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BIOMIMETIC SYNTHESIS OF *ANTRODIA* MALEIMIDES AND MALEIC ANHYDRIDES[‡]

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‡Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday and in recognition of his significant contributions to heterocyclic chemistry

Abstract – A simple and efficient biomimetic synthesis of *Antrodia* maleimides and maleic anhydrides, including the HCV protease inhibitor antrodin A, is described. The key step is a Perkin-type condensation performed under exceptionally mild conditions.

The development of practical methods for constructing 3,4-disubstituted maleic anhydrides and maleimides continues to attract a great deal of attention due to the important biological properties of many such compounds.¹ In 2004, Hattori and co-workers reported the isolation of a small family of closely related natural products, exemplified by antrodins A-C (**1-3**),² from the treasured Taiwanese medicinal fungus *Antrodia camphorata* (a.k.a. *Antrodia cinnamomea*).³ Subsequently, in 2008 and 2013, additional members of the antrodin family were reported (e.g. **4-7**, Figure 1).⁴⁻⁶ Despite their simple structures, the antrodins display a range of highly sought biological activities. Anhydride **1** is a non-cytotoxic, potent and selective inhibitor of hepatitis C virus (HCV) protease (IC₅₀ = 0.9 µg/mL).⁷ In contrast, maleimide **2** is devoid of HCV-protease inhibitory activity⁷ but suppresses the growth of estrogen-independent, highly metastatic MDA-MB-231 breast cancer cells in nude mice at a dose as low as 3 mg/kg (x3/week, i.p.).⁸ Furthermore, newer members of this family, including **5-7**, have been shown to inhibit the production of pro-inflammatory mediators such as IL-6^{4a} and NO.^{5,6} So far, antrodins **1-3** have been synthesized by four groups including our own.⁹⁻¹² The shortest available route¹⁰ requires a total of six steps to assemble anhydride **1** from which the maleimides **2-3** are derived.⁹⁻¹²

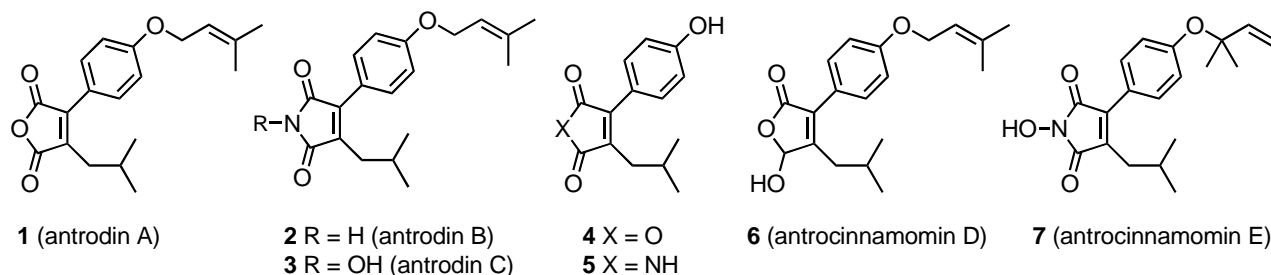
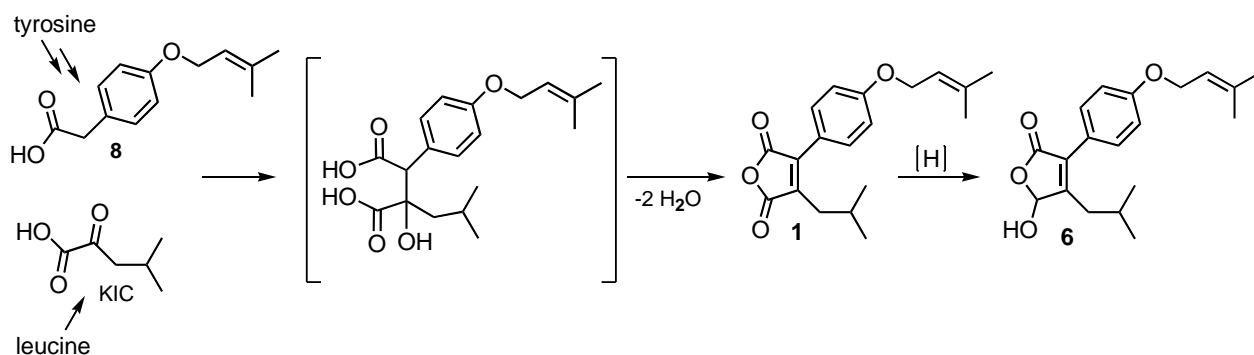


Figure 1. Representative members of the antrodin family

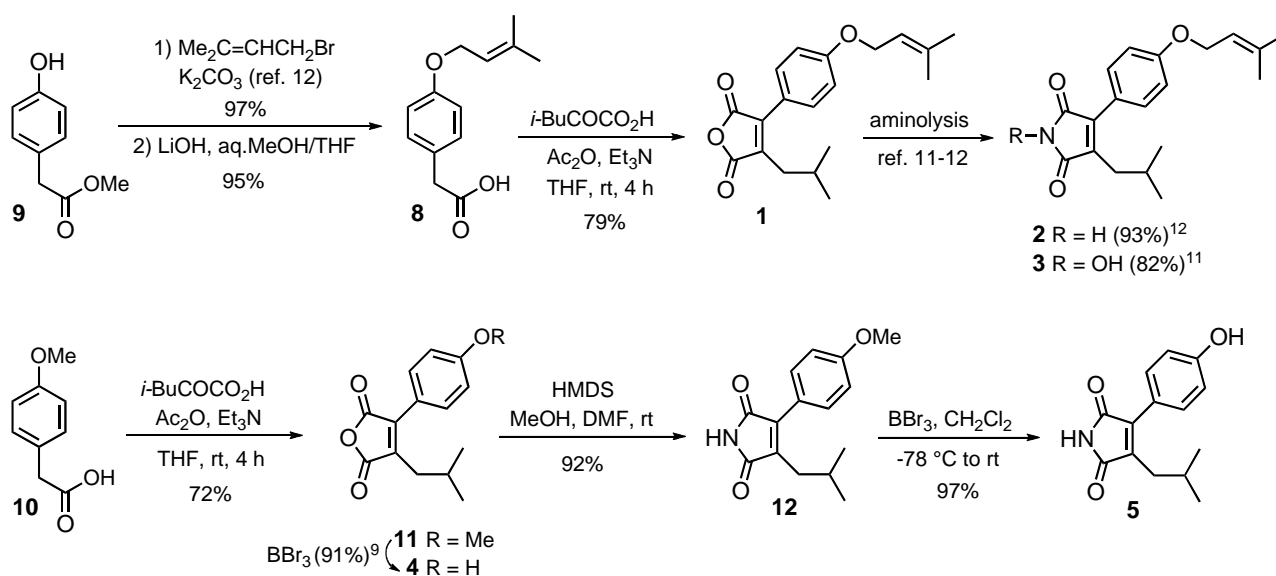
On the other hand, γ -hydroxybutenolide **6** has only been prepared once¹² through oxyfunctionalization¹³ of the corresponding butenolide. Our quest for a shorter route to **1-7** led us to consider the biosynthesis of these compounds,¹⁴ thought to arise via Perkin-type condensation of α -ketoisocaproic acid (KIC) with **8** (Scheme 1). Interestingly, the only mention of **8** in the literature pertains to its isolation from a fungus,¹⁵ which somewhat increases the likelihood of being a biosynthetic precursor of **1**. We now report that this biomimetic pathway is not only realizable but provides a remarkably short and efficient synthesis of **1-3** and their congeners.



Scheme 1. Proposed biosynthesis of **1** and **6**

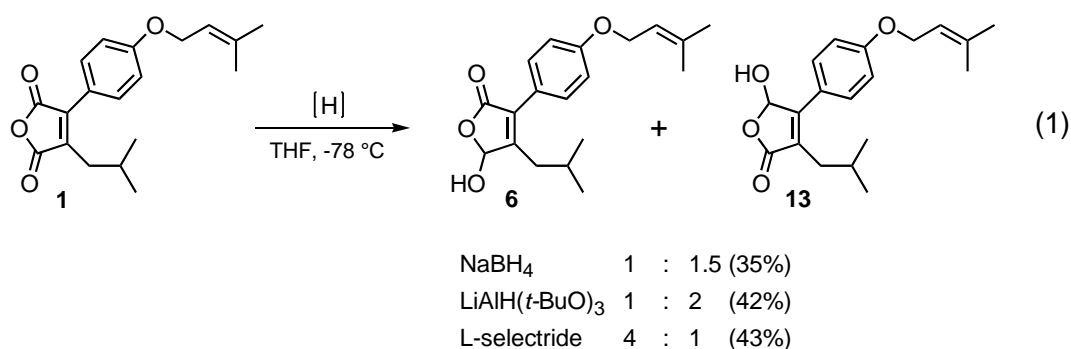
Gram-quantities of the requisite homovalenic acid **8** were easily obtained from commercial phenol **9** by prenylation¹² and subsequent ester hydrolysis (Scheme 2).¹⁶ In a seminal study of the Perkin condensation, Fields and co-workers have shown that this process works well for preparing 3,4-diarylmaleic anhydrides but rather poorly when one of the aryl groups is replaced by an alkyl.¹⁷ Furthermore, a literature survey revealed that all documented applications of the Fields method pertain to the synthesis of diaryl-substituted maleic anhydrides.¹⁸ Unsurprisingly, initial attempts at condensing **8** with commercial α -ketoisocaproic acid (or its potassium salt) using the Fields conditions (Ac₂O, 140 °C) led only to traces of **1** (<10%). To our delight, however, a systematic investigation of various reaction parameters enabled an optimal procedure to be found, which consists in the use of triethylamine and acetic anhydride (5 equiv.

each) and the free α -keto acid in THF at room temperature. Under these mild conditions, antrodin A (**1**) was obtained in a respectable yield of 79% after flash chromatography.¹⁹ Since the conversion of **1** to antrodins B-C (**2-3**) has been reported,^{11,12} our route also delivers the latter in step-economical fashion. The usefulness of this chemistry is further demonstrated by the first synthesis of the anti-inflammatory norprenyl antrodin **5** and an exceptionally short formal synthesis⁹ of antrodin **4** (Scheme 2). Thus, commercial *p*-methoxyphenylacetic acid (**10**) was transformed in a single step (72%) to anhydride **11**, which had previously been prepared by a 7-step route from citraconic anhydride (15.4% overall).⁹ Conversion of **11** to maleimide **12**²⁰ followed by demethylation afforded antrodin **5** (mp 202-205 °C, lit.^{4a} 199-201 °C) whose NMR data were in good agreement with those reported for the natural product.⁴



Scheme 2. Short synthesis of antrodins **1-5** from commercial chemicals

With easy access to anhydride **1**, its reduction to antrocinnamomin D (**6**) was also explored (Eq. 1). The contrasting steric and electronic effects operating on either of the two carbonyl groups of **1** suggested that the task of attaining good regioselectivity would be challenging.²¹ After screening several metal hydrides,



including NaBH₄, LiAlH(*t*-BuO)₃, and K, N and L-selectride, it was found that the three selectrides gave some selectivity in favor of **6**, with the best ratio (ca. 4:1) obtained using the L-version (Eq. 1). Nonetheless, the difficulties encountered in separating the two isomers from each other and the modest yields of the so obtained **6/13** mixtures (35-50%) led us to abandon this approach, especially when considering the availability of a highly efficient, regiospecific method for constructing **6** and related γ -hydroxybutenolides.^{12,13}

In conclusion, we have described a remarkably short, biomimetic synthesis of the potent HCV protease inhibitor antrodin A (3 steps, 73% overall), which represents a significant improvement over the previous synthetic routes.⁹⁻¹² The approach is modular, amenable to scale-up and demonstrates the serviceability of Perkin condensation for assembling 3-alkyl-4-aryl substituted maleic anhydrides.

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16. Data for homovalencic acid (**8**): white powder, mp 73-75 °C (lit.¹⁵ brown powder); IR (NaCl, film): ν 3030 (br), 2965, 2915, 2865, 1694, 1614, 1514, 1442, 1423, 1407, 1385, 1300, 1251, 1179, 1011, 925, 816 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.18 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.49 (t, $J = 7.0$ Hz, 1H), 4.48 (d, $J = 7.0$ Hz, 2H), 3.58 (s, 2H), 1.79 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 178.0, 158.3, 138.4, 130.5, 125.3, 119.8, 114.9, 64.9, 40.2, 26.0, 18.3$; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{17}\text{O}_3$ [$\text{M} + \text{H}$] $^+$: 221.1172; found: 221.1172.
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19. **Synthesis of Antrodin A (General Procedure)**: To a solution of **8** (100.7 mg, 0.457 mmol, 1.0 equiv) and α -ketoisocaproic acid (65.4 mg, 0.503 mmol, 1.1 equiv) in THF (2.5 mL), acetic anhydride (216 μL , 233.4 mg, 2.286 mmol, 5 equiv) and triethylamine (318 μL , 231.3 mg, 2.286 mmol, 5 equiv) were successively added. After 4 h at rt, the mixture was partitioned between 40 mL of ethyl acetate and 40 mL of water. The organic layer was separated and the aq. phase was extracted

with ethyl acetate (2 x 40 mL). The combined organic phases were dried (MgSO₄) and concentrated. Purification by flash chromatography (CombiFlash, 10% EtOAc/hexanes) afforded antrodin A (**1**) as a fluorescent yellow oil (113.7 mg, 79 %) whose ¹H and ¹³C NMR spectra were identical to those described in the literature.¹²

20. Data for maleimide **12**: fluorescent yellow solid, mp 134-136 °C; IR (NaCl, film): ν 3247 (br), 2961, 2933, 2871, 2847, 1764, 1710, 1606, 1513, 1464, 1353, 1336, 1297, 1253, 1177, 1029, 841, 825 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.51 (d, J = 9.0 Hz, 2H), 7.25 (br s, 1H), 6.98 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 2.51 (d, J = 7.5 Hz, 2H), 2.05 (m, 1H), 0.90 (d, J = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃): δ = 171.7, 171.1, 160.8, 139.4, 138.9, 131.1, 121.4, 114.3, 55.5, 33.0, 28.3, 22.9; HRMS (ESI): m/z calcd for C₁₅H₁₈NO₃ [M + H]⁺ : 260.1281; found: 260.1280.
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