

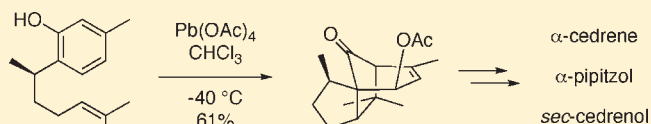
An Oxidative Dearomatization-Induced [5 + 2] Cascade Enabling the Syntheses of α -Cedrene, α -Pipitzol, and *sec*-Cedrenol

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S Supporting Information

ABSTRACT: Efficient syntheses of α -cedrene (**1**), α -pipitzol (**2**), and *sec*-cedrenol (**3**) were carried out using a new method, which was inspired by the proposed biosynthesis of the tricyclic skeleton of cedrol (**12**). The key transformation begins with the oxidative dearomatization of curcuphenol (**5a**) followed by an intramolecular [5 + 2] cycloaddition of the respective phenoxonium intermediate across the tethered olefin. The benzylic stereocenter effectively guides the formation of the first two stereocenters during the [5 + 2] reaction. The cascade then terminates with the selective incorporation of acetic acid to generate a third stereocenter, setting it apart from other previous cationic [5 + 2] reactions. The phenolic precursors (**5a–h**) are constructed from readily available salicylaldehydes, either as the racemate (one pot) or as a specific enantiomer (four pots) by a modification to our method for the generation of *ortho*-quinone methides (*o*-QMs).



INTRODUCTION

The cedranoids comprise a venerable family of unique natural sesquiterpenes (Figure 1). α -Cedrene (**1**), an approved food preservative,¹ conveys antimicrobial,² insecticidal, and termiticidal properties³ to the timber of the American red cedar *Juniperus virginiana* from which it is isolated.⁴ Its characteristic tricyclo-[5.3.1.0^{1,5}]-undecane skeleton was first proposed and then verified by Stork more than a century after its isolation.⁵ Many creative strategies for building its congested skeleton have since emerged,⁶ culminating in the arene-olefin *meta*-photocycloaddition strategy championed by Wender.⁷ Similarly, α -pipitzol (**2**), which was isolated from the root extracts of *Perezias cuernavacana*, remained unsolved for over a hundred years.⁸ The relatively few approaches to α -pipitzol (**2**) include a semisynthesis from perezone,⁹ a racemic synthesis featuring a [4 + 2] tropone olefin cyclization,¹⁰ and the lone enantioselective synthesis requiring more than 30 steps from methyl α -D-mannopyranoside.¹¹ *sec*-Cedrenol (**3**) is a relative newcomer to the cedranoid family. It is produced by the *Rhodococcus* bacterium sp. KSM-7358 upon exposure to feed stocks of α -cedrene (**1**).¹² It has been shown to be a potent stimulant of the histamine H3 receptor, and it might prove useful for the prevention and treatment of bronchial asthma, hyperlipidemia, and inflammation.¹³

A number of cationic intramolecular [5 + 2] cycloadditions have been described in the literature.¹⁴ All prior examples, however, necessitate the use of highly oxygenated aromatic precursors capable of forming a cationic species resembling a *para*-quinone, either by the addition of a Lewis acid to a *para*-quinone monoketal, or by the oxidation of a monoprotected *para*-quinol, or by addition of a Lewis acid to a *para*-quinone itself. To the best of our knowledge, there are no reports of *ortho*-(pent-4-enyl)-phenols, such as curcuphenol (**5a**),¹⁵ parti-

cipating in a [5 + 2] cycloaddition, nor are there any examples whereby the cascade terminates by the incorporation of a separate nucleophile.

Our inspiration for this cascade arose from the biosynthesis of cedrol (**12**), which is proposed to commence from nerolidyl pyrophosphate **8** as shown in Scheme 1.¹⁶ A sesquiterpene cyclase triggers the ionization of the tertiary alcohol, whereupon cyclization with the adjacent olefin and a 1,2-hydride shift affords the bisabolyl cation **9**, which upon further reaction leads to the spirocyclic acorane intermediate **10**. Subsequent cyclization to the cedryl cation **11** and addition of water affords cedrol (**12**). We therefore hypothesized that oxidative dearomatization of curcuphenol (**5a**) would provide the intermediate phenoxonium **7** that might behave in an analogous manner, whereby the benzylic stereocenter would govern the assembly of the tricyclic skeleton with the cascade terminating by the addition of an oxygen nucleophile.

RESULTS AND DISCUSSION

Syntheses of Curcuphenol (5a) and Its Derivatives. To test our hypothesis, we required efficient access to an assortment of *ortho*-(pent-4-enyl)-phenols including curcuphenol (**5a**). After some experimentation, we found that a slight modification to our previously reported low temperature *o*-QM generation procedure enables the direct use of unprotected salicylaldehydes **6** in a one-pot process (Scheme 2).¹⁷ For the racemic process, the sequence commences with the addition of 2 equiv of MeLi to the appropriate salicylaldehyde **6a** ($\text{R}^1 = -\text{Me}$, $\text{R}^2 = -\text{H}$). This results in both deprotonation of the phenol and addition to the

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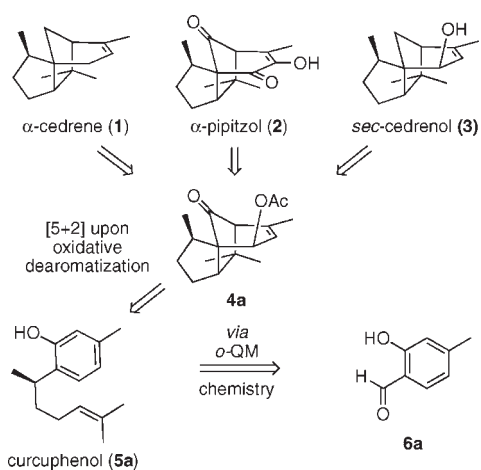
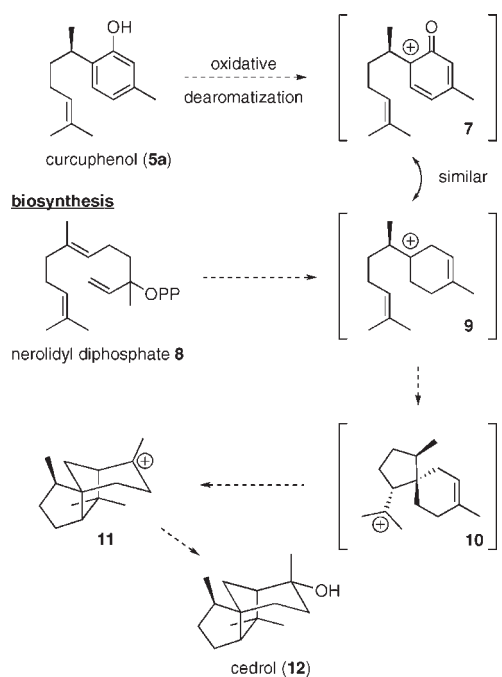
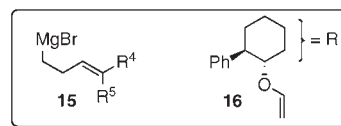
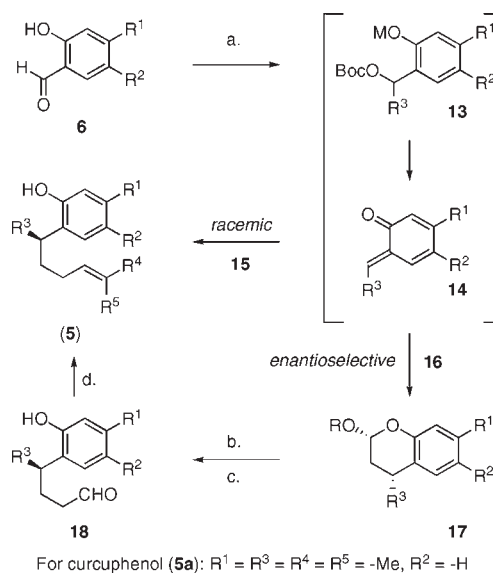


Figure 1. Retrosyntheses of the cedranoid family.

Scheme 1. Biosynthetically Inspired [5 + 2] Cycloaddition



aldehyde, thereby yielding an intermediate dianion that undergoes *mono* carbonylation with di-*tert*-butyl dicarbonate. Upon addition of the Grignard reagent **15**, elimination occurs after formation of the magnesium phenoxide **13a** ($M = -MgX$, $R^1 = R^3 = -Me$, $R^2 = -H$), thereby producing the intermediate *o*-QM **14a** ($R^1 = R^3 = -Me$, $R^2 = -H$). This intermediate is intercepted in a 1,4-addition and rearomatization reaction with the Grignard reagent **15** to produce (\pm)-**5a** ($R^1 = R^3 = R^4 = R^5 = -Me$, $R^2 = -H$) in 84% yield in a single pot. If, however, optically enriched material is required, the procedure begins by addition of 2 equiv of MeMgBr to a flask containing the salicylaldehyde **6a** and the enol ether **16**. The resulting dianion similarly undergoes *mono* carbonylation leading to generation of the same *o*-QM **14a** intermediate. However, in this case without a nucleophile to induce the 1,4-addition and rearomatization, a diastereoselective inverse-demand Diels–Alder reaction proceeds to afford the chroman ketal **17a** ($R^1 = R^3 = -Me$, $R^2 = -H$) in 73% yield (16:1 dr). Hydrolysis

Scheme 2. Racemic and Enantioselective Syntheses of Various *ortho*-(Pent-4-enyl)-phenols^a

^a Reagents and conditions for curcuphenol (**5a**) synthesis: Racemic [one pot: **6a** to **5a**] (a). MeLi (2.05 equiv), Et₂O, 0 °C; then Boc₂O (1.1 equiv), -40 °C; then **15** (1.1 equiv), 84%. Enantioselective [four pots: **6a** to **17**] (a) MeMgBr (2.05 equiv), **16** (3 equiv), Et₂O, 0 °C; then Boc₂O (1.1 equiv), -40 °C, 73%, 16:1 dr; (b) CSA (0.1 equiv), CH₃CN, H₂O, 92%; (c) ClPh₃PCH₂OCH₃ (2.5 equiv), *n*-BuLi (2.3 equiv), THF; then aqueous HCl, 84% over two steps; (d) IPH₃PCH(CH₃)₂ (2.5 equiv), *n*-BuLi (2.4 equiv), THF, 78%.

to the corresponding lactol and sequential elaboration with the respective Wittig reagents produces (–)-curcuphenol **5a** in four pots (48% overall yield from **6a**).

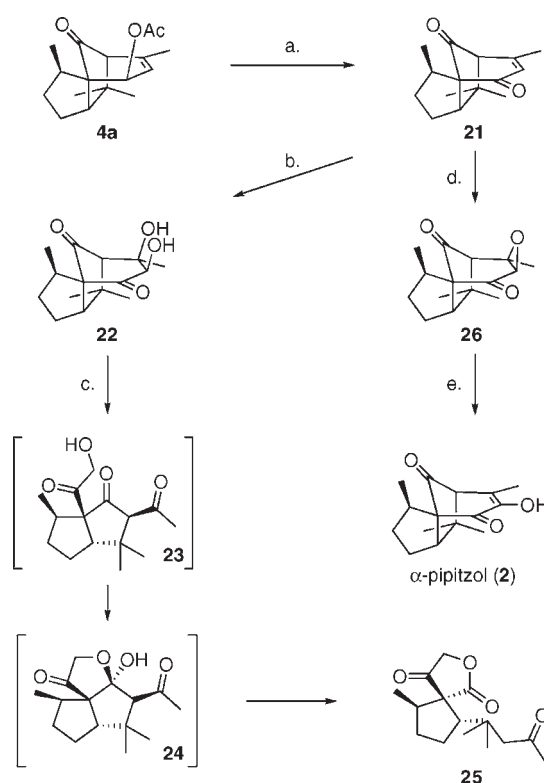
With an assortment of *ortho*-(pent-4-enyl)-phenols (**5a–h**) in hand, we were poised to test the proposed dearomatization reaction (Table 1). Unfortunately, various hypervalent iodine oxidants failed to provide any of the desired tricyclic products. However, we were gratified to find that addition of Pb(OAc)₄ (1.1 equiv) to **5a** (1.0 M in AcOH) provided a trace (6%) of the tricyclic compound **4a**, presumably from acetic acid addition to the allyl cation **19**, along with a 44% yield of the *ortho*-acetoxylation diastereomers **20**. We suspect that the latter arises from the stereoischemic addition of acetic acid to the phenoxonium **7**.¹⁸ Nevertheless, the formation of the tricyclic adduct **4a** as a single diastereomer, the relative stereochemistry of which was secured by single crystal X-ray analysis, indicated that the single benzylic stereocenter had governed the creation of two additional rings before a selective incorporation of acetic acid. In view of the molecular complexity afforded from the simple starting material in this transformation, we sought conditions to favor the intramolecular cycloaddition reaction. The key optimization involved changing the solvent to chloroform, thus allowing for a lower reaction temperature and limiting the equivalents of acetic acid to those liberated from the Pb(OAc)₄, which increased the yield of the tricyclic compound **4a** to 61%.

Table 1. Dearomatization of *ortho*-(Pent-4-enyl)-phenols

Entry	Phenol	Conditions ^a	[5 + 2] Product	Ratio 4 : 20 ^c
1		A	 61% yield	2.6 : 1
2		A	 54% yield	1.6 : 1
3		A	 32% yield	1 : 1.4
4		A	 65% yield & 8% α -OAc	4.6 : 1
5		A	 52% yield & 7% α -OAc	2.2 : 1
6		A	 6% yield	1 : 14
7		B	 7% yield	1 : 7.6 ^c
8		C	 44% yield	d

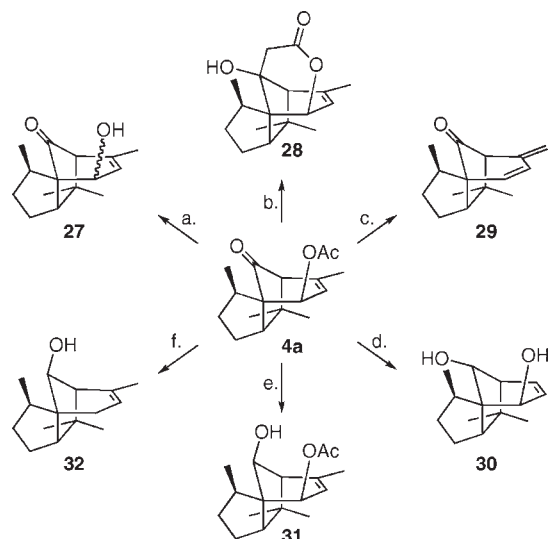
^a Conditions: (A) $\text{Pb}(\text{OAc})_4$ (1.05 equiv), CHCl_3 , -40°C . (B) 1.05 equiv of $\text{Pb}(\text{OAc})_4$, CHCl_3 , -40°C , remove **4g** by column chromatography, submit the remaining fractions to 5 M aqueous HCl. (C) $\text{Pb}(\text{OAc})_4$ (1.05 equiv), CHCl_3 , -40°C ; 5 M aqueous HCl. ^b Determined by crude $^1\text{H NMR}$. ^c Ratio of [5 + 2] adduct to *p*-acetoxylation products. ^d Complex mixture of regioisomers and diastereomers in the crude $^1\text{H NMR}$.

Stripping the aromatic core of its substitution resulted in a slight decrease in the overall efficiency as the reaction afforded **4b** in 54% yield (entry 2). Remarkably, we observed the same regio-

Scheme 3. α -Pipitzol (**2**) Synthesis and Unexpected Fragmentation^a

^a Reagents and conditions: (a) CrO_3 , H_2SO_4 , H_2O , 96%; (b) OsO_4 , THF, 79%; (c) *p*-TsOH, benzene, 80°C , 85%; (d) DMDO, acetone, 78%; (e) H_2SO_4 , AcOH, THF, silica gel, <15 mmHg, 70°C , 72%.

and stereoselective outcome for the acetic acid incorporation, as the addition reaction could be expected to produce a mixture of regioisomers. Removal of the benzylic stereocenter (R_3) proved most detrimental as the oxidation ceded a meager 32% yield of the compound **4c** (entry 3). We therefore believe that the benzylic substituent assists in positioning the tethered olefin for the subsequent cyclization. Indeed, the dearomatization of achiral bis-prenylated substrate **5d** afforded the anticipated adduct **4d** in 65% yield along with 8% of the diastereomeric acetate (entry 4). The ethylated derivative **5e** afforded a similar diastereomeric ratio upon oxidation, although the yield was not as high (entry 5). Oxidation of the disubstituted olefin derivative **5f** yielded **4f** as the sole tricyclic product in a poor yield (entry 6). This outcome likely suggests an olefin capable of stabilizing the incipient charge during the course of the reaction as a critical component for success. In the case of a *para*-methoxy residue **5g**, oxidation followed by acidic workup results mostly in the corresponding curcuquinone by hydrolysis of the *para*-acetoxy mixed ketal. However, a small amount of the desired adduct **4g** could be obtained (entry 7). This result implies that the predominate cation character rests with the *p*-phenoxonium contributor, which is intercepted by acetic acid, as opposed to the corresponding *o*-phenoxonium species **7**, which is intercepted by the tethered olefin in all the preceding reactions. In a somewhat similar manner, exchange of the aryl methyl residue for a methoxy group provided a mixture of tricyclic allylic acetates upon oxidation of **5h**. These crude materials subsequently converge to the β -diketone **4h** upon acidic workup (entry 8).

Scheme 4. Reactivity of the [5 + 2] Adduct 4a^a

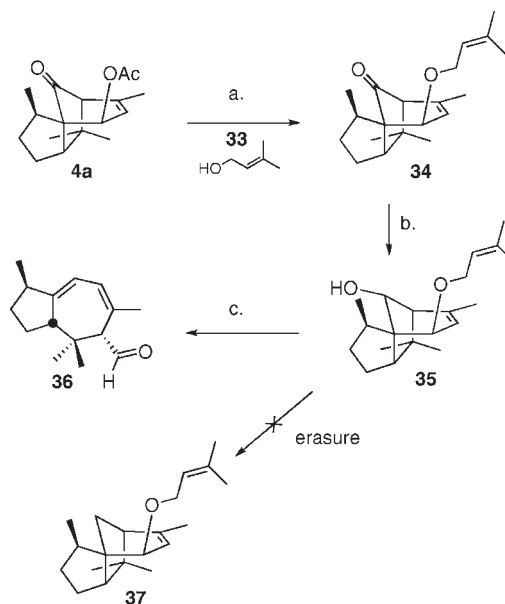
^a Reagents and conditions: (a) KCN, MeOH, 94%; (b) LDA, THF, 75%; (c) TBSOTf, Et₃N, 91%; (d) LiAlH₄, Et₂O, 62%; (e) Li⁰, NH₃, 35%; (f) Na⁰, NH₃, 83%.

Having established the scope for this new intramolecular cationic cascade replete with an unprecedented intermolecular termination step, we now chose to pursue the synthesis of compounds 1–3 from the tricyclic adduct 4a. The construction of α -cedrene (1) would require global erasure of both the acetate and the bridge ketone, whereas the synthesis of *sec*-cedrenol (3) would require the selective removal of the ketone. α -Pipitzol (2), on the other hand, would only require two oxidations of activated regions, and thus seemed the most straightforward target.

Synthesis of α -Pipitzol (2). Submission of the allylic acetate 4a to a Jones oxidation smoothly proceeded to afford the enone 21 (Scheme 3).¹⁹ At this juncture, we had imagined dihydroxylation followed by β -elimination would furnish α -pipitzol (2). Treatment of 21 with osmium tetroxide (1 equiv) and subsequent reductive workup (NaHSO₃) furnished the expected diol 22. However, its treatment with *p*-TsOH (0.3 equiv in benzene) failed to deliver α -pipitzol (2). Instead, the spiro lactone 25 emerged in a respectable 85% yield. We believe this material may result from a series of fragmentation reactions commencing with an acid catalyzed retro-aldol reaction to afford the α -hydroxy ketone 23. This intermediate undergoes hemiketalization to give compound 24, whereupon a second retro-aldol reaction furnishes the spirocyclic lactone 25.

To circumvent this rather debilitating series of events, we next considered epoxidation of the enone 21. All typical nucleophilic epoxidation reagents, as usually applied to enones, failed. Epoxidation was eventually carried out by prolonged exposure of the enone 21 to dimethyldioxirane (0.08 M in acetone, 4.5 equiv). Application of Hu's mixed-acid catalyst (H₂SO₄, AcOH, 70 °C, reduced pressure) for ring-opening of α,β -epoxyketones provided α -pipitzol (2) in good yield.²⁰

Approaches for *sec*-Cedrenol (3) and α -Cedrene (1). Our attention then turned toward the synthesis of *sec*-cedrenol (3), which initially seemed to be a simple exercise, as it only required selective erasure of the bridge ketone in 4a (Scheme 4). Attempts to affect this transformation, however, were beset by two factors: the congested nature of the ketone and the frailty of the allylic

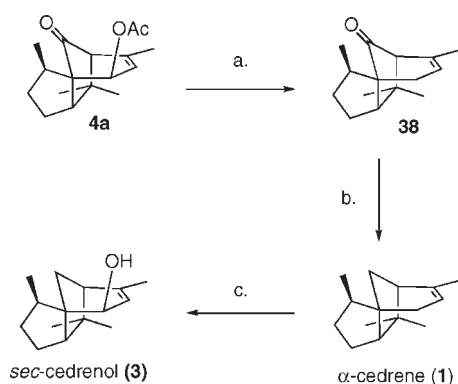
Scheme 5. Acetate Manipulation and Grob Fragmentation^a

^a Reagents and conditions: (a) BF₃·OEt₂, ROH, CH₂Cl₂, 77%, 4:1 dr; (b) LiAlH₄, Et₂O, 89%; (c) CDCl₃, 48 h, 88%.

acetate. For example, basic conditions, as required of most Wolff–Kishner reductions, led to saponification and epimerization of the allylic alcohol, presumably as a result of a retro-aldol/aldol equilibration. This outcome even occurred under mild conditions, such as deacylation by addition of KCN (0.5 equiv) to the acetate 4a (0.2 M in MeOH). This prevented consideration of any obvious alterations of the acetate protecting group on the allylic alcohol. A second drawback to basic conditions was the formation of the tetracycle 28, as observed upon treatment of 4 (0.5 M in THF) with lithium diisopropyl amide (1.2 equiv, 1.0 M in THF).

On the other hand, the allylic acetate in compound 4a did not fair better under acidic conditions, as might be required for formation of certain hydrazones.²¹ Treatment of 4a with a number of Lewis or Brønsted acids led to formation of the diene 29. Optimal conditions involved treatment of 4a (0.05 M in Et₃N) with *tert*-butyldimethylsilyltriflate (1.1 equiv). We suspect that this reaction proceeds by regeneration of the corresponding allylic cation 19, which undergoes elimination.

With our synthetic options disappearing before us, we next considered removal of the bridge ketone by application of a Barton–McCombie deoxygenation reaction of the properly outfitted carbonyl reduction product. Unable to effect a chemoselective hydride reduction, we eventually found that both carbonyls in 4a (0.48 M in THF, –78 °C) undergo reduction with LiAlH₄ (2.2 equiv) to produce the diol 30, as the result of hydride addition to the least sterically encumbered face of the bridge ketone. However, distinguishing between the alcohols in a subsequent derivatization process was problematic. Application of a single-electron reduction to 4a (16 equiv of Li⁰, 0.10 M in NH₃) solved this problem to some degree, resulting in a 41% yield of the alcohol 31. Similarly, employing sodium (35 equiv of Na⁰, 0.35 M in NH₃) as the dissolving metal provided the globally reduced product 32 in 83% yield.²² Despite our best efforts, after conversion of 31 and 32 into their respective xanthate ester,²³ phosphite,²⁴ or triflate²⁵ derivatives, all attempted

Scheme 6. Endgame for α -Cedrene (1) and *sec*-Cedrenol (3)^a

^a Reagents and conditions: (a) $\text{BF}_3 \cdot \text{OEt}_2$, Et_3SiH , CH_2Cl_2 , 94%; (b) KOH , H_2NNH_2 , $\text{O}(\text{CH}_2\text{CH}_2\text{OH})_2$, 125–215 °C, 52%; (c) $\text{Pb}(\text{OAc})_4$, benzene, 100 °C; NaOMe , MeOH , 68%.

radical erasures failed to provide the desired material and instead afforded complex mixtures of unassigned products.

With the shortcomings of the allylic acetate as a protecting group becoming all the more evident, we now sought to exchange it for a more robust residue by regeneration of the allylic cation **19** and interception with another oxygen nucleophile (Scheme 5). Several alcohols were investigated. However, of those tested, prenyl alcohol **33** afforded the highest diastereoselectivity ($\sim 4:1$) to provide the desired product **34**. Lithium aluminum hydride reduction of the ketone **34** proceeded with addition of the hydride occurring from the more accessible face to furnish the alcohol **35** (6.3:1 dr). However, the product proved unstable. Prolonged exposure of **35** to acidic media (CDCl_3) resulted in a fragmentation to afford the fused-[5.3]-decane skeleton **36** found in the hydroazulene family of natural products.²⁶ This Grob-like fragmentation deviates from the classical orbital alignment, and it is suggestive of a stepwise mechanism involving formation of corresponding allylic cationic intermediate. We were able to convert the alcohol **35** under basic conditions into its corresponding xanthate ester, phosphite, and triflate derivatives. Once again, application of the customary radical reduction reactions with these materials failed to afford the desired compound **37**.

We therefore chose to settle on a route to reach α -cedrene (**1**) by intercepting the penultimate intermediate **38** from the Wender synthesis,⁷ by using the propensity of the allylic acetate in **4a** to ionize to our advantage. We found that addition of Et_3SiH (4.5 equiv) and $\text{BF}_3 \cdot \text{OEt}_2$ (1.5 equiv) to compound **4a** (0.01 M in CH_2Cl_2) cleanly erased the acetate functionality and afforded the corresponding ketone **38**. Steric hindrance prohibits the required anti- $\text{S}_{\text{N}}2'$ approach of palladium required for a formate reduction of this allylic acetate. Treatment of **38** to a Wolff–Kishner reduction, as previously outlined by Wender, concluded our formal synthesis of α -cedrene (**1**).

Fortunately, an interesting observation that was reported during the synthesis of verbenone suggested a means for us to address *sec*-cedrenol (**3**) from α -cedrene (**1**) (Scheme 6).²⁷ During the initial step of the verbenone synthesis, oxyplumbation of α -pinene with $\text{Pb}(\text{OAc})_4$ in refluxing benzene resulted in the formation of the corresponding allylic tertiary acetate. However, in a footnote Paquette indicated that failure to remove lead oxide

upon the reaction's completion resulted in an allylic 1,3-transposition of the acetate. Because we ultimately desired the secondary alcohol, we chose to reflux α -cedrene **1** (0.9 M in benzene) with $\text{Pb}(\text{OAc})_4$ (1.05 equiv) for an extended time. The reaction proceeded as expected, whereupon the initial tertiary allylic acetate transformed entirely into the desired secondary allylic acetate. Upon completion of the reaction as determined by TLC, saponification with NaOMe afforded *sec*-cedrenol (**3**).

CONCLUSION

The complexity created during the biosynthesis of cedrol (**12**) inspired us to develop its synthetic equivalent. Phenols with various *ortho*-(pent-4-enyl) motifs were directly prepared from salicylaldehydes by a modification to our method for low temperature *o*-QM generation and consumption. The key transformation features the oxidative dearomatization of an *ortho*-(pent-4-enyl)-phenol (**5a–h**) followed by an intramolecular [5 + 2] cycloaddition of the respective phenoxonium intermediate across the tethered olefin to afford the respective derivatives of the tricyclo-[5.3.1.0^{1,5}]-undecane skeleton. This oxidative dearomatization-induced cascade reaction is unique as it proceeds in the absence of *para*-oxygen substituent. This distinction necessitates an unprecedented termination step, whereby a nucleophile engages the allylic cation that emerges from the [5 + 2] cycloaddition in a regioselective, diastereoselective, and intermolecular fashion, much like water engages the cedryl cation **11** that concludes the cascade leading to cedrol (**12**). Thus, by a combination of these two methods, we have succinctly demonstrated an ability to harness the reactivity of *o*-QMs and phenoxoniums, thereby leading to an unprecedented streamlined construction of many tricyclo-[5.3.1.0^{1,5}]-undecane derivatives.

In particular, three members of the cedranoid family were synthesized from **4a** and several remarkable fragmentations that are unique to the tricyclo-[5.3.1.0^{1,5}]-undecane skeleton were discovered from our efforts. α -Pipitzol (**2**) was constructed (racemic, five pots, 28% overall yield; enantioselective, eight pots, 14% overall yield). This is a significant improvement over prior efforts toward α -pipitzol (**2**). A formal synthesis of α -cedrene (**1**) was completed (racemic, four pots, 25% overall yield; enantioselective, seven pots, 13% overall yield), signifying the quickest and most efficient route to date. Finally, the first total synthesis of *sec*-cedranol (**3**) was completed (racemic, five pots, 17% overall yield; enantioselective, eight pots, 9% overall yield) and provides the first synthetic access to the most biologically active member of the cedranoid family.

ASSOCIATED CONTENT

S Supporting Information. Detailed experimental procedures, spectral characterization, and X-ray data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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