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Natural Products

Total Synthesis of the Antiviral Natural Product Houttuynoid B

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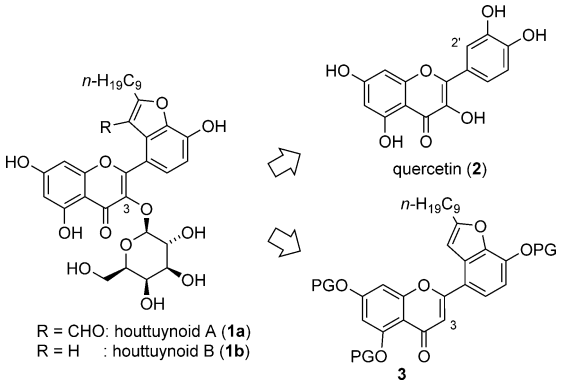
Dedicated to Professor Henning Hopf on the occasion of his 75th birthday

Abstract: The first total synthesis of houttuynoid B, a powerful antiviral flavonoid glycoside from the Chinese plant *Houttuynia cordata*, is described. In a key step, a Baker–Venkataraman rearrangement employing an already glycosylated substrate was used to efficiently set up the fully functionalized carbon skeleton. The required benzofuran building block was prepared through a domino Sonogashira coupling/5-*endo-dig* cyclization and converted into a stable 1-hydroxybenzotriazole-derived active ester prior to linking with a galactosylated hydroxyacetophenone unit. The elaborated synthesis requires only nine steps (11% overall yield) along the longest linear sequence and paves the way for the preparation of structurally related compounds for further biological evaluation.

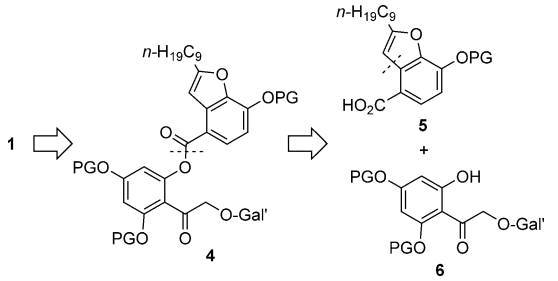
Viral infections such as influenza, hepatitis, HIV, and dengue fever are still a leading cause of death worldwide and the development of new powerful antiviral agents represents an important challenge for scientific research.[1] In this context, the testing of natural products has led to the identification of several promising antiviral agents.[2] A relevant example is the houttuynoids, a small group of structurally related flavonoid glycosides, isolated in 2012 by Yao and co-workers from *Houttuynia cordata*.[3] This plant belongs to the family of *Sauruaceae* and is used in traditional Chinese medicine inter alia for the treatment of viral diseases.[4] It was shown that the houttuynoids are responsible for the antiviral activity of *Houttuynia cordata*.[3] For instance, houttuynoids A (**1a**) and B (**1b**) were found to inhibit herpes simplex virus with IC_{50} values of 23.5 and 57.7 μM, respectively. Biosynthetically, the houttuynoids, which all carry a β-galactosyloxy unit at C-3, are supposed to be derived from quercetin (**2**) and 3-oxo-dodecanal (houttuynin).[3]

Due to their pronounced antiviral activities and their limited availability from natural sources, the houttuynoids represent attractive target molecules for chemical synthesis; however, they have never been synthesized so far.[5] This may be due to the fact that particular structural features, for example, the benzofuran unit in **1a**/**1b**, hamper the application of some obvious strategies. For instance, initial experiments in our laboratory revealed that the regioselective functionalization of properly protected derivatives of quercetin (**2**) cannot be achieved through metalation or halogenation at C-2′ (Scheme 1).[6] Also, all our attempts to introduce an oxy-substituent of intermediates of type **3** at C-3 under various established conditions[7] failed, possibly due to the strong electron-donating effect of the benzofuran moiety.

Nevertheless, we finally succeeded to accomplish an efficient synthesis of houttuynoid B (**1**), as reported herein. According to the retrosynthetic analysis shown in Scheme 2, our strategy is based on the consideration that the chromenone core could eventually be built up by means of a Baker–Venkataraman rearrangement/cyclization[8] employing a substrate of type **4** already containing the glycosyloxy substituent. The ester **4** in turn would be derived from a benzofuran building block **5** and a hydroxyacetophenone derivative of type **6**.



Scheme 1. Houttuynoids A and B, and the two initially considered potential synthetic precursors **2** and **3**.



Scheme 2. Retrosynthetic analysis of houttuynoid B (**1**) based on a Baker–Venkataraman rearrangement.

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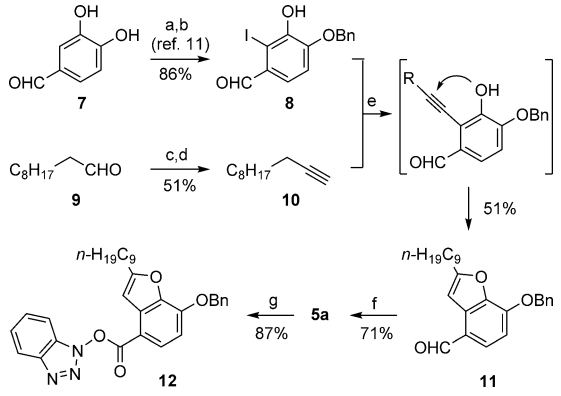
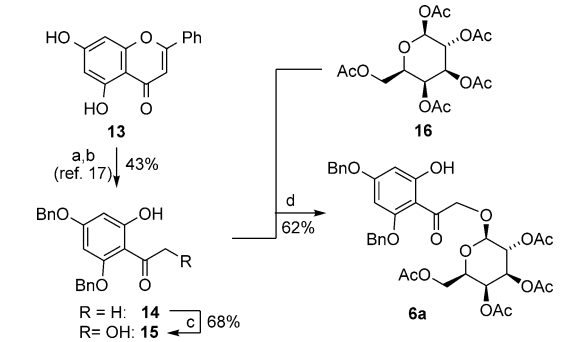
To generate a benzofuran building block of type **5** we intended to use a Sonogashira coupling[9] with a consecutive 5-*endo-dig* cyclisation.[10] For this purpose, we first prepared the known 2-iodo-3-hydroxybenzaldehyde derivative **8** following slightly modified literature protocols.[11] After treatment of 3,4-dihydroxybenzaldehyde (**7**) with benzyl bromide in the presence of K_2CO_3 in acetone,[12] the mono-protected product was further reacted with iodine monochloride to afford the iodide **8** in high yield as a pure regioisomer (Scheme 3). Separately, 1-undecyne (**10**) was prepared from decanal (**9**) under Corey–Fuchs conditions.[13] On heating the iodo-phenol **8** and the alkyne **10** with 10 mol% of $Pd(PPh_3)_2Cl_2$ and CuI in the presence of NEt_3 in DMF, the domino Sonogashira coupling/5-*endo-dig* cyclisation proceeded smoothly to afford the benzofuran **11** in 51% isolated yield. Subsequent Pinnick oxidation[14] of the aldehyde function gave the carboxylic acid **5a**. To prepare for the planned ester formation (see Scheme 2), this building block was further converted into the HOBT-activated ester **12**,[15] which proved to be easy to handle and was stable for months without significant decomposition.[16]



Scheme 3. Synthesis of the benzofuran building block **5a** and its activated derivative **12**. Reagents and conditions: a) benzyl-Br, K_2CO_3, KI, acetone, reflux, 93%; b) ICl, pyridine, CH_2Cl_2, RT, 93%; c) CBr_4, PPh_3, CH_2Cl_2, 0 °C to RT, 73%; d) *n*BuLi, THF, −78 °C to RT, then H_2O, 70%; e) $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI, NEt_3, DMF, 60 °C, 51%; f) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, THF/water, 40 °C, 71%; g) HOBT, EDC·HCl, CH_2Cl_2, RT, 87%; HOBT = 1-hydroxybenzotriazole; EDC = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide.

The synthesis of the second building block **6a** (Scheme 4) started from the inexpensive commercially available natural product chrysin (**13**), which after double *O*-benzylation was degraded by retro-aldol reaction to the resulting acetophenone derivative (**14**) as described by Caldwell et al.[17] α-Oxidation under Rubottom conditions[17,18] then furnished the hydroxylated product **15**. It is worth noting that, despite the modest yield, this method opened a reliable and practical access to **15** on a multigram scale. Lastly, the installation of a β-galactose moiety was accomplished in good yield by reacting a mixture of the alcohol **15** with peracetylated β-galactose in the presence of BF_3-etherate as a Lewis acid at room temperature.[19]

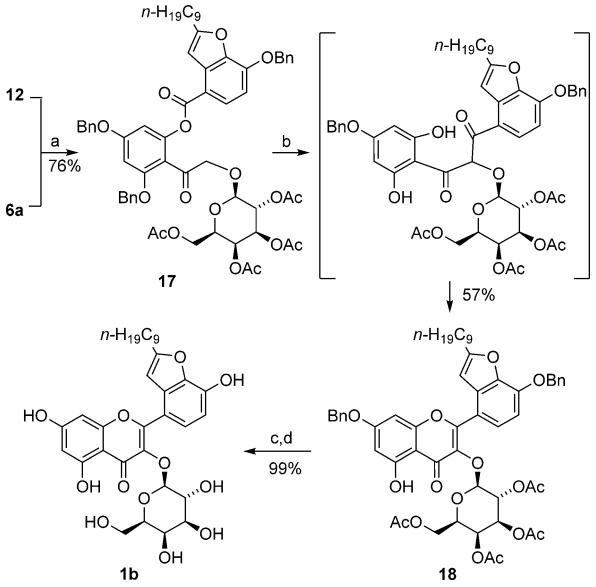
With the *ortho*-hydroxyacetophenone building block **6a** in our hands the next goal was the esterification with the acid building block **5a**. Though initial experiments to connect **5a** and **6a** under Steglich conditions[20] only resulted in the formation of the acid anhydride, the arylester **17** was obtained in good yield when the phenol **6a** was reacted with the HOBT-activated acid derivative **12** in the presence of NaH at 0 °C in THF (Scheme 5).



Scheme 4. Synthesis of the acetophenone building block **6a**. Reagents and conditions: a) benzyl-Br, K_2CO_3, DMF, 70 °C, 57%; b) 18 M KOH, pyridine, diethylene glycol, 120 °C, 75%; c) i. LDA, TMSCl, THF, 0 °C; ii. *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C; iii. *p*TsOH, THF/water, RT, 68%; d) BF_3·OEt_2, CH_2Cl_2, RT, 62%; *m*-CPBA = *meta*-chloroperbenzoic acid; *p*TsOH = *para*-toluenesulfonic acid.

Having successfully constructed the ester **17**, the stage was set to probe the planned key transformation, that is, the conversion of **17** into the chromenone **18**. Much to our satisfaction, using potassium carbonate as a base in the presence of TBAB as a phase-transfer catalyst, the ester **17** smoothly underwent the desired Baker–Venkataraman rearrangement with concomitant in situ cyclization of the intermediate 1,3-diketone to afford the chromenone **18** in 57% yield after purification (Scheme 5).

The remaining task was the deprotection of **18**.[21] The hydrogenolytic cleavage of the benzyl ethers proceeded smoothly using palladium on carbon in a mixture of THF and ethanol



Scheme 5. Completion of the total synthesis of houttuynoid B (**1**). Reagents and conditions: a) NaH, THF, 0 °C, 76%; b) K_2CO_3, TBAB, toluene, 70 °C, 57%; c) Pd-C, H_2, THF/EtOH, RT; d) NaOMe, MeOH, RT, 99% (2 steps). TBAB = tetra-*n*-butylammonium bromide.

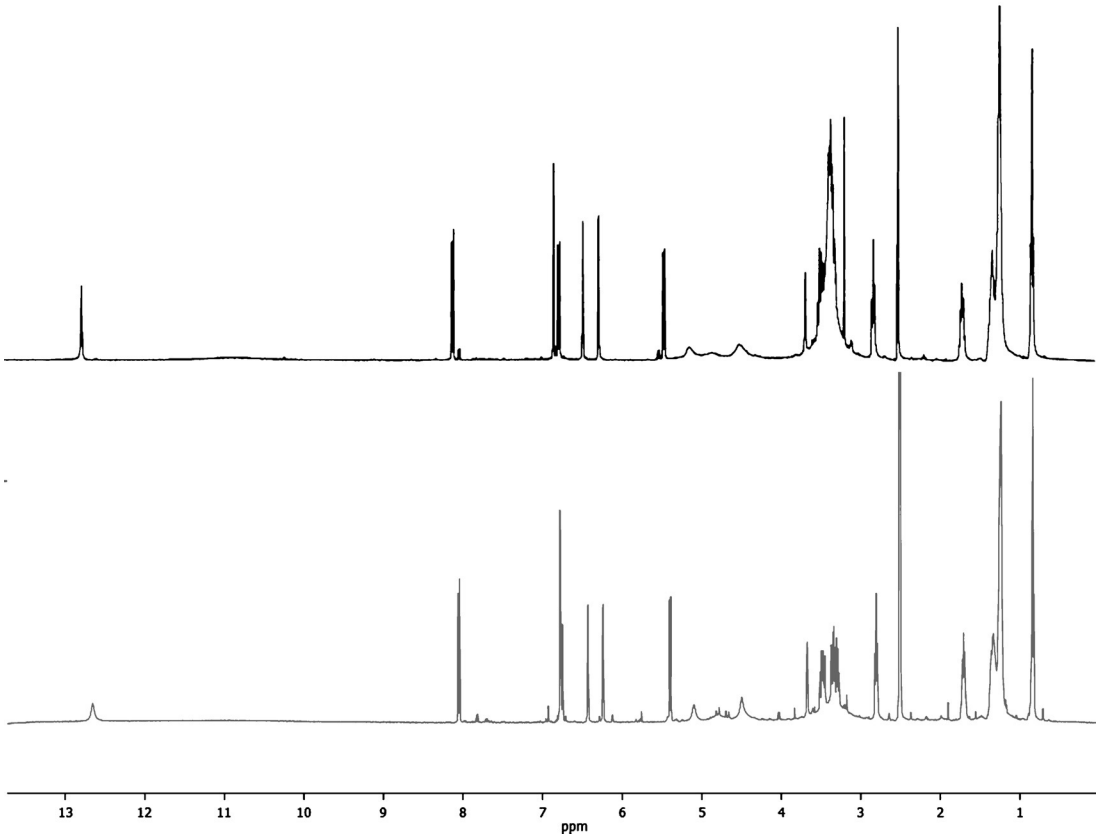


Figure 1. Comparison of the ^{1}H NMR spectra of natural (top) and synthetic (bottom) houttuynoid B (**1**) in [D_6]DMSO.

to afford a pure crude product that was used directly without further purification. The final deprotection of the sugar moiety (acetate cleavage) was achieved by addition of sodium methoxide in methanol to afford the natural product houttuynoid B (**1**) in almost quantitative yield. The ^{1}H and ^{13}C NMR spectra of the synthetic sample of **1** perfectly matched those reported for natural houttuynoid B (Figure 1).[3]

In summary, we have achieved the first total synthesis of a member of the houttuynoid family of natural products. Starting from 3,4-dihydroxybenzaldehyde, the synthesis of **1** requires only nine linear steps and proceeds with an overall yield of 11%. As key features the synthesis exploits: 1) a domino Sonogashira coupling/*5-endo-dig*-cyclization to build up the benzofuran system; 2) a stable HOBT-derived active ester as a building block for the arylester formation; and 3) a Baker–Venkataraman rearrangement/cyclisation to establish the flavone skeleton in the presence of the (protected) galactosyloxy substituent. We are optimistic that the developed strategy will pave the way for the synthesis of other natural and unnatural houttuynoids and their biological investigation as promising antiviral agents.

Acknowledgements

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Keywords: antiviral agents · benzofurans · cross-coupling · flavonoids · glycosides

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