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Total Syntheses of (−)-Majucin and (−)-Jiadifenoxolane A, Complex Majucin-Type *Illicium* Sesquiterpenes

Matthew L. Condakes, Kevin Hung, Stephen J. Harwood, and Thomas J. Maimone*

Department of Chemistry, University of California-Berkeley, 826 Latimer Hall, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: We report the first chemical syntheses of both (−)-majucin and (−)-jiadifenoxolane A via 10 net oxidations from the ubiquitous terpene (+)-cedrol. Additionally, this approach allows for access to other majucin-type sesquiterpenes, like (−)-jiadifenolide, (−)-jiadifenin, and (−)-(1*R*,10*S*)-2-oxo-3,4-dehydroxyneomajucin (ODNM) along the synthetic pathway. Site-selective aliphatic C(sp^3)-H bond oxidation reactions serve as the cornerstone of this work which offers access to highly oxidized natural products from an abundant and renewable terpene feedstock.

Exclusive to the *Illicium* species of plants, *seco*-prezizaane sesquiterpenes are noted for their highly oxidized polycyclic architectures. Within this family, over 20 members possess the majucin core, including the eponymous member (−)-majucin (**1**), first isolated in 1988 from pericarps of the Chinese flowering plant *Illicium majus* (Figure 1A).[1,2] Majucinoids are among the most highly oxidized members of the *seco*-prezizaane family, and **1** in particular features a complex scaffold containing both a bridging δ-lactone and a fused γ-lactone, along with four stereodefined hydroxyl groups in close proximity.[2] These attributes loom as challenges to chemical synthesis efforts, and indeed, majucin stands as one of the few flagship *Illicium* sesquiterpenes yet to succumb to chemical synthesis. Work toward the synthesis of other majucin-type natural products, however, has been prolific. Jiadifenin (**4**), the first member of this subtype to fall to synthetic efforts, has been prepared on multiple occasions.[3] (−)-(1*R*,10*S*)-2-Oxo-3,4-dehydroxyneomajucin (ODNM, **3**) serves as the direct precursor to **4** in the aforementioned syntheses and thus has also been synthesized.[3] By far though, (−)-jiadifenolide (**5**) has received the most attention from the synthetic community with a multitude of impressive formal and total syntheses reported.[4,5] No doubt such interest has arisen from the long-known GABA-modulatory properties of members of this *Illicium* class and especially the ability of **2**−**5** (and derivatives) to promote neurotrophic phenotypes in both cultured rat cortical neurons and, more recently, human induced pluripotent stem cells.[3a,d,5k,6−8] To the best of our knowledge, the neurotrophic activity of **1** has not been reported.

As part of our continued efforts directed toward a unifying synthesis of all *Illicium* sesquiterpenes using C(sp^3)−H activation strategies,[9] we recently disclosed an oxidative approach to the simpler family member (+)-pseudoanisatin (**6**) from the abundant sesquiterpene (+)-cedrol (Figure 1B).[10]

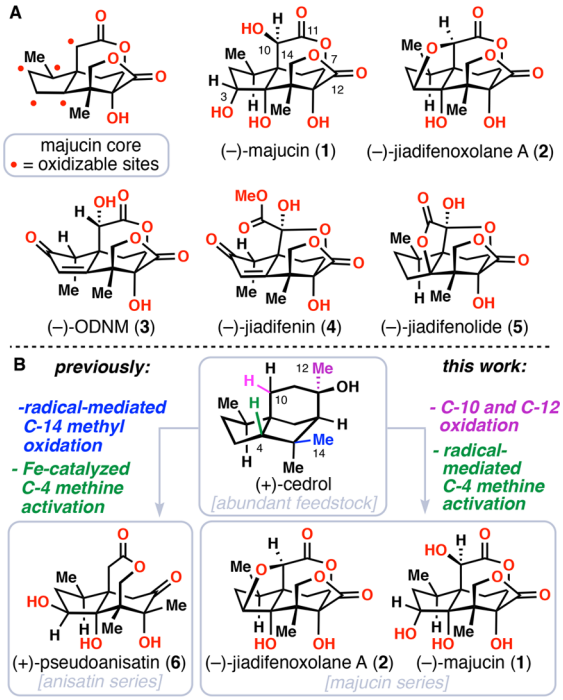

Figure 1. (A) Complex majucinoids from *Illicium sp.* (B) An oxidative strategy for the construction of *Illicium* sesquiterpenes from the feedstock chemical (+)-cedrol.

During our work, iron- and radical-mediated oxidations of the cedrol C-4 methine (shown in green) and C-14 methyl positions (shown in blue) respectively were employed as key steps. In extending this strategy to the more highly oxidized majucinoids, such as **1** and **2**, it is also necessary to oxidize all the C−H bonds of the C-12 methyl group and the indicated C−H bond of the C-10 methylene (both shown in magenta, *seco*-prezizaane numbering). Moreover, the low yields encountered in previous studies using acid-directed Fe-catalysis prompted us to seek alternative solutions to the C-4 methine oxidation problem. Herein, we present our studies toward realizing these—and other—goals which have culminated in the first chemical syntheses of (−)-majucin (**1**) and (−)-jiadifenoxolane A (**2**) via 10 net oxidations from (+)-cedrol. Moreover, formal syntheses of (−)-ODNM (**3**), (−)-jiadifenin (**4**), and (−)-jiadifenolide (**5**) have also been accomplished along the way.

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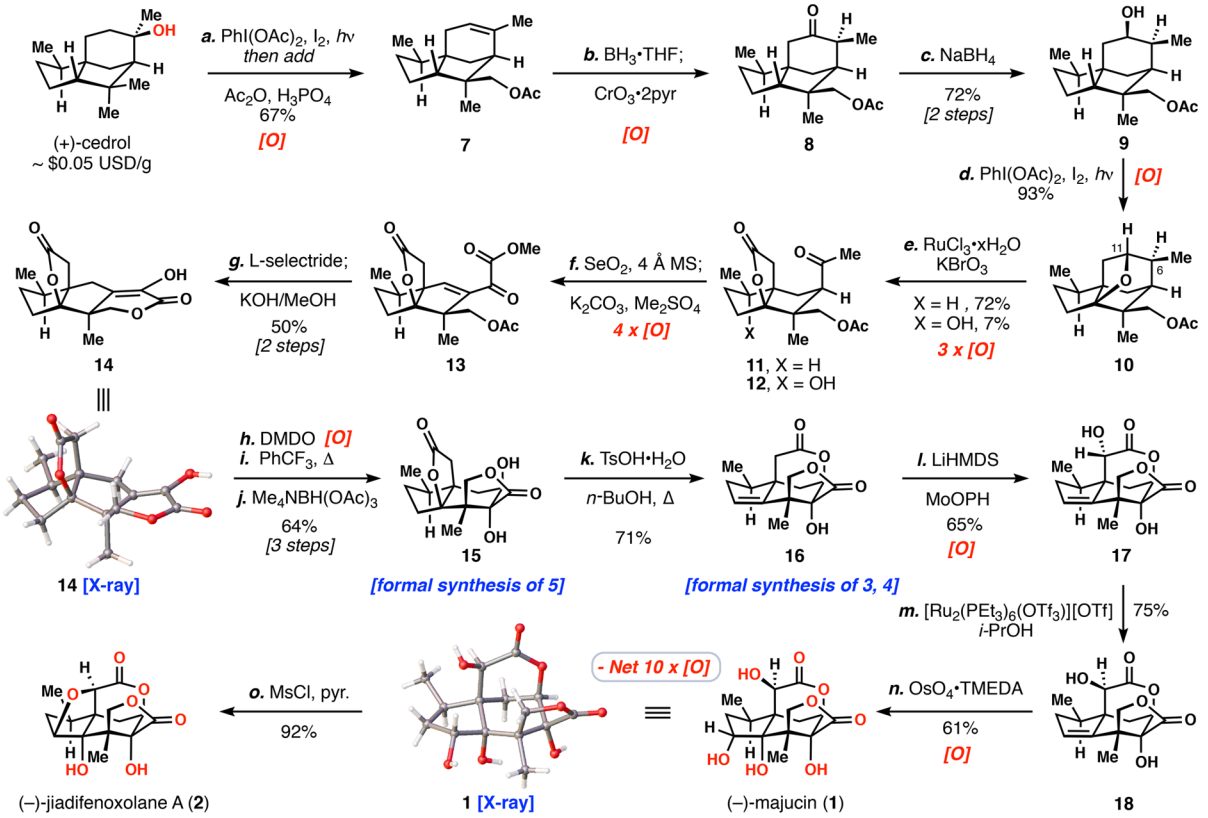
Scheme 1. Synthesis of Complex Majucinoids[a]



[a]Reagents and conditions: (a) $PhI(OAc)_2$ (1.1 equiv), I_2 (0.4 equiv), cyclohexane, *hν* (visible), 1.5 h *then* Ac_2O (10.0 equiv), H_3PO_4 (2.0 equiv), 67%; (b) BH_3·THF (1.3 equiv), THF, 1.5 h *then* CrO_3·2pyr (25.0 equiv), DCM, 30 min; (c) $NaBH_4$ (1.5 equiv), MeOH, 30 min, 72% *over two steps*; (d) $PhI(OAc)_2$ (3.0 equiv), I_2 (1.0 equiv), DCM, *hν* (visible), 0 °C, 1.5 h, 93%; (e) $KBrO_3$ (2 × 5.0 equiv), $RuCl_3$·xH_2O (3 × 0.03 equiv), MeCN/CCl_4/H_2O (2:2:3), 75 °C, 3 d, 72% of **11**, 7% of **12**; (f) SeO_2 (3.5 equiv), 4 Å MS (1.0 mass equiv), diglyme, 130 °C, 4 h *then* K_2CO_3 (3.0 equiv), Me_2SO_4 (1.5 equiv), 1 h; (g) L-selectride (1.2 equiv), THF, −78 °C, 30 min *then* KOH (10.0 equiv), MeOH, 0 °C, 30 min, 50% *over two steps*; (h) DMDO (1.5 equiv), 12 h; (i) $PhCF_3$, 170 °C, 2 h; (j) $Me_4NBH(OAc)_3$ (7.0 equiv), MeCN/AcOH (3:1), − 40 °C, 16 h, 64% *over three steps*; (k) TsOH·H_2O (2.2 equiv), *n*-BuOH, 150 °C, 26 h, 71%; (l) LHMDS (3.0 equiv), MoOPH (5.0 equiv), THF, −78 → 0 °C, 2.5 h, 65%; (m) $[Ru_2(PEt_3)_6(OTf)_3](OTf)$ (0.1 equiv), NMM (0.2 equiv), TFE/dioxane (1:1), 120 °C, 18 h *then* *i*-PrOH (3.0 equiv), 120 °C, 5 h, 75%; (n) OsO_4·TMEDA (1.0 equiv), DCM, −78 → 0 °C, 2 h *then* $NaHSO_3$ (10.0 equiv), H_2O, 16 h, 61%; (o) MsCl (5.0 equiv), pyr. (10.0 equiv), DCE, rt →80 °C, 15 h, 92%. DMDO = dimethyldioxirane, LHMDS = lithium bis(trimethylsilyl)amide, MoOPH = oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide).

We began our synthetic studies in analogy to previous work on **6**, but found that the strained THF ring formed in the initial Suárez oxidation (I_2, $PhI(OAc)_2$, *hν*) could be conveniently converted to acetoxy cedrene (**7**) simply by adding acetic anhydride and phosphoric acid directly to the reaction mixture (Scheme 1). This procedure delivered **7** in 67% yield and on 120 mmol scale.[11] Diverging from past work, in which an olefin oxidative cleavage reaction was used to generate a keto acid,[10] we found that **7** could be converted into ketone **8** directly via a hydroboration/double oxidation sequence (BH_3·THF/CrO_3·2pyr.). The use of Collin's reagent avoided hydrolysis of the acetate protecting group as compared to many other oxidants examined. Ketone **8** was then easily reduced ($NaBH_4$) from the convex face to give alcohol **9** in 72% yield over 2 steps as essentially a single diastereomer. Taking inspiration from the work of Waegell on simpler cedrene scaffolds,[12] we explored the use of Suárez conditions to oxidize the C-4 methine position at this stage. Owing to the very close spatial proximity of the secondary hydroxyl to the ring junction C-4 methine, an exceptionally high yielding (93%) C−H functionalization ensued (I_2, $PhI(OAc)_2$, *hν*). In contrast to our previous work employing iron complexes to oxidize this position, the presence of preexisting C-14 oxidation had little impact on this transformation. Next, prolonged stirring with *in situ* generated RuO_4 ($RuCl_3$·xH_2O, $KBrO_3$) accomplished a remarkably clean triple oxidation reaction, cleaving the C-6/C-11 bond and delivering ketone lactone **11**.[12,13] While not optimized, we were also able to isolate quadruple oxidation product **12** wherein an additional C−H bond has been hydroxylated.[14]

With the construction of the tricyclic propellane-like core accomplished in five steps, we were poised to address the crucial majucin-type *γ*-lactone which called for the exhaustive oxidation of the cedrol C-12 methyl group (*vide supra*). In a single, remarkable step, we found that a quadruple oxidation of *all* C−H bonds *α* to the ketone group in **13** was achieved under anhydrous Riley oxidation conditions (SeO_2, 4 Å MS, Δ).[15] In order to facilitate handling of this compound, it proved essential to methylate the intermediate acid (K_2CO_3, Me_2SO_4) prior to workup, thus delivering unsaturated keto ester **13**. Upon treatment of **13** with L-selectride, a diastereomeric mixture of allylic alcohols was obtained via 1,2-reduction of the ketone moiety. When the reaction was quenched with basic methanol, both intermediates converged to enol lactone **14**, presumably via an acetate cleavage/translactonization/alkene isomerization

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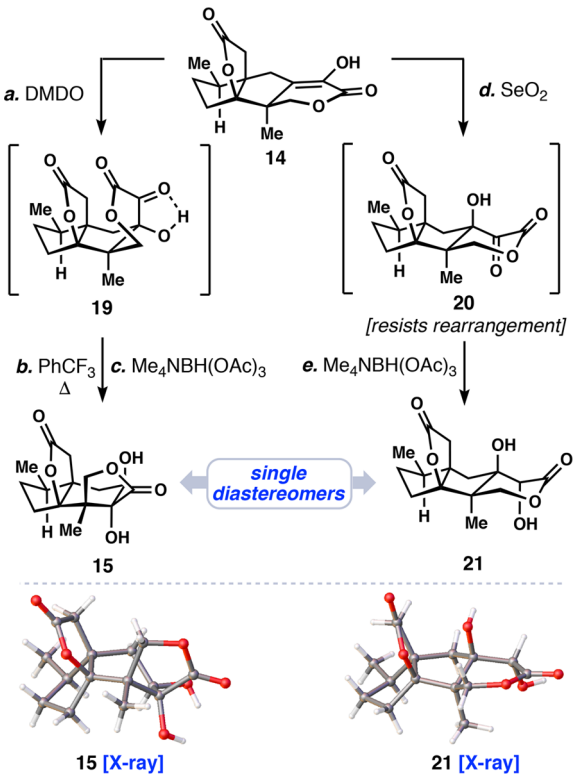
cascade process. Overall **14**, whose rigid tetracyclic skeleton was confirmed by X-ray crystallographic analysis, was obtained in 50% yield from **11** without intermediate silica-gel purification.

In order to rearrange the 5,5-fused ring system found in tetracycle **14** into the majucinoid 5,6-fused core typified by **1**−**5**, we envisioned employing an α-ketol rearrangement. However, unlike our previous work on **6**, this system required a transannular bond migration event (Scheme 2). Experimentally,

Scheme 2. Stereochemical Considerations for the α-Ketol Rearrangement of Enol Lactone 14[a]



[a]Reagents and conditions: (a−c) See Scheme 1; (d) SeO_2 (2.0 equiv), pyr, 110 °C, 16 h; (e) $Me_4NBH(OAc)_3$ (7.0 equiv), MeCN/AcOH (3:1), −40 °C, 16 h, 51% over two steps.

we found that enol lactone **14** could be oxidized to a single, somewhat unstable, α-hydroxyketone diastereomer (see **19**) using DMDO. A solvent swap from acetone to trifluorotoluene followed by heating to 170 °C elicited clean bond reorganization to the majucin core. Precedented directed reduction ($Me_4NBH(OAc)_3$) of the α-ketol group then furnished known tetracyclic diol **15** in 76% yield over 3 steps, without the need for intermediate silica-gel purification, and as essentially a single diastereomer. The structure of **15**, which completes a formal synthesis of **5**,[3d,4,16] was secured by X-ray crystallographic analysis.

Exploration into the diastereoselective oxidation of the enol lactone **14** revealed that while DMDO gave α-ketol **19** selectively, formation of the epimeric α-ketol **20** could be accomplished with SeO_2 (Scheme 2).[17] Reduction of **20** gave diol **21** and X-ray crystallographic analysis unambiguously assigned its stereochemistry. Although the rearrangement of α-ketol **19** was facile, **20** did not rearrange under a variety of conditions.[18]

To gain access to **1** and **2**, we first converted the jiadifenolide-type γ-lactone ring system into the δ-lactone system via simple treatment with acid (TsOH/*n*-BuOH, Δ) which unveiled trisubstituted alkene-containing **16** in 71% yield (Scheme 1). Theodorakis and co-workers have demonstrated the synthesis of (−)-ODNM (**3**) and (−)-jiadifenin (**4**) in two and three steps, respectively, from **16**.[3d,16] Direct α-hydroxylation of δ-lactone **16** from the convex face had been reported using the Davis oxaziridine, although reagent byproduct removal proved problematic.[3d] Seeking an alternative method, we found that enolate oxidation with the molybdenum(VI) reagent MoOPH led to the isolation of clean hydroxy lactone **17**.[19] We viewed **17** as an excellent testing grounds for Hartwig's recently reported epimerization methodology via Ru-catalyzed transfer hydrogenation.[20] Much to out delight, the catalyst $[Ru_2(PEt_3)_6(OTf)_3][OTf]$ in combination with isopropanol delivered diastereomer **18**, a recently isolated natural product itself,[21] cleanly in 75% yield. To complete the synthesis of majucin (**1**) a challenging dihydroxylation was required. While we observed no desired reactivity of **18** with OsO_4, application of precomplexed osmium tetroxide and tetramethylethylenediamine (OsO_4·TMEDA) ultimately provided (−)-majucin (**1**) in 61% yield.[22] X-ray crystallographic analysis unambiguously confirmed the structure of **1**. Finally, selective monomesylation (MsCl, pyr.) of (−)-majucin followed by heating elicited a high-yielding intramolecular etherification to give neurotrophic natural product (−)-jiadifenoxolane A (**2**) in 92% yield. While the enzymatic pathways to **1**−**5** are not known, this facile displacement could have relevance to the biosynthetic connection between **1** and **2**.

In summary, we have demonstrated the first chemical synthesis of the complex majucin-type natural products (−)-majucin (**1**) and (−)-jiadifenoxolane A (**2**) in 14 and 15 steps, respectively, and the formal synthesis of (−)-ODNM (**3**), (−)-jiadifenin (**4**), and (−)-jiadifenolide (**5**) from the chiral-pool feedstock (+)-cedrol, a building block available for ∼$0.05 USD/gram.[23] During this process, 13 oxidations were employed; however, 3 reduction steps were necessary for oxidation state and stereochemical adjustments,[24] highlighting existing gaps in the oxidative synthetic repertoire. Nevertheless, combined with our previous C−H hydroxylation strategy for the anisatin series, this work definitively establishes (+)-cedrol as a versatile platform for the synthesis of nearly all subtypes of *seco*-prezizaane natural products. Moreover, the formation of C−H hydroxylated intermediate **12** hints to the possibility of accessing even further oxidized, unnatural analogs of these sesquiterpenoids using similar chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b11493.

X-ray crystallographic data for **1** (CIF)
X-ray crystallographic data for **14** (CIF)
X-ray crystallographic data for **15** (CIF)
X-ray crystallographic data for **21** (CIF)
Experimental procedures and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*maimone@berkeley.edu

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ORCID

Kevin Hung: 0000-0001-6177-3427

Thomas J. Maimone: 0000-0001-5823-692X

Notes

The authors declare no competing financial interest.

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(16) See the Supporting Information for the precise routes to the indicated natural products.

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