Synthesis of Harounoside, A Naturally Occurring Pentalongin Hydroquinone Bisglucoside

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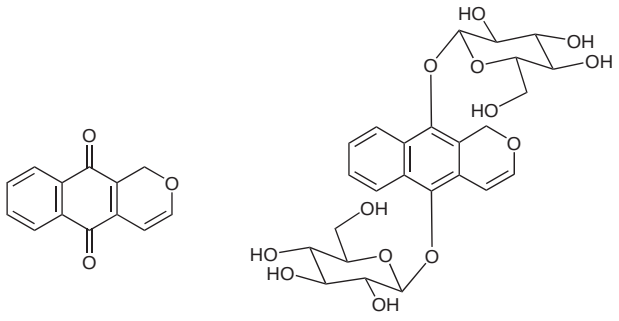
Abstract: The recently isolated natural product harounoside, namely 5,10-dihydroxy-2*H*-naphtho[2,3-*c*]pyran-β-D-bisglucopyranoside, was conveniently synthesized for the first time from pentalongin in 84% yield over three steps.

Key words: natural products, total synthesis, glucosidation

Mitracarpus scaber Zucc. is an annual plant used in African traditional medicine for its antifungal and antiparasitic activities.[1] Recently, a new pentalongin hydroquinone bisglucoside, named harounoside **2**, has been isolated from this plant (Figure 1).[2] Salient structural features of harounoside are the reduced pentalongin structure and the bisglucoside unit with β-stereochemistry. The natural product pentalongin **1**, which showed pronounced antifungal and antiparasitic activities, has been isolated from the roots of *Pentas longiflora* Oliv. (Rubiacea).[3–5] The powder of the roots of *P. longiflora* is used by traditional healers in the dispensary of traditional medicine of Curphametra (Butare, Rwanda) to treat the skin disease pityriasis versicolor.[4] All these physiological activities of pentalongin and its reduced form underline the importance of this class of natural products as a potential drug candidate.



1 (pentalongin) **2** (harounoside)

Figure 1

In continuation of our synthetic efforts towards physiologically active pentalongin derivatives,[6–9] we now report the first synthesis of the natural product harounoside **2**.

Concerning the synthesis of arylglucosides and naturally occurring glycosides, various glucosylation methods have been developed since the classical Koenigs–Knorr synthesis.[10] These procedures usually require an activated glucosyl donor, such as glucosyl halides.[11,12] However, it has been shown that the reaction of per(*O*-acetyl)glucosyl bromide with an aglycone in the presence of various silver salts as promoter, often led to a complex mixture of reaction products.[13] The directed glucosylation of hydroquinone with penta-*O*-acetylglucose in the presence of one equivalent of $BF_3{\cdot}OEt_2$ in dichloromethane has been shown to be a convenient method to obtain tetra-*O*-acetyl-β-D-glucopyranosides of hydroquinone.[14] Unfortunately, in our hands, this procedure completely failed with the hydroquinone derived from pentalongin **6**, resulting in a complex mixture of reaction products. Recently, the imidate methodology[15] has been shown as a good method for the synthesis of naturally occurring β-glycosides in the presence of Lewis acid catalysis, as exemplified for 7-hydroxycoumarin glucuronosides[16] and retinoic acid glucoconjugates.[17] We have applied this methodology to the synthesis of harounoside **2** because of the mild reaction conditions (cf. the enol ether moiety in the structure) and the fact that the reaction product could be selectively directed towards the desired β-isomer.[16,17]

The hemiacetal **4** has been obtained by selective deacetylation of 1,2,3,4,6-pentaacetyl-D-glucose (**3**) in various ways.[17–19] The 1-*O*-acetyl group was removed by treatment of 1,2,3,4,6-pentaacetyl-D-glucose (**3**) with hydrazinium acetate in dimethyl formamide at room temperature (Scheme 1),[18] giving rise to hemiacetal **4** (α/β, 5:1, measured by NMR spectroscopy[19]) in 99% yield.

Treatment of compound **4** with trichloroacetonitrile[14] in the presence of DBU in dichloromethane at room temperature afforded the corresponding trichloroacetimidate **5** in 85% yield (Scheme 1).[14] *O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetimidate (**5**) was obtained as the α-isomer as indicated by the typical acetal carbon signal at 92.6 ppm in the ^{13}C NMR spectrum and the doublet of the acetal hydrogen at 6.56 ppm (J = 3.9 Hz) in the ^{1}H NMR spectrum. The configuration of the anomeric carbon

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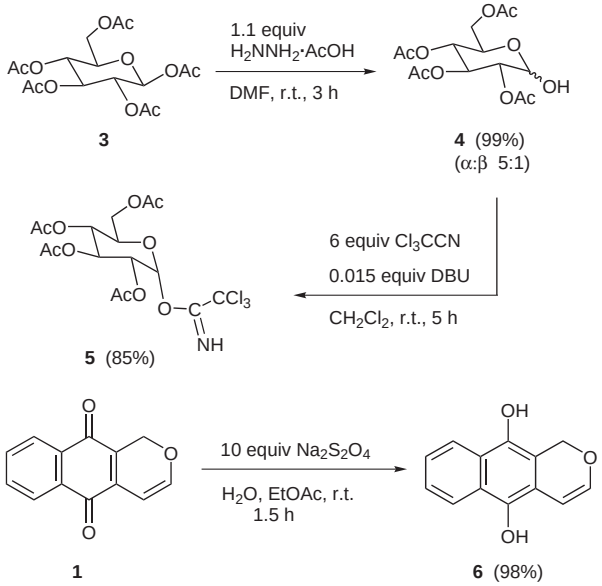
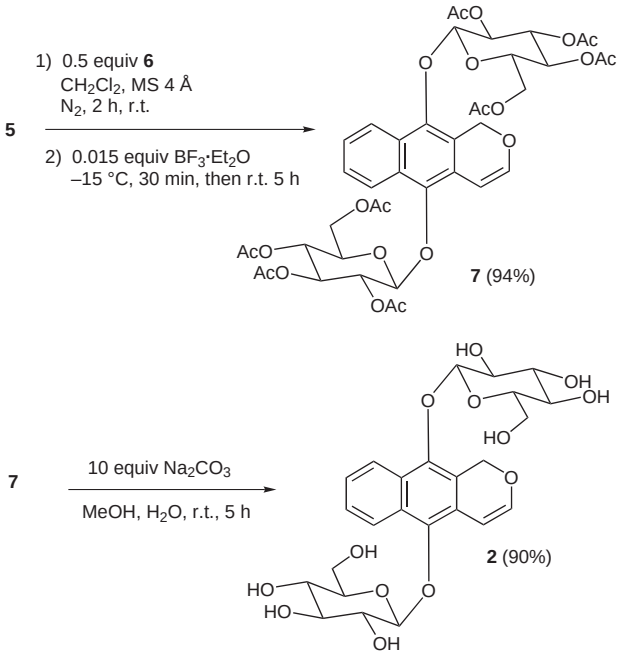


Scheme 1



Scheme 2

of this trichloroacetimidate **5** did not change after one month at –20 °C. *O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetimidate (**5**) was used as the condensing agent with 5,10-dihydroxy-2*H*-naphtho[2,3-*c*]pyran (**6**).

The new aglycone **6**, the hydroquinone derived from pentalongin **1**, was obtained in 98% yield by the treatment of pentalongin **1** with sodium dithionite[20] in a biphase system with ethyl acetate and water at room temperature. The new aglycone **6** was characterized especially by its typical double bond appearing as an AB system at 6.25 and 6.63 ppm (J = 5.9 Hz; $CDCl_3$) in the ^{1}H NMR spectrum.

The glucosylating agent *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetimidate (**5**) was reacted with the aglycone pentalongin hydroquinone **6** in the presence of a Lewis acid catalyst (BF_3·OEt_2) in dichloromethane, leading to glycoside **7** in 94% yield (Scheme 2). The glycoside **7** was obtained solely as the double β-isomer, as indicated by the signals of the two anomeric carbons at 102.1 and 102.4 ppm in the ^{13}C NMR spectrum. In addition, the anomeric proton doublet in the ^{1}H NMR ($CDCl_3$) spectrum at 6.56 ppm (J = 7.7 Hz) was very characteristic. The olefinic double bond in the hydroquinone pentalongin derivative **7** was indicated by the AB system at 6.30 and 6.67 ppm (J = 5.9 Hz) in the ^{1}H NMR spectrum ($CDCl_3$).

The acetyl groups in the glycoside **7** were removed by treatment with sodium carbonate in a mixture of methanol–water (2.5:1) at room temperature for four hours.[15] By means of this reaction, harounoside **2** was obtained in 90% isolated yield. The structure of harounoside **2** was determined by spectral techniques (^{1}H NMR, ^{13}C NMR, IR, MS) and was compared with the spectral data of the authentic compound.[2] The glycoside **2** was obtained as the β-isomer, which was identical to the natural product.

In conclusion, 5,10-dihydroxy-2*H*-naphtho[2,3-*c*]pyran-*O*-β-D-bis-(2,3,4,6-tetra-*O*-acetyl-glucopyranoside) (**7**) was conveniently synthesized for the first time in good yield by a glucosidation reaction of pentalongin hydroquinone **6** and the donor *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetimidate (**5**). The acetyl groups of the latter compound were removed by using sodium carbonate to afford the natural 5,10-dihydroxy-2*H*-naphtho[2,3-*c*]pyran-5,10-β-bisglucopyranoside (**2**) in 85% overall yield.

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