Iron-catalyzed hydrobenzylation: stereoselective synthesis of (−)-eugenial C

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Metal-hydride hydrogen atom transfer (MHAT) has emerged as a useful tool to form quaternary carbons from alkenes via hydrofunctionalization. Here, we report a monometallic cross-coupling via putative MHAT/Si₂ steps that solves a key stereochemical problem in the synthesis of meroterpenoid eugenial C and obviates the need for nickel in these hydrobenzylation reactions. The concise synthesis benefits from a conformationally-locked α,α′-disubstituted benzyl bromide and a locally-sourced chiral pool terpene coupling partner.

Eugenial C (1, Figure 1a), a meroterpenoid isolated from the fruit of *Eugenia umbelliforma*, was reported to exhibit selective antibacterial activity against *S. aureus*, including MRSA strains (resistant to β-lactams), at minimal inhibitory concentrations lower than 1 μg/mL, comparable to vancomycin, daptomycin and bithionol. Its challenging structure consists of two lobes—a non-symmetric hexasubstituted benzene and an aromadendrene—merged at a quaternary carbon stereocenter. We were curious to understand the role of both moieties in bactericidal activity and whether they acted independently or in concert—a question best answered by modular synthesis. Eugenial C and its congeners are thought to arise via α,β-unsaturated methine-initiated cyclization of a bicyclogermacrene followed by E1 elimination. This cationic approach significantly reduces complexity but at the cost of modularity. An alternative carbon radical disconnection, we thought, would allow for selective cross-coupling of simple building blocks in a way that would lend itself to focused library synthesis and biological interrogation.

We previously reported a method for the synthesis of quaternary carbons via alkene hydroalkylation by alkylhalides. This transformation occurred via Mn/Ni dual catalysis: the Mn catalyst reacted with an alkene via a proposed MHAT step and the Ni catalyst reacted with the alkylhalide to forge a C–C bond after C* capture and reductive elimination of a putative dialkylnickel (Figure 1b, left). Direct application to the synthesis of eugenial C, however, failed due to: 1) the steric encumbrance of the 2,6-disubstituted benzyl halide coupling partner and 2) the inability of ligands on nickel to favor the 4'R-stereoisomer of the natural product (1). Here, we report a solution to both problems using monometallic catalysis: engagement of both alkene and benzyl halide by iron. The predominant pathway to stereoselective C–C bond formation appears to involve sequential MHAT and Si₂ steps.

Development of an effective cross-coupling method required access to appropriate coupling partners on large scale so that optimization of multiple parameters could be carried out. The phloroglucinol portion, while superficially trivial, could be introduced in numerous forms—fully functional or protected, symmetric or non-symmetric, hexasubstituted or partly substituted (see Scheme 2 below)—each of which required independent synthesis. Identification of a successful strategy involved extensive trial and error. Access to the aromadendrene moiety (2) benefited from local sourcing: closely related terpenoids aromadrene and globulol occur in abundance in the fruits of *Eucalyptus globulus* (Figure 1b, right), which grow throughout the San Diego region where we live.

Figure 1. Overview. a. Proposed biosynthesis versus proposed chemical synthesis; b. Prior coupling via reductive elimination versus proposed coupling via Si₂ (left), and convenient source of starting materials (right). Aromadendrene (3, Scheme 1) was noted as an optimal starting material due to its commercial availability, but pandemics and regional shortages in commercial samples of *Eucalyptus* leaf oils prevented access. We identified *Eucalyptus globulus* as a high-abundance producer species and found its regions of abundant growth using the publicly available Plant Atlas Project administered by the San Diego Natural History Museum. Fortunately, this species abounds in our local region due to 19th century planting efforts to establish *Eucalyptus* species as arid-region economy crops. *E. globulus* fruits litter the ground among stands of *ca*. 20 trees located about 2 km from our laboratory. Fallen fruits were ground to a fibrous mass using a Marada 2 kg stainless-steel high power electric screwdriver.
spice grinder (see SI), extracted with Et2O and concentrated in vacuo to a crude oil that contained 10.6% aromadendrene (3, average of 10 extractions), in addition to 2.2% 10-epi-globulol (eugenial C numbering) and 4.8% globulol (4). In a typical isolation, 3.2 kg of fallen E. globulus fruits were gathered in 1 h; extraction yielded 284 g of a light oil that could be separated into 13.2 g globulol and 29.3 g aromadendrene. Studer’s dia-
steroselective Mukaiyama hydration11 of 3 to 4, followed by acetylation converged the separate E. globulus fruit extract constituents into a single material 5 for large-scale processing.22

Aromadendrene (3) had been reported to undergo regio-
and stereoselective C–H oxidation at C4’ using ozone, but con-
comitantly with alkyl cleavage.21 A similar oxidation of 5 could be accomplished with dimethyldioxirane (DMDO), methyl(trifluoromethyl) dioxirane (TFDO), or RuO2 (generated in situ), but reproducibly high yields of 6 were observed only with CrO3/n-Bu4NCl via a putative Cr(VI) peroxide.23 Methanesul-
fonyl anhydride mediated an endo-selective alcohol elimination of 6 (5:1 Δ3,5 : Δ2,10). Decacylation by potassium hydroxide delivered 2 in good yield on multigram scale.

Identification of an effective hydrobenzylation coupling partner required extensive work at the strategic and methodo-
logical level to optimize steric and electronic features that led to high yields while also searching for substrate/catalyst combinations that led to high diastereoselectivity (Scheme 2a). First, we explored a fully functional, non-symmetric benzyl bromide (7) that contained all functionalities or equivalent groups. O,o’-
disubstitution of the arene, however, led to low yields and never favored the desired diastereomer. Second, we removed the offending ortho-substituents to probe cross-coupling and late-
stage C-H hydroxylation. Hydrobenzylation of 8 occurred in modest yield using variations on our reported protocol.5 However, o,o’-dihydroxylation of the products failed with nine separate procedures24 using nitrite, amide, carboxylic acid and ox-
ime directing groups, largely stalling at mono-functionalization under dozens of variations to the published protocols. Third and
finally, we reasoned that o,o’-disubstitution might be tolerated if the groups were restrained into an acetal that 1) limited steric clash with benzylmetal complexes and 2) delocalized Lewis basic ortho-oxygen non-bonding orbitals into the σ* 5.1 of the ester oxygen to limit chelation. This strategy was modestly successful: the symmetric bis-dioxirane 9 engaged alkene 2 in hy-
drobenzylation using Mn/Ni dual catalysis—the first example of a o,o’-substituted partner in hydrobenzylation. Our excite-
ment was short-lived. Diastereoselectivity proved consistently poor across hundreds of variations to substrate, ligand, solvent, additives and temperatures.

As we struggled with stereocontrol, a study of a novel iron porphyrin-catalyzed decarboxylative cross-coupling of NHPI esters and alkyl bromides reported an increase in diastereose-
levity (1:1.1 dr to 3:2:1 dr) in the presence of an iron porphyrin as one piece of evidence consistent with C–C bond for-
mation via alkyl-Fe(III) S2O52. Similarly, if dialkynickel dia-
stereomers (Scheme 2b) or radical heterodimerization led to low dr, differentiation of globulyl radical (2*) re- and si-faces might better occur by irreversible S2O52 of an alkyl-iron porphyrin, where steric repulsion from the geminal dimethyl cyclopro-
pane would obstruct pseudo-equatorial approach. Independent of this question of diastereoselectivity, it was unclear whether benzyl radicals could engage iron porphyrins productively versus dimerize competitively, or whether an S2O52 elementary step could effectively outcompete common pathways in MHAT cata-
lytic cycles like hydrogenation and isomerization.25

Table 1 displays the optimal conditions after extensive screen-
ing (entry 1; see Figure 2 for a proposed catalytic cycle) and deviations from these conditions. To our relief, capture of the proposed globulyl radical (2*) resulted in high selectivity to

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\text{Table 1.} \quad \text{0.1 mmol 2, 0.05 mmol 9; } ^\circ \text{TPP = tetrakis[3,5-bis(4-pyridyl)-2,4,6-trimethylphenyl]porphyrin, } 28\% \text{ dehydration of the C10’ alcohol}
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favor the desired C4' (R) diastereomer (for NOE and X-ray data, see SI). Whereas we had investigated Fe(dpmp)$_2$ originally due to the proposed ability of bulky dpmp (dipivaloylmethane) ligands to limit off-cycle hydrogen evolution, 28,27 the less expensive Fe(acac)$_3$ was more effective in this case (entry 2), likely due to clash of the hindered substrate alkene 2 with dpmp metal hydride complexes. Mn(dpmp)$_2$ proved too efficient a hydrogenation catalyst and limited cross-coupling yields (entry 3). However, we did observe small amounts of product using Mn(dpmp)$_3$, likely arising from direct radical-radical heterodimerization but delivering 1:1 dr (entry 4). Mono-iso-propoxynaphenyl silane (PhSiH$_3$O-i-Pr, RubenSilane) resulted in significantly higher yields than phenylsilane (entries 5 and 6), consistent with prior studies that demonstrated its higher rate of metal hydride formation.26,11d Both Fe(acac)$_3$ and Fe(TPP)Cl (TPP = tetraphenylporphyrin) catalysts were necessary (entries 7 and 8), although ongoing work in our lab suggests that the iron porphyrins can mediate the MHAT step in other contexts.27 Weak base was essential for substrate 9 (entry 9), whose C10' tertiary alcohol can undergo acid-catalyzed elimination. As in prior reports, an atmosphere of air was employed, likely to turn over the HAT catalytic cycles and/or rescue off-cycle reduced catalysts.28

This diastereoselective MHAT / Si$_2$2 cross-coupling proved crucial to the development of a streamlined, 11-step synthesis of (−)-eugenial C (Scheme 3). Conformationally-restricted benzyl bromide 9 was synthesized from dimethyl phloroglucinol 11 (listed commercially or accessible from 2,4,6-trihydroxy-benzaldehyde) by a short sequence of double formylation, double oxidation and quadruple alkylation. Bisphenol 11 was formylated by heating with formamidine acetate followed by acidic hydrolysis to 12. Facile Pinnick oxidation allowed us to explore cyclization strategies. Formation of the intermediate bis-dioxinone in this latter step required extensive optimization due to the build-up of strain resulting from electron repulsion between non-bonding orbitals on the three oxygen atoms that line the northern border (see X-ray of 9 for dihedral angles). The use of CICH$_2$Br was ultimately successful, while alternative procedures29 that relied on CH$_2$Br$_2$, FCHO$_3$, formaldehyde,31 or trioxane and catalytic Brønsted or Lewis acids32 all failed. Radical C–H bromination occurred smoothly to deliver 9 on gram-scale. The optimized cross-coupling reaction with globulol-derivative 2 proceeded as reported above, and was followed by phosphonic anhydride-mediated elimination of the C10' tertiary alcohol13 that delivered a crystalline material to support prior NOE-based assignments of relative stereochemistry; X-ray crystallography also assigned the absolute configurations conclusively (Flack parameter = 0.01(7)). Selective derivatization of the symmetrical bis-dioxinone to the n-propyl ketone / benzaldehyde motif was carried out by a variant of Takai olefination using catalytic PbCl$_2$,34 which resulted in selective mono-olefination and an inconsequential 1:1 mixture of E/Z stereoisomers. This olefination served to install the 3 carbons of the n-propyl ketone of 1 while also allowing for selective mono-reduction of the remaining dioxinone with DIBAL; work-up with acetic acid/SiO$_2$ hydrolyzed the enol ether ketal to its n-propyl ketone. Unsuccessful attempts to achieve the same selective functionalizations included conversion of 14 to the bis-(N-alkoxy) (Weinreb) amide, which only yielded either the bis-aldol and tertiary alcohol upon nucleophile addition. Alternative olefinations using Peterson or Takeda conditions were similarly unsuccessful. Finally, O-demethylation by lithium p-thiocresolate completed the synthesis of (−)-eugenial C, whose spectroscopic properties ($^1$H, $^{13}$C NMR, HRMS) proved identical in all respects to those from its isolation.35 The optical rotation of synthetic 1 ([$\alpha$]$_D$ = -4, c 0.05, CHCl$_3$) differed slightly from that of isolated 1 ([$\alpha$]$_D$ = -7, c 0.13, CHCl$_3$), perhaps a result of the error associated with low specific rotation.

The iron-catalyzed cross-coupling optimized for 2 and 9 could be applied to a broad range of substrates and provided general access to hindered, methylene-bridged products (Table 2). The remarkable alignment of catalytic cycles helped suppress side-products commonly associated with our first-generation conditions, such as alkene hydrogenation, isomerization and hydration, as well as benzyl bromide proto-dehalogenation and oxidation to a benzaldehyde. Due to the large-scale availability of aromadendrene via isolation from *E. globulus*, we first explored the breadth of benzyl bromide tolerance with this complex 1,1-disubstituted alkene. Very little difference in reaction efficiency was observed between electron-poor and electron-rich arenes; the only effect of ortho substitution was to vary diastereoselectivity, which in most cases exceeded 10:1 dr. We also investigated several heterocyclic benzyl bromides, which have wide commercial availability (~2000) and are simple to access by radical bromination. The few that we tested all coupled with high stereoselectivity, although reductively labile rings like isoxazoles led to modest yields (39–43%). The breadth of the alkene scope surprised us, especially given the
restricted scope of our first-generation Mn/Ni hydrobenzylation. In addition to complex sesquiterpenes like aromadendrene (3) and Δ^{5,9}-dehydrollobulol (2, see Scheme 1), nootkatone (to 16o) and a Δ^4-tetrahydrocannabinoid derivative (to 16p) coupled efficiently with pyridylmethyl bromides. Monoterpenes like pinene (to 16q), complex steroids like cholesteryl chloride (see 16r) and pregnenolone (to 16s), and meroterpenoids like O-methyl mycophenolate (to 16t) were also productive substrates. In this latter case, the alkene could isomerize into conjugation with both the arene and the ester, but the Sn2 reaction outcompetes these reactions, which would likely be mediated by HAT to (TPP)Fe^{3+}. The proposed, intersecting catalytic cycles are depicted in Figure 2 (for a longer discussion, see SI). The alkene is likely to undergo MHAT with a fleeting metal hydride generated from silane and Fe(acac); the low-BDE Fe^{3+}-H is thought to react\textsuperscript{11d} at the hexet spin state\textsuperscript{11c} and prefer outer-sphere MHAT over an inner-sphere coordination/migratory insertion\textsuperscript{11i} driven by the weak-field β-diketonate ligands.\textsuperscript{11e,11i,11d,11k} The resulting tertiary carbon radical (R,C\textsuperscript{•}) can either undergo equilibrium collapse to a tert-alkyl organoiron\textsuperscript{11j,17} (R,C-Fe^{3+}) or engage the benzyliron(TPP) complex directly.\textsuperscript{12i} The benzyliron(TPP) is likely to form by capture of benzyl radical (Bn\textsuperscript{•}) by (TPP)Fe^{2+}, which may itself form via hydrogen evolution from 2 (TPP)Fe^{3+}-H or the proposed Sn2 reaction. The origin of Bn\textsuperscript{•} is unclear but control experiments suggest its formation by both (TPP)Fe^{3+}-H and (acac)Fe^{3+}-H by analogy to Leonori’s HAT/XAT mechanism (see SI).\textsuperscript{38} We did not observe any reaction of the BnBr with (TPP)Fe^{2+}. We consider Sn2 more likely than persistent radical effect (PRE)-driven heterodimerization because of the low dr (1:1) associated with background coupling in the absence of Fe(TPP)Cl (Table 1, entry 4), low dr

Table 2. Preliminary scope of iron-catalyzed hydrobenzylation via MHAT/Sn2. All reactions conducted with 0.2 mmol of alkene and 0.1 mmol of benzyl bromide; diastereomeric product ratios >10:1 unless otherwise noted. a 5 mol% Fe(acac)\textsubscript{3} and 5 mol% Fe(TPP)Cl; b 10 mol% Fe(acac)\textsubscript{3} and 10 mol% Fe(TPP)Cl; c solvent = 4:1 i-PrOH/acetone; d solvent = 1:1 i-PrOH/acetone.

in the variations to our 1st generation hydrobenzylation conditions,\textsuperscript{39} and the precedent of Ref. 12–16. These data suggest
Eugenial C and its analogs are now available by a modular route that relies on an iron-catalyzed alkene/benzyl bromide cross-coupling through a putative MHAT/Sn2 sequence, the first of its kind. This terpene hydrobenzylation transformation differs significantly from prior disconnections to access terpenephenoic meroterpenoids and may prove generally simplifying. For example, symmetric partner allows for late-stage diversification after coupling with diverse alkenes like chiral pool terpenes. Whether the arene primarily undergoes redox reactions, disrupts membranes or adds lysines through its salicylaldehyde and whether the terpene serves as a lipophilic vehicle or binds a hydrophobic pocket can now be interrogated by synthesis. The iron-catalyzed cross-coupling offers a new jumping-off point for the development of a suite of branched-selective alkene hydrofunctionalizations that obviate the need for nickel, whose toxicity can present problems for large-scale pharmaceutical applications. Numerous paths are now made available through this study in natural product synthesis.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

Materials and methods, experimental procedures, copies of NMR spectra (PDF).
X-ray structure reports (PDF).
X-ray structure files (CIF).

REFERENCES


18. Essential oils from Eucalyptus globulus were purchased from MilliporeSigma but only contained trace amounts of 3 and 4.

19. sdplantatlas.org


22. Ref. 21 reports the hydration of aromadendrene (3) but depicts opposite C10 diastereomers between the manuscript and supporting information. The SI of Ref. 21 contains 1D NOE spectra that support the configuration (4) shown in Scheme 1.


25. Reductive elimination, not carbon radical capture, has been proposed as the stereochemistry-determining step in certain nickel-catalyzed cross-couplings. See Ref. 7a.


35. 1 is a mixture of rotamers in CDCl3 due to phenol-carbonyl hydrogen-bonding.


39. We cannot rule out that our prior Mn/Ni cross-coupling did not proceed via PRE heterodimerization (with benzyl bromides specifically, see Ref. 5). Nor can we rule out S22 in Ref. 5, but we consider it unlikely due to its similarity to well-studied Ni-catalyzed cross-coupling via reductive elimination (see Ref. 8). For a Ni-catalyzed cross-coupling proposed to proceed by S22, see Ref. 13.


44. Egorova, K. S.; Ananikov, V. P. "Which Metals are Green for Catalysis? Comparison of the Toxicities of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts" Angew. Chem. Int. Ed. 2016, 55, 12150.

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