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Alternative routes to the acylphloroglucinol rhodomyrtone

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ABSTRACT

Two novel routes to the acylphloroglucinol rhodomyrtone (**1**) which has antibiotic properties are presented. In the first route an *ortho*-quinone methide, generated from dioxaborinine **23**, is reacted with syncarpic acid (**10**) leading to xanthenedione **25**. Cleavage of the methyl ether functions led to the known rhodomyrtone precursor **16**. In the second route the bis-ester derivative **28** of trihydroxybenzaldehyde **26** is condensed with syncarpic acid (**10**) to give tricyclic hemiacetal **29**. Acetalization and cuprate addition to the enone function led to bis-ester **32** which gave rhodomyrtone (**1**) by $TiCl_4$-induced regioselective Fries rearrangement.

1. Introduction

The isolation of small molecules from the myrtle family of plants has led to a range of novel biologically active natural products. In Asia and other regions of the planet extracts of Myrtaceae plants have traditionally been used for the treatment of various health problems. Besides terpenoids and flavonoids acylphloroglucinols are quite often found in plants of this family. For example, from *Eucalyptus globulus* Labill, rhodomyrtone (**1**) and eucalyptone G (**2**) were isolated (Fig. 1).[1,2] Both of these acylphloroglucinols display antibiotic activity. Extraction of the leaves of *Callistemon lanceolatus* DC allowed isolation of several acylphloroglucinols with callistenone A (**3**) showing very strong antibacterial activity.[3] From *rhodomyrtus tomentosa* leaves, besides the two isomeric acylphloroglucinols rhodomyrtone (**1**) and rhodomyrtosone B (**4**) several other rhodomyrtosones were isolated.[4] One of them tomentosone A (**6**), illustrates a double coupling of the central acylphloroglucinol part with an aldehyde and syncarpic acid.[5,6] The acylphloroglucinol family of natural products also includes the well-known hyperforin (**7**).[7] Because of the prenyl groups polycyclic structures are quite common within this type of natural products.[8] In particular the antibiotic activity of rhodomyrtone has been studied in more detail[9] but so far the exact mode of action is not known. Quite recently the isolation of a hybrid consisting of a phloroglucinol derivative and the terpene myrcene from *Callistemon viminalis* was described.[10] A new compound rhodomyrtosone E (**5**) was recently found in *Eucalyptus citriodora* Hook leaves.[11]

The retrosynthesis of these acylphloroglucinols is rather obvious. Thus, opening of the heterocyclic ring leads to precursor **9** which can be simplified further to syncarpic acid (**10**), an aldehyde **11**, and an acylated phloroglucinol derivative **12** (Fig. 2). Most likely, similar intermediates are involved in the biosynthesis of acylphloroglucinols.[12] The question is whether aldehyde **11** first reacts with syncarpic acid **10** or with the phloroglucinol derivative **12**. Both **10** and **12** can be prepared from phloroglucinol (**13**).[13]

We recently described the first total synthesis of rhodomyrtone (**1**) and rhodomyrtosone B (**4**) where initially syncarpic acid (**10**) was combined with the aldehyde **14** in a Knoevenagel condensation followed by a Michael addition of the phloroglucinol (**13**) to the enedione **15** (Scheme 1).[13] A similar strategy towards the rhodomyrtones A and B was recently disclosed by Porco et al.[14] The recent synthesis of the calliviminones via a final Diels–Alder reaction of myrcene to a related Knoevenagel intermediate supports this order of events during the biosynthesis.[10] However, the initial reaction of the aldehyde **14** with the phloroglucinol part to form a *ortho*-quinone methide intermediate **20** seems likely as well. Therefore, we set out to investigate this and another option toward rhodomyrtone (**1**).

2. Results and discussion

2.1. Quinone methide strategy

ortho-Quinone methides hold a prominent place as intermediates in synthesis and they are also implicated in many

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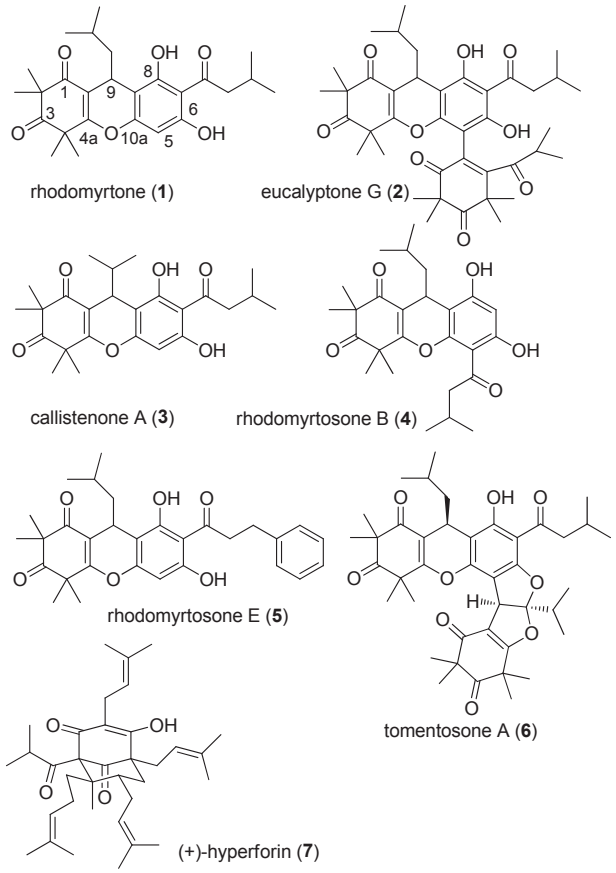


Fig. 1. Structures of some natural acylphloroglucinols.

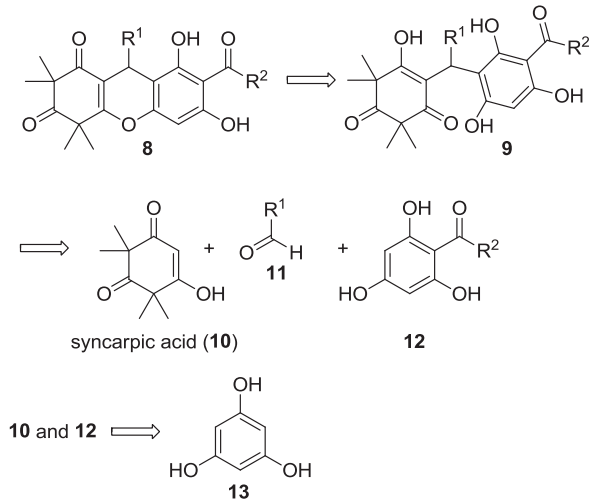
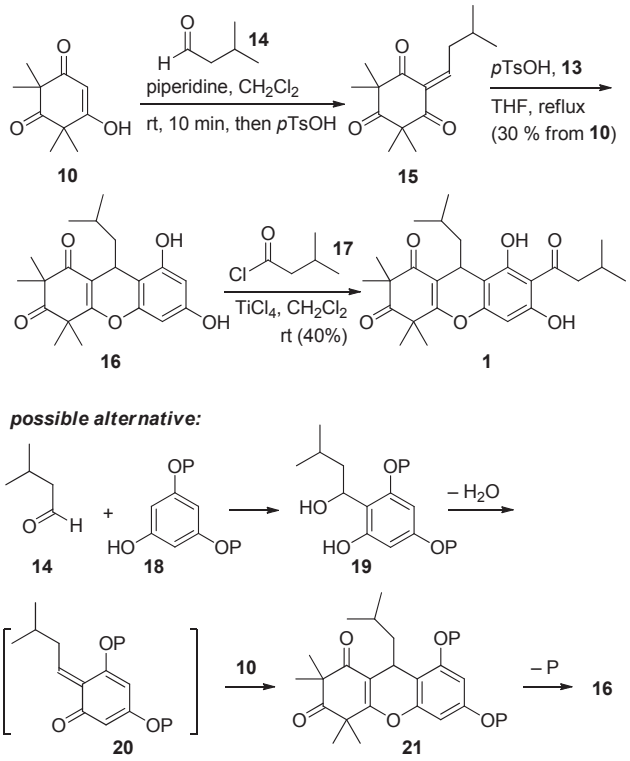
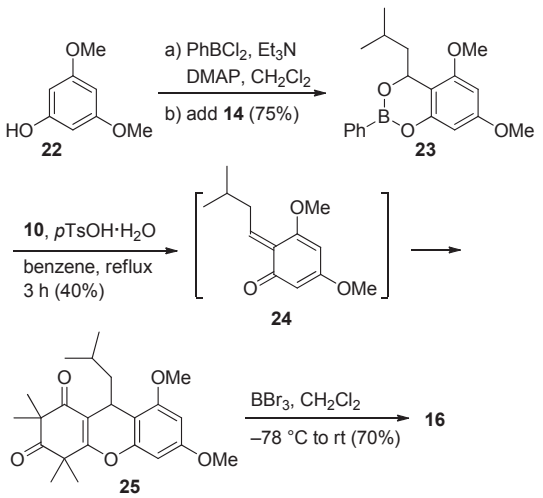


Fig. 2. Retrosynthetic disconnection of acylphloroglucinols of the rhodomyrtone type to the three components **10**, **11**, and **12**.



Scheme 1. Summary of our previous synthesis of rhodomyrtone (**1**) and alternative order of assembly; P=protecting group.



Scheme 2. Synthesis of rhodomyrtone precursor **16** via an *ortho*-quinone methide strategy.

biological processes.[15] For example, natural phloroglucinol-terpene adducts are believed to be formed by cycloaddition between an *ortho*-quinone methide as heterodiene, and a double bond of the terpene component.[16]

Since we knew from our previous work that the isovaleryl group would have to be installed in the last step of the synthesis, we started with commercially available 3,5-dimethoxyphenol (**22**). Using the method of Dufresne et al.[17] phenol **22** was reacted with isovaleraldehyde (**14**) in presence of dichlorophenylborane, Et_3N and catalytic amounts of DMAP. This way the 2-phenyl-4*H*-1,3,2-dioxaborinine **23** was produced in 75% yield (Scheme 2). It turned out to be stable towards chromatography. Such dioxaborinines are known to be precursors of *ortho*-quinone methides.[18] Indeed, when a solution of dioxaborinine **23**, syncarpic acid (**10**) and pTsOH·H_2O (3 equiv) in benzene was refluxed for 3 h, xanthenedione **25** was obtained in 40% yield after chromatographic purification. Most likely, syncarpic acid reacts with the intermediate quinone methide **24** in a Michael addition reaction followed by acid-catalyzed cyclization. The alternative would be a Hetero-Diels–Alder reaction with the enol form of syncarpic acid serving as dienophile. In order to reach the known rhodomyrtone precursor **16**,[13] the methyl ethers of **25** had to be cleaved. This was possible with BBr_3 in CH_2Cl_2 at low temperature. It is worth to mention that other methods of generating *ortho*-quinone methide **24** were unsuccessful. For example, the diol precursor of **23** turned out to be unstable in our hands.[19]

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