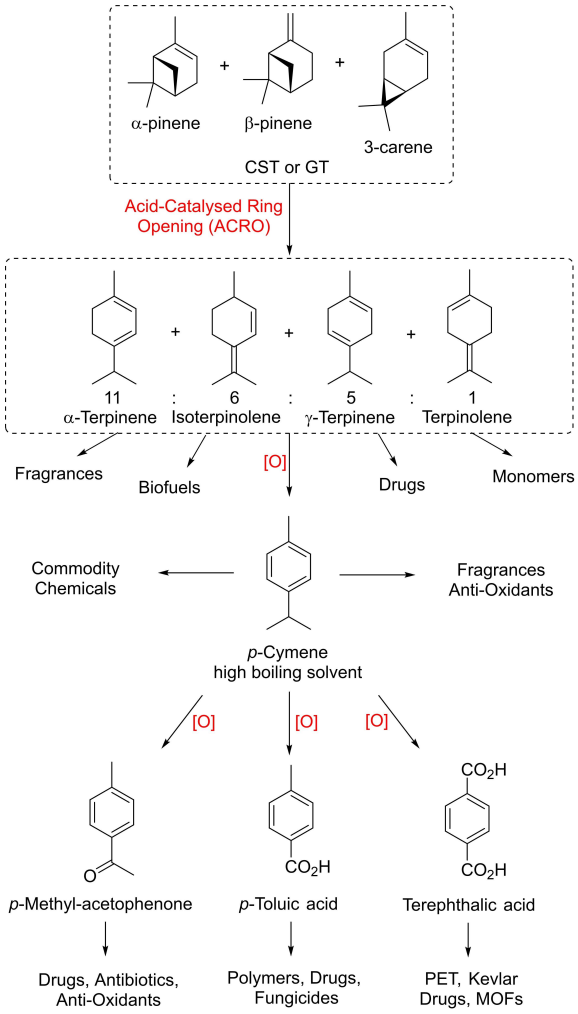


Scheme 1. Terpene biorefinery model for the synthesis of sustainable platform aromatics that are used to manufacture commercial aromatic products.[9a–c] Crude sulfate turpentine (CST). Gum turpentine (GT).

and (*rac*)-ibuprofen. Both these painkillers are on the World Health Organisation list of essential medicines, with highly optimised processes used to manufacture multi-tonne quantities of both drugs annually (See Figure SI2 for details).[11] Therefore, the availability of potentially scalable routes to manufacture sustainable versions of these painkillers from monoterpene feedstocks would be potentially attractive, both from an environmental and economic perspective.[12,13]

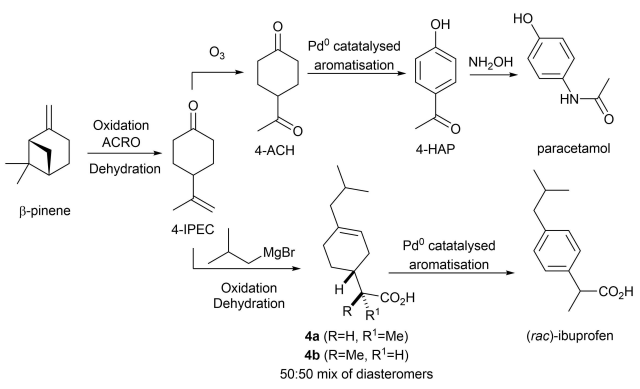
Results and Discussion

The synthetic strategy targeted to prepare sustainable versions of these painkillers first required development of an oxidation-ring-opening-dehydration protocol to transform bicyclic β-pinene into monocyclic 4-isopropenylcyclohexanone (4-IPEC). This key intermediate would then be used as a bioderived feedstock for the divergent synthesis of paracetamol (3 steps) and (*rac*)-ibuprofen (5-steps). Both synthetic routes would use key late-stage Pd^0 catalysed oxidative aromatisation reactions to convert the cyclohexyl ring systems of key intermediates (4-ACH and cyclohexene acids **4a/b**) into the benzenoid ring systems of each painkiller (Scheme 2).

Our study commenced with the aim of identifying a three-step scalable route to transform β-pinene into 4-IPEC on a decagram scale. Standard ozonolysis conditions (O_3 in methanol at −78 °C; Me_2S work-up) were used to oxidatively cleave the alkene bond of β-pinene to afford nopinone in 91% yield on a 20 g scale.[14] Although this ozonolysis reaction was carried out at −78 °C for safety reasons, a full process study on the continuous flow ozonolysis of β-pinene has previously described production of nopinone at RT on a large scale.[15]

Acid catalysed ring opening (ACRO) of nopinone to give 4-(1-hydroxy-1-methylethyl)-cyclohexanone (4-HMEC) was achieved through modification of conditions first reported by Boelens and co-workers.[16] Bicyclic nopinone (unpurified) was stirred with 12 M H_2SO_4 at −5 °C for 45 min to give 4-HMEC in 86% yield (Scheme 3a).[17] Inspired by our previous success of carrying out biphasic reactions in flow,[18] we then carried out the ACRO reaction of nopinone in a continuous manner. This involved flowing separate streams of nopinone and 12 M H_2SO_4 into a microreactor (4.5 mL LTF static mixer, residence time 10 min) at 5 °C which produced 4-HMEC in 89% yield (Scheme 3a, see SI for details).

Attempts to carry out the ACRO reaction of nopinone under milder conditions using 6 M H_2SO_4 at 35 °C did not produce 4-HMEC, instead affording mixtures of 4-IPEC and 4-isopropylidenecyclohexanone (4-IPIC), which isomerised over time to produce the α,β-unsaturated ketone, cryptone. Treatment of 4-HMEC with 6 M H_2SO_4 at 35 °C produced similar results. These findings are consistent with both reactions proceeding through formation of a tertiary carbenium ion **A** that eliminates a proton to give the alkene bonds of 4-IPEC and 4-IPIC that then isomerise to give cryptone (Scheme 3b). However, this means that the low temperature ACRO reaction of nopinone to afford 4-HMEC (12 M H_2SO_4, −5 °C; Scheme 3c) does not proceed via direct ring fragmentation of oxocarbenium ion **B** to give carbenium ion **A**, otherwise similar mixtures of 4-IPEC and 4-



Scheme 2. Conversion of β-pinene into 4-isopropenylcyclohexanone (4-IPEC), which is then used as a bioderived feedstock for the sustainable syntheses of paracetamol and (*rac*)-ibuprofen. ACRO = acid-catalysed ring opening. 4-ACH = 4-acetylcyclohexanone. 4-HAP = 4-hydroxy-acetophenone.

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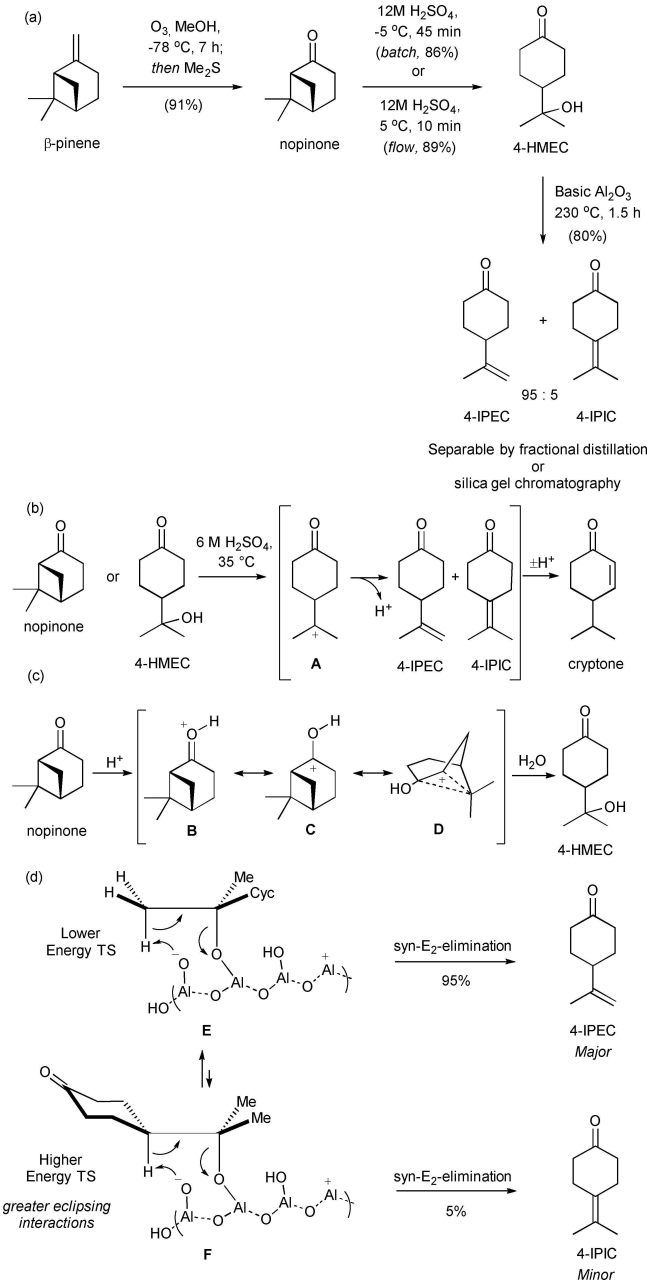
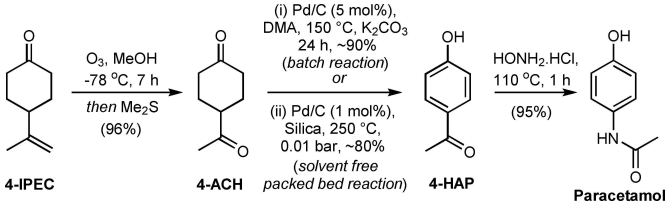


Scheme 3. (a) Conversion of biorenewable β-pinene into 95% pure 4-IPEC in 65% yield over three steps. (b) Acid-catalysed dehydration reaction of 4-HMEC. (c) Mechanism of ACRO reaction of nopinone. (d) Competing *syn*-E_2 elimination reactions of alkoxides **E** and **F** produce 4-IPEC and 4-IPIC, respectively. Cyc = Cyclohexan-4-one. TS = transition state.

IPIC would be formed. Instead, we propose that the low temperature ACRO reaction of nopinone proceeds through participation of non-classical carbenium ion **D**, with water acting as a nucleophile at its gem-dimethyl carbon to trigger ring fragmentation to directly afford 4-HMEC (Scheme 3c).[19]

Thermolysis of 4-HMEC in the presence of basic Al_2O_3 at 230 °C for 1 h resulted in a clean dehydration reaction to afford a 95:5 mixture of 4-IPEC (Hofmann product) and 4-IPIC (Saytzeff product) in a combined ~80% yield (Scheme 3a). These heterogeneous dehydration reactions proceed via E_2 elimination of surface bound alkoxides **E** and **F**, with *syn*-elimination pathways favoured by surface Lewis basic sites abstracting β-protons from the bound alkoxides.[20] *Syn*-abstraction of a methyl proton from alkoxide **E** to produce 4-IPEC is likely to proceed through an eclipsed transition state that is significantly lower in energy than the corresponding eclipsed transition state required for the β-ring proton of alkoxide **F** to be abstracted to produce 4-IPIC (Scheme 3d). This transition state energy difference results in thermodynamically less stable 4-IPEC being formed as the major elimination product under kinetic control. Clearly no competing alkene isomerisation reactions occur under these basic thermal dehydration conditions, otherwise greater amounts of 4-IPIC (and cryptone) would accumulate. The 95:5 mixture of 4-IPEC and 4-IPIC could be separated by careful fractional distillation (90–95 °C at 5 mm Hg, three consecutive distillations), which allowed >99% pure 4-IPEC to be isolated in 67% yield. However, mass losses incurred during this purification step meant we chose to use 95% pure 4-IPEC (80% yield) as a feedstock for the subsequent syntheses of paracetamol and (*rac*)-ibuprofen (*vide infra*). This approach allowed minor side-product impurities (<5%) derived from 4-IPIC to be more easily removed in downstream recrystallisation steps.[21,22]

Having developed an effective three-step route from β-pinene to multigram quantities of 4-IPEC in an overall 65% yield, we then set about identifying conditions that would allow it to be transformed into a sustainable version of paracetamol (Scheme 4). Treatment of 4-IPEC (95%) with O_3 in methanol at −78 °C and work-up with Me_2S, afforded 4-acetylcyclohexanone (4-ACH) in 96% yield.[23] Treatment of unpurified 4-ACH with 5 mol% Pd/C in dimethylacetamide (DMA) at 150 °C for 24 h then resulted in a clean oxidative aromatisation reaction occurring to afford 4-hydroxyacetophenone (4-HAP) (Scheme 4).[24] This heterogeneous aromatisation reaction was worked up by filtering off the Pd/C catalyst, removing the DMA solvent *in vacuo* and recrystallizing the resulting crude solid from water to give >99% pure 4-HAP in ~90% yield. Recovered Pd/C catalyst could be reused to carry out four subsequent 4-ACH aromatisation reactions with essentially no losses in catalytic activity, which enabled four consecutive batches of crystalline 4-HAP to be produced in 85–90% yield. An alternative solvent-free packed bed approach to carry out this aromatisation reaction was then developed, involving passing 4-ACH vapour over Pd/C adsorbed onto microporous silica gel at 250 °C and 0.01 bar. These reactive distillation conditions



Scheme 4. Conversion of 4-IPEC into paracetamol in 82% yield over three steps.

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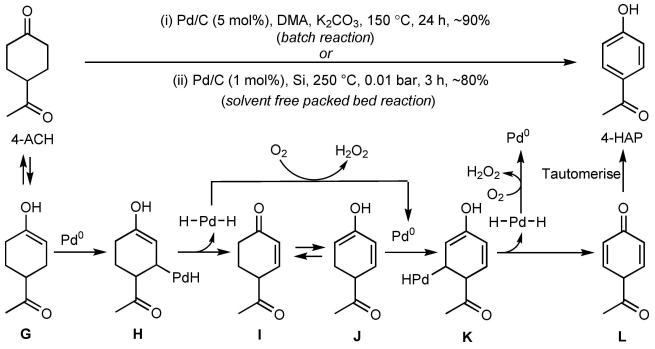
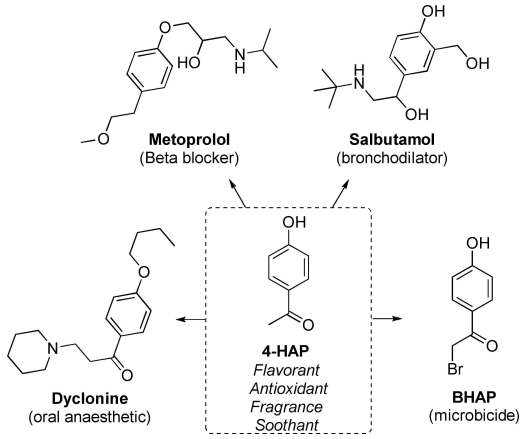
produced a distillate that solidified to afford >95% pure 4-HAP in ~80% yield (see Figure SI3 for details).

A reasonable mechanism for the Pd^0 catalysed conversion of 4-ACH into 4-HAP is shown in Scheme 5. Consecutive oxidative insertion of Pd^0 species into allylic C–H bonds of enol intermediates **G** and **J** will generate palladium-enol intermediates **H** and **K** respectively. Consecutive losses of H_2 from enol intermediates **H** and **K** to O_2 can then occur to produce enedione **I** and dienedione **L** respectively, with concomitant formation of H_2O_2 and Pd^0 catalytic species. Once formed, dienedione **L** can tautomerize irreversibly to afford the phenolic ring system of 4-HAP.

A modification of the Hoechst-Celanese process was then used to transform 4-HAP into paracetamol,[25] based on addition of $HONH_2 \cdot HCl$ to molten 4-HAP at 110 °C (no solvent) over a period of 1 h. These conditions result in formation of an oxime intermediate (not isolated) that undergoes a clean Beckmann rearrangement to produce paracetamol. The crude paracetamol produced in this reaction was purified by recrystallisation from hot water to afford >99% pure paracetamol in 95% yield (Scheme 4). Therefore, three potentially scalable steps can be used to convert bioderived 4-IPEC into a sustainable version of paracetamol in 82% overall yield, with all eight of its carbon atoms originating from β-pinene (Scheme 4).



Scheme 5. Mechanism of palladium catalysed dehydrogenation reaction of 4-ACH to produce 4-HAP.



Scheme 6. Potential uses of bioderived 4-HAP in the cosmetic, pharmaceutical and chemical industries.

Although the focus of this study was to develop a scalable route from β-pinene to paracetamol, access to large quantities of bioderived 4-HAP provides an opportunity to use it to prepare other valuable sustainable aromatic products. Non-sustainable petrochemical 4-HAP is widely used as a flavouring, antioxidant, fragrance and soothing agent by the cosmetic industry, as well as being used as a platform aromatic feedstock to prepare numerous other drugs, anaesthetics and pesticides (Scheme 6).[26] Therefore, potential use of bioderived 4-HAP as a drop-in feedstock replacement could significantly broaden the range of valuable sustainable aromatic products that are available from a terpene biorefinery.

Our attention then turned to devising a viable oxidative aromatisation-based protocol to transform 4-IPEC into (*rac*)-ibuprofen (Scheme 7a).[27] The first step of this synthesis would require addition of a bioderived version of ^{i}BuMgCl to the ketone group of 4-IPEC. Bioisobutanol is available as a microbial fermentation product of lignocellulosic biomass,[28] which is easily converted into ^{i}BuCl ($SOCl_2$, DMF) as a precursor to prepare bioderived ^{i}BuMgCl (Mg/THF) (Scheme 7b).[29] Addition of ^{i}BuMgCl to 4-IPEC in THF at 0 °C produced a mixture of the desired tertiary alcohol **1** and significant amounts of unwanted 4-isopropenylcyclohexanol (4-IPECOL). Tertiary alcohol **1** is formed from nucleophilic attack of a coordinated isobutyl nucleophile at the least hindered face of the carbonyl of 4-IPEC, whilst competing intramolecular transfer of a hydride equivalent from an *O*-coordinated isobutylmagnesium species produces 4-IPECOL (Scheme 7c). However, inclusion of stoichiometric amounts of $CeCl_3$ in the Grignard reaction fixed this selectivity problem,[30] resulting in clean formation of achiral tertiary alcohol **1** as a single product in 88% yield (Scheme 7a).[31]

Hydroboration of the alkene bond of achiral tertiary alcohol **1** using $BH_3 \cdot SMe_2$ in THF at 0 °C, followed by oxidative work-up with $NaOH/H_2O_2$, gave (*rac*)-diol **2** as a crude solid that was used in the next catalytic alcohol oxidation step without further purification (Scheme 7a). The facial selectivity of the previous step (addition of ^{i}BuMgCl) was also confirmed through X-ray crystallographic analysis of diol **2** (Scheme 7a and SI). Noyori's solvent-free tungsten catalysed oxidation protocol was then chosen to sustainably oxidise the primary alcohol of (*rac*)-diol **2** to the carboxylic acid group of (*rac*)-ε-hydroxy-acid **3**. This involved treating (*rac*)-diol **2** with 1% Na_2WO_4, 1% methyltrioctyl-ammonium hydrogen sulfate (phase transfer catalyst) and 30% $H_2O_{2(aq)}$ which gave (*rac*)-ε-hydroxy-acid **3** in 91% yield over two steps (Scheme 7a).[32]

The tertiary alcohol group of unpurified (*rac*)-ε-hydroxy-acid **3** was then dehydrated through treatment with 120 wt% Amberlyst-15 resin in EtOAc at RT for 1 h, which selectively gave the trisubstituted alkene bonds of (*rac*)-cyclohexene acids **4a**/**4b** as a 1:1 mixture of diastereomers in 95% yield.[33] Attempts to oxidatively aromatise cyclohexene acids **4a**/**4b** using Pd/C catalysed conditions previously employed to aromatise 4-ACH (see Scheme 4) proved unsuccessful, affording complex mixtures of products. However, treatment of cyclo-

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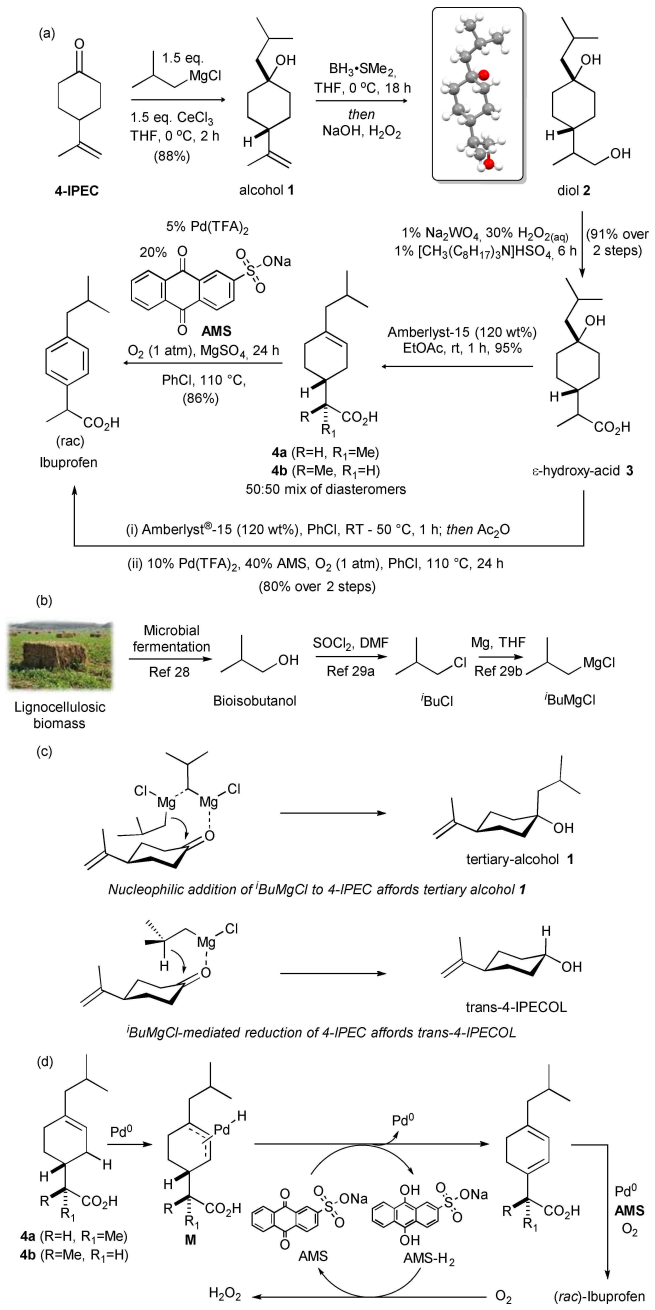

Scheme 7. (a) Conversion of 4-IPEC into ibuprofen in 64% yield over 5 steps. (b) Potential route from bioisobutanol to bioderived ^{i}BuMgCl. (c) Competing addition and reduction pathways produce tertiary alcohol 1 and *trans*-4-IPECOL. (d) AMS acts as a hydrogen acceptor in the Pd^0-catalysed aromatisation reactions of cyclohexene acids **4a**/**4b**.

hexene acids **4a**/**4b** with 5% $Pd(TFA)_2$ and 20% sodium anthraquinone-2-sulfonate (AMS) cocatalyst under one atmosphere of O_2 in chlorobenzene at 110 °C for 24 h,[34] resulted in clean aromatisation to afford a crude solid that was recrystallised to afford (*rac*)-ibuprofen in 86% isolated yield. The role of the AMS cocatalyst is to accept H_2 from incipient palladium-π-allyl complexes (e.g. intermediate **M**) that are formed when the Pd^0 catalyst reacts with cyclohexene acids **4a**/**4b** (see Scheme 7d). Failure to include AMS in this aromatisation reaction resulted in competing catalytic disproportionation of the alkene bonds of the parent cyclohexene acids **4a**/**4b** to produce saturated cyclohexane side-products that are difficult to separate, leading to lower yields of (*rac*)-ibuprofen.[35]

An alternative 'one-pot' dehydration/aromatisation procedure was also developed to directly convert (*rac*)-ε-hydroxy-acid **3** into (*rac*)-ibuprofen. Treatment of (*rac*)-ε-hydroxy-acid **3** with Amberlyst-15 in chlorobenzene at 50 °C for 1 h, followed by addition of Ac_2O and stirring at RT for 30 min, gave a solution of cyclohexene-acids **4a**/**4b**. 10% $Pd(TFA)_2$ and 40% AMS were then added to the solution of cyclohexene acids **4a**/**4b** in chlorobenzene (no workup) which was then heated at 110 °C under 1 atm of O_2 for 24 h to produce (*rac*)-ibuprofen in 80% yield over two steps. Addition of Ac_2O after the first step is necessary for the subsequent aromatisation reaction to proceed effectively, with Ac_2O acting as a scavenger of the water produced in the dehydration step to produce acetic acid.

Therefore, five potentially scalable steps have been used to convert 4-IPEC into a sustainable version of (*rac*)-ibuprofen in an overall yield of ~64%, with nine of its carbons originating from β-pinene and the other four carbon atoms of its isobutyl fragment potentially sourced from bioisobutanol.

Conclusions

Scalable synthetic routes have been developed to transform biorenewable β-pinene into sustainable versions of two widely used non-prescription painkillers, paracetamol and (*rac*)-ibuprofen. The bicyclic ring system of β-pinene is first ring-opened to afford the monocyclic cyclohexyl ring system of 4-IPEC that is then used as a key bioderived intermediate for the divergent syntheses of both drugs. Key late stage Pd^0-catalysed oxidative aromatization reactions of cyclohexenyl intermediates are used to install the benzenoid ring systems of each analgesic. The potential of using bioderived 4-HAP as a biorenewable feedstock for the sustainable synthesis of aromatic products within a monoterpene biorefinery context is also discussed. We hope the success of this study will inspire others to design their own sustainable routes from biorenewable feedstocks to industrially important benzenoid products that are currently sourced from non-sustainable petrochemical feedstocks.

Experimental Section

Detailed experimental procedures including additional diagrams are included in the Supporting Information.

General experimental details

^{1}H and ^{13}C NMR spectra were run in $CDCl_3$ using Bruker Avance 250/300/400/500 MHz spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to the residual solvent peak. The multiplicities and general assignments of spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of doublets (td), quartet of doublets (qd), triplet of triplets (tt), multiplet (m), aromatic (Ar), and

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apparent (app.). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Infrared spectra (4000 cm^{-1} to 0 cm^{-1}) were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a Universal ATR accessory for sampling. The machine has internal calibration and only selected peaks are quoted in ν (wavenumbers, cm^{-1}). Mass spectra were recorded on a Bruker Daltonics micrOTOF electrospray time-of-flight (ESITOF) mass spectrometer. Samples were introduced either by syringe pump or flow injection using an auto-sampler. Samples were diluted in either methanol or acetonitrile. All capillary melting point determinations were carried out using Büchi 535 melting point apparatus and reported to the nearest degree Celsius. Analytical thin layer chromatography was carried out using commercially available polyethylene backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, *p*-anisaldehyde or phosphomolybdic acid, followed by heating. Flash chromatography was performed under medium pressure using Merck 60 H silica gel (35–75 μm). Samples were loaded as saturated solutions in an appropriate solvent.

Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried apparatus, which was allowed to cool under nitrogen prior to use. Anhydrous solvents were obtained by passing them through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All commercially available compounds were used as obtained from the chemical suppliers.

Ozonolysis of β-pinene to nopinone

β-Pinene (20.0 g, 147 mmol) was dissolved in methanol (200 mL) and cooled to −78 °C. A stream of O_3 was passed through the solution until its colour became bright blue (approx. 8 h) showing the presence of excess ozone. The reaction was sparged for 5 min with O_2 then N_2 for 10 min, fully dissipating the colour. Dimethyl sulfide (21.8 mL, 294 mmol, 2 equiv.) was added dropwise to this stirred solution (still at −78 °C) over 30 min, with the solution then allowed to warm to rt. After stirring for 18 h the reaction was concentrated *in vacuo*, diluted with Et_2O (300 mL) and washed with sat. NaCl (3×150 mL) before the organic extracts were evaporated to dryness *in vacuo* to yield nopinone (18.4 g, 133 mmol, 91 %) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.66–2.45 (m, 3H), 2.38–2.17 (m, 2H), 2.11–1.87 (m, 2H), 1.56 (d, J = 10.0 Hz, 1H), 1.30 ppm (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 215.1, 58.1, 41.4, 40.6, 32.9, 26.0, 25.4, 22.3, 21.6 ppm. Analytical data were in accordance with a commercial sample of nopinone (CAS 38651-65-9).

4-(1-Hydroxy-1-methylethyl)-cyclohexanone (4-HMEC)

Method 1 (batch protocol)

Nopinone (2.00 mL, 1.96 g, 14.4 mmol) was added dropwise over 5 min to a stirred solution of 12 M H_2SO_4 (20 mL) at −5 °C. The resulting mixture was stirred at this temperature for an additional 40 min before being poured onto ice (~50 g), followed by extraction with hexane (50 mL) and this organic layer then discarded. The aqueous layer was then saturated with NaCl and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried over $MgSO_4$ and the solvent removed in vacuo to give 4-HMEC (1.91 g, 12.4 mmol, 86 %) as a yellow oil.

Method 2 (continuous flow protocol)

Following a modification of a previously described setup,[18] a Little Things Factory (LTF) GmbH XXL-ST-04 microreactor was cooled to 5 °C. Nopinone and 12 M H_2SO_4 were loaded into syringes and pumped at 0.05 mL min^{-1} and 0.45 mL min^{-1}respectively (total flow rate of 0.5 mL min^{-1}) through the central 4.5 mL microreactor with a residence time of 9 min. The output stream was collected for 40 min (20 mL) into a flask containing ice and worked up in the same way described for method 1 to give 4-HMEC (1.98 g, 12.8 mmol, 89 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47–2.27 (m, 4H), 2.21–2.11 (m, 2H), 1.78 (tt, J = 12.1, 3.3 Hz, 1H), 1.51 (qd, J = 12.9, 4.7 Hz, 2H,), 1.23 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.1, 72.5, 47.5, 41.0, 27.6, 27.4 ppm. Analytical data was in accordance with literature.[36]

4-Isopropenylcyclohexanone (4-IPEC)

4-HMEC (1.90 g, 12.4 mmol) and basic alumina (3.80 g) were heated at 220 °C for 1 h with a distillation apparatus used to collect the distillate (1.14 g, 8.3 mmol, ~80 %) comprised of 95 % 4-IPEC and 5 % 4-isopropylidene-cyclohexanone (4-IPIC). Further purification could be carried out to obtain a pure sample of 4-IPEC if required *via* distillations (90–95 °C@5 mm Hg, three consecutive distillations, 67 %) or silica gel chromatography (2 % Et_2O in pentane). Alternatively, the crude 4-IPEC (95 %) could also be used directly as a feedstock in subsequent synthetic steps with no adverse effects. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.78–4.76 (m, 2H), 2.46–2.32 (m, 5H), 2.12–2.04 (m, 2H), 1.76 (s, 3H), 1.74–1.61 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 211.7, 148.2, 109.8, 43.7, 41.2, 31.6, 21.6. Analytical data was in accordance with literature.[37]

4-acetylcyclohexanone (4-ACH)

4-IPEC (14.7 g, 106.5 mmol) was subjected to the general ozonolysis procedure and work-up used for nopinone (see above) to yield **4-ACH** (14.3 g, 102.1 mmol, 96 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.78 (tt, J = 10.2, 3.9 Hz, 1H), 2.52–2.42 (m, 2H), 2.41–2.28 (m, 2H), 2.22 (s, 3H), 2.21–2.12 (m, 2H), 1.97–1.83 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.1, 209.8, 48.7, 39.9, 28.3, 28.0 ppm. Analytical data was in accordance with literature.[38]

4-Hydroxyacetophenone (4-HAP)

Method 1

Following a modification of the procedure reported by Liu and co-workers,[39] a stirred solution of 4-ACH (1.40 g, 10 mmol), K_2CO_3 (280 mg, 2 mmol), 10 wt% Pd/C (500 mg, 0.052 mmol Pd) and dimethylacetamide (20 ml) was degassed and then heated at 150 °C under N_2 for 24 h. The reaction was then cooled to rt, Pd/C filtered off and 5 ml of saturated $NaHCO_{3(aq)}$ added. The filtrate was then extracted with EtOAc (3×6 mL) and the combined organic layer dried over anhydrous $MgSO_4$. The product was concentrated in vacuo and the crude residue purified by silica gel chromatography (25 % EtOAc in Pet. Ether) to give 4-HAP in 92 % yield (1.26 g. 9.2 mmol) as a white solid. The filtered Pd/C catalyst could be reused four times in subsequent aromatisation reactions producing 4-HAP in 80–92 % yield.

Method 2

Following a modification of the procedure reported by Frost and co-workers,[24] high purity grade silica gel (60 Å pore size, 200–400 mesh particle size, 8.5 g) was oven dried (150 °C) overnight before being cooled under an inert atmosphere and thoroughly mixed with 10 wt% Pd/C (1.2 g, 1.1 mmol). This material was then packed into a small Kugelrohr bulb (20 mL capacity) using glass

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wool to immobilize the supported catalyst. 4-ACH (14 g, 100 mmol) was charged to a 50 mL Kugelrohr bulb which was attached to the inlet of the catalyst containing bulb whose outlet was attached to an empty 25 mL receiver bulb (Figure SI2). The flasks containing 4-ACH and the catalyst were then inserted into a Kugelrohr oven and heated to 250 °C under a constant vacuum (0.01 bar) with slow rotation (Figure SI3). The receiver flask was continuously cooled, with a white solid accumulating over several hours which was recovered by washing with methanol. Evaporation *in vacuo* led to 4-HAP (10.7 g, 80 %) being isolated as an off-white solid that could either be used directly in the subsequent Beckmann rearrangement reaction or purified *via* recrystallization from water. m.p. 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.82$ (s, 1H), 7.93 (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 2.60 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.5$, 162.0, 131.5, 129.2, 115.8, 26.4 ppm. Analytical data were in accordance with a commercial sample of 4-HAP (CAS: 99-93-4).

Paracetamol

Following a modification of the procedure reported by Ronchin and co-workers,[25] 4-HAP (1.36 g, 10 mmol) was charged to a 25 mL flask and heated to 110 °C so that the white solid melted. Hydroxylamine hydrochloride (834 mg, 12 mmol) was added in one portion to the gently stirred melt to form a homogeneous yellow oil that was heated at 110 °C for 1 h until the starting material was consumed. Upon cooling, the product was isolated by first washing with ice cold water and then recrystallized from hot water to yield paracetamol as a white solid (1.43 g, 95 %). m.p. 170–172 °C; ^{1}H NMR (300 MHz, acetone-d_6): $\delta = 9.03$ (s, 1H), 8.25 (s, 1H), 7.45 (d, $J = 8.9$ Hz, 2H), 6.76 (d, $J = 8.9$ Hz, 2H), 2.04 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 168.5$, 154.3, 132.5, 121.8, 115.8, 24.0 ppm. Analytical data were in accordance with a commercial sample of paracetamol (CAS 103-90-2).

(rac)-1-Isobutyl-4-(prop-1-en-2-yl)cyclohexan-1-ol (1)

Following a modification of the procedure by Imamoto and co-workers,[30] $CeCl_3.7H_2O$ (22.3 g, 60 mmol) was charged to a 250 mL Schlenk tube and slowly heated over 4 h with stirring to 140 °C under a vacuum of 0.01 bar. The $CeCl_3$ was then cooled, quickly ground with a pestle and mortar, placed back into the Schlenk tube and heated quickly to 140 °C under vacuum at 0.01 bar and held at this temperature for 2 h. The flask was backfilled with N_2 while hot, cooled to 0 °C in an ice bath and anhydrous THF (200 mL) then added in one portion with rapid stirring. The solution was allowed to warm to RT and stirred for 18 h under N_2. Following this, the flask was cooled again in ice and isobutylmagnesium chloride (30 mL, 2 M in THF, 60 mmol) added dropwise over 10 min. 4-IPEC (5.50 g, 40 mmol) was then added dropwise to the white suspension and the reaction mixture stirred for 2 h at 0 °C. 10 % acetic acid (100 mL) was added to quench the reaction and the solution extracted with Et_2O (3×100 mL). The organic layers were combined, washed with sat. $NaHCO_3$, dried over $MgSO_4$ and evaporated *in vacuo to yi*eld alcohol **1** (6.90 g, 88 %) as a clear oil that was used in the subsequent hydroboration reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.72$–4.66 (m, 2H), 1.91–1.77 (m, 2H), 1.76–1.66 (m, 5H), 1.63–1.49 (m, 4H), 1.44–1.32 (m, 4H), 1.14–1.02 (m, 1H), 0.96 ppm (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (126 MHz, chloroform-*d*): $\delta = 150.6$, 108.4, 71.5, 53.2, 45.2, 37.7, 27.0, 25.2, 23.7, 21.1 ppm; IR: $\nu = 3467$, 2928, 2868, 1643, 1443, 954, 885 cm^{-1}; HRMS (ESI+) *m/z* calculated for $C_{13}H_{24}O$: $[M+H^+]$ theoretical *m/z* 197.1900 measured *m/z* 197.1905.

(rac)-4-(1-Hydroxypropan-2-yl)-1-isobutylcyclohexan-1-ol (2)

Unpurified (*rac*)-alcohol **1** (6.90 g, 35.2 mmol) was dissolved in anhydrous THF (80 mL) under N_2 and cooled in an ice bath. $BH_3{\bullet}SMe_2$ (24.6 mL, 2 M in THF, 49.3 mmol) was then added dropwise allowing the generated gas to vent from an outlet needle and the reaction stirred at 0 °C for 18 h. NaOH (6.48 g, 161.9 mmol dissolved in 60 mL H_2O) was then added dropwise over 30 min, followed by dropwise addition of H_2O_2 (30 % aq., 18.3 mL, 161.9 mmol) over 15 min, with the reaction then allowed to warm to rt. After 1 h at rt, sat. $NaHCO_3$ (100 mL) was added and the reaction extracted with Et_2O (3×150 mL). The combined organic layers were then dried ($MgSO_4$) and evaporated *in vacuo* to afford a crude white solid (7.01 g, > 95 %). This crude reaction mixture could be purified *via* column chromatography (40 % EtOAc in petroleum ether) to afford purified (*rac*)-diol **2** or used directly in the subsequent oxidation step. m.p. = 61–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.63$ (dt, $J = 10.1$, 4.9 Hz, 1H), 3.50 (dt, $J = 10.1$, 5.4 Hz, 1H), 1.89–1.77 (m, 1H), 1.74–1.63 (m, 2H), 1.55–1.25 (m, 10H), 0.95 (d, $J = 6.7$ Hz, 6H), 0.92 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 71.7$, 66.5, 53.2, 40.7, 39.0, 37.8, 37.7, 26.0, 25.2, 23.9, 23.7, 13.7 ppm; IR: $\nu = 3284$, 2954, 2926, 2869, 1459, 1433, 1045, 1026 cm$^{-1;}$ HRMS (ESI+) *m/z* calculated for $C_{13}H_{26}O_2$: $[M+H^+]$ theoretical *m/z* 213.1855 measured *m/z* 213.1854.

(rac)-2-(4-Hydroxy-4-isobutylcyclohexyl)propanoic acid (3)

Unpurified (*rac*)-diol **2** (7.01 g, ~33.4 mmol), $Na_2WO_4.2H_2O$ (1 mol%, 110 mg, 0.33 mmol) and methyltrioctylammonium hydrogen sulfate (1 mol%, 155 mg, 0.33 mmol) were charged to a large Radleys flask and the resultant reaction mixture stirred at 1000 rpm at rt. H_2O_2 (30 % aq, 11.3 mL, 100 mmol) was then added dropwise over 10 min and the reaction then heated to 90 °C for 2 h. A further portion of H_2O_2 (30 % aq, 5.6 mL, 50 mmol) was then added dropwise and the reaction mixture heated for a further 4 h. The reaction was then cooled to RT, the organic layer separated off and the aqueous layer extracted with Et_2O (2×15 mL). The combined organic fractions were then dried ($MgSO_4$) and solvent removed in vacuo to produce a crude solid that was recrystalised (EtOAc/hexane) to give (*rac*)-acid **3** (7.3 g, 32.0 mmol, 91 % over 2 steps from **1**). m.p. = 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.33$ (p, $J = 7.0$ Hz, 1H), 1.88–1.78 (m, 1H), 1.75–1.63 (m, 2H), 1.63–1.42 (m, 4H), 1.42–1.29 (m, 5H), 1.16 (d, $J = 7.0$ Hz, 3H), 0.95 ppm (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 181.0$, 71.5, 53.1, 44.8, 40.2, 37.4, 37.3, 26.2, 25.2, 24.5, 23.7, 14.0 ppm; IR: $\nu = 3424$, 2923, 1711, 1456, 1232, 954 cm^{-1}. HRMS (ESI+) *m/z* calculated for $C_{13}H_{24}O_3$: $[M\text{-}H^+]$ theoretical *m/z* 227.1647 measured *m/z* 227.1644.

(rac)-2-(4-Isobutylcyclohex-3-en-1-yl)propanoic acids 4 a/4 b

Following a modified literature procedure of Frija and Afonso,[33] Amberlyst-15 (dry) (1.64 g) was added to a stirred solution of (*rac*)-acid **3** (1.37 g, 6.0 mmol) in 100 mL of ethyl acetate at RT was added and the resulting mixture stirred for 16 h. The acidic resin was then filtered off and the solvent removed *in vacuo* to afford acids **4 a/4 b** as a colourless oil (1.20 g, 5.7 mmol, 95 %) that could be purified by column chromatography (20 % Et_2O in petrol) as desired or used directly in the next aromatisation step. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.35$ (s, 1H), 2.45–2.31 (m, 1H), 2.17–1.65 (m, 9H), 1.44–1.24 (m, 1H), 1.20 (t, $J = 7.0$ Hz, 3H), 1.06–0.89 (m, 1H), 0.86 ppm (t, $J = 6.4$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 182.74$, 182.68, 137.11, 136.90, 121.02, 120.87, 47.60, 44.83, 44.25, 36.77, 29.85, 28.59, 28.57, 28.39, 27.75, 26.12, 25.89, 22.86, 22.37, 22.35, 14.14, 14.12 ppm; IR: $\nu = 2953$, 2908, 1703 cm^{-1}. HRMS (ESI+) *m/z* calculated for $C_{13}H_{22}O_2$: $[M-H^+]$ theoretical *m/z* 209.1542 measured *m/z* 209.1546.

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(rac)-Ibuprofen

Method 1

Following a modified literature procedure of Iosub and Stahl:[34] A stirred solution of acids **4a**/**4b** (1.05 g, 5.0 mmol), $Pd(TFA)_2$ (80 mg, 0.25 mmol), sodium anthraquinone-2-sulfonate (310 mg, 1.0 mmol) and $MgSO_4$ (500 mg) in chlorobenzene (5.0 mL) was purged for 10 min with O_2 before being sealed under a balloon of O_2. The reaction mixture was heated for 24 h at 110 °C, then cooled and the mixture then purified directly using silica chromatography (10 to 30% Et_2O in petrol) to afford ibuprofen (885 mg, 4.3 mmol, 86%) as a white crystalline solid.

Method 2–One pot dehydration/aromatization procedure

Amberlyst-15 (dry) (1.30 g) was added to a stirred solution of acid **3** (1.06 g, 5.0 mmol) in chlorobenzene (5 mL) and the resulting mixture stirred at 50 °C for 1 h. The reaction was cooled to rt, acetic anhydride (1.1 mL, 11.5 mmol) then added and the reaction left to stir for a further 30 min. $Pd(TFA)_2$ (166 mg, 0.5 mmol) and sodium anthraquinone-2-sulfonate (620 mg, 2.0 mmol) were then added. The reaction mixture was then purged for 10 min with O_2 before being sealed under a balloon of O_2 and heated for 24 h at 110 °C. Upon cooling, the mixture was purified directly by silica gel chromatography (10 to 30% Et_2O in petrol) to afford ibuprofen (825 mg, 4.0 mmol, 80%) as a white solid. m.p. 76–79 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.30$ (m, 2H), 7.20–7.14 (m, 2H), 3.77 (q, $J =$ 7.1 Hz, 1H), 2.52 (d, $J = 7.1$ Hz, 2H), 2.00–1.84 (m, 1H), 1.57 (d, $J =$ 7.1 Hz, 3H), 0.97 ppm (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 181.5$, 140.9, 137.1, 129.5, 127.4, 45.2, 45.2, 30.3, 22.5, 18.2 ppm. Analytical data were in accordance with a commercial sample of ibuprofen (CAS: 15687-27-1).

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article. Deposition Number 2256121 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: terpenes · biorefinery · biomass · paracetamol · ibuprofen

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