Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2429–2439

TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic syntheses of naturally occurring β-glucosides

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Received 21 April 1999; revised 24 May 1999; accepted 27 May 1999

Abstract

Enzymatic glycosidation of the various kinds of primary alcohols **5**, **7**, **9**, **11**, **13** and **15** and 4-nitrophenyl-β-D-glucopyranoside **4** using β-glucosidase from almonds gave stereoselectively β-D-glucosides **6**, **8**, **10**, **12**, **14** and **16** including the naturally occurring β-glucosides in moderate yield. Among them, the β-glucosides **6**, **8** and **10** were converted to the cyanoglycosides, rhodiocyanoside A **20a**, osmaronin **24a** and sutherlandin **29**, respectively.

1. Introduction

The development of stereoselective methods for the synthesis of glycosidic linkages offers a considerable challenge to synthetic chemists.[1] Although the well described chemical synthesis of glycosidic structures is becoming increasingly established, several steps of selective protection, activation and coupling are necessary. This problem in chemical synthesis has enhanced the development of enzymatic approaches because a large number of the enzymes involved in carbohydrate biosynthesis are well described and some enzymes are commercially available. For example, β-glucosidase catalyzes the stereospecific hydrolytic cleavage of the β-glucosidic bond in the substrate **1** to give glucose **2** (Scheme 1, path a). Meanwhile, the reaction of the β-glucoside **1** and a nucleophile such as an alcohol are reported to afford a new glucoside **3** exclusively with the β-configuration (Scheme 1, path b).[2] In the case where the alcohol is cheap and readily available, the use of high concentrations of the alcohol acceptor in order to favor formation of **3** over **2** is reported to provide good yields of the β-glucosides. However, the need for using high concentrations of the alcohol clearly limits the scope and application of this reaction. We are attracted by this transglycosylation reaction since if a second nucleophile was a suitably selected functionalized alcohol used in limited amounts it might provide an effective method of glycosidation under aqueous conditions without the need for any protection of the hydroxyl group. We now describe

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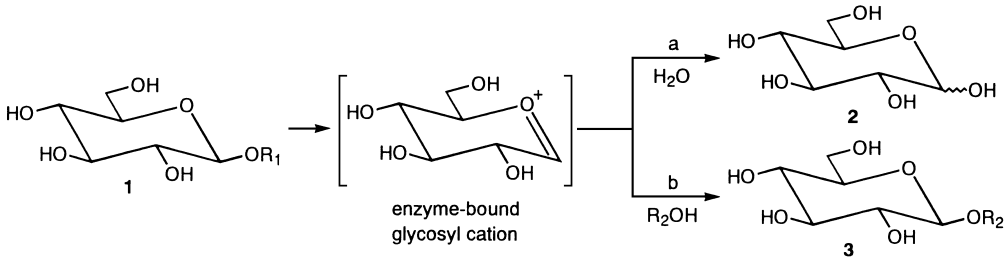
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00228-1

the syntheses of β-glucosides using β-glucosidase from almonds and its application to the short path synthesis of naturally occurring β-glucosides.

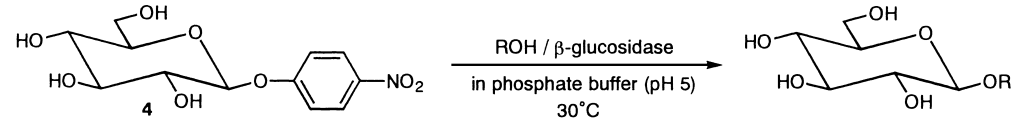


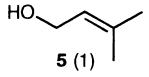
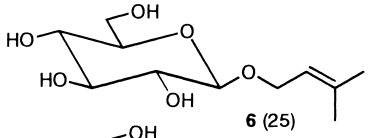
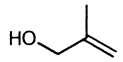
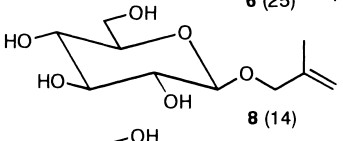
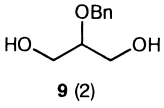
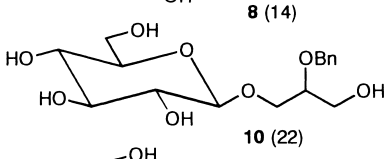
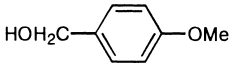
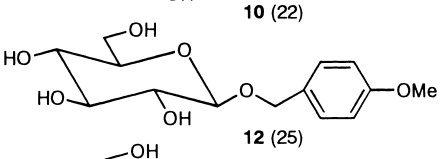
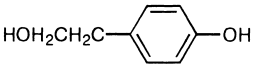
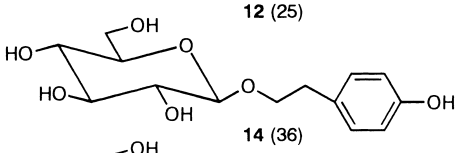
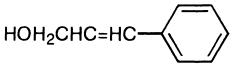
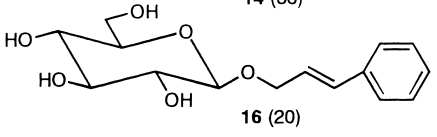
Scheme 1.

2. Results and discussion

In order to determine the effective enzyme and glycosyl donor, the synthesis of benzyl-β-D-glucoside or *n*-hexyl-β-D-glucoside was selected as a model transglycosylation reaction. From a screening experiment using either glycosyl transferases or glucosidases as catalysts, β-D-glucosidase (EC 3.2.1.21) from almonds was effective for transglycosylation. This enzyme was purchased from the Sigma Chemical Co. (G-0395, 2.5–3.4 U/mg). Meanwhile, 4-nitrophenyl-β-D-glucopyranoside **4**[3] as a glycosyl donor was chosen from either several kinds of phenyl-β-D-glucopyranoside congeners or cellobiose. The following functionalized alcohols such as 3-methyl-2-buten-1-ol **5**, 2-methyl-2-propen-1-ol **7**, 2-benzyloxy-1,3-diol **9**, 4-methoxybenzyl alcohol **11**, 4-hydroxyphenethyl alcohol **13**, and cinnamyl alcohol **15** were selected as nucleophiles. Addition of the glycosyl donor **4** to a solution of the acceptor substrate dissolved in phosphate buffer containing β-glucosidase was carried out over a period of 3–26 h. The reaction can be easily monitored by reverse phase HPLC and terminated when the formation of the desired product is at a maximum. The results are summarized in Table 1. The structures of all products were determined by either conversion to the corresponding acetates or direct comparison with the corresponding natural β-glucosides. Identification of the β-configuration of the anomeric center was easily achieved via analysis of the C_1-H/C_2-H coupling constant. The spectral data of the synthetic β-D-glucosides (**6**: mp 78–81°C, $[\alpha]_D$ −40.8 (c=0.54, MeOH); **12**: mp 139–140°C, $[\alpha]_D$ −57.5 (c=0.55, MeOH); **14**: mp 159–160°C, $[\alpha]_D$ −28.4 (c=0.5, MeOH); **16**: mp 114–116°C, $[\alpha]_D$ −48.8 (c=0.3, MeOH)) were identical with those of the reported naturally occurring β-D-glucosides (3-methyl-2-buten *O*-β-glucopyranoside **6**:[4] mp 68–70°C, $[\alpha]_D$ −23.6 (c=0.2, MeOH), ^{1}H and ^{13}C NMR; 4-methoxybenzyl *O*-β-glucopyranoside **12**:[5] mp 137–138°C, $[\alpha]_D$ −51.1 (MeOH), ^{1}H and ^{13}C NMR; salidroside (rhodioside) **14**:[6] mp 161–164°C, $[\alpha]_D$ −28.3 (MeOH), ^{1}H and ^{13}C NMR; cinnamyl *O*-β-glucopyranoside **16**:[7] mp 114–116°C, $[\alpha]_D$ −48.1 (c=1.0, MeOH), ^{1}H and ^{13}C NMR), respectively. The β-glucoside **16** was reported to exhibit potential anti-tumor-promoting activity which corresponds with the inhibitory effects on Epstein–Barr virus (EBV) activation induced by 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA).[7b] In spite of the moderate chemical yield, in all cases only the β-glucoside was obtained. Prolonged reaction times (>24 h) generally resulted in decreased yields of the glucosides presumably due to competing hydrolysis of the product by β-glucosidase. In the case of the transglucosylation of an alcohol with 2-nitrophenylglucopyranoside or 4-nitrophenylglucopyranoside **4** in the presence of β-glucosidase in phosphate buffer, the chemical yield of the β-glucoside is reported to be low and less than 30%.[2] In order to avoid the cleavage of the glycosidic bond of the produced β-glucoside, transglucosylation of 5-phenyl-1-pentanol with **4** using lipid-coated β-glucosidase in dry isopropyl ether is reported to give the corresponding β-glucoside in 23% yield.[8]

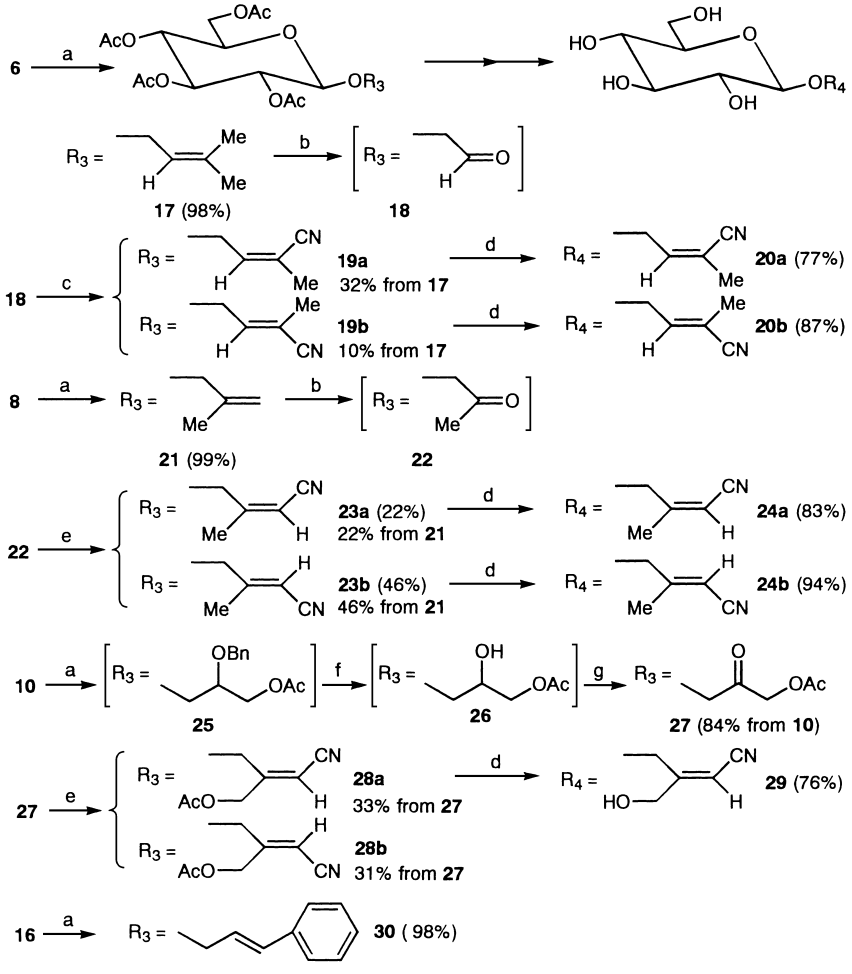
Table 1



entry	ROH (eq)	enzyme/buffer (U/ml)	time (hr)	product (yield, %)
1	 **5** (1)	5	24	 **6** (25)
2	 **7** (2)	5	4	 **8** (14)
3	 **9** (2)	7	3	 **10** (22)
4	 **11** (1)	10	26	 **12** (25)
5	 **13** (5)	8	26	 **14** (36)
6	 **15** (1)	6	16	 **16** (20)

Enzymatic formation of the glycosidic bond is thought to be mechanistically similar to the acid-catalyzed formation of glycosides. By the use of appropriate glycosyl donor **1**, the enzyme-bound glycosyl cation (Scheme 1) can be captured by an alcohol to yield a glycoside. A proximal carboxylate moiety appears as a common structural feature among β-glucosidases and presumably acts to stabilize this glycosyl cation with an α-configuration at the anomeric carbon.[9] Nucleophilic alcohol presumably attacks at the anomeric carbon from the β-side to afford exclusively β-glucoside.

The synthetic β-glucopyranoside **6** was converted to the cyanoglucoside rhodiocyanoside A **20a** which was isolated from the underground part of *Rhodiola quadrifida* (Pall.) Fisch. et Mey. (Crassulaceae) and found to show antiallergic activity in a passive cutaneous anaphylaxis test in rat (Scheme 2).[10] Acetylation of **6** gave an acetate **17** (98% yield, $[\alpha]_D$ −27.6 (c=0.38, $CHCl_3$)) which was subjected to ozonolysis to afford the aldehyde **18**. The Horner–Emmons reaction of **18** using diethyl (1-cyanoethyl)phosphonate furnished (*Z*)-**19a** (32% yield from **17**, $[\alpha]_D$ −2.65 (c=0.68, MeOH)) and (*E*)-**19b** (10% yield from **17**, $[\alpha]_D$ −25.3 (c=0.43, $CHCl_3$)). The physical data of (*Z*)-**19a** were identical with those (^1H and ^{13}C NMR) of the reported (*Z*)-**19a**.[10] Deprotection of (*Z*)-**19a** and (*E*)-**19b** provided the β-D-glucosides **20a** (77% yield, $[\alpha]_D$ −15.3 (c=0.34, MeOH)) and unnatural **20b** (87% yield, $[\alpha]_D$ −23.5 (c=0.34, MeOH)), respectively. The physical data ($[\alpha]_D$, ^1H and ^{13}C NMR) of the synthetic **20a** were identical with those ($[\alpha]_D$ −16.1 (c=0.4, MeOH), ^1H and ^{13}C NMR) of the natural rhodiocyanoside A (**20a**).[10]



Scheme 2. (a) Ac_2O/pyridine; (b) (1) O_3, (2) Me_2S; (c) $(EtO)_2POCH(CN)CH_3$/NaH, THF; (d) K_2CO_3/MeOH; (e) $(EtO)_2POCH_2CN$/NaH, THF; (f) H_2/10% Pd–C; (g) Jones reagent

The synthetic **8** was converted into the cyanoglucoside osmaronin **24a** which was isolated from a methanolic extract of the leaves of *Osmaronia cerasiformis*.[11] Acetylation of **8** gave an acetate **21** (99% yield, $[\alpha]_D$ −26.8 (c=0.6, $CHCl_3$)) which was subjected to ozonolysis to afford a ketone **22**. The Horner–Emmons reaction of **22** using diethyl cyanomethylphosphonate furnished (*Z*)-**23a** (22% yield from **21**, $[\alpha]_D$ +10.3 (c=0.6, $CHCl_3$)) and (*E*)-**23b** (10% yield from **21**, $[\alpha]_D$ −26.2 (c=0.68, $CHCl_3$)). Deprotection of (*Z*)-**23a** and (*E*)-**23b** gave the β-D-glucosides **24a** (83% yield, $[\alpha]_D$ +20.0 (c=0.7, MeOH)) and **24b** (94% yield, $[\alpha]_D$ −17.5 (c=0.51, MeOH)), respectively. The spectral data of the synthetic **24a** were identical with those (^1H and ^{13}C NMR) of the natural osmaronin (**24a**).[11]

Then the synthetic **10** was converted to the cyanoglucoside sutherlandin **29** which was isolated from leaves of *Acacia sutherlandii*.[12] Acetylation of a diastereomeric mixture of **10** gave the corresponding acetate **25** which was subjected to the hydrogenation (**26**) and the subsequent oxidation to yield the α-acetoxyl ketone **27** (84% overall yield from **25**, $[\alpha]_D$ −7.55 (c=1.10, $CHCl_3$)). The Horner–Emmons reaction of **27** using diethyl cyanomethylphosphonate furnished the (*Z*)-**28a** (33% yield from **27**, $[\alpha]_D$ −2.48 (c=1.10, $CHCl_3$)) and (*E*)-**28b** (31% yield from **27**, $[\alpha]_D$ −23.0 (c=1.10, $CHCl_3$)). Deprotection of

the presumably desired (*Z*)-**28a** afforded the (*Z*)-**29a** (76% yield, $[\alpha]_D$ −14.6 (c=0.54, MeOH)) whose ^{13}C NMR spectra were identical with those of the natural sutherlandin **29**.[12]

In summary, we have demonstrated the practical syntheses of a series of β-glucosides **6**, **8**, **10**, **12**, **14**, and **16** directly from the sugar donor and an alcohol acceptor using β-glucosidase from almonds. Among them, the first syntheses of the cyanoglucosides, rodionoside A **20a**, osmaronin **24a**, and sutherlandin **29** were achieved from the β-glucosides **6**, **8**, and **10**, respectively.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Jeol EX 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FABMS) were obtained with a Jeol LMS-DX 303 spectrometer. IR spectra were recorded on a Jasco FT/IR-300 spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

3.2. 3-Methyl-2-buten-1-ol β-D-glucopyranoside *6*

A mixture of **4** (1 g, 3.32 mmol), 3-methyl-2-buten-1-ol **5** (287 mg, 3.32 mmol), and β-glucosidase (50 mg, 170 units) in phosphate buffer (pH 5, 34 ml) was incubated for 24 h at 30°C. After the reaction mixture was boiled for 5 min and evaporated under reduced pressure, the residue was chromatographed on silica gel (50 g, $CHCl_3$:MeOH (30:1)) to afford **6** (205 mg, 25%) as a colorless amorphous powder. **6**: Mp 78–81°C; $[\alpha]_D^{26}$ −40.8 (c=0.54, MeOH); IR (KBr): 3346, 2882, 1073, 1025 cm^{-1}; ^1H NMR (pyridine-d_5): δ 1.54 (3H, s), 1.60 (3H, s), 3.94–3.97 (1H, m), 4.06 (1H, t, J=8 Hz), 4.21–4.29 (2H, m), 4.38 (1H, d, J=11.7 Hz), 4.36–4.40 (1H, m), 4.59 (1H, d, J=11.7 Hz), 4.54–4.55 (1H, m), 4.90 (1H, d, J=7.3 Hz), 5.52 (1H, t, J=6.3 Hz); ^{13}C NMR (pyridine-d_5): δ 135.9, 121.9, 103.5, 78.6, 78.5, 75.2, 71.7, 65.7, 62.8, 25.6, 17.9; FABMS *m/z*: 249 $(M+1)^+$. Anal. found: C, 52.78; H, 8.24. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12%.

3.3. Acetylation of *6*

A solution of **6** (200 mg, 0.81 mmol) in pyridine (2 ml, 24.8 mmol), 4-dimethylaminopyridine (10 mg, 0.08 mmol) was treated with Ac_2O (0.5 ml, 5.3 mmol) and the reaction mixture was stirred for 15 min at room temperature. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (50 ml×3). The AcOEt extract was washed with sat. brine (100 ml), dried over $MgSO_4$, and filtered. Removal of the solvent gave a residue which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt (2:1)) to give **17** (329 mg, 98%) as colorless needles. **17**: Mp 81–83°C; $[\alpha]_D^{27}$ −27.6 (c=0.38, $CHCl_3$); IR (KBr): 2969, 1754, 1384, 1209 cm^{-1}; ^1H NMR: δ 1.67 (3H, s), 1.76 (3H, s), 2.00 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 3.67 (1H, ddd, J=2.4, 4.9, 9.8 Hz), 4.14–4.27 (4H, m), 4.53 (1H, d, J=7.8 Hz), 4.99 (1H, dd, J=7.8, 9.8 Hz), 5.08 (1H, t, J=9.8 Hz), 5.21 (1H, t, J=9.8 Hz), 5.24–5.28 (1H, m); FABMS *m/z*: 455 $(M+K)^+$. Anal. found: C, 54.69; H, 6.74. Calcd for $C_{19}H_{28}O_{10}$: C, 54.79; H, 6.78%.

3.4. Rhodiocyanoside A tetraacetate **19a** and its isomer **19b**

(i) A solution of **17** (837 mg, 2.01 mmol) in CH_2Cl_2 (15 ml) was subjected to ozonolysis at −78°C for 2 h and treated with Me_2S (1 ml, 13.6 mmol). The whole reaction mixture was stirred at room temperature for 30 min and evaporated under reduced pressure to provide a crude aldehyde **18**. (ii) NaH (60%, 77 mg, 2.01 mmol) was washed with dry *n*-hexane (5 ml×3) and added to dry THF (8 ml) under an argon atmosphere at 0°C. A solution of diethyl (1-cyanoethyl)phosphonate (384 mg, 2.01 mmol) in dry THF (2 ml) was added to the above mixture and the whole mixture was stirred for 15 min at 0°C. A solution of the crude **18** in dry THF (6 ml) was added to the above reaction mixture and the whole mixture was stirred for 30 min at 0°C. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (30 ml×3). The organic layer was washed with sat. brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica gel (30 g, *n*-hexane:AcOEt (3:2)) to afford **19a** (288 mg, 33% from **17**) as a colorless oil and **19b** (85 mg, 10% from **17**) as colorless needles in elution order. **19a**: $[\alpha]_D^{24}$ −2.65 (c=0.68, MeOH); IR (neat): 2956, 2220, 1752, 1046 cm^{-1}; ^1H NMR: δ 2.00 (3H, d, J=1.5 Hz), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.70–3.74 (1H, m), 4.17 (1H, dd, J=2.4, 12.2 Hz), 4.26 (1H, dd, J=4.9, 12.2 Hz), 4.40–4.53 (2H, m), 4.55 (1H, d, J=7.8 Hz), 5.00 (1H, dd, J=7.8, 9.8 Hz), 5.09 (1H, t, J=9.8 Hz), 5.21 (1H, t, J=9.3 Hz), 6.22–6.26 (1H, m); ^{13}C NMR (MeOH-d_4): δ 172.3 (s), 171.6 (s), 171.2 (s), 171.1 (s), 143.7 (s), 118.0 (s), 113.8 (s), 101.1 (d), 74.2 (d), 73.0 (d), 72.7 (d), 69.8 (d), 68.2 (t), 63.0 (t), 20.7 (q), 20.6 (q), 20.6 (q), 20.6 (q), 20.3 (q); FABMS *m/z*: 428 $(M+1)^+$. Anal. found: C, 52.49; H, 5.92; N, 3.37. Calcd for $C_{19}H_{25}NO_{10}\cdot 1/2H_2O$: C, 52.28; H, 6.01; N, 3.21%. **19b**: Mp 86–87°C; $[\alpha]_D^{23}$ −25.3 (c=0.43, $CHCl_3$); IR (KBr): 2229, 1756, 1647, 1212, 1068 cm^{-1}; ^1H NMR: δ 1.90 (3H, d, J=1.5 Hz), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.71 (1H, ddd, J=2.4, 4.9, 9.8 Hz), 4.16 (1H, dd, J=2.4, 12.2 Hz), 4.25 (1H, dd, J=4.9, 12.2 Hz), 4.28 (1H, ddd, J=1.0, 6.3, 14.2 Hz), 4.44 (1H, ddd, J=1.0, 6.3, 14.2 Hz), 4.54 (1H, d, J=7.8 Hz), 5.01 (1H, dd, J=7.8, 9.8 Hz), 5.09 (1H, t, J=9.8 Hz), 5.21 (1H, t, J=9.8 Hz), 6.38 (1H, dt, J=1.5, 6.3 Hz); FABMS *m/z*: 428 $(M+1)^+$. Anal. found: C, 53.23; H, 5.76; N, 3.14. Calcd for $C_{19}H_{25}NO_{10}$: C, 53.38; H, 5.90; N, 3.28%.

3.5. Rhodiocyanoside A **20a**

A mixture of **19a** (249 mg, 0.58 mmol) and K_2CO_3 (166 mg, 1.2 mmol) in MeOH (10 ml) was stirred for 30 min at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (5 g, $CHCl_3$:MeOH (4:1)) to give **20a** (117 mg, 77%) as a colorless syrup. **20a**: $[\alpha]_D^{26}$ −15.3 (c=0.34, MeOH); IR (KBr): 3397, 2224, 1646, 1075 cm^{-1}; ^1H NMR (MeOH-d_4): δ 1.98 (3H, s), 3.19 (1H, dd, J=7.8, 8.9 Hz), 3.27–3.37 (3H, m), 3.68 (1H, dd, J=4.9, 11.7 Hz), 3.87 (1H, br. d, J=11.7 Hz), 4.30 (1H, d, J=7.8 Hz), 4.43 (1H, dd, J=6.4, 13.7 Hz), 4.55 (1H, dd, J=6.4, 13.7 Hz), 6.46 (1H, br. t, J=6.4 Hz); ^{13}C NMR (MeOH-d_4): δ 145.0, 118.2, 112.6, 104.0, 77.9, 77.9, 74.9, 71.4, 68.4, 62.5, 20.2; FAB MS *m/z*: 260 $(M+1)^+$.

3.6. Rhodiocyanoside A isomer **20b**

A mixture of **19b** (90 mg, 0.21 mmol) and K_2CO_3 (58 mg, 0.42 mmol) in MeOH (4 ml) was stirred for 30 min at room tempertaure. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (5 g, $CHCl_3$:MeOH (4:1)) to give **20b** (48 mg, 87%) as a colorless syrup. **20b**: $[\alpha]_D^{25}$ −23.5 (c=0.34, MeOH); IR (KBr): 3394, 2224, 1646, 1073 cm^{-1}; ^1H NMR (MeOH-d_4): δ 1.91 (3H, d, J=1.5 Hz), 3.19 (1H, dd, J=7.8, 9.3 Hz), 3.27–3.38 (3H, m), 3.64–3.68 (1H, m), 3.88 (1H, br. d, J=11.7 Hz), 4.29 (1H, d, J=7.8 Hz), 4.38 (1H, ddd, J=1.0, 6.4, 14.7 Hz), 4.54 (1H,

ddd, J=1.0, 5.9, 14.7 Hz), 6.53 (1H, ddd, J=1.5, 5.9, 6.3 Hz); ^{13}C NMR (MeOH-d_4): δ 145.4 (d), 120.8 (s), 112.5 (s), 103.9 (d), 78.1 (d), 78.0 (d), 75.0 (d), 71.6 (d), 65.8 (t), 62.7 (t), 15.6 (t); FABMS *m/z*: 298 $(M+K)^+$.

3.7. 2-Methyl-2-propen-1-ol β-D-glucopyranoside **8**

A mixture of **4** (250 mg, 0.83 mmol), 2-methyl-2-propen-1-ol **7** (116 mg, 1.61 mmol), β-glucosidase 17 mg (42.5 unit) in phosphate buffer (pH 5, 8.5 ml) was incubated for 4 h at 30°C. After the reaction mixture was boiled for 5 min and evaporated under reduced pressure, the residue was chromatographed on silica gel (6 g, $CHCl_3$:MeOH (7:1)) to afford **8** (28 mg, 14%) as colorless needles. **8**: Mp 123–125°C; $[\alpha]_D^{25}$ −51.7 (c=0.24, MeOH); IR (KBr): 3434, 1648, 1455, 1380, 1082 cm^{-1}; ^{1}H NMR (D_2O): δ 1.63 (3H, s), 3.14–3.37 (4H, m), 3.58 (1H, dd, J=5.9, 12.2 Hz), 3.77 (1H, dd, J=1.0, 12.2 Hz), 4.08 (1H, d, J=12.7 Hz), 4.15 (1H, d, J=12.7 Hz), 4.33 (1H, d, J=7.8 Hz), 4.88 (1H, s), 4.93 (1H, s); ^{13}C NMR (D_2O): δ 142.3 (s), 114.4 (t), 101.7 (d), 76.6 (d), 76.6 (d), 73.9 (d), 73.9 (t), 70.5 (d), 61.5 (t), 19.5 (q); FABMS *m/z*: 273 $(M+K)^+$. Anal. found: C, 51.12; H, 7.79. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75%.

3.8. Acetylation of **8**

A solution of **8** (55 mg, 0.24 mmol) in pyridine (1 ml, 12.4 mmol), 4-dimethylaminopyridine (10 mg, 0.08 mmol) was treated with Ac_2O (240 mg, 2.4 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (20 ml×3). The AcOEt extract was washed with sat. brine (50 ml) and dried over $MgSO_4$, and filtered. Removal of the solvent gave a residue which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt (2:1)) to give **21** (94 mg, 99%) as colorless prisms. **21**: Mp 108–109°C; $[\alpha]_D^{24}$ −26.8 (c=0.6, $CHCl_3$); IR (KBr): 2950, 1761, 1656, 1226, 1042 cm^{-1}; ^{1}H NMR: δ 1.71 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 3.68 (1H, ddd, J=2.2, 4.7, 9.8 Hz), 4.02 (1H, d, J=12.7 Hz), 4.19 (1H, dd, J=2.2, 12.2 Hz), 4.22 (1H, d, J=12.7 Hz), 4.26 (1H, dd, J=4.7, 12.2 Hz), 4.53 (1H, d, J=7.8 Hz), 4.93 (1H, s), 4.95 (1H, s), 5.04 (1H, dd, J=7.8, 9.3 Hz), 5.01 (1H, t, J=9.8 Hz), 5.21 (1H, t, J=9.3 Hz); FABMS *m/z*: 441 $(M+K)^+$. Anal. found: C, 53.52; H, 6.45. Calcd for $C_{18}H_{26}O_{10}$: C, 53.71; H, 6.52%.

3.9. Osmaronin tetraacetate **23a** and its isomer **23b**

(i) A solution of **21** (137 mg, 0.34 mmol) in CH_2Cl_2 (8 ml) was subjected to ozonolysis at −78°C for 20 min and treated with Me_2S (1 ml, 13.6 mmol). The whole reaction mixture was stirred at room temperature for 30 min and evaporated under reduced pressure to provide a crude ketone **22**. (ii) NaH (60%, 25 mg, 0.61 mmol) was washed with dry *n*-hexane (6 ml×2) and added to dry THF (8 ml) under an argon atmosphere at 0°C. A solution of diethyl cyanomethylphosphonate (108 mg, 0.61 mmol) in dry THF (2 ml) was added to the above mixture and the whole mixture was stirred for 15 min at 0°C. A solution of the crude **22** in dry THF (2 ml) was added to the above reaction mixture and the whole mixture was stirred for 30 min at 0°C. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (20 ml×3). The organic layer was washed with sat. brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt (3:2)) to afford **23a** (32 mg, 22% from **21**) as a colorless oil and **23b** (67 mg, 46% from **21**) as colorless needles in elution order. **23a**: $[\alpha]_D^{28}$ +10.3 (c=0.6, $CHCl_3$); IR (neat): 2221, 1751, 1373, 1231, 1045 cm^{-1}; ^{1}H NMR: δ 1.94 (3H, d, J=1.5 Hz), 1.99 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 3.71 (1H, ddd, J=2.4, 4.9, 9.8 Hz), 4.15 (1H, dd, J=2.4, 12.5 Hz), 4.24 (1H, dd, J=4.9, 12.5 Hz), 4.46 (2H, s), 4.51 (1H, d, J=8.1

Hz), 5.01 (1H, dd, J=8.1, 9.3 Hz), 5.07 (1H, t, J=9.8 Hz), 5.20 (1H, t, J=9.3 Hz), 5.26 (1H, d, J=1.5 Hz); FABMS *m/z*: 428 $(M+1)^+$. Anal. found: C, 52.69; H, 5.74; N, 3.19. Calcd for $C_{19}H_{25}NO_{10}\cdot 1/2H_2O$: C, 52.28; H, 6.01; N, 3.21%. **23b**: Mp 109–110°C; $[\alpha]_D^{26}$ −26.2 (c=0.68, $CHCl_3$); IR (KBr): 2228, 1752, 1376, 1217, 1041 cm^{-1}; ^1H NMR: δ 2.00 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.70 (1H, ddd, J=2.0, 4.4, 9.6 Hz), 4.08 (1H, d, J=15.9 Hz), 4.15 (1H, dd, J=2.0, 12.2 Hz), 4.25 (1H, dd, J=4.4, 12.2 Hz), 4.37 (1H, d, J=15.9 Hz), 4.54 (1H, d, J=8.0 Hz), 5.03–5.12 (2H, m), 5.22 (1H, t, J=9.6 Hz), 5.43 (1H, s); FABMS *m/z*: 428 $(M+1)^+$. Anal. found: C, 53.27; H, 5.76; N, 3.15. Calcd for $C_{19}H_{25}NO_{10}$ C, 53.38; H, 5.90; N, 3.28%.

*3.10. Osmaronin **24a***

A mixture of **23a** (170 mg, 0.4 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in MeOH (4 ml) was stirred for 10 min at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (5 g, $CHCl_3$:MeOH (6:1)) to give **24a** (86 mg, 83%) as a colorless syrup. **24a**: $[\alpha]_D^{26}$ +20.0 (c=0.7, MeOH); IR (KBr): 3388, 2224, 1645, 1383, 1073 cm^{-1}; ^1H NMR (MeOH-d_4): δ 2.03 (3H, d, J=1.5 Hz), 3.23 (1H, dd, J=7.8, 9.3 Hz), 3.29–3.37 (3H, m), 3.70 (1H, dd, J=5.4, 12.2 Hz), 3.88 (1H, dd, J=2.4, 12.2 Hz), 4.29 (1H, d, J=7.8 Hz), 4.46 (1H, d, J=13.2 Hz), 4.56 (1H, d, J=13.2 Hz), 5.46 (1H, m); ^{13}C NMR (MeOH-d_4): δ 162.9 (s), 117.1 (s), 103.9 (d), 97.5 (d), 78.0 (d), 78.0 (d), 74.9 (d), 71.4 (d), 70.6 (t), 62.5 (t), 20.8 (q); FABMS *m/z*: 260 $(M+1)^+$.

*3.11. Osmaronin isomer **24b***

A mixture of **23b** (370 mg, 0.87 mmol) and K_2CO_3 (239 mg, 1.73 mmol) in MeOH (7 ml) was stirred for 20 min at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (5 g, $CHCl_3$:MeOH (7:1)) to give **24b** (212 mg, 94%) as a colorless syrup. **24b**: $[\alpha]_D^{24}$ −17.5 (c=0.51, MeOH); IR (KBr): 3395, 2224, 1645, 1382, 1076 cm^{-1}; ^1H NMR (MeOH-d_4): δ 2.01 (3H, s), 3.23 (1H, dd, J=7.8, 8.8 Hz), 3.27–3.38 (3H, m), 3.65 (1H, dd, J=5.6, 11.7 Hz), 3.87 (1H, d, J=11.7 Hz), 4.23 (1H, d, J=16.9 Hz), 4.28 (1H, d, J=7.8 Hz), 4.43 (1H, d, J=16.9 Hz), 5.75 (1H, m); ^{13}C NMR (MeOH-d_4): δ 162.5 (s), 118.0 (s), 103.7 (d), 95.1 (d), 77.9 (d), 77.8 (d), 74.9 (d), 71.7 (t), 71.4 (d), 62.6 (t), 17.9 (q); FABMS *m/z*: 282 $(M+Na)^+$.

*3.12. 2-Benzyloxy-3-hydroxy-propan-1-ol β-D-glucopyranoside **10***

A mixture of **4** (1 g, 3.32 mmol), 2-benzyloxy-1,3-propanediol **9** (1.2 g, 6.59 mmol), β-glucosidase (93 mg, 232 unit) in phosphate buffer (pH 5, 34 ml) was incubated for 4 h at 30°C. After the reaction mixture was boiled for 5 min and evaporated under reduced pressure, the residue was chromatographed on silica gel (20 g, $CHCl_3$:MeOH (5:1)) to afford **10** (253 mg, 22%) as a colorless syrup. **10**: $[\alpha]_D^{26}$ −3.0 (c=0.37, MeOH); IR (KBr): 3394, 1635, 1343, 1252, 1075 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O): δ 2.96–3.17 (3.5H, m), 3.32–3.90 (7H, m), 4.19 (1H, t, J=7.8 Hz), 4.50–4.68 (2.5H, m), 7.22–7.53 (5H, m); FABMS *m/z*: 383 $(M+K)^+$. Anal. found: C, 53.30; H, 6.96. Calcd for $C_{16}H_{24}O_8.H_2O$: C, 53.03; H, 7.23%.

*3.13. 3-Acetoxy-2-oxopropan-1-ol β-D-glucopyranoside **27***

(i) A solution of **10** (180 mg, 0.52 mmol) in pyridine (2 g, 25.3 mmol), 4-dimethylaminopyridine (10 mg, 0.08 mmol) was treated with Ac_2O (534 mg, 5.24 mmol) and the reaction mixture was stirred for 1 h

at room temperature. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (20 ml×3). The AcOEt extract was washed with sat. brine (50 ml), dried over $MgSO_4$, and filtered. Removal of the solvent gave a crude acetate **25**. (ii) A mixture of the crude **25** and 10% Pd–C (50 mg) in MeOH (7 ml) was subjected to catalytic hydrogenation at ordinary temperature for 2 h and the reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give a residue **26**. A mixture of the crude **26** and PCC (552 mg, 2.1 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 48 h. The reaction mixture was directly subjected to chromatography on Florisil (20 g, AcOEt) to provide a ketone **27** (203 mg, 84% from **10**) as a colorless oil. **27**: $[\alpha]_D^{24}$ −7.55 (c=1.1, $CHCl_3$); IR (KBr): 1752, 1375, 1241, 1044 cm^{-1}; ^1H NMR: δ 2.02 (3H, s), 2.03 (3H, s), 2.09 (3H, s), 2.09 (3H, s), 2.16 (3H, s), 3.72 (1H, ddd, J=2.4, 4.9, 9.8 Hz), 4.13 (1H, dd, J=2.4, 12.5 Hz), 4.26 (1H, dd, J=4.9, 12.5 Hz), 4.30 (1H, d, J=16.9 Hz), 4.36 (1H, d, J=16.9 Hz), 4.57 (1H, d, J=7.8 Hz), 4.86 (2H, s), 5.06 (1H, dd, J=7.8, 9.3 Hz), 5.09 (1H, t, J=9.8 Hz), 5.23 (1H, dd, J=9.3, 9.8 Hz); FABMS *m/z*: 501 $(M+K)^+$. Anal. found: C, 49.26; H, 5.80. Calcd for $C_{19}H_{26}O_{13}$: C, 49.34; H, 5.67%.

*3.14. Sutherlandin pentaacetate **28a** and its isomer **28b***

NaH (60%, 62 mg, 1.56 mmol) was washed with dry *n*-hexane (6 ml×3) and added to dry THF (8 ml) under an argon atmosphere at 0°C. A solution of diethyl cyanomethylphosphonate (287 mg, 1.62 mmol) in dry THF (2 ml) was added to the above mixture and the whole mixture was stirred for 15 min at 0°C. A solution of **27** (500 mg, 1.8 mmol) in dry THF (4 ml) was added to the above reaction mixture and the whole mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (20 ml×3). The organic layer was washed with sat. brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt (3:2)) to afford **28a** (176 mg, 33% from **27**) as a colorless syrup and **28b** (164 mg, 31% from **27**) as a colorless syrup in elution order. **28a**: $[\alpha]_D^{27}$ −2.48 (c=1.1, $CHCl_3$); IR (KBr): 2226, 1752, 1374, 1228, 1048 cm^{-1}; ^1H NMR: δ 2.01 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.10 (3H, s), 2.13 (3H, s), 3.73 (1H, ddd, J=2.0, 4.7, 9.8 Hz), 4.18 (1H, dd, J=2.0, 12.3 Hz), 4.25 (1H, dd, J=4.7, 12.3 Hz), 4.55 (1H, d, J=7.8 Hz), 4.58 (2H, d, J=2.9 Hz), 4.74 (2H, dd, J=2.0, 3.4 Hz), 5.01 (1H, dd, J=7.8, 9.8 Hz), 5.09 (1H, t, J=9.8 Hz), 5.21 (1H, t, J=9.8 Hz), 5.54 (1H, s); FABMS *m/z*: 524 $(M+K)^+$. Anal. found: C, 51.78; H, 5.56; N, 2.78. Calcd for $C_{21}H_{27}NO_{12}$: C, 51.94; H, 5.61; N, 2.89%. **28b**: $[\alpha]_D^{28}$ −23.0 (c=1.1, $CHCl_3$); IR (KBr): 2226, 1752, 1228, 1044 cm^{-1}; ^1H NMR: δ 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 2.13 (3H, s), 3.72 (1H, ddd, J=2.4, 4.4, 9.8 Hz), 4.15 (1H, dd, J=2.4, 12.7 Hz), 4.20 (1H, dd, J=2.0, 15.9 Hz), 4.26 (1H, dd, J=4.4, 12.7 Hz), 4.47 (1H, dd, J=1.8, 15.9 Hz), 4.56 (1H, d, J=7.8 Hz), 4.84 (2H, br. s), 5.04 (1H, dd, J=7.8, 9.3 Hz), 5.09 (1H, t, J=9.8 Hz), 5.22 (1H, t, J=9.8 Hz), 5.62 (1H, br. d, J=1.0 Hz); FABMS *m/z*: 524 $(M+K)^+$. Anal. found: C, 51.64; H, 5.58; N, 2.63. Calcd for $C_{21}H_{27}NO_{12}$: C, 51.94; H, 5.61; N, 2.89%.

*3.15. Sutherlandin **29***

A mixture of **28a** (239 mg, 0.49 mmol) and K_2CO_3 (68 mg, 0.49 mmol) in MeOH (10 ml) was stirred for 30 min at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (5 g, $CHCl_3$:MeOH (4:1)) to give **29** (103 mg, 76%) as a colorless syrup. **29**: $[\alpha]_D^{22}$ −14.6 (c=0.54, MeOH); IR (KBr): 3405, 2227, 1645, 1075 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.97 (1H, dt, J=4.4, 7.8 Hz), 3.07–3.26 (3H, m), 3.46 (1H, dd, J=5.9, 12.0 Hz), 3.67 (1H, dd, J=6.4, 12.0 Hz), 4.15 (1H, d, J=7.8 Hz), 4.22 (2H, d, J=3.4 Hz), 4.37 (1H, d, J=13.0 Hz), 4.50 (1H, d, J=13.0 Hz), 4.51 (1H, d, J=5.9 Hz), 4.93 (1H, d, J=3.9 Hz), 4.98 (1H, d, J=4.4 Hz), 5.10 (1H, d, J=4.9

Hz), 5.38 (1H, t, J=5.4 Hz), 5.72 (1H, br. s); ^{13}C NMR (DMSO-d_6): δ 165.0 (s), 116.5 (s), 102.5 (d), 94.0 (d), 76.9 (d), 76.5 (d), 73.2 (d), 69.8 (d), 66.4 (t), 61.0 (t), 60.8 (t); FABMS *m/z*: 276 $(M+1)^+$.

*3.16. 4-Methoxybenzyl β-D-glucopyranoside **12***

A mixture of **4** (1 g, 3.32 mmol), 4-methoxybenzyl alcohol **11** (463 mg, 3.35 mmol), β-glucosidase (100 mg, 340 unit) in phosphate buffer (pH 5, 34 ml) was incubated for 26 h at 30°C. After the reaction mixture was boiled for 5 min and evaporated under reduced pressure, the residue was chromatographed on silica gel (50 g, $CHCl_3$:MeOH (30:1)) to afford **12** (249 mg, 25%) as a colorless amorphous powder. **12**: Mp 139–140°C; $[\alpha]_D^{26}$ −57.5 (c=0.55, MeOH); IR (KBr): 3338, 2900, 1514, 1075, 1031 cm^{-1}; ^{1}H NMR (pyridine-d_5): δ 3.66 (3H, s), 3.95–4.00 (1H, m), 4.09–4.13 (1H, m), 4.24–4.29 (2H, m), 4.42 (1H, dd, J=5.4, 11.7 Hz), 4.60 (1H, d, J=2.4, 11.7 Hz), 4.81 (1H, d, J=11.2 Hz), 4.98 (1H, d, J=7.8 Hz), 5.13 (1H, d, J=11.2 Hz), 6.95 (2H, d, J=8.8 Hz), 7.48 (2H, d, J=8.8 Hz); ^{13}C NMR (pyridine-d_5): δ 159.7, 130.8, 130.0, 114.1, 114.1, 103.7, 78.6, 78.5, 75.2, 71.7, 70.6, 62.8, 55.2; EIMS *m/z*: 300 M^+. Anal. found: C, 55.98; H, 6.73. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71%.

*3.17. 4-Hydroxyphenethyl β-D-glucopyranoside **14***

A mixture of **4** (600 mg, 1.99 mmol), 4-hydroxyphenethyl alcohol **13** (1.377 g, 9.97 mmol), β-glucosidase (47 mg, 160 unit) in phosphate buffer (pH 5, 20 ml) was incubated for 26 h at 30°C. After the reaction mixture was boiled for 5 min and evaporated under reduced pressure, the residue was chromatographed on silica gel (30 g, $CHCl_3$:MeOH (30:1)) to afford **14** (217 mg, 36%) as colorless needles. **14**: Mp 159–160°C (recrystallized from AcOEt); $[\alpha]_D^{26}$ −28.4 (c=0.5, MeOH); IR (KBr): 3324, 2956, 1520, 1075, 1060 cm^{-1}; ^{1}H NMR (pyridine-d_5): δ 1.54 (3H, s), 1.60 (3H, s), 4.38 (1H, dd, J=11.7, 6.1 Hz), 4.59 (1H, d, J=11.7 Hz), 4.90 (1H, d, J=7.3 Hz), 5.52 (1H, t, J=6.3 Hz); ^{13}C NMR (MeOH-d_4): δ 156.8, 130.9, 130.9, 130.7, 116.1, 116.1, 104.4, 78.1, 77.9, 75.1, 72.1, 71.6, 62.7, 36.4; FABMS *m/z*: 301 $(M+1)^+$. Anal. found: C, 55.63; H, 6.77. Calcd for $C_{14}H_{20}O_7$: C, 55.91; H, 6.71%.

*3.18. Cinnamyl β-D-glucopyranoside **16***

A mixture of **4** (500 mg, 1.66 mmol), cinnamyl alcohol **15** (228 mg, 1.7 mmol), β-glucosidase (30 mg, 102 unit) in phosphate buffer (pH 5, 17 ml) was incubated for 16 h at 30°C. After the reaction mixture was boiled for 5 min and evaporated under reduced pressure, the residue was chromatographed on silica gel (25 g, $CHCl_3$:MeOH (30:1)) to afford **16** (97 mg, 20%) as a colorless amorphous powder. **16**: Mp 114–116°C; $[\alpha]_D^{28}$ −48.8 (c=0.3, MeOH); IR (KBr): 3378, 2924, 1075, 1031 cm^{-1}; ^{1}H NMR (pyridine-d_5): δ 3.95–3.99 (1H, m), 4.12 (1H, t, J=7.8 Hz), 4.24–4.31 (2H, m), 4.40 (1H, dd, J=5.4, 11.7 Hz), 4.48 (1H, ddd, J=1.0, 5.9, 13.0 Hz), 4.58 (1H, dd, J=2.4, 11.7 Hz), 4.75 (1H, ddd, J=1.5, 5.9, 13.0 Hz), 4.98 (1H, d, J=7.8 Hz), 6.48 (1H, dt, J=5.9, 16.1 Hz), 6.78 (1H, d, J=16.1 Hz), 7.24 (1H, t, J=6.8 Hz), 7.31 (2H, t, J=6.8 Hz), 7.41 (2H, d, J=6.8 Hz); ^{13}C NMR (pyridine-d_5): δ 137.4, 132.1, 129.0, 127.9, 126.9, 126.9, 103.9, 78.5, 78.5, 75.2, 71.7, 69.7, 62.8; EIMS *m/z*: 296 M^+. Anal. found: C, 60.29; H, 6.79. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80%.

*3.19. Acetylation of **16***

A solution of **16** (100 mg, 0.34 mmol) in pyridine (1 ml, 12.4 mmol), 4-dimethylaminopyridine (10 mg, 0.08 mmol) was treated with Ac_2O (276 mg, 2.7 mmol) and the reaction mixture was stirred for 1 h

at room temperature. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (20 ml×3). The AcOEt extract was washed with sat. brine (50 ml), dried over $MgSO_4$, and filtered. Removal of the solvent gave a residue which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt (3:1)) to give **30** (154 mg, 98%) as colorless needles. **30**: Mp 81–83°C (recrystallized from *n*-hexane/benzene); $[\alpha]_D^{27}$ −27.6 (c=0.38, $CHCl_3$); IR (KBr): 3430, 2929, 1745, 1228, 1043 cm^{-1}; ^1H NMR: δ 2.01 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.71 (1H, ddd, J=2.4, 4.9, 9.8 Hz), 4.16 (1H, dd, J=2.4, 12.2 Hz), 4.25–4.31 (2H, m), 4.50 (1H, ddd, J=1.5, 5.4, 13.2 Hz), 4.63 (1H, d, J=7.8 Hz), 5.05 (1H, dd, J=7.8, 9.3 Hz), 5.11 (1H, t, J=9.8 Hz), 5.21 (1H, t, J=9.8 Hz), 6.22 (1H, ddd, J=5.4, 6.4, 16.1 Hz), 6.59 (1H, d, J=16.1 Hz), 7.23–7.39 (5H, m); ^{13}C NMR ($CDCl_3$): δ 170.7 (s), 170.3 (s), 169.4 (s), 169.3 (s), 136.3 (s), 133.1 (d), 128.6 (d), 127.9 (d), 126.5 (d), 124.4 (d), 99.5 (d), 72.9 (d), 71.8 (d), 71.3 (d), 69.8 (t), 68.4 (d), 61.9 (t), 20.7 (q), 20.7 (q), 20.5 (q), 20.5 (q); FABMS *m/z*: 503 $(M+K)^+$. Anal. found: C, 59.57; H, 6.14. Calcd for $C_{23}H_{28}O_{10}$: C, 59.47; H, 6.08%.

Acknowledgements

The authors are grateful to Dr. Junichi Kitajima, Showa College of Pharmaceutical Sciences, Japan, for generously giving the spectral data of **6**, **12**, to Dr. Kenichiro Inoue, Gifu Pharmaceutical University, Japan, for generously providing the spectral data of **14** and to Dr. Takao Konoshima, Kyoto Pharmaceutical University, Japan, for generously donating the spectral data of **16**. This work was supported by a grant for the 'Biodesign Research Program' from The Institute of Physical and Chemical Research (RIKEN, Japan) to H.A.

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