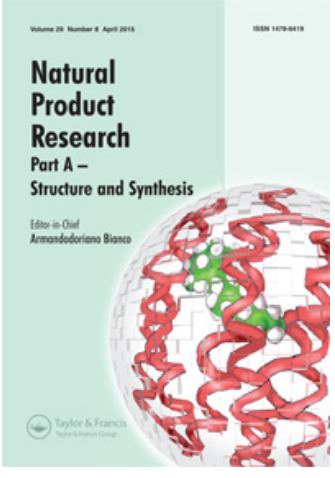

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Chemistry of α-mangostin. Studies on the semisynthesis of minor xanthones from Garcinia mangostana

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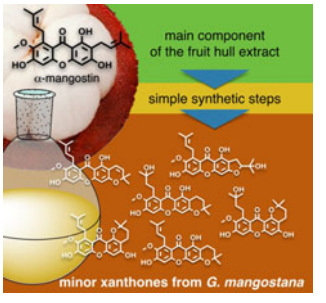

α-Mangostin is the major prenylated xanthone from *Garcinia mangostana* and it has been used also in recent times as starting material for the semisynthetic preparation of various biologically active derivatives. Its structure is characterised by the presence of few functional groups amenable to chemical manipulations, but present in the molecule in multiple instances (three phenolic hydroxyl groups, two prenyl chains and two unsubstituted aromatic carbons). This study represents a first approach to the systematic investigation of the reactivity of α-mangostin and describes the semisynthesis of some minor xanthones isolated from *G. mangostana*.

Keywords: α-mangostin; *Garcinia mangostana*; semisynthesis; acid-catalysed cyclisation; oxidative cyclisation

1. Introduction

α-, β- and γ-Mangostin (**1**, **2** and **3**, Figure 1) represent the most abundant prenylated xanthones in *Garcinia mangostana* L. (Guttiferae) (Obolskiy et al. 2009), and several biological activities have been ascribed to the former (Larson et al. 2010; Krajarng et al. 2011; Quan et al. 2012; Wang et al. 2012; Koh et al. 2013). However, interesting biological properties have been attributed also to some minor components of the plant (Ho et al. 2002; Suksamrarn et al. 2003; Jung et al. 2006; Suksamrarn et al. 2006). Among these, 9-hydroxycalabaxanthone (**11**, Figure 1) showed cytotoxic activity towards HT-29 human colon cancer cell line (Han et al. 2009) and a moderate inhibitory activity towards neuraminidase (Ryu et al. 2010). Also 3-isomangostin (**14**, Figure 1) has cytotoxic activity (Han et al. 2009) and it is an inhibitor of mammalian DNA polymerases (Mizushina et al. 2013) and a selective inhibitor of acetylcholinesterase (Khaw et al. 2014). Its hydrate form **16** is an inhibitor of the catalytic subunit of cyclic AMP-dependent

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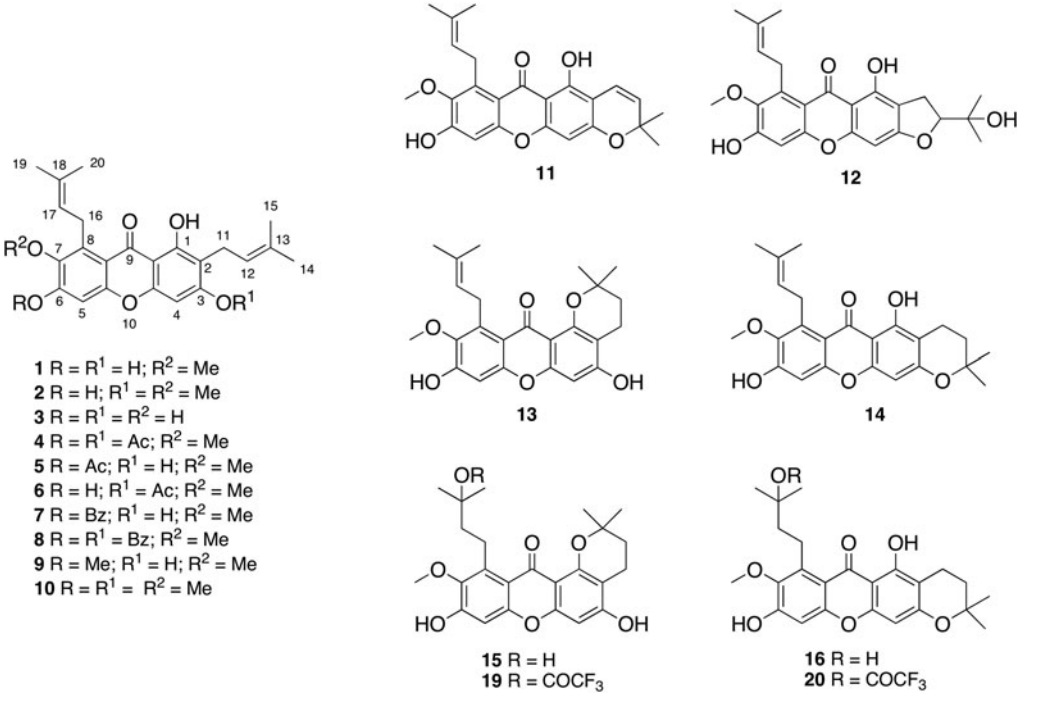

Figure 1. Prenylated xanthones from *G. mangostana* (**1**–**3** and **11**–**16**) and synthetic derivatives of α-mangostin.

protein kinase (Lu et al. 1998). Mangostanin (**12**, Figure 1) showed cancer chemopreventive properties due to a quinone reductase-inducing activity comparable to that of liquiritigenin used as the positive control (Chin et al. 2008). Some of these studies give, however, an incomplete description of the biological activities, due often to the insufficient amounts of material obtained from the plant. Difficulties in the isolation of such minor constituents led to the development of semisynthetic analogues (see for example Ren et al. 2011; Keiser et al. 2012; Sudta et al. 2013; Zou et al. 2013; Fei et al. 2014). Chemical modification of α-mangostin is a matter of selectivity, in that it possesses more than one instance of otherwise few types of functional groups (phenolic hydroxyls, prenyl chains and unsubstituted aromatic carbons) (Figure 1). Even if the chemical behaviour of α-mangostin can emerge through the comparison of already published results, a comprehensive and not fragmentary analysis of its reactivity is lacking. This paper describes the first systematic approach to the manipulation of functional groups of α-mangostin, in the search for reaction conditions aimed at the preparation of minor xanthones of *G. mangostana* using the most abundant component α-mangostin as the starting material.

2. Results and discussion

2.1. *Reactivity of the hydroxyl groups of α-mangostin*

The acetylation reactions of the phenolic hydroxyl groups of α-mangostin have been already reported both as a tool for structure elucidation (Yates & Bhat 1970) and in the search for biologically active derivatives (recent examples: Ren et al. 2011; Keiser et al. 2012; Sudta et al. 2013; Fei et al. 2014). The most accessible phenolic hydroxyl groups are those in positions 3 and

Table 1. Acylation and alkylation reactions of the hydroxyl groups of α-mangostin.

Entry	Conditions	Product(s) (%)
1	Ac_2O (1.1 equiv.), Et_3N (4 equiv.), CH_2Cl_2, 0°C	**4** (30); **5** (33)
2	*N*-Acetylimidazole (2 equiv.), CH_2Cl_2, rt	**4** (8); **6** (44)
3	Ac_2O (4 equiv.), Et_3N (4 equiv.), toluene, rt	**4** (99)
4	Benzoyl chloride (1.1 equiv.), Et_3N (4 equiv.), CH_2Cl_2, 0°C	**7** (39); **8** (36)
5	MeI (18 equiv.), $NaHCO_3$ (4.5 equiv.), DMF, rt	**9** (29); **10** (51)

6, while the hydroxyl group in 1 hardly reacts (Ren et al. 2011), probably due to its involvement in an intramolecular hydrogen bond with the carbonyl oxygen in position 9.

Using 1 equiv. of acetic anhydride in the presence of triethylamine at low temperature, the 3,6-diacetyl derivative **4** (Table 1, entry 1) and the monoacetyl derivative **5** were obtained in nearly equal molar amount. The preferential acetylation of the 6-hydroxyl group with respect to that in position 3 is a recurrent motif in the chemistry of α-mangostin (Sudta et al. 2013; Fei et al. 2014), and it was noticed also using benzoyl chloride as the acylating agent (Table 1, entry 4) and in the methylation reaction with methyl iodide (Table 1, entry 5).

Using the mild acetylating agent *N*-acetylimidazole, the 3-acetyl derivative **6** was obtained as the main product (Table 1, entry 2). This result is the opposite with respect to that observed previously and to the best of our knowledge it was never reported before. The different regioselectivity could be ascribed to the increased reactivity of the protonated form of *N*-acetylimidazole towards the transfer of the acetyl group (Fife 1993). Although no reports exist about the different acidities of the phenolic hydroxyl groups of α-mangostin, we hypothesise that the imidazole ring could abstract a proton preferentially from the 3-phenolic hydroxyl, affording both a more powerful acetylating agent (the protonated form of *N*-acetylimidazole) and the more nucleophilic phenolate anion.

2.2. *Reactions involving the prenyl groups of α-mangostin*

Several xanthones from *G. mangostana* have one or more additional oxygenated ring, originating from reactions involving prenyl and phenolic hydroxyl groups through oxidative cyclisations (e.g. 9-hydroxycalabaxanthone **11** and mangostanin **12**) or addition reactions, e.g. 1-isomangostin **13** and 3-isomangostin **14**.

By reacting α-mangostin with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 9-hydroxycalabaxanthone **11**, also known as garciniafuran (Nilar & Harrison 2002), was obtained in 70% yield. In the meantime the same approach was reported by Dharmaratne et al. (2013).

Mangostanin **12**, a furanoxanthone from the heartwood of *G. mangostana* (Nilar & Harrison 2002), could originate from the putative epoxide intermediate **17** through attack of the 3-phenolic oxygen on the less substituted carbon atom of the oxirane ring (Figure 2). The reaction is enzymatically controlled, as the stereocentre has (*R*) configuration (Han et al. 2009). Using a

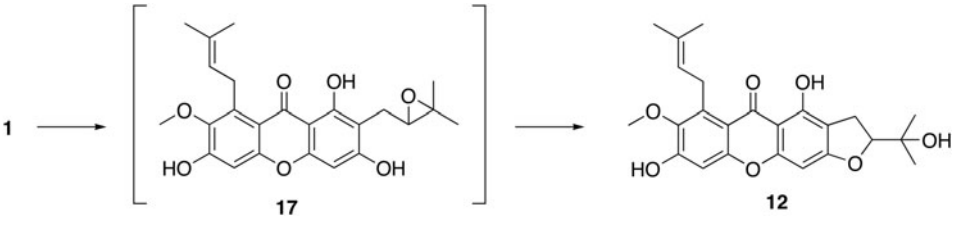

Figure 2. Proposed biosynthetic route and biomimetic approach to mangostanin **12**.

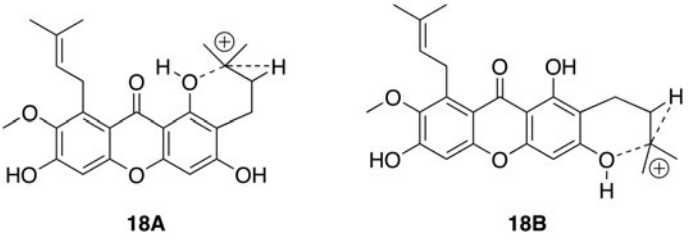

Figure 3. Hypotetical intermediates in the synthesis of isomangostins.

Table 2. Acid-catalysed and acid-promoted cyclisation reactions of α-mangostin.

Entry	Acid (equiv.)	Reaction conditions	Product(s) (%)
1	*p*-TsOH (cat)	Toluene/CH_2Cl_2 2:1, rt	**13** (27), **14** (15), **15** (9), **16** (15)
2	H_2SO_4 (0.2)[a]	Toluene, rt	**14** (20)[b]
3	H_2SO_4 (1)[a]	Toluene, 40°C	**14** (30), **15** (63)
4	BF_3Et_2O (cat)	CH_2Cl_2, 0°C to rt	**13** (29), **15** (9)
5	CF_3COOH (1)	CH_2Cl_2, rt	**19** (25), **20** (56)

[a] Molecular sieves of 4 Å were added to the reaction mixture.
[b] Seventy-four percent of unreacted α-mangostin was recovered.

biomimetic approach, racemic mangostanin **12** was obtained in 25% yield by reacting α-mangostin with *m*-chloroperbenzoic acid, and up to 46% yield when oxone® was used as the oxidising agent in a biphasic system.

1- and 3-Isomangostin (**13**, **14**) and their hydrate forms **15** and **16** were isolated from *G. mangostana* in 1987 (Mahabusarakam et al. 1987), but some of them were already known synthetic compounds (Yates & Bhat 1970). As the prenyl group in position 2 is flanked by two phenolic hydroxyls, both intermediates **18A** and **18B** could be formed (Figure 3). Due to the carbocationic character of **18A** and **18B**, nucleophilic attack of the phenolic oxygen atom occurs at the tertiary carbon, leading to the six-membered pyranose derivatives **13** and **14**.

Depending on the reaction conditions, the corresponding hydrated derivatives **15** and **16** could also be obtained. By reacting α-mangostin with a catalytic amount of *p*-toluenesulphonic acid, the four compounds **13**–**16** were isolated (Table 2, entry 1). In an attempt to reduce the complexity of the reaction mixture, several different acid/solvent systems were tested. With the dehydrating sulphuric acid in toluene in the presence of molecular sieves at 40°C, 1-isomangostin hydrate **15** was the main product together with minor amounts of 3-isomangostin **14** (Table 2, entry 3). The latter was the only isolated product at lower temperature and in the presence of a catalytic amount of acid, albeit the conversion of the starting material was low (Table 2, entry 2). Using the Lewis acid BF_3 in anhydrous conditions, 1-isomangostin **13** was isolated in 29% yield (Table 2, entry 4). In the light of these results, we tried the use of the protic trifluoroacetic acid in anhydrous conditions (Table 2, entry 5). The trifluoroacetyl derivatives of 1-isomangostin hydrate **19** and 18-*O*-trifluoroacetyl-3-isomangostin hydrate **20** were isolated in 25% and 56% yield, respectively, with complete conversion of the starting material.

3. Conclusions

Our results constitute the first attempt to give a comprehensive and systematic picture of the chemical behaviour of α-mangostin. Among the obtained results, the different reactivity of the

phenolic hydroxyl groups in 3 and 6 positions, depending on the experimental conditions (acetic anhydride vs *N*-acetylimidazole), could be of interest for a temporary selective protection of one of them. Both oxidative and non-oxidative cyclisation reactions involving the 2-prenyl group could represent an alternative entry to the minor xanthones from *G. mangostana* with respect to cumbersome and low-yielding extractive procedures, in view of detailed biological studies requiring some amount of material.

Supplementary material

Experimental details relating to this article are available online.

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