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

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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 (−)-(1R,10S)-2-oxo-3,4-dehydroxynemo-majucin (ODNM) along the synthetic pathway. Site-selective aliphatic C(sp³)-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 (−)-(1R,10S)-2-Oxo-3,4-dehydroxynemo-majucin (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,3d,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(sp³)-H activation strategies,7 we recently disclosed an oxidative approach to the simpler family member (−)-pseudoanisatin (6) from the abundant sesquiterpene (+)-cedrol (Figure 1B).10

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.
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 (I2, PhI(OAc)2, hv) 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.10 We found that 7 could be converted into ketone 8 directly via a hydroboration/double oxidation sequence (BH3·THF/CrO3·2pyr). The use of Collin’s reagent avoided hydrolysis of the ketone protecting group as compared to many other oxidants employed in this stage. Owing to the very close spatial proximity of the secondary hydroxyl to the ring junction C-4 methine, an allylic alcohol was obtained via 1,2-reduction of the ketone (vide supra).10 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 ketone oxidation reaction, cleaving the C-6/C-11 bond and delivering ketone lactone 11. Upon treatment of 13 with L-selectride, a diastereomeric mixture of allylic alcohols was obtained via 1,2-reduction of the ketone α,β bonds (vide supra).15 In order to facilitate handling of this compound, it proved essential to methylate the intermediate acid (K2CO3, Me2SO4) prior to workup, thus delivering unsaturated keto ester 14.12,13 While not optimized, we were also able to achieve exceptionally high yielding (93%) C–H functionalization ensued (I2, PhI(OAc)2, hv). 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 Ru4O12 (RuCl3·xH2O, KBrO4) accomplished a remarkably clean triple oxidation reaction, cleaving the C-6/C-11 bond and delivering ketone lactone 11.15,12

Reagents and conditions: (a) PhI(OAc)2 (1.1 equiv), I2 (0.4 equiv), cyclohexane, hv (visible), 1.5 h then Ac2O (10.0 equiv), H3PO4 (2.0 equiv), 67%; (b) BH3·THF (1.3 equiv), THF, 1.5 h then CrO3·2pyr. (25.0 equiv), DCM, 30 min; (c) NaBH4 (1.5 equiv), MeOH, 30 min, 72% over two steps; (d) PhI(OAc)2 (3.0 equiv), I2 (1.0 equiv), DCM, hv (visible), 0 °C, 1.5 h, 93%; (e) KBrO4 (2 x 2.5 equiv), RuCl3·xH2O (3 x 0.03 equiv), MeCN/CCl4/H2O (2:2:3), 75 °C, 3 d, 72% of 11, 7% of 12; (f) SeO2 (3.5 equiv), 4 Å MS (1.0 mass equiv), diglyme, 130 °C, 4 h then K2CO3 (3.0 equiv), Me2SO4 (1.5 equiv), 1 h; (g) t-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) PhCF3, 170 °C, 2 h; (j) Me4NBH(OAc)3 (7.0 equiv), MeCN/AcOH (3:1), −40 °C, 16 h, 64% over three steps; (k) TsOH·H2O (2.2 equiv), n-BuOH, 150 °C, 26 h, 71%; (l) LHMDS (3.0 equiv), MoOPH (5.0 equiv), THF, −75 to −5 °C, 2.5 h, 65%; (m) [Ru2{(PET)3}2(OtO)2]2(OtO) (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) OsO4·TMEDA (1.0 equiv), DCM, −78 to 0 °C, 2 h then NaHSO3 (10.0 equiv), H2O, 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)-(hexamethylphosphoramide triamide).
we found that enol lactone 14 could be oxidized to a single, somewhat unstable, α-hydroxyketone diastereomer (see 19) using DMO. A solvent swap from acetone to trifluorotoluene followed by heating to 170 °C elicited clean bond reorganization to the majucin core. Precedent directed reduction (Me$_4$NBH(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 $S_5^{3,4,6}$. was secured by X-ray crystallographic analysis.

Exploration into the diastereoselective oxidation of the enol lactone 14 revealed that while DMO gave α-ketol 19 selectively, formation of the epimeric α-ketol 20 could be accomplished with SeO$_2$ (Scheme 2). 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. 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, $\Delta$) which unveiled triunsubstituted alkene-containing 16 in 71% yield (Scheme 1). Theodorakis and co-workers have demonstrated the synthesis of (−)-ODDNM (3) and (−)-jiadifenin (4) in two and three steps, respectively, from 16.$^{16,3d}$ Direct α-hydroxylation of δ-lactone 16 from the convex face had been reported using the Davis oxaziridine, although reagent byproduct removal proved problematic.$^{34}$ 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 hydro-}

**Scheme 2. Stereochemical Considerations for the α-Ketol Rearrangement of Enol Lactone 14**

- a) DMDO
- b) PhCF$_3$  
- c) Me$_4$NBH(OAc)$_3$  
- d) SeO$_2$  
- e) Me$_4$NBH(OAc)$_3$

Reagents and conditions: (a–c) See Scheme 1; (d) SeO$_2$ (2.0 equiv), pyr, 110 °C, 16 h; (e) Me$_4$NBH(OAc)$_3$ (7.0 equiv), MeCN/AcOH (3:1), −40 °C, 16 h, 51% over two steps.

**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)

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Notes
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