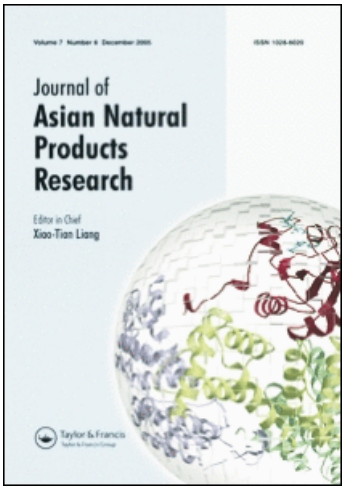

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A novel total synthesis of kinsenoside and goodyeroside A relying on the efficient reaction of the chiral 2(5H)-furanones

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A novel total synthesis of kinsenoside and goodyeroside A relying on the efficient reaction of the chiral 2(5H)-furanones

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A new total synthesis of the bioactive compounds, kinsenoside (**1**) and goodyeroside A (**2**), has been accomplished from readily available starting materials. The chiral 2(5H)-furanone **5a** and its enantiomer **5b** were employed as the key chiral intermediates to construct the chiral glycosides **8a** and **8b** with the appropriate stereochemistry. The spectral data of the target compounds and their acetylated derivatives **1a** and **2b** are identical with those of the natural and corresponding acetylated products.

Keywords: Kinsenoside; Goodyeroside A; Total synthesis

1. Introduction

In 1993, Ito and co-workers reported the isolation and structural characterisation of 4R-4-*O*-(β-D-glucopyranosyl)-2(5H)-furanone, kinsenoside (**1**), which exists in *Anoectochilus koshunensis* [1] and *Anoectochilus formosanus* plants [2]. These plant drugs are used as a folk remedy in China for treatment of lung disease, pleurodynia pain, fever, hypertension and snake-bites [3]. Goodyeroside A (**2**), 4S-4-*O*-(β-D-glucopyranosyl)-2(5H)-furanone, the epimer of **1,** was discovered and isolated from the sprouts of *Crocus sativus* by Gao and co-workers [4] and later from the plants of three *Goodyera* species, G. *schlechtendaliana* REICHB. fil., G. *matsumurana* SCHLTR. and G. *discolor* KER-GAWL, natively grown in Japan and Southeast Asia [5]. Some species of the genus *Goodyera* have been used since ancient times in Chinese folk medicine for fever, pain, snake-bite, and lung disease [6,7]. This type of compound, 4R (or S)-*O*-(β-D-glucopyranosyl)-2(5H)-furanone, exhibits high levels of anti-hyperliposis activity, and a hepatoprotective effect as well as decreasing the triglyceride level [5,8].

The molecule of kinsenoside (**1**) and goodyeroside A (**2**) possesses five contiguous chiral centres in the glucopyranosyl moiety and one chiral centre in the butyrolactone ring. Their interesting unique structural features coupled with their low natural content and promising pharmacological profiles have attracted much attention from us. Yoshizawa and co-workers [9] recently reported the synthesis of these two natural products. In Yoshizawa's

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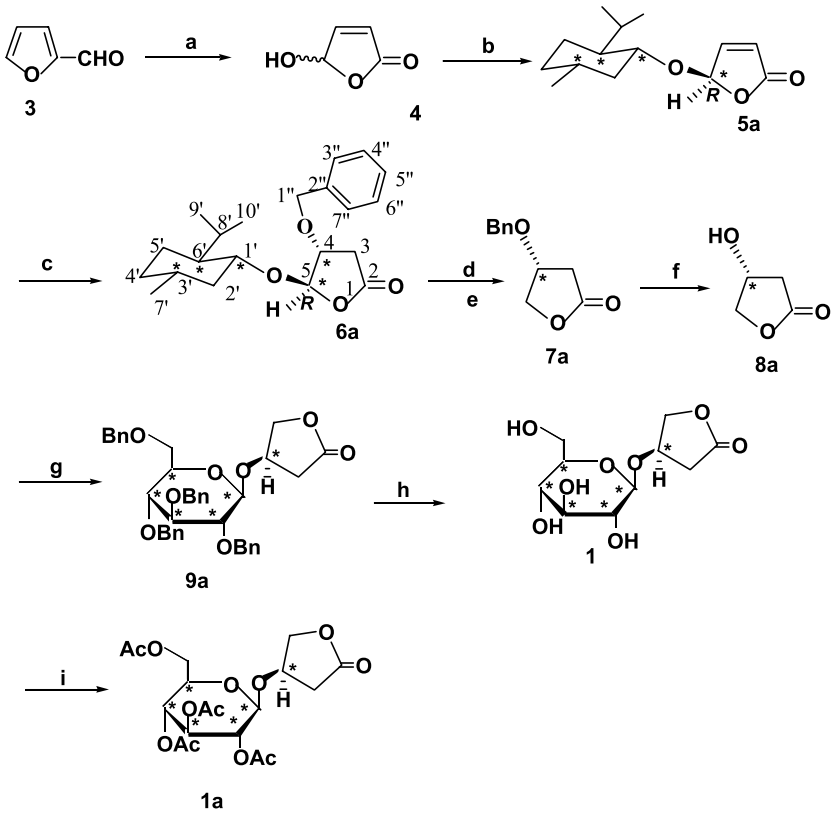


Scheme 1. The synthetic route for kinsenoside (**1**). Reagents and conditions: (a) O_2, R.B, 95% EtOH, *hv*, 70%; (b) (−)-menthol, conc. H_2SO_4, benzene, 63%; (c) $PhCH_2OH$, K_2CO_3, TBAB, CH_3CN, 60%; (d) acetone, 12% HCl; (e) $NaBH_4$, MeOH, 42% (two steps); (f) 10% Pd-C, EtOH, HOAc, 83%; (g) *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-trichloroacetimidate, 4 Å MS, TMSOTf, CH_3CN, 60% ($\alpha : \beta = 1 : 1$); (h) 10% Pd-C, EtOH, EtOAc, 90%; (i) Ac_2O, pyridine, 73%.

approach, 4-*O*-allyl-1-*O*-benzyl-1,2,4-butanetriol and *O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-trichloroacetimidate were used as the starting materials; the key step was the separation of isomer (R and S) of an aglycon part via column chromatography. Structurally, **1** and **2** contain D-glucose and (R)- or (S)-4-hydroxytetrahydrofuran-2-one (**8a**, **8b**). Inspired by the recent successful research on the 5-(R)-[(1R,2S,5R)-menthyloxy]-2(5H)-furanone (**5a**) [10 – 15], a useful chiral synthon with the dual functionality and high stereocontrol, we decided to develop a less complicated procedure for the synthesis of **8a** and **8b** using **5a** and 5-(S)-[(1S,2R,5S)-menthyloxy]-2(5H)-furanone (**5b**) as the respective valuable chiral building blocks. We describe here a novel synthesis of these two natural products via the glycosidation of the benzyl protected D-glucose with (R)- or (S)-4-hydroxy-tetrahydrofuran-2-one (**8a**, **8b**), which were prepared through a novel synthetic strategy with furfural (**3**) as the starting material, as shown in Schemes 1 and 2.

2. Results and discussion

Kinsenoside (**1**) and goodyeroside A (**2**) are epimers in which only the configuration of C-4 is different (Figure 1). In our approach, we focused on the generation of the two important

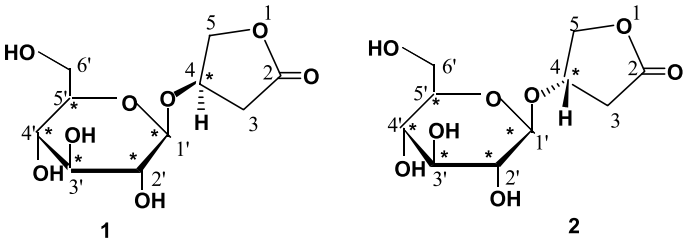


Figure 1. Structure of kinsenoside (**1**) and goodyeroside A (**2**).

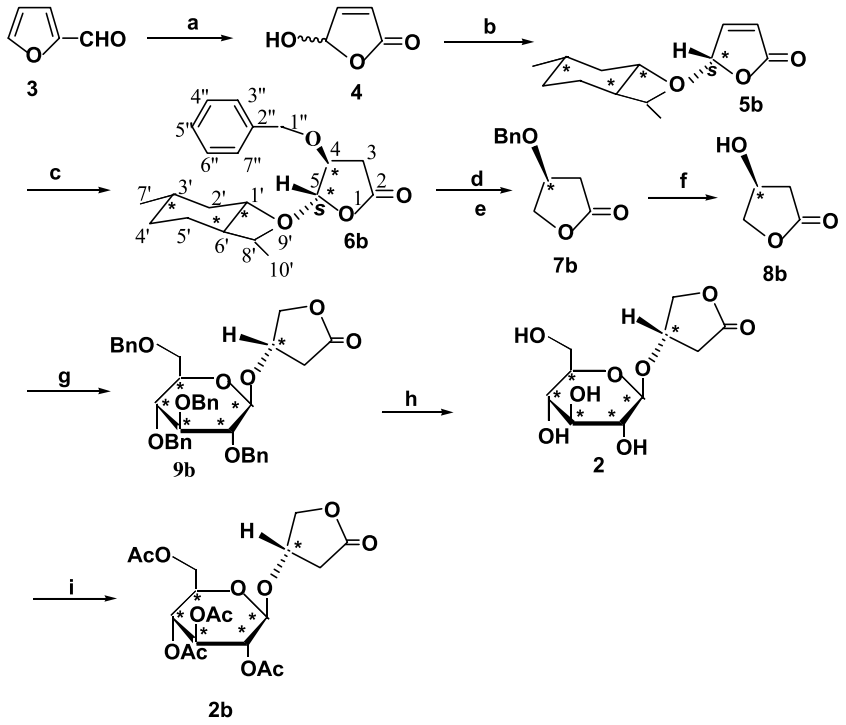
synthons (R)- and (S)-4-hydroxytetrahydrofuran-2-one (**8a**, **8b**), which are the versatile chiral sources for the synthesis of chiral three-carbon building blocks [16], prepared by the chemical transformation of unnatural or natural malic acid [17], or starting from L-ascorbic acid and D-isoascorbic acid [18]. We now designed the new synthetic strategy to construct the exact chiral centre of these compounds as the extension of our series of research on the application of 5-(R)-[(1R,2S,5R)-menthyloxy]-2(5H)-furanone (**5a**) in asymmetric synthesis.

With our experience on the improved photo-oxidation of furfural (**3**) to obtain 5-hydroxy-2(5H)- furanone (**4**) [12], enantiomerically pure **5a** was easily obtained by the acetalisation of **4** with natural (−)-menthol which is readily available and inexpensive as a chiral auxiliary, and then by the recrystallisation of the crude product. Stereoselective Michael addition of **5a** with benzyl alcohol under a mild reaction condition gave the optically active compound **6a**. Acidic hydrolysis (12% HCl/acetone) succeeded by reduction ($NaBH_4$/MeOH) afforded **7a** (42% yield over two steps). The benzyl group was easily removed by hydrogenation under acidic conditions to give the key intermediate (R)-4-hydroxytetrahydrofuran-2-one (**8a**) (Scheme 1).

With the chiral aglycon **8a** in hand, we continued the glycosylation with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate in the presence of an equivalent amount of TMSOTf in CH_2Cl_2. In an effort to improve the productivity of the β-glycoside in this reaction, we selected CH_3CN as the solvent normally showed highly selective β-glycoside formation in most cases [19]. However, we only obtained a mixture of α- and β-glucoside ($\alpha : \beta = 1 : 1$ from ^{1}H NMR analysis of the crude reaction mixture) due to the minor steric hindrance of the acceptor. The β-glycoside **9a** and its α-isomer were separated by chromatography on a large amount of silica gel ($W_{\text{silica}}/W_{\text{sample}} = 500 : 1$). The final product **1** was achieved by debenzylation of **9a** with 10% Pd/C in very high yield, 90%. As the lactone ring of kinsenoside (**1**) is sensitive to the chromatography condition of silica gel and methanol used in the purification step [8], we selected methylene chloride-ethanol as the eluant system.

The ^{1}H and ^{13}C NMR, IR and FAB-HRMS spectra of the synthesised target compound **1** were identical with those of the natural product. However, the optical rotation of the synthetic material was not in correspondence with that of the isolated compound. The difference was probably caused by the inaccurate weight of sample since the target compound **1** was oil. To this end, the synthetic kinsenoside (**1**) was acetylated (Ac_2O/Pyridine) to give solid product **1a**, which exhibited identical physical and spectroscopic properties to that of natural product.

8b, the enantiomer of **8a**, was the key building block for the synthesis of goodyeroside A (**2**). We attempted to transform **8a** to **8b** through the Mitsunobu Reaction [20] in the presence of Ph_3P, DEAD, and chloroacetic acid in order to change the chiral centre configuration of C-4 from R to S. Unfortunately, we only obtained α,β-unsaturated



Scheme 2. The synthetic route for goodyeroside A (**2**). Reagents and conditions: (a) O_2, R.B, 95% EtOH, *hv*, 70%; (b) (+)-menthol, conc. H_2SO_4, benzene, 79%; (c) $PhCH_2OH$, K_2CO_3, TBAB, CH_3CN, 55%; (d) acetone, 12% HCl; (e) $NaBH_4$, MeOH, 25% (two steps); (f) 10% Pd-C, EtOH, HOAc, 46%; (g) *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-trichloroacetimidate, 4 Å MS, TMSOTf, CH_3CN, 65% ($\alpha : \beta = 1 : 1$); (h) 10% Pd-C, EtOH, EtOAc, 70%; (i) Ac_2O, pyridine, 60%.

γ-lactone. With the same synthetic method as **8a**, we obtained **8b** through five steps using unnatural (+)-menthol as the chiral auxiliary. After glycosylation and debenzylation, goodyeroside A (**2**) was successfully obtained (Scheme 2).

In summary, we developed the total synthesis of kinsenoside (**1**) and goodyeroside A (**2**) in seven steps. The α-glucoside isomers of kinsenoside, goodyeroside A and their total acetylated derivatives were obtained also. This demonstrated that 5-(R)-[(1R,2S,5R)-menthyloxy]-2(5H)-furanone (**5a**) and 5-(S)-[(1S,2R,5S)-menthyloxy]-2(5H)-furanone (**5b**) could be used in the synthesis of optically active natural products as the important chiral building blocks.

3. Experimental

3.1 General experimental procedures

Melting points were determined with a Yanaco micrometer and are uncorrected. NMR spectra were taken on a Mercury-300 or INOVA-500 spectrometer with TMS as the internal reference. IR spectra were obtained on an Impact 400 FTIR spectrometer. EI–MS was obtained on a ZAB-2F spectrometer. FAB-MS and FAB-HRMS were obtained on an Autospec-Ultima ETOF spectrometer. The optical rotation was recorded on a Perkin–Elmer 241 polarimeter. TLC was carried out on silica gel (GF_{254}). Vacuum liquid chromatography

was performed on silica gel H and column chromatography was run on silica gel (200 – 300 mesh). Benzene was distilled from sodium benzophenone ketyl; CH_3CN, CH_2Cl_2 was distilled from P_2O_5; pyridine was dried with KOH; and acetic anhydride was distilled at 136 – 138°C. Commercially available regents were used as received except as indicated.

3.2 5-(R)-[(1R,2S,5R)-menthyloxy]-2(5H)-furanone (5a) and 5-(S)-[(1S,2R,5S)-menthyloxy]-2(5H)-furanone (5b)

5a and **5b** were easily obtained according to methods described in the literature [11 – 13,21,22], by the photo-oxidation of furfural (**3**) as the starting material, followed by the acetalisation with natural (−)-menthol and unnatural (+)-menthol as chiral auxiliary, respectively. The enantiomerically pure **5a** or **5b** were obtained on the recrystallisation of the corresponding crude product.

5a: mp 78.5 – 79.5°C; $[\alpha]_D^{20}$ −133.5 (C 1.0, $CHCl_3$) (lit [12], mp 76 – 77°C; $[\alpha]_D^{20}$ −141.5 (C 1.0, $CHCl_3$)).

5b: mp 76.9 – 77.4°C; $[\alpha]_D^{23}$ +130.7 (C 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.79 ∼ 1.44 (m, 3′, 4′, 6′, 7′, 8′, 9′, 10′-H, 14H), 1.64 ∼ 1.70 (m, 5′-H, 2H), 2.07 ∼ 2.17 (m, 2′-H, 2H), 3.61 ∼ 3.70 (m, 1′-H, 1H), 6.08 (s, 5-H, 1H), 6.20 (d, J = 5.7 Hz, 3-H, 1H), 7.16 (d, J = 5.7 Hz, 4-H, 1H); FAB-HRMS *m/z* 238.1575 (calcd for $C_{14}H_{22}O_3$, 238.1569) (lit [22], mp 74.2 – 74.4°C; $[\alpha]_D^{20}$ +139.7 (C 1.0, $CHCl_3$)).

3.3 4R,5R-4-benzyloxy-5-[(1R,2S,5R)-menthyloxy]-2(5H)-furanone (6a)

Benzyl alcohol (8.89 g, 82.35 mmol) was added to a mixture of powdered anhydrous K_2CO_3 (12.52 g, 90.62 mmol), tetrabutylammonium bromide (8.85 g, 27.45 mmol) and anhydrous CH_3CN (135 ml) under nitrogen. The mixture was stirred at room temperature (RT) for 0.5 h, then the chiral synthon **5a** (13.06 g, 54.9 mmol) was added. The resulting mixture was stirred at RT for 24 h. Additional K_2CO_3 (6.26 g, 45.29 mmol) and benzyl alcohol (4.45 g, 41.2 mmol) were added into the mixture obtained above. The mixture was stirred for 24 h continuously. The reaction mixture was filtered and washed with a little CH_3CN. The filtrate was combined and the solvent was removed under reduced pressure to give brown oil. The crude product was purified by vacuum liquid chromatography (20:1 PE/EtOAc) to yield the title compound **6a**: white solid (11.45 g, 60.3%); mp 82 – 83°C; $[\alpha]_D^{15}$ −106 (C 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.74 ∼ 1.34 (m, 3′, 4′, 6′, 7′, 8′, 9′, 10′-H, 14H), 1.60 ∼ 1.70 (m, 5′-H, 2H), 1.95 ∼ 2.07 (m, 2′-H, 2H), 2.53 (dd, J = 18 Hz, 1.8 Hz, 3-H, 1H), 2.81 (dd, J = 18 Hz, 6 Hz, 3-H, 1H), 3.48 ∼ 3.57 (m, 1′-H, 1H), 4.05(dd, J = 6 Hz, 1.8 Hz, 4-H, 1H), 4.58 (s, $PhCH_2$-H, 2H), 5.58 (s, 5-H, 1H), 7.29 ∼ 7.40 (m, Ar-H, 5H); FAB-HRMS *m/z* 369.2056 (calcd for $C_{21}H_{30}O_4$ + Na, 369.2041).

3.4 4S,5S-4-benzyloxy-5-[(1S,2R,5S)-menthyloxy]-2(5H)-furanone (6b)

6b was prepared by the same procedure for **6a** using the chiral synthon **5b** (2.29 g, 9.6 mmol). The title compound **6b**: white solid (1.71 g, 51.2%); mp 80 – 82°C; $[\alpha]_D^{11}$ +103.3 (C 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.74 ∼ 1.34 (m, 3′, 4′, 6′, 7′, 8′, 9′, 10′-H, 14H), 1.61 ∼ 1.69 (m, 5′-H, 2H), 1.95 ∼ 2.07 (m, 2′-H, 2H), 2.62 (dd, J = 18 Hz, 3-H, 1H), 2.81 (dd, J = 18 Hz, 6 Hz, 3-H, 1H), 3.48 ∼ 3.57 (m, 1′-H, 1H), 4.05 (d, J = 6 Hz, 4-H, 1H), 4.58 (s, $PhCH_2$-H, 2H), 5.58 (s, 5-H, 1H), 7.29 ∼ 7.39 (m, Ar-H, 5H); ^{13}C NMR

($CDCl_3$, 75 MHz): δ 15.5 (10′-C), 20.8 (9′-C), 22.2 (7′-C), 23.0 (4′-C), 25.5 (3′-C), 31.3 (8′-C), 34.2 (5′-C), 34.3 (3-C), 39.5 (6′-C), 47.6 (2′-C), 71.6 (1″-C), 77.4 (4-C), 78.5 (1′-C), 102.8 (5-C), 128.1 (5″-C), 127.7 (3″, 7″-C), 128.6 (4″, 6″-C), 136.9 (2″-C), 174.8 (2-C); FAB-HRMS *m/z* 347.2204 (calcd for $C_{21}H_{30}O_4$ + H, 347.2222).

3.5 4R-4-benzyloxy-2(5H)-furanone (7a)

The aqueous HCl (12%, 120 ml) was added to a solution of **6a** (8.89 g, 25.7 mmol) in acetone (160 ml) under stirring. The mixture was stirred at 50°C for 6 h. Then the acetone was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (200 ml, 2 × 100 ml). The combined organic layer was washed with water (100 ml), saturated aqueous NaCl (100 ml) separately, dried over Na_2SO_4 and then concentrated in vacuum. The residue obtained was purified by vacuum liquid chromatography (10:1 PE/EtOAc) to give a colourless oil (4.31 g). The oil above was dissolved in CH_3OH (100 ml) at 0°C, then $NaBH_4$ (3.14 g, 83 mmol) was added portion-wise. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with water (50 ml), and then aqueous HCl (18%, 25 ml) was added. The mixture was stirred at RT for 4 h. The partial solvent was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (2 × 100 ml, 50 ml). The organic layer was washed with water (50 ml), saturated aqueous NaCl (50 ml) separately, dried over Na_2SO_4 and then concentrated in vacuum to give a brown oil. The crude product was purified by vacuum liquid chromatography (200:1 CH_2Cl_2/CH_3OH) to give the title compound **7a**: white solid (2.08 g, 42.2%); mp 65 – 67 °C; $[\alpha]_D^{15}$ +33.7 (C 0.61, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.62 ~ 2.72 (m, 3-H, 2H), 4.35 ~ 4.42 (m, 4-H, 5-H, 3H), 4.51 ~ 4.57 (m, $PhCH_2$-H, 2H), 7.31 ~ 7.39 (m, Ar-H, 5H); EI-MS *m/z* [M]: 192(20) (lit [23], $[\alpha]_D^{20}$ +35.9 (C 0.6, CH_2Cl_2)).

3.6 4S-4-benzyloxy-2(5H)-furanone (7b)

7b was prepared by the same procedure for **7a** using the corresponding starting material **6b** (1.6 g, 4.6 mmol). The title compound **7b**: white solid (0.22 g, 25%); mp 70 – 72°C; $[\alpha]_D^{12}$ −28.4 (C 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.66 ~ 2.69 (m, 3-H, 2H), 4.36 ~ 4.40 (m, 4-H, 5-H, 3H), 4.54 ~ 4.55 (m, $PhCH_2$-H, 2H), 7.31 ~ 7.37 (m, Ar-H, 5H); FAB-MS *m/z* [M + H]: 193(55) (lit [24], 70 – 72°C; $[\alpha]_D^{25}$ −28.7 (C 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 80 MHz): δ 2.65 (m, 2H), 4.34 (m, 3H), 4.52 (s, 2H), 7.30 (s, 5H)).

3.7 4R-4-hydroxy-2(5H)-furanone (8a)

The 10% Pd-C (0.2 g) was added to a solution of **7a** (1.67 g, 8.7 mmol) in ethanol (80 ml) and glacial acid (1.0 ml). The mixture was hydrogenated under middle pressure about 2.5 atm. When the reaction was over by detected with TLC, the Pd-C was removed by filtration. The residue was concentrated under reduced pressure. The crude product was purified by vacuum liquid chromatography (80:1 CH_2Cl_2/CH_3OH) to give a colourless oil **8a** (0.75 g, 83.2%); $[\alpha]_D^{14}$ +72.2 (C 1.25, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.53 (d, J = 17.7 Hz, 3-H, 1H), 2.76 (dd, J = 17.7 Hz, 5.7 Hz, 3-H, 1H), 4.30 (d, J = 10.2 Hz, 5-H, 1H), 4.43 (dd, J = 10.2 Hz, 4.5 Hz, 5-H, 1H), 4.68 ~ 4.72 (m, 4-H, 1H); FAB-MS *m/z* [M]: 103 (100) (lit [18], $[\alpha]_D^{23}$ +88.9 (C 1.36, EtOH)).

3.8 4S-4-hydroxy-2(5H)-furanone (8b)

8b was prepared by the same procedure for **8a** using the corresponding starting material **7b** (0.2 g, 1.04 mmol). The title compound **8b**: colourless oil (0.05 g, 45.7%); $[\alpha]_D^{11}$ −71.1 (C 1.31, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.53(d, J = 18 Hz, 3-H, 1H), 2.76 (dd, J = 18 Hz, 6 Hz, 3-H, 1H), 4.30 (d, J = 10 Hz, 5-H, 1H), 4.42 (dd, J = 10 Hz, 5 Hz, 5-H, 1H), 4.68 ∼ 4.71 (m, 4-H, 1H); FAB-MS *m/z* [M]: 103(100) (lit [18], $[\alpha]_D^{21}$ −86.1 (C 3.1, EtOH)).

3.9 4R-4-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-2(5H)-furanone (9a) and its α-isomer

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (1.54 g, 2.25 mmol) and **8a** (0.26 g, 2.5 mmol) were dissolved in dry acetonitrile (20 ml). Then 4 Å molecular sieves (0.5 g) were added into the above solution under nitrogen. The mixture was stirred at −40°C for 20 min, then a solution of TMSOTf (0.56 g, 2.5 mmol) in dry acetonitrile (5 ml) was added slowly. The mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with triethylamine (5 ml) and filtered, the filtration was concentrated in vacuum to obtain slight brown oil (2.25 g). The residue was purified by vacuum liquid chromatography (2:1 PE/EtOAc) to give a white solid (0.94 g, 60.3%) containing α- and β-isomer with the ratio of 1:1 that was confirmed by ^{1}H NMR.

The pure product was obtained by column chromatography with $CHCl_3/CH_3OH$ = 200:1 as eluant, which gave the title compound **9a** as a white solid: mp 121 – 123°C; $[\alpha]_D^{20}$ +24.9 (C 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.59 (dd, J = 18.5 Hz, 3 Hz, 3-H, 1H), 2.71 (dd, J = 18.5 Hz, 6.5 Hz, 3-H, 1H), 3.43 ∼ 3.46 (m, G2-H, G5-H, 2H), 3.56 (t, J = 9.5 Hz, G4-H, 1H), 3.61 ∼ 3.69 (m, G3-H, G6-H, 3H), 4.40 ∼ 4.43 (m, $PhCH_2$-H, 2H), 4.50 ∼ 4.57 (m, $PhCH_2$-H, 5-H, 4H), 4.59 ∼ 4.62 (m, 4-H, 1H), 4.75 (dd, J = 40 Hz, 10.5 Hz, $PhCH_2$-H, 2H), 4.82 (d, J = 7.5 Hz, G1-H, 1H), 4.79 ∼ 4.93 (m, $PhCH_2$-H, 2H), 7.15 ∼ 7.35 (m, Ar–H, 20H); FAB-HRMS m/z 647.2619 (calcd for $C_{38}H_{40}O_8$ + Na, 647.2621).

α-Isomer of **9a**: colourless oil; $[\alpha]_D^{20}$ +50.6(C 2.83, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.68 (dd, J = 17.5 Hz, 6 Hz, 3-H, 1H), 2.73 (dd, J = 17.5 Hz, 3 Hz, 3-H, 1H), 3.55 (dd, J = 10 Hz, 3.5 Hz, G2-H, 1H), 3.62 (t, J = 9.5 Hz, G4-H, 1H), 3.63 (t, J = 6.5 Hz, G6-H, 1H), 3.68 (dd, J = 5.5 Hz, 4 Hz, G6-H, 1H), 3.72 ∼ 3.76 (m, G5-H, 1H), 3.93 (t, J = 9.5 Hz, G3-H, 1H), 4.27 (dd, J = 10.5 Hz, 2.5 Hz, 5-H, 1H), 4.31 (dd, J = 10.5 Hz, 5 Hz, 5-H, 1H), 4.40 ∼ 4.43 (m, 4-H, 1H), 4.46 (d, J = 12 Hz, $PhCH_2$-H, 2H), 4.58 (dd, J = 12 Hz, 8.5 Hz, $PhCH_2$-H, 2H), 4.70 (d, J = 3.5 Hz, G1-H, 1H), 4.83 (dd, J = 12.5 Hz, 5.5 Hz, $PhCH_2$-H, 2H), 4.89 (dd, J = 16.5 Hz, 10 Hz, $PhCH_2$-H, 2H), 7.12 ∼ 7.36 (m, Ar-H, 20H); FAB-HRMS *m/z* 647.2619 (calcd for $C_{38}H_{40}O_8$ + Na, 647.2621).

3.10 4S-4-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-2(5H)-furanone (9b) and its α-isomer

9b and its α-isomer were prepared by the same procedure for **9a** using the corresponding starting material **8b** (0.26 g, 2.5 mmol). The title compound **9b** as a white solid: mp 104 – 108°C; $[\alpha]_D^{10}$ −19.1 (C 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.75 (dd, J = 18 Hz, 6 Hz, 3-H, 1H), 2.83 (dd, J = 18 Hz, 2 Hz, 3-H, 1H), 3.43 ∼ 3.46 (m, G2-H, G5-H, 2H), 3.56 (t, J = 9 Hz, G4-H, 1H), 3.61 ∼ 3.70 (m, G3-H, G6-H, 3H), 4.36 ∼ 4.43 (m, $PhCH_2$-H, 2H), 4.51 ∼ 4.59 (m, $PhCH_2$-H, 5-H, 4H), 4.62 ∼ 4.63 (m, 4-H, 1H), 4.76 (dd, J = 44.5 Hz, 10.5 Hz,

$PhCH_2$-H, 2H), 4.81 (d, $J = 9$ Hz, G1-H, 1H), 4.78 ~ 4.93 (m, $PhCH_2$-H, 2H), 7.14 ~ 7.34 (m, Ar–H, 20H); FAB-HRMS *m/z* 647.2569 (calcd for $C_{38}H_{40}O_8$ + Na, 647.2621).

α-Isomer of **9b**: white solid, mp 78 – 79.5°C; $[\alpha]_D^{10}$ +16.4 (C 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.53 (dd, $J = 18$ Hz, 2.5 Hz, 3-H, 1H), 2.63 (dd, $J = 18$ Hz, 6.5 Hz, 3-H, 1H), 3.54 (dd, $J = 10$ Hz, 3.5 Hz, G2-H, 1H), 3.59 (t, $J = 10$ Hz, G4-H, 1H), 3.57 ~ 3.67 (m, G6-H, 2H), 3.73 ~ 3.75 (m, G5-H, 1H), 3.92 (t, $J = 10$ Hz, G3-H, 1H), 4.35 (dd, $J = 10$ Hz, 5 Hz, 5-H, 1H), 4.40 ~ 4.47 (m, 4-H, 5-H, $PhCH_2$-H, 4H), 4.55 (dd, $J = 12$ Hz, 5 Hz, $PhCH_2$-H, 2H), 4.65 (d, $J = 3.5$ Hz, G1-H, 1H), 4.80 ~ 4.97 (m, 2 × $PhCH_2$-H, 4H), 7.12 ~ 7.34 (m, Ar-H, 20H); FAB-HRMS *m/z* 647.2603 (calcd for $C_{38}H_{40}O_8$ + Na, 647.2621).

3.11 4R-4-O-(β-D-glucopyranosyl)-2(5H)-furanone (1, kinsenoside) and its α-isomer

The 10% Pd-C (0.1 g) was added to a solution of **9a** (0.16 g, 0.26 mmol) in EtOH and EtOAc (30 ml, 9:1). The mixture was hydrogenated under 2.5 atm for 5 h. The Pd-C was removed by filtration. The filtration was concentrated under reduced pressure. The crude product was purified by column chromatography with CH_2Cl_2/EtOH = 7 : 3 as eluant, which gave the title compound **1** as a colourless oil (0.06 g, 89.7%): $[\alpha]_D^{17}$ +17.9 (C 1.24, EtOH); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.84 (d, $J = 4$ Hz, 3-H, 2H), 3.93 ~ 3.95 (m, G5-H, 1H), 3.98 (dd, $J = 9.0$ Hz, 7.5 Hz, G2-H, 1H), 4.21 ~ 4.23 (m, G3-H, G4-H, 2H), 4.34 ~ 4.39 (m, 5-H, G6-H, 2H), 4.54 (dd, $J = 12.0$ Hz, 2.5 Hz, G6-H, 1H), 4.67 (dd, $J = 10.5$ Hz, 1.5 Hz, 5-H, 1H), 4.81 ~ 4.83 (m, 4-H, 1H), 4.89 (d, $J = 7.5$ Hz, G1-H, 1H); ^{13}C NMR (d^5-pyridine, 125 MHz): δ 35.7 (3-C), 62.8 (G6-C), 71.5 (G4-C), 74.8 (5-C), 74.9 (G2-C), 75.3 (4-C), 78.4 (G5-C), 78.8 (G3-C), 104.1 (G1-C), 176.1 (2-C); FAB-HRMS *m/z* 287.0733 (calcd for $C_{10}H_{16}O_8$ + Na, 287.0743); IR (KBr) ν_{max}: 3394 (OH), 2918 (CH), 1770 (γ-lactone).

Lit [1], colourless oil: $[\alpha]_D^{16}$ +48.4 (C 2.07, EtOH); ^{1}H NMR (d^5-pyridine, 400 MHz): δ 2.87 (dd, $J = 17.5$ Hz, 2.8 Hz, 3-H), 2.91 (dd, $J = 17.5$ Hz, 5.1 Hz, 3-H), 3.95 (m, G5-H), 3.99 (t, $J = 7.9$ Hz, G2-H), 4.21 (m, G4-H), 4.24 (m, G3-H), 4.35 (dd, $J = 11.7$ Hz, 5.7 Hz, G6-H), 4.44 (dd, $J = 10.3$ Hz, 4.6 Hz, 5-H), 4.55 (dd, $J = 11.7$ Hz, 2.4 Hz, G6-H), 4.71 (dd, $J = 10.3$ Hz, 1.5 Hz, 5-H), 4.88 (dddd, $J = 5.1$ Hz, 4.6 Hz, 2.8 Hz, 1.5 Hz, 4-H), 4.91 (d, $J = 7.9$ Hz, G1-H); ^{13}C NMR (d^5-pyridine, 100 MHz): δ 35.7 (3-C), 62.7 (G6-C), 71.4 (G4-C), 74.8 (5-C), 74.9 (G2-C), 75.3 (4-C), 78.3 (G5-C), 78.7 (G3-C), 104.1 (G1-C), 176.1 (2-C); FAB-HRMS *m/z* 263.0808 (calcd for $C_{10}H_{16}O_8$-H, 263.0767); IR(KBr) ν_{max}: 3400 (OH), 2967 (CH), 1770 (γ-lactone).

The α-isomer of kinsenoside (**1**) was prepared by the same procedure using the corresponding starting material α-isomer of **9a** (0.28 g, 0.45 mmol). α-Isomer of **1**: colourless oil (0.11 g, 93.2%); $[\alpha]_D^{17}$ +159.1 (C = 2.3, EtOH); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.90 (dd, $J = 18$ Hz, 6 Hz, 3-H, 1H), 2.95 (dd, $J = 18$ Hz, 3 Hz, 3-H, 1H), 4.14 (dd, $J = 4$ Hz, 2 Hz, G2-H, 1H), 4.19 (t, $J = 3$ Hz, G4-H, 1H), 4.30 ~ 4.36 (m, G6-H, 5-H, 3H), 4.47 ~ 4.58 (m, G3-H, G5-H, 5-H, 3H), 4.79 ~ 4.82 (m, 4-H, 1H), 5.43 (d, $J = 3.5$ Hz, G1-H, 1H); FAB-HRMS *m/z* 287.0754 (calcd for $C_{10}H_{16}O_8$ + Na, 287.0743).

3.12 4S-4-O-(β-D-glucopyranosyl)-2(5H)-furanone (2, goodyeroside A) and its α-isomer

2 was prepared by the same procedure for **1** using the corresponding starting material **9b** (0.26 g, 0.41 mmol). The title compound **2** was obtained by recrystallised from EtOH as a white crystal (0.07 g, 64.8%): mp 165 – 166°C; $[\alpha]_D^{10}$ −69.9 (C 0.55, H_2O); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.86 (dd, $J = 17.8$ Hz, 5.6 Hz, 3-H, 1H), 2.91 (dd, $J = 17.8$ Hz,

2.2 Hz, 3-H, 1H), 3.93 (ddd, $J = 9.5$ Hz, 5.4 Hz, 2.4 Hz, G5-H, 1H), 3.98 (dd, $J = 9.0$ Hz, 7.8 Hz, G2-H, 1H), 4.19 ~ 4.22 (m, G3-H, G4-H, 2H), 4.35 (dd, $J = 10.0$ Hz, 4.4 Hz, 5-H, 1H), 4.36 (dd, $J = 12.0$ Hz, 5.4 Hz, G6-H, 1H), 4.54 (dd, $J = 12.0$ Hz, 2.4 Hz, G6-H, 1H), 4.64 (d, $J = 10.0$ Hz, 5-H, 1H), 4.85 ~ 4.88 (m, 4-H, 1H), 4.93 (d, $J = 7.8$ Hz, G1-H, 1H); ^{13}C NMR (d^5-pyridine, 125 MHz): δ 36.4 (3-C), 62.7 (G6-C), 71.5 (G4-C), 74.0 (5-C), 74.6 (4-C), 74.8 (G2-C), 78.4 (G5-C), 78.8 (G3-C), 103.7 (G1-C), 176.3 (2-C); FAB-HRMS *m/z* 287.0763 (calcd for $C_{10}H_{16}O_8$ + Na, 287.0743).

Lit [5], colourless needles: mp 156 – 157°C; $[\alpha]_D^{17}$ −71.2 (C 0.55, H_2O); ^{1}H NMR (d^5-pyridine, 400 MHz): δ 2.84 (dd, $J = 17.8$ Hz, 2.5 Hz, 3-H), 2.88 (dd, $J = 17.8$ Hz, 5.2 Hz, 3-H), 3.94 (ddd, $J = 8.9$ Hz, 5.3 Hz, 2.3 Hz, G5-H), 3.98 (dd, $J = 8.9$ Hz, 7.9 Hz, G2-H), 4.19 (dd, $J = 8.9$ Hz, 8.9 Hz, G4-H), 4.22 ($J = 8.9$ Hz, 8.9 Hz, G3-H), 4.35 (dd, $J = 11.7$ Hz, 5.3 Hz, G6-H), 4.41 (dd, $J = 10.2$ Hz, 4.7 Hz, 5-H), 4.54 (dd, $J = 11.7$ Hz, 2.3 Hz, G6-H), 4.69 (dd, $J = 10.2$ Hz, 1.5 Hz, 5-H), 4.85 (m, 4-H), 4.94 (d, $J = 7.9$ Hz, G1-H); ^{13}C NMR (d^5-pyridine, 100 MHz): δ 36.4 (3-C), 62.8 (G6-C), 71.5 (G4-C), 74.0 (5-C), 74.7 (4-C), 74.8 (G2-C), 78.4 (G5-C), 78.7 (G3-C), 103.7 (G1-C), 176.2 (2-C); FAB-HRMS *m/z* 287.0843 (calcd for $C_{10}H_{16}O_8$ + Na, 287.0743).

The α-isomer of goodyeroside A (**2**) was prepared by the same procedure using the corresponding starting material α-isomer of **9b** (0.22 g, 0.35 mmol). α-Isomer of **2**: colourless syrup (0.07 g, 76.3%); $[\alpha]_D^{15}$ +83.2 (C 0.27, H_2O); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.77 ~ 2.82 (m, 3-H, 2H), 4.13 (dd, $J = 9.5$ Hz, 4 Hz, G2-H, 1H), 4.14 (t, $J = 9.5$ Hz, G4-H, 1H), 4.31 ~ 4.38 (m, G6-H, 2H), 4.42 (dd, $J = 10$ Hz, 4.5 Hz, 5-H, 1H), 4.51 (d, $J = 10$ Hz, 5-H, 1H), 4.52 ~ 4.55 (m, G5-H, 1H), 4.71 ~ 4.73 (m, G3-H, 1H), 4.77 ~ 4.80 (m, 4-H, 1H), 5.41 (d, $J = 4$ Hz, G1-H, 1H); ^{13}C NMR (d^5-pyridine, 125 MHz): δ 35.6 (3-C), 62.9 (G6-C), 72.2 (G4-C), 73.4 (5-C), 74.7 (4-C, G2-C), 75.0 (G5-C), 75.3 (G3-C), 100.4 (G1-C), 176.8 (2-C); FAB-HRMS *m/z* 287.0759 (calcd for $C_{10}H_{16}O_8$ + Na, 287.0743).

3.13 4R-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2(5H)-furanone (1a) and its α-isomer

A solution of kinsenoside (**1**) (0.05 g, 0.2 mmol) in Ac_2O (0.5 ml) and dry pyridine (1 ml) was left standing at RT overnight. The reaction was quenched with the aqueous $CuSO_4$ (60 ml) and extracted with ethyl acetate (2 × 20 ml). The combined organic portion was washed with 0.05 M HCl (10 ml) and saturated aqueous NaCl (10 ml) before it was dried (Na_2SO_4), filtered, and evaporated in vacuum. The crude product was purified by column chromatography with PE/EtOAc = 3 : 1 as eluant, which gave the title compound **1a** as a white crystal (0.06 g, 73.4%): mp 151 – 152.5°C; $[\alpha]_D^{18}$ −6.7 (C 0.18, $CHCl_3$); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.00, 2.01, 2.02, 2.04 (each 3H, S, CH_3CO, 12H), 2.78 (d, $J = 17.5$ Hz, 3-H, 1H), 2.93 (dd, $J = 17.5$ Hz, 6 Hz, 3-H, 1H), 4.15 (ddd, $J = 10$ Hz, 4.5 Hz, 2.5 Hz, G5-H), 4.40 ~ 4.55 (m, 5-H, G6-H, 4H), 4.84 ~ 4.87 (m, 4-H, 1H), 5.10 (d, $J = 8.0$ Hz, G1-H, 1H), 5.44 (t, $J = 8.0$ Hz, G2-H, 1H), 5.50 (t, $J = 10$ Hz, G4-H, 1H), 5.74 (t, $J = 10$ Hz, G3-H, 1H); ^{13}C NMR (d^5-pyridine, 125 MHz): δ 20.4 (CH_3 × 3), 20.6 (CH_3), 35.5 (3-C), 62.3 (G6-C), 68.9 (G4-C), 71.7 (5-C), 72.5 (G2-C), 73.2 (4-C), 74.2 (G5-C), 75.5 (G3-C), 99.9 (G1-C), 169.6, 169.8, 170.3, 170.5 (CH_3CO × 4), 175.3 (2-C); FAB-HRMS *m/z* 455.1174 (calcd for $C_{18}H_{24}O_{12}$ + Na, 455.1165).

Lit [2], colourless prisms: mp 157 – 159°C; ^{1}H NMR (d^5-pyridine, 270 MHz): δ 2.03, 2.04, 2.05, 2.07 (each 3H, S, CH_3CO), 2.78 (dd, $J = 17.8$ Hz, 1.2 Hz, 3-H), 2.97

(dd, $J = 17.8$ Hz, 5.9 Hz, 3-H), 4.43 (dd, $J = 12.5$ Hz, 2.8 Hz, 5-H), 4.51 (dd, $J = 12.5$ Hz, 4.6 Hz, G6-H), 4.88 (dddd, $J = 5.9$ Hz, 4.6 Hz, 2.8 Hz, 1.2 Hz, 4-H), 5.13 (d, $J = 7.9$ Hz, G1-H); ^{13}C NMR (d^5-pyridine, 67.5 MHz): δ 20.4 ($CH_3 \times 3$), 20.6 (CH_3), 99.9 (G1-H), 169.6, 169.8, 170.3, 170.5 ($CH_3CO \times 4$), 175.3 (2-C); FAB-MS *m/z* $[M + H]^+$: 433.

The α-isomer of **1a** was prepared by the same procedure using the corresponding starting material α-isomer of **1** (0.11 g, 0.40 mmol). α-Isomer of **1a**: white crystal (0.14 g, 83.1%); mp 119 – 120°C; $[\alpha]_D^{18}$ +168.8 (C 0.35, $CHCl_3$); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 1.96, 2.03, 2.04, 2.06 ($CH_3 \times 4$, s, 12H), 3.00 ~ 3.05 (m, 3-H, 2H), 4.35 ~ 4.50 (m, G5-H, G6-H, 5-H, 5H), 4.80 ~ 4.81 (m, 4-H, 1H), 5.33 (dd, $J = 10.5$ Hz, 4 Hz, G2-H, 1H), 5.50 (t, $J = 10$ Hz, G4-H, 1H), 5.64 (d, $J = 3.5$ Hz, G1-H, 1H), 5.93 (t, $J = 10$ Hz, G3-H, 1H); FAB-HRMS *m/z* 455.1174 (calcd for $C_{18}H_{24}O_{12}$ + Na, 455.1165).

3.14 4S-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2(5H)-furanone (2b) and its α-isomer

2b was prepared by the same procedure for **1a** using the corresponding starting material **2** (0.05 g, 0.2 mmol). The title compound **2b** as a white crystal (0.05 g, 59%): mp 126 – 127.5°C; $[\alpha]_D^{15}$ −47.4 (C 0.09, $CHCl_3$); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.01 ~ 2.10 ($CH_3 \times 4$, s), 2.74 ~ 2.75 (m, 3-H, 2H), 3.69 ~ 3.72 (m, G5-H, 1H), 4.15 (dd, $J = 12.5$ Hz, 2.5 Hz, G6-H, 1H), 4.23 (dd, $J = 12.5$ Hz, 5 Hz, G6-H, 1H), 4.31 (dd, $J = 10.5$ Hz, 2 Hz, 5-H, 1H), 4.39 (dd, $J = 10.5, 5$ Hz, 5-H, 1H), 4.62 (d, $J = 8$ Hz, G1-H, 1H), 4.63 ~ 4.65 (m, 4-H, 1H), 4.98 (dd, $J = 9.5$ Hz, 8 Hz, G2-H, 1H), 5.08 (t, $J = 10$ Hz, G4-H, 1H), 5.21(t, $J = 9.5$ Hz, G3-H, 1H); ^{13}C NMR (d^5-pyridine, 125 MHz): δ 20.4 ($CH_3 \times 3$), 20.6 (CH_3), 35.6 (3-C), 61.7 (G6-C), 68.1 (G4-C), 70.8 (G2-C), 72.2 (G5-C), 72.4 (G3-C), 72.6 (5-C), 74.0 (4-C), 99.5 (G1-C), 169.3, 169.5, 170.4, 170.7($CH_3CO \times 4$), 174.9(2-C); FAB-HRMS *m/z* 455.1171 (calcd for $C_{18}H_{24}O_{12}$ + Na, 455.1165); IR (KBr) ν_{max}: 1786, 1755, 1379, 1228, 1043.

Lit [4], colourless needles: mp 108 – 110°C; $[\alpha]_D$ −8.2 (C 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.98 ~ 2.07 ($CH_3 \times 4$), 2.54 (dd, $J = 18.0$ Hz, 6.9 Hz, 3-H), 2.70 (dd, $J = 18.0$ Hz, 2.7 Hz, 3-H), 3,68 (m, G5-H), 4.12 (dd, $J = 12.0$ Hz, 2.4 Hz, G6-H), 4.19 (dd, $J = 12.0$ Hz, 5.8 Hz, G6-H), 4.40 (d, $J = 4.0$ Hz, 5-H), 4.55 (d, $J = 7.9$ Hz, G1-H), 4.60 (m, 4-H), 4.94 (t, $J = 7.9$ Hz, G2-H), 5.02 (m, G4-H), 5.16 (m, G3-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2 ($CH_3 \times 3$), 20.5 (CH_3), 34.8 (3-C), 61.6 (G6-C), 68.0 (G4-C), 70.7 (G2-C), 72.3 (G5-C), 72.6 (G3-C), 74.0 (5-C), 74.2 (4-C), 99.3 (G1-C), 168.0, 169.2, 170.0, 170.4 ($CH_3CO \times 4$), 174.3 (2-C); EI-MS *m/z* [M]: 432; IR (KBr) ν_{max}: 1786, 1760, 1759, 1755, 1381, 1228, 1043.

The α-isomer of **2b** was prepared by the same procedure using the corresponding starting material α-isomer of **2** (0.02 g, 0.08 mmol). α-Isomer of **2b**: colourless oil (0.02 g, 70.3%); mp 44 – 46°C; $[\alpha]_D^{18}$ +98.6 (C 0.12, $CHCl_3$); ^{1}H NMR (d^5-pyridine, 500 MHz): δ 2.02 ~ 2.10 ($CH_3 \times 4$, s), 2.53 (d, $J = 18$ Hz, 3-H, 1H), 2.71 (dd, $J = 18$ Hz, 6 Hz, 3-H, 1H), 4.02 ~ 4.05 (m, G5-H, 1H), 4.12 (d, $J = 12.5$ Hz, G6-H, 1H), 4.22 (dd, $J = 12.5$ Hz, 5.5 Hz, G6-H, 1H), 4.42 (dd, $J = 10.5$ Hz, 5 Hz, 5-H, 1H), 4.53 (d, $J = 10.5$ Hz, 5-H, 1H), 4.55 ~ 4.57 (m, 4-H, 1H), 4.80 ~ 4.83 (m, G2-H, 1H), 5.05 (t, $J = 10$ Hz, G3-H, 1H), 5.21 (d, $J = 4$ Hz, G1-H, 1H), 5.43 (t, $J = 10$ Hz, G4-H, 1H); ^{13}C NMR (d^5-pyridine, 125 MHz): δ 20.54 ($CH_3 \times 3$), 20.64 (CH_3), 34.81 (3-C), 61.84 (G6-C), 68.17 (G4-C), 68.29 (G2-C), 69.61 (G5-C), 70.55 (G3-C), 72.95 (5-C), 74.14 (4-C), 95.09 (G1-C), 169.50, 169.90, 170.31, 170.43

($CH_3CO \times 4$), 174.00 (2-C); FAB-HRMS *m/z* 455.1159 (calcd for $C_{18}H_{24}O_{12} + Na$, 455.1165).

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