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Expedient Total Syntheses of Rhein and Diacerhein via Fries Rearrangement

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Received May 7, 2004

Abstract: Short and practical total syntheses of rhein (**1**) and diacerhein (**2**) have been achieved via a Fries rearrangement and bis-carbonylation strategy followed by cyclization in molten salt, starting from dibromoester **7**.

Isolated in the free state and as the glucoside in *Rheum polygonaceae* species (rhubarb), Senna leaves, and several species of *Cassia* (Peguminosae),[1] rhein (**1**, Figure 1) is well-known for its applications in antiarthritic drugs.[2] Indeed, rhein is recognized to be the active metabolite of diacerhein (**2**), which inhibits interleukin-1 activity by reducing the collagenase production in articular cartilage.

Rhein (**1**) is also known to inhibit superoxide anion production, chemotaxis, phagocytic activity of neutrophils, macrophage migration, and phagocytosis.[2] Diacerhein (**2**) has been produced by semisynthesis on industrial scale via oxidation of the natural occurring aloin (**4**).[3] However, this route affords compounds which are difficult to purify and, importantly, may be contaminated with the mutagenic byproduct aloe-emodin (**3**). To overcome this crucial problem, several innovative strategies have been designed for the total synthesis of rhein and related anthraquinones.

Approaches, based on Diels−Alder reactions,[4] tandem processes[5,6] (Stobbe condensation or Michael addition followed by cyclization), or organometallic routes[7] (condensation of lithium salts with benzynes) are often lengthy and low yielding. In this paper, we report an efficient and practical synthesis of rhein (**1**) and diacerhein (**2**) using a highly convergent approach based on a

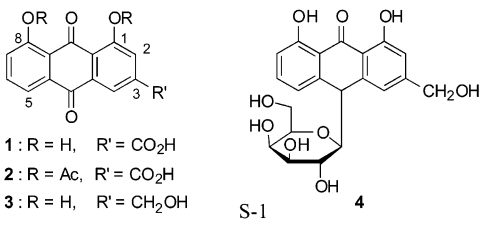
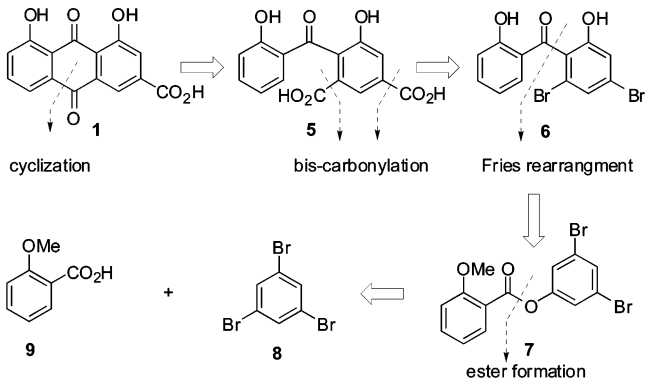


FIGURE 1. Structure of rhein (**1**), diacerhein (**2**), aloe-emodin (**3**), and aloin **(4)**.

SCHEME 1. Retrosynthetic Plan for the Synthesis of Rhein (1)



Fries rearrangement followed by bis-carbonylation. Moreover, our synthetic plan avoids any intermediates containing the undesirable hydroxymethyl group at the C-8 position of the anthraquinone core, precluding mutagenic aloe-emodin (**3**) as a contaminate. Scheme 1 outlines our strategy toward the synthesis of the target.

The cyclization precursor **5** could be derived from dibromobenzophenone **6** via a bis-carbonylation process. This key building block **6** could conveniently be obtained by a Fries rearrangement of precursor **7** which in turn could easily be synthesized starting from the cheap and commercially available materials 1,3,5-tribromobenzene **8** and anisic acid **9**.

The synthesis began with the preparation of 3,5-dibromophenol **10** from 1,3,5-tribromobenzene **8** by reaction with potassium methoxide in DMF at 80 °C (Scheme 2).[8] Methyl ether deprotection was performed by treatment with BBr_3 using a standard method (98%, overall yield).[9]

Phenol **10** was then coupled to anisic acid **9** in the presence of trifluoroacetic anhydride[10] affording key ester **7** in quantitative yield.[13] With **7** in hand, we were able

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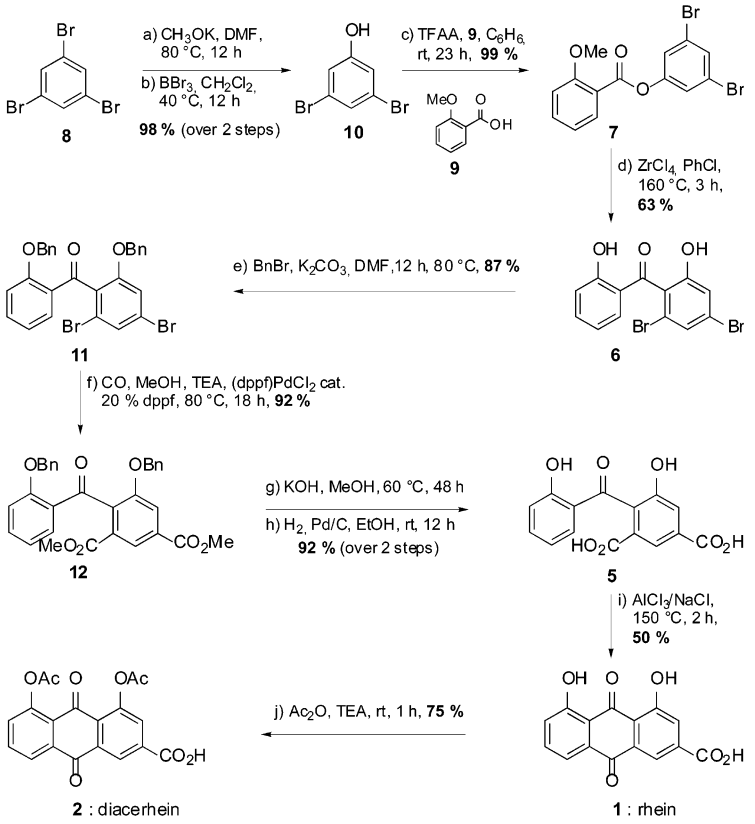
(13) See the Supporting Information for the optimization.

10.1021/jo049228l CCC: $27.50
Published on Web 11/17/2004

SCHEME 2. Total Synthesis of Rhein (1) and Diacerhein (2)



to evaluate our hypothesis on the feasability of the crucial Fries rearrangement.[11,12] Numerous conditions using different Lewis acid ($AlCl_3$, $Sc(OTf)_3$, $BF_3{\cdot}Et_2O$) catalysts have been tested to explore the reactivity of substrate **7**. Unfortunately, the desired product was not isolated under these conditions.[13] Either no reaction or ester bond hydrolysis were observed. This lack of reactivity might be due to the nature of the substituents on the phenolic moiety of **7**. Indeed, it is well established that the rearrangement of substrates containing electron-withdrawing groups such as nitriles, esters, or halogens are often difficult to perform.[11a] Eventually, we found that an excess of $ZrCl_4$ in chlorobenzene at 160 °C converted **7** to the dihydroxy benzophenone derivative **6** in good yield. During the reaction, the methyl ether was cleaved and the desired deprotected dihydroxy ketone was isolated in 63%.

Compound **6** was subsequently dibenzylated with benzyl bromide in the presence of potassium carbonate to afford **11** in 87% yield. Subsequent treatment of **11** with a catalytic amount of $Pd(PPh_3)_4$ or $Pd(OAc)_2$ under carbonylation conditions[14] (CO (1 atm), MeOH, TEA) gave unsatisfactory results.[13] Mixtures of the desired product **12**, monocarbonylated compound, and starting material were obtained. Careful screening of palladium catalysts allowed an effective carbonylation method to be identified. Indeed, $Pd(dppf)Cl_2$ with an additional amount of diphenylphosphinoferrocene (20 mol %) in DMF (80 °C, 18 h) furnished the desired diester **12** in 92% isolated yield (8% of the monocarbonylated intermediate was also isolated and recycled). Saponification of the methyl esters (KOH, MeOH) followed by debenzylation (H_2, Pd/C) afforded the key diacid **5** (92% over two steps) which was converted into rhein (**1**) upon treatment at 150 °C in molten salt[15] ($AlCl_3$/NaCl) (50% isolated yield). Compound **1** exhibited chromatographic and spectroscopic data identical to those of an authentic sample.[16] Finally, diacetylation of **1** (Ac_2O, TEA) afforded diacerhein (**2**) in 75% yield.

In conclusion, we have reported a short and efficient synthesis of rhein (**1**) (nine steps, 22% overall yield) and diacerhein (**2**) via a Fries rearrangement followed successively by a bis-carbonylation reaction and a cyclization effected in molten salt. This efficient process should allow for facile syntheses of rhein analogues, benzoquinones, and anthracyclines derivatives.

Acknowledgment. We acknowledge the contribution of Cyril Antheaume and Alain Valleix for NMR and MS analysis. We thank Laboratoires Pierre Fabre (Plantes et Industries) and the CNRS for financial support of S.T.

Supporting Information Available: General experimental details, optimization for the synthesis of ester **7**, the Fries rearrangement, and the bis-carbonylation reaction, and ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049228L

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(16) We would like to thank Laboratoires Pierre Fabre for providing an authentic sample of rhein and diacerhein.