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Oxidative Entry into the *Illicium* Sesquiterpenes: Enantiospecific Synthesis of (+)-Pseudoanisatin

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Supporting Information

ABSTRACT: *Illicium* sesquiterpenes have been the subject of numerous synthetic efforts due to their ornate and highly oxidized structures as well as significant biological activities. Herein we report the first chemical synthesis of (+)-pseudoanisatin from the abundant feedstock chemical cedrol (~$50 USD/kg) in 12 steps using extensive site-selective C(sp^3)−H bond functionalization. Significantly, this work represents a novel oxidative strategic template for future approaches to these natural products and their analogs.

Since the report of pseudoanisatin (**1**) and anisatin (**2**) in 1968 by Yamada and co-workers from Japanese star anise (*Illicium anisatum*), more than 50 sesquiterpenes containing the *seco*-prezizaane skeleton have been isolated from plants of the *Illicium* genus.[1,2] For decades, these natural products have attracted significant synthetic attention owing to their diverse oxidation patterns and notable biological activities (Figure 1). Pseudoanisatin (**1**) and its congeners contain a bridging ϵ-lactone, while anisatin (**2**) and associated compounds present an unusual spiro β-lactone motif. Other members present elaborate variations on this theme; most notably, hydroxylation is found at every potentially oxidizable position on the 15-carbon framework. Each of these structures is also marked by unique and varied phenotypic outputs, although such effects appear to stem from modulation of the γ-aminobutyric acid (GABA) receptors.[2,3] For instance, anisatin (**2**) is one of the most powerful poisons of plant origin (murine LD_{50} < 1 mg/kg),[4] whereas pseudoanisatin (**1**) is nontoxic and shows marked selectivity for insect GABA receptors (IC_{50}^{fly} = 376 nM, IC_{50}^{rat} > 10^4 nM) implying potential as an insecticide.[5] Related jiadifenolide (**4**) and jiadifenin (**5**) promote neurite outgrowth at low concentrations,[3c] whereas **1** and **2** are not reported to have this ability.[2]

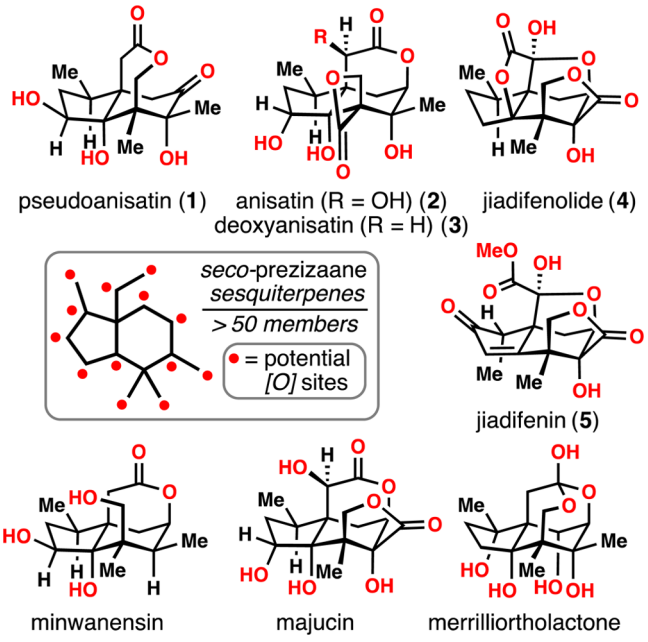

Figure 1. *Illicium* sesquiterpenes possessing the *seco*-prezizaane framework.

Many highly creative syntheses have been disclosed for various *seco*-prezizaane *Illicium* family members, with anisatin (**2**),[6] jiadifenolide (**4**),[7] and jiadifenin (**5**)[8] attracting the most synthetic attention to date.[9] The efficiency with which these compounds can be prepared synthetically, however, varies greatly according to structural type and oxidation pattern, with syntheses ranging from a remarkable 8 steps to **4**,[7e] 22 steps to **3**,[6c] and over 40 steps to **2**.[6a,b] Given that the hydroxylation pattern of the *Illicium* sesquiterpenes also appears to govern their biological effects, we sought a synthetic strategy that would be flexible in its introduction of such units and viewed **1** as an entry point to this family. To accomplish this objective, we drew upon the proposed biosynthesis of these compounds as inspiration.

The biosynthesis of *seco*-prezizaane sesquiterpenes has not been fully elucidated biochemically, but has been proposed to commence with cyclization of farnesyl pyrophosphate to the bisabolyl cation (**6**) (Figure 2).[2] Through a series of hydride shifts and cationic cyclizations, the polycyclic cedrane skeleton (**7**) is rapidly forged. A 1,2-alkyl shift converts **7** into the *allo*-cedrane framework (**8**), which undergoes C−C bond cleavage furnishing the core *seco*-prezizaane ring system (**9**).

Individual members are then tailored by extensive C−H hydroxylation. In contemplating a semisynthetic approach to this family, a strategy which has had a profound impact on the synthesis of steroids,[10] we were dismayed to find that no readily abundant starting materials with the skeleton of **9** are available. The sesquiterpene (+)-cedrol (**10**), however, which bears the ring system of **7**, is an exceedingly inexpensive terpene feedstock extracted from Texas cedarwood ($52 USD/kg). Our goal therefore became the conversion of this abundant and unfunctionalized terpene into the rare *Illicium* sesquiterpenes.

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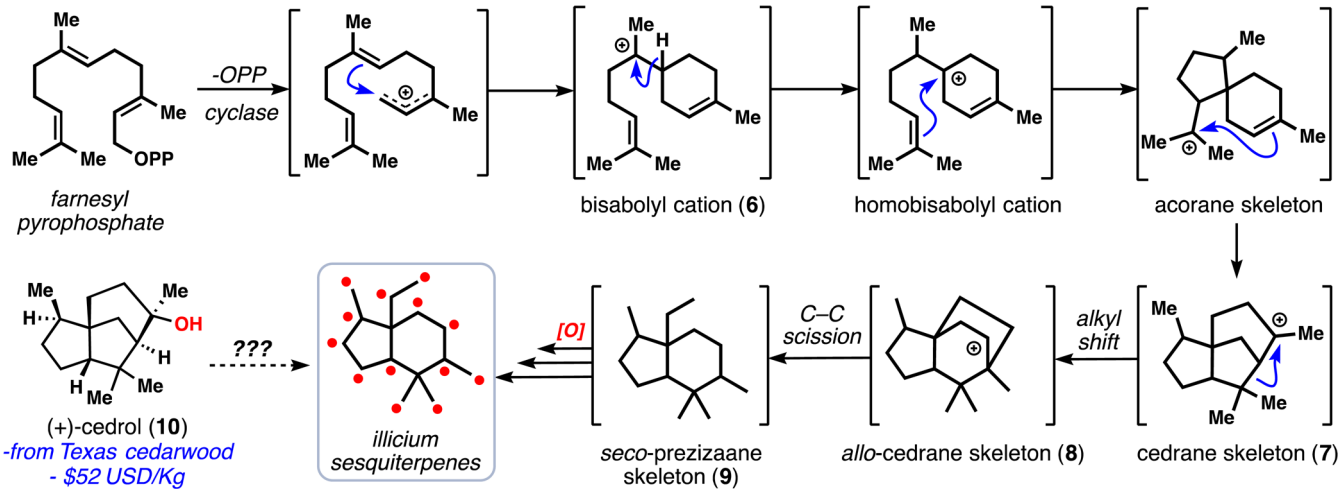

Figure 2. Proposed biosynthetic pathway to *seco*-prezizaane *Illicium* sesquiterpenes inspires a semisynthetic approach.

Such an endeavor entails not only the exploration of extensive C(sp^3)–H bond functionalization[11,12] but also carbon–carbon bond reorganization. Herein we document the realization of this blueprint resulting in the first chemical synthesis of pseudoanisatin (**1**) in 12 steps from cedrol.

We began our synthetic studies by first oxidizing the gem-dimethyl group of cedrol, a task easily accomplished with Suarez's radical-based method (I_2/PhI(OAc)$_2$, floodlamp) on 50–100 mmol scales.[13] The strained tetrahydrofuran ring subsequently formed could be methylated and eliminated via the action of Meerwein's salt (Me_3OBF_4) and mild base (proton sponge) affording methoxy cedrene **11** in near quantitative yield (10-g scale). The trisubstituted olefin of **11** was oxidatively cleaved using *in situ* generated RuO_4 (via $NaIO_4$/cat. $RuCl_3$) and afforded keto-acid **12** in good yield on decagram scales. Significant difficulties were quickly encountered in attempting to elicit an α-oxidation of the methyl ketone at the hindered internal position. Canonical strategies such as thermodynamic enolate formation and subsequent oxidation all failed. Ultimately, it was found that simply heating keto-acid **12** to 150 °C in the presence of anhydrous $CuBr_2$ (3.0 equiv) and *t*-BuOH (3.0 equiv) cleanly forged lactone **13** via direct, intramolecular acyloxylation.[14]

With lactone **13** in hand, we were poised to investigate methods to convert the 5,5-fused ring system of the cedranes into the 5,6-fused *seco*-prezizaane skeleton and the venerable α-ketol rearrangement appeared to be a logical choice.[15] After extensive experimentation, we found that treating **13** with KOH/KO*t*-Bu in DMSO initiated lactone hydrolysis, presumably forming potassium alkoxide **14**, which then underwent an α-ketol rearrangement to generate **15** as a 4:1 mixture of diastereomers in 45% combined yield. This reaction could be easily scaled to the gram level, and the stereochemistry of the major product, which bears the correct stereochemistry for all *seco*-prezizaane *Illicium* sesquiterpenes, was confirmed by X-ray crystallographic analysis. Although many conditions, both acidic and basic, have been reported to promote α-ketol rearrangements, we found the potassium counterion to be crucial in our system. Furthermore, subjecting either pure diastereomer of **15** to the reaction conditions established the same 4:1 mixture implying the observed diastereoselectivity is a result of thermodynamic control.

Moving forward, the tertiary alcohol of **15** was silylated (NaH, TBSCl) affording compound **16** and setting the stage for a crucial C–H activation reaction of the unactivated tertiary methine center. Considering quaternary carbons on both sides flank its position, we reasoned that a successful oxidation of this position would likely need to be directed by the internal carboxylic acid moiety. Taking inspiration from the general observations of White and others, we reasoned that nonheme iron catalysis could potentially forge a lactone ring directly.[16–18] Nevertheless, with an alkyl ether, silyl ether, and several C–H bonds within reach of the pendant carboxylic acid present, substrate **16** would test the limits of this chemistry. After extensive experimentation, we found that iron catalysts bearing the pinene-based mepp ligand architecture popularized by Costas were able to promote this reaction, resulting in a combined 37% yield of lactone products (see **17**–**19**) along with 18% recovered starting material.[19,20] The structure of the major product (**17**) was confirmed by X-ray crystallographic analysis of a desilylated derivative (Scheme 1). Loss of the silicon-based protecting group during the reaction was significantly problematic, as the iron catalyst was found to decompose this unprotected material competitively, without promoting the desired, directed C–H oxidation. Nevertheless, both **17** and **18** could be directly utilized in the synthesis without further manipulation, and thus the combined 30% yield of these products proved to be workable in completing exploratory studies.[21] Lactone **17** was then ethylated and eliminated (Et_3OPF_6, proton sponge) affording alkene **20**. Much to our delight, *in situ* formed TMSI (TMSCl, NaI) cleanly dealkylated the methyl ether and following treatment with TBAF, compound **21**, which contains the ε-lactone characteristic of pseudoanisatin was formed. Dihydroxylation of the trisubstituted alkene in **21** was then attempted and previous work, particularly Kende's pioneering synthesis of **3**, hinted that reagent approach would come from the desired α-face.[6] However, treatment of **21** with OsO_4 in pyridine afforded exclusively the undesired diastereomer (**22**) in which the jiadifenolide-type lactone has been reconstructed and the primary hydroxyl group has formed a hemiketal. Fortunately, Donohoe's procedure for dihydroxylation directed by a homoallylic alcohol (OsO_4·TMEDA), overrode this facial bias resulting in the formation of **23**.[22] Finally, mesylation of **23** (MsCl/pyridine) followed by treatment with aqueous sodium hydroxide promoted secondary alcohol inversion thus completing a 12-step synthesis of (+)-pseudoanisatin (**1**) from (+)-cedrol.

In summary, biosynthesis-guided synthetic planning coupled with the exploration of selective C(sp^3)–H oxidation reactions

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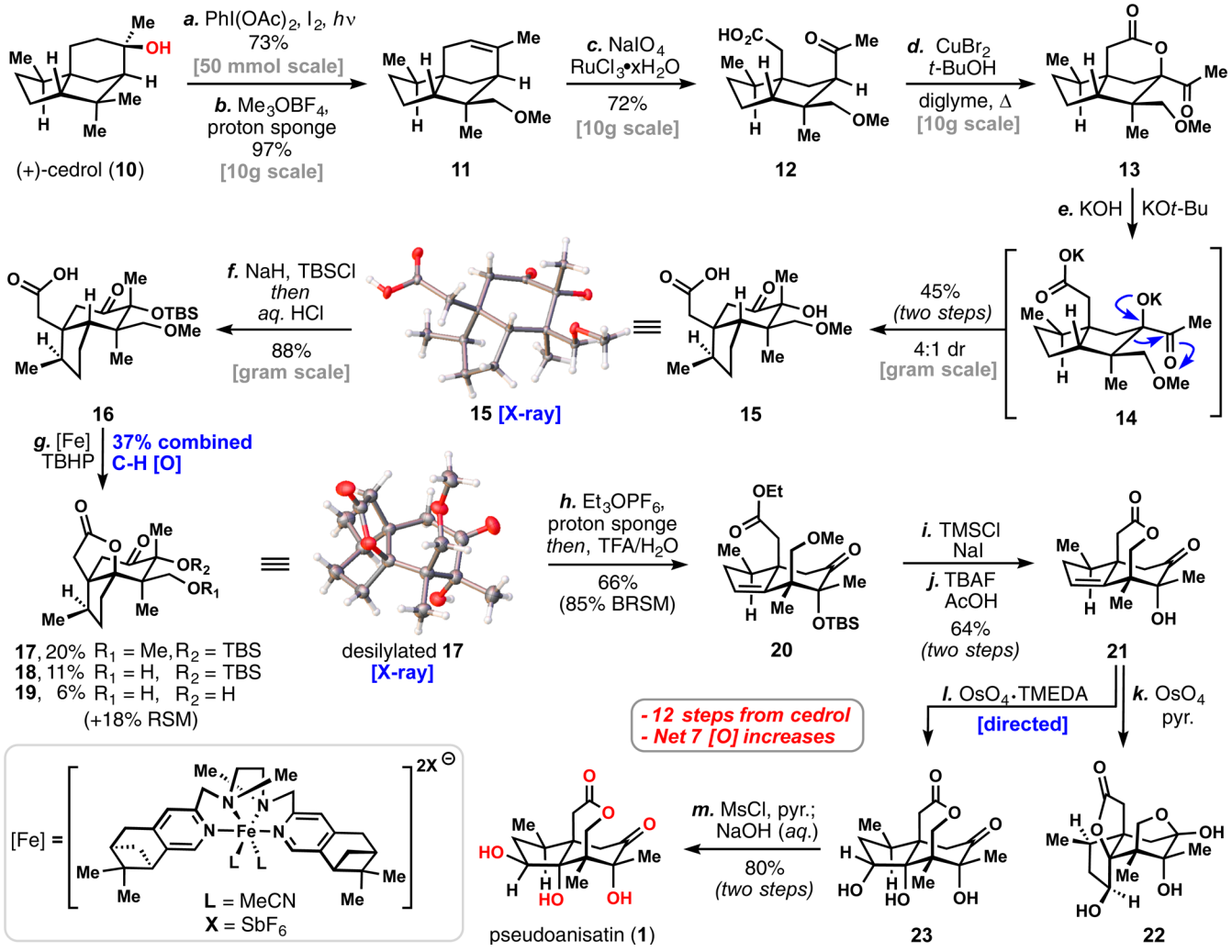
Scheme 1. 12-Step Synthesis of (+)-Pseudoanisatin (1) from (+)-Cedrol (10)[a]



[a]Reagents and conditions: (a) $PhI(OAc)_2$ (3.0 equiv), I_2 (1.0 equiv), cyclohexane, $h\nu$ (visible), 1.5 h, 73%; (b) Me_3OBF_4 (1.5 equiv), proton sponge (1.5 equiv), DCM, 55 °C, 12 h, 97%; (c) $NaIO_4$ (5.0 equiv), $RuCl_3{\cdot}xH_2O$ (0.1 equiv), CCl_4:MeCN:H_2O (3:3:4), 1 h, 72%; d) $CuBr_2$ (3.0 equiv), *t*-BuOH (3.0 equiv), diglyme, 150 °C, 12 h; (e) KOH (1.0 equiv), KO*t*-Bu (3.0 equiv), DMSO, 14 h, 45% (*two steps*), d.r. = 4:1; (f) NaH (5.0 equiv), TBSCl (4.0 equiv), THF, 65 °C, 8 h *then add* 3.0 M HCl (16 equiv), 65 °C, 16 h, 88%; (g) TBHP (5.0 equiv), [Fe] (0.5 equiv), Tl(OTf) (0.5 equiv), MeCN, 1 h, 20% **17**, 11% **18**, 6% **19**; (h) Et_3OPF_6 (3.0 equiv), proton sponge (3.0 equiv), DCE, 85 °C, 12 h *then add* TFA/H_2O (1:1), rt, 45 min, 66%; (i) TMSCl (10.0 equiv), NaI (5.0 equiv), MeCN, 80 °C, 12 h; (j) TBAF (5.0 equiv), AcOH (1.0 equiv), THF, 1 h, 64% (*two steps*); (k) OsO_4 (1.5 equiv), pyr., 12 h, 63%; l) OsO_4·TMEDA (1.5 equiv), DCM, −78 °C to rt, 2 h; (m) MsCl (10.0 equiv), pyr. (10.0 equiv), DCM, 12 h, *then add aq.* NaOH (2.0 M), 2 h, 80% (*two steps*). Proton sponge = 1,8-bis(dimethylamino)naphthalene, TBS = *tert*-butyldimethylsilyl, [Fe] = [Fe((*R*)-mepp) $(MeCN)_2$][$(SbF_6)_2$], TBHP = *tert*-butyl hydroperoxide, DCE = 1,2-dichloroethane, TMS = trimethylsilyl, TMEDA = tetramethylethylenediamine.

and a skeletal rearrangement strategy, has allowed for the first chemical synthesis of (+)-pseudoanisatin (**1**) in 12-steps. The route to **1** from cedrol represents the first fully oxidative strategy toward this coveted sesquiterpene family, a blueprint we envision allowing for both the synthesis of numerous *Illicium* sesquiterpenes and their heteroatom analogs. Moreover, this work further attests to both the power, as well as current practical limitations, of C−H oxidation pathways in complex synthetic planning.[23] We foresee future efforts in this area leading to an enhanced toolset of compounds for neuroscience as well as improved reagents for oxidative chemistry in complex molecular settings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11739.

Experimental procedures and spectroscopic data for all compounds and X-ray crystallographic data for **15** and **17-TBS** (PDF)

Data for **15** (CIF)

Data for **17-TBS** (CIF)

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Notes

The authors declare no competing financial interest.

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