Tetrahedron 69 (2013) 8559–8563

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of the acylphloroglucinols rhodomyrtone and rhodomyrtosone B

Marius Morkunas [a], Linda Dube [b], Friedrich Götz [b], Martin E. Maier [a,*]

[a] *Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany*
[b] *Interfakultäres Institut für Mikrobiologie und Infektionsmedizin (IMIT), Mikrobielle Genetik, Universität Tübingen, Auf der Morgenstelle 28, 72076 Tübingen, Germany*

ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form 22 July 2013
Accepted 29 July 2013
Available online 4 August 2013

Keywords:
Acylphloroglucinols
Natural products
Antibiotics
Knoevenagel condensation
Retro Friedel–Crafts acylation

ABSTRACT

In a sequential three-component coupling syncarpic acid, 3-methylbutanal and an acylated phloroglucinol were combined to the hydroxy ketone **3**. Acid catalysis converted **3** directly to the natural product rhodomyrtosone B (**2**). The other isomer, the antibiotic rhodomyrtone (**1**) was obtained from **3** in a sequence of acid-catalyzed cyclization, retro Friedel–Crafts reaction, and reacylation. In preliminary assays both compounds showed potent antibiotic activity.

1. Introduction

Plants continue to be a rich source of biologically active compounds. In particular promising are medicinal plants. For example, the flowering plant *Rhodomyrtus tomentosa* (Aiton) Hassk. of the family Myrtaceae is used in Thailand to treat a variety of ailments. From the ethanol extract rhodomyrtone (**1**) was isolated (Fig. 1).[1] The same compound was also found in the ethyl acetate fraction of the bark of small twigs of *Eucalyptus globulus* Labill, which also belongs to the Myrtaceae family.[2,3] This acylphloroglucinol displays significant antibacterial activity against several Gram-positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA). While a proteome analysis of cellular proteins in MRSA in presence of rhodomyrtone already was carried out, the exact mode of action is not yet clear.[4,5] Further acylphloroglucinols could be isolated from the acetone extract of the leaves of *R. tomentosa*. These include the isomer called rhodomyrtosone B (**2**).[6] The biological properties of rhodomyrtosone B were not known so far. Some structural modifications on rhodomyrtone indicated that the hydroxyl and ketone groups are essential for the antibiotic property.[7]

As acylphloroglucinols they are derived from phloroglucinol, which itself originates from a diketoheptanedioate precursor.[8,9] One part of acylphloroglucinol is converted to syncarpic acid (**4**) and another part probably is acylated with activated 3-methylbutanoic acid (Fig. 1). A third component would be 3-methylbutanal (**5**). Here the order of assembly (first **4**+**5** or **5**+**6**) of the three components **4**, **5**, and **6** is left open. The recent announcement[10] of the synthesis of **1** and **2**, prompted us to report our own results in this field.

2. Results and discussion

We thought to carry out the synthesis of both compounds **1** and **2** along these lines. This also would follow some literature precedence.[11] However, the problem of the regioselectivity in the cyclization of the ultimate precursor **3** would have to be solved. In analogy to the literature the cyclization of **3** most likely would provide rhodomyrtosone B (**2**) and not rhodomyrtone (**1**). Nevertheless, we hoped to find conditions that eventually would provide either one of the natural products in a selective manner. In this paper we describe the realization of these goals.

First, syncarpic acid (**4**) was synthesized essentially according to the literature, starting with the acylation of phloroglucinol (**8**) to the acyl derivative **7** (Scheme 1).[12] Most likely, this acylation favours the desired C-alkylation over O-alkylation in the subsequent reaction of **7** with methyl iodide in presence of sodium

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* Corresponding author. Tel.: +49 7071 2975247; fax: +49 7071 295137; e-mail address: martin.e.maier@uni-tuebingen.de (M.E. Maier).

http://dx.doi.org/10.1016/j.tet.2013.07.091

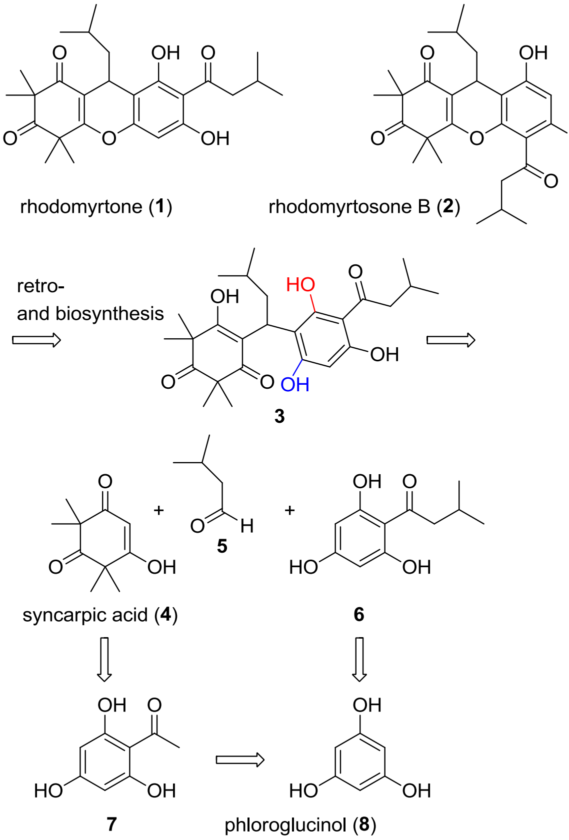
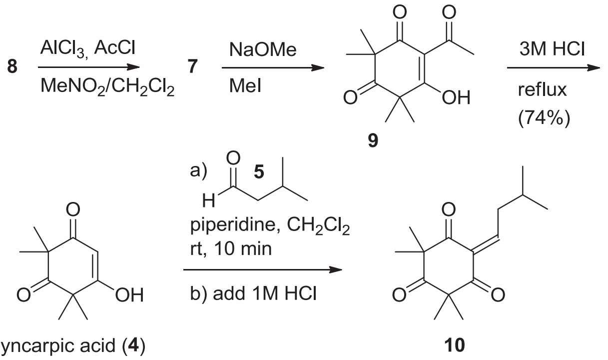


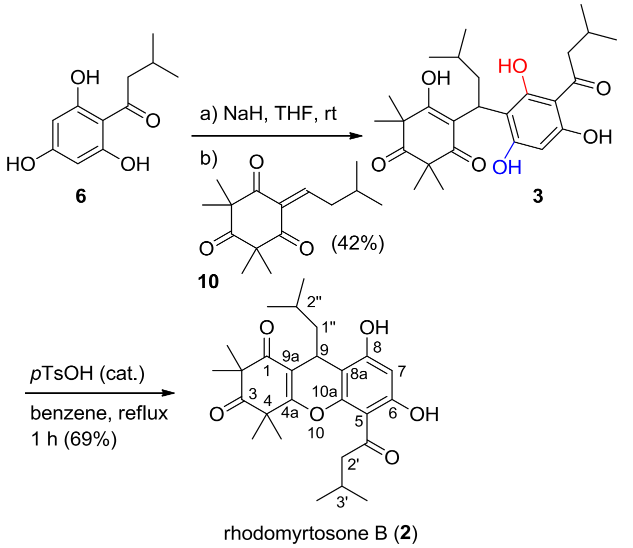
Fig. 1. Possible biosynthesis and retrosynthetic analysis of the acylphloroglucinols rhodomyrtone (**1**) and rhodomyrtosone B (**2**) from phloroglucinol (**8**).



Scheme 1. Synthesis of syncarpic acid (**4**) from acylphloroglucinol **7** and condensation of **4** with aldehyde **5** to the enetrione **10**.

methanolate.[13,14] A final acid induced retro-Claisen condensation furnished syncarpic acid (**4**) in good overall yield.[15] The crucial three-component coupling to hydroxy ketone **3** was initiated with the Knoevenagel condensation between syncarpic acid (**4**) and 3-methylbutanal (**5**). This condensation reaction was realized via the intermediate Mannich addition product.[11] Treatment of the crude reaction mixture with 1 M HCl led to the cross-conjugated enedione **10**.

The right fragment, acylphloroglucinol **6**, was obtained as well by simple Friedel–Crafts acylation using 3-methylbutanoyl chloride and $AlCl_3$ in a mixture of nitromethane and dichloromethane. Since enone **10** was prone to isomerization[16] it was immediately reacted with the enolate generated by treatment of acylphloroglucinol **6** with 1 equiv of NaH (Scheme 2). This way a reasonable yield of the key intermediate **3** could be obtained. Larger amounts of NaH (2 equiv) did not make a difference in the outcome of the coupling reaction. As expected, refluxing a benzene solution of hydroxy ketone **3** in presence of catalytic amounts of *p*-toluenesulfonic acid (5 mol %) led to rhodomyrtosone B (**2**) in 69% yield. The most striking difference in the ^{1}H NMR spectrum of **2** to the reported data for **1** is the relative large shift difference of the two diastereotopic methylene protons of the acyl side chain. These protons (2′-H) appear as doublet of doublet at 2.95 and 3.18 ppm, respectively.



Scheme 2. Synthesis of rhodomyrtosone B (**2**) by acid-catalyzed cyclization of hydroxy ketone **3**.

If this ring closing reaction of hydroxy ketone **3** was carried out in presence of 3 equiv of *p*-TsOH·H_2O a surprising result was obtained. Thus, neither rhodomyrtone nor rhodomyrtosone B was formed. Rather, the deacylated dihydroxanthene derivative **11** was isolated in 61% yield (Scheme 3). As it appeared, a retro-Fries rearrangement followed by cleavage of the phenolic ester must have taken place. Reactions of this type have been described, but under much more drastic conditions.[17] Compound **11** allowed us then to study its regioselective acylation. Gratifyingly, reaction of phloroglucinol derivative **11** with 3-methylbutanoyl chloride in presence of $TiCl_4$ (4 equiv) in dichloromethane led indeed to rhodomyrtone (**1**), essentially as the only isomer. With $AlCl_3$ this reaction did not take place. The crude rhodomyrtone could be recrystallized from petroleum ether/acetone to provide white needles of rhodomyrtone (**1**). The spectral data were in full agreement with the reported ones. Analysis of the acylation by TLC indicated that the reaction proceeds through the two possible monoesters that slowly undergo Fries rearrangement to rhodomyrtone. The conversion of one of the monoesters seems to stop after some time. The diacylated derivative **12** forms slowly as minor product in presence of 6 equiv of $TiCl_4$. One might speculate that compound **11** is an intermediate in the biosynthesis of **1** and **2**. The phloroglucinol derivative **11** could also be obtained by acid-catalyzed reaction of phloroglucinol with the enetrione **10** (1.5 equiv) in moderate yield.

Both synthetic compounds **1** and **2** were tested for growth-inhibiting activity of *S. aureus*. Cells of the strain *S. aureus* SA113 were diluted and inoculated to an OD578 of 0.05 and cultivated overnight in Mueller-Hinton broth (MHB) medium without and with rhodomyrtone and its isomer solubilized in DMSO. Both compounds were able to inhibit the growth in liquid medium (Fig. 2A) and on MHB-agar (Fig. 2B). The minimal inhibition concentration (MIC) was in the range of 1 μg mL^{-1}. DMSO was also tested as control, it showed no inhibition.