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Letter

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Sequential Ketene Generation from Dioxane-4,6-dione-keto-dioxinones for the Synthesis of Terpenoid Resorcylates

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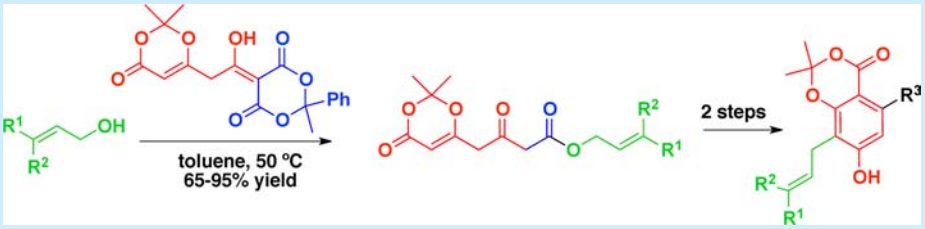
Supporting Information

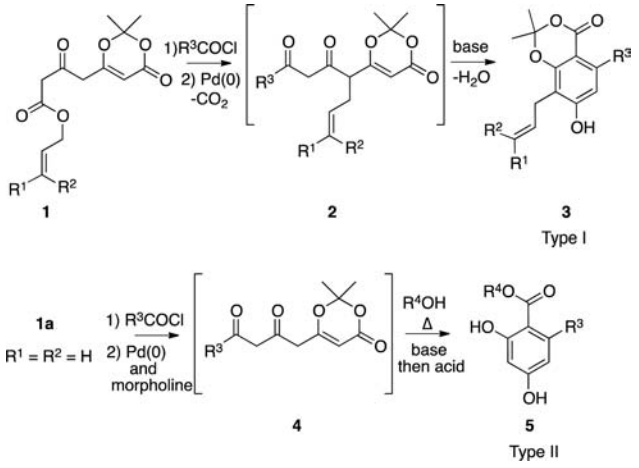


ABSTRACT: Trapping of the ketene generated from the thermolysis of 2-methyl-2-phenyl-1,3-dioxane-4,6-dione-keto-dioxinone at 50 °C with primary, secondary, or tertiary alcohols gave the corresponding dioxinone β-keto-esters in good yield under neutral conditions. These intermediates were converted by palladium(0)-catalyzed decarboxylative allyl migration and aromatization into the corresponding β-resorcylates. These transformations were applied to the syntheses of the natural products (±)-cannabiorcichromenic and (±)-daurichromenic acid.

The 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylic acid moiety is a structural entity embedded in diverse biologically active natural products. Many members of the resorcylates show useful biological effects and have complex and intriguing molecular structures. As such, resorcylates remain attractive targets for both total synthesis studies and as possible drug candidates.

Over the past decade our group has developed a general strategy for the synthesis of β-resorcylates (Scheme 1).[1] Palladium-catalyzed decarboxylative allylic migration and aromatization of dioxinone β-keto-esters **1** provided β-resorcylates in which the allyl moiety was transferred specifically to the arene C-3 position giving the allyl-resorcylate **3** (Type I).[2] This sequence provided diverse meroterpenoids in two steps. Alternatively, reaction of *C*-acylated dioxinone β-keto-esters, derived from allyl ester **1a** with a palladium(0) catalyst and morpholine followed by ketene trapping with an alcohol and subsequent aromatization, gave resorcylates **5** (Type II). We have employed this second process for the total synthesis of many biologically important resorcylic acid lactones.[3]

Scheme 1. Biomimetic Strategies for the Synthesis of β-Resorcylates



The use of dioxinone β-keto-esters **1** is fundamental to our strategy for the synthesis of meroterpenoids. Previously we have applied three different reactions to synthesize these key intermediates **1** (Scheme 2): (1) Claisen condensation of the lithium enolate **9** with β-keto acid derivatives (**8a** or **8b**) (pathway A); (2) condensation of the dienolate **11** with imidazoyl carbamates **10** (pathway B); and (3) bismuth(III) triflate catalyzed Muikayama-type reactions of acyl chlorides **8b** with enol silane **12** (pathway C).

Although we have demonstrated these methods are synthetically useful, they have limitations. Each method employed excess enolate or enol silane relative to the acyl donor. After workup, separation of the β-keto-ester from residual dioxinone or keto-dioxinone usually required chromatography, which is inappropriate when the reaction is scaled up. In addition, these reactions resemble more classical procedures to construct 1,3-dicarbonyl systems (i.e., ketone enolate acylations); as such, yields obtained are often modest and can be capricious.[4] Others

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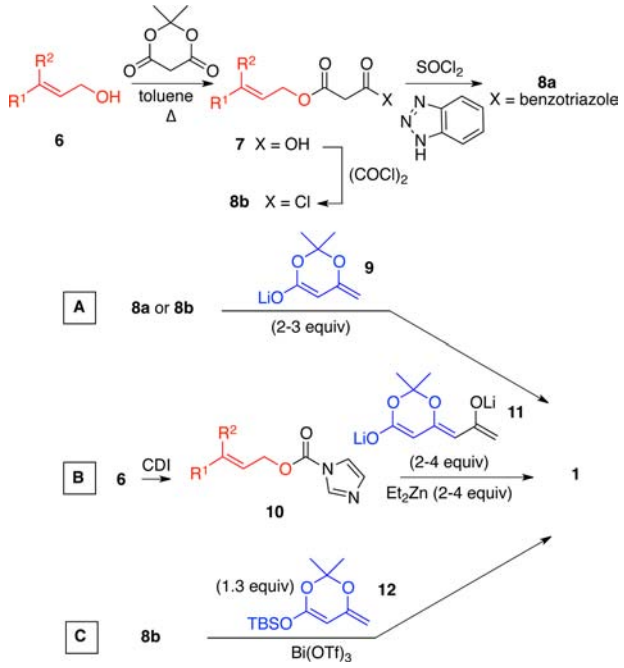
Scheme 2. Literature Methods for the Synthesis of Dioxinone β-Keto-esters

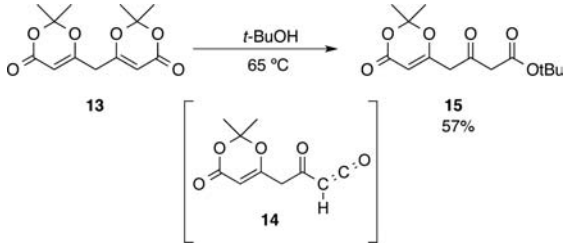


have reported similar findings with enolates derived from dioxinones in Claisen condensation reactions.[5]

In light of our continued interest in the parallel synthesis of increasingly complex β-resoryclates in programs of medicinal chemistry and for scale-up use, we sought to remedy these limitations in the reaction sequence. In this letter we report a new and more reliable method for the synthesis of dioxinone β-keto esters based on the reaction of an alcohol with a dioxanedione-dioxinone. This procedure is operationally simple, mild, and versatile.

At the outset of this work, the only alternative method reported for construction of dioxinone β-keto-esters was by Kiegiel and co-workers (Scheme 3).[6] Under controlled conditions, they successfully converted double-dioxinone **13** into the corresponding *tert*-butyl β-keto-ester **15** in 57% yield.

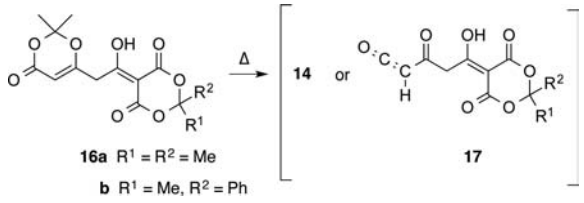
Scheme 3. Kiegiel's Reaction of *tert*-Butanol with Double-Dioxinone 15



In Kiegiel's report, double-dioxinone **13** was prepared from ketene. Since the preparation and handling of ketene (from the high temperature pyrolysis of acetone at or above 700 °C) is an inconvenient process,[7] and there was no information available on whether or not it was possible to effect monoaddition of primary or secondary alcohols to bis-dioxinone **13**,[8] we did not investigate its use for the preparation of compound **1**.

Herein we report the use of dioxane-4,6-dione-keto-dioxinones **16a** and **16b** as synthetic equivalents for double-dioxinones (Scheme 4). Mindful of a possible regioselectivity

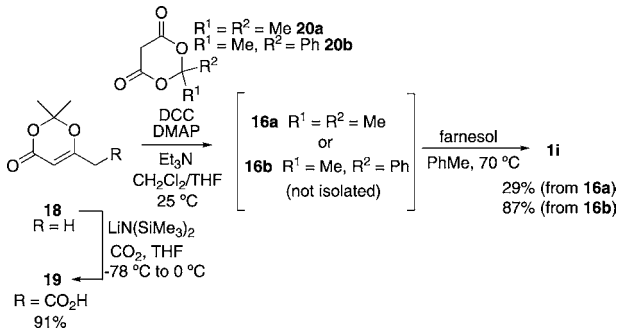
Scheme 4. Thermolysis of Dioxane-4,6-dione-keto-dioxinones



problem in the key initial monoketene generation reaction, we considered that, if necessary, we could modulate the reactivity by modification of the Meldrum's acid moiety. The thermally induced retro-Diels–Alder reaction of compound **16b** (R^1 = Me, R^2 = Ph) should form ketene **14** faster than ketene **17** because of arene π-delocalization into the O–CO σ^* orbital. This has precedent with simple dioxinone thermolysis reactions.[9]

Dioxanedione-dioxinones **16a** and **16b** were prepared in two steps from commercially available dioxinone **18**. Dioxinone acid **19** was prepared in 91% yield by trapping of the lithium enolate **9** with carbon dioxide. A DCC coupling reaction of dioxinone acid **19** with Meldrum's acid **20a** or **20b** gave adducts **16a** and **16b** respectively. For our initial experiments, we screened the reaction of adducts **16a** and **16b** with farnesol (Scheme 5).

Scheme 5. Synthesis of Dioxane-4,6-dione-keto-dioxinones and Reaction with Farnesol



Reaction of dioxanedione-dioxinone **16a** with farnesol in toluene at 70 °C was not regioselective and gave keto ester **1i** in only 29% yield. On the other hand, reaction of dioxanedione-dioxinone **16b** gave keto ester **1i** in 87% yield. We extended this reaction to a range of allylic alcohols (Scheme 6), and in all cases monoesterification was effective for primary, secondary, and tertiary allylic alcohols at 50 °C.

With a series of keto esters **1** available, we examined their conversion to the corresponding resorcylates **3** (Scheme 7). Following our earlier publications,[2a−c,f−h] we screened the allylic rearrangement and aromatization sequence by allowing the keto esters **1b** to **1l** to react with $Pd(PPh_3)_4$ followed by aromatization with cesium carbonate or silica gel. In general, we found this catalyst system gave low yields (<20%) and was not compatible with substrates bearing an endocyclic alkene, which gave only intractable mixtures. After screening a range of catalysts, we found that Pd_2dba_3 in the presence of tri-2-

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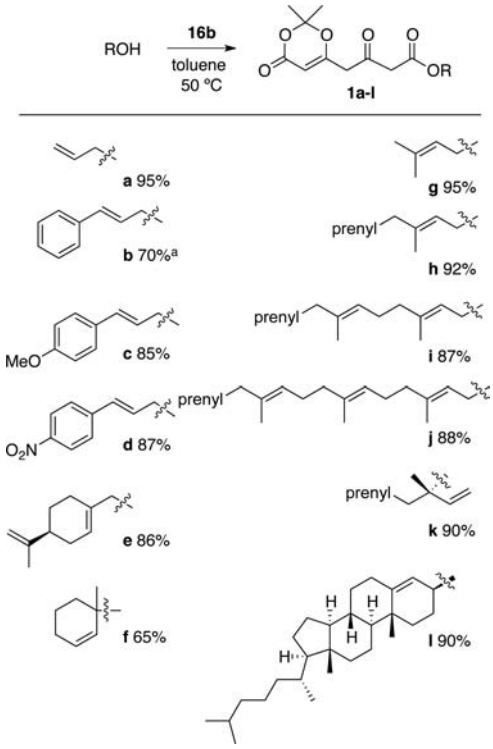
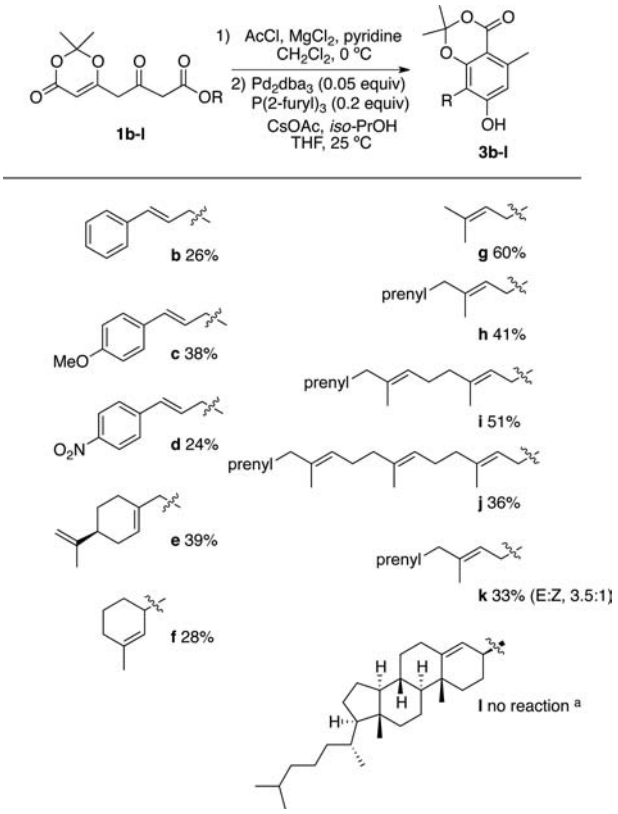
Scheme 6. Reaction of Allylic Alcohols with Dioxanedione-dioxinone 16b[a]



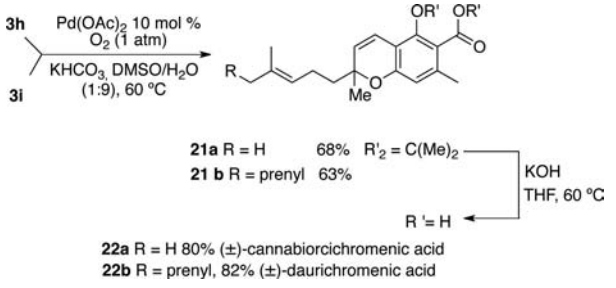
[a]The remaining product could not be isolated from the crude reaction mixture.

Scheme 7. Conversion of Dioxinone Keto Esters 1b−1l to Resorcylates 3b−3l[a]



[a]Starting material recovered.

Scheme 8. Total Synthesis of (±)-Cannabiorcichromenic and (±)-Daurichromenic Acids 22a and 22b



furylphosphine gave acceptable conversions with most substrates **1**.[10]

For substrates that underwent reaction, the rearrangement of acylated keto esters **1** to produce the diketo-ester intermediates **2** was complete within 1 h but these were not isolated but directly converted into the corresponding resorcylates. These aromatization reactions were more rapid (1 h for completion) using the soluble cesium acetate in isopropanol rather than cesium carbonate or silica gel. Steroid **1l** did not undergo reaction, possibly due to the steric hindrance imparted by the C-19 methyl group.

Finally, we applied the reaction to the total syntheses of the antibiotic (±)-cannabiorcichromenic acid (**22a**)[11] and the anti-HIV agent (±)-daurichromenic acid[11,12] (**22b**) (Scheme 8).

For the elaboration of the 2*H*-chromene ring system, we examined a number of oxidative cyclization conditions reported to be effective for *o*-allylic phenols. Reaction of phenol **3h** or **3i** with DDQ or potassium dichromate in benzene gave the corresponding chromene but in low yield (<30%).[13] On the other hand, the palladium-catalyzed aerobic oxidative cyclization reaction reported by Larock and co-workers was highly effective.[14] Thus, treatment of resorcylate **3h** or **3i** with palladium(II) acetate under 1 atm of oxygen[15] gave chromenes **21a** and **21b** in 68% and 63% yields, respectively. Saponification with potassium hydroxide in THF gave the desired (±)-cannabiorcichromenic and (±)-daurichromenic acids **22a** and **22b**. The spectral properties displayed by both compounds (^{1}H,^{13}C NMR and HRMS) were in excellent agreement with data reported for the natural products.[16]

In conclusion, we have developed a simple and reliable procedure for the synthesis of dioxinone *β*-keto-esters and derived resorcylates and meroterpenoids. The application of this new methodology to the total synthesis and medicinal chemistry of biologically relevant resorcylates is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00533.

Spectral data for all new compounds (PDF)
X-ray data and structure of **3h** (PDF)
Crystallographic data for **3h** (CIF)
Experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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