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An unprecedented gedunin rearrangement reaction converts a methyl group into the methylene group of a cyclopropyl ring

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ABSTRACT

Herein we describe an unprecedented formation of a cyclopropane ring through the conversion of a methyl group that was not functionalized for the purpose. In a one-step reaction, 7-deacetoxy-7α-hydroxygedunin (**4**) afforded two new gedunin derivatives, namely 7-deacetoxy-13,14,18-cyclopropyl-7α,15β, 17ξ-trihydroxy-gedu-16-oic acid (**7**) and 7-deacetoxy-9,11-en-7α,15β-dihydroxygedunin (**8**) along with the known 7-deacetoxy-7,9-diene-15β-hydroxygedunin (**5**).

1. Introduction

Gedunin (**1**) is one of the biologically important bitter principles that are found in the plant families Rutaceae and Meliaceae.[1] It was first isolated from the extracts of the plant *Entandrophragma angolense*.[2] Limonin (**2**) was the first of such bitter principles to be fully studied for the purpose of structure determination.[3] Gedunin continues to attract interest because of the many biological activities associated with it. It possesses antimalarial,[4] antifungal,[5] anticancer[6] and insect antifeedant[7] activities. It is the recognized active principle of extracts of *Azadirachta indica*, which has been formulated and is being distributed as an antimalarial.[8] It is therefore of interest to make derivatives of gedunin for the purpose of structure–activity studies, chemosystematics and drug discovery.

The chemistry of gedunin is well documented.[2,9] One of the ways of making new partially synthesized compounds from gedunin is the exploitation of its rearrangement reactions under alkaline and mostly under acidic conditions. Under alkaline conditions gedunin gives the quassinoid-like merogedunol (**3**, Fig. 1) with the elimination of β-furfural together with a minor glycidic ester decarboxylation product.[9] Essentially the same reaction takes place when the potassium salt of 7-deacetoxy-7-hydroxygedunin is heated.[10]

7-Deacetoxy-7α-hydroxygedunin (**4**), on treatment with acid in benzene, gave two compounds,[11] namely the 7,9-diene-15β-hydroxy compound (**5**) in which the methyl group at the 8-position has migrated to the 14-position followed by the dehydration of a postulated 7-hydroxy-8-ene allylic alcohol intermediate compound that was not isolated, and the 15-oxo derivative (**6**) (Fig. 2).

We needed to make 2-halogeno derivatives of gedunin and 7-deacetoxy-7α-hydroxygedunin. We modified the method described[9] for the partial synthesis of 2-bromogedunin, which involves treating 1,2-epoxygedunin in acetic acid for half an hour with hydrobromic acid. When 7-deacetyl-7α-hydroxy-1,2-epoxygedunin was treated in separate reactions with hydrochloric acid and hydrobromic acid, the expected 2-chloro- and 2-bromo- derivatives were obtained, respectively[12] Trace amounts of side products were observed when thin layer chromatography was used to analyse the composition of the reaction mother liquor. It was suspected that the 14,15-epoxy group, which is known to trigger rearrangement reactions in acid medium, may have led to the side products. Modification of the reaction procedure starting with 7-deacetoxy-7α-hydroxygedunin (**4**) led to a new reaction. We

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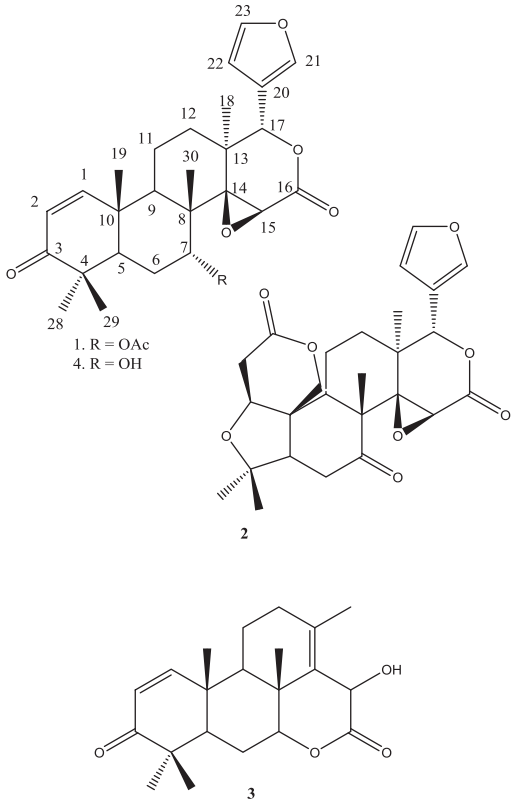

Fig. 1. Some naturally occurring bioactive gedunin limonoids and derivatives.

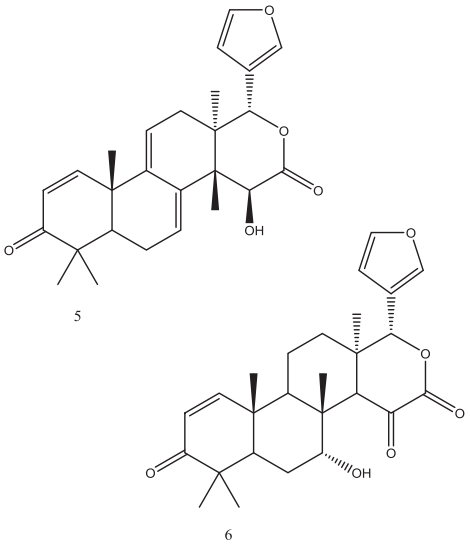

Fig. 2. Previously reported products of acid-catalysed gedunin rearrangement.

herein report an unprecedented rearrangement reaction leading to the formation of the cyclopropane gedunin derivative product **7**, along with the diene derivative **5** and the new 9,11-ene derivative **8** (Scheme 1), when 7-deacetoxy-7α-hydroxygedunin (**4**) in acetic acid was treated with concentrated hydrochloric acid.

2. Results and discussion

Initially, we carried out the rearrangement reaction of 7-deacetoxy-7α-hydydroxygedunin **4** (2 g, 4.5 mmol) and concentrated hydrochloric acid (8 mL), using glacial acetic acid (33 mL) as solvent at 15 °C for 1 h and then maintained at room temperature of 29–30 °C for 11 h (Scheme 2, condition A).

After work up and monitoring with thin layer chromatography, the bicarbonate fraction gave a mixture of four compounds from which a trace amount of 7-deacetoxy-13,14,18-cyclopropyl-7α,15β,17ξ-trihydroxy-gedu-16-oic acid **7** was obtained by fractional crystallization and as the major product. The reaction was then performed at 20 °C for 4 h and the desired product **7** was obtained in 4.0% yield as the only product in the bicarbonate fraction (Scheme 2, condition B). Furthermore, the reaction was performed at 40 °C for 4 h and the desired product **7** was obtained in 1.8% yield as the only product in the bicarbonate fraction along with some charred residue (Scheme 2, condition C). Thus the reaction at 20 °C gave the highest yield of the cyclopropane gedunin derivative **7** in 4 h. Column chromatography of the neutral fraction of the rearrangement product yielded 7-deacetoxy-9,11-en-7α,15β-dihydroxygedunin **8** along with the known diene **5** in 47.0% yield.

The structures of the rearrangement reaction products were determined using infrared spectroscopic, NMR, high resolution mass spectral data and comparison with data in the literature.

The starting compound **4** for the reaction was prepared[9,10] from gedunin. Its spectra were in agreement with published data for the same compound and its 2D NMR spectra and assignments determined for the first time in this work were in agreement with the data published[13] for the natural product.

The IR spectrum of 7-deacetoxy-7,9-diene-15β-hydroxygedunin **5** agreed with the published[11] data. The chemical shifts for the carbon and hydrogen atoms of this compound have not, before now, been assigned. Analysis of the 2D ^{1}H and ^{13}C NMR spectra led to assignments of the ^{1}H and ^{13}C chemical shifts (Table 1).

The FT-IR spectrum of 7-deacetoxy-(13,14,18)-cyclopropyl-7α, 15β,17α,β,-trihydroxy-ged-16-oic acid **7** showed very intense absorptions at 3400–2600 cm^{-1} (OH of the carboxylic acid and the other OH groups), 1705 and 1669 cm^{-1} (C=O for the carboxylic acid and α,β unsaturated ketone), 1501 and 873 cm^{-1} for the β-substituted furan. The analysis of the full 2-D spectra (Table 2) including H–H COSY, HSQC and HMBC spectra enabled the assignment of the chemical shifts of the C and H atoms of (**7**). The ^{1}H NMR spectrum had only four methyl group absorptions at δ 1.14 (C-14), 1.17 (C-28), 1.11 (C-29) and 1.34 (C-30) instead of five methyl groups of the starting material (4), and four sets of methylene protons instead of the three sets of (4).

One of these methylene protons belonging to the C-18 H_2 of the cyclopropyl ring showed absorptions as a pair of doublets at δ 0.90 (d, J=6 Hz) and 1.38 (d, J=6 Hz). There were seven methine protons, three of which were geminal with OH at 4.20 (H-7), 4.94 (d, H-15) and 5.13 (H-17). The protons of H-1 and H-2 were observed at δ 7.03 (d, J=10 Hz) and 5.86 (d, J=10 Hz), respectively. The orientation of the C-17 OH group could not be assigned.

The ^{13}C NMR had 26 carbon atom absorptions in agreement with the same number of carbon atoms in the starting material **4**. The four methyl groups had absorptions at δ 19.5, 27.5, 21.3 and 20.1, respectively and the absorption of the methylene carbon of the cyclopropane ring had a chemical shift of δ 21.9. This latter assignment was confirmed by the observation that the J_{C-H} for the C-18 H_2 group was 162 Hz as in the cneorins[14] and glabretals.[15] The rest of the spectrum was in accordance with expectations.

The HMBC connectivity is shown in Fig. 3. There are correlations between H-18 and C-15 as well as between H-17 and C-18. ROESY spectral correlations (Table 2) led to the assignment of stereochemistry of the cyclopropyl ring and the conformational structure of **7**. The β face of the molecule is relatively more crowded with methyl groups than the α face so that the methylene group of the cyclopropyl ring should be formed at the face opposite to that of the methyl groups.

The HRMS had $[M+H-18]^{+}$ at m/z 441.2273 for $C_{26}H_{33}O_6$ calculated as 441.2275, which may have arisen through lactonization