Communication

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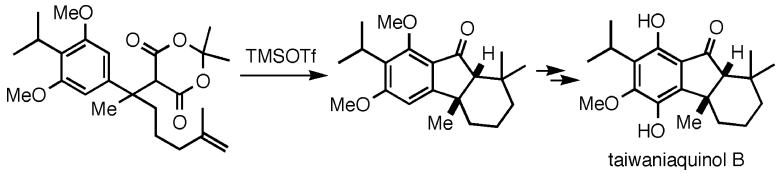

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Total Synthesis of (±)-Taiwaniaquinol B via a Domino Intramolecular Friedel−Crafts Acylation/Carbonyl α-*tert*-Alkylation Reaction

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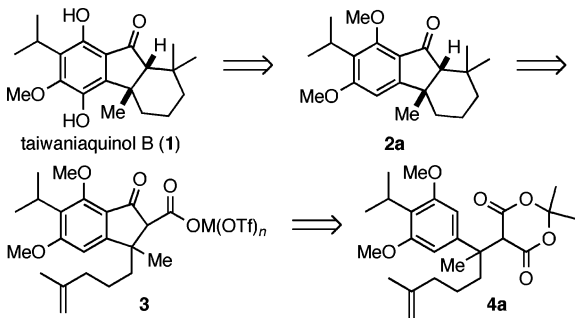
Meldrum's acid has established synthetic utility as an acylating agent for heteroatomic nucleophiles,[1] and our group has recently demonstrated it to be a potent electrophile for catalytic carbon−carbon bond formation via intramolecular Friedel−Crafts acylation.[2] Under specific reaction conditions, the acylation of benzylic Meldrum's acid occurs via the intermediacy of an acyl ketene that produces a 1-indanone-2-carboxylic acid species, which decarboxylates to provide the 1-indanone product.[3,4] It was envisaged that this unique reactivity of Meldrum's acid could be exploited in the design of a multiple carbon−carbon bond forming reaction. This Communication describes a conceptually new approach to sterically congested 1-indanones via metal triflate-mediated intramolecular Friedel−Crafts acylation/carbonyl α-*tert*-alkylation domino reaction and its application to the concise total synthesis of taiwaniaquinol B (**1**).

Taiwaniaquinol B (**1**), isolated from *Taiwania cryptomerioides*, a common Taiwanese pine tree, is a 6-*nor*-5(6→7)*abeo*-abietane-type diterpenoid exhibiting the uncommon fused 6−5−6 tricyclic carbon skeleton.[5] The biochemistry of this family of diterpenoids has yet to be examined comprehensively, but aromatase inhibitory activity has been identified for standishinal, which could lead to the development of valuable therapeutic agents in the treatment of estrogen-dependent cancers.[6] In light of this bioactivity, the distinctive 6−5−6 fused ring system found in these compounds has received considerable attention,[7] and the total synthesis of dichroanone and dichroanal B was recently reported.[8]

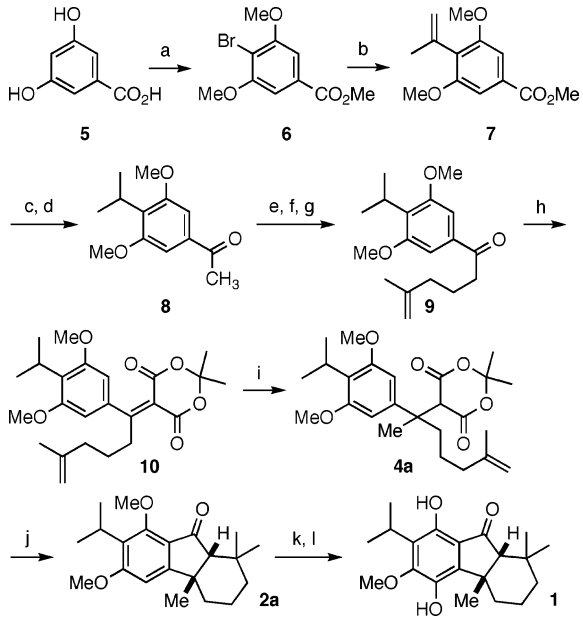
The challenges associated with the development of a flexible synthetic strategy to **1**, amenable to structure activity relationship studies, are the presence of a hexasubstituted aromatic core and two all-carbon quaternary centers located at the carbonyl β-positions. Scheme 1 illustrates the assembly of **1** from tricycle **2a**, which would emanate from the intramolecular α-*tert*-alkylation of the highly substituted 1-indanone **3** with an appropriately tethered alkene.[9,10] This pivotal intermediate would arise from the metal triflate-promoted intramolecular acylation of benzyl Meldrum's acid **4a**.

Scheme 1



The synthesis began with the symmetrically substituted 3,5-dihydroxybenzoic acid (**5**), which upon regioselective monobromination, followed by permethylation, furnished ester **6** (Scheme 2). The isopropyl moiety was introduced in two steps via the Stille cross-coupling of tributyl(isopropenyl)stannane using Fu's protocol[11] to yield **7**. Catalytic hydrogenation followed by saponification of the ester and treatment with excess MeLi provided methyl ketone **8**. The installation of the tethered terminal alkene was accomplished in three steps by preparing the corresponding β-ketoester, which was alkylated with 3-methyl-1-iodobut-3-ene, saponified, and then decarboxylated. Knoevenagel condensation of aryl ketone **9** with Meldrum's acid yielded alkylidene **10**, which was further reacted with methylmagnesium bromide to efficiently introduce the all-carbon benzylic quaternary center and set the stage for the key tandem dicyclization reaction.

Scheme 2 [a]



[a] Reagents and conditions: (a) i. Br_2, AcOH, 100 °C; ii. $(MeO)_2SO_2$, K_2CO_3, acetone, reflux, 72% over two steps; (b) $Pd(P(t\text{-}Bu)_3)_2$ (1 mol %), tributyl(isopropenyl)stannane, CsF (2 equiv), THF, reflux, 88%; (c) i. H_2 (1 atm), Pd/C, EtOAc; ii. 6 N NaOH, reflux, then HCl, 95% over two steps; (d) MeLi (4 equiv), Et_2O, rt, 96%; (e) NaH, $CO(OMe)_2$, THF, reflux, 93%; (f) NaH, 3-methyl-1-iodo-3-butene, DMF, 70 °C, 79%; (g) 6 N NaOH, reflux, then 6 N HCl, 83%; (h) Meldrum's acid, $TiCl_4$, pyridine, 61%; (i) MeMgBr, THF, −15 °C, 90%; (j) TMSOTf (1.2 equiv), CH_3NO_2, reflux, 1 h, 70%; (k) BCl_3, CH_2Cl_2, 0 °C, 90%; (l) i. CAN, H_2O, CH_3CN, 0 °C, 1 h; ii. H_2 (1 atm), Pd/C, EtOAc, 52% over two steps.

Upon treatment of **4a** with 10 mol % of $Sc(OTf)_3$, tricycle **2a** was obtained in 17% yield, accompanied by an inseparable mixture of indanones **11a** and **11b** in a 2.5:1 ratio and 29% yield (Figure 1). Similar results were obtained when either TfOH or TMSOTf catalyzed the reaction. It was rationalized that the acylation proceeded smoothly, but that the α-*tert*-alkylation was problematic

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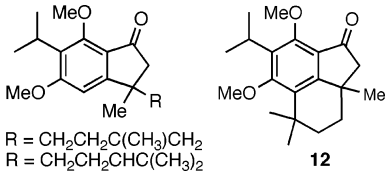
under catalytic conditions due to a low concentration of the reactive species—the enol form of the β-keto carboxylate **3** that may undergo decarboxylation over time, in combination with the metal triflate- or triflic acid-activated alkene. Indeed, when TMSOTf was used in a stoichiometric amount, tricycle **2a** was isolated in 70% yield, and no trace of indanones **11a**/**11b** was detected by analysis of the crude reaction mixture.

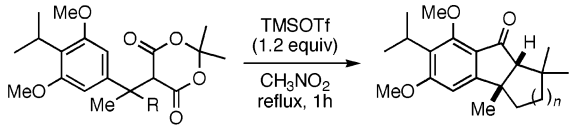


11a, R = $CH_2CH_2C(CH_3)CH_2$
11b, R = $CH_2CH_2CHC(CH_3)_2$ **12**

Figure 1. Byproducts of the domino reactions.

The location and substitution of the tethered alkene had no impact on the efficiency of the tandem process, as shown by the cyclization of trisubstituted alkene **4b** to **2a** in 73% yield (Scheme 3). The methodology was further applied to the synthesis of the analogous fused 6−5−5 tricyclic carbon skeleton. Substrate **4c** provided a 53% yield of two tricyclic products, in a 2:1 ratio (Scheme 3). Tricycle **2b** was the major product and tricycle **12** the minor component (Figure 1). The latter arose from a competing Friedel−Crafts alkylation reaction at the highly congested 4-position of the 1-indanone intermediate, installing two contiguous all-carbon quaternary centers on the aromatic moiety.[12] This mode of cyclization was not observed for **4a** and **4b**, likely due to the relatively slow formation of seven-membered ring carbocycles.

Scheme 3

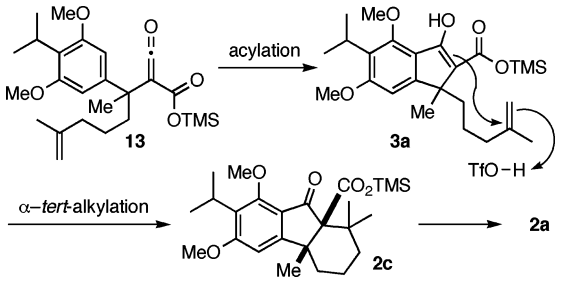


4b, R = $CH_2CH_2CHC(CH_3)_2$
4c, R = $CH_2CH_2C(CH_3)CH_2$

2a, n = 2 (73%)
2b, n = 1 (53%, 2:1 **2b**:**12**)

A proposed mechanism of the TMSOTf-mediated intramolecular Friedel−Crafts acylation/carbonyl α-*tert*-alkylation domino reaction is depicted in Scheme 4. Treatment of **4a** with TMSOTf forms the corresponding 6-siloxy-1,3-dioxin-4-one with release of 1 equivalent of TfOH. Acyl ketene **13**, generated via cycloreversion,[4a] undergoes Friedel−Crafts acylation[3] to **3a**. α-*tert*-Alkylation of **3a** with the triflic acid-activated alkene leads to **2c**, providing tricycle **2a** after workup. The involvement of β-keto trimethylsilyl carboxylate enol **3a**, in lieu of enolized **11a** or its TMS enol ether, is supported by the failure of the indanone mixture **11a**/**11b** to produce **2a** under the optimized reaction conditions.

Scheme 4



The synthesis of **1** was completed by selective deprotection of the methoxy group adjacent to the carbonyl group in 90% yield.[13] Installation of the phenoxy group was realized by treatment of **2a** with CAN to provide a quinone, which was reduced using H_2, culminating in taiwaniaquinol B (**1**) in 52% for the two steps.

In conclusion, the first synthesis of taiwaniaquinol B was accomplished in 15 steps and 6% overall yield. The crux of the approach is a TMSOTf-mediated intramolecular Friedel−Crafts acylation/carbonyl α-*tert*-alkylation domino reaction that exploits the unique reactivity of Meldrum's acid. The facile precursor synthesis makes this a powerful methodology for the modification and assembly of sterically congested indanone-containing ring systems.

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Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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