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Original article

Synthesis of (S)-(+)-decursin and its analogues as potent inhibitors of melanin formation in B16 murine melanoma cells

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Melanin inhibitors

1. Introduction

Melanin is a heterogeneous biopolymer that is synthesized by specialized cells known as melanocytes, dendritic cells that comprise a relatively minor portion of the cells present in the dermal—epidermal border of the skin. Melanin plays a vital role in protecting human skin from the harmful effects of sunlight, toxic drugs, and chemicals. However, increased levels of melanin synthesis can cause diverse hyperpigmentary disorders such as melasma, freckles, age spots or liver spots, and actinic damage, resulting in the accumulation of excessive levels of epidermal and dermal pigmentation [1–6]. Consequently, inhibition of abnormal deposition of melanin is expected to provide therapeutic means for the treatment of dermatological disorders and in the development

ABSTRACT

We report the synthesis of a novel series of highly potent melanin inhibitors which were obtained through structural modification of an anticancer compound S-(+)-decursinol. The *in vitro* inhibitory potencies of the newly synthesized compounds were evaluated against α -MSH induced melanin production in B16 murine melanoma cells. Among the compounds evaluated, compounds **2**, **3**, **6b**, **7a**, **7b**, **8a** and **8b** emerged as highly potent inhibitors of melanin production. Besides, these compounds demonstrated significantly low cytotoxicity.

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of cosmetic whitening agents. In this context, several inhibitors of melanin production have been reported in the literature [7-17].

Angelica gigasNakai has been traditionally known as a medicinal plant in East Asia. Recently, Park et al. reported the significant inhibition of isobutylmethylxanthine-induced melanogenesis by ethanolic extract of A.gigas in B16 melanoma cells [18]. (+)-Decursinol (1), (+)-decursin (2) and (+)-decursinol angelate (3) are novel cancer chemotherapeutic candidates isolated from A.gigas Nakai and were shown to display diverse range of interesting biological properties. In view of their remarkable biological activities, decursin and decursinol angelate have recently attracted considerable attention of global researchers (Fig. 1) [19-25]. Based on these findings, we hypothesized that decursin and their analogues may elicit potent inhibition of melanin production. Moreover, to the best of our knowledge, there have been no reports on the structure activity relationship (SAR) studies of decursin analogues as melanin inhibitors. These key findings prompted us to investigate a series of decursin analogues for their potential to inhibit melanin production in B16 melanoma cells. Herein, we report discovery of a novel series of decursinol analogues as potent melanin inhibitors identified by preliminary SAR studies of 1.

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Fig. 1. Structure of (+)-decursinol, (+)-decursin and (+)-decursinol angelate.

2. Chemistry

The synthesis of (+)-decursin, (+)-decursinol angelate and their analogues 4–8 and 13 was accomplished according to the synthetic protocols as outlined in Schemes 1 and 2. The key starting material 1 was efficiently obtained from *A.gigas* by following our previously developed method [26]. As shown in Scheme 1, DCC mediated coupling of 1 with appropriate acids in presence of DMAP in dichloromethane afforded compounds 2-4 and 6-8 in excellent yields. Compounds **5a**–**c** were prepared in good yield by reacting **1** with appropriate acid chlorides in presence of catalytic amount of pyridine in dichloromethane. Demethylation of compounds 7b, 7e, **7h**, **7k** and **7n** was accomplished using BBr₃ to obtain compounds 7c, 7f, 7i, 7l and 7o, respectively in good yield, which underwent further acetylation by reaction with acetyl chloride to provide corresponding acetylated compounds 7d, 7g, 7j, 7m and 7p, respectively. Scheme 2 describes the synthesis of compound 13. Cinnamic acid 9 underwent esterification, followed by DIBALH mediated reduction to produce 11, which upon subsequent bromination furnished 12. Reaction of 12 with 1 at -30 °C in DMF in presence of NaH afforded 13 in good yield.

3. Results and discussion

The newly synthesized compounds were evaluated for their potential to inhibit melanin formation in B16 murine melanoma cells and the results are tabulated in Table 1. All the assays were performed under standard assay conditions by following the previously described assay protocol. Cell viability, as measured by the MTT assay, showed that most of the compounds had no significant cytotoxicity at their effective concentrations for the



Scheme 2. Reagents and conditions: (a) Concentrated H_2SO_4 , MeOH, Reflux, 12 h; (b) DIBALH in toluene 1 M solution, Dichloromethane, $-78 \degree C$ to rt, MeOH, Rochelle's salt, 6 h; (c) PBr₃, Diethyl ether, $-3 \degree C$, 4 h; (d) (+)-Decursinol, NaH, DMF anhydrous, $-20 \degree C$, 3 h.

inhibition of melanin production (Table 1). Arbutin [27], *p*-hydroxyphenyl β -D-glucopyranoside, a well-known skin-whitening agent was used as a reference compound for a comparison, which showed moderate inhibition (41%) without cytotoxicity.

In order to define the key structural requirements for melanin inhibitory activity, our structure activity relationship studies centered on the derivatisation of hydroxyl group present at 7-position of (+)-decursinol (1), to its corresponding ester and ether derivatives. Accordingly, we first investigated the effect of the natural products (+)-decursinol (1) having free hydroxyl group, (+)-decursin (2) and (+)-decursinol angelate (3) with ester groups. Interestingly, esters 2 and 3 demonstrated significant inhibition of melanin formation (71% and 74.5%, respectively) without exhibiting cytotoxicity. On the other hand, compound **1** without any side chain on ether linkage demonstrated poor inhibitory activity, suggesting that alkyl-ester linkage is optimal for potency. Encouraged by these results, we prepared various alkenyl substituted carboxylic acid derivatives 4a-e. Although compounds 4a and 4c exhibited appreciably high inhibitory activity (71.5% and 79.4%, respectively), displayed cytotoxicity as well (16.4% and 39.5%, respectively). Compound 4b exhibited moderate inhibition (58%) and compounds **4d**–**e** were found to be inactive. Replacement of alkenoyl groups by alkanoyl substitutions was investigated by synthesizing analogues 5a-c. Of the three compounds, 5b and 5c are the most potent melanin inhibitors with 76.5% and 79.3% inhibition, respectively,



Scheme 1. Reagents and conditions: (a) Alkenyl substituted carboxylic acid, DCC, 4-DMAP, Dichloromethane, 5–12 h, rt; (b) Alkanoyl chloride, Pyridine, Dichloromethane, rt, 6–12 h; (c) 3-Aryl-Acrylic acid, DCC, 4-DMAP, Dichloromethane, rt, 5–12 h; (d) Substituted Cinnamic acid, DCC, 4-DMAP, Dichloromethane, rt 6–12 h; or Substituted Cinnamic acid, SOCl₂, DMF (catalytic), Benzene, Reflux, 5–12 h, then Pyridine, Dichloromethane, rt, 6–12 h; (e) BBr₃, Dichloromethane, 0 °C, 5 h; (f) Acetyl chloride, Pyridine, Dichloromethane, rt, 8 h; (g) Phenyl- or 2-Methoxy-phenyl- propionic acid, DCC, 4-DMAP, Dichloromethane, 5–12 h, rt.

Table 1

Melanin inhibitory activity and cytotoxicity of compounds $1{-}8$ and 13 in B16F10 murine melanoma cells.^a $\,$



Compounds	R	% Inhibition at	Cytotoxicity
		100 µM	(%)
1	Н	12.2 ± 6.9	1.4 ± 14.4
2	$-COCH = C(CH_3)_2$	71.0 ± 12.0	-9.7 ± 11.5
3	-COcis-C(CH ₃)=CHCH ₃	74.5 ± 2.7	-2.4 ± 10.6
4a	-COtrans-C(CH ₃)=CHCH ₃	71.5 ± 10.2	16.4 ± 0.9
4b	$-COC(CH_3)=CH_2$	58.1 ± 10.6	58.4 ± 0.5
4c	-COCH=CHCH ₂ CH ₃	$\textbf{79.4} \pm \textbf{2.8}$	39.5 ± 0.6
4d	-COCH ₂ CH=CH ₂	-8.1 ± 4.3	0.6 ± 3.5
4e	-COCH ₂ CH ₂ CH=CH ₂	$\textbf{36.4} \pm \textbf{8.0}$	-0.4 ± 2.7
5a	-COCH ₃	-5.7 ± 8.0	3.7 ± 5.1
5b	$-CO(CH_2)_3CH_3$	$\textbf{76.5} \pm \textbf{4.4}$	10.4 ± 1.3
5c	$-CO(CH_2)_8CH_3$	$\textbf{79.3} \pm \textbf{3.5}$	$\textbf{28.2} \pm \textbf{1.8}$
6a	-COCH=CH-3-Pyridyl	53.5 ± 14.2	5.0 ± 13.0
6b	-COCH=CH-2-Thienyl	$\textbf{71.6} \pm \textbf{9.8}$	-15.4 ± 1.8
6c	-COCH=CH-2-Furanyl	$\textbf{33.0} \pm \textbf{1.9}$	-1.4 ± 7.0
7a	-COCH=CH-Phenyl	72.1 ± 1.6	$\textbf{0.8} \pm \textbf{11.9}$
7b	-COCH=CH-C ₆ H ₄ -OCH ₃ -2	63.7 ± 1.6	-5.1 ± 11.0
7c	-COCH=CH-C ₆ H ₄ -OH-2	76.8 ± 1.5	74.2 ± 10.6
7d	-COCH=CH-C ₆ H ₄ -OAc-2	65.9 ± 9.1	63.1 ± 6.9
7e	-COCH=CH-C ₆ H ₄ -OCH ₃ -3	$\textbf{37.9} \pm \textbf{9.4}$	14.5 ± 2.2
7f	-COCH=CH-C ₆ H ₄ -OH-3	$\textbf{73.8} \pm \textbf{10.2}$	47.9 ± 11.8
7g	-COCH=CH-C ₆ H ₄ -OAc-3	80.7 ± 3.6	31.4 ± 10.7
7h	$-COCH = CH - C_6H_4 - OCH - 4$	40.3 ± 7.4	-3.5 ± 11.1
7i	$-COCH = CH - C_6H_4 - OH - 4$	$\textbf{66.4} \pm \textbf{11.2}$	65.8 ± 7.2
7j	$-COCH = CH - C_6H_4 - OAc - 4$	76.1 ± 9.1	58.0 ± 1.6
7k	$-COCH = CH - C_6H_3 - (OCH_3)_2 - 3,4$	$\textbf{42.4} \pm \textbf{7.4}$	-1.4 ± 7.1
71	$-COCH = CH - C_6H_3 - (OH)_2 - 3,4$	43.5 ± 0.5	67.6 ± 3.9
7m	$-COCH = CH - C_6H_3 - (OAc)_2 - 3.4$	$\textbf{30.7} \pm \textbf{11.5}$	49.4 ± 2.0
7n	$-COCH = CH - C_6H_2 - (OCH_3)_3 - 3,4,5$	18.8 ± 8.7	4.1 ± 9.8
7 o	$-COCH = CH - C_6H_2 - (OH)_3 - 3,4,5$	59.2 ± 5.9	42.9 ± 3.1
7p	$-COCH = CH - C_6H_2 - (OAc)_3 - 3,4,5$	35.4 ± 2.6	54.8 ± 7.2
8a	-COCH ₂ CH ₂ -Phenyl	62.8 ± 1.7	-0.6 ± 0.6
8b	$-COCH_2CH_2-C_6H_4-OCH_3-2$	68.9 ± 0.5	6.1 ± 10.4
13	-CH ₂ CH=CH-Phenyl	$\textbf{33.8} \pm \textbf{1.9}$	-12.53 ± 7.8
Arbutin (evaluated at 500 µM)		41.0 ± 4.0	-6.2 ± 2.4

^a Values are means of three experiments.

however showed moderate cytotoxicity (10.4% and 28.2%, respectively). We then explored the effect of various acrylic acid derivatives represented by analogues 6a-c and 7a-p. Interestingly, this modification yielded highly potent melanin inhibitors 6b, 7a and 7b, which displayed highly potent melanin inhibitory activity without cytotoxicity (71.6%, 72.1% and 63.7%, respectively). On the other hand, compounds 7c, 7d, 7f, 7g, 7i, and 7j which potently suppressed the melanin formation, were also found to be cytotoxic and all of other derivatives exhibited poor inhibitory activity. Based on these results, we prepared further modified analogues **8a–b** and **13**. Compounds with saturated carboxylic acids 8a and 8b possessing significantly low cytotoxicity greatly inhibited the production of melanin with 62.8% and 68.9% inhibition, respectively. However, compound 13 having ether linkage showed poor inhibitory activity, in addition did not show any cytotoxicity. These results strongly suggested that the hydroxyl group or replacement of hydroxyl group with an ether moiety caused significant loss of activity, and that the presence of ester substitution is essential for effective inhibition of melanin formation.

4. Conclusions

In summary, a novel series of (+)-decursinol analogues were prepared and evaluated for their ability to inhibit the production of melanin in B16 murine melanoma cells and assessed for their cytotoxicity. Preliminary SAR studies involving structural modification of (+)-decursinol led to the identification of highly potent melanin inhibitors having no cytotoxicity represented by compounds **2**, **3**, **6b**, **7a**, **7b**, **8a** and **8b**, which demonstrated appreciably high inhibitory activity than that of reference compound arbutin. These compounds could serve as valuable leads for the treatment of dermatological disorders and in the development of cosmetic whitening agents.

5. Experimental

5.1. Chemistry

The reactions were monitored by TLC on silica gel GF254. Detection was effected by examination under UV light. Silica gel Column chromatography was performed on silica gel (250–400 mesh, Silicycle). ¹H and ¹³C NMR spectra were performed on a JEOL JNM-AL 400 spectrometer. Melting points were recorded on a Yamako MD-S3. Low resolution mass spectra were acquired using a PE SCIX API 2000 MS/MS. Optical rotations were measured in a 1.0 dm tube with JASCO DIP-370 polarimeter in CHCl₃ and MeOH. Elemental analyses were performed on a Thermo Fisher Scientific (Flash EA 1112 series).

5.2. (+)-Decursinol (1) [26]

White solid, mp: 177.6 °C, $R_f = 0.20$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +12.3 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.57 (1H, d, J = 9.6 Hz, H-4), 7.17 (1H, s, H-5), 6.77 (1H, s, H-10), 6.21 (1H, d, J = 9.6 Hz, H-3), 3.87 (1H, q, J = 5.6 Hz, H-7), 3.11 (1H, dd, J = 5.6, 17.2 Hz, H-6a), 2.83 (1H, dd, J = 5.6, 17.2 Hz, H-6b), 1.93 (1H, d, J = 6.8 Hz, OH-7), 1.39 (3H, s, CH₃-8), 1.36 (3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C ; 160.9(C-2), 157.6(C-9a), 154.9(C-10a), 144.3(C-4), 130.0(C-5), 118.6(C-5a), 113.3(C-3), 113.3(C-4a), 104.2 (C-10), 79.2(C-8), 69.1(C-7), 31.3(C-6), 25.9(CH₃-8), 21.2(CH₃-8); ESI-MS: m/z = 247 [M + H]⁺. Anal. Calc. for C₁₄H₁₄O₄: C, 68.28; H, 5.73; Found: C, 68.22; H, 5.71.

5.3. General method for the synthesis of compounds (2-3, 4a-e)

The mixture of alkenyl substituted carboxylic acid (4.06 mmol), DCC (8.12 mmol) and 4-DMAP (1.62 mmol) were dissolved in anhydrous dichloromethane. (S)-(+)-Decursinol (1, 4.06 mmol) was added thereto to react together with stirring to room temperature for 5–12 h. The mixture was washed with dichloromethane, filtrated and concentrated in vacuo. The residue was purified by flash silica gel column chromatography.

5.3.1. (S)-(+)-Decursin (**2**)

Yield 64.0%, white solid, mp: 93–94 °C, $R_f = 0.35$ (2:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25}$ +132.7 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.58(1H, d, J = 9.6 Hz, H-4), 7.16(1H, s, H-5), 6.78(1H, s, H-10), 6.22(1H, d, J = 9.6 Hz, H-3), 5.66(1H, s, H-2'), 5.08(1H, t, J = 4.8 Hz, H-7), 3.19(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.86(1H, dd, J = 4.8, 17.2 Hz, H-6b), 2.14(3H, d, J = 1.0 Hz, CH₃-3'), 1.88(3H, d, J = 1.0 Hz, 3H-4'), 1.38(3H, s, CH₃-8), 1.36(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 165.7(C-1'), 161.2(C-2), 158.4(C-3'), 156.4 (C-9a), 154.1(C-10a), 143.1(C-4), 128.6(C-5), 115.9(C-5a), 115.5(C-2'), 113.2(C-3), 112.8(C-4a), 104.7(C-10), 76.6(C-8), 69.1(C-7), 27.9(C-6), 27.4(C-4'), 25.0(CH₃-8), 23.1(CH₃-8), 20.3(CH₃-3'); ESI-MS: m/z = 329 [M + H]⁺. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.23; H, 6.12.

5.3.2. (S)-(+)-Decursinol angelate (**3**)

Yield 56.3%, white solid, mp: 93–94 °C, $R_f = 0.35$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +93.0 (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃) δ_H 7.57(1H, d, J = 9.6 Hz, H-4), 7.15(1H, s, H-5), 6.79(1H, s, H-10), 6.23(1H, d, J = 9.6 Hz, H-4), 7.15(1H, s, H-5), 6.79(1H, s, H-10), 6.23(1H, d, J = 9.2 Hz, H-3), 6.10(1H, q, J = 7.6 Hz, H-3'), 5.12 (1H, t, J = 4.4 Hz, H-7), 3.22(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.89(1H, dd, J = 4.8, 17.2 Hz, H-6b), 1.88(3H, d, J = 6.8 Hz, 3H-4'), 1.83(3H, s, CH₃-2'), 1.39(3H, s, CH₃-8), 1.38(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 167.1(C-1'), 161.2(C-2), 156.4(C-9a), 154.1(C-10a), 143.1 (C-4), 139.5(C-3'), 128.6(C-5), 127.3(C-2'), 115.8(C-5a), 113.2(C-3), 112.8(C-4a), 104.6(C-10), 77.1(C-8), 70.0(C-7), 27.9(C-6), 25.0 (CH₃-8), 23.1(CH₃-8), 20.5(CH₃-2'), 15.7(C-4'); ESI-MS: m/z = 329 [M + H]⁺. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.47; H, 6.11.

5.3.3. (7S)-(+)-trans-2-Methyl-but-2-enoic acid 8,8-dimethyl-2oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**4a**)

Yield 43.9%, white solid, mp: 93–94 °C, $R_f = 0.48$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +68.9 (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.59(1H, d, J = 9.6 Hz, H-4), 7.16(1H, s, H-5), 6.81(2H, m, H-10, H-3'), 6.22(1H, d, J = 9.6 Hz, H-3), 5.08(1H, t, J = 4.8 Hz, H-7), 3.21(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.89(1H, dd, J = 4.8, 17.2 Hz, H-6b), 1.80(3H, s, CH₃-2'), 1.76(3H, m, 3H-4'), 1.35(3H, s, CH₃-8), 1.31 (3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 167.1(C-1'), 121.2(C-2), 156.4(C-9a), 154.1(C-10a), 143.1(C-4), 138.3(C-3'), 128.6(C-5), 128.1 (C-2'), 115.8(C-5a), 113.2(C-3), 112.8(C-4a), 104.6(C-10), 76.6(C-8), 70.1(C-7), 27.7(C-6), 25.0(CH₃-8), 23.0(CH₃-8), 14.4(CH₃-2'), 11.9 (C-4'); ESI-MS: m/z = 329 [M + H]⁺. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.41; H, 6.11.

5.3.4. (7S)-(+)-2-Methyl-acrylic acid 8,8-dimethyl-2-oxo-6,7dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**4b**)

Yield 93.3%, white solid, mp: 80–81 °C, $R_f = 0.52$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +80.5 (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.56(1H, d, J = 9.6 Hz, H-4), 7.14(1H, s, H-5), 6.78(1H, s, H-10), 6.21(1H, d, J = 9.6 Hz, H-3), 6.05(1H, s, H-3a'), 5.56(1H, s, H-3b'), 5.07(1H, t, J = 5.2 Hz, H-7), 3.20(1H, dd, J = 4.8, 16.8 Hz, H-6a), 2.88(1H, dd, J = 5.6, 17.2 Hz, H-6b), 1.90(3H, s, CH₃-2'), 1.38 (3H, s, CH₃-8), 1.37(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 166.5(C-1'), 161.2(C-2), 156.3(C-9a), 154.1(C-10a), 143.0(C-4), 135.8 (C-3'), 128.6(C-5), 126.4(C-2'), 115.7(C-5a), 113.3(C-3), 112.8(C-4a), 104.6(C-10), 76.6(C-8), 70.5(C-7), 27.7(C-6), 25.0(CH₃-8), 22.9 (CH₃-8), 18.1(CH₃-2'); ESI-MS: m/z = 315 [M + H]⁺. Anal. Calc. for C₁₈H₁₈O₅: C, 68.78; H, 5.77. Found: C, 68.59; H, 5.75.

5.3.5. (7S)-(+)-Pen-2-enoic acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**4c**)

Yield 92.1%, light yellow solid, mp: 58–59 °C, $R_f = 0.40$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_{2}^{25}$ +91.3 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.58(1H, d, J = 9.6 Hz, H-4), 7.15(1H, s, H-5), 7.02(1H, m, H-3'), 6.79(1H, s, H-10), 6.22(1H, d, J = 9.6 Hz, H-3), 5.80 (1H, d, J = 15.6 Hz, H-2'), 5.11(1H, t, J = 4.8 Hz, H-7), 3.20(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.88 (1H, dd, J = 4.8, 17.2 Hz, H-6b), 2.19(2H, m, 2H-4'), 1.39(3H, s, CH₃-8), 1.36(3H, s, CH₃-8), 1.04(3H, t, J = 7.6 Hz, 3H-5'); ¹³C NMR (100 MHz, CDCl₃) δ_C 165.9(C-1'), 161.2 (C-2), 156.3(C-9a), 154.1(C-10a), 152.1(C-3'), 143.1(C-4), 128.6(C-5), 119.6(C-2'), 115.7(C-5a), 113.2(C-3), 112.8(C-4a), 104.6(C-10), 76.6 (C-8), 69.8(C-7), 27.7(C-6), 25.2(C-4'), 24.9(CH₃-8), 23.1(CH₃-8), 11.9 (C-5'); ESI-MS: m/z = 329 [M + H]⁺. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.43; H, 6.11.

5.3.6. (7S)-(+)-But-3-enoic acid acid 8,8-dimethyl-2-oxo-6,7dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**4d**)

Yield 90.2%, white solid, mp: 78–79 °C, $R_f = 0.65$ (1:1 *n*-hexane–ethyl acetate); [α]_D²⁵ +71.0 (c = 3, CHCl₃); ¹H NMR

(400 MHz, CDCl₃): $\delta_{\rm H}$ 7.58(1H, d, J = 9.6 Hz, H-4), 7.15(1H, s, H-5), 6.79(1H, s, H-10), 6.23(1H, d, J = 9.6 Hz, H-3), 5.86(1H, m, H-3'), 5.17(2H, m, H-4a', H-4b'), 5.06(1H, t, J = 4.8 Hz, H-7), 3.19(1H, dd, J = 4.8, 17.2 Hz, H-6a), 3.09(2H, m, 2H-2'), 2.85(1H, dd, J = 5.2, 17.2 Hz, H-6b), 1.37(3H, s, CH₃-8), 1.35(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) $\delta_{\rm C}$ 170.8(C-1'), 161.1(C-2), 156.2(C-9a), 154.1(C-10a), 143.0(C-4), 129.6(C-3'), 128.5(C-5), 119.0(C-4'), 115.5(C-5a), 113.3(C-3), 112.8(C-4a), 104.7(C-10), 76.6(C-8), 70.4(C-7), 39.0(C-2'), 27.7(C-6), 24.9(CH₃-8), 22.9(CH₃-8); ESI-MS: m/z = 315 [M + H]⁺. Anal. Calc. for C₁₈H₁₈O₅: C, 68.78; H, 5.77. Found: C, 68.64; H, 5.76.

5.3.7. (7S)-(+)-Pent-4-enoic acid acid 8,8-dimethyl-2-oxo-6,7dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**4e**)

Yield 81.0%, light orange-yellow solid, mp: 94–95 °C, $R_f = 0.51$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +62.6 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.58(1H, d, J = 9.6 Hz, H-4), 7.14(1H, s, H-5), 6.79(1H, s, H-10), 6.23(1H, d, J = 9.6 Hz, H-3), 5.79–5.71(1H, m, H-4'), 5.05–4.95(3H, m, H-7, H-5a', H-5b'), 3.17(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.83 (1H, dd, J = 5.2, 17.2 Hz, H-6b), 2.43(2H, m, 2H-3'), 2.35(2H, t, J = 6.4 Hz, 2H-2'), 1.37(3H, s, CH₃-8), 1.35(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 172.4(C-1'), 161.2(C-2), 156.3 (C-9a), 154.1(C-10a), 143.0(C-4), 136.2(C-4'), 128.5(C-5), 115.7(C-5a), 115.7(C-5'), 113.3(C-3), 112.8(C-4a), 104.7(C-10), 76.4(C-8), 70.1 (C-7), 33.4(C-2'), 28.7(C-3'), 27.7(C-6), 24.9(CH₃-8), 23.0(CH₃-8); ESI-MS: m/z = 329 [M + H]⁺. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.47; H, 6.13.

5.4. General method for the synthesis of compounds (5a-c)

A solution of (S)-(+)-decursinol (**1**, 0.406 mmol) in anhydrous dichloromethane was added to pyridine (0.812 mmol) and alkanoyl chloride (0.812 mmol). The mixture was stirred to room temperature for 6-12 h and the solvent was removed in vacuum. The residue was purified by flash silica gel column chromatography.

5.4.1. (7S)-(+)-Acetic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**5a**)

Yield 89.8%, white solid, mp: 125–126 °C, $R_f = 0.38$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +61.7 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.57(1H, d, J = 9.6 Hz, H-4), 7.15(1H, s, H-5), 6.79(1H, s, H-10), 6.22(1H, d, J = 9.6 Hz, H-3), 5.05(1H, t, J = 4.8 Hz, H-7), 3.18(1H, dd, J = 4.0, 17.2 Hz, H-6a), 3.00(1H, dd, J = 4.8, 17.4 Hz, H-6b), 2.04(3H, s, 3H-2'), 1.42(3H, s, CH₃-8), 1.37(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.4(C-1'), 161.2(C-2), 156.2(C-9a), 154.1 (C-10a), 143.1(C-4), 128.6(C-5), 115.5(C-5a), 113.3(C-3), 112.8(C-4a), 104.7(C-10), 76.4(C-8), 70.1(C-7), 27.7(C-6), 24.8(CH₃-8), 23.1 (CH₃-8), 21.0(C-2'); ESI-MS: m/z = 289 [M + H]⁺. Anal. Calc. for C₁₆H₁₆O₅: C, 66.66; H, 5.59. Found: C, 66.52; H, 5.58.

5.4.2. (7S)-(+)-Pentanoic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**5b**)

Yield 90.7%, light yellow solid, mp: 55–56 °C, $R_f = 0.39$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_2^{D5}$ +79.0 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.57(1H, d, J = 9.6 Hz, H-4), 7.14(1H, s, H-5), 6.78(1H, s, H-10), 6.22(1H, d, J = 9.6 Hz, H-3), 5.04(1H, t, J = 5.2 Hz, H-7), 3.18(1H, dd, J = 4.8, 16.8 Hz, H-6a), 2.83(1H, dd, J = 4.8, 16.8 Hz, H-6b), 2.31(2H, t, J = 7.6 Hz, 2H-2'), 1.58(2H, m, 2H-3'), 1.37 (3H, s, CH₃-8), 1.35(3H, s, CH₃-8), 1.37–1.25(2H, m, 2H-4'), 0.87(3H, t, J = 7.2 Hz, 3H-5'); ¹³C NMR (100 MHz, CDCl₃) δ_C 173.2(C-1'), 161.2 (C-2), 156.3(C-9a), 154.1(C-10a), 143.1(C-4), 128.5(C-5), 115.6(C-5a), 113.3(C-3), 112.8(C-4a), 104.7(C-10), 76.5(C-8), 69.9(C-7), 34.0(C-2'). 27.7(C-6), 26.9(C-3'), 24.9(CH₃-8), 23.0(CH₃-8), 22.1(C-4'), 13.6 (C-5'); ESI-MS: m/z = 331 [M + H]⁺. Anal. Calc. for C₁₉H₂₂O₅: C, 69.07; H, 6.71. Found: C, 68.93; H, 6.68.

5.4.3. (7S)-(+)-Decanoic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**5c**)

Yield 93.0%; yellow Oil; $R_f = 0.49$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25} + 43.8$ (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.57(1H, d, J = 9.2 Hz, H-4), 7.14(1H, s, H-5), 6.78(1H, s, H-10), 6.22(1H, d, J = 9.2 Hz, H-3), 5.04(1H, t, J = 4.8 Hz, H-7), 3.17(1H, dd, J = 4.8, 16.8 Hz, H-6a), 2.83(1H, dd, J = 4.8, 17.2 Hz, H-6b), 2.32(2H, t, J = 8.0 Hz, 2H-2'), 1.61(2H, m, 2H-3'), 1.40(3H, s, CH₃-8), 1.37(3H, s, CH₃-8), 1.33–1.22(12H, m, 2H-4', 2H-5', 2H-6', 2H-7', 2H-8', 2H-9'), 0.88(3H, t, J = 7.2 Hz, 3H-10'); ¹³C NMR (100 MHz, CDCl₃) δ_C 173.2(C-1'), 161.2(C-2), 156.3(C-9a), 154.1 (C-10a), 143.1(C-4), 128.5(C-5), 115.6(C-5a), 113.3(C-3'), 29.3(C-4'), 29.2(C-5'), 29.1(C-6'), 29.0(C-7'), 27.7(C-6), 24.9(CH₃-8), 24.6 (C-8'), 23.1(CH₃-8), 22.6(C-9'), 14.0(C-10'); ESI-MS: m/z = 401 [M + H]⁺. Anal. Calc. for C₂₄H₃₂O₅: C, 71.97; H, 8.05. Found: C, 71.87; H, 8.03.

5.5. General method for the synthesis of compounds (6a-c)

The mixture of aryl-acrylic acid (0.812 mmol), DCC (0.812 mmol) and 4-DMAP (0.162 mmol) were dissolved in anhydrous dichloromethane. (S)-(+)-Decursinol (**1**, 0.406 mmol) was added thereto to react together with stirring to room temperature for 5-12 h. The mixture was washed with dichloromethane, filtrated and concentrated in vacuo. The residue was purified by flash silica gel column chromatography.

5.5.1. (7S)-(+)-3-(3-Pyridyl)-acrylic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**6a**)

Yield 96.7%, white solid, mp: 105 °C, $R_{\rm f} = 0.24$ (1:1 *n*-hexane-ethyl acetate); $[\alpha]_D^{25}$ +48.5 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta_{\rm H}$ 8.72(1H, d, J = 2.2 Hz, H-5'), 8.60(1H, dd, J = 1.5, 4.9 Hz, H-7'), 7.81(1H, d, J = 8.4 Hz, H-9'), 7.67(1H, d, J = 16.0 Hz, H-3'), 7.58(1H, d, J = 9.6 Hz, H-4), 7.32(1H, dd, J = 4.8, 8.0 Hz, H-8'), 7.18(1H, s, H-5), 6.83(1H, s, H-10), 6.49(1H, d, J = 16.4 Hz, H-2'), 6.24(1H, d, J = 9.6 Hz, H-3), 5.21(1H, t, *J* = 4.8 Hz, H-7), 3.26(1H, dd, *J* = 4.8, 17.2 Hz, H-6a), 2.95(1H, dd, J = 4.8, 17.2 Hz, H-6b), 1.44(3H, s, CH₃-8), 1.39(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 165.6(C-1'), 161.2(C-2), 156.3(C-9a), 154.2(C-10a), 151.2(C-5'), 149.8(C-7'), 143.1(C-4), 142.1(C-3'), 134.2 (C-9'), 129.8(C-4'), 128.7(C-5), 123.7(C-8'), 119.5(C-2'), 115.5(C-5a), 113.4(C-3), 112.9(C-4a), 104.8(C-10), 76.5(C-8), 70.5(C-7), 27.8(C-6), 24.9(CH₃-8), 23.4(CH₃-8); ESI-MS: $m/z = 378 [M + H]^+$. Anal. Calc. for C₂₂H₁₉ NO₅: C, 70.02; H, 5.07; N, 3.71. Found: C, 69.92; H, 5.05; N, 3.70.

5.5.2. (7S)-(+)-3-(2-Thienyl)-acrylic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**6b**)

Yield 48.0%, white solid, mp: 149 °C, $R_{\rm f} = 0.67$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +33.0 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta_{\rm H}$ 7.77(1H, d, J = 15.6 Hz, H-3'), 7.58(1H, d, J = 9.2 Hz, H-4), 7.38(1H, d, J = 4.8 Hz, H-6'), 7.25(1H, d, J = 3.6 Hz, H-8'), 7.17(1H, s, H-5), 7.04(1H, dd, J = 3.6, 4.8 Hz, H-7'), 6.83(1H, s, H-10), 6.23(1H, d, J = 9.6 Hz, H-3), 6.20(1H, dd, J = 15.6 Hz, H-2'), 5.18(1H, t, J = 4.8 Hz, H-7), 3.23(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.92(1H, dd, J = 4.8, 17.2 Hz, H-6b), 1.42 (3H, s, CH₃-8), 1.38(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) $\delta_{\rm C}$ 166.1(C-1'), 161.2(C-2), 156.3(C-9a), 154.1(C-10a), 143.1(C-4), 139.1 (C-4'), 138.2(C-3'), 113.4(C-6'), 128.9(C-7'), 128.6(C-5), 128.1(C-8'), 115.9(C-2'), 115.6(C-5a), 113.3(C-3), 112.9(C-4a), 104.7(C-10), 76.6 (C-8), 70.1(C-7), 27.8(C-6), 24.9(CH₃-8), 23.3(CH₃-8); ESI-MS: m/z = 383 [M + H]⁺. Anal. Calc. for C₂₁H₁₈O₅S: C, 65.95; H, 4.74; S, 8.38; Found: C, 65.90; H, 4.74; S, 8.36.

5.5.3. (7S)-(+)-3-(2-Furanyl)-acrylic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**6c**)

Yield 73.6%, light orange solid, mp: 96 °C, $R_f = 0.62$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} +62.4$ (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.64(1H, s, H-6'), 7.58(1H, d, J = 9.6 Hz, H-4), 7.56(1H, d, J = 16.0 Hz, H-3'), 7.41(1H, d, J = 1.6 Hz, H-7'), 7.17(1H, s, H-5), 6.82(1H, s, H-10), 6.55(1H, d, J = 1.6 Hz, H-8'), 6.23(1H, d, J = 9.6 Hz, H-3), 6.13(1H, d, J = 16.0 Hz, H-2'), 5.17 (1H, t, J = 4.4 Hz, H-7), 3.23(1H, dd, J = 4.4, 17.6 Hz, H-6a), 2.92 (1H, dd, J = 4.4, 17.6 Hz, H-6b), 1.42(3H, s, CH₃-8), 1.38(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 166.3(C-1'), 161.3(C-2), 156.3(C-9a), 154.1(C-10a), 144.8(C-4'), 144.5(C-6'), 143.1 (C-4), 135.8(C-3'), 128.7(C-5), 117.0(C-2'), 115.6(C-5a), 113.3(C-3), 112.9(C-7'), 112.9(C-4a), 107.2(C-8'), 104.7(C-10), 76.6(C-8), 70.0 (C-7), 27.8(C-6), 24.8(CH₃-8), 23.3(CH₃-8); ESI-MS: m/z = 367[M + H]⁺. Anal. Calc. for C₂₁H₁₈O₆: C, 68.85; H, 4.95. Found: C, 68.82; H, 4.94.

5.6. General method for the synthesis of compounds (7a-p)

Two drops of *N*,*N*-dimethyl formamide and thionyl chloride (20.3 mmol) were added to a solution of cinnamic acid (6.09 mmol) in 20 ml of anhydrous benzene. After refluxing for 5–12 h at 70–80 °C, the reaction solution was cooled to room temperature and concentrated under reduced pressure to obtain cinnamoyl chloride. (S)-(+)-Decursinol (**1**, 4.06 mmol) was added to a solution of cinnamoyl chloride and pyridine (12.2 mmol) in anhydrous dichloromethane at room temperature. After stirring for 2–5 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography to obtain cinnamoyl- or methoxy-cinnamoyl decursin derivatives (**7a**, **7b**, **7e**, **7h**, **7k** and **7n**).

A solution of methoxy-cinnamoyl decursin derivatives (0.49 mmol) in anhydrous dichloromethane (5 ml) was added to 1 M boron tribromide solution in dichloromethane (1.47–2.46 mmol) in ice bath. The mixture was stirred to room temperature for 5 h. The reaction solution was purified by silica gel short-column chromatography and re-purified by C18 column chromatography to obtain hydroxy-cinnamoyl decursin derivatives (**7c**, **7f**, **7i**, **7l** and **7o**).

A solution of hydroxy-cinnamoyl decursin derivatives (0.51 mmol) in anhydrous dichloromethane was added to pyridine (0.76–2.29 mmol) and acetyl chloride (0.76–2.29 mmol). The mixture was stirred to room temperature for 8 h and the solvent was removed in vacuum. The residue was purified by flash silica gel column chromatography to obtain acetoxy-cinnamoyl decursin derivatives (**7d**, **7g**, **7j**, **7m** and **7p**).

5.6.1. (7S)-(+)-3-Phenyl-acrylic acid acid 8,8-dimethyl-2-oxo-6,7dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**7a**)

Yield 49.3%, white solid, mp: 136–137 °C, $R_f = 0.40$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +42.0 (c = 3, CHCl₃); ¹H NMR (400 MHz, acetone-d₆): δ_H 7.88(1H, d, J = 9.6 Hz, H-4), 7.70(3H, m, H-3', H-5', H-9'), 7.43(4H, m, H-5, H-6', H-7', H-8'), 6.75(1H, s, H-10), 6.56(1H, d, J = 16.0 Hz, H-2'), 6.21(1H, d, J = 9.2 Hz, H-3), 5.24(1H, t, J = 4.6 Hz, H-7), 3.34(1H, dd, J = 4.6, 17.6 Hz, H-6a), 2.99(1H, dd, J = 4.4, 17.6 Hz, H-6b), 1.43(3H, s, CH₃-8), 1.42(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 166.4(C-1'), 160.8(C-2), 157.1(C-9a), 155.0(C-10a), 146.1(C-3'), 144.2(C-4), 135.0(C-4'), 131.3(C-7'), 130.2 (C-6'), 130.2(C-8'), 129.7(C-5'), 129.7(C-9'), 129.1(C-5), 118.4(C-2'), 116.7(C-5a), 113.8(C-3), 113.7(C-4a), 104.5(C-10), 77.5(C-8), 70.8(C-7), 28.2(C-6), 25.0(CH₃-8), 23.6(CH₃-8); ESI-MS: m/z = 377 [M + H]⁺. Anal. Calc. for C₂₃H₂₀O₅: C, 73.39; H, 5.36. Found: C, 73.25; H, 5.38.

5.6.2. (7S)-(+)-3-(2-Methoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7b**)

Yield 81.8%, white solid, mp: 72 °C, $R_f = 0.48$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +57.7 (c = 3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ_H 7.99(1H, d, J = 16.4 Hz, H-3′), 7.58(1H, d, J = 9.6 Hz, H-4), 7.47(1H, d, J = 6.4 Hz, H-9′), 7.35(1H, t, J = 7.8 Hz, H-7′), 7.17(1H, s, H-5), 6.96–6.89(2H, m, H-6′, H-8′), 6.80(1H, s, H-10), 6.50(1H, d, J = 16.0 Hz, H-2′), 6.23(1H, d, J = 9.6 Hz, H-3), 5.19(1H, t, J = 5.0 Hz, H-7/), 3.87(3H, s, OCH₃-5′), 3.24(1H, dd, J = 5.0, 17.2 Hz, H-6a), 2.94 (1H, dd, J = 5.0, 17.2 Hz, H-6b), 1.43(3H, s, CH₃-8), 1.39(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 166.8(C-1′), 161.3(C-2), 158.4(C-5′), 156.4(C-9a), 154.1(C-10a), 143.1(C-4), 141.4(C-3′), 131.8(C-7′), 129.1 (C-9′), 128.7(C-5), 122.9(C-8′), 120.6(C-4′), 117.7(C-2′), 115.8(C-5a), 113.2(C-3), 112.8(C-4a), 111.0(C-6′), 104.7(C-10), 77.1(C-8), 69.9 (C-7), 55.4(OCH₃-5′), 27.8(C-6), 25.0(CH₃-8), 23.2(CH₃-8); ESI-MS: m/z = 407 [M + H]⁺. Anal. Calc. for C₂₄H₂₂O₆: C, 70.92; H, 5.46. Found: C, 70.85; H, 5.45.

5.6.3. (7S)-(+)-3-(2-Hydroxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7c**)

Yield 58.5%, white solid, m.p 106 °C, $R_{\rm f} = 0.39$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_{D}^{25}$ +16.3 (c = 1, CHCl₃); ¹H NMR(400 MHz, acetone-d₆): $\delta_{\rm H}$ 9.18(1H, s, OH-5'; disappeared after addition of D₂O), 8.00(1H, d, *J* = 16.4 Hz, H-3'), 7.85(1H, d, *J* = 9.6 Hz, H-4), 7.61 (1H, d, J = 7.6 Hz, H-9'), 7.43(1H, s, H-5), 7.25(1H, t, J = 6.8 Hz, H-7'), 6.95(1H, d, *J* = 8.4 Hz, H-6'), 6.88(1H, t, *J* = 7.4 Hz, H-8'), 6.74(1H, s, H-10), 6.61(1H, d, *J* = 16.0 Hz, H-2'), 6.20(1H, d, *J* = 9.6 Hz, H-3), 5.23 (1H, t, *J* = 4.4 Hz, H-7), 3.33(1H, dd, *J* = 4.4, 17.6 Hz, H-6a), 2.98(1H, dd, J = 4.4, 17.6 Hz, H-6b), 1.43(3H, s, CH₃-8), 1.42(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_{C} 167.0(C-1'), 160.8(C-2), 157.5(C-5'), 157.2(C-9a), 155.1(C-10a), 144.3(C-4), 141.8(C-3'), 132.5(C-7'), 130.2 (C-9'), 130.0(C-5), 122.0(C-8'), 120.8(C-4'), 118.0(C-2'), 116.9(C-6'), 116.9(C-5a), 113.8(C-3). 113.7(C-4a), 104.5(C-10), 77.6(C-8), 70.6 (C-7), 28.3(C-6), 25.0(CH₃-8), 23.6(CH₃-8); ESI-MS: m/z = 393 $[M + H]^+$. Anal. Calc. for C₂₃H₂₀O₆: C, 70.40; H, 5.14. Found: C, 70.33; H, 5.14.

5.6.4. (7S)-(+)-3-(2-Acetoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (7d)

Yield 95.1%, white solid, mp: 61 °C, $R_f = 0.47$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 8.7$ (c = 0.5, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.73(1H, d, J = 16.0 Hz, H-3'), 7.66—7.63(2H, m, H-9', H-4), 7.43—7.39(1H, m, H-7'), 7.25—7.23(2H, m, H-5, H-8'), 7.11(1H, d, J = 6.8 Hz, H-6'), 6.80(1H, s, H-10), 6.45(1H, d, J = 16.4 Hz, H-2'), 6.22(1H, d, J = 9.6 Hz, H-3), 5.19(1H, t, J = 4.8 Hz, H-7), 3.27(1H, dd, J = 4.4, 17.6 Hz, H-6a), 3.00(1H, dd, J = 4.4, 17.6 Hz, H-6b), 2.31(3H, s, OAc-5'), 1.43(3H, s, CH₃-8), 1.41(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 169.1(OC=O-5'), 165.7(C-1'), 161.2(C-2), 156.3(C-9a), 154.1(C-10a), 149.3(C-5'), 143.1(C-4), 138.9(C-3'), 131.5(C-7'), 128.7 (C-5), 127.3(C-9'), 126.7(C-8'), 126.3(C-4'), 123.1(C-6'), 119.2(C-2') 115.5(C-5a), 113.3(C-3), 112.8(C-4a), 104.6(C-10), 77.2(C-8), 70.2 (C-7), 27.8(C-6), 24.8(CH₃-8), 23.4(CH₃-8), 20.7(OCOCH₃-5'); ESI-MS: m/z = 435 [M + H]⁺. Anal. Calc. for C₂₅H₂₂O₇: C, 69.12; H, 5.10.

5.6.5. (7S)-(+)-3-(3-Methoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7e**)

Yield 90.9%, white solid, mp: 72 °C, $R_f = 0.51$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +37.9 (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.64(1H, d, J = 16.0 Hz, H-3'), 7.58(1H, d, J = 9.6 Hz, H-4), 7.29(1H, d, J = 8.4 Hz, H-9'), 7.17(1H, s, H-5), 7.08(1H, d, J = 8.0 Hz,

H-7'), 7.01(1H, s, H-5'), 6.93(1H, dd, J = 4.0, 8.4 Hz, H-8'), 6.83(1H, s, H-10), 6.40(1H, d, J = 15.6 Hz, H-2'), 6.23(1H, d, J = 9.6 Hz, H-3), 5.19 (1H, t, J = 4.8 Hz, H-7), 3.81(3H, s, OCH₃-6'), 3.24(1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.94(1H, dd, J = 4.8, 17.2 Hz, H-6b), 1.44(3H, s, CH₃-8), 1.39(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_{C} 166.2 (C-1'), 161.2(C-2), 159.8(C-6'), 156.3(C-9a), 154.1(C-10a), 145.8(C-3'), 143.1(C-4), 135.3(C-4'), 129.8(C-8'), 128.7(C-5), 120.9(C-9'), 117.5 (C-2'), 116.5(C-7'), 115.6(C-5a), 113.3(C-3), 112.9(C-5'), 112.8(C-4a), 104.7(C-10), 77.2(C-8), 70.1(C-7), 55.2(OCH₃-6'), 27.87(C-6), 24.9 (CH₃-8), 23.3(CH₃-8); ESI-MS: m/z = 407 [M + H]⁺. Anal. Calc. for C₂₄H₂₂O₆: C, 70.92; H, 5.46. Found: C, 70.77; H, 5.43.

5.6.6. (7S)-(+)-3-(3-Hydroxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7f**)

Yield 88.1%, white solid, mp: 105 °C, $R_f = 0.21$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 12.0$ (c = 1, CHCl₃); ¹H NMR(400 MHz, acetone-d₆): δ_H 8.61(1H, s, OH-6'; disappeared after addition of D₂O), 7.86(1H, d, J = 9.2 Hz, H-4), 7.62(1H, d, J = 15.6 Hz, H-3'), 7.44 (1H, s, H-5), 7.25(1H, t, J = 7.8 Hz, H-8'), 7.16(1H, d, J = 7.6 Hz, H-9'), 7.11(1H, s, H-5'), 6.91(1H, d, J = 8.4 Hz, H-7'), 6.75(1H, s, H-10), 6.48 (1H, d, J = 16.0 Hz, H-2'), 6.21(1H, d, J = 9.6 Hz, H-3), 5.22(1H, t, J = 4.6 Hz, H-7), 3.33(1H, dd, J = 4.2, 17.2 Hz, H-6a), 2.98(1H, dd, J = 4.4, 17.6 Hz, H-6b), 1.43(3H, s, CH₃-8), 1.42(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 166.4(C-1'), 160.8(C-2), 158.6(C-6'), 157.2 (C-9a), 155.0(C-10a), 146.2(C-3'), 144.3(C-4), 136.4(C-4'), 130.8(C-8'), 130.2(C-5), 120.5(C-9'), 118.5(C-7'), 118.3(C-2)'), 116.8(C-5a), 115.5(C-5'), 113.8(C-3), 113.7(C-4a), 104.6(C-10), 77.5(C-8), 70.8(C-7), 28.2(C-6), 25.0(CH₃-8), 23.5(CH₃-8); ESI-MS: m/z = 393 [M + H]⁺. Anal. Calc. for C₂₃H₂₀O₆: C, 70.40; H, 5.14. Found: C, 70.29; H, 5.13.

5.6.7. (7S)-(+)-3-(3-Acetoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7g**)

Yield 87.0%, white solid, mp: 181 °C, $R_f = 0.31$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 35.0$ (c = 3, CHCl₃); ¹H NMR(400 MHz, acetone-d₆): δ_H 7.84(1H, d, J = 9.6 Hz, H-4), 7.68(1H, d, J = 16.0 Hz, H-3'), 7.55(1H, d, J = 7.6 Hz, H-9'), 7.45(3H, m, H-5, H-5', H-7'), 7.18 (1H, dd, J = 2.4, 7.6 Hz, H-8'), 6.73(1H, s, H-10), 6.57(1H, d, J = 15.6 Hz, H-2'), 6.19(1H, d, J = 9.6 Hz, H-3), 5.23(1H, t, J = 4.4 Hz, H-7), 3.33(1H, dd, J = 4.2, 17.6 Hz, H-6a), 2.98(1H, dd, J = 4.8, 17.6 Hz, H-6b), 2.25(3H, s, OAc-6'), 1.43(3H, s, CH₃-8), 1.42(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 169.5(OC=O-6'), 166.2(C-1'), 160.8 (C-2), 157.1(C-9a), 155.0(C-10a), 152.3(C-6'), 145.0(C-3'), 144.2(C-4), 136.5(C-4'), 130.7(C-8'), 130.2(C-5), 126.5(C-9'), 124.7(C-7'), 122.1 (C-5'), 119.5(C-2'), 116.7(C-5a), 113.8(C-3), 113.7(C-4a), 104.6(C-10), 77.5(C-8), 71.0(C-7), 28.2(C-6), 25.0(CH₃-8), 23.5(CH₃-8), 20.8 (OCOCH₃-6'); ESI-MS: m/z = 435 [M + H]⁺. Anal. Calc. for C₂₅H₂₂O₇: C, 69.12; H, 5.10. Found: C, 68.93; H, 5.08.

5.6.8. (7S)-(+)-3-(4-Methoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7h**)

Yield 91.2%, white solid, mp: 68 °C, $R_f = 0.20$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25} + 21.9$ (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.63(1H, d, J = 16.0 Hz, H-3'), 7.58(1H, d, J = 9.6 Hz, H-4), 7.45(2H, d, J = 8.8 Hz, H-5', H-9'), 7.17(1H, s, H-5), 6.85(2H, d, J = 8.0 Hz, H-6', H-8'), 6.78(1H, s, H-10), 6.28(1H, d, J = 16.0 Hz, H-2'), 6.23(1H, d, J = 9.6 Hz, H-3), 5.18(1H, t, J = 4.8 Hz, H-7), 3.82(3H, s, OCH₃-7'), 3.23 (1H, dd, J = 4.4, 17.6 Hz, H-6a), 2.93(1H, dd, J = 4.4, 17.6 Hz, H-6b), 1.43(3H, s, CH₃-8), 1.39(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C ; 166.7(C-1'), 162.6(C-7'), 160.8(C-2), 157.2(C-9a), 155.0(C-10a), 145.9(C-3'), 144.2(C-4), 130.8(C-5'), 130.8(C-9'), 130.2(C-5), 127.6(C-4'), 116.8(C-5a), 115.6(C-2'), 115.1(C-6'), 115.1(C-8'), 113.8(C-3), 113.7 (C-4a), 104.5(C-10), 77.5(C-8), 70.6(C-7), 55.7(OCH₃-7'), 28.3(C-6),

25.0(CH₃-8), 23.5(CH₃-8); ESI-MS: $m/z = 407 [M + H]^+$. Anal. Calc. for C₂₄H₂₂O₆: C, 70.92; H, 5.46. Found: C, 70.88; H, 5.49.

5.6.9. (7S)-(+)-3-(4-Hydroxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7i**)

Yield 82.3%, white solid, mp: 104 °C, $R_f = 0.32$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +11.3 (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.61(1H, d, J = 16.0 Hz, H-3'), 7.59(1H, d, J = 9.6 Hz, H-4), 7.40(2H, d, J = 8.8 Hz, H-5', H-9'), 7.17(1H, s, H-5), 6.84(2H, d, J = 8.8 Hz, H-6', H-8'), 6.83(1H, s, H-10), 6.26(1H, d, J = 16.0 Hz, H-2'), 6.24(1H, d, J = 9.6 Hz, H-3), 5.82(1H, s, OH-7'; disappeared after addition of D₂O), 5.18(1H, t, J = 4.6 Hz, H-7), 3.23(1H, dd, J = 4.6, 17.6 Hz, H-6a), 2.93(1H, dd, J = 4.6, 17.6 Hz, H-6b), 1.43(3H, s, CH₃-8), 1.38(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 166.8 (C-1'), 160.8(C-2), 160.7(C-7'), 157.2(C-9a), 155.0(C-10a), 146.2(C-3'), 144.3(C-4), 131.0(C-5'), 131.0(C-9'), 130.2(C-5), 126.6(C-4'), 116.8 (C-5a), 116.6(C-2'), 114.8(C-6'), 114.8(C-8'), 113.7(C-3), 113.7(C-4a), 104.5(C-10), 77.5(C-8), 70.5(C-7), 28.2(C-6), 25.0(CH₃-8), 23.5 (CH₃-8); ESI-MS: m/z = 393 [M + H]⁺. Anal. Calc. for C₂₃H₂₀O₆: C, 70.40; H, 5.14. Found: C, 70.26; H, 5.13.

5.6.10. (7S)-(+)-3-(4-Acetoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7***j*)

Yield 63.3%, white solid, mp: 181 °C, $R_f = 0.39$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 3.6$ (c = 0.3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.65(1H, d, J = 16.0 Hz, H-3'), 7.58(1H, d, J = 9.6 Hz, H-4), 7.51(2H, d, J = 8.4 Hz, H-5', H-9'), 7.17(1H, s, H-5), 7.11(2H, d, J = 8.4 Hz, H-6', H-8'), 6.83(1H, s, H-10), 6.37(1H, d, J = 16.0 Hz, H-2'), 6.23(1H, d, J = 9.2 Hz, H-3), 5.19(1H, t, J = 4.8 Hz, H-7), 3.24 (1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.94(1H, dd, J = 4.8, 17.2 Hz, H-6b), 2.30(3H, s, OAc-7'), 1.39(3H, s, CH₃-8), 1.35(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 169.2(OC=O-7'), 166.7(C-1'), 160.8(C-2), 157.2(C-9a), 155.0(C-10a), 150.3(C-7'), 145.1(C-3'), 144.2(C-4), 130.2 (C-5), 129.2(C-4'), 126.5(C-5'), 126.5(C-9'), 121.4(C-6'), 121.4(C-8'), 119.2(C-2'), 116.8(C-5a), 113.8(C-3), 113.7(C-4a), 104.5(C-10), 77.5 (C-8), 70.6(C-7), 28.2(C-6), 25.0(CH₃-8), 23.5(CH₃-8), 20.7 (OCOCH₃-7'); ESI-MS: m/z = 435 [M + H]⁺. Anal. Calc. for C₂₅H₂₂O₇: C, 69.12; H, 5.10. Found: C, 69.08; H, 5.09.

5.6.11. (7S)-(+)-3-(3,4-Dimethoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7k**)

Yield 45.8%, white solid, mp: 83 °C, $R_f = 0.35$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 41.5$ (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.62(1H, d, J = 16.0 Hz, H-3'), 7.58(1H, d, J = 9.6 Hz, H-4), 7.17(1H, s, H-5), 7.09(1H, d, J = 8.4, H-9'), 7.01(1H, s, H-5'), 6.85(1H, d, J = 7.2 Hz, H-8'), 6.84(1H, s, H-10), 6.28(1H, d, J = 16.0 Hz, H-2'), 6.24(1H, d, J = 9.6 Hz, H-3), 5.20(1H, t, J = 4.4 Hz, H-7), 3.91(3H, s, OCH₃-6'), 3.90(3H, s, OCH₃-7'), 3.23(1H, dd, J = 4.4, 16.8 Hz, H-6a), 2.96(1H, dd, J = 4.4, 16.8 Hz, H-6b), 1.44(3H, s, CH₃-8), 1.39(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃) δ_C 166.8(C-1'), 160.8(C-2), 157.2 (C-9a), 155.0(C-10a), 152.6(C-6'), 150.5(C-7'), 146.4(C-3'), 144.2(C-4), 130.2(C-5), 127.9(C-4'), 124.0(C-9'), 116.8(C-5a), 115.6(C-2'), 113.8 (C-3), 113.7(C-4a), 112.1(C-8'), 110.7(C-5'), 104.6(C-10), 77.5(C-8), 70.5(C-7), 56.0(OCH₃-6'), 55.9(OCH₃-7'), 28.3(C-6), 25.0(CH₃-8), 23.7(CH₃-8); ESI-MS: m/z = 437 [M + H]⁺. Anal. Calc. for C₂₅H₂₄O₇: C, 68.80; H, 5.54. Found: C, 68.70; H, 5.52.

5.6.12. (7S)-(+)-3-(3,4-Dihydroxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7**I)

Yield 93.2%, white solid, mp: 115 °C, $R_f = 0.36$ (1:2 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ +19.3 (c = 3, CHCl₃); ¹H NMR(400 MHz,

DMSO-d₆): $\delta_{\rm H}$ 9.63(1H, s, OH-7'; disappeared after addition of D₂O), 9.10(1H, s, OH-6'; disappeared after addition of D₂O), 7.90(1H, d, J = 9.6 Hz, H-4), 7.46(1H, s, H-5), 7.45(1H, d, J = 15.2 Hz, H-3'), 7.00 (1H, s, H-5'), 6.99(1H, d, J = 8.4 Hz, H-9'), 6.81(1H, s, H-10), 6.71(1H, d, J = 8.4 Hz, H-8'), 6.25(1H, d, J = 9.6 Hz, H-3), 6.22(1H, d, J = 15.6 Hz, H-2'), 5.14(1H, t, J = 4.0 Hz, H-7), 3.24(1H, dd, J = 4.0, 17.6 Hz, H-6a), 2.88(1H, dd, J = 4.0, 17.6 Hz, H-6b), 1.35(3H, s, CH₃-8), 1.31(3H, s, CH₃-8); ¹³C NMR (100 MHz, CDCl₃): $\delta_{\rm C}$ 166.9(C-1'), 162.3 (C-2), 156.6(C-9a), 154.0(C-10a), 147.0(C-7'), 146.2(C-6'), 144.2 (C-3'), 143.9(C-4), 128.8(C-5), 126.8(C-4'), 122.5(C-9'), 116.0(C-5a), 115.3(C-8'), 114.3(C-2'), 114.1(C-3), 112.8(C-4a), 112.7(C-5'), 104.7 (C-10), 76.8(C-8), 70.0(C-7), 27.8(C-6), 24.8(CH₃-8), 23.3(CH₃-8); ESI-MS: m/z = 409 [M + H]⁺. Anal. Calc. for C₂₃H₂₀O₇: C, 67.64; H, 4.94. Found: C, 67.58; H, 4.95.

5.6.13. (7S)-(+)-3-(3,4-Diacetoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7m**)

Yield 84.5%, white solid, mp: 92 °C, $R_f = 0.27$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25} + 28.0$ (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.60(1H, d, J = 16.0 Hz, H-3'), 7.59(1H, d, J = 9.6 Hz, H-4), 7.38–7.33(2H, m, H-5', H-9'), 7.25–7.17(2H, m, H-5, H-8'), 6.82(1H, s, H-10), 6.35(1H, d, J = 16.0 Hz, H-2'), 6.23(1H, d, J = 9.2 Hz. H-3), 5.19(1H, t, J = 4.6 Hz, H-7), 3.24(1H, dd, J = 4.6, 17.6 Hz, H-6a), 2.93 (1H, dd, J = 4.6, 17.6 Hz, H-6b), 2.29(3H, s, OAc-6'), 2.29(3H, s, OAc-7'), 1.42(3H, s, CH₃-8), 1.38(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 168.5(OC=O-6'), 168.4(OC=O-7'), 166.2(C-1'), 160.8 (C-2), 157.1(C-9a), 155.0(C-10a), 145.0(C-3'), 144.3(C-6'), 144.3(C-7'), 143.7(C-4), 133.7(C-4'), 130.2(C-5), 127.4(C-9'), 124.9(C-8'), 123.9 (C-5'), 119.4(C-2'), 116.7(C-5a), 113.8(C-3), 113.7(C-4a), 104.6(C-10), 77.5(C-8), 70.9(C-7), 28.2(C-6), 25.0(CH₃-8), 23.6(CH₃-8), 20.4 (OCOCH₃-6'), 20.4(OCOCH₃-7'); ESI-MS: m/z = 493 [M + H]⁺. Anal. Calc. for C₂₇H₂₄O₉: C, 65.95; H, 4.91. Found: C, 65.88; H, 4.90.

5.6.14. (7S)-(+)-3-(3,4,5-Trimethoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7n**)

Yield 52.9%, white solid, mp: 87 °C, $R_f = 0.23$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 22.5$ (c = 3, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.59(1H, d, J = 16.0 Hz, H-3'), 7.58(1H, d, J = 10.0 Hz, H-4), 7.18(1H, s, H-5), 6.84(1H, s, H-10), 6.72(2H, s, H-5', H-9'), 6.32(1H, d, J = 16.0 Hz, H-2'), 6.24(1H, d, J = 9.2 Hz, H-3), 5.20(1H, t, J = 4.4 Hz, H-7), 3.90(9H, s, OCH₃-6', OCH₃-7', OCH₃-8'), 3.25(1H, dd, J = 4.4, 16.8 Hz, H-6a), 2.95(1H, dd, J = 4.4, 16.8 Hz, H-6b), 1.45(3H, s, CH₃-8), 1.395(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 166.7(C-1'), 160.8(C-2), 157.2(C-9a), 155.1(C-10a), 154.5(C-6'), 154.5 (C-8'), 146.5(C-3'), 144.3(C-4), 141.3(C-7'), 130.3(C-4'), 130.2(C-5), 117.4(C-2'), 116.8(C-5a), 113.8(C-3), 113.7(C-4a), 106.7(C-5'), 106.6 (C-9'), 104.6(C-10), 77.5(C-8), 70.6(C-7), 60.5(OCH₃-7'), 56.4 (OCH₃-6'), 56.4(OCH₃-8'), 28.3(C-6), 24.9(CH₃-8), 23.7(CH₃-8); ESI-MS: m/z = 467 [M + H]⁺. Anal. Calc. for C₂₆H₂₆O₈: C, 66.94; H, 5.62.

5.6.15. (7S)-(+)-3-(3,4,5-Trihydroxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7o**)

Yield 18.2%, white solid, mp: 144 °C, $R_f = 0.44$ (5:1 chloroformmethanol); $[\alpha]_D^{25} + 24.4$ (c = 3, MeOH); ¹H NMR(400 MHz, acetoned₆): δ_H 8.16(2H, br, OH-6', OH-8'; disappeared after addition of D₂O), 7.93(1H, br, OH-7'; disappeared after addition of D₂O), 7.84 (1H, d, J = 9.6 Hz, H-4), 7.47(1H, d, J = 15.6 Hz, H-3'), 7.42(1H, s, H-5), 6.73(1H, s, H-10), 6.72(2H, s, H-5', H-9'), 6.22(1H, d, J = 16.0 Hz, H-2'), 6.20(1H, d, J = 9.6 Hz, H-3), 5.19(1H, t, J = 4.8 Hz, H-7), 3.31(1H, dd, J = 4.8, 16.8 Hz, H-6a), 2.93(1H, dd, J = 4.8, 16.8 Hz, H-6b), 1.42(3H, s, CH₃-8), 1.41(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_{C} 166.7(C-1'), 160.9(C-2), 157.2(C-9a), 155.0 (C-10a), 146.9(C-3'), 146.6(C-6'), 146.6(C-8'), 144.3(C-4), 136.8(C-7'), 130.2(C-5), 126.3(C-4'), 116.9(C-5a), 115.0(C-2'), 113.7(C-3), 113.7(C-4a), 108.5(C-5'), 108.5(C-9'), 104.5(C-10), 77.6(C-8), 70.5(C-7), 28.3 (C-6), 25.0(CH₃-8), 23.5(CH₃-8); ESI-MS: m/z = 425 [M + H]⁺. Anal. Calc. for C₂₃H₂₀O₈: C, 65.09; H, 4.75. Found: C, 65.05; H, 4.74.

5.6.16. (7S)-(+)-3-(3,4,5-Triacetoxy-phenyl)-acrylic acid acid 8,8dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-ylester (**7p**)

Yield 19.5%, white solid, mp: 118 °C, $R_{\rm f} = 0.38$ (1:2 *n*-hexane–ethyl acetate); $[\alpha]_{D}^{25}$ +8.7 (c = 1, CHCl₃); ¹H NMR(400 MHz, $CDCl_3$): $\delta_H 6.58(1H, d, J = 9.6 Hz, H-4), 6.55(1H, d, J = 17.2 Hz, H-3'),$ 7.28-7.25(2H, s, H-5', H-9'), 7.17(1H, s, H-5), 6.82(1H, s, H-10), 6.34 (1H, d, J = 16.0 Hz, H-2'), 6.23(1H, d, J = 9.6 Hz, H-3), 5.18(1H, t, t)*J* = 4.8 Hz, H-7), 3.23(1H, dd, *J* = 4.8, 17.6 Hz, H-6a), 2.92(1H, dd, J = 4.8, 17.6 Hz, H-6b), 2.29(9H, s, OAc-6', OAc-7', OAc-8'), 1.41(3H, s, CH₃-8), 1.38(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 168.3 (OC=O-6'), 168.3(OC=O-8'), 167.4(OC=O-7'), 166.0(C-1'), 160.8 (C-2), 157.2(C-9a), 155.1(C-10a), 145.0(C-3'), 144.3(C-4), 143.7(C-6'), 143.7(C-8'), 133.3(C-7'), 132.6(C-4'),130.2(C-5), 121.4(C-5'), 121.4 (C-9'), 120.4(C-2'), 116.7(C-5a), 113.8(C-3), 113.8(C-4a), 104.6(C-10), 77.5(C-8), 71.1(C-7), 28.2(C-6), 25.0(CH₃-8), 23.6(CH₃-8), 20.4 (OCOCH₃-6'), 20.4(OCOCH₃-8'), 19.9(OCOCH₃-7'); ESI-MS: *m*/ $z = 551 [M + H]^+$. Anal. Calc. for C₂₉H₂₆O₁₁: C, 63.27; H, 4.76. Found: C, 63.22; H, 4.74.

5.7. General method for the synthesis of compounds (8*a*-*b*)

The mixture of phenylpropionic acid (0.812 mmol), DCC (0.812 mmol) and 4-DMAP (0.162 mmol) was dissolved in anhydrous dichloromethane. (S)-(+)-Decursinol (**1**, 0.406 mmol) was added thereto to react together with stirring to room temperature for 5–12 h. The mixture was washed with dichloromethane, filtrated and concentrated in vacuo. The residue was purified by flash silica gel column chromatography.

5.7.1. (7S)-(+)-Phenylpropionic acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**8a**)

Yield 76.8%, white solid, mp: 106 °C, $R_f = 0.63$ (1:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25} +55.05$ (c = 6, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.57(1H, d, J = 9.6 Hz, H-4), 7.22(2H, d, J = 7.6 Hz, H-5', H-9'), 7.19–7.12(3H, m, H-6', H-7', H-8'), 7.10(1H, s, H-5), 6.78(1H, s, H-10), 6.23(1H, d, J = 9.6 Hz, H-3), 5.02(1H, t, J = 4.8 Hz, H-7), 3.12 (1H, dd, J = 4.8, 17.2 Hz, H-6a), 2.92(1H, t, J = 7.6 Hz, H-6b), 2.74(2H, dd, J = 5.2, 17.6 Hz, 2H-3'), 2.65(2H, t, J = 7.2 Hz, 2H-2'), 1.29(3H, s, CH₃-8), 1.29(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 172.4 (C-1'), 160.8(C-2), 157.1(C-9a), 155.0(C-10a), 144.2(C-4), 141.3(C-4'), 130.1(C-5), 129.1(C-6'), 129.1(C-8'), 129.0(C-5'), 129.0(C-9'), 126.9 (C-7'), 116.7(C-5a), 113.8(C-3), 113.6(C-4a), 104.5(C-10), 77.3(C-8), 70.7(C-7), 36.0(C-2'), 31.3(C-3'), 28.1(C-6), 24.9(CH₃-8), 23.4 (CH₃-8); ESI-MS: m/z = 379 [M + H]⁺. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14, Found: C, 69.43; H, 6.13.

5.7.2. (7S)-(+)-2-Methoxy-phenylpropionic acid acid 8,8-dimethyl-2-oxo-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-7-yl-ester (**8b**)

Yield 77.7%, Colorless oil, $R_f = 0.65$ (1:1 *n*-hexane—ethyl acetate); $[\alpha]_D^{25} + 48.4(c = 10, CHCl_3)$; ¹H NMR(400 MHz, CDCl_3): δ_H 7.57(1H, d, J = 9.6 Hz, H-4), 7.17(1H, t, J = 9.8 Hz, H-7'), 7.10(1H, s, H-5), 7.06(1H, d, J = 8.8 Hz, H-9'), 6.83–6.80(2H, m, H-6', H-8'), 6.78(1H, s, H-10), 6.23(1H, d, J = 9.6 Hz, H-3), 5.01(1H, t, J = 4.8 Hz, H-7), 3.76(3H, s, OCH₃-5'), 3.13(1H, dd, J = 4.4, 17.2 Hz, H-6a), 2.90(2H, t, J = 7.4 Hz, 2H-3'), 2.75(1H, dd, J = 5.2, 17.6 Hz, H-6b), 2.63(2H, t, J = 8.0 Hz, 2H-2'), 1.31(6H, s, 2× CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 172.6 (C-1'), 160.8(C-2), 158.3(C-5'), 157.1(C-9a), 155.0(C-10a), 144.2(C-4), 130.4(C-9'), 130.1(C-5), 129.1(C-7'), 128.4(C-4'), 121.0(C-8'), 116.7 (C-5a), 113.7(C-3), 113.6(C-4a), 111.1(C-6'), 104.5(C-10), 77.3(C-8), 70.6(C-7), 55.5(OCH₃-5'), 34.4(C-2'), 30.3(C-3'), 28.1(C-6), 25.0(CH₃-8), 23.4(CH₃-8); ESI-MS: $m/z = 409 [M + H]^+$. Anal. Calc. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.41; H, 6.15.

5.8. Method for the synthesis of compound (13)

A solution of trans-cinnamic acid (9, 34.2 mmol) and concentrated sulfuric acid (5 drops) in MeOH (20 ml) was warmed to reflux overnight. After cooling to room temperature, the solvent was removed under the reduced pressure. The residue was purified by flash silica gel column chromatography to obtain 3-phenyl-acrylic acid methylester (10). A solution of 3-phenyl-acrylic acid methyl-ester (10, 24.7 mmol) in dichloromethane anhydrous was cooled to -78 °C under the nitrogen gas. The mixture was slowly added to 1 M solution of diisobutylalluminum hydride (DIBALH) in hexane (74 mmol). After stirring at 0 °C for 1 h, the mixture was added with methanol (22 ml) and stirred for 30 min to room temperature. The mixture was added with aqueous saturated Rochelle's salt (88 ml) and vigorously stirred for 2 h. The reaction mixture was separated with dichloromethane, dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography to obtain 3-phenyl-pro-2-pen-1-ol (11). 3-Phenyl-pro-2-pen-1-ol (11, 7.45 mmol) was dissolved in dichloromethane anhydrous and added 1 M solution of boron tribromide in dichloromethane (2.61 mmol) in ice bath. After stirring 1 h. the mixture was added ice water (50 ml) and stirred for 10 min. The reaction mixture was separated using saturated sodium bicarbonate and diethyl ether. Organic layer was dried with sodium sulfate and concentrated in vacuo. The residue was purified by flash silica gel column chromatography to obtain (3-bromo-prophenyl)benzene (12). A solution of (+)-decursinol (1, 0.41 mmol) in N,N-dimethyl formamide anhydrous was cooled to -20 °C and added to (3-bromo-prophenyl)-benzene (12, 0.609 mmol). After stirring to -20 °C for 24 h, the reaction mixture was fastly filtrated on silica gel short-column chromatography using 5:1 *n*-hexane–ethyl acetate. After the solvent was removed under the reduced pressure, the residue was purified by silica gel column chromatography to obtain (S)-(+)-2,2-dimethyl-3(3-phenyl-allyloxy)-3,4-dihydro-4H-pyrano [3,2-g]chromen-8-one (13).

5.8.1. (S)-(+)-8,8-Dimethyl-7-(3-phenyl-allyloxy)-6,7-dihydro-2H,8H-pyrano[3,2-g]chromen-2-one(**13**)

Yield 32.7%, white solid, mp: 143 °C, $R_f = 0.39$ (2:1 *n*-hexane–ethyl acetate); $[\alpha]_D^{25}$ + 117.6 (c = 1, CHCl₃); ¹H NMR(400 MHz, CDCl₃): δ_H 7.56(1H, d, J = 9.6 Hz, H-4), 7.38–7.23(5H, m, H-5', H-6', H-7', H-8', H-9'), 7.15(1H, s, H-5), 6.76(1H, s, H-10), 6.59(1H, d, J = 16.0 Hz, H-3'), 6.30–6.23(1H, m, H-2'), 6.20(1H, d, J = 9.6 Hz, H-3), 4.34(1H, dd, J = 6.0, 12.8 Hz, H-1a'), 4.21(1H, dd, J = 6.0, 12.4 Hz, H-1b'), 3.59(1H, dd, J = 5.2, 7.6 Hz, H-7), 3.07(1H, dd, J = 4.8, 16.0 Hz, H-6a), 2.85(1H, dd, J = 7.2, 16.4 Hz, H-6b), 1.41(3H, s CH₃-8), 1.36(3H, s, CH₃-8); ¹³C NMR (100 MHz, acetone-d₆) δ_C 160.9 (C-2), 157.6(C-9a), 155.0(C-10a), 144.3(C-4), 132.7(C-4'), 130.2(C-5), 129.4(C-3'), 129.3(C-6'), 129.3(C-8'), 128.4(C-7'), 127.3(C-5'), 127.3 (C-9'), 127.2(C-2'), 118.1(C-5a), 113.5(C-3), 113.4(C-4a), 104.3(C-10), 78.6(C-7), 76.2(C-8), 20.7(C-1'), 27.7(C-6), 26.0(CH₃-8), 22.1 (CH₃-8); ESI-MS: m/z = 363 [M + H]⁺. Anal. Calc. for C₂₃H₂₂O₄: C, 76.22; H, 6.12; Found: C, 76.20; H, 6.10.

5.9. Biology

5.9.1. Melanogenesis inhibition assay

B16 murine melanoma cells were obtained from the Korean Cell Line Bank (Seoul, Korea). Cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heatinactivated fetal bovine serum (Invitrogen, Carlsbad, NM, USA) and 1% penicillin-streptomycin (10,000 U/ml and 10,000 µg/ml, respectively) in 5% CO₂ at 37 °C. Extracellular melanin release was measured as described previously [28]. Cells were incubated at a density of 1×10^5 cells in six-well plates overnight. Alpha-MSH (Sigma, St. Louis, MO, USA) was then added and cells were treated with or without chemicals in phenol red free DMEM for 2 d. Amounts of melanin in the media were measured at 405 nm.

5.9.2. Cytotoxicity test

After treatment the cells with or without chemicals for 24 h, 5 mg/ml MTT in PBS was added to each well. Cells were incubated at 37 °C for 3 h and DMSO was added to dissolve the formazan crystals. The absorbance was measured at 570 nm with a microplate reader (Molecular Devices, USA).

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