Efficient Syntheses of Mollugin

Pascal Habonimana, Sven Claessens, Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, 9000 Ghent, Belgium
Fax +32(9)2646243; E-mail: norbert.dekimpe@UGent.be

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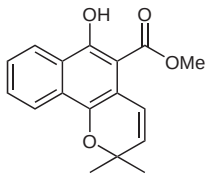
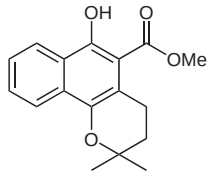
Abstract: Two different strategies are presented to synthesize mollugin, based upon a close investigation of possible natural precursors. The best total synthesis of mollugin, a natural product isolated from rubiaceous herbs, is achieved in an overall yield of 61% starting from 1,4-dihydroxynaphthalene-2-carboxylic acid. The key reaction is the prenylation and spontaneous pyran ring formation. Subsequent oxidation of the intermediate 3,4-dihydromollugin with DDQ afforded mollugin.

Key words: quinones, natural products, oxidations

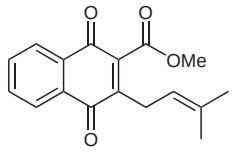
Many naturally occurring naphthoquinones possess interesting physiological properties. Among them, mollugin (**1**), 3,4-dihydromollugin (**2**), and their analogues have shown anti-tumor activity,[1] antiviral activity against the hepatitis B virus,[2] antibacterial, and mutagenic[3] activities. Chung et al. reported that mollugin strongly inhibited collagen-induced and arachidonic acid induced platelet aggregation.[4]



mollugin (**1**)



3,4-dihydromollugin (**2**)



methyl 3-(3-methyl-2-butenyl)-
1,4-naphthoquinone-2-carboxylate (**3**)

Figure 1

Mollugin (**1**) was isolated first from the rhizome of *Gallium mollugo* (Rubiaceae) and has been found in many rubiaceous herbs growing in Europe, Africa, and Asia.[1,2,4,5] At our department, mollugin (**1**) was isolated from *Pentas longiflora* (Rubiaceae), a very important plant species used by traditional African healers to treat skin diseases like pityriasis versicolor, itchy rashes, or mycoses. This medicinal plant is also used in Kenya and Rwanda against malaria, diarrhea, tapeworm, gonorrhea, syphilis, and as a purgative.[6] An earlier report mentioned the synthesis of mollugin (**1**) in 23% yield in two steps by the condensation of 3-chloro-3-methyl-1-butyne and 1,4-dihydroxynaphthalene-2-carboxylic acid in the presence of aluminum(III) chloride and subsequent esterification of the intermediate molluginic acid with diazomethane.[7] Heide and Leistner reported, without mentioning the yield, the synthesis of 3,4-dihydromollugin (**2**) by condensing 2-methyl-3-buten-2-ol and methyl 1,4-dihydroxynaphthalene-2-carboxylate (**5**) in dioxane, in the presence of BF_3 as a Lewis acid catalyst.[8] In a recent publication,[9] the synthesis of mollugin (**1**) was achieved in two steps from methyl 1,4-dihydroxynaphthalene-2-carboxylate (**5**) in 39% yield. According to this report, 3,4-dihydromollugin (**2**) was obtained after electrophilic aromatic addition of 2-methyl-3-buten-2-ol onto methyl 1,4-dihydroxynaphthalene-2-carboxylate (**5**). Subsequent pyran ring closure in the presence of $BF_3 \cdot OEt_2$ resulted in 3,4-dihydromollugin (**2**) in 54% yield. Refluxing 3,4-dihydroxymollugin **2** in dioxane in the presence of DDQ yielded mollugin (**1**) in 72% yield. Recently, a lengthy but promising synthesis of mollugin was published in which the methoxycarbonyl moiety was adhered at the end of the route.[10]

In this report, two new and alternative pathways towards mollugin (**1**) are presented. In order to facilitate the search for promising reaction pathways, the design of the strategy was based on the search and observation of possible precursors in the biosynthesis of mollugin in the plant material. By looking in the literature at isolated compounds in *Gallium mollugo* and *Pentas longiflora*, two possible precursors were selected.

The first route (Scheme 1) was based upon the idea that the biosynthesis of mollugin proceeds via the formation of methyl 3-(3-methyl-2-butenyl)-1,4-naphthoquinone-2-carboxylate (**3**), since this compound **3** is often isolated from plant materials together with mollugin.[8,11] An important feature of prenylated naphthoquinones is their ability to tautomerize to orthoquinone methides.[12] It is expected that this compound **3** would give rise to an electrocyclization reaction and subsequent pyran-ring formation resulting in mollugin. This mechanism is also responsible for the photoracemization of cyclopropyl chromenes.[13] During the course of our research, this strategy was applied independently by Trauner's research group.[14] In their research, triethylamine was used as a base in dichloromethane resulting in an elegant synthesis of mollugin in

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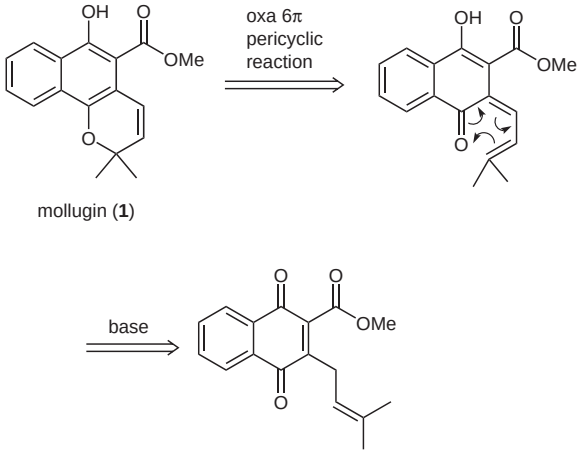
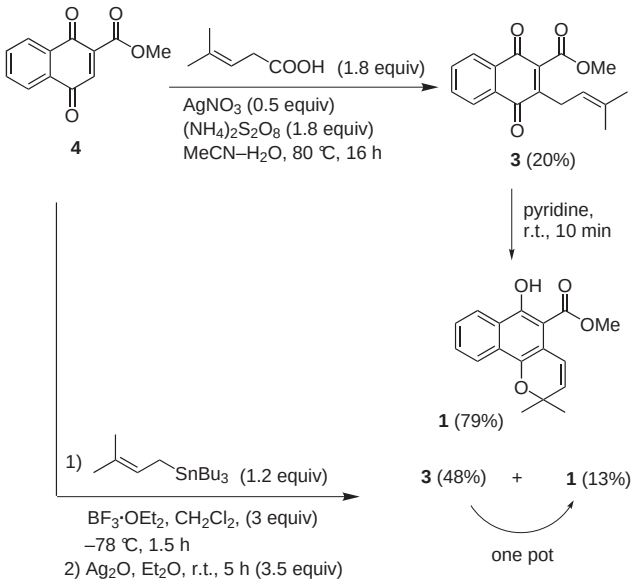
81% yield. Their synthesis of methyl 3-(3-methyl-2-butenyl)-1,4-naphthoquinone-2-carboxylate (**3**) as a precursor was performed by an allylation reaction and subsequent Grubbs cross-metathesis with 2-methyl-2-butene to yield the precursor **3** in a total yield of 33%.



Scheme 1

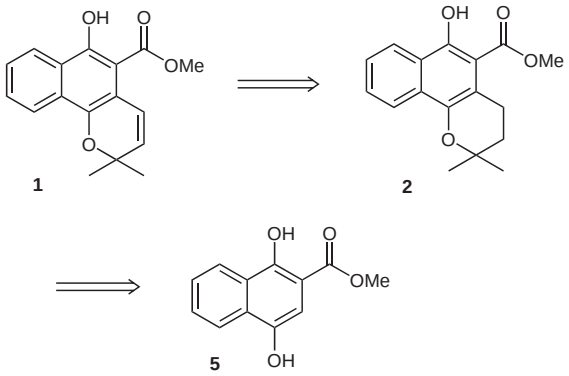
The C-3 allylation of 2-acetyl-1,4-naphthoquinone had been achieved using either 3-butenoic acid in the presence of silver(I) nitrate and potassium persulfate (43% yield)[15] or using allyltrimethylstannane in the presence of $BF_3{\cdot}OEt_2$.[16]

We chose to introduce the prenyl chain directly without making the detour via the allyl side chain and Grubbs cross-metathesis. Radical C-3 prenylation of methyl 1,4-naphthoquinone-2-carboxylate (**4**) with 4-methyl-3-pentenoic acid in the presence of 0.5 equivalent of silver(I) nitrate and 1.8 equivalents of ammonium peroxydisulfate[17] yielded methyl 3-(3-methyl-2-butenyl)-1,4-naphthoquinone-2-carboxylate (**3**) in 20% yield together with unreacted and unidentified material. The nucleophilic addition of tributylprenyltin to methyl 1,4-naphthoquinone-2-carboxylate (**4**) in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at –78 °C, followed by silver(I) oxidation gave the prenylated naphthoquinone **3** in 48% yield. The initial yield of this prenylated naphthoquinone **3** was higher but, surprisingly, under the given conditions, already a part of the prenylated naphthoquinone **3** is converted into the desired mollugin (**1**) (13% yield). This unexpected result is a positive indication for the usefulness of the proposed strategy (Scheme 2). Unfortunately, the efforts to improve the yield (13%) of mollugin in this reaction by varying the reaction conditions were not successful. It seemed better to synthesize mollugin in a two-step protocol. In this way, the precursor **3** was treated in basic conditions by using a 10% solution in pyridine affording the desired mollugin in 79% yield, together with some unidentified materials. The low-yielding radical prenylation (20%) next to the higher-yielding tributyltin prenylation (48% and part converted to mollugin) give an indication of the non-radical character of the prenylation in nature.



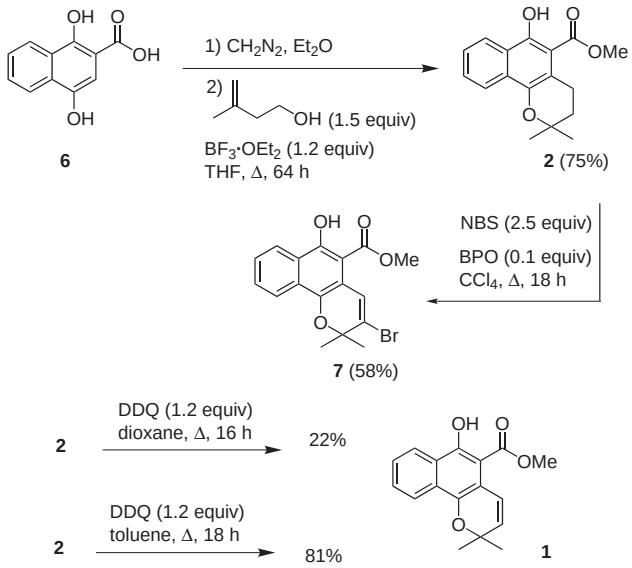
Scheme 2

The above-mentioned strategy worked out as outlined but the synthesis of the precursor **3** was merely low-yielding (48%). Taking a closer look at the isolated compounds in Rubiaceae species suggests another possible synthetic route (Scheme 3). The next scheme is based upon the synthesis of the key intermediate 3,4-dihydromollugin (**2**), which was isolated together with mollugin from *Gallium mollugo*.[5b,18] If 3,4-dihydromollugin (**2**) can be synthesized in a reasonable yield, it would constitute a suitable route to synthesize mollugin by an oxidation process.



Scheme 3

Therefore, methyl 1,4-dihydroxynaphthalene-2-carboxylate (**5**) was prepared by esterification of the carboxylic acid **6** with diazomethane. In the following step, the methyl ester **5** was heated under reflux with 3-methyl-3-buten-1-ol in tetrahydrofuran in the presence of 1.2 equivalents of $BF_3{\cdot}OEt_2$ to give rise to 3,4-dihydromollugin (**2**)



Scheme 4

in 75% yield. The reaction proceeded faster when performed in dioxane for 16 hours but the observed yield was a little lower (61%). BF_3 activates the alcohol moiety by borate formation. Subsequent *ortho*-alkylation of the aromatic alcohol by the homoallylborate and cyclization by attack of the phenol oxygen onto the proton-activated carbon–carbon double bond of the isoprenyl group afforded 3,4-dihydromollugin (**2**).

In a next step, 3,4-dihydromollugin was oxidized to the desired mollugin. The literature[9] revealed an existing method using DDQ in dioxane resulting in mollugin in 72% yield, but in our hands the yields were much lower (22%), even after repeated attempts. In an attempt to search for alternatives, oxidation using Pd/C in toluene was tried, but only starting material was recovered. The reaction of 3,4-dihydromollugin (**2**) with one equivalent of NBS and 0.1 equivalent of benzoyl peroxide (BPO) in tetrachloromethane did not result in the expected mollugin (**1**) but instead gave rise to the interesting and new compound 3-bromomollugin (**7**) in 40% yield.[19] Apparently, the radical bromination–dehydrobromination sequence afforded mollugin, but in the given conditions mollugin reacts further with NBS to give rise to 3-bromomollugin. The yield of this reaction could be improved to 58% by using 2.5 equivalents of NBS in tetrachloromethane. Finally, it was found that mollugin could be obtained in 81% yield by using a DDQ oxidation of dihydromollugin (**2**) in toluene, which is an improved oxidation procedure compared to the literature.[9]

In summary, in this report, the present synthetic strategies for mollugin are based upon the observation of possible biosynthetic precursors. Two alternative precursors were presented and this resulted in two different approaches. Both worked out well but the second strategy, based upon 3,4-dihydromollugin as a precursor is the most promising. In this way, a synthesis which produced the naturally occurring 3,4-dihydromollugin (**2**) (75% total yield) and mollugin (**1**) (61% total yield) in a short reaction sequence was developed. The reaction sequence was based upon electrophilic addition of 3-methyl-3-buten-1-ol onto the *ortho* position of an aromatic alcohol in the presence of BF_3, immediately followed by pyran ring formation and subsequent DDQ oxidation. This pathway reveals the highest-yielding synthesis of mollugin at this moment.

Acknowledgment

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(19) 3-Bromomollugin **7**: IR (KBr): 1650 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.59 (6 H, s, 2 × CH_3), 4.04 (3 H, s, OCH_3), 7.54 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz, CH-8 or CH-9), 7.56 (1 H, s, CH), 7.63 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz, CH-8 or CH-9), 8.13 (1 H, ddd, *J* = 8.2, 1.4, 0.8 Hz, CH-7), 8.37 (1 H, ddd, *J* = 8.2, 1.4, 0.8 Hz, CH-10), 12.27 (1 H, s, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.82 (2 × CH_3), 52.62 (OMe), 78.73 (=CBr), 101.24 (C_{quat}), 113.15 (C_{quat}), 121.85 (CH-7), 123.80 (C_{quat}), 124.29 (CH-10), 125.25 (C_{quat}), 125.31 (=CH), 126.73 (CH-8 or CH-9), 128.81 (C_{quat}), 129.77 (CH-8 or CH-9), 140.32 (C_{quat}), 157.27 (C_{quat}), 172.20 (C=O). MS (ES^+): *m*/*z* (%) = 362/364 $[M]^+$(100).