Mono- and Di-benzyl Derivatives of α-Mangostin from *Garcinia mangostana* Linn.

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**Abstract.** A major prenylated xanthone from *Garcinia mangostana* L., α-mangostin has been used as a starting material for structural modification in terms of discovering various biologically active derivatives. The presence of three hydroxyl groups and two prenyl chains leads to chemical manipulation of α-mangostin which the *O*-alkylation often takes place on the hydroxyl group at positions 1, 3, and 6. In this study, the benzylation of α-mangostin was performed using benzyl bromide at 0°C to room temperature in DMF affording the derivatives in moderate yield. The characterization was carried out using 1H-NMR, FTIR spectroscopic methods, and HRMS analysis.

# INTRODUCTION

α-Mangostin **1** is a noticeable xanthone derivative isolated from the mangosteen (*Garcinia mangostana* Linn.) pericarp. The mangosteen which known for its bright purple hue has been utilized in traditional medicine across Southeast Asia for centuries [1]. Modern research has validated many of these traditional uses, attributing a diverse of pharmacological properties to α-mangostin **1**, including anti-inflammatory, antioxidant [2], antimicrobial [3], antidiabetic [4] and anticancer properties [5]. Moreover, a recent in silico study revealed that it has good potential as an antivirus [6]. The compound's various biological activities have made it a significant focus of extensive research in the quest to develop new therapeutic agents.

Due to its potent bioactivities, structural modifications of α-mangostin **1** are a promising approach to further enhance its pharmacological efficacy and optimize its drug-like properties [7]. Structurally characterized by its xanthone core with multiple hydroxyl groups (**FIGURE 1**), α-mangostin **1** provides a versatile scaffold for chemical modifications. This transformation can influence the stability and bioavailability of α-mangostin **1**, potentially leading to derivatives with improved therapeutic profiles [8]. Various strategies, including hydroxyl group protection, alkylation, and glycosylation, have been employed to modify the xanthone core of α -mangostin **1**, aiming to expand its utility and effectiveness in medicinal chemistry [1].



**FIGURE 1.** Structure of α-mangostin **1**

Among these modification techniques, *O*-alkylation is particularly noteworthy. This process involves the introduction of alkyl groups to the hydroxyl functionalities f α-mangostin, resulting in derivatives with altered physicochemical properties. The *O*-alkylated derivatives of α-mangostin **1** have shown enhanced bioactivity, potentially due to increased cellular uptake and improved metabolic stability [1]. Several studies have afforded the *O*-alkylated derivatives of α-mangostin **1** (**FIGURE 2**) using different methods [9-12]. This study as continuation of our interest in the development of natural-based active molecules [13-17] explores the *O*-alkylation of α-mangostin **1**, detailing the reaction conditions and characterization of the alkylated products.



**FIGURE 2.** Structure of some *O*-alkylated a-mangostin derivatives. Reagent and conditions: **2a-b** (allyl chloride, K2CO3, acetone, reflux 4h, 20-59%), **2c** (**2b**, CH3I, K­2CO3, acetone, reflux 4h, 80%), **3a-b** (CH3I, NaHCO3, DMF, r.t 24h, 29-51%), **3c-d** (benzoyl chloride, Et3N, DCM, stirring 0°C, 36-39%), **4a-b** (bromopropane/benzyl bromide, K2CO3, AcN, M.W 10 min), **5a-d** (alkyl halide, K2CO3,acetone, reflux o.n, yield 34-80%).

# EXPERIMENTAL

## General

Chemicals were used as purchased from Merck (Darmstadt, Germany) or Sigma Aldrich (Massachusetts, United States). Thin layer chromatography (TLC) analyses were performed on a pre-coated silica gel plate (0,20 mm, 60 F 254) (Merck, Darmstadt, Germany). Melting points were determined by using Fischer John apparatus (Cole Parmer, Illinois, USA) and are uncorrected. Infared (FTIR) spectra were recorded on Shimadzu 8400S spectrophotometer (Kyoto, Japan) using KBr technique. The NMR spectra were recorded on Bruker Avance 500 Mhz (Bruker, Germany) (1H, 500Hz) in deuterated solvents. The chemical shifts (*δ*) are reported in ppm relative to TMS as internal standard and coupling constant (*J*) are reported in Hz. Mass spectrometry (HRMS) was conducted using Waters QTOF (Waters, Hertfordshire, UK).

## Isolation of α-Mangostin 1

The dark purple pericarps of mangosteen fruits were washed, chopped, and dried in the shade at room temperature. The dried pericarps were fine powdered using a grinding mill. Eight (8) kilograms of the powder of *G. mangostana* was completely soaked in ethyl acetate (5L) at rt for 3×24 h. The residue was filtered from the extract and the solvent was evaporated at a reduced pressure to give 535 g of a condensed extract (6.69%). The extract was successively partitioned into *n*-hexane, methylene chloride, ethyl acetate, and methanol. The obtained fractions were concentrated by rotavapor and combined for the fractions with α-mangostin **1** for the next isolation with column chromatography. The pure α-mangostin **1** was obtained by recrystallization from *n*-hexane/ethyl acetate its structure was established by using NMR.

## Synthesis of Mono-and Di-benzyl Derivatives of α-Mangostin 1

A solution of α-mangostin **1** (0.1848 g; 0.45 mmol) in DMF (2 mL) was stirred at 0°C (ice bath) for 15 minutes. Next, K2CO3 (0.0730 g; 0.51 mmol) was added to the mixture with stirring at 0°C (ice bath). After 30 minutes, benzyl chloride (0.52 mL; 4.5 mmol) was added dropwise and the reaction was continued with stirring at 0°C for 1 hour then at room temperature overnight. The reaction mixture was poured into crushed ice and washed with cold distilled water. The extraction was performed with dichloromethane (3×5 mL) and distilled water (1×10 mL). The organic phase was collected and dried over Na2SO4, followed by filtration. The filtrate was then mixed with ethyl acetate (5 mL) and washed with distilled water (3×10 mL) and brine (10 mL). The organic layer was combined and dried over Na2SO4, followed by filtration, and dried under vacuum. The crude solid was purified using column chromatography with *n*-hexane: ethyl acetate 100:20 v/v to give the products.

## 6-Benzyl-1,3-dihidroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one 6a

A pale yellow solid (49 mg, 19.2%). m.p 102-103°C. FTIR (KBr, *v* cm-1): 3408, 2917, 1636, 1579. 1H NMR (CDCl3, 500 MHz): δ 13.51 (s, 1H), 7.34-7.47 (m, 6H), 6.78 (S, 1H), 6.35 (s, 1H), 5.20 (m, 1H), 5.16 (m, 1H), 4.14 (d, *J* = 7 Hz, 2H), 3.83 (s, 3H), 3.4 (d, *J* = 7 Hz, 2H), 1.67-1.85 (s, 12H), 1.57 (s, 2H). HRMS [ES+, *m/z*]: 501.2277 [M+H]+. Anal. Calcd for C31H34O6:501.2277.

## 3,6-Dibenzyl-1-hidroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one 6b

A pale orange solid (49.7 mg, 18.7%. m.p 127-128°C. FTIR (KBr, *v* cm-1): 3271, 2924, 1589. 1H NMR (CDCl3, 500MHz): δ 13.84 (s, 1H), 7.34-7.48 (m, 10H), 6.79 (s, 1H), 6.27 (s, 1H), 5.19 (m, 2H), 4.14 (d, *J* = 7 Hz, 2H), 3.83 (s, 3H), 3.45 (d, *J* = 7 Hz, 2H), 1.68-1.85 (s, 12H), 1.25 (m, 4H). HRMS [ES+, *m/z*]: 591.2749 [M+H]+. Anal. Calcd for C38H39O6:591.2749.

# RESULTs AND DISCUSSION

α-Mangostin **1** (21.6643 g, 0.27%) was obtained as a yellow solid. The IR spectrum (KBr disc) showed the absorptions for hydroxyl (3421 and 3267 cm-1), carbonyl (1643 cm-1), CC double bond (1456 cm-1), and CO bond (1240 cm-1) groups, respectively. The 1H NMR spectrum (recorded in (CD3)2CO-*d6*) displayed one signal as a singlet at *δ* 13.77 ppm (OH). It also exhibited signals attributed to the methine group adjacent to aromatic double bond as singlets at *δ* 6.79 (H-5) and 6.36 ppm (H-4). The presence of a signal at 5.25 ppm (t, *J* = 7.0 Hz, 2H) corresponded to two methines (H-12, H-17) adjacent to the olefinic double bond was suggested by the 1H NMR spectrum. Two doublet signals at *δ* 4.10 (*J* = 7.0 Hz) and 3.33 ppm (*J* = 7.0 Hz) fit the methylene group (H-11, H-16). A singlet signal at *δ* 3.76 ppm (3H) is characteristic of a methoxy group (OCH3) and four methyl group signals as singlets at *δ* 1.80 (H3-14), 1.75 (H3-15), 1.62 (H3-19), and 1.62 ppm (H3-20) in 1H NMR spectrum confirmed the α-mangostin **1** framework. The 13C NMR spectrum of α-mangostin **1** showed peaks at *δ* 182.02, 162.12, 160.88, 158.69, 156.55, 155.40, 154.87, 143.60, 137.30, 130.59, 123.95, 122.59, 111.17, 110.24, 102.77, 101.82, 92.34, 60.53, 26.05, 25.12, 25.08, 21.15, 17.49, 17.09. The presence of 24 carbon atoms was further classified into the categories of five methyls (*δ* 17.09, 17.49, 25.08, and 25.12 ppm) including methoxy (*δ* 60.53 ppm), two methylenes (*δ* 21.15 and 26.05 ppm), four methynes (*δ* 92.34, 102.77, 122.59, and 123.95 ppm), thirteen quarternary carbon atoms including one carbonyl (*δ* 182 ppm).

Next, modification of a-mangostin can occur in free hydroxyl groups of xanthone frameworks [1]. In this study, the synthesis of α-mangostin **1** derivativeswas conducted by *O*-alkylation of the hydroxyl group of theα-mangostin **1** with benzyl substituent from benzyl chloride (**FIGURE 3**). The phenolic hydroxyl located at positions 3 and 6 are the most easily accesible, while the hydroxyl group in position 1 largely unreactive probably it forms an intramolecular hydrogen bond with the carbonyl oxygen in position 9 [9].

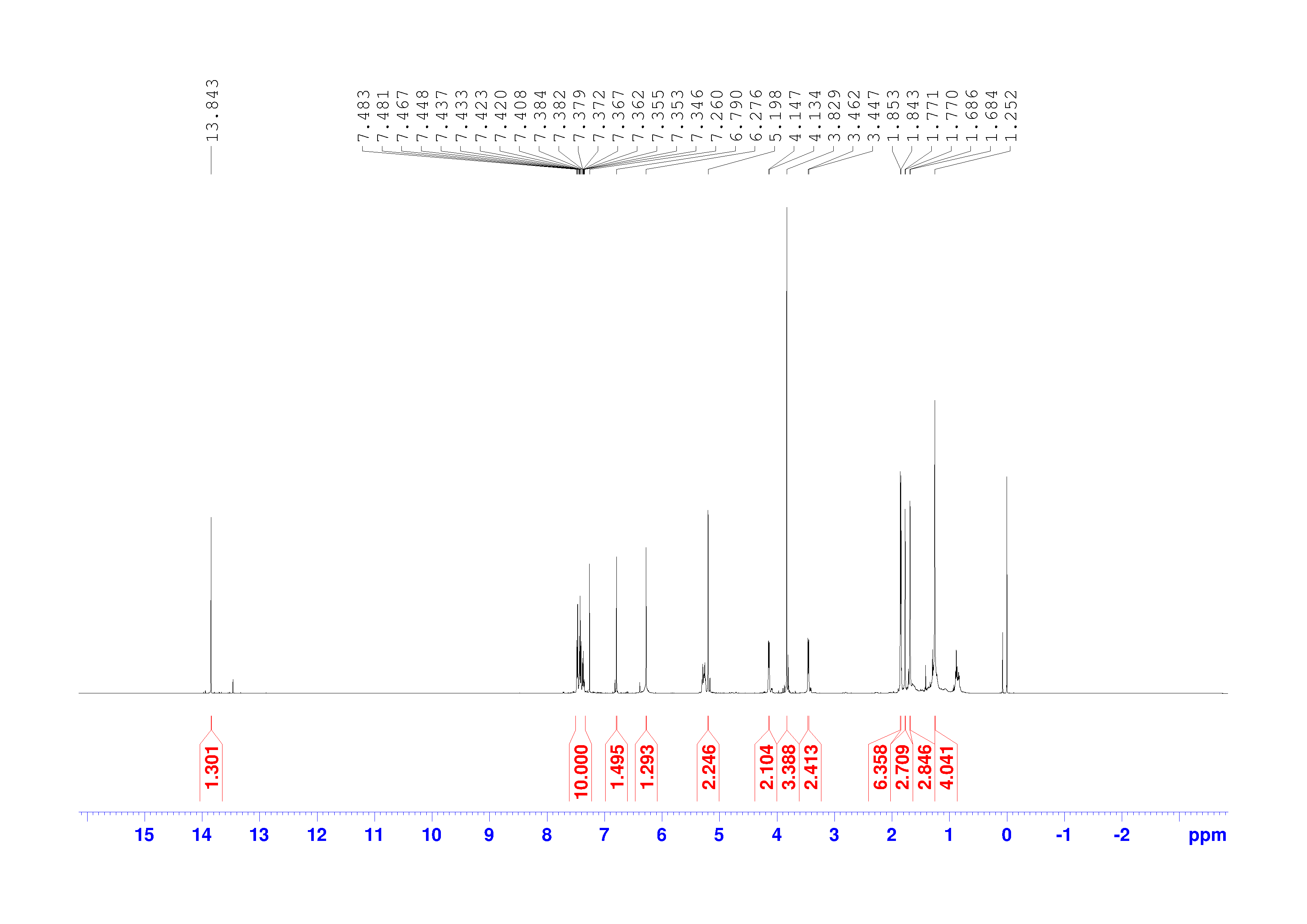
**FIGURE 3.** Synthesis of *O*-alkylated α-mangostin **1** derivatives

The structure modification of α-mangostin **1** was conducted in DMF at 0°C (ice bath) for 1 hour to room temperature overnight. TLC monitor indicated two distinct spots with *Rf* values of 0.6 and 0.4 (*n*-hexane: ethyl acetate = 1:3), differing from the α-mangostin **1** spot. A literature review supports the hypothesis that the reaction products may be mono-substituted and di-substituted benzyl derivatives [11]. To determine the number of free hydroxy groups substituted by benzyl, the sample was analyzed by 1H NMR and compared to the spectrum of α-mangostin **1**. The increased number of H in the 1H NMR spectrum of α-mangostin **1** derivatives reflects the number of benzyls substituted in the framework. The 1H NMR spectrum as shown in **FIGURE 4** gives the multiplet signal at *δ* 7.34-7.47 ppm (5H) and singlet signal at *δ* 1.57 ppm (2H) associated with the benzyl substituent. The HRMS spectrum displays the molecular ion peak [M+H]+ at *m/z* 501.2277 for which corresponds to the calculated *m/z* for 6-benzyl-1,3-dihidroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one **6a**. The 1H NMR spectrum as shown in **FIGURE 5** attributes the two benzyl substituent in the structure with a multiplet signal (10H) at *δ* 7.34-7.47 ppm and singlet signal at *δ* 1.25 ppm (4H). The molecular ion peak [M+H]+ of the compound shows at *m/z* 590.2749 for which suits with the calculated *m/z* for 3,6-dibenzyl-1-hidroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one **6b**.

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**FIGURE 4.** The 1H NMR spectrum of compound 6-benzyl-1,3-dihydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one **6a**



**FIGURE 5.** The 1H NMR spectrum of compound 3,6-dibenzyl-1-hydroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one **6b**

# CONCLUSION

In this study, mono-and di-benzyl derivatives of α-mangostin **1** namely 6-benzyl-1,3-dihidroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one **6a** (19.2% yield) and 3,6-dibenzyl-1-hidroxy-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one **6b** (18.7% yield) were afforded by *O*-alkylation of α-mangostin **1** using benzyl chloride at low to room temperature for 3 hours. The structure of the derivatives was established by spectroscopic methods.

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