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Efficient two directional syntheses of a homophthalate ester and novel resorcylate oligomers

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ABSTRACT

Thermolysis of 6,6′-(2-oxopropane-1,3-diyl)bis(2,2-dimethyl-4*H*-1,3-dioxin-4-one) in the presence of methanol gave a triketo-ester which subsequently aromatized to provide a synthetically useful homophthalate ester. Enolate C-acylation in the presence of diethylzinc was used to synthesize other double diketo-dioxinones, which on cyclization, aromatization and dioxinone ring opening gave novel double resorcylate derivatives.

1. Introduction

Numerous biologically active natural products contain the β-resorcylate unit **1**,[1] including the fungal metabolites W1278A–C (**2**) in which the unit serves as the backbone (Fig. 1).[2] These oligo-esters are antibiotics and possess activity against the influenza A virus. We have recently reported the total syntheses of such natural products,[3] and marine antifungal agent 15G256τ (**3**),[4] which were designed following consideration of their polyketide biosynthesis.[5] The symmetrical nature of these resorcylate structures along with their interesting bioactivities lead us to undertake the synthesis of novel resorcylate oligomers **4** with two resorcylic ester entities linked by a generic bridge R.

Biomimetic syntheses of simple resorcylates were first reported by Harris,[6] and we have shown that functionalized diketo-dioxinones **5** are ideal intermediates for this purpose. They can be aromatized either by thermolysis, ketene trapping and aldol reaction and dehydration sequence to give resorcylates **6**, or cyclized by base mediated cycloaromatization to give isopropylidene protected resorcylates **7** (Scheme 1).[7]

Double dioxinones are intriguing building blocks for the two directional syntheses of the target double resorcylates **4** and we initially targeted the synthesis of homophthalate ester **8**, an important building block for the synthesis of DNA-binding ligands[8] and the total synthesis of other bioactive natural products.[9] We considered that **8** should be available from double dioxinone **9** (Scheme 2), whereas the symmetrical double resorcylates **4** should be avail-

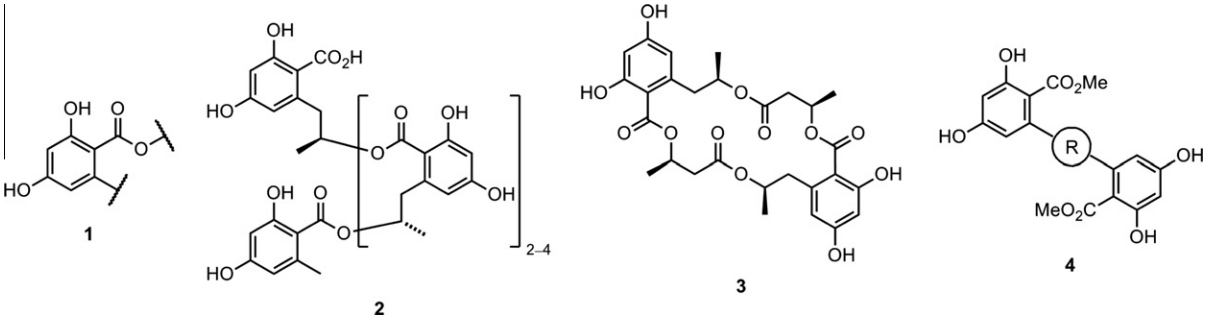

Figure 1. β-Resorcylate unit **1**, resorcylate antibiotic oligo-esters W1278A–C (**2**), resorcylate natural product 15G256τ (**3**) and novel resorcylate oligomers **4**.

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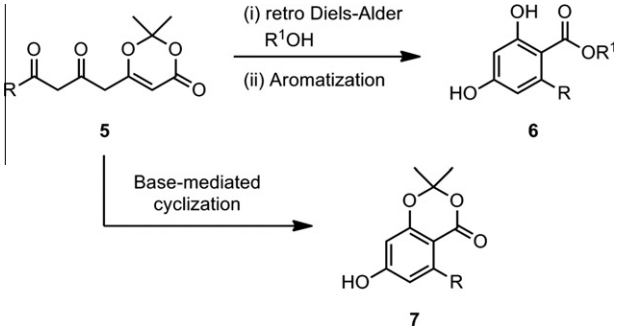
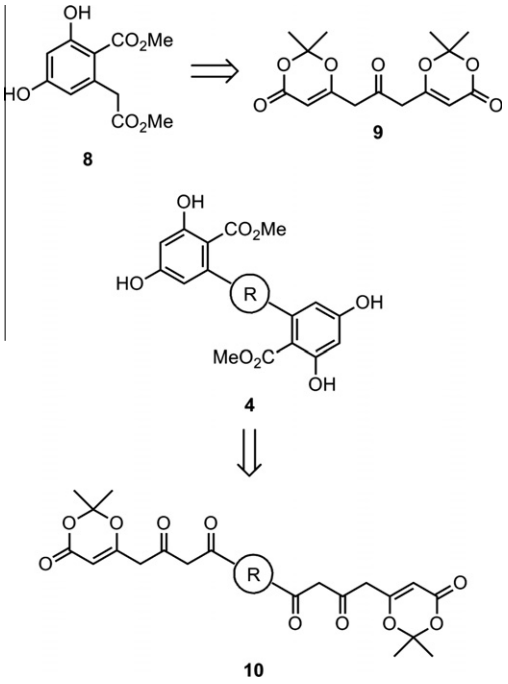


Scheme 1. Two alternate transformations of diketo-dioxinones **5**.



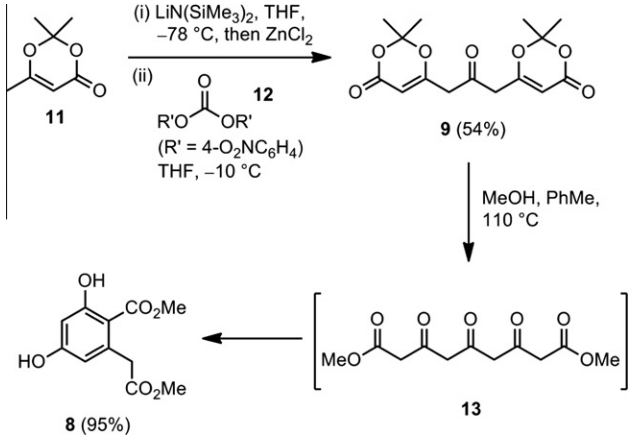
Scheme 2. Retrosynthesis: resorcylates from double dioxinones.

able from double diketo-dioxinones **10**. As such, we sought to find a general, efficient and robust method for the synthesis of such double dioxinones and their derived resorcylates. Herein we report our initial studies in this area, which is notable for concise synthetic sequences, two-directional synthesis and the absence of any phenolic protection.

2. Results and discussion

A double Claisen condensation between the lithium enolate of **11** and bis(4-nitrophenyl) carbonate **12** in the presence of zinc chloride[10] provided double dioxinone **9** in 54% yield (Scheme 3). Thermolytic retro-Diels–Alder reaction[11] of **9** at 110 °C and ketene trapping by methanol gave triketo-diester **13**. Upon further heating at 110 °C, **13** underwent cyclization and aromatization, giving resorcylate **8** in 95% yield.

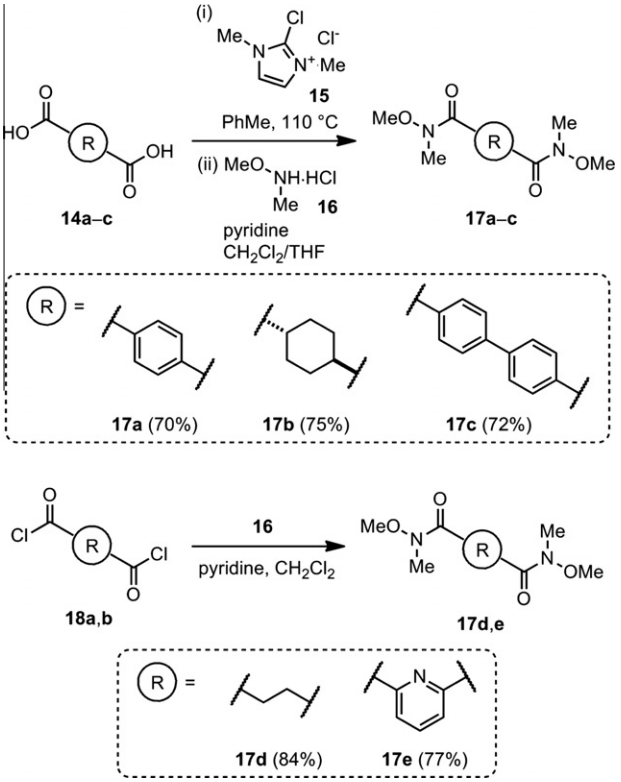
This novel and convenient two-step synthesis provides the first example of an acid and base free cyclization and aromatization without the use of elevated pressure or drying agents. It also underscores the value of dioxinones in controlling the regioselectivity of biomimetic multi-keto-ester cyclization reactions to give specific aromatic products.



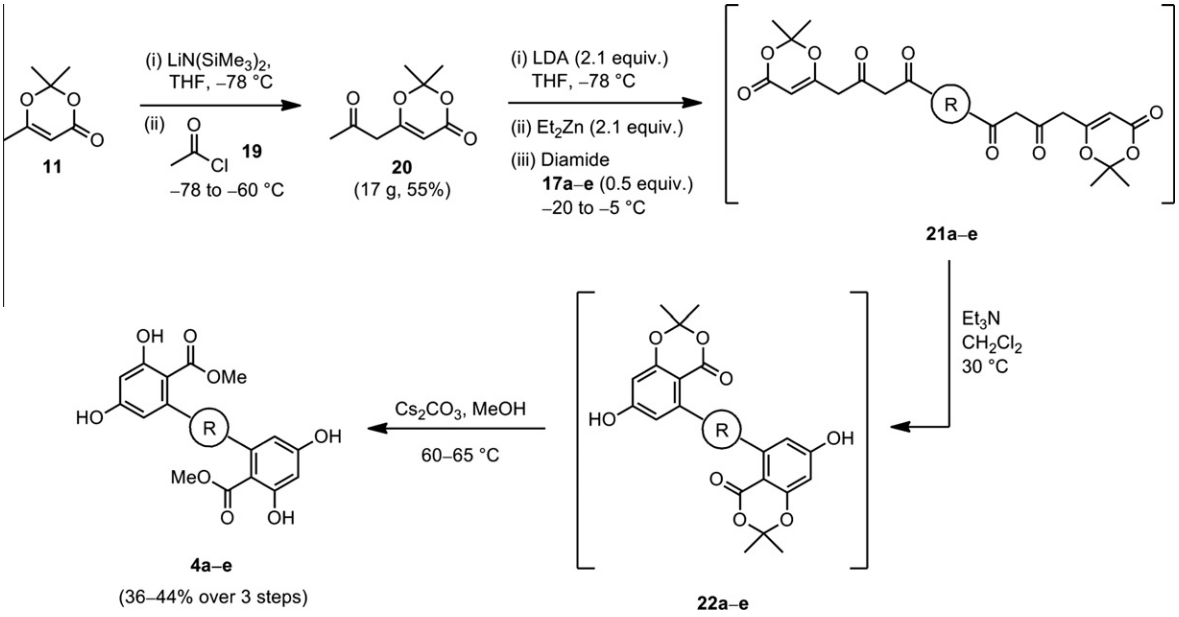
Scheme 3. Synthesis of double dioxinone **9** leading to homophthalate ester **8**.

Our approach towards double diketo-dioxinones was based on extending our previously reported use of Weinreb amides for crossed Claisen condensation reactions.[3] The symmetric diacids **14a–c** were heated with 2-chloro-1,3-dimethyl-1*H*-imidazolium chloride **15** to form the corresponding diacid chlorides[12] which were directly reacted with *N*,*O*-dimethylhydroxylammonium chloride **16** in the presence of base to give the desired double Weinreb amides with 1,4-phenylene- **17a**, *trans*-1,4-cyclo-hexylene- **17b** and 4,4′-biphenylene- **17c** linkers in 70–75% yield (Scheme 4). Other commercially available diacid chlorides **18a**,**b** were converted in a similar fashion to the corresponding diamides with ethylene- **17d** and 2,6-pyridylene- **17e** linkers in 77% and 84% yields, respectively.

Keto-dioxinone **20** was synthesized on a 17 g scale by the Claisen condensation of the lithium enolate of **11** with acetyl chloride



Scheme 4. Synthesis of functionalized double Weinreb amides.



Scheme 5. Synthesis of novel resorcylate oligomers **4a–e**.

19 (Scheme 5).[13] Following on from our previous observations on Claisen condensations of dioxinone derivatives, generation of the dilithium enolate of **20**, transmetallation with diethylzinc,[14] and reaction with diamides **14a–e** gave the diketo-dioxinones **21a–e**.[15] The incorporation of diethylzinc along with temperatures above −10 °C was essential for complete consumption of the Weinreb amides. These successful extensions to dioxinone functionalization presumably were the result of the reduction in basicity of the enolate dianion from **20** through transmetallation with zinc(II). It is also worth noting that of the diamides discussed, there are no reported examples of double Claisen condensation reactions.

Compounds **21a–e** proved to be slightly unstable and therefore were directly subjected to double cyclization catalyzed by triethylamine rather than thermolysis in methanol solution (Scheme 5). The rates of these cyclization reactions were variable and the course of reaction in each case was followed by ^{1}H NMR spectroscopy.[16] The crude adducts **22a–e** were directly methanolyzed in the presence of cesium carbonate to provide the double resorcylates **4a–e** in 36–44% yield over the three steps.

This efficient and reproducible multi-step synthesis gave several novel symmetrical resorcylate dimers (Fig. 2). Some of these compounds portrayed significant and rather interesting physical properties especially with regards to thermal stability and solubility. Double resorcylates **4a–c**, all have melting points in the range of 250–280 °C, and that of **4e** is greater than 310 °C. Compound **4e** also did not readily dissolve in organic solvents except for DMSO.

In conclusion, we have shown that double dioxinones are useful intermediates for the efficient two-step synthesis of 2,4-dihydroxy-homophthalates, and the four-step synthesis of double resorcylates. It should be possible to extend the methodology for the synthesis of a wider range of resorcylates with additional structural complexity. Further applications of dioxinones in synthesis will be reported in due course.

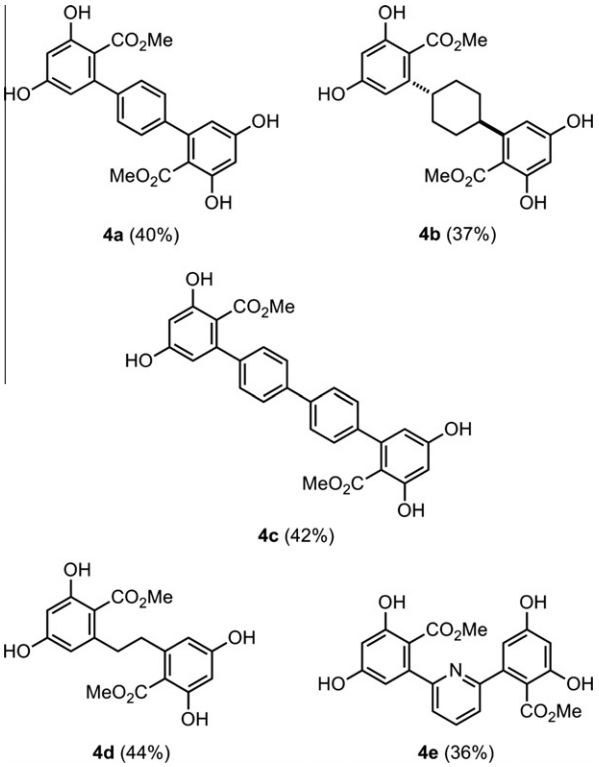


Figure 2. Structures of novel resorcylate oligomers synthesized and the associated multi-step reaction yield.

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Supplementary data

Supplementary (experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds)

data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.100.

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15. The diketo-dioxinones exist as keto-enol mixtures and the reaction was monitored by ^{1}H NMR spectroscopy to observe complete consumption of diamides.
16. In each case, the course of reaction was carefully monitored by ^{1}H NMR spectroscopy to observe the disappearance of enol protons of the precursor diketo-dioxinone units, and the appearance of aromatic protons.