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Total synthesis of rhein and diacerhein via a directed *ortho* metalation of an aromatic substrate

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Dedicated to the memory of Charles Mioskowski who dies on June 2nd 2007

Abstract—An efficient total synthesis of rhein and diacerhein has been accomplished by relying on a remarkable regioselective directed *ortho* metalation (DOM) followed by a one-pot two step addition-cyclization reaction, generating phthalide **5** intermediate efficiently.

Rhein **1** and diacerhein **2**, the parent members of the anthraquinone-type natural products, have attracted the attention of synthetic chemists because of their use as drugs in the degenerative process osteoarthritis (OA) of the joints,[1] characterized by a progressive destruction and erosion of cartilage (Fig. 1). Recently, it has been found that these molecules might be used for the treatment of chronic inflammation, the prevention and the treatment of organ and tissue transplant rejection,[2] the treatment or prevention of vascular diseases[3] and in treating insulin resistance.[4] According to the recent resurgence of interest of this significant class of molecules, the need of material for clinical trials and biochemical evaluations is therefore obvious.

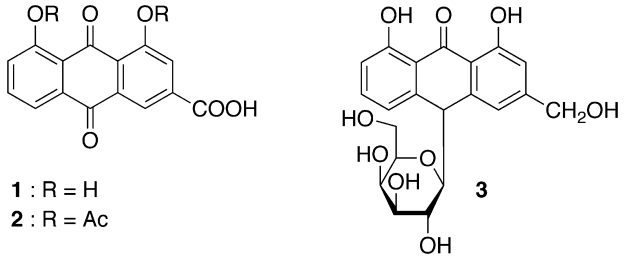

Figure 1. Structure of rhein **1**, diacerhein **2**, and aloin **3**.

Because of the limited supplies, the high cost, the difficulty of isolation from natural sources and the tedious industrial production from aloin **3** (Fig. 1) via semisynthesis,[5] several total syntheses of **1** and **2** have been reported.

However, most general approaches based on Diels–Alder reactions,[6] tandem processes[7,8] (Stobbe condensation or Michael addition followed by cyclization), or organometallic route[9] (condensation of lithium salts with benzynes) remain synthetically intricate. As a consequence, we published quite recently a convenient syntheses of **1** and **2** based on the Fries rearrangement in combination with a bis-carbonylation reaction.[10] To further explore this field, we envisioned a second-generation strategy, which had two goals: (1) the development of a highly convergent process, and (2) the realization of an efficient and practical gram scale synthesis. The retrosynthetic analysis of the anthraquinone system, based on a selective direct *ortho* metalation (DOM) of **6** strategy is shown in Scheme 1.

Directed *ortho* metalation (DOM) of *N*,*N*-diethylbenzamides and related tandem strategy (DOM followed by

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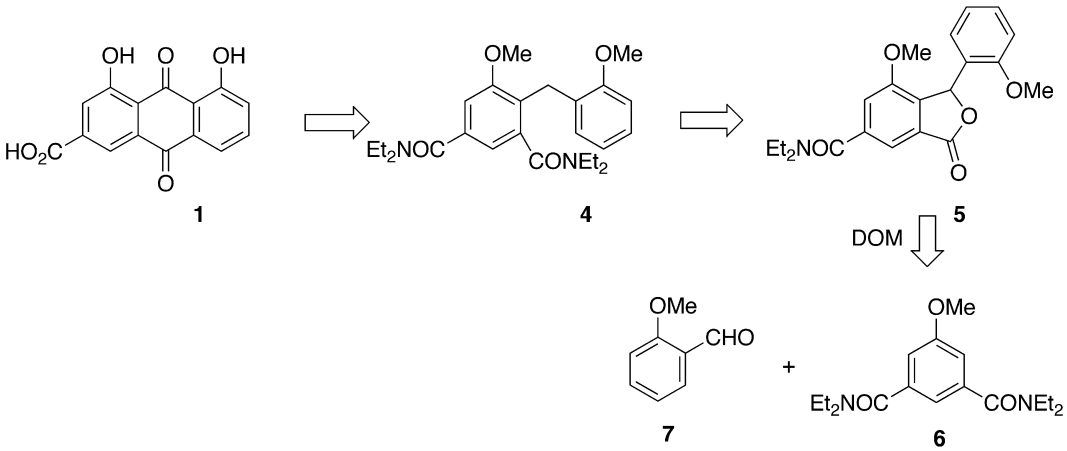
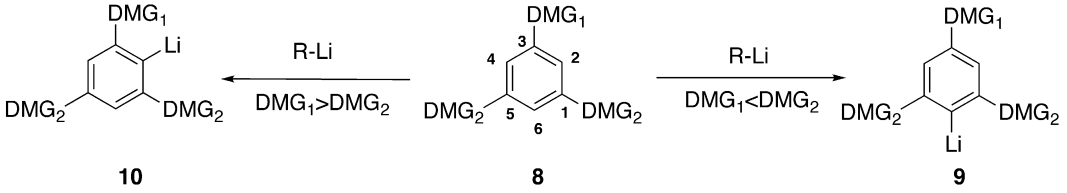


Scheme 1. Retrosynthetic analysis.

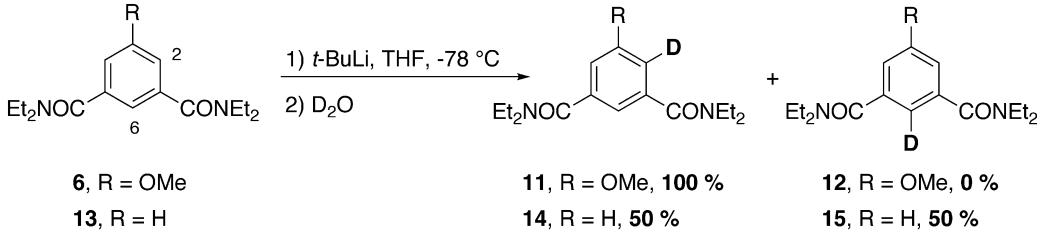


Scheme 2. DOM of 1,3,5-trisubstituted symmetrical substrates.

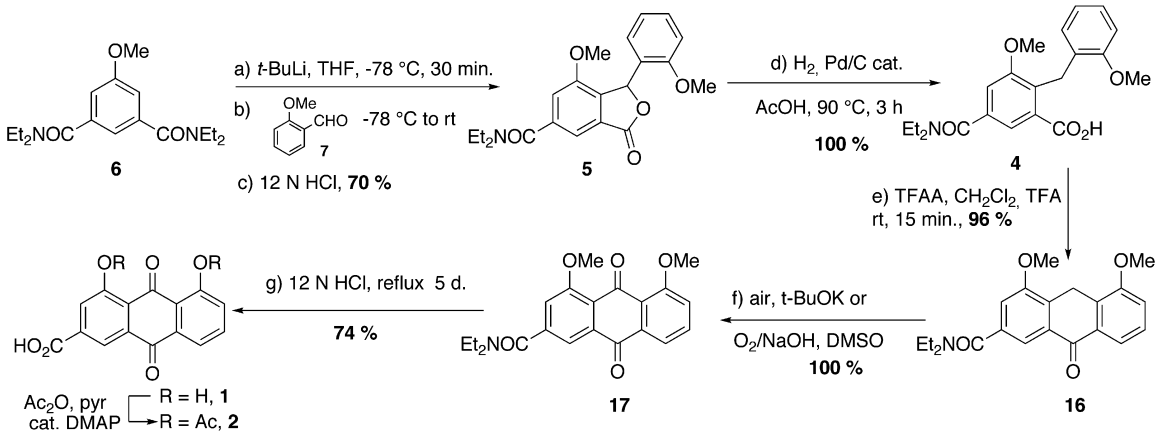
metal-halogen exchange) have been extensively studied by Snieckus and others for the generation of anthraquinone natural products.[11–17] In this context, DOM of alkoxy-bis-*N*,*N*-diethylbenzamides has not been studied yet, despite the fact that a sporadic generation of a lithiated derivative followed by reaction with a Michael acceptor has been published.[18] Particularly, DOM of symmetrical 1,3,5-trisubstituted aromatic derivatives such as **8** should occur either in position 2 (C2) or 6 (C6), depending on the strength of the directing metalation groups (DMG_1 or DMG_2) (Scheme 2).

In the case of compound **6**, due to the relative hierarchy of both *N*,*N*-diethylamide groups over the methoxy group, for the DOM, one would expect that the lithiation would occur at position 6 of the substrate. Interestingly, despite the fact that the $-CONEt_2$ function has a stronger ability than the methoxy group (–OMe) to direct *ortho* metalation, we observed experimentally by deuteration experiments, that the DOM occurs at position 2 with a remarkable regioselectivity 100/0 C2/C6. Indeed, the deuterated compound **11** is isolated in quantitative yield (Scheme 3). One could infer from this result that position 6 is not favored due to the steric hindrance provoked by the two *N*,*N*-diethyl groups. However, when the DOM is performed with derivative **13** (R = H) under the same conditions, followed with D_2O quenching, a mixture of isomers **14** and **15** is formed in equal amounts. These results prove two facts: (1) the existence of the steric hindrance at position 6 does not prevent DOM, (2) the crucial influence of the 3-OMe group for the control of the regioselectivity that can be ascribed to the strong cooperation between the $-CONEt_2$ and –OMe groups.

Having set the selectivity of compound **6** for DOM, we decided to apply this reaction to the total synthesis of rhein **1**. Our efforts were focused then, on the conversion of the tri-substituted symmetrical aromatic system **6** to the tetra-substituted variation by reaction of the lithiated species with the appropriate electrophile. Toward this goal the treatment of compound **6** with *sec*-Buli at −78 °C in THF for 30 min, followed by addition of *ortho*-anisaldehyde **7** afforded the adduct, which upon 12 N HCl treatment was directly converted to phthalide **5** at room temperature.[19,20] This one-pot two step transformation has been further optimized to 70% of isolated yield **5**.



Scheme 3. Regioselective directed *ortho* metalation of **6**.



Scheme 4. Completion of the synthesis.

Interestingly at this stage of the synthesis, due to the high convergence of our approach, the intermediate **5** contains the entire carbon unit necessary to reach the targets. The resulting phthalide **5** was therefore reacted with hydrogen in the presence of palladium catalyst on carbon in acetic acid to afford *O*-benzyl benzoic acid **4** in quantitative yield (Scheme 4). Subsequent treatment with trifluoroacetic anhydride in a 1/1 mixture of DCM and TFA effected smooth Friedel–Craft acylation to give anthracenone **16** in 96% of yield. Quantitative and clean benzylic oxidation was then optimized using mild experimental conditions (air, *t*-BuOK in DMSO at room temperature) leading to the anthraquinone **17**.[21] Global deprotection and amide cleavage were then effected by treating **17** with concentrated HCl for four days at 120 °C, resulting in the formation of rhein **1** in 70% of yield. Acetylation of **1** under usual conditions (Ac_2O, pyr, cat. DMAP) gave substrate **2** quantitatively.

In summary, we have accomplished a new and practical total synthesis of rhein **1** and diacerhein **2** utilizing a remarkable regioselective directed *ortho* metalation of diamide **6**. New optimized one-pot conditions for the generation of the key phthalide **5** have been used. This highly convergent five-step synthesis of **1** has been successfully performed in a scale larger than 5 g in a global yield of 49%, starting from **6**. Moreover, this practical preparation can be performed without any purification by column chromatography on silica starting from **6**.

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Supplementary data

Supplementary data for the synthesis of compounds **4**–**6**, **16**, and **17**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.218.

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