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p-Menthadienes as Biorenewable Feedstocks for a Monoterpene-Based Biorefinery

*Joshua D. Tibbetts and Steven D. Bull**

A terpene-based biorefinery is described that uses crude sulfate turpentine (CST) and gum turpentine (GT) to produce mixtures of *p*-menthadienes (*p*-MeDs) as biorenewable terpene feedstocks. An acid catalyzed ring opening reaction (6 M aq. H_2SO_4, 90 °C) is first used to convert the major bicyclic monoterpenes (α-pinene, β-pinene, and 3-carene) in untreated CST (or GT with 5 mol% Me_2S) into mixtures of monocyclic *p*-MeDs. These unpurified sulfurous *p*-MeD mixtures (α-terpinene, γ-terpinene, and isoterpinolene) are then used as feedstocks for oxidative aromatization (OA), ozonolysis, Diels–Alder, and hydrogenation reactions to produce *p*-cymene, fragrances, anti-oxidants, drugs, biopolymers, and biofuels. Mechanistic studies of the OA reaction used to convert the *p*-MeDs into *p*-cymene reveal that *p*-cymene hydroperoxide acts as an initiator to produce polar radical intermediates that are stabilized by DMSO generated in situ through aerobic oxidation of Me_2S. This enables CST and GT to be converted into biorenewable *p*-cymene in 50–60% yields (two steps) using a process that only requires aqueous acid, oxygen, heat, and a final distillation step.

1. Introduction

The International Energy Agency has defined a biorefinery as "the sustainable processing of biomass into a spectrum of marketable products and energy."[1] Any kind of biomass can be used in principal, including forestry and agricultural by-products, aquaculture sources, and industrial/household waste. The aim of any biorefinery is to use sustainable processes to transform these biorenewable feedstocks into a wide range of value-added chemical products, such as fragrances, flavorings, polymers, and biofuels, that are currently obtained from non-renewable petrochemical sources. This transition to a biobased chemical industry means that new biorefining technologies for the upgrading of biomass into biofuels and platform chemicals will need to be developed and integrated into new/existing chemical processes.[2] The large volumes and wide geographical distribution of lignocellulosic biomass means that it will undoubtedly play a key role as a biorenewable feedstock for bulk chemical production.[3] In this approach, fermentative processes are used to depolymerize lignocellulose biomass into sugars (e.g., glucose and fructose), with these monomers then transformed into low-value feedstocks such as bioethanol, succinic acid, glutamic acid, and 5-hydroxymethylfurfural.[4] Although highly promising, technological difficulties associated with large-scale catalytic upgrading of these highly oxygenated biopolymers cause significant problems that still need to be overcome before lignocellulose-based biorefineries become more widely established.[5]

Monoterpenes (and monoterpenoids) represent an alternative biomass source for the production of biofuels, polymers, and chemicals that are available in significant volumes at low cost. Significant amounts of commercially available monoterpenes are currently produced as products and waste from the forestry and agricultural industries, all of which can be considered as potentially useful biorenewable feedstocks for fuel and chemical production. These include turpentine (≈360 000 tonnes pa), limonene-containing citrus oil (≈30 000 tonnes pa), menthol-containing mint oil (≈20 000 tonnes pa), and 1,8-cineole from eucalyptus oil (≈7000 tonnes pa with an estimated multimillion tonne production potential per annum).[6] The structures of these energy-dense, lightly oxygenated, alkene-containing C_{10} building blocks more closely resemble those of petroleum-based hydrocarbons, which means they can potentially be catalytically upgraded using existing refining technologies to produce a wide range of chemical products (including aromatics).

Crude sulfate turpentine (CST) is the cheapest and most widely available source of monoterpene biomass, with around 260 000 tonnes of CST produced as a waste by-product of the paper industry annually. High pressure cooking of wood chips to produce paper pulp in the Kraft process generates around 15 kg of CST per tonne of pulp,[7] which is comprised of a mixture of monoterpenes and around 5% volatile sulfur compounds (e.g., Me_2S).[6a] A further annual 100 000 tonnes of pinene-rich gum turpentine (GT) is also produced through sustainable tapping of the trunks of living trees. The major monoterpene components of turpentine are α-pinene, β-pinene, 3-carene, and limonene, along with small amounts of camphene and C_{15}

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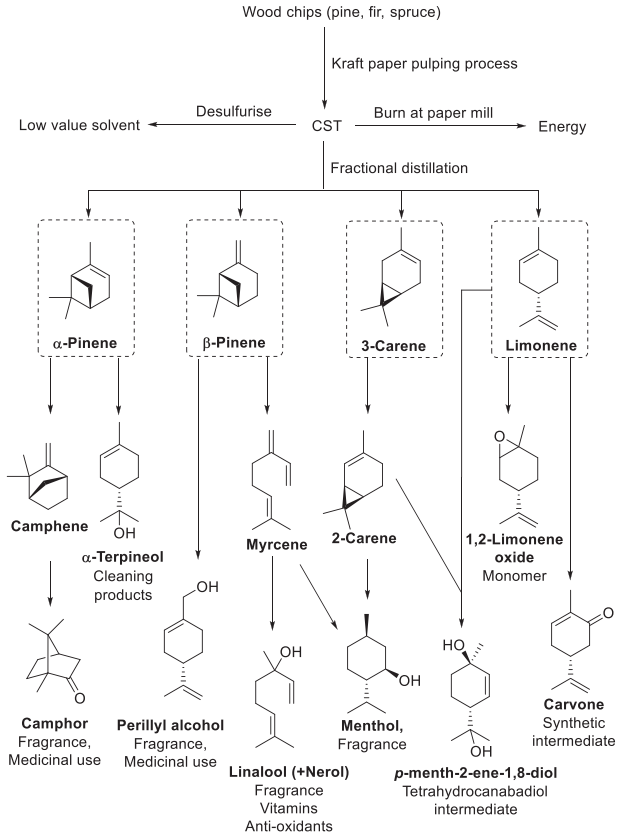


Figure 1. Major uses of CST for the production of solvent, biofuels, and commercially important flavors and fragrances.

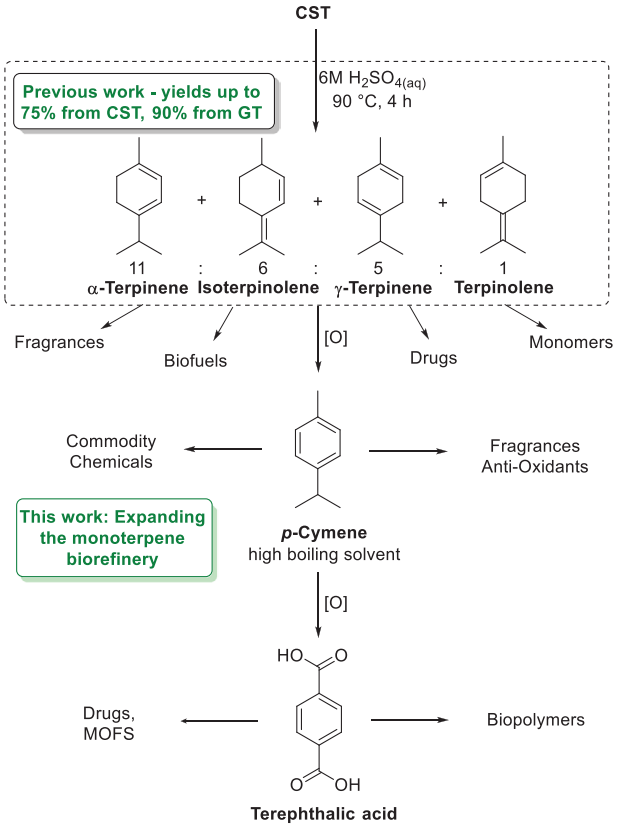


Figure 2. Terpene biorefinery model based on sequential conversion of CST into *p*-MeDs, *p*-cymene, and terephthalic acid that are then used as feedstock intermediates for the synthesis of a wide range of biofuels, biopolymers, and biorenewable chemical products.

sesquiterpenes, with turpentine composition dependent on its geographical origin.[6] Currently, CST and GT are either distilled into their individual monoterpene components for use as biorenewable feedstocks by the flavor/fragrance industries, or used in their unfractionated form as cheap solvents or biofuels (**Figure 1**).[6,7]

The number of commercial products (e.g., menthol and camphor) that can be produced from these purified monoterpene fractions is impressive (Figure 1). In addition, many recent reports of new methodologies for catalytic upgrading of purified monoterpene feedstocks could be used to expand the potential of a future terpene-based biorefinery. These include metal-catalyzed hydroalkylation reactions of alkene bonds,[8a] photocatalytic arylation of allylic sp^3 C−H bonds,[8b] electrochemical allylic oxidation (e.g., α-pinene to verbenone),[8c] and catalytic allylic C−H amination reactions.[8d] Although not yet applicable industrially, these promising transformations could potentially be employed to generate valuable products with high molecular complexity from purified monoterpene feedstocks.

However, there are still significant operating costs associated with the distillative processes required to fractionate CST into its individual monoterpene components. Furthermore, the sulfur contaminants present in CST can interfere with catalytic processes used to upgrade monoterpene feedstocks, with the oxidative desulfurization processes required to remove these sulfur impurities adding costs to the overall process. Therefore, the availability of sulfur-tolerant processes that enable untreated commercial sulfurous CST to be transformed into value-added chemical products would be potentially useful for further establishing the commercial viability of monoterpene-based biorefineries.

We have recently reported the development of a process to convert the major bicyclic monoterpenes (α-pinene, β-pinene, and 3-carene) in CST into sulfurous mixtures of *p*-menthadienes (*p*-MeDs) as a potential biorenewable monoterpene feedstock for synthesis. This organic solvent-free process involves heating CST with 6 M aq. H_2SO_4 (recyclable) at 90 °C for 4 h which results in acid-catalyzed ring opening (ACRO) of its bicyclic terpene components to afford 70–75% yields of *p*-MeD mixtures (α-terpinene, γ-terpinene, and isoterpinolene) and around 20–25% terpene oligomers (**Figure 2**). These studies revealed that the Me_2S present as a contaminant in CST[6a] was critical for achieving good yields of *p*-MeDs, which led us to add 5 mol% Me_2S to ACRO reactions of GT, which resulted in >80% yields of *p*-MeD mixtures.[9]

Other biorenewable *p*-MeD sources that could potentially be used as feedstocks for a monoterpene biorefinery include limonene that is available from citrus oil (waste by-product of peel from the citrus juice industry), or *p*-MeD mixtures available from ACRO/dehydration reactions of 1,8-cineole (major component of eucalyptus oil). Importantly, *p*-MeD mixtures

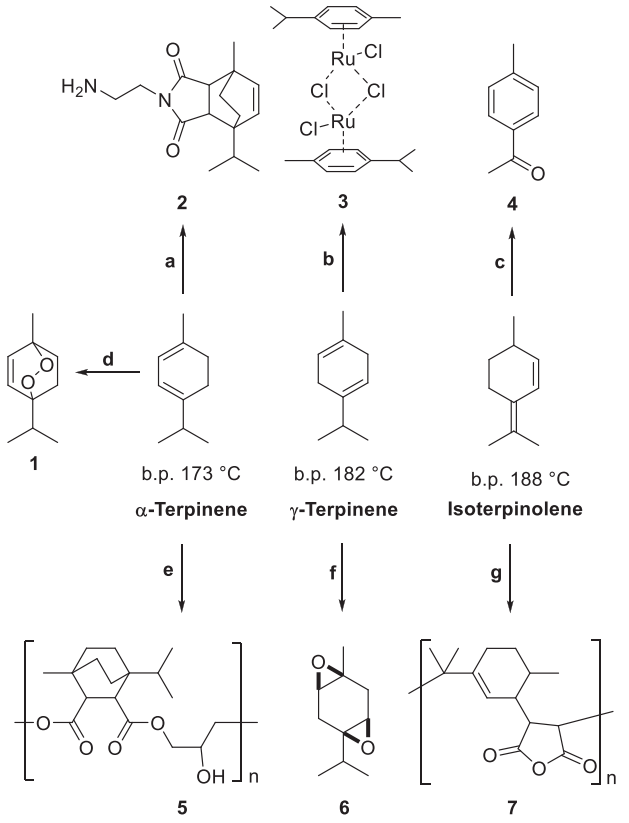


Figure 3. Selected transformations of α-terpinene, γ-terpinene, and isoterpinolene. Conditions:[12b,14] a) Maleic anhydride, 140 °C; then $NH_2CH_2CH_2NH_2$, EtOH; b) $RuCl_3$, MeOH; c) O_2, DMSO, 100 °C; d) *hν*, O_2, MeOH, rose bengal; e) See ref. [14e]. f) $PW_4O_{24}[PTC]_3$ (1%), 30% aq. H_2O_2; g) maleic anhydride, AIBN, toluene, 75 °C See ref. [12b].

are also produced as waste by-products of industrial processes used to convert turpentine (and α-pinene) feedstocks into commercially valuable α-terpineol (pine-oil fragrance) or camphene (camphor precursor) products. These mild acid-catalyzed hydration (α-terpineol) and rearrangement (camphene) reactions invariably produce monoterpene mixtures containing 30–40% *p*-MeDs as major side-products.[10] These low-value *p*-MeD mixtures are currently sold as technical grade dipentene for solvent and cleaning applications, or fractionally distilled into their individual monoterpene components (limonene, terpinolene, α-terpinene, and γ-terpinene).[6]

The plentiful supply of *p*-MeD mixtures from a number of different cheap biomass sources clearly affords an opportunity to develop processes to diversify the range of commercial products available from a terpene biorefinery. Consequently, this study now describes how unpurified mixtures of sulfurous *p*-MeDs generated from the ACRO reaction of CST (most abundant monoterpene feedstock) can be used to produce a range of biorenewable fragrances, drugs, polymers, and biofuels. The approach taken involves establishing a series of transformations (CST→*p*-MeDs→*p*-cymene→terephthalic acid) that could function as the central spine of a multilevel biorefinery that could be used to produce a wide range of value-added chemical products. This approach would enable the volumes of products produced in these multilevel processes to be varied in response to demand, thus providing operational flexibility and greater economic viability to the monoterpene biorefining process (Figure 2).

2. Results and Discussion

2.1. Existing Processes for Converting Crude Sulfate Turpentine-Derived *p*-Menthadienes Mixtures into Valuable Chemical Products

Separation of the mixtures of *p*-MeDs (α-terpinene [b.p. 173 °C], γ-terpinene [b.p. 182 °C], and isoterpinolene [b.p. 188 °C][11]) produced in the ACRO reactions of CST and GT by fractional distillation is challenging, with impure fractions often requiring multiple redistillations to produce pure *p*-MeD products in low yield. Nevertheless, reports have described the successful use of fractional distillation, spinning band distillation, and preparative gas chromatography to fractionate these type of *p*-MeD mixtures into their pure components.[12,13] Efficient fractionation of ACRO generated *p*-MeD mixtures on an industrial scale would produce large volumes of α-terpinene and γ-terpinene to complement existing sources that are currently available as by-products from industrial processes used to generate α-terpineol and camphene.[10] Potential value-added products that can be prepared from α-terpinene include ascaridole **1** (anthelmintic), the Diels–Alder product **2** (fungicide), and the terpene polyester **5**, whilst γ-terpinene can be used to prepare ruthenium complex **3** (catalyst precursor) and bis-epoxide **6** (monomer for ring-opening polymerization) (see **Figure 3**).[14]

Access to significant quantities of pure isoterpinolene would provide a new bulk monoterpene feedstock for production of new types of biorenewable products. Promisingly, >50 g of pure isoterpinolene has been obtained in 11% overall yield through fractional distillation (atmospheric pressure) of a 5:3:1 mixture of α-terpinene, isoterpinolene, and γ-terpinene generated from a base-catalyzed isomerization reaction of (*rac*)-limonene.[13] Potential uses for isoterpinolene include its conversion into the important bulk chemical *p*-methylacetophenone **4** or its use as a monomer for copolymerization with maleic anhydride to afford biorenewable terpene polymers such as **7**.

Hydrogenation strategies have also been developed to fractionate *p*-MeD mixtures, with nickel catalysts used to selectively reduce the diene fragments of the α-terpinene and isoterpinolene fractions to produce mixtures of *p*-menth-3-ene and unreacted γ-terpinene that are easier to separate by fractional distillation.[15] *p*-Menth-3-ene (also sourced from 3-carene)[16] has previously been used for the industrial synthesis of 200 tonnes of menthol,[17] thus demonstrating the potential of using *p*-MeD mixtures for the industrial production of a commercially important flavor/fragrance molecule (**Figure 4**).

Building on this precedent, we wanted to demonstrate that the unfractionated mixture of sulfurous *p*-MeDs generated by the ACRO reactions of CST (and cineole and GT) could be used to generate a wider range of chemical targets. These new protocols would also be applicable to transform low-value *p*-MeD mixtures available as by-products of other industrial processes into value-added products (vide supra). Therefore, we now describe a series of transformations that can be used

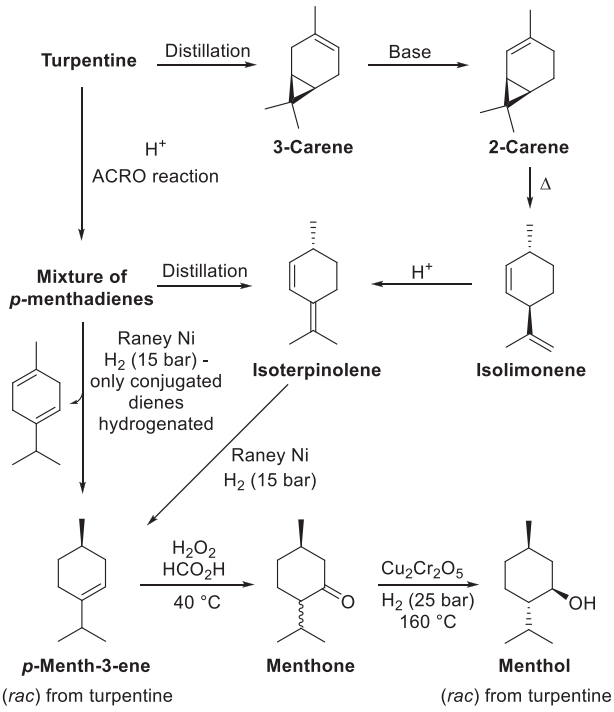


Figure 4. Divergent industrial routes from turpentine to menthol that proceed through a common *p*-menth-3-ene intermediate.

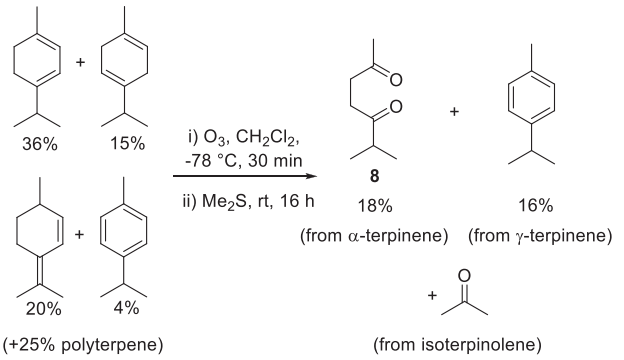


Figure 5. Ozonolysis of the sulfurous mixture of *p*-MeDs produces 6-methylheptan-2-5-dione (**8**), *p*-cymene and acetone.

to transform untreated sulfurous mixtures of *p*-MeDs generated in ACRO processes into a range of low-volume, high-value products (e.g., flavors and drugs), and high-volume, low-value bulk chemicals (e.g., biofuels and biopolymers). The crude sulfurous *p*-MeD mixtures that have been used as feedstocks in these transformations are unpurified crude reaction products obtained from ACRO reactions of CST that contain ≈75% *p*-MeDs and ≈25% soluble terpene oligomers. Therefore, all product yields are quoted relative to the theoretical amount of *p*-MeD available for transformation (e.g., 75%), and do not consider the terpene oligomers (e.g., 25%) content that is present as ballast in these reactions.

2.2. Ozonolysis of Sulfurous *p*-Menthadienes Mixtures to Afford 6-Methylheptan-2,5-Dione and *p*-Cymene

Previous reports on the ozonolysis of α-terpinene and γ-terpinene have focused on atmospheric studies investigating their degradation kinetics and/or the structure of the ozonides formed. Ozonolysis of the diene fragment of α-terpinene has been reported to afford cyclic peroxide intermediates (e.g., 1,2-dioxines) that are further oxidized to multiple products (including small amounts of 6-methylheptan-2,5-dione **8**) on work-up.[18] No synthetically useful reports of the ozonolysis of γ-terpinene have been described, with multiple ozonolysis pathways leading to complex mixtures of low molecular weight products.[19] A few isolated reports of low-yielding ozonolysis of isoterpinolene have been reported, with mono-ozonolysis protocols affording (*R*)-4-methyl-2-cyclohexen-1-one and di-ozonolysis protocol affording (-)-α-methyl glutaric acid after oxidative work-up with CrO_3.[20] Therefore, whilst recognizing that ozonolysis of the mixtures of sulfurous *p*-MeDs might be problematic and low yielding, we reasoned that it would provide a practically scalable method of producing a range of synthetically useful oxygenated products.

Ozonolysis of the sulfurous *p*-MeD mixture with excess O_3 in CH_2Cl_2 at –78 °C for 30 min, followed by reductive work-up with Me_2S, led to a crude product that was purified by chromatography to give 6-methylheptan-2,5-dione **8** in 18% yield and *p*-cymene in 16% yield (**Figure 5**). Ozonolysis of a pure sample of α-terpinene produced 1,4-diketone **8** in 60% yield, thus indicating that ozonolysis of the 36% α-terpinene fraction of the *p*-MeD mixture is responsible for production of 1,4-diketone **8** in 50% theoretical yield. Previous reports have described that ozonolysis of unconjugated cyclohexadienes results in oxidative aromatization (OA) reactions to produce aromatic products such as *p*-cymene. We found that ozonolysis of pure γ-terpinene produced *p*-cymene in 68% yield,[21] thus confirming that ozonolysis of the γ-terpinene fraction (15%) present in the *p*-MeD mixtures is likely to be responsible for its origin. The starting mixture of sulfurous *p*-MeDs contains 15% γ-terpinene and 4% *p*-cymene, meaning that *p*-cymene is formed in this ozonolysis reaction in 87% theoretical yield. Although acetone was seen in the ^{1}H NMR spectrum of the crude ozonolysis product of the sulfurous *p*-MeDs (no work-up), no resonances corresponding to oxidative cleavage products (e.g., 4-methyl-2-cyclohexen-1-one or 2-methyl-pentanedial) that might be expected from the isoterpinolene fraction were detected.[22]

The two major components (b.p. of 1,4-diketone **8** = 220 °C; b.p. of *p*-cymene = 177 °C) present in the crude product of the ozonolysis reaction could be easily purified by fractional distillation at atmospheric pressure. In terms of synthetic utility, 6-methylheptan-2,5-dione **8** is a potentially useful building block for five-membered heterocyclic synthesis, having previously been used to prepare medicinally active pyrroles **9**/**10** (via Paal–Knorr reactions) that exhibit hypocholesterolemic and radioprotective activities (**Figure 6**).[23] Alternatively, 1,4-diketone **8** has be used as an intermediate for the synthesis of *trans*-sabinene hydrate **11**, which is a commercially desirable fragrance compound.[24] The lower value *p*-cymene coproduct has multiple industrial uses (vide infra). Therefore, whilst this ozonolysis process is low-yielding, it cleanly converts the unfractionated sulfurous

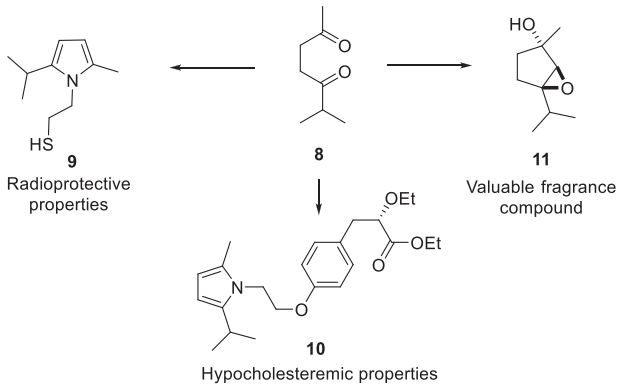


Figure 6. Uses of α-terpinene-derived ozonolysis product 6-methylheptan-2,5-dione (**8**) for the synthesis of medicinally active and fragrance compounds.

mixture of *p*-MeDs into three products (ketone **8**, *p*-cymene, and acetone) that can be easily separated by fractional distillation on a large scale.

2.3. Diels–Alder Reaction of the α-Terpinene Fraction of Sulfurous *p*-Menthadienes Mixtures with Maleic Anhydride

The α-terpinene fraction of the sulfurous mixture of *p*-MeDs contains a *cis*-configured diene fragment that can undergo a Diels–Alder cycloaddition reaction with an appropriate dienophile. This Diels–Alder reactivity profile has been exploited previously to remove minor α-terpinene contaminants from impure isoterpinolene fractions through its reaction with maleic anhydride to afford a more easily separable cycloadduct **12**.[12c] Furthermore, a recent report has described that treatment of limonene with I_2 at 180 °C afforded an interconverting mixture of *p*-MeDs whose α-terpinene component was reacted with maleic anhydride to afford a bicyclic Diels–Alder adduct **12** in 77% yield.[25] Consequently, we decided to investigate whether these iodine mediated alkene isomerization conditions could be applied to convert our sulfurous mixture of *p*-MeDs into cycloadduct **12**.

Solvent-free treatment of the mixture of sulfurous *p*-MeDs with maleic anhydride (1.4 eq.) in the presence of 0.05 mol% I_2 at 180 °C resulted in clean formation of endo-adduct **12** in 83% isolated yield (**Figure 7**). Since the fraction of α-terpinene present in the starting mixture of *p*-MeDs was 48%, this meant that the iodine was effectively catalyzing isomerization of the alkene bonds of the *p*-MeDs in the presence of the sulfur impurities. The cycloadduct **12** produced in this Diels–Alder reaction has a number of uses, including its use as an effective curing agent for the production of biorenewable epoxy resins that is currently sold under the trade name JERCure YH309. It has also been used in block copolymerization reactions with various epoxides to afford a range of alternating polyesters **13** with narrow polydispersities and good thermal/mechanical properties.[26] Alternatively, reaction of cycloadduct **12** with amines enables access to medicinally active maleimides **14–16**, that have been shown to have promising antifungal and anticancer properties, whilst diester derivatives exhibit strong insect larvicidal activity.[14a,27,28]

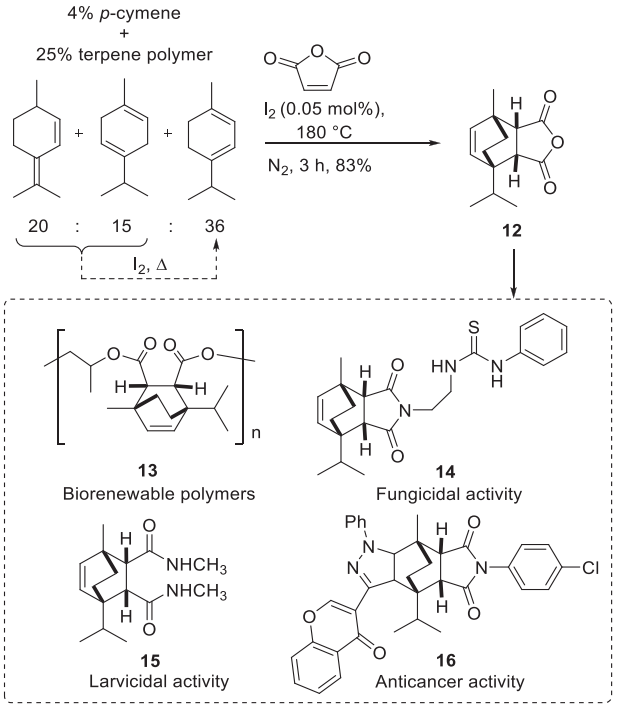


Figure 7. I_2-mediated isomerization of the mixture of sulfurous *p*-MeDs, whose α-terpinene component undergoes Diels–Alder reaction with maleic anhydride to afford endo-cycloadduct (**12**) that can be transformed into a range of biopolymers and medicinally active products.[14a,26–28]

2.4. Hydrogenation of Desulfurized *p*-Menthadienes Mixtures to Afford a Mixture of *p*-Menthane and *p*-Cymene as a Potential Biofuel

We next explored the potential of globally hydrogenating the alkene bonds of *p*-MeD mixtures from the ACRO reaction of CST to afford *p*-menthane which has considerable potential as a biofuel.[29] For example, *p*-menthane has been used previously as a biorenewable diesel fuel additive to produce 10% fuel blends whose combustion performance and low soot levels satisfy the regulatory standards required for transportation fuel emissions.[30] *p*-Menthane blends have also been reported as promising biorenewable high energy jet fuel additives in a number of patents and academic studies.[31]

Initial experiments focused on identifying conditions for the hydrogenation of a non-sulfurous "mock" sample of *p*-MeDs containing a 4:3:3 mixture of α-terpinene, γ-terpinene, and terpinolene (commercially available substitute for isoterpinolene) using 10 mol% Pd/C at room temperature in hexane under 1 atmosphere of H_2. This hydrogenation reaction gave a mixture of *p*-menthane and *p*-cymene in a 3:1 ratio in 79% isolated yield.[32] Attempts to carry out solvent-free hydrogenation reactions were less successful, leading to lower yields of a 1:2 mixture of *p*-menthane and *p*-cymene in the statistical ratio expected from a classical disproportionation reaction. The loadings of the Pd catalyst were then lowered to reduce the amount of *p*-cymene produced through disproportionation,[32] with dropwise addition of a degassed "mock" mixture of *p*-MeDs to a prestirred suspension of 2.5 mol% Pd/C in hexane

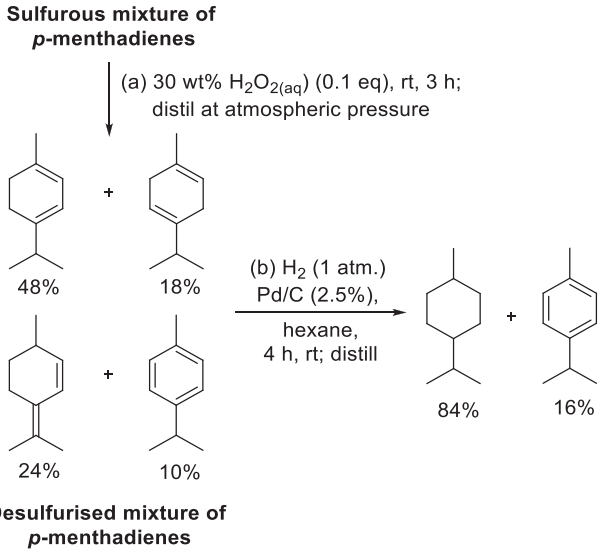


Figure 8. a) Desulfurization of mixtures of *p*-MeDs from the ACRO reaction of CST b) Hydrogenation of desulfurized *p*-MeDs to afford a biofuel containing an 84:16 ratio of p-menthane and *p*-cymene.

under 1 atmosphere of H_2 producing an improved 9:1 mixture of *p*-menthane and *p*-cymene in 76% isolated yield.

As expected, attempts to apply these hydrogenation conditions to our crude sulfurous mixture of *p*-MeDs (from an ACRO reaction of CST) proved unsuccessful, resulting in poor yields of hydrogenated products caused by rapid poisoning of the palladium catalyst by the sulfur impurities. Accordingly, the mixture of sulfurous *p*-MeDs was desulfurized by stirring it with 30 wt% aq. H_2O_2 (0.1 eq.) for 3 h at rt, followed by washing with water to remove oxidized sulfur products (e.g., DMSO) and distilling the residue at atmospheric pressure. This oxidative pretreatment process resulted in a "sulfur-free" *p*-MeD mixture that contains a 48:18:24:10 mixture of α-terpinene, γ-terpinene, isoterpinolene, and *p*-cymene. Pleasingly, this *p*-MeD mixture could then be reproducibly hydrogenated using 2.5 mol% Pd/C and 1 atmosphere H_2 to afford a 84:16 mixtures of *p*-menthane and *p*-cymene in 70–75% yields (**Figure 8**) after fractional distillation to remove the hexane solvent (recyclable).

Mixtures of *p*-menthane (b.p. 168 °C) and *p*-cymene (b.p. 177 °C) can be separated through azeotropic or extractive distillation processes,[33] with pure *p*-menthane useful as a green solvent for cleaning applications[34] and natural product extraction,[35] as well as for the production of *p*-menthane hydroperoxide as an initiator for polymerization reactions.[36] Importantly, combining the low soot combustion properties of *p*-menthane with the greater engine seal compatibility of aromatic *p*-cymene (minimum of 8% aromatic content required for good seal compatibility for military jet fuel specifications) means that use of unfractionated mixtures of *p*-menthane and *p*-cymene as biofuel blends is also potentially attractive.[37] Furthermore, the ratio of *p*-menthane:*p*-cymene produced in these hydrogenation reactions can potentially be varied by changing catalyst loadings/H_2 pressure levels and process conditions, thus providing a potentially attractive method for fine-tuning its fuel properties for different automotive/aviation applications.[38]

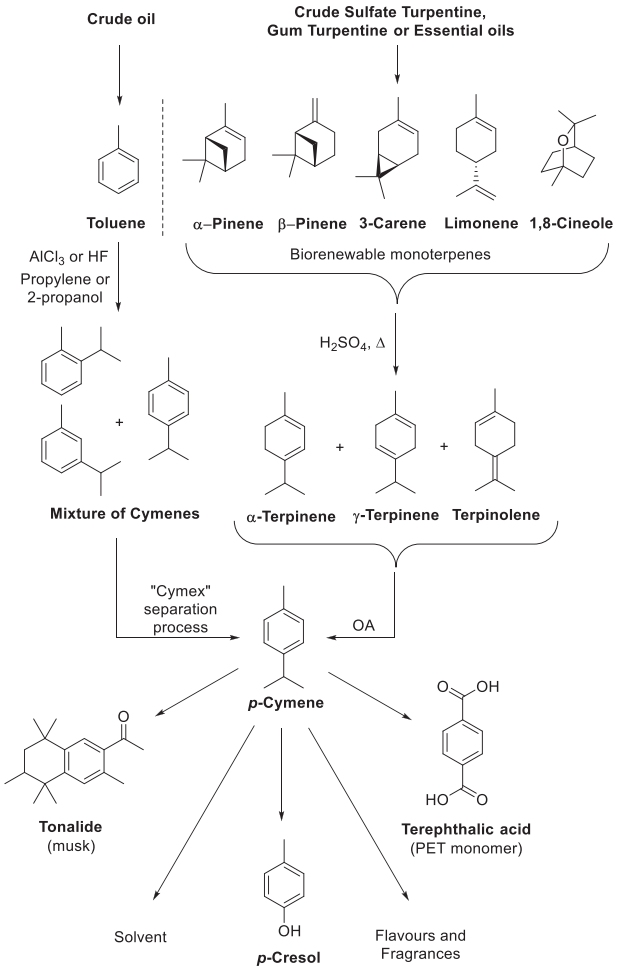


Figure 9. Synthetic routes used to convert toluene and biorenewable monoterpene feedstocks into *p*-cymene that has various commercial applications.

The development of a simple H_2O_2 mediated desulfurization method that enables the *p*-MeD mixture to be used in a palladium catalyzed hydrogenation reaction is particularly noteworthy, since this pretreatment process should enable other types of transition metal catalyzed reaction (e.g., rhodium-catalyzed hydroformylation) to be used to catalytically upgrade this cheap source of *p*-MeDs.

2.5. Oxidative Aromatization Reactions to Transform Sulfurous *p*-Menthadienes Mixtures into *p*-Cymene

Our attention then turned to establishing the spine of the terpene biorefinery by developing scalable conditions that would enable the mixture of sulfurous *p*-MeDs to be converted into synthetically versatile *p*-cymene. This commodity chemical is commonly used as a high boiling solvent and synthetic precursor to produce *p*-cresol and various flavor and fragrance compounds (musks). It has also been proposed as a replacement biorenewable feedstock for *p*-xylene for the synthesis of "green" terephthalic acid for PET production (**Figure 9**).[39]

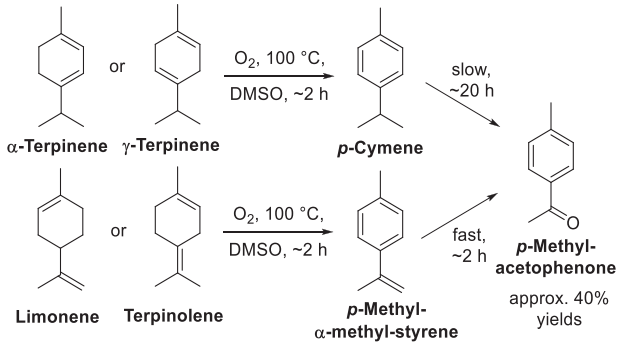


Figure 10. OA reaction of various *p*-MeDs using O_2 in DMSO at 100 °C.[14c]

p-Cymene is currently produced on a kilotonne scale through Friedel–Crafts alkylation of toluene with propylene or 2-propanol using acid catalysts (e.g., $AlCl_3$ and HF), sometimes in stoichiometric amounts. This process produces mixtures of *para*- and *meta*-cymene isomers that then need to be separated using the Cymex process using an energy intensive route that generates significant amounts of waste.[40] Therefore, a more sustainable, economically competitive method to produce isomerically pure, biorenewable *p*-cymene from CST would be highly beneficial.

Many reports have described OA reactions of limonene to produce *p*-cymene, with other two-step processes employing *p*-MeDs feedstocks generated from ACRO reactions of terpene feedstocks (e.g., α-pinene, cineole) (see Table S1, Supporting Information, for details). A number of these OA processes employ transition metal-catalyzed methods[41] that are unsuitable for transforming untreated sulfurous mixtures of *p*-MeDs. Other methods employ relatively expensive zeolite catalysts and high temperatures/pressures,[42] or require the use of stoichiometric amounts of reagents/additives such as metallic sodium, iodine, DDQ, and $FeCl_3$ that were unsuited to our needs.[43] Scalable aerobic protocols are widely used for the controlled catalytic oxidation of petrochemical feedstocks to produce value-added chemicals (e.g., terephthalic acid, ethylene oxide, phenol, and *p*-cresol) on multitonne scales.[44] Therefore, we decided to develop a simple aerobic OA approach to convert our untreated mixtures of sulfurous *p*-MeDs into *p*-cymene. Harlin and coworkers have previously described that bubbling air through γ-terpinene at 120 °C for 27 h gave *p*-cymene in 81% yield, whilst flow reaction of γ-terpinene under 30 bar of air at 250 °C gave a 77% yield of *p*-cymene in 6 h.[42b] However, we found that bubbling oxygen through crude sulfurous *p*-MeD mixtures at 120 °C for 4 h gave large amounts of viscous oligomeric material, with <10% yield of *p*-cymene being produced. Some success was achieved by repeating these aerated reactions using modified clays (montmorillonite[45] or sepiolite[42a]) as additives in reactions at 100–140 °C for 6 h, which gave 30–40% isolated yields of *p*-cymene. However, all of these OA reactions produced significant amounts of terpene oligomers, as well as *p*-menthane and *p*-menth-3-ene by-products.

A comprehensive review of the literature revealed a promising report by Matsubara and coworkers who reported that heating *p*-MeD mixtures under O_2 in polar solvents such as DMSO or DMF resulted in clean OA reactions.[14c] Importantly, α-terpinene and γ-terpinene were reported to aromatize to

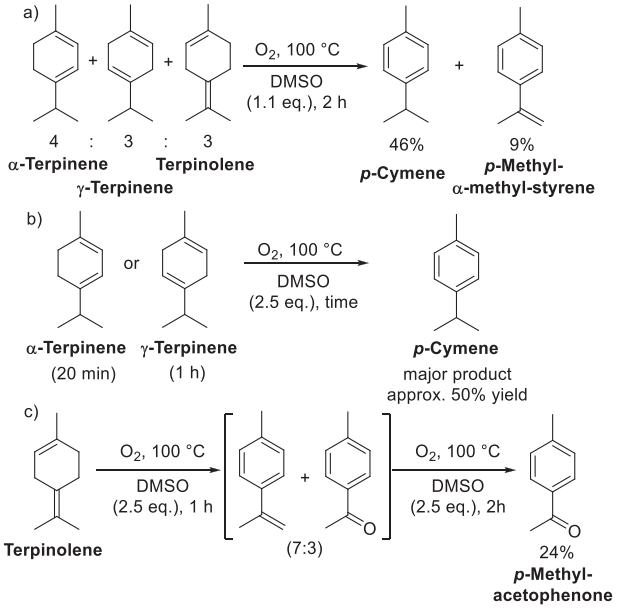


Figure 11. DMSO-mediated OA reactions of *p*-MeDs using O_2 in DMSO at 100 °C: a) Aromatization of a "mock" mixture of *p*-MeDs affords 46% *p*-cymene and 9% *p*-methyl-α-methylstyrene. b) OA of α-terpinene or γ-terpinene affords *p*-cymene. c) OA of terpinolene (exocyclic alkene) affords a 7:3 mixture of *p*-methyl-α-methylstyrene and *p*-methylacetophenone that is then oxidized to *p*-methylacetophenone.

produce *p*-cymene, whilst *p*-MeDs containing exocyclic alkene bonds (e.g., limonene or terpinolene) produced *p*-methyl-α-methyl-styrene that was rapidly oxidized to *p*-methylacetophenone (**Figure 10**). Repeating these conditions by bubbling O_2 through a "mock" *p*-MeD sample in 1.1 eq. DMSO at 100 °C for 2 h produced a crude product containing a 5:1 mixture of *p*-cymene and *p*-methyl-α-methylstyrene (see Supporting Information) in a combined 55% yield (**Figure 11**a). OA of pure *p*-MeDs under similar conditions (O_2, 100 °C, 2.5 eq. DMSO) confirmed that α-terpinene (20 min) and γ-terpinene (1 h) produced *p*-cymene, whilst terpinolene (commercial substitute for isoterpinolene) afforded a 7:3 mixture of *p*-methyl-α-methylstyrene and *p*-methyl acetophenone after 1 h (Figure 11c).

The ability to produce *p*-cymene, *p*-methyl-α-methylstyrene, and *p*-methylacetophenone in these oxidation reactions is potentially valuable from a terpene biorefinery perspective, as each of these biorenewable aromatic products could potentially be used for chemical production on an industrial scale. Oxidation in air under similar conditions led to similar product ratios but extended reaction times (100 °C, >6 h). These conditions may be preferred industrially as an alternative to using a pure O_2 atmosphere that can produce an explosion hazard in combination with volatile organic compounds.[46]

A brief solvent screen (EtOH, CH_3CN, and EtOAc) revealed that *p*-cymene (1 eq.) could be used as a replacement solvent for DMSO in these oxidation reactions, with the "mock" *p*-MeD mixture being oxidized (100 °C, 2 h) to afford a 39% yield of *p*-cymene (**Figure 12**a). This promising result was consistent with the good solubility of O_2 in *p*-cymene (1.4×10^{-3} mole fraction of O_2),[47] as well as its ability to produce *p*-cymene hydroperoxide as a radical initiator of these OA reactions.[48]

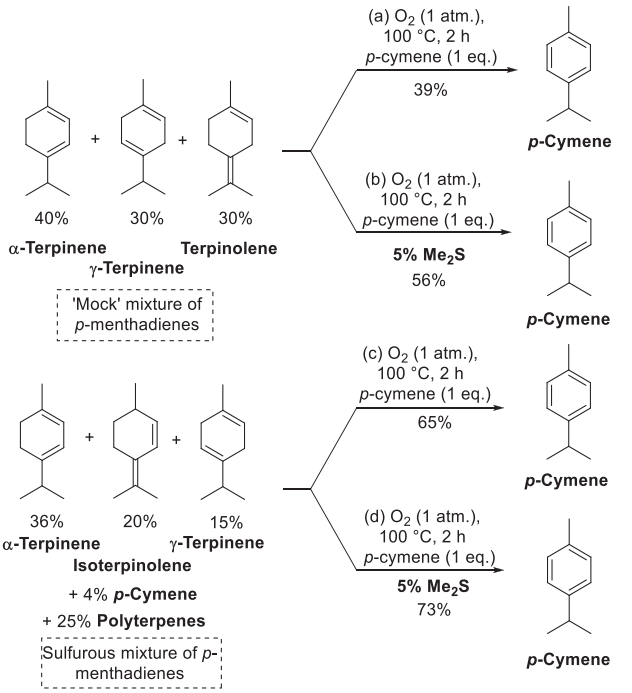


Figure 12. a) OA of a "mock" sample of *p*-MeDs using *p*-cymene as solvent. b) OA of a "mock" mixture of *p*-MeDs using 5 mol% Me_2S and *p*-cymene as solvent. c) OA of a sulfurous mixture of *p*-MeDs using *p*-cymene as solvent. d) OA of a sulfurous mixture of *p*-MeDs using 5 mol% Me_2S and *p*-cymene as solvent.

Although the use of *p*-cymene as a solvent gave slightly lower overall yields of *p*-cymene (product) than when DMSO was used as solvent, it gave a much cleaner reaction profile with no *p*-methyl-α-methylstyrene or *p*-methylacetophenone by-products present, even after extended reaction at 100 °C. This increase in selectivity resulted in a much simpler reaction work-up, enabling simple flash distillation of the crude product at atmospheric pressure to be used to isolate *p*-cymene in >95% purity.

Applying these oxidative reaction conditions (1 eq. *p*-cymene, 100 °C, 2 h) to an unpurified mixture of sulfurous *p*-MeDs (containing 25% terpene oligomers) gave a significantly higher 65% yield of *p*-cymene (Figure 12c) than observed for the corresponding OA reaction of the "mock" sample of *p*-MeDs, which only gave a 39% yield of *p*-cymene (Figure 12a). The only difference between the "mock" and sulfurous samples of *p*-MeDs was the substitution of isoterpinolene by commercial terpinolene in the "mock" sample, which we reasoned was unlikely to cause the large differences in *p*-cymene yield. This led us to suspect that Me_2S might be playing a key role in increasing the yield of *p*-cymene in the OA reaction of the sulfurous *p*-MeD mixture.

This hypothesis was confirmed by repeating the OA reaction of a "mock" sample of *p*-MeDs doped with 5 mol% Me_2S, which resulted in an increase in yield of *p*-cymene from 39% (no Me_2S) to 56% under otherwise identical conditions (Figure 12b). ^{1}H NMR spectroscopic analysis of the crude product produced from the Me_2S-catalyzed OA reaction of the "mock" mixture of *p*-MeDs revealed the presence of DMSO. Bubbling O_2 through a solution of Me_2S in *p*-cymene (100 °C) only resulted in small amounts of DMSO (≈3%) and *p*-cymene hydroperoxide (≈0.2%) being formed after 1 h.[49] However, aerobic OA reactions of cyclic dienes are known to produce H_2O_2 as a by-product,[50] and we found that stirring 1 eq. of Me_2S with 3 eq. of aq. H_2O_2 in *p*-cymene at rt resulted in its rapid transformation to DMSO. Examination of the crude products of larger scale *p*-MeD OA reactions revealed the presence of visible amounts of water, whose formation implied that H_2O_2 had been generated in these OA reactions (vide infra). Therefore, it is proposed that H_2O_2 generated in the early stages of these OA reactions oxidizes DMS to DMSO, which then acts as a polar cosolvent to stabilize the polar radical intermediates that are required to produce improved yields of *p*-cymene.

It appears that the lower concentration of DMSO (max 5 mol%) generated in these OA reactions is sufficient to promote formation *p*-cymene, but insufficient to enable formation of *p*-methyl-α-methylstyrene (or *p*-methyl-acetophenone) that are generated when DMSO is used as a solvent (*cf* results in Figures 11 and 12). This mechanistic rationale was confirmed by adding 5 mol% Me_2S (or 5 mol% DMSO) to the OA reactions of the "mock" and sulfurous samples of the *p*-MeDs in *p*-cymene at 100°C, which both gave higher yields (up to 75%) of *p*-cymene after 2 h. The 8% increase in yield observed in the OA reactions of the sulfurous *p*-MeD mixtures (cf Figure 12c and 12d) originating from CST is likely to be due to replenishment of Me_2S levels to ≥5 mol% to replace losses that occur in the preceding ACRO step of CST. Addition of >5% DMSO during the OA reaction resulted in slightly faster reaction times but significant (≈10%) formation of *p*-methyl-α-methylstyrene and, so, higher concentrations of DMSO were not pursued further.

Plausible mechanisms to explain the OA reactions of the different α-terpinene, γ-terpinene, and isoterpinolene fractions of the *p*-MeD mixtures are shown in **Figure 13**. Initial reaction of the *p*-cymene solvent with oxygen will produce small amounts of H_2O_2 (that can oxidize Me_2S to DMSO) and *p*-cymene peroxide radical **17**. This *p*-cymene peroxide radical **17** then acts as an initiator to abstract allylic hydrogen atoms from the *p*-MeDs to afford allyl radical species **18a**/**18b** that react with oxygen to afford cyclohexadienyl peroxy radical species **19a**/**19b**. These peroxy radical species (19a/19b) then disproportionate to afford *p*-cymene and hydroperoxide radicals that propagate the OA reaction further. Radical termination reactions will then occur through disproportionation of the hydroperoxyl radical to produce H_2O_2 and O_2, with H_2O_2 also undergoing disproportionation to produce H_2O and more O_2.[50]

With optimal conditions in hand, and a mechanistic understanding of the role of Me_2S in the OA reaction, we sought to demonstrate this transformation on a larger scale. Our previously developed ACRO conditions (20 vol% 6 M aq. H_2SO_4, 90 °C, 4 h) were used to transform 10 g of CST into a mixture of sulfurous *p*-MeDs that were then oxidized (O_2, 100 °C, 1 eq. *p*-cymene) to afford *p*-cymene (>95% purity after distillation) in 47% isolated yield over two steps (**Figure 14**).

Addition of 5 mol% Me_2S to the crude sulfurous mixture of *p*-MeDs before carrying out the second OA step gave an improved 53% isolated yield of *p*-cymene over both steps. Applying a similar two-step ACRO/OA protocol to 10 g of GT containing 5 mol% Me_2S as an additive resulted in an

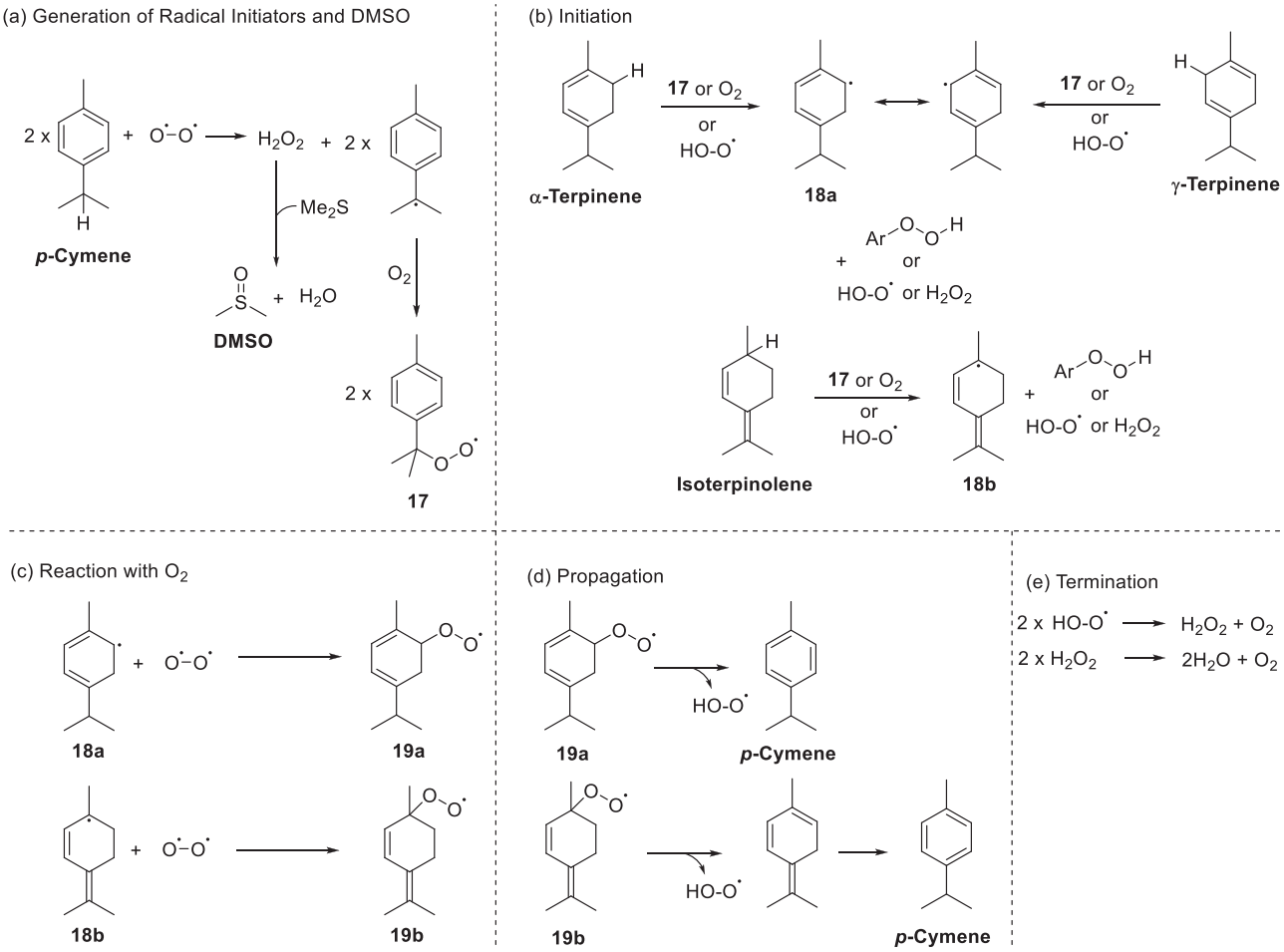


Figure 13. Proposed mechanism for Me_2S/Me_2SO catalyzed oxidation of α-terpinene, γ-terpinene, and isoterpinolene into *p*-cymene. a) Generation of *p*-cymene hydroperoxide radical initiatior and DMSO. b) Initiation step involving hydrogen atom abstraction from *p*-MeDs. c) Reaction of allyl radical species **18a**/**18b** with O_2 to form peroxy radical species **19a**/**19b**. d) Propagation step to afford *p*-cymene and hydroperoxide radicals through disproportionation. e) Radical termination through disproportionation reactions to generate H_2O_2, O_2 and H_2O.

improved 58% isolated yield of *p*-cymene, with addition of a second dose of 5 mol% Me_2S to the OA step increasing the isolated yield of *p*-cymene further to 61% isolated yield from CST. On an industrial scale, addition of Me_2S to CST may not be required due to the use of more efficient condensers and fewer losses to evaporation. Indeed, CST from the Kraft paper process contains ≥5% Me_2S and so the same handling precautions to address volatility, flammability, and malodor issues could be applied to this downstream OA protocol, with the added advantage that the Me_2S is converted to DMSO during the process.[6a]

Therefore, this optimal two-step process can be used to convert 3-carene-rich CST (or GT) into *p*-cymene in 50–60% isolated yields using catalytic amounts of 6 M aq. H_2SO_4 (recyclable), Me_2S (converted to DMSO), and O_2 as reagents and *p*-cymene as solvent (100% recoverable) at temperatures of ≤100 °C. The two-step process proceeds with minimal reaction work-up and allows *p*-cymene of >95% purity to be obtained from a final atmospheric distillation of crude reaction products. These sulfide/sulfoxide-catalyzed OA conditions should prove equally applicable to other *p*-MeD feedstocks (e.g., limonene, technical grade dipentene), allowing multiple terpene biomass sources to be used as feedstocks to produce biorenewable *p*-cymene.

2.6. Recovery of Waste Terpene Oligomers as a Potential Biofuel

The untreated sulfurous *p*-MeD mixtures used as feedstocks in the reactions reported in this study contain 20–25% soluble terpene oligomers as ballast that are generated as by-products from the preceding ACRO reaction of CST. Many of the crude reaction products produced in this study were purified by fractional distillation to afford purified product distillates and viscous brown terpene oligomer residues (20–30% by weight of mainly dimeric/trimeric species).[9] All these gummy terpene residues were shown to be highly flammable, burning fiercely in air when lit with an open flame (**Figure 15**). The combustibility of these viscous terpene biopolymers should enable them to be burnt as biofuels to generate energy to power terpene biorefinery processes. Alternatively, the solubility of these oligomeric terpene residues in common organic solvents (e.g., acetone, *p*-cymene, and hexane) indicates that they may have potential as sustainable fuel blends that could be incorporated into common transport fuels.[51]

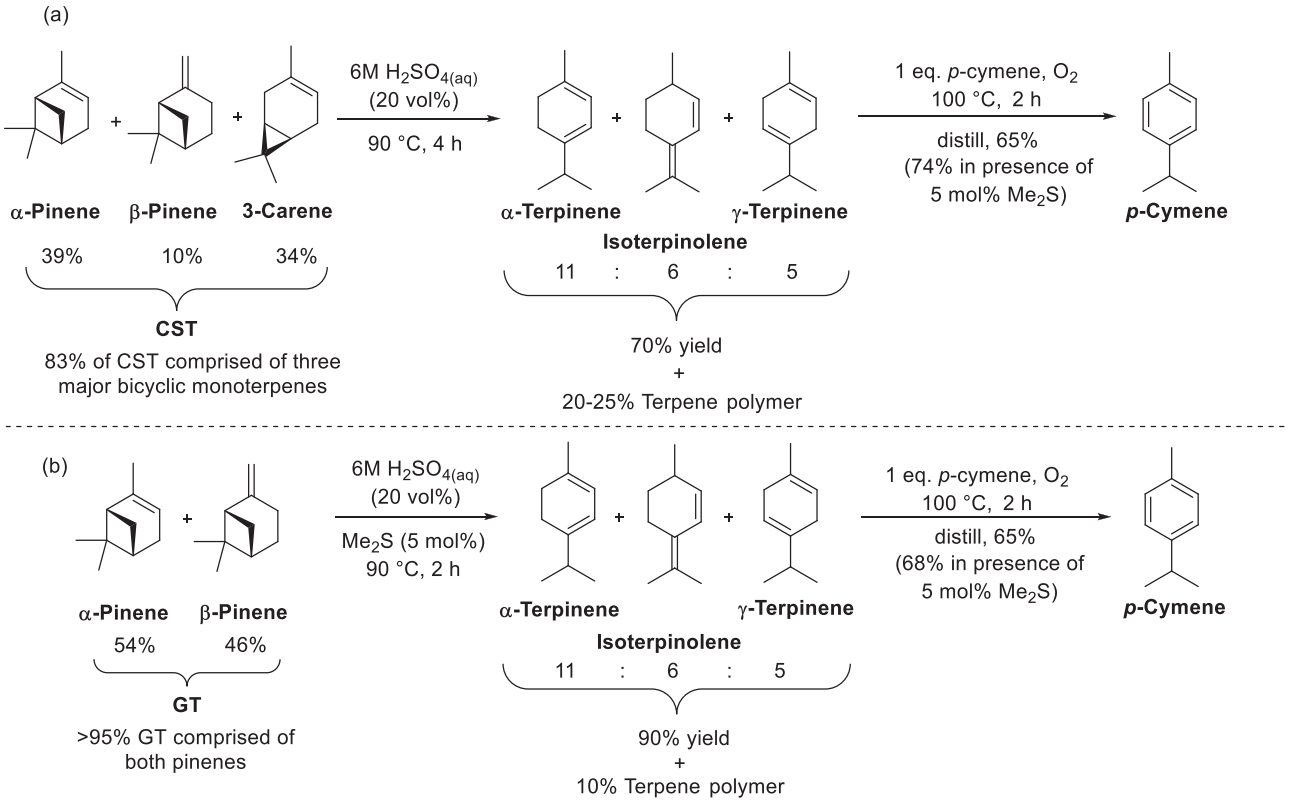


Figure 14. Use of a) CST and b) GT as biorenewable terpene feedstocks for the two-step synthesis of "green" *p*-cymene. Me_2S plays a key role in improving the efficiency of both the ACRO and OA reactions in this two-step process.

3. Conclusion

This paper describes the development of processes (e.g., ozonolysis and Diels–Alder reactions) to transform untreated sulfurous mixtures of *p*-MeDs from ACRO reactions of CST, GT, and 1,8-cineole into a range of useful chemical products within a terpene biorefinery context. Most of these protocols have been applied directly to unpurified sulfurous *p*-MeD mixtures, thus avoiding the need for difficult/costly separation steps that are required for their effective fractionation. A simple desulfurization pretreatment approach based on treatment with 30% aq. H_2O_2 also enables these *p*-MeD mixtures to be used as feedstocks in transition metal-catalyzed reactions, with palladium-catalyzed hydrogenation reactions used to produce *p*-menthane-based biofuels. Untreated sulfurous *p*-MeD mixtures have been transformed into the bulk commodity chemical *p*-cymene through a simple OA protocol that employs O_2 at 100 °C in the presence of 5 mol% Me_2S. These transformations significantly broaden the range of useful chemical products that can be produced from CST, GT, and other biorenewable sources of *p*-MeDs, thus increasing the synthetic versatility and economic viability of the monoterpene biorefinery process.

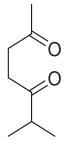
Figure 15. A terpene oligomeric residue burning vigorously in air after being lit with an open flame.

4. Experimental Section

General Experimental Details: All reagents were purchased from commercial suppliers apart from CST which was obtained from a Swedish paper mill owned by Södra Forestry and Barrettine genuine turpentine that was purchased from a local hardware store. All reactions were carried out under air unless otherwise specified. Nuclear magnetic resonance spectra were recorded using either a Bruker Avance 300, 400, or 500 MHz spectrometer, or an Agilent Technologies 500 MHz spectrometer. All ^{13}C spectra were proton decoupled ($^{13}C\{^1H\}$) and all

spectra were run in $CDCl_3$. Chemical shifts (δ) were reported in parts per million (ppm) and were referenced to residual solvent peaks.

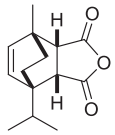
6-Methyl-2,5-Heptanedione (8):



A crude *p*-MeD mixture (0.544 g, 4.0 mmol, [3.0 mmol *p*-MeDs when 25% terpene oligomers taken into account]) was dissolved in CH_2Cl_2 (10 mL) and the stirred reaction mixture was cooled to –78 °C. Ozone was bubbled through the solution until a blue color was observed after ≈30 min, at which point oxygen was bubbled through the solution for 5 min, followed by bubbling nitrogen through the solution for 5 min. Me_2S (0.88 mL, 12.0 mmol) was then added and the reaction mixture stirred at rt overnight. The reaction mixture was then washed with aq. $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), before being dried ($MgSO_4$), and the solvent removed in vacuo. The resulting yellow oil was purified by silica chromatography (petroleum ether: ethyl acetate (4:1), $R_f = 0.33$) to afford the title compound as a colorless oil (0.101 g, 0.7 mmol) in 50% yield (based on the 36% α-terpinene present in the starting *p*-MeD mixture).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73–2.61 (m, 5H), 2.19 (s, 3H), 1.11 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 213.4, 207.5, 41.0, 37.0, 34.0, 30.1, and 18.4. Spectroscopic data in accordance with literature data.[52]

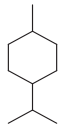
4,7-Ethanoisobenzofuran-1,3-Dione, 3a,4,7,7a-Tetrahydro-4-Methyl-7-(1-Methylethyl)-[JERCure YH309] (12):



A crude *p*-MeD mixture produced from the ACRO reaction of CST (3.40 g, 25 mmol [18.75 mmol *p*-MeDs when ≈25% terpene oligomers taken into account]) and I_2 (0.003 g, 0.01 mmol) was added dropwise (over 5 min) to maleic anhydride (2.45 g, 25 mmol) and the reaction stirred at 180 °C under N_2 for 4 h. The reaction mixture was then cooled to rt and the resulting crude oil was purified by silica chromatography (petroleum ether: ethyl acetate [19:1], R_f = 0.50) to give the title compound a viscous yellow oil (3.40 g, 15 mmol) in 83% yield (based on the ≈72% *p*-MeD present in the starting mixture).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (d, J = 8.5 Hz, 1H, C=CH), 6.01 (d, J = 8.5 Hz, 1H, C=CH), 3.21 (d, J = 8.7 Hz, 1H, C[=O]CH), 2.84 (d, J = 8.7 Hz, 1H, C[=O]CH), 2.55 (h, J = 6.9 Hz, 1H, $CH[CH_3]_2$), 1.50 (s, 3H, CCH_3), 1.48–1.37 (m, 2H, CH_2), 1.36–1.23 (m, 2H, CH_2), 1.08 (d, J = 6.9 Hz, 3H, $CH[CH_3][CH_3]$), 1.00 (d, J = 6.9 Hz, 3H, $CH[CH_3][CH_3]$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 171.0, 137.1, 136.4, 51.1, 47.4, 43.6, 36.8, 33.8, 29.5, 22.8, 22.3, 18.4, and 16.8. Spectroscopic data was in accordance with literature data.[25a]

Mixture of trans-/cis-p-Menthane and p-Cymene:

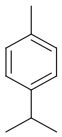


A mixture of *p*-MeDs produced from the ACRO reaction of CST was desulfurized by stirring it with 30 wt% aq. H_2O_2 (0.1 eq.) for 3 h at rt. The organic layer was separated, washed with water, and distilled under reduced pressure (b.p. = 60–65 °C, 10 mmHg) to afford a *p*-MeD mixture comprised of 48% α-terpinene, 24% isoterpinolene, 18% γ-terpinene, and 10% *p*-cymene. A degassed sample of this desulfurized mixture of *p*-MeDs (3.00 g, 22.0 mmol) was then added dropwise to a stirred suspension of 10% Pd on activated carbon (0.583 g, 0.55 mmol) in hexane (10 mL) under a hydrogen atmosphere. Hydrogen was then bubbled through the solution for 15 min, with the reaction then stirred under an atmosphere of hydrogen for 4 h. Nitrogen was then bubbled through the reaction for 5 min which was then filtered through celite to remove the Pd catalyst. The hexane solvent was then removed in vacuo to afford a colorless oil (2.33 g, 16.5 mmol) that was then distilled to afford a fluid oil containing 84% *p*-menthane (4:1 mixture of *trans*- and *cis*- and isomers) and 16% *p*-cymene in a combined 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71–1.55 (m, 3H), 1.49–1.19 (m, 5H), 0.94–0.73 (m, 12H) ^{13}C NMR (101 MHz, $CDCl_3$): peaks for *cis-p*-menthane: δ 43.2, 31.6, 29.4, 25.5, 24.2, 20.5, and 19.5; peaks for *trans-p*-menthane: 44.0, 35.8, 33.1, 33.1, 30.0, 22.9, and 20.0; peaks for *p*-cymene: 146.0, 135.3, 129.1, 126.4, 33.9, 24.3, and 21.1.

Spectroscopic data was in accordance with literature data.[53]

p-Cymene:



Method 1 (Two step synthesis from CST): Step 1) CST (12.0 mL, 10.44 g, 77 mmol) was stirred at 500 rpm at 90 °C. H_2SO_4 (2.4 mL, 6 M aq.) was added in one portion and the reaction stirred at 90 °C for 4 h. Stirring was then stopped and the organic and aqueous layers allowed to cool and separate. The organic layer containing the desired *p*-MeDs mixture was then decanted off and used directly in (Step 2), with the acidic aqueous layer recovered and reused in subsequent ACRO reactions as required.

Step 2) *p*-Cymene (12.0 mL, 10.29 g, 77 mmol) and Me_2S (0.28 mL, 0.24 g, 3.8 mmol) were added to the crude sulfurous mixture of *p*-MeDs (containing 25% terpene oligomers) from (Step 1) and the resultant mixture then heated to 100 °C. A steady stream of O_2 was bubbled through the stirred solution for 2 h. The O_2 stream was stopped, the reaction cooled to rt, and the mixture then distilled under reduced pressure to afford *p*-cymene (b.p. = 70 °C at 10 mmHg) as a colorless liquid (15.74 g, 118 mmol) in 53% yield (allowing for 1 eq. of *p*-cymene used as solvent) and a viscous brown terpene oligomeric residue (4.28 g, 41% yield).

Method 2 (Two step synthesis from GT): Step 1) GT (12.0 mL, 10.44 g, 77 mmol) and Me_2S (0.28 mL, 0.24 g, 3.8 mmol) was stirred at 500 rpm at 90 °C. H_2SO_4 (2.4 mL, 6 M aq.) was added in one portion and the reaction stirred at 90 °C for 2 h. The organic layer containing the desired mixture of *p*-MeDs was then decanted off and used directly in (Step 2), with the acidic aqueous layer recovered and reused in subsequent ACRO reactions as required.

Step 2) *p*-Cymene (12.0 mL, 10.29 g, 77 mmol) and Me_2S (0.28 mL, 0.24 g, 3.8 mmol) were added to the crude sulfurous mixture of *p*-MeDs (containing 10% terpene oligomers) from (Step 1) and the resultant mixture was then heated to 100 °C. A steady stream of O_2 was then bubbled through the stirred solution for 2 h. The oxygen stream was stopped, the reaction cooled to rt, and the mixture then distilled under reduced pressure to afford *p*-cymene as a colorless liquid (16.63 g, 124 mmol) in 61% yield (allowing for 1 eq. of *p*-cymene used as solvent) and a viscous brown terpene oligomeric residue (3.02 g, 29% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (m, 4H, Ar*H*), 2.89 (sep, J = 7.0 Hz, 1H, $CH[CH_3]_2$), 2.34 (s, 3H, $PhCH_3$), 1.25 (d, J = 7.0 Hz, 6H, $CH[CH_3]_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 135.3, 129.1, 126.4, 33.8, 24.3, and 21.1. Spectroscopic data in accordance with literature data.[54]

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

Keywords

biorefinery, CST, monoterpenes, terpenes, turpentine

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