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Synthesis of new UV-B light absorbents: (Acetylphenyl)glycosides with antioxidant activities

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ABSTRACT

m-Acetylphenyl-β-D-glucopyranosides and *m*-acetylphenyl-α/β-D-mannopyranosides were synthesized by the Koenigs–Knorr, Mitsunobu, and Helferich reactions as key glycosylation reactions, respectively. Their spectroscopic properties and antioxidative activities were characterized as potential ultraviolet B-ray absorbents.

Ultraviolet (UV) light in the sunlight is an environmental human carcinogen. UV light in sunlight is divided into three regions, viz. UV-A (320–400 nm), UV-B (280–320 nm), and UV-C (200–280 nm). The stratospheric ozone layer effectively blocks UV-C light from reaching the earth's surface. Both UV-A and UV-B light reach the earth's surface in sufficient amounts to give rise to serious biological consequences to the skin and eyes. Although UV-A light is the predominant component of terrestrial UV radiation and believed to be rather weak in the carcinogenesis, excessive exposure to UV-A light causes aging and wrinkling of the skin.[1] On the other hand, UV-B light is known to be absorbed into the skin, producing erythema, burns, and eventually skin cancer as a consequence of DNA damage.

The eye lenses of diurnal primates contain glucosides that act as UV filters. Glucosides **1**–**4** were isolated and their structures identified.[2–5] (3-Acetyl-2-aminophenyl)-β-D-glucopyranoside (**3**: AAP-β-D-Glu) is known to be the precursor of yellow pigments, whose intensity increases with age.[4,6] Therefore, AAP-β-Glu (**3**) containing an acetylaminophenyl group as an aglycon is expected to serve as a UV-A absorbent in sunscreen for cosmetics. It should be noted that an aromatic amino group of a liberated aglycon has been suspected of being venomous. Satoh et al.[6] showed that AAP-β-Glu (**3**) would be involved in photodynamic processes at work in the aging human lens. Moreover, they suggested that photooxidation proceeded with an increase in accumulation of active oxygen generated through the aglycon, and that the active oxygen formed is diminished by the in situ presence of the glycon of the glucoside, acting as an antiphotooxidant. With regard to the antioxidant functions of sugars, West et al. presented the radical scavenger processes for hydroxyl radical ($^{\cdot}OH$).[7] In the sugar species, it has been reported that the antioxidant activity increases in the order glucose < mannose ≤ fructose.[8]

The objective of this study was to develop a new UV-B light absorbent by modification of the glycoside **3**. In taking account of the foregoing context, including the order of the sugar species for antioxidant activity, we synthesized *m*-acetylphenyl-β-D-mannopyranosides (**5**: AP-β-Man) composed of an acetylphenyl group as an aglycon and mannose as a glycon. The removal of the electron-releasing amino group ($-NH_2$) from 2-amino-3-hydroxyacetophenone (AHA) of the aglycon in AAP-β-Glu (**3**) is predicted to give rise to a blue shift of the characteristic absorption band from the UV-A range to the UV-B range. For comparison, *m*-acetylphenyl-β-D-glucopyranosides (**6**: AP-β-Glu) and *m*-acetylphenyl-α-D-mannopyranoside (**7**: AP-α-Man) were also synthesized. The spectroscopic properties such as the UV–vis absorption and fluorescence spectra were probed for the glycosides **5**–**7**. Moreover, their antioxidant activities were evaluated by monitoring the increments of the absorbances at 550 nm responsible for the photogeneration of superoxide anion radical ($O_2^{\cdot-}$) using the cytochrome-*c* reduction assay[9] (see the Supplementary Data for details). The effects of the sugar species and anomer on the physicochemical properties of the glycosides will be discussed below.

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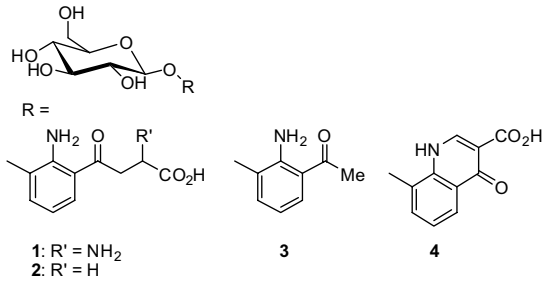
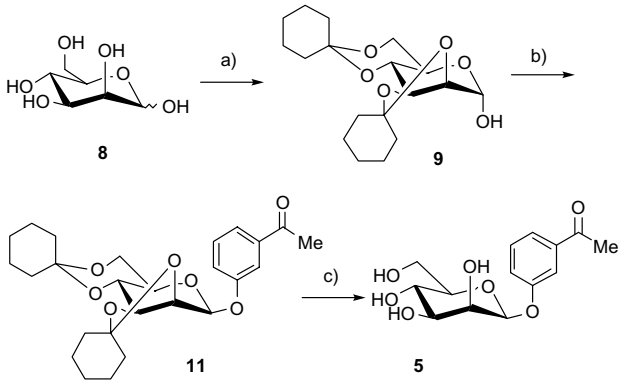


The AP-β-Man **5** was synthesized by the Mitsunobu reaction[10] as a key reaction by a two-step procedure without resorting to chromatographic purification (Scheme 1).[11] First, D-mannose (**8**) was converted to crystalline 2,3;4,6-di-*O*-cyclohexylidene-α-D-mannopyranose (**9**) by reaction with 1-ethoxycyclohexene. The protected mannose **9** was glycosylated with *m*-hydroxyacetophenone (**10**) under the Mitsunobu conditions to produce mannopyranoside **11**, which was hydrolyzed with acetic acid to give AP-β-Man (**5**) in 56% yield.[12]

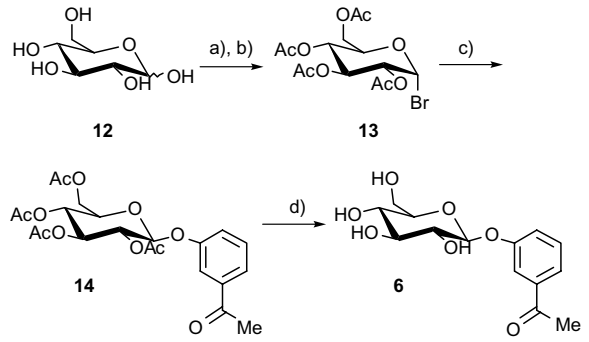
The glucosides **6** were prepared by Koenigs–Knorr glycosylation (Scheme 2).[13] D-Glucose (**12**) was converted to 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**13**) in high yield, which was then glycosylated with *m*-hydroxyacetophenone (**10**) by the Koenigs–Knorr glycosylation to produce β-glycoside **14** (29%). Deprotection of the acetyl groups of **14** with sodium methoxide gave AP-β-Glu (**6**) (60%).[14]

The α-mannopyranoside **7** was prepared by the Helferich reaction[15] as a key reaction (Scheme 3).[16] Treatment of D-mannose (**8**) with acetic anhydride in the presence of pyridine gave the pentaacetate **15** in high yield.[17] The pentaacetate **15** was reacted with **10** upon heating in the presence of $ZnCl_2$ to give α-glycosylated mannose **16** in 41% yield. Deprotection of **16** under basic conditions produced AP-α-Man (**7**) in 30% yield.[18]

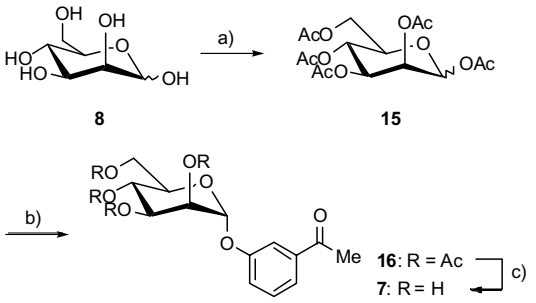
Figure 1 shows the UV–vis absorption spectra of HA (**10**), AP-β-Man (**5**), AP-β-Glu (**6**), and AP-α-Man (**7**), which were measured with a JASCO V-570 spectrophotometer. All the samples including the aglycon HA (**10**) gave absorption spectra with three peaks at around 210, 250, and 300 nm in the UV-B region. Compared with the spectral feature of HA, the glycosides **5**–**7** exhibited blue shifts for each of the peaks, accompanied by a slight hypochromic effect for the band near 300 nm and bathochromic effects for the bands near 210 and 250 nm. Each of the glycosides **5**–**7** has a moderate UV-B absorbance with molar extinction coefficients $\varepsilon_{300} \approx 2000\ M^{-1}\ cm^{-1}$ at 300 nm, regardless of the sugar species and anomer. The ε_{300} values of all the samples are summarized



Scheme 1. Reagents and conditions: (a) 1-ethoxycyclohexene, *p*-TsOH (cat.), DMF 44%; (b) *m*-hydroxyacetophenone (**10**), DEAD, TPP, toluene; (c) AcOH, H_2O 56% in two steps.



Scheme 2. Reagents and conditions: (a) Ac_2O, cat. $HClO_4$; (b) P, Br_2, H_2O; (c) **10**, Ag_2O, $CaSO_4$, pyridine, I_2 29%; (d) NaOMe, MeOH, H_2O, 60%.



Scheme 3. Reagents and conditions: (a) Ac_2O, pyridine; (b) **10**, $ZnCl_2$, AcOH/Ac_2O 150 °C 41%; (c) MeONa, MeOH 30%.

in Table 1, including the antioxidation efficiencies (AO). It should be noted that the ε_{360} value of the AAP-β-Glu (**3**) at 360 nm in the UV-A region is ca. $3400\ M^{-1}\ cm^{-1}$.[4] Typical excitation (Ex) and fluorescence spectra (Em) of AP-β-Man (**5**) in aqueous solution are shown in Figure 2, where the emission wavelength for the former and excitation wavelength for the latter were $\lambda_{em} = 400$ nm and $\lambda_{ex} = 320$ nm, respectively. Likewise, the other glycosides, AP-β-Glu (**6**) and AP-α-Man (**7**) besides HA (**10**) exhibited similar Ex and Em spectra to those of AP-β-Man (**5**). The Ex spectra showed peaks at around 275 and 325 nm, whereas the Em spectra showed a peak at around 400 nm, regardless of the sugar species and anomer.

Table 1 shows the AO values estimated by the following formula (Eq. 1) from the cytochrome-*c* reduction assay[9]:

$$AO(\%) = \left(1 - \frac{\Delta A_{550}}{\Delta A^{o}_{550}}\right) \times 100, \quad (1)$$

where ΔA^{o}_{550} and ΔA_{550} refer to the increments in the absorbances at 550 nm over the reaction time of 1 h for aglycon HA (**10**) and each of the glycosides **5**–**7**. All of the glycosides **5**–**7** show antioxidant activities, in particular, the AO value of AP-β-Man (**5**) is the largest.

It should be noted that the synthesized glycoside **5** has also efficient antioxidant activity for singlet oxygen generated in the photo reaction (based on the squaleneperoxide assay, see the Supplementary Data for details).

In conclusion, new UV-B absorbent glycosides **5**–**7** with efficient antioxidant activity were synthesized. The results show that AP-β-Man (**5**) is expected to serve as a potential UV-B absorbent in sunscreen for cosmetics.[19]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.05.006.

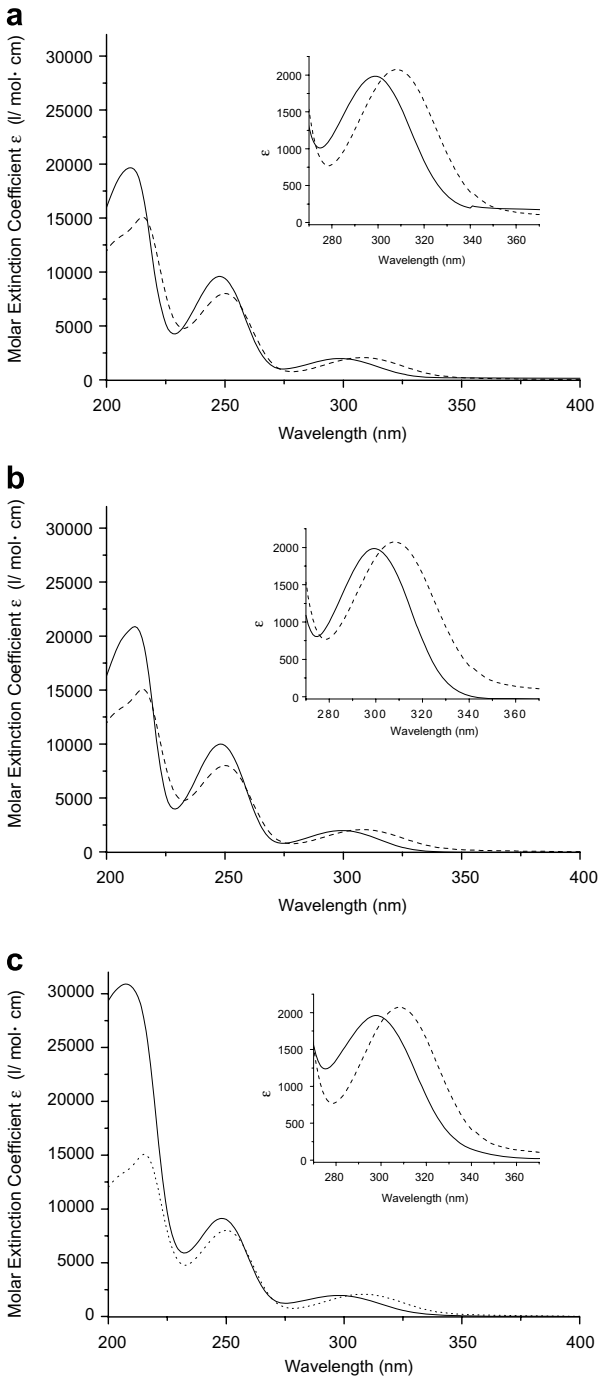


Figure 1. Absorption spectra of glycosides (**5**, a; **6**, b; **7**, c) in solid line and aglycon HA (**10**) in a dashed line. Insets: magnification of UV-B region of spectra.

Table 1
Molar extinction coefficients ε_{300} at 300 nm and degree of antioxidant activity (AO) for HA (**10**) and the glycosides **5**–**7**

Compound	ε_{300} (M^{-1} cm^{-1})	AO (%)
HA (**10**)	1870	0.0
AP-β-Man (**5**)	1946	71.5
AP-β-Glu (**6**)	1982	51.7
AP-α-Man (**7**)	1976	66.9

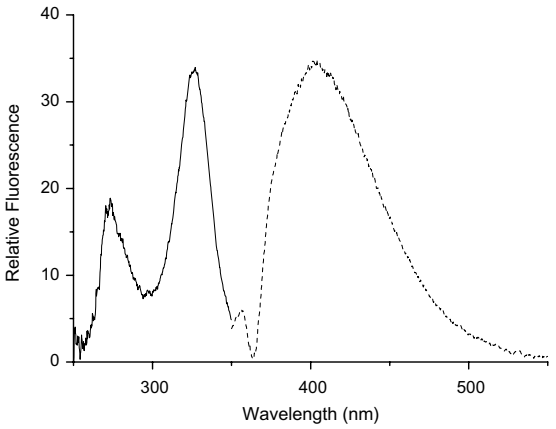


Figure 2. Excitation (solid line) and emission (dashed line) spectra of AP-β-Man (**5**).

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12. **5**: colorless solid, mp 64.4–65.0 °C; ^{1}H NMR (500 MHz, D_2O, δ): 7.72 (d, J = 7.8 Hz, 1H, 4′-H), 7.62 (s, 1H, 2′-H), 7.51 (t, J = 8.0 Hz, 1H, 5′-H), 7.37 (dd, J = 2.6, 8.2 Hz, 1H, 6′-H), 5.41 (s, 1H, 1-H), 4.23 (d, J = 3.3 Hz, 1H, 2-H), 3.92 (dd, J = 2.2, 12.4 Hz, 1H, 6-H), 3.80–3.76 (m, 1H, 3-H), 3.75 (d, J = 6.6 Hz, 1H, 6-H), 3.69 (t, J = 9.8 Hz, 1H, 4-H), 3.62–3.57 (m, 1H, 5-H), 2.65 (s, 3H, CH_3); ^{13}C NMR (150 MHz, D_2O, δ): 203.1 (C=O), 156.3 (C), 137.7 (C), 130.1 (CH), 123.2 (CH), 121.8 (CH), 115.3 (CH), 97.4 (CH), 76.4 (CH), 72.6 (CH), 70.4 (CH), 66.6 (CH), 60.1 (CH_2), 26.2 (CH_3); HRMS-FAB (m/z): $[M+H]^+$ Calcd for $C_{14}H_{19}O_7$, 299.1131; found 299.1129.
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14. **6**: Colorless solid, mp 172.0–173.1 °C; ^{1}H NMR (600 MHz, D_2O, δ): 7.74 (d, J = 7.7 Hz, 1H, 4′-H), 7.66 (s, 1H, 2′-H), 7.53 (t, J = 8.0 Hz, 1H, 5′-H), 7.40 (dd, J = 2.4, 9.1 Hz, 1H, 6′-H), 5.18 (d, J = 7.1 Hz, 1H, 1-H), 3.94 (dd, J = 1.7, 12.4 Hz, 1H, 6-H), 3.74 (dd, J = 6.1, 12.4 Hz, 1H, 6-H), 3.62–3.56 (m, 1H, 5-H), 3.56–3.48 (m, 2H, 2-H and 3-H), 3.50 (t, J = 9.2 Hz, 1H, 4-H), 2.66 (s, 3H, CH_3); ^{13}C NMR (150 MHz, D_2O, δ): 206.8 (C=O), 159.4 (C), 140.8 (C), 133.0 (CH), 126.3 (CH), 124.9 (CH), 118.5 (CH), 102.9 (CH), 79.0 (CH), 78.3 (CH), 75.6 (CH), 72.2 (CH), 63.3 (CH_2), 29.1 (CH_3); HRMS-FAB (m/z): $[M+H]^+$ Calcd for $C_{14}H_{19}O_7$, 299.1131; found 299.1130.
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18. **7**: colorless solid, mp 161.2–162.2 °C; ^{1}H NMR (600 MHz, D_2O, δ): 7.72 (d, J = 3.3 Hz, 1H, 4′-H), 7.69 (s, 1H, 2′-H), 7.51 (dd, J = 7.8, 8.2 Hz, 1H, 5′-H), 7.43 (dd, J = 1.7, 8.2 Hz, 1H, 6′-H), 5.67 (d, J = 1.7 Hz, 1H, 1-H), 4.20 (dd, J = 1.7, 3.7 Hz, 1H, 2-H), 4.06 (dd, J = 3.4, 9.2 Hz, 1H, 3-H), 3.82–3.68 (m, 4H, 4-H, 5-H, and 6-H), 2.65 (s, 3H, CH_3); ^{13}C NMR (150 MHz, D_2O, δ): 203.3 (C=O), 155.5 (C), 137.9 (C), 130.1 (CH), 123.2 (CH), 122.5 (CH), 116.4 (CH), 98.1 (CH), 73.4 (CH), 70.3 (CH), 69.8 (CH), 66.5 (CH), 60.6 (CH_2), 26.3 (CH_3); HRMS-ESI (m/z): $[M+Na]^+$ Calcd for $C_{14}H_{18}NaO_7$, 321.0945; found 321.0934.
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