Tetrahedron 73 (2017) 1503–1510

Contents lists available at ScienceDirect

Tetrahedron

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

C8-selective biomimetic transformation of 5,7-dihydroxylated flavonoids by an acid-catalysed phenolic *Mannich reaction*: Synthesis of flavonoid alkaloids with quercetin and (−)-epicatechin skeletons

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ARTICLE INFO

Article history:
Received 22 July 2016
Received in revised form
14 January 2017
Accepted 27 January 2017
Available online 1 February 2017

Keywords:
Flavonoid alkaloids
Biomimetic synthesis
Regioselective phenolic *Mannich reaction*
Flavonoid chemistry
N-Acylaminocarbinol
Iminium chemistry

ABSTRACT

We hereby report the biomimetic synthesis of three flavonoid alkaloids, namely 8-(2″-pyrrolidinon-5″-yl)quercetin, 6-(2″-pyrrolidinon-5″-yl)-(−)-epicatechin and 8-(2″-pyrrolidinon-5″-yl)-(−)-epicatechin. These known natural products were prepared *via* an acid-catalysed regioselective phenolic Mannich reaction involving the electrophilic attack of an *N*-acyliminium ion on the corresponding flavonoidal precursors. The products were purified by preparative HPLC. The reactions showed high C8-regioselectivity. The major isomers of the synthesized flavonoid alkaloids were further characterized in terms of their medicinal-chemical properties.

1. Introduction

Flavonoid alkaloids constitute a unique group of natural products. They contain − in almost all cases − a five- or six-membered nitrogen heterocycle which is connected to the C6 or C8 position of the A-ring of the flavonoid skeleton. Almost all molecules in this group are found in plants which are used in folk medicine as herbal remedy for the treatment of a wide range of conditions. Some compounds were reported to possess valuable pharmacological activity themselves.[1] Research into the field of flavonoid alkaloids gained even more attention when a synthetic flavonoid alkaloid derivative, namely flavopiridol[2] (brand name: Alvocidib, by Tolero Pharmaceuticals®) performed promisingly in phase II clinical trials and was granted the orphan drug designation by the FDA for the treatment of acute myeloid leukaemia in the United States in 2014.[3] Based on the still unexploited potential that lies in this family of natural products in terms of bioactivity and structural diversity, it can be rightfully stated that the isolation and synthesis of flavonoid alkaloids and their derivatives is a highly important field of research today.

The flavonoid alkaloid 8-(2″-pyrrolidinone-5″-yl)quercetin (**1**, Fig. 1) was isolated as a racemate from *Senecio argunensis* by N. Li and co-workers in 2008.[4] This molecule has a 2-pyrrolidone moiety attached to the C8 position of the A-ring of quercetin (**4**, Fig. 1). *Senecio argunensis* is a perennial herb distributed in northeast and northwest China. It is used in traditional Chinese medicine as a

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http://dx.doi.org/10.1016/j.tet.2017.01.068
0040-4020/

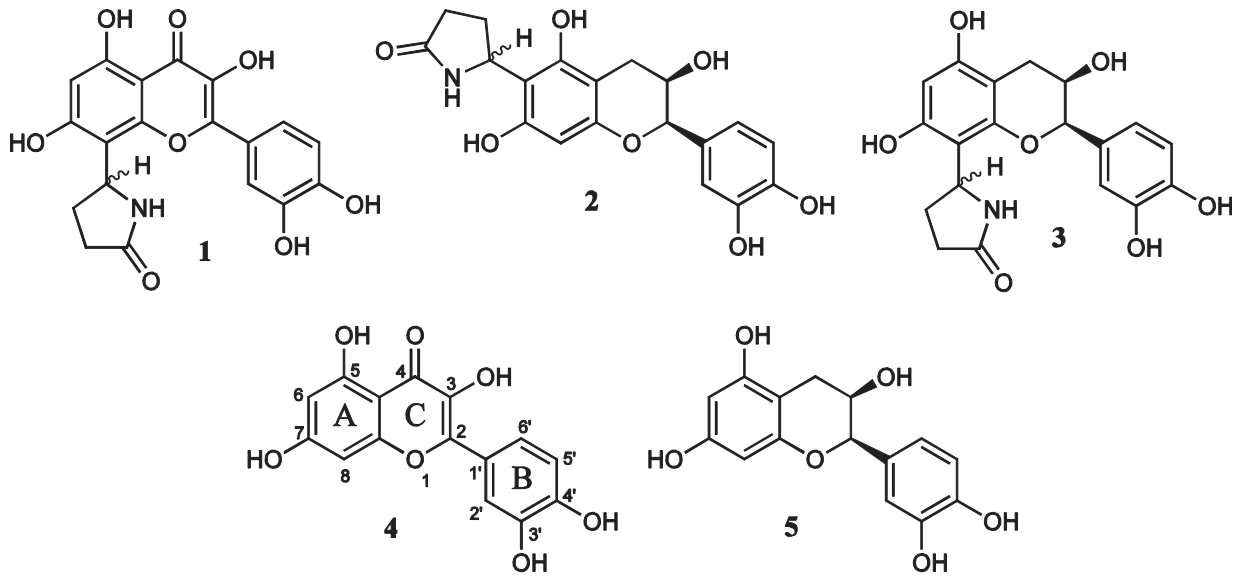

Fig. 1. Structure of flavonoid alkaloids **1**–**3** and their flavonoid precursors (**4**, **5**).

remedy for the treatment of, among other conditions, sore throat, dysentery and snake bite.

6-(2″-Pyrrolidinone-5″-yl)-(−)-epicatechin (**2**, Fig. 1) and 8-(2″-pyrrolidinone-5″-yl)-(−)-epicatechin (**3**, Fig. 1) are both derivatives of the flavan-3-ol (−)-epicatechin (**5**, Fig. 1). They were isolated from the roots of *Actinidia arguta* by D. S. Jang and co-workers in 2009.[5] *Actinidia arguta* (or hardy kiwi) is a perennial vine native to northern China, Japan, Korea and Siberia. It produces an edible kiwi-like fruit used in traditional Chinese medicine to improve general health. In *in vitro* biological tests compounds **2** and **3** were both found to exhibit significant inhibitory effect against the formation of advanced glycation end products (AGEs), which play a key role in the pathogenesis of diabetic complications, cataracts, atherosclerosis and other neurodegenerative diseases.[5]

The biosynthesis of these flavonoid-pyrrolidone conjugates is hypothesized[6,7] to proceed *via* an aminocarbinol-derived iminium intermediate, which presumably arises through the *Strecker-degradation* of the corresponding amino acids present in the plants – in the case of molecules **1**–**3**, L-glutamine (**6**). The spontaneous cyclization of Strecker aldehyde **7** gives rise to 5-hydroxypyrrolidin-2-one (**8**), which is transformed into the *N*-acyliminium ion **9** upon protonation and subsequent loss of water. This *N*-acyliminium ion is a reactive electrophile, which attacks the activated A-ring of the flavonoids present in the plants to yield the C6- and C8-isomers of pyrrolidone-substituted flavonoids (Scheme 1). Plausible explanations of this biosynthetic route for similar cases are given by E. Leete[6] and by Tanaka et al.[7]

The aim of our work was to synthetically prepare flavonoid alkaloids **1**–**3** from their flavonoid precursors (**4**, **5**) in order to further investigate the desired products from a medicinal chemistry point of view.

2. Results and discussion

We have devised a feasible methodology for the synthesis of lactam-containing flavonoid alkaloids, utilizing a cyclic *N*-acylaminocarbinol reagent,[8] which can be easily prepared from succinimide in one step. This *N*-acylaminocarbinol is allowed to react with the appropriate flavonoid compound in a suitable solvent to yield the desired flavonoid alkaloids *via* an acid-catalysed regioselective phenolic *Mannich reaction*.[9] This type of transformation was applied in recent works by Tanaka et al. in the synthesis of a black tea polyphenol-type flavonoid alkaloid,[7] and also by Nguyen and co-workers in the selective synthesis of the C6- and C8-isomers of chrysin-derived flavonoid alkaloids and other pyrrolidine- and piperidine-substituted chrysin derivatives.[10] Complementarily to their work, our biomimetic synthetic route provides a convenient way to pyrrolidone-substituted flavonoids and can be generally applied to various flavonoid substrates.

First we prepared the *N*-acylaminocarbinol reagent 5-ethoxypyrrolidin-2-one (**11**) by the partial reduction of succinimide (**10**) with sodium borohydride (Scheme 2), as described in the literature.[11]

Quercetin (**4**) was allowed to react with reagent **11** with acid catalysis in refluxing THF (Scheme 3). The crude product was subjected to preliminary purification in order to dispose of the remaining quercetin by refluxing its suspension in ethyl acetate (dissolving unreacted **4**), and filtering the purified product. The obtained solid was purified by preparative HPLC, after which the desired flavonoid alkaloid **1** was obtained together with its C6-isomer (**12**) in a ratio of 94:6, indicating an electrophilic attack predominantly directed towards C8 in the reaction. We note that the C8-substituted regioisomer was the only isomer of this natural product which was isolated from its natural source (*Senecio argunensis*).[4]

In the next step, (−)-epicatechin (**5**) was allowed to react with 5-ethoxypyrrolidin-2-one (**11**) in the presence of an acid catalyst in refluxing THF (Scheme 4). A suspension of the crude product in ethyl acetate was refluxed (dissolving unreacted **5**) and filtered, in order to get rid of the remaining starting material contaminating the product. The obtained solid was purified by preparative HPLC, which gave the epimeric mixtures of the C8- (**3**) and the C6-substituted isomers (**2**) in a ratio of 87:13. The epimers of the regioisomers could not be separated by the applied method. The C8-regioselectivity observed in the reaction involving (−)-epicatechin is somewhat lower than in the case of quercetin, but