Chemical Plants: High-Value Molecules from Essential Oils

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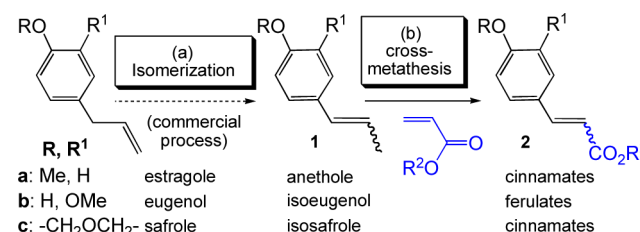
Ⓢ Supporting Information

ABSTRACT: As society faces a future of dwindling petrochemical supplies at increasing cost, much attention has been focused on methods to degrade biomass into renewable commodity-chemical building blocks. Reported here is a powerful complementary approach that *amplifies* the complexity of molecular structures present in plant materials. Essential-oil phenylpropenoids are transformed via acrylate cross-metathesis into potent antioxidants that are widely used in perfumery and cosmetics, and in treating disorders associated with oxidative damage.

Olefin metathesis, as a technology that enables direct modification of the internal C=C bonds of unsaturated fats and oils, has enormous potential in the transition from petrochemicals to renewable feedstocks.[1−4] The dominant focus is on degrading seed oils into α-olefin,[2−5] ester,[6,7] or nitrile[7,8] building blocks for commodity manufacturing (Figure 1a). Terpenes can be treated similarly, yielding products that span the commodity and fine-chemicals sectors (Figure 1b).[9,10] Essential oils, in comparison, offer potential access to high-value, low-tonnage products. Abundant in these volatile oils are phenylpropenoids, functionalized phenol derivatives that are challenging to synthesize but represent important fine-chemical building blocks. Here we describe the use of olefin metathesis to elaborate essential-oil phenylpropenoids into powerful antioxidants that represent key products and platforms for the personal care market (Figure 1c). This represents a paradigm shift in biomass utilization from degradation to enhancement: that is, adding to the complexity of structures assembled by nature rather than breaking these entities down into simple building blocks that must then be reassembled.

Phenylpropenoids such as safrole, eugenol, and estragole are major constituents of essential oils. Existing commercial processes (Scheme 1a) transform these allylbenzenes into

Scheme 1. Strategy for Elaboration of Phenylpropenoids[a]

a: Me, H   estragole   anethole   cinnamates
b: H, OMe   eugenol   isoeugenol   ferulates
c: -CH₂OCH₂-   safrole   isosafrole   cinnamates

[a]For specific acrylates explored, see Table 2.

their conjugated isomers isosafrole, isoeugenol, and anethole; the latter two are also abundant in some essential oils.[11] These compounds have long been regarded as renewable synthons.[12−14] Anethole (1a) is produced on the largest scale (750 000 tons/yr), from star anise, anise, and fennel as well as from turpentine oils from wood processing; additional amounts are generated by isomerization of estragole.[11,15] Production of eugenol and safrole is lower, approaching 2000 tons/yr each from commercial and clandestine sources,[16] but all three represent low-tonnage, high-value renewables. Notable derivatives range from fragrance components to piperonyl butoxide (an essential synergist for natural pyrethum insecticides) and the recreational drug 3,4-methylenedioxymethamphetamine (MDMA).[16]

Olefin metathesis creates new opportunities to amplify the scope and value of these building blocks via elaboration into, for example, conjugated esters (2) (Scheme 1b).[17] Such entities are important in the billion-dollar perfumery and cosmetics industries. UVB-absorbing cinnamates that are potentially
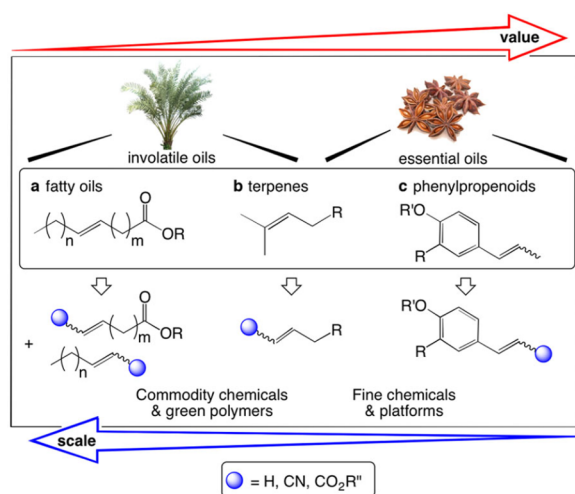

Figure 1. (a, b) Existing and (c) proposed approaches to "renewable metathesis".

accessible from anethole, for example, are now widely used as the active ingredients in sunscreens and cosmetics.[12,18] More generally, the potent antioxidant properties of these compounds have focused attention on their potentially protective role in disorders associated with oxidative damage, including arthritis and other inflammatory diseases, coronary thrombosis, neurodegeneration, and some cancers.[19−23]

The classical Perkin condensation route to cinnamic acid itself requires 8−12 h at >180 °C, and yields reach only ca. 80%.[24] Conventional routes to *functionalized* cinnamates rely on multistep stoichiometric processes.[25] Catalytic cross-coupling of halogenated aromatics offers improvements but remains wasteful.[26] Cross-metathesis (CM) of β-methylstyrene phenylpropenoids offers a potentially succinct, powerful alternative with several compelling features. First, nature has already addressed the challenge of conjugating a C=C bond with the functionalized phenol. Second, CM of the near-terminal olefin in 1 eliminates the unwanted olefinic substituent as volatile propylene (Scheme 2). This sidesteps the

Scheme 2. CM of Anethole with Methyl Acrylate
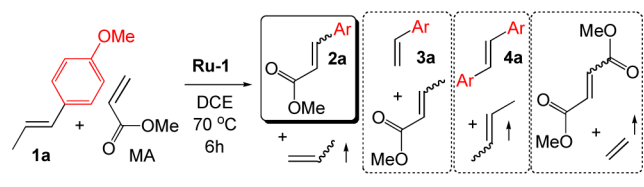
purification issues inherent in metathesis of "deep-internal" unsymmetrical olefins (Figure 1a), namely, formation of two product streams requiring separation. Third, the electron deficiency of the acrylate olefin inhibits self-metathesis,[27] enabling the use of excess acrylate to minimize homocoupling of 1. In sum, these features offer a powerful opportunity for clean capture and elaboration of the valuable phenylpropenoid moiety.

While self-metathesis[28] and CM[17] of anethole have been reported, the intended CM reaction poses a greater challenge to reactivity due to electronic deactivation of the acrylate combined with steric deactivation of the predominantly trans-configured double bond in the precursors 1. However, impressive efficiencies have been achieved in CM of internal olefins with acrylates using the Hoveyda catalyst Ru-1,[4,6,29] and we thus sought to build on these advances. In probe experiments, we employed anethole with a 4-fold excess of methyl acrylate (MA) at high catalyst loadings (2 mol %); elevated temperatures were also required (Scheme 2).

Efficient volatilization of propylene and ethylene byproducts is essential to promote selectivity for the desired CM reaction. Near-quantitative yields of 2a were attained within 6 h by stirring in open vessels in the glovebox (Table 1, entry 1).[30] Yields of 2a declined as the headspace was reduced, as shown most dramatically in entry 2. When the catalyst loading was decreased to 0.1 mol % Ru-1 (entry 3), the yield of 2a dropped to 78% at 6 h and increased by only 2% after 12 h, consistent with catalyst deactivation. Dropwise infusion of Ru-1, a protocol that has proven effective in other contexts,[6,31] gave essentially identical results (entry 4). At a catalyst loading of 0.5 mol %, however, the yield of 2a was restored to 97% (entry 5), and this was used as a baseline for further improvement.

In the experiments above, we employed excess acrylate to minimize self-metathesis of 1a (i.e., formation of stilbenoid 4a).

Table 1. Maximizing the CM Selectivity for Cinnamate 2a[a]

entry	mol % Ru-1	equiv of MA	% conv	% Yield			%E (for 2a)
				2a	3a	4a	
1	2	4	100	99	0	0	97
2[b]	2	4	100	72	15	6	99
3	0.1	4	99	78	2	18	>99
4[c]	0.1	4	99	82	2	15	>99
5	0.5	4	100	97	0	3	99
6	0.5	2	100	90	2	7	99
7	0.5	10	100	93	0	5	98
8	0.5	20	97	89	1	6	99
9	0.5	6	100	99	0	1	99

[a]Conversions are based on 1a; yields are relative to the sum of anisole derivatives. [b]10% headspace; unidentified byproducts were present. [c]Catalyst was added over 4 h via syringe pump.

A disadvantage of high acrylate concentrations, however, is faster catalyst deactivation. Efficient CM of acrylates is promoted by reaction of the catalyst with the olefinic coupling partner. Direct reaction with acrylate would give unstable ester−alkylidene Ru-2 (eq 1) and hence accelerate decomposition.[32]
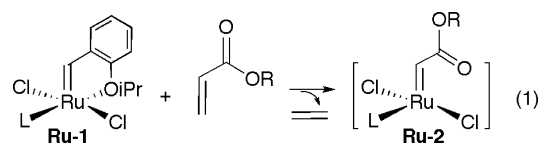
Additional experiments were therefore carried out to establish the optimal acrylate loading. At 2 equiv of MA (Table 1, entry 6), 1a was fully consumed, but the yield of 2a dropped to 90% because of buildup of the sterically deactivated stilbenoid 4a. At 10 equiv (entry 7), the yield of 2a was likewise poor, in this case reflecting increased catalyst decomposition. (Indeed, at 20 equiv of MA, this effect was sufficient to inhibit complete conversion of anethole; entry 8). The use of 6 equiv MA, however, represented a "sweet spot" at which the formation of 2a was essentially quantitative: no evidence of the vinylanisole intermediate 3a was seen, and the proportion of 4a dropped to 1% (entry 9; also see Table 2, entry 1).

The corresponding reactions of isoeugenol and isosafrole yielded 2b (99%) and 2c (97%) (Table 2, entries 2 and 3). Indicative of the potentially broad scope of this methodology, comparable or higher yields were achieved with ethyl acrylate (entries 4−6) and, of particular note, 2-ethylhexyl acrylate

Table 2. Expanding the Scope of Arylpropenoid CM[a]

entry	acrylate	phenylpropenoid	% conv	% yield[b]	%E
1	methyl	1a	100	99 (83)	99
2		1b	100	99 (90)	98
3		1c	100	97 (85)	99
4	ethyl	1a	100	99 (85)	>99.5
5		1b	100	100 (95)	99.5
6		1c	100	98 (90)	99
7	2-ethylhexyl	1a	100	99 (89)	99.5
8		1b	100	>99 (98)	>99.5
9		1c	100	98 (81)	99.5

[a]Conditions as in Scheme 2 (6 equiv of acrylate). Conversions are based on 1 and yields on 2. [b]Isolated yields are given in parentheses.

(entries 7−9). Reaction of the latter with anethole generated the important sunscreen agent octyl methoxycinnamate in 99% yield (entry 7). Reactions on a 1 g scale proceeded over 15−22 h to give the desired compounds in 81−98% isolated yield. The lower values reflect the similar polarity of the targets versus the maleate/fumarate products of acrylate coupling.

To date, the overwhelming focus in biomass utilization has been on degrading renewable resources into the basic chemical building blocks central to chemical manufacturing. Olefin metathesis creates new opportunities in two respects: it enables net augmentation rather than degradation of biomass, and it enables the capture of complex structures relevant to fine-chemicals markets. These concepts have been illustrated above by the succinct synthesis of high-value (E)-cinnamate and (E)-ferulate esters from the renewable phenylpropenoids anethole, isoeugenol, and isosafrole. The general approach, in which metathesis is used to capture and elaborate synthetically demanding structural motifs assembled by nature, represents a powerful, potentially versatile platform for sustainable synthesis. From a broader perspective, these methodologies offer the potential for economic expansion via the sustainable cultivation and elaboration of high-return source species in the tropical countries that represent the major producers of essential oils.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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