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Graphical Abstract

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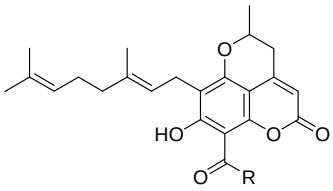
[a]*Faculty of Pharmacy,* [b]*Pharmaceutical Research and Technology Institute, and* [c]*Joint Research Center, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan.*



mammeasin C (**1**): R = ^{i}Pr, mammeasin D (**2**): R = ^{n}Pr

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[a]*Faculty of Pharmacy,* [b]*Pharmaceutical Research and Technology Institute, and* [c]*Joint Research Center, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan.*

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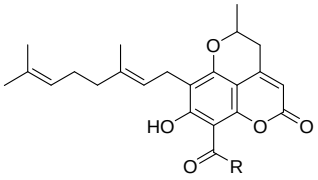
ABSTRACT

The first total syntheses of the geranylated pyranocoumarins, mameasins C (**1**) and D (**2**), aromatase inhibitors isolated from the flowers of *Mammea siamensis*, were accomplished in five steps, starting from phloroglucinol **3**. In this strategy, the characteristic pyran ring-fused coumarin core of **1** and **2** was effectively constructed by Friedel-Crafts acylation of **3**, followed by Reformatsky reaction of the resultant ketone to give a key coumarin intermediate **9**. Compound **9** was converted to targets **1** and **2** in a stepwise manner by successive *C*-acylation and *O*-geranylation, followed by a [1,3]-sigmatropic geranyl shift. Furthermore, screening of intermediates obtained in the synthetic pathway to **1** and **2** revealed that de-geranylated pyranocoumarins (**10** and **11**) show superior aromatase inhibitory activity as compared to the natural products **1** and **2**.

1. Introduction

Coumarins constitute an important class of heterocyclic compounds that are known as benzo-α-pyrones, wherein a pyran ring is fused with a benzene ring. Natural and synthetic coumarins have attracted considerable interest because they exhibit a diverse range of biological activities, which depend on the substitution pattern on the coumarin ring. A number of studies focusing on a broad array of pharmacological and biochemical properties such as anti-coagulant,[1] anti-alzheimer,[2] anti-viral,[3] anti-bacterial,[4] anti-fungal,[4b,4c,5] anti-inflammatory,[6] and anti-oxidant[4e,7] properties have been reported. In addition, the anti-proliferative and anti-tumor activities of various coumarins have been extensively investigated.[8] Some coumarins have also been used in clinical trials to demonstrate activity against breast cancer, prostate cancer, malignant melanoma, and metastatic renal cell carcinoma.[8k,8l,9] Furthermore, coumarins are used as additives in food and cosmetics, and as optical brightening agents.[10] Coumarins also find application in photochemotherapy for the treatment of certain skin diseases such as psoriasis, vitiligo, eczema, and mycosis.[11]

In the course of our characterization studies on bioactive constituents in Thai natural medicine,[13,14] we reported that a methanol extract of the flowers of *Mammea siamensis*, which have been used for preparing a heart tonic in Thai traditional medicine (“Sarapi” in Thai). The coumarin constituents



mammeasin C (**1**): R = ^{i}Pr, mammeasin D (**2**): R = ^{n}Pr

Figure 1 The structure of Mammeasin C (**1**) and D (**2**)

showed inhibitory effects on nitric oxide production in lipopolysaccharide-activated RAW264.7 cells.[13] Moreover, our continuing studies revealed that the methanol extract shows inhibitory activity against aromatase. The enzyme is responsible for a key step in the biosynthesis of estrogens, which plays a crucial role in the pathogenesis of breast cancer and is known to express itself at higher levels in breast cancer cells than in non-cancerous breast cells. Consequently, aromatase is a key therapeutic target in the treatment and prevention of estrogen-dependent breast cancer.[8m,8n] Based on bioassay-guided separation, two new geranylated coumarins, mammeasins C and D (**1** and **2**), were isolated together with 20 known coumarins[14] (Figure 1). Compounds **1** and **2** are rare coumarins, wherein a dioxaphenalene type framework is constructed by fusing a pyran ring to the coumarin unit. Both these compounds showed potent aromatase inhibitory activity [IC_{50} (μM): **1** = 2.7, **2** = 3.6]

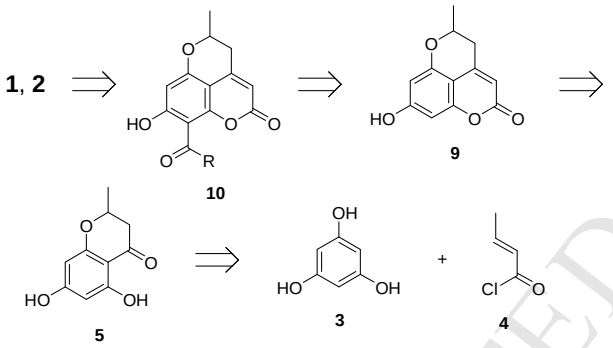
*Corresponding authors. *e-mail address:* g-tanabe@phar.kindai.ac.jp (G.T.), morikawa@kindai.ac.jp (T.M.)

comparable to that of aminoglutethimide (IC_{50} = 2.0 μM), which was used as a reference standard.[14] Compounds **1** and **2** find potential application as seeds for the development of therapeutic agents against breast cancer; hence, ensuring ready availability of analogues for structure-activity relationship (SAR) studies is an important research goal. In this regard, establishing a practical and short-step approach for the construction of the three-ring-fused coumarin core in **1** and **2** is imperative. Therefore, beginning with an SAR study on mammeasins C and D (**1** and **2**), we report herein the first total syntheses of **1** and **2** in five steps starting from commercially available phloroglucinol **3**. Furthermore, we compared the aromatase inhibitory activity of synthetic intermediates (**15** and **16**) to **1** and **2** with those of the parent coumarins, demonstrating that de-geranylation effectively enhanced the inhibitory activity against aromatase.

2. Results and discussion

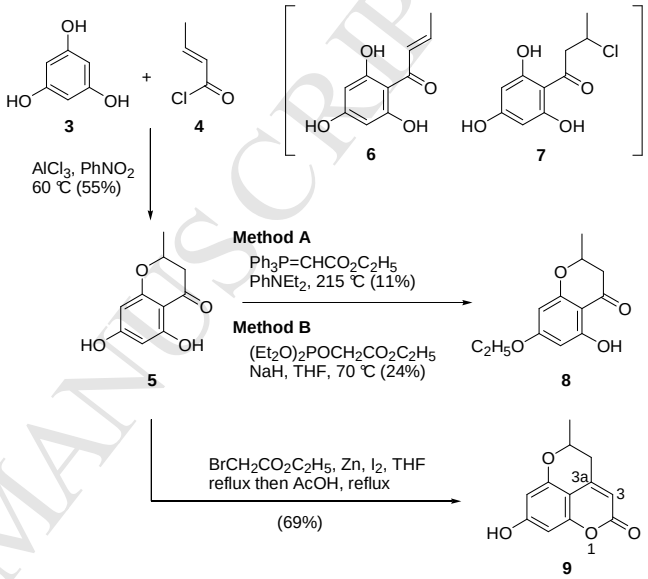
2.1. Syntheses of mammeasins C (1) and D (2)

As shown in the retrosynthetic analysis, compound **9**, the key pyranocoumarin motif of **1** and **2**, was constructed by coumarin synthesis from an known ketone **5** prepared by Friedel-Crafts acylation of phloroglucinol **3**, and subsequent internal conjugated addition of the resultant enone intermediate. Compound **9** was then converted to targets **1** and **2** via Friedel-Crafts acylation and subsequent geranylation of ketone **10** (Scheme 1).



Scheme 1 Retrosynthetic analysis of Mammeasins C (**1**) and D (**2**)

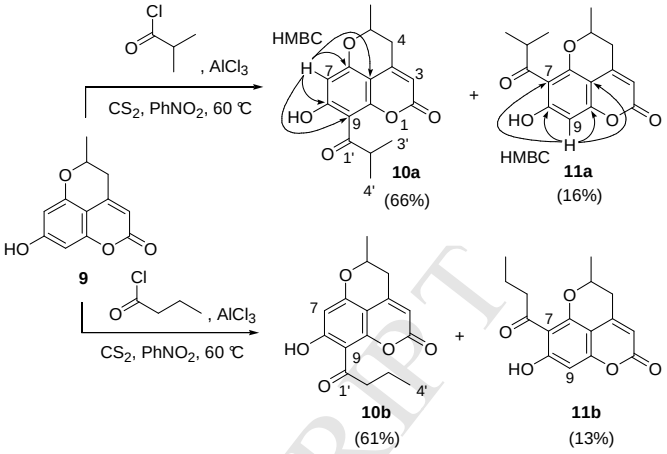
Based on the modified version of a published method,[15] phloroglucinol **3** was subjected to Friedel-Crafts acylation with crotonyl chloride, as an alternative to crotonic anhydride. The reaction afforded the desired chromanone 5,7-dihydroxy-2-methylchroman-4-one **5**, albeit in a disappointing yield of 31%. This yield was close to the reported value (36%)[15] and did not improve despite several attempts. Careful examination of the crude mixture revealed the formation of (2*E*)-(2,4,6-trihydroxyphenyl)-but-2-en-1-one **6** (an intermediate of **5**) and its HCl adduct, 3-chloro-(2,4,6-trihydroxyphenyl)-butan-1-one **7** (a by-product), which significantly decreased the yield of **5**. Fortunately, both **6** and **7** could be converted to the desired ketone **5** by NaOH treatment of the crude mixture prior to purification, and chemical yield of **5** was successfully improved up to 51%. Compound **5** was sequentially subjected to a Wittig reaction with $Ph_3P{=}CHCO_2C_2H_5$ as per a reported to a coumarin synthesis;[16] however, the reaction afforded 7-*O*-ethylated compound **8**, which is the ester-exchange product between the non-hydrogen-bonded hydroxyl of **5** and the ethoxy moiety of the Wittig reagent, in 11% yield. There was no evidence for the formation of the desired pyranocoumarin, 4,5-dihydro-8-hydroxy-5-methyl-2*H*-pyrano[4,3,2-*de*]coumarin **9**, despite careful chromatographic examination of the reaction mixture. Horner-Emmons reaction with $(Et_2O)_2POCH_2CO_2C_2H_5$[17] also resulted in the formation of **8**. On the other hand, the coumarin ring core was successfully constructed by Reformatsky[18] reaction with bromoacetate, followed by treatment with AcOH, to furnish the desired pyranocoumarin **9** in 69% yield. The structural motif of **9** was evidenced by the ^{13}C NMR spectrum, which displayed three kinds of sp^2-carbon signals at δ_{C3} 105.6, δ_{C3a} 152.0, and $\delta_{C=O}$ 164.0, attributed to the α,β-unsaturated enone system. No signal due to the ketonic carbonyl carbon was observed in the case of **8** ($\delta_{C=O}$ 197.9). The ^1H NMR spectrum also showed a signal due to an olefin proton at the α–position to the carbonyl at δ_H 5.86. No signal due to the hydrogen-bonded hydroxyl proton was observed at around 12 ppm (Scheme 2).



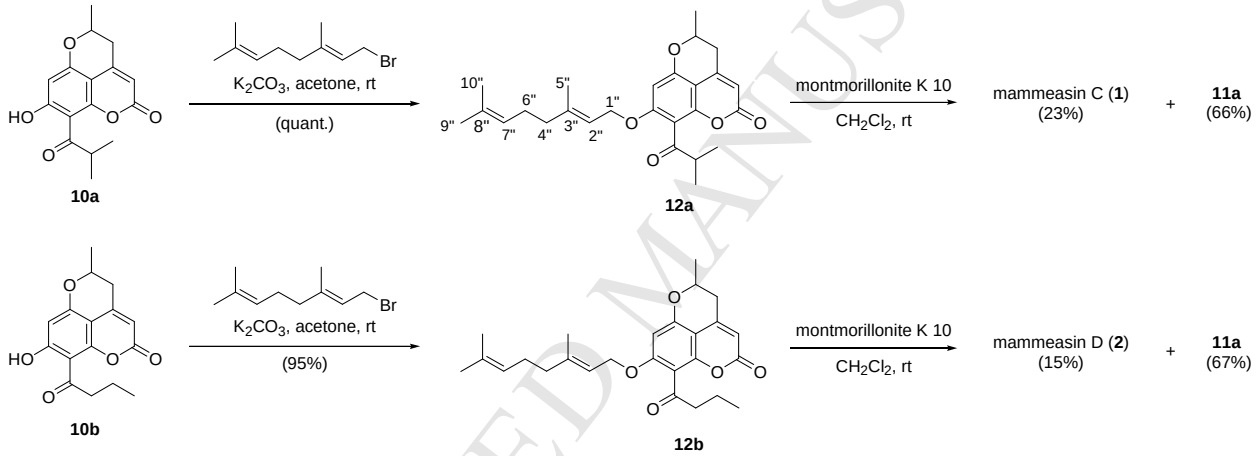
Scheme 2 Construction of pyranocoumarin framework (**9**) from phloroglucinol (**3**)

With the key pyranocoumarin core in hand, we attempted the functionalization of the benzene ring from **9** via a three-step sequence. First, Friedel-Crafts acylation of **9** with butyryl chloride or isobutyryl chloride was carried out under the standard conditions for the acylation of phenolic compounds,[19] and two regioisomers (**10**/**11**) in 4:1 and 5:1 ratio were obtained. The fact acylation of phenol ethers tends to occur at the para position[20] and the difference in electron density between the C6a- and C9a-oxygens of **9** suggested that the major isomers were 9-butyryl-4,5-dihydro-8-hydroxy-5-methyl-2*H*-pyrano[4,3,2-*de*]coumarin **10a** and 9-isobutyryl-4,5-dihydro-8-hydroxy-5-methyl-2*H*-pyrano[4,3,2-*de*]coumarin **10b**, while the minor isomers were the corresponding C7 regioisomers **11a** and **11b**. However, these products were not easily distinguishable from each other on the basis of their ^1H and ^{13}C NMR spectra. For example, the ^1H NMR spectrum of the major product **10a** showed a singlet due to the H7 proton at δ_H 6.33, while the spectrum of the minor product **11a** showed a singlet due to the H9 proton at δ_H 6.44. Because of the close chemical shifts of these signals, structure identification of these products was not possible. The ^{13}C NMR spectra showed a slight difference in the chemical shift with respect to signals due to the quaternary carbon α to the carbonyl of the acyl moiety (**10a**: δ_{C9} 103.5, **11a**: δ_{C7} 106.3); however, there was no conclusive evidence for the identification of their structures. Finally, the structures of the products were confirmed by heteronuclear multiple-bond correlation (HMBC) spectroscopy, as depicted in Scheme 3.

A final geranylation at the C7 position of **10a** and **10b** would have led to the target natural products, mammeasins C and D (**1** and **2**), but the usual mild reaction conditions for *C*-geranylation[21] using geranyl bromide in the presence of K_2CO_3 exclusively gave the corresponding *O*-geranylated products (**12a** and **12b**) in good yield. When the base was changed to NaH, a complex mixture was obtained, which did not contain the desired C7-geranylated products (**1** and **2**). When potassium *tert*-butoxide was used as an alternative base, trace amounts of **1** and **2** were detected in the crude mixture. Thus, the final transformation was not successful despite the aforementioned trials. Therefore, we abandoned our initial strategy for the direct *C*-geranylation of **10a** and **10b**, and turned our attention to the [1,3]-sigmatropic rearrangement of *O*-geranyl moiety of **12a** and **12b** using montmorillonite K10.[22] The reaction of **12a** and **12b** smoothly proceeded at room temperature to give the desired **1** and **2** in 23% and 15% yield, respectively. However, cleavage of the geranyl ether bond of **12a** and **12b** competed with the rearrangement, giving de-*O*-geranylated compounds **11a** and **11b** in 66% and 67% yield, respectively. Major products **11a** and **11b** were again converted to **1** and **2**, respectively, *via* the same sequence (*O*-geranylation/[1,3]-sigmatropic rearrangement). The physical and spectroscopic properties of the synthesized compounds were consistent with those of natural products (Scheme 4).



Scheme 3 The Friedel-Crafts acylation of **9**



Scheme 4 Conversion of **10** to Mammeasins C (**1**) and D (**2**)

2.2. Aromatase inhibitory activity

As shown in Table 1, our preliminary SAR study[14] revealed that kayeassamin A (**14**) and surangin D (**15**) inhibit aromatase at IC_{50}= 10 and 18 μM, respectively (entries 4 and 5). In contrast, the inhibitory activities of pyrano ring-fused coumarins **1**, **2**, and **13** were found to be almost 5 times stronger than those of ring-cleavage type compounds **14** and **15** (entries 1, 2, and 3). In particular, **1** and **2** showed potent inhibitory activity comparable to that of the aromatase inhibitor aminoglutethimde, which was used as the reference standard. These results indicated that fusion of the pyran ring to the coumarin framework was necessary to strengthen the inhibitory activity.

As the related heterocycles (**10**, **11a**, **12a**, **11b**, **12b**) with a 2*H*-pyrano[4,3,2-*de*]coumarin framework were obtained in this study, their aromatase inhibitory activities were tested *in vitro* and compared with those of natural **1** and **2** as well as the related coumarins **13**, **14** and **15** (Table 1).

Although both **1** and **2** effectively inhibited the enzyme aromatase, the simplest analogue **9** showed approximately 10-fold inferior activity than **1** and **2** (entry 7). The removal of both geranyl and acyl moieties caused one-order loss of activity relative to **1** and **2**. On the other hand, the IC_{50} values for aromatase inhibition of the de-geranylated versions **10a** and **10b** were in the same range as those of **1** and **2**; however, the potency of **10a** and **10b** was slightly higher (entries 8 and 10). Thus, it is noteworthy that the geranyl moiety of **1** and **2** was no longer essential for the aromatase inhibitory activity. Regioisomers **11a** and **11b** maintained almost equivalent or higher potent activities, irrespective of the position of the acyl moiety, as compared with **10a** and **10b** (entries 9 and 11). Introduction of an acyl moiety into the benzene ring, at either C7 or C9, was revealed to be imperative for the onset of potent inhibitory activity.

3. Conclusion

To summarize, the first total syntheses of **1** and **2** have been accomplished in five steps, from the commercially available phloroglucinol (**3**), thereby making these compounds readily accessible for further medical research. The potent aromatase inhibitory activity of intermediates **10a**, **10b**, **11a**, and **11b** obtained in the synthesis of **1** and **2** proved that these would be good lead compounds for further modification in drug development. Further SAR studies on the strong aromatase inhibitory activity are in progress.

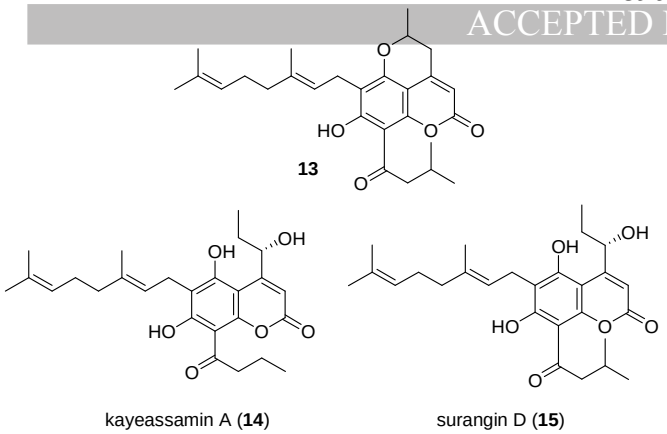


Figure 2 The coumarins (**13**, **14**, **15**) isolated from *Mammea siamensis*

Table 1. IC_{50} Values (μM) of 2*H*-pyrano[4,3,2-*de*]coumarin type intermediates (**9**, **10a**, **11a**, **10b 11b**) and mammeasins C (**1**) and D (**2**) against human recombinant aromatase.

Entry	Compound	activity	Entry	Compound	activity
1	**1**[a]	2.7	7	**9**	23
2	**2**[a]	3.6	8	**10a**	1.1
3	**13**[a]	8.8	9	**11a**	2.1
4	**14**[a]	10	10	**10b**	1.4
5	**15**[a]	18	11	**11b**	0.43
6	Aminoglutethimide[a]	2.0			

[a]lit.14.

4. Experimental section

4.1 General information

Mps were determined on a AS ONE ATM-02 melting point apparatus, and mps are uncorrected. IR spectra were measured on a Shimadzu IRAffinity-1 spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 400 (400 MHz ^{1}H, 100 MHz ^{13}C), a JEOL JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C) or a JEOL JNM-ECA 800 (800 MHz ^{1}H, 200 MHz ^{13}C) spectrometer. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-700T spectrometer. Optical rotations were determined with a JASCO P-2200 polarimeter. Column chromatography was effected over Fuji Silysia silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

*4.1.1. 5,7-Dihydroxy-2-methyl-chroman-4-one (**5**)*

To a suspension of phloroglucinol (**3**, 2.00 g, 15.9 mmol) in nitrobenzene (40 mL) was added anhydrous aluminum chloride (10.6 g, 79.5 mmol) at room temperature, and the mixture was stirred at room temperature for 1 h. Crotonyl chloride (**4**, 1.8 mL, 18.8 mmol) was added to the mixture at room temperature, and reaction mixture was stirred at 60 ºC for 4 h. The reaction mixture was poured into ice-water (300 mL), and extracted with EtOAc (3 × 100 mL). The EtOAc layer was re-extracted with 10% aq. NaOH (2 × 50 mL), and the combined aqueous layers were neutralized with concentrated hydrochloric acid. The resulting mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with brine, and concentrated *in vacuo*. The residue was purified by means of column chromatography (*n*-hexane–EtOAc, 10/1) to give the title compound **5** (1.69 g, 55%).

For analytical purpose a small portion of the EtOAc layer prior to treatment with NaOH was evaporated in *vacuo*, and the residue was purified by means of column chromatography (*n*-hexane–EtOAc, 15/1) to give (2*E*)-(2,4,6-trihydroxyphenyl)-but-2-en-1-one (**6**), 3-chloro-(2,4,6-trihydroxyphenyl)-butan-1-one (**7**) and the title compound **5**.

*Chromanone **5***: A colorless solid. Mp: 177–178 ºC (lit.[15], 176–178 °C). IR (nujor) cm^{-1}: 3148, 1632, 1605, 1504, 1466, 1346, 1304, 1165, 1115, 1084. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 (3H, d, J = 6.3, CH_3), 2.61 (1H, dd, J = 17.2, 3.5, H-3a), 2.69 (1H, dd, J = 17.2, 12.3, H-3b), 4.53 (1H, dqd, J = 12.3, 6.3, 3.5, H-2), 5.92 (1H, d, J = 2.3, H-8), 5.93 (1H, br s, 7-O*H*), 5.96 (1H, d, J = 2.3, H-6), 12.1 (1H, s, 5-O*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8 (CH_3), 43.2 (C-3), 74.0 (C-2), 95.1 (C-8), 96.4 (C-6), 103.1 (C-4a), 163.4/164.3/164.4 (C-5, C-7 and C-8a), 196.4 (C-4). FABMS *m/z*: 195 $[M+H]^+$ (pos.). FABHRMS *m/z*: 195.0667 ($C_{10}H_{11}O_4$ requires 195.0658).

*But-2-en-1-one **6***: A pale yellow oil. IR (neat) cm^{-1}: 3264, 1643, 1601, 1555, 1516, 1454, 1339, 1293, 1227, 1169, 1080, 1038. ^{1}H NMR (500 MHz, CD_3OD) δ: 1.92 (3H, dd, J = 6.9, 1.7 Hz, H-4), 5.80 (2H, s, Arom.), 6.99 (1H, dq, J = 15.2, 6.9 Hz, H-2), 7.50 (1H, dq, J = 15.2, 1.7 Hz, H-3). ^{13}C NMR (125 MHz, CD_3OD) δ: 18.6 (C-4), 95.9 (C-3′ and C-5′), 105.3 (C-1′), 133.3 (C-2), 142.7 (C-3), 166.1 (2C, C-2′ and C-6′), 166.3 (C-4′) 194.4 (C-1). FABMS *m/z*: 195 $[M+H]^+$ (pos.). FABHRMS *m/z*: 195.0654 ($C_{10}H_{11}O_4$ requires 195.0657).

*Butan-1-one **7***: A colorless oil. IR (neat) cm^{-1}: 3325, 1632, 1601, 1520, 1454, 1373, 1304, 1223, 1169, 1076. ^{1}H NMR (400 MHz, CD_3OD) δ: 1.55 (3H, d, J = 6.6, H-4), 3.39 (1H, dd, J = 16.8, 5.9, H-2a), 3.55 (1H, dd, J = 16.8, 7.3, H-2b), 4.60 (1H, dqd, J = 7.3, 6.6, 5.9, H-3), 5.80 (2H, s, Arom.). ^{13}C NMR (100 MHz, CD_3OD) δ: 25.8 (C-4), 54.4 (C-3), 54.9 (C-2), 95.8 (2C, C-3′ and C-5′), 105.4 (C-1′), 165.8 (2C, C-2′ and C-6′), 166.5 (C-4′), 202.5 (C-1). FABMS *m/z*: 231 $[M+H]^+$ (pos.). FABHRMS *m/z*: 231.0415 ($C_{10}H_{12}ClO_4$ requires 231.0424).

*4.1.2. 4,5-Dihydro-8-hydroxy-5-methyl-2H-pyrano[4,3,2-de]coumarin (**9**)*

A mixture of zinc (2.10 g, 32.1 mmol), iodine (80 mg, 0.32 mmol) and THF (4.0 mL) was refluxed for 1h. To the mixture was slowly added a solution of chromanone **5** (623 mg, 3.21 mmol) and ethyl bromoacetate (1.42 mL, 12.8 mmol) in THF (4.0 mL), and the mixture was heated under reflux for further 1 h. The reaction mixture was poured into water (50 mL), the resulting suspension was filtered off through Celite. The filtrate was extracted with EtOAc (3 × 50 mL). The extract was washed with brine, and concentrated *in vacuo*. The residue (981 mg) was heated under reflux in acetic acid (5.3 mL) for 4 h. After being cooled, the reaction mixture was diluted with water (30 ml) and the resulting mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with brine, and concentrated *in vacuo*. The residue was purified by means of column chromatography (*n*-hexane–EtOAc, 8/1) to give the title compound **9** (483 mg, 69%) as a pale orange solid, mp. 262–263 ºC. IR (nujor) cm^{-1}: 3089, 1694, 1624, 1597, 1470, 1393, 1373, 1285, 1161, 1096, 1076, 1041, 833. ^{1}H NMR (800 MHz, CD_3OD) δ: 1.46 (3H, d, J = 6.2, CH_3), 2.74 (1H, ddd, J = 17.0, 11.5, 1.8, H-4a), 2.93 (1H, ddd, J = 17.0, 2.8, 0.9, H-4b), 4.29 (1H, dqd, J = 11.5, 6.2, 2.8, H-5), 5.86 (1H, dd, J = 1.8, 0.9, H-3), 6.21 (1H, d, J = 2.3, H-7), 6.28 (1H, d, J = 2.3, H-9). ^{13}C NMR (200 MHz, CD_3OD) δ: 20.8 (CH_3), 35.5 (C-4), 74.3 (C-5), 96.7 (C-9), 100.2 (C-7), 101.6 (C-9b), 105.6 (C-3), 152.0 (C-3a), 156.5 (C-9a), 157.5 (C-6a), 164.0 (C-2), 164.3 (C-8). FABMS *m/z*: 219 $[M+H]^+$ (pos.). FABHRMS *m/z*: 219.0657 ($C_{12}H_{11}O_4$ requires 219.0657).

*4.1.3. The Friedel-Crafts acylation of **9***
4.1.3.1. with isobutyryl chloride

A mixture of **9** (300 mg, 1.37 mmol), aluminum chloride (915 mg, 6.88 mmol), carbon disulfide (5.4 mL) and nitrobenzene (2.1 mL) was strred at room temperature for 1 h. Isobutyryl chloride (0.26 mL, 2.47 mmol) was added to the mixture, and the resulting mixture was heated under reflux for 2 h. The resulting mixture was poured into ice-water (50 mL) and extracted with EtOAc (3 × 30 mL). The extract was washed with brine, and concentrated *in vacuo*. The residue was purified by means of column chromatography (*n*-hexane–EtOAc, 6/1) to give 9-acylated compound, 4,5-dihydro-8-hydroxy-9-isobutanoyl-5-methyl-2*H*-pyrano[4,3,2-*de*]coumarin (**10a**, 262 mg, 66%) and its 7-acylated isomer **11a** (62.3 mg, 16%).

*9-Acylated isomer **10a***: A colorless solid. Mp 175–177 °C. IR (KBr) cm^{-1}: 3059, 1732, 1589, 1404, 1373, 1230, 1184, 1126, 1084, 1042. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26/1.27 (each 3H, d, *J* = 6.9, H-3' and H-4'), 1.53 (3H, d, *J* = 6.5, CH_3), 2.78 (1H, ddd, *J* = 16.8, 11.1, 2.0, H-4a), 2.91 (1H, ddd, *J* = 16.8, 3.0, 0.7, H-4b), 4.05 (1H, hept, *J* = 6.9, H-2'), 4.37 (1H, dqd, *J* = 11.1, 6.5, 3.0, H-5), 5.95 (1H, dd, *J* = 2.0, 0.7, H-3), 6.33 (1H, s, H-7), 14.2 (1H, s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0/19.1 (C-3' and C4'), 20.6 (CH_3), 34.9 (C-4), 40.0 [C2'], 72.8 (C-5), 100.0 (C-9b), 100.8 (C-7), 103.5 (C-9), 105.8 (C-3), 148.8 (C-3a), 156.1 (C-9a), 159.47/159.54 (C-2 and C-6a), 169.6 (C-8), 210.0 (C-1'). FABMS *m/z*: 289 $[M+H]^+$ (pos.). FABHRMS *m/z*: 289.1074 ($C_{16}H_{17}O_5$ requires 289.1076).

7-*Acylated isomer **11a***: A colorless solid. Mp 178–179 °C. IR (KBr) cm^{-1}: 3082, 1759, 1628, 1593, 1578, 1431, 1381, 1265, 1234, 1200, 1150, 1111, 1076, 1030. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21/1.22 (each 3H, d, *J* = 6.9, H-3' and H-4'), 1.61 (3H, d, *J* = 6.1, CH_3), 2.81 (1H, ddd, *J* = 16.8, 11.5, 1.9, H-4a), 2.90 (1H, ddd, *J* = 16.8, 3.1, 1.1, H-4b), 3.79 (1H, hept, *J* = 6.9, H-2'), 4.46 (1H, dqd, *J* = 11.5, 6.1, 3.1, H-5), 5.89 (1H, dd, *J* = 1.9, 1.1, H-3), 6.44 (1H, s, H-7), 13.8 (1H, s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.8/19.2 (C3' and C-4'), 20.5 (CH_3), 34.3 (C-4), 40.2 (C-2'), 74.2 (C-5), 98.3 (C-9), 99.7 (C-9b), 106.3 (C-7), 106.6 (C-3), 148.0 (C-3a), 157.6 (C-6a), 158.2 (C-9a), 160.0 (C-2), 168.3 (C-8), 210.7 (C-1'). FABMS *m/z*: 289 $[M+H]^+$ (pos.). FABHRMS *m/z*: 289.1054 ($C_{16}H_{17}O_5$ requires 289.1076).

4.1.3.2. with butyryl chloride

Following the method used for the acylation of **9** with isobutylyl chloride, **8** (213 mg, 0.976 mmol) was acylated with butyryl chloride (182 µL, 1.76 mmol). The usual work-up and chromatographic purification (*n*-hexane–EtOAc, 15/1) gave 9-acylated compound, 9-butanoyl-4,5-dihydro-8-hydroxy-5-methyl-2*H*-pyrano[4,3,2-*de*]coumarin (**10b**, 171 mg, 61%) and its 7-acylated isomer **11b** (35.6 mg, 13%).

*9-Acylated isomer **10b***: A colorless solid. Mp 177–178 °C. IR (KBr) cm^{-1}: 3059, 1748, 1635, 1616, 1597, 1566, 1543, 1454, 1404, 1381, 1303, 1121, 1188, 1111, 1080, 1042. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.05 (3H, t, *J* = 7.3, H-4'), 1.53 (3H, d, *J* = 6.1, CH_3), 1.79 (2H, tq, *J* = 7.3, 7.3, H-3'), 2.78 (1H, ddd, *J* = 16.8, 11.1, 1.9, H-4a), 2.91 (1H, ddd, *J* = 16.8, 3.1, 1.1, H-4b), 3.26 (2H, t, *J* = 7.3, H-2'), 4.37 (1H, dqd, *J* = 11.1, 6.1, 3.1, H-5), 5.95 (1H, dd, *J* = 1.9, 1.1, H-3), 6.32 (1H, s, H-7), 14.2 (1H, s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8 (C-4'), 17.8 (C-3'), 20.6 (CH_3), 34.8 (C-4), 46.2 (C-2'), 72.8 (C-5), 99.9 (C-9b), 100.6 (C-7), 104.4 (C-9), 105.8 (C-3), 148.7 (C-3a), 156.4 (C-9a), 159.5/159.6 (C-2 and C-6a), 169.2 (C-8), 205.6 (C-1'). FABMS *m/z*: 289 $[M+H]^+$ (pos.). FABHRMS *m/z*: 289.1070 ($C_{16}H_{17}O_5$ requires 289.1076).

7-*Acylated isomer **11b***: A colorless solid. Mp 211–212 °C. IR (KBr) cm^{-1}: 3059, 1744, 1628, 1598, 1578, 1435, 1389, 1265, 1192, 1157, 1115, 1072, 1034. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 7.3, H-4'), 1.62 (3H, d, *J* = 6.1, CH_3), 1.73 (2H, tq, *J* = 7.6, 7.3 H-3'), 2.80 (1H, ddd, *J* = 16.8, 11.5, 1.9, H-4a), 2.90 (1H, ddd, *J* = 16.8, 3.1, 0.8, H-4b), 3.04/3.07 (each 1H, dt-like, *J* = 16.4, 7.6 Hz, H-2′a and H-2b'), 4.47 (1H, dqd, *J* = 11.5, 6.1, 3.1, H-5), 5.89 (1H, dd, *J* = 1.9, 0.8, H-3), 6.43 (1H, s, H-9), 13.9 (1H, s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8 (C-4'), 17.9 (C-3'), 20.6 (CH_3), 34.3 (C-4), 46.7 (C-2'), 74.1 (C-5), 98.2 (C-9), 99.6 (C-9b), 106.5 (C-3), 107.0 (C-7), 148.0 (C-3a), 157.9 (C-6a), 158.3 (C-9a), 160.0 (C-2) 168.1 (C-8), 206.4 (C-1′). FABMS *m/z*: 289 $[M+H]^+$ (pos.). FABHRMS *m/z*: 289.1076 ($C_{16}H_{17}O_5$ requires 289.1076).

*4.1.4. 4,5-Dihydro-8-geranyloxy-9-isobutanoyl-5-methyl-2H-pyrano[4,3,2-de]coumarin (**12a**)*

To a mixture of **11a** (20.0 mg, 0.0694 mmol), potassium carbonate (19.2 mg, 0.139 mmol) and acetone (0.6 mL) was added geranyl bromide (21 µL, 0.104 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (1 × 10 mL, 2 × 5 mL,). The extract was washed with brine, and concentrated *in vacuo*. The residue was purified by means of column chromatography (*n*-hexane–EtOAc, 10/1) to give **12a** (29.4 mg, quant.) as a colorless oil. IR (neat) cm^{-1}: 1740, 1701, 1632, 1605, 1570, 1454, 1369, 1204, 1184, 1107, 1076. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.18/1.19 (each 3H, d, *J* = 6.9, H-3' and H-4'), 1.51 (3H, d, *J* = 6.3, CH_3), 1.60 (3H, br s, H-10"), 1.67 (3H, br s, H-9"), 1.70 (3H, br s H-5"), 2.04–2.13 (4H, m, H-4" and H-6"), 2.74 (1H, ddd, *J* = 16.9, 11.2, 1.7, H-4a), 2.86 (1H, ddd, *J* = 16.9, 2.9, 0.9, H-4b), 3.11 (1H, hept, *J* = 6.9, H-2'), 4.33 (1H, dqd, *J* = 11.2, 6.3, 2.9, H-5), 4.57 (2H, d, *J* = 6.3, H-1"), 5.06 (1H, tm, *J* = ca. 6.6, H-7"), 5.39 (1H, tm, *J* = ca. 6.3, H-2"), 5.88 (1H, dd, *J* = 1.7, 0.9, H-3), 6.34 (1H, s, H-7). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.7 (C-5"), 17.6/17.66/17.73 (C-3', C-4' and C-9"), 20.6 (CH_3), 25.6 (C-10"), 26.2 (C-6"), 34.7 (C-4), 39.4 (C-4"), 42.2 (C-2'), 66.0 (C-1'), 73.0 (C-5), 96.0 (C-7), 100.6 (C-9b), 106.6 (C-3), 112.5 (C-9), 118.3 (C-2"), 123.5 (C-7"), 131.9 (C-8"), 142.2 (C-3"), 147.9 (C-3a), 151.1 (C-9a), 156.0 (C-6a), 159.9 (C-8), 160.2 (C-2), 205.3 (C-1'). FABMS *m/z*: 425 $[M+H]^+$ (pos.). FABHRMS *m/z*: 425.2311 ($C_{26}H_{33}O_5$ requires 425.2328).

*4.1.5. 9-Butanoyl-4,5-dihydro-8-geranyloxy-5-methyl-2H-pyrano[4,3,2-de]coumarin (**12b**)*

Following the method used for the preparation of **12b**, **11b** (20.0 mg, 0.0694 mmol) was alkylated with geranyl bromide (21 µL, 0.104 mmol) The usual work-up and chromatographic purification (*n*-hexane–EtOAc, 10/1) gave **12b** (28.1 mg, 95%) as a colorless oil. IR (neat) cm^{-1}: 1736, 1701, 1632, 1605, 1570, 1454, 1366, 1204, 1180, 1107, 1088. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, t, *J* = 7.2, H-4′), 1.51 (3H, d, *J* = 6.3, CH_3), 1.60 (3H, br s, H-10"), 1.67 (3H, d, *J* = 1.1, H-9"), 1.71 (3H, d, *J* = 1.2, H-5"), 1.72 (2H, qt, *J* = 7.2, 7.2 Hz, H-3′), 2.04–2.13 (4H, m, H-4" and H-6"), 2.74 (1H, ddd, *J* = 16.9, 11.2, 1.7, H-4a), 2.81 (2H, t, *J* = 7.2, H-2'), 2.86 (1H, dd, *J* = 16.9, 2.9, 0.8, H-4b), 4.33 (1H, dqd, *J* = 11.2, 6.3, 2.9, H-5), 4.57 (2H, d, *J* = 6.4, H-1"), 5.07 (1H, tm, *J* = ca. 6.9, H-7"), 5.40 (1H, tm, *J* = 6.4, H-2"), 5.88 (1H, dd, *J* = 1.7, 0.8 Hz, H-3), 6.33 (1H, s, H-7). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8 (C-4'), 16.8 (C-5"), 17.3 (C-3'), 17.8 (C-10"), 20.7 (CH_3), 25.7 (C-9"), 26.3 (C-6"), 34.8 (C-4), 39.5 (C-4"), 47.0 (C-2'), 66.2 (C-1") 73.1 (C-5), 96.2 (C-7), 100.7 (C-9b), 106.7 (C-3), 113.1 (C-9), 118.3 (C-2"), 123.7 (C-7"), 132.0 (C-8"), 142.3 (C-3"), 148.0 (C-3a), 151.2 (C-9a), 156.2 (C-6a), 160.0 (C-8), 160.3

(C-2), 201.6 (C-1'). FABMS *m/z*: 425 $[M+H]^+$ (pos.). FABHRMS *m/z*: 425.2301 ($C_{26}H_{33}O_5$ requires 425.2328).

4.1.6. Mammeasin C (1)

To a solution of **12a** (30 mg, 0.0707 mmol) in CH_2Cl_2 (0.4 mL) was added montmorillonite K 10 (35 mg) at 0 ºC, and the mixture was stirred at room temperature for 1.5 h. The catalyst was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were condensed *in vacuo*. The residue was purified by means of column chromatography (*n*-hexane–Et_2O, 20/1) to give **1** (7.0 mg, 23%) and the de-*O*-geranylated compound **11a** (13.4 mg, 66%).

*Compound **1***: A colorless solid. Mp 92–93 °C. The spectral properties of **1** were in accord with those reported.[14]

4.1.7. Mammeasin D (2)

Following the method used for the preparation of **1**, **12b** (20.4 mg, 0.0481 mmol) was treated with montmorillonite K 10 (25 mg). The usual work-up and chromatographic purification (*n*-hexane–Et_2O, 20/1) gave **2** (3.2 mg, 15%) and the de-*O*-geranylated compound **11b** (9.3 mg, 67%).

*Compound **2***: A colorless solid. Mp 99–100 °C. The spectral properties of **2** were in accord with those reported.[14]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/??.????/j.tet.????.??.???.

References and notes

1. (a) Manolov, I.; Maichle-Moessmer, C.; Danchev, N. *Eur. J. Med. Chem.* **2006**, *41*, 882–890; (b) Nicholson, J. H.; Leavitt, T Jr. *New Engl. J. Med.* **1956**, *255*, 491-501.

2. (a) Zhou, X.; Wang, X.-B.; Wang, T.; Kong, L.-Y. *Bioorg. Med. Chem.* **2008**, *16*, 8011–8021; (b) Zawia, N. H.; Lahiri, D. K.; Cardozo-Pelaez, F.; *Free Radic. Biol. Med.***2009**, *46*, 1241–1251.

3. (a) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K. H. *J. Med. Chem.* 44, 2001, 664–671; (b) Matsuda, K.; Hattori, S.; Kariya, R.; Komizu, Y.; Kudo, E., Goto, H., Taura, M.; Ueoka, R.; Kimura, S.; Okada, S. *Biochem. Biophys. Res. Commun*. **2015**, 457 288–294.

4. (a) Khubeiz, M. J. Int. *J. ChemTech Res*., **2016**, *9*, 508–515; (b) Karatas, M. O., Olgundeniz, B., Günal, S., Özdemir, I., Alici, B., Çetinkaya, E. *Bioorg. Med. Chem*. **2016**, *24*, 643–650; (c) Patil, S. A., Prabhakara, C. T., Halasangi, B. M., Toragalmath, S. S,, Badami, P. S. *Spectrochim. Acta A: Mol. Biomol. Spectrosc*. **2015**, *137*, 641–651; (d) Vazquez-Rodriguez, S.; López, R. L,; Matos, M. J.; Armesto-Quintas, G.; Serra, S., Uriarte, E., Santana, L.; Borges, F.; Crego, A. M.; Santos, Y. *Bioorg. Med. Chem*. **2015**, *23*, 7045–7052; (e) Govindhan, M.; Subramanian, K.; Sridharan, S.; Rao, K. C.; Eswaramoorthi, K. Int. *J. ChemTech Res*., **2015**, *8*, 1897–1904; (f) Kasumbwe, K.; Venugopala, K.; Mohanlall, V.; Odhav, B. *J. Med. Plants Res.***2014**, *8*, 274–281; (g) Wang, S.-F.; Yin, Y.; Wu, X.; Qiao, F.; Sha, S.; Lv, P.-C.; Zhao, J.; Zhu, H.-L. *Bioorg. Med. Chem.***2014**, *22*, 5727–5737; (h) Naik, R. J.; Kulkarni, M. V.; Sreedhara Ranganath Pai, K.; Nayak, P. G. *Chem. Biol. Drug Des*. **2012**, *80*, 516–523.

5. Ayine-Tora, D. M.; Kingsford-Adaboh, R.; Asomaning, W. A.; Harrison, J. J. E. K.; Mills-Robertson, F. C.; Bukari, Y.; Sakyi, P. O.; Kaminta, S.; Reynisson. J. *Molecules* **2016**, *21*, 1369 doi:10.3390/molecules21101369.

6. (a) Khode, S.; Maddi, V.; Aragade, P.; Palkar, M.; Ronad, P. K.; Mamledesai, S.; Thippeswamy, A. H.; Satyanarayana, D. *Eur. J. Med. Chem.* **2009**, *44*, 1682–1688; (b) Luchini, A. C.; Rodrigues-Orsi, P.; Cestari, S. H.; Seito, L. N.; Witaicenis, A.; Pellizzon, C. H.; Di Stasi, L. C.; *Biol. Pharm. Bull.* **2008**, *31*, 1343; (c) Bylov, I. E.; Vasylyev, M. V.; Bilokin, Y. V. *Eur. J. Med. Chem*. 1999, 34, 997–1001.

7. (a) Matos, M. J.; Mura, F.; Vazquez-Rodriguez, S.; Borges, F.; Santana, L.; Uriarte, E.; Olea-Azar, C. *Molecules* **2015**, *20*, 3290–3308 doi:10.3390/molecules20023290; (b) Matos, M. J.; Pérez-Cruz, F.; Vazquez-Rodriguez, S.; Uriarte, E.; Santana, L.; Borges, F.; Olea-Azar, C.; *Bioorg. Med. Chem.* **2013**, *21*, 3900–3906; (c) Singh, O. M.; Devi, N. S.; Thokchom, D. S.; Sharma, G. J. *Eur. J. Med. Chem.* **2010**, 2250–2257; (d) Stanchev, S.; Hadjimitova, V.; Traykov, T.; Boyanov, T.; Manolov, I. *Eur. J. Med. Chem.* **2009**, *4*, 3077–3082.

8. Bisi, A.; Cappadone, C,; Rampa, A.; Farruggia, G.; Sargenti, A.; Belluti, F., Di Martino, R. M. C.; Malucelli, E.; Meluzzi, A.; Iotti, S.; Gobbi, S. *Eur. J. Med. Chem.* **2017**, *4*, 577–585; (b) Nocentini, A,; Carta, F.; Ceruso, M.; Bartolucci, G.; Supuran, C. T. *Bioorg. Med. Chem.* **2015**, *23*, 6955–6966; (c) Elhalim, S. M. A.; Ibrahim, I. T. *Appl. Radiat. Isot.* **2015**, *9*,:153–158; (d) Musa, M. A.; Latinwo, L. M.; Virgile, C.; Badisa, V. L. D.; Gbadebo, J. *Bioorg. Chem*. **2015**, *58*, 96–103; (e) Rauf, A.; Khan, R.; Khan, H.; Tokuda, H. *Nat. Prod. Res.* **2015**, *29*, 1775–1778; (f) Klenkar, J.; Molnar, M. *J. Chem. Pharm. Res.* **2015**, *7*, 1223–1238; (g) Thakor, T.; Savjani, J. *Int. J. PharmTech Res.* **2014**, *6*, 1397–1406; (h) Kielbus, M.; Skalickawozniak, K.; Grabarska, A.; Jeleniewicz, W.; Dmoszynska, M.; Marston, A.; Polberg, K., Gawda, P.; Klatka, J.; Stepulak, A. *Anticancer Res*. **2013**, *33*, 4347–4356; (i) Tung, N. H.; Uto, T.; Sakamoto, A.; Hayashida, Y.; Hidaka, Y.; Morinaga, O.; Lhieochaiphant, S.; SHoyama, Y. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 158–162; (j) Jin, L.; Tabe, Y.; Kimura, S.; Zhou, Y.; Kuroda, J.; Asou, H.; Inaba, T.; Konopleva, M.; Andreeff, M.; Miida, T. *Brit. J. Cancer* **2011**, *104*, 91-100; (k) Musa, M. A.; Cooperwood, J. S.; Khan, M. O. F. *Curr. Med. Chem*. **2008**, *15*, 2664–2679; (l) Kostova, I. *Curr. Med. Chem. - Anti-Cancer Agents*, **2005**, 5, 29–46; (m) Ahmad, I.; Shagufta. *Eur. J. Med. Chem.* **2015**, *102*, 375–386; (n) Kanomata, N.; Matsuura, S.; Nomura, T.; Kurebayashi, J.; Mori, T.; Kitawaki, J. Moriya, T. *PLoS ONE* **2017**, *12*, e0177439/1–e0177439/16.

9. (a) Venkata, S. K.; Gurupadayya, B. M.; Chandan, R. S.; Nagesha, D. K.; Vishwanathan, B. *Curr. Drug. Deliv*. **2016**, *13*, 186–201; (b) Rohini, K.; Srikumar, P. S. *J. Thermodyn. Catal.* **2014**, *5*: 130. doi: 10.4172/2157-7544.1000130; (c) Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des.* **2004**, *10*, 3797–3811; (d) Mohler, J. L.; Gomella, L. G.; Crawford, E. D.; Glode, L. M.; Zippe, C. D.; Fair, W. R.; Marshall, M. E. *Prostate* 1992, 20, 123–131.

10. (a) O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*, John Wiley & Sons, Chichester, 1997; (b) Zahradnik, M. *The Production and Application of Fluorescent Brightening Agents*, John Wiley & Sons; Chichester, 1982.

11. (a) Grundmann-Kollmann, M.; Ludwig, R.; Zollner, T. M.; Ochsendorf, F.; Thaci, D.; Boehncke, W.-H.; Krutmann, J.; Kaufmann, R.; Podda, R. *J. Am. Acad. Dermatol*. **2004**, *50*, 734–73; (b) Park, J.-H.; Lee, M.-H. *Int. J. Dermatol*. **2004**, *43*, 138–139; (c) Petering, H.; Breuer, C.; Herbst, R.; Kapp, A.; Werfel, T. *J. Am. Acad. Dermatol* .**2004**, *50*, 68–72; (d) Diederen, P. V. M. M.; van Weelden, H.; Sanders, C. J. G.; Toonstra, J.; van Vloten, W. A. *J. Am. Acad. Dermatol*.; **2003**, *48*, 215–219.

12. (a) Mahidol, C.; Prawat, H.; Kaweetripob, W.; Ruchirawat, S. *Nat. Prod. Commun.* **2007,** 2, 557–564; (b) Prachyawarakorn, V.; Mahidol, C.; Ruchirawat, S. *Phytochemistry* **2006**, *67*, 924–928; (c) Mahidol, C.; Kaweetripob, W.; Prawat, H.; Ruchirawat, S. *J. Nat. Prod*. **2002**, *65*, 757–760; (d) Kaweetripob, W.; Mahidol, C.; Prawat, H.; Ruchirawat, S. *Pharm. Biol.* **2000**, *38* (Suppl. 1), 55–57.

13. Morikawa, T.; Sueyoshi, M.; Chaipech. S.; Matsuda, H.; Nomura, Y.; Yabe, M.; Matsumoto, T.; Ninomiya, K.; Yoshikawa, M.; Pongpiriyadacha, Y.; Hayakawa, T.; Muraoka O. *Bioorg. Med. Chem.* **2012**, *20*, 4968–4977.

14. Ninomiya, K.; Shibatani, K.; Sueyoshi, M.; Chaipech, S.; Pongpiriyadacha, Y.; Hayakawa, T.; Muraoka, O.; Morikawa, T. *Chem. Pharm. Bull*. **2016**, *64*, 880–885.

15. Chandler, I. M.; Mclntyre, C. R.; Simpson, T. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2271–2284.

16. (a) Tanaka, T.; Kumamoto, T.; Ishikawa, T. *Tetrahedron: Asymmetry* **2000**, **11**, 4633-4637; (b) Ishii, H.; Kaneko, Y.; Miyazaki, H.; Harayama, T. Chem. Pharm. Bull. **1991**, *39*, 3100–3102.

17. Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron* **2013**, *59*, 8375–8381.

18. Sousa, C. M.; Pina, J.; de Melo J. S.; Berthet, J.; Delbaere, S.; Coelho, P. J. *Eur. J. Org. Chem*. **2012**, 1768–1773.

19. (a) Müller, H.; Paul, M.; Hartmann, D.; Huch, V.; Blaesius, D.; Koeberle, A.; Werz, O.; Jauch, J. *Angew. Chem. Int. Ed*. **2010**, *49*, 2045–2049; (b) George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. M. Org Lett. 2010, 12, 3532–3535.

20. Effenberger, F.; Epple, G. *Angew. Chem. Int. Ed*. **1972**, *11*, 300–301; (b) Wang, Q. L.; Ma, Y.; Ji, X.; Yan, H.; Qiu, Q. *J. Chem. Soc., Chem. Commun*.,

1995, 2307–2308; (c) Sarvari, M. H.; Shaeghi, H. *Synthesis*, **2004**, 2165–2168.
21. (a) Sun, Q.; Schmidt, S.; Tremmel, M.; Heilmann, J. König, B. *Eur. J. Med. Chem*. **2014**, *85*, 621–628; (b) Yang, J. H.; Huang, W. Q.; Luo, J. S.; Guo, D. D.; Zhang, Y. H.; Li, H. J. *Chin. Che. Lett*. **2012**, *23*, 127–129; (c) Heilmann, J.; Vogel, S. *J. Nat. Prod*. **2008**, *71*, 1237–1241.
22. Sugamoto, K.; Matsusita, K.; Matsui, K.; Kurogi, C.; Matsui, T. *Tetrahedron*, **2011**, *67*, 5346–5359.

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