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Synthesis of the Glycosidic Precursor of Isomeric Marmelo Lactones, Volatile Components of the Quince Fruit, *Cydonia oblonga*

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The glucosidic precursor of marmelo lactones was synthesized by employing a common intermediate which had been used for the synthesis of the glucosidic precursor of marmelo oxides. The synthesis was performed by modifying the former procedure. Monochloroacetyl was adopted to protect both the glucose and aglycon hydroxyl groups for selective transesterification in the presence of the glycosyl ester. Glycosylation of the aglycon carboxyl group with 1-α-bromopermonochloroacetylglucose and final selective alcoholysis yielded the target glucoside.

Key words: quince fruit; *Cydonia oblonga* Mill.; glycosidic precursor; volatile component; selective alcoholysis

Progress in analytical technology has enabled more than 200 kinds of natural glycosidic bound components to be found, including terpenoids and nonterpenoids, and their structures, biosyntheses and roles in the plant kingdom have been elucidated since the 1980s.[1–4]

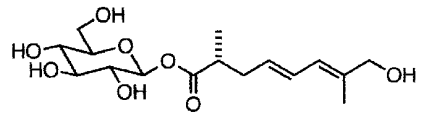
Monoterpene glycosides **1** and **2** are precursors of the main volatile components, marmelo lactones **3** and marmelo oxides **4**, in quince fruit, *Cydonia Oblonga* Mill., which are important for the characteristic odor of this fruit (Fig. 1). In 1991, Schreier and co-workers isolated and characterized the structures of **1**[5] and **2**,[6] and at almost the same time, Näf and Velluz reported several non-glycosidic bound acyclic precursors, including that of **1** and **2**,[7] from an enzymatic hydrolysate of the glycosidic fraction extracted from quince fruit.

Synthetic studies to enable a stable supply of the glycosidic precursors of volatile compounds would be very useful for further research in this area such as revealing the mechanism for generating the volatile components, clarifying the metabolisms and signals in the plant and preparing for future industrial uses. We thus embarked upon the syntheses of compounds **1** and **2**, at the synthesis of **2** already having been achieved and reported.[8] We now report the synthesis of ester glycoside **1** by using a similar strategy.

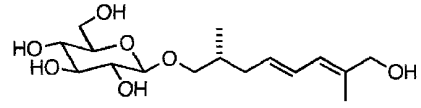
Results and Discussion

As shown in Scheme 1, the acetyl-protected aglycon **6** of **1** was prepared from alcohol **5** which had been used for the synthesis of **2**.[8] A two-step sequence involving Dess-martin oxidation and successive chlorite oxidation enabled alcohol **5** to be converted to carboxylic acid **6**. The glycosylation reaction was initially performed with glucosyl trichloroacetimidate **7** and TMSOTf in the same manner as that for the synthesis of **2**[9] to give glucoside **8** in a 33% yield. However, during deprotection of the acetate groups with methanolic sodium methoxide, the glycosyl ester was simultaneously methanolyzed.

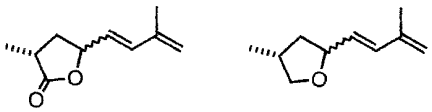
In order to overcome this difficulty, we adopted the monochloroacetyl group instead of the acetyl group for protecting both the glucose and aglycon hydroxyl groups, since monochloroacetate is known to be more labile than acetate during hydrolysis[10] (Scheme 2). Known intermediate **10** for the synthesis of **2**[8] was converted to monochloroacetyl ester **11**. Under strongly acidic or basic conditions such as HF-



Glycosidic precursor of marmelo lactones (**1**)



Glycosidic precursor of marmelo oxides (**2**)



Marmelo lactones (**3**) Marmelo oxides (**4**)

Fig. 1.

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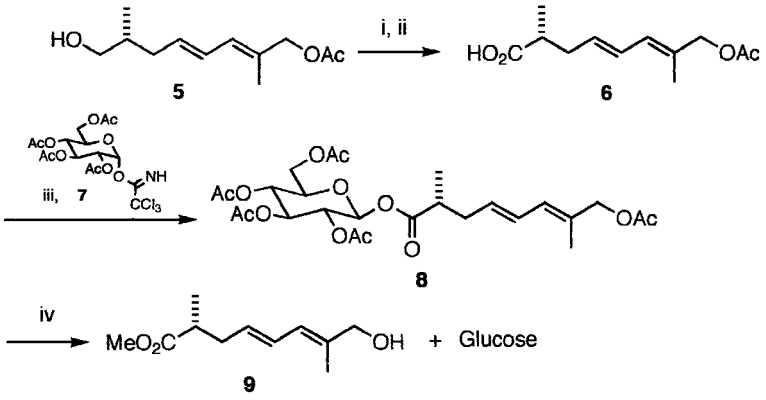
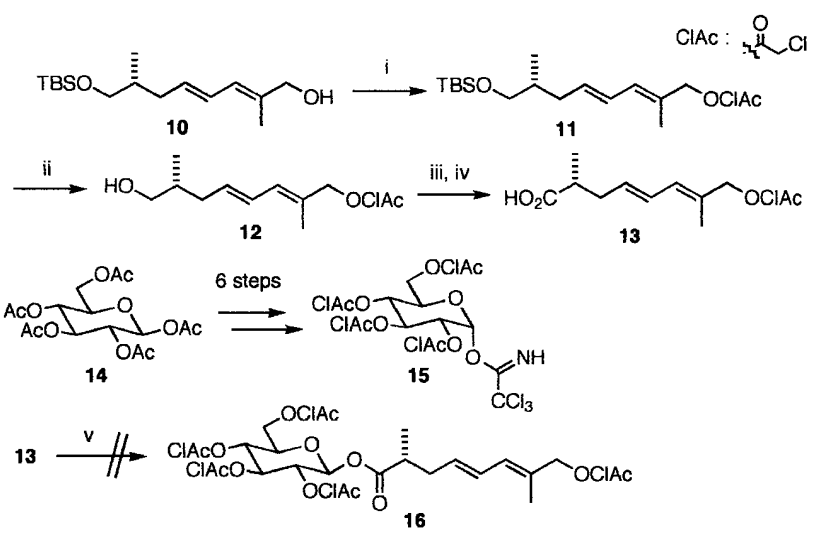


Key: (i) Dess-Martin periodinane, CH_2Cl_2; (ii) $NaClO_2$, KH_2PO_4, $(CH_3)_2C{=}CHCH_3$, H_2O–*t*-BuOH (1:4); (iii) **7**, TMSOTf, MS AW300, CH_2Cl_2, -78°C; (iv) NaOMe, MeOH

Scheme 1.

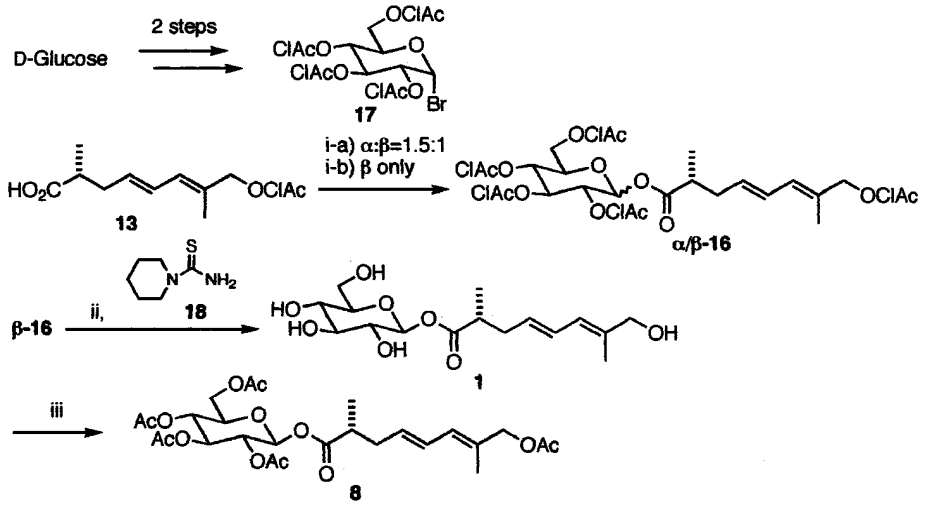


Key: (i) monochloroacetic anhydride, Et_3N, CH_2Cl_2, (ii) AcOH-THF-H_2O (13:7:3); (iii) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2; (iv) $NaClO_2$, KH_2PO_4, $(CH_3)_2C{=}CHCH_3$, H_2O–*t*-BuOH (1:4); (v) **15**, TMSOTf, MS AW300, CH_2Cl_2, -78°C

Scheme 2.

pyridine or TBAF, the diene moiety was isomerized to give an (*E*, *Z*) mixture during desilylation. Consequently, deprotection was carried out with THF–AcOH–H_2O to give pure (*E*,*E*)-**12**,[11] whose hydroxyl group was oxidized with the Dess-Martin reagent and then with sodium chlorite to give carboxylic acid **13**. The gylcosylation reaction was also attempted with **13** and permonochloroacetylated glucosyl trichloroacetimidate **15**,[12] but the adduct decomposed and the desired glycosyl ester could not be obtained. The Mitsunobu reaction was then attempted to couple **13** and **15**,[13] but only a trace amount of the α/β mixture of glucoside **16** was afforded.

We finally examined the coupling of tetra-monochloroacetylglucosyl bromide **17**[14] with aglycon **13** in the presence of Ag_2CO_3 (Scheme 3). The effect of the solvent on the stereochemistry of the product was remarkable and, in the case of methylene chloride, the ratio of glucoside isomers was $\alpha:\beta = 3:2$. In the case of acetonitrile (r.t. for 2d),[15] only β-glucoside **16** (41%) was produced. The last step, deprotection of the monochloroacetyl group, was attempted under various conditions. During the transesterification of **16** with MeOH and ion-exchange resin[16] of the strongly basic type (Dowex 1 × 8 20–50 mesh), the aglycon methyl ester emerged before the glucoside had been completely deprotected. Neither the monochloroacetyl nor glycosyl ester was cleaved with resin of the weakly base type (Amberlite IR-45 or IR-4B). When hydrazine dithiocarbonate was used,[17] deprotection seemed to be successful by TLC observation, although purification was much too difficult since both the product and



Key: (i) a) **17**, Ag_2CO_3, MS AW300, CH_2Cl_2, rt b) **17**, Ag_2CO_3, MS AW300, CH_3CN, rt; (ii) **18**, CH_2Cl_2-MeOH(3:1), rt; (iii) Ac_2O, Pyridine, DMAP, CH_2Cl_2

Scheme 3.

reagents were extremely polar. When thiourea derivative **18** was employed,[18] transesterification was achieved to give **1** in a 79% yield. The total yield was 16% in 6 steps from **10**. The structure of synthetic glycoside **1** was identified by its transformation to the peracetyl derivative. ^{1}H-NMR data for the product were indistinguishable from those of **8**.[5]

In conclusion, we synthesized ester-type glycosidic precursor **1** that had been isolated from quince fruit by employing common intermediate **10** which had also been used for our synthesis of glycoside **2**. In this particular case, the key step was selective removal of the ester protecting groups in the glucosyl moiety by using the more labile monochloroacetyl groups. The synthesis was achieved in a 5.1% overall yield by 13 steps from methyl (*S*)-3-hydroxy-2-methylpropanoate.

Experimental

General experimental procedure. NMR spectra were recorded at 90 MHz by a Jeol JMN-EX90 instrument in $CDCl_3$ and at 300 MHz by a Bruker AC-300 instrument in $CDCl_3$ or MeOH-d_4. IR spectra were measured as films by a Jasco A-102 spectrometer, and HRMS measurements were performed with Jeol JMS-SX102/SX102 and Jeol JMS700 instruments. Optical rotation values were measured by a Jasco DIP 371 polarimeter. Merck Kieselgel 60 (Art. no. 7734) and Kanto Chemical silica gel 60 N were used for column chromatography.

(R,2E,4E)-8-t-Butyldimethylsilyloxy-2,7-dimethyl-2,4-octadien-1-yl chloroacetate (11). To a solution of **10** (0.15 g, 0.522 mmol) in CH_2Cl_2 (3 ml) were added monochloroacetic anhydride (0.464 g, 2.71 mmol) and triethylamine (0.253 ml, 1.08 mmol) while ice-cooling. After stirring for 15 minutes at r.t., the reaction mixture was poured into cooled sat. $NaHCO_3$ aq. and extracted with EtOAc. The organic layer was washed with sat. NaCl aq., dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-Hexane:EtOAc = 35:1) to give 0.190 g (quant.) of **11** as a colorless oil. $[\alpha]_D^{23}$ +1.6° (*c* 0.12, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2955 (S), 1761 (S), 1471 (m), 1255 (m), 1164 (m), 1094 (m), 966 (m), 837 (S), 776 (m), 667 (w). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 0.03 (6H, s, CH_3-Si), 0.86 (3H, d, J=6.8, CH_3-7), 0.89 (9H, s, *t*-Bu-Si), 1.69 (1H, m, H-7), 1.78 (3H, brs, CH_3-2), 1.95 (1H, ddd, J=7.3 and 14.6, H-6a), 2.24 (1H, ddd, J=7.3 and 13.8, H-6b), 3.41 (2H, d, J=6.0, H-8), 4.08 (2H, s, $ClCH_2C(O)$), 4.62 (2H, s, H-1), 5.75 (1H, dt, J=7.1 and 14.3, H-5), 6.17 (1H, d, J=11.3, H-3), 6.22 (1H, dd, J=11.3 and 14.3, H-4). *Anal.* Calcd. for $C_{18}H_{33}ClO_3Si$: C, 59.89; H, 9.21%. Found: C, 59.79; H, 9.03%.

(R,2E,4E)-2,7-Dimethyl-8-hydroxy-2,4-octadien-1-yl chloroacetate (12). Chloroacetate **11** was dissolved in AcOH–H_2O–THF (13:3:7, 40 ml) and stirred for 4.5 h at r.t. The reaction mixture was poured into sat. $NaHCO_3$ aq. and extracted with EtOAc. The organic layer was washed with sat. NaCl aq., dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (*n*-Hexane:EtOAc = 14:1) to give 0.720 g (quant.) of **12** as a colorless oil. $[\alpha]_D^{22}$ +13.0° (*c* 0.12, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3361 (br.s, OH), 2925 (S), 1755 (S), 1454 (m), 1308 (m), 1170 (S), 1035 (m), 967 (m), 759 (w). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 0.92 (3H, d, J=6.7, CH_3-7), 1.75 (1H, m, H-7), 1.78 (3H, s, CH_3-2), 2.02 (1H, ddd, J=6.6 and 13.7, H-6a), 2.24 (1H, ddd, J=6.9 and 13.4), 3.48 (2H, ddd,

J=5.9 and 6.2, H-8), 4.08 (2H, s, $ClCH_2C(O)$), 4.61 (2H, s, H-1), 5.75 (1H, dt, J=7.4 and 15.0, H-5), 6.07 (1H, d, J=10.7, H-3), 6.25 (1H, dd, J=10.7 and 15.0, H-4). *Anal.* Calcd. for $C_{12}H_{19}ClO_3$: C, 58.42; H, 7.76%. Found: C, 58.51; H, 7.68%.

(R,4E,6E)-8-Chloroacetoxy-2,7-dimethyl-4,6-octadienoic acid (13). To a solution of **12** (0.74 g, 2.88 mmol) in CH_2Cl_2 (30 ml) was added Dess-Martin periodinane (1.34 g, 3.17 mmol) while ice-cooling in an N_2 atmosphere. After stirring for 30 min, the reaction mixture was poured into 5% $Na_2S_2O_3$ aq. and extracted with CH_2Cl_2. The organic layer was successively washed with sat. $NaHCO_3$ aq. and sat. NaCl aq., dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (*n*-Hexane:EtOAc=12:1) to give 0.43 g (66%) of an aldehyde as a colorless oil. $[\alpha]_D^{22}$ −3.3° (*c* 0.32, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2932 (S), 2720 (m), 1730 (S), 1455 (m), 1413 (m), 1373 (m), 1309 (m), 1169 (S), 969 (m), 760 (w). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.11 (3H, d, J=6.9, CH_3-7), 1.78 (3H, s, CH_3-2), 2.23 (1H, ddd, J=7.4 and 14.8, H-6a), 2.39–2.58 (2H, m, H-6b and H-7), 4.08 (2H, s, $ClCH_2C(O)$), 4.62 (2H, s, H-1), 5.57 (1H, dt, J=7.4 and 14.8, H-5), 6.06 (1H, d, J=10.2, H-3), 6.26 (1H, dd, J=10.2 and 14.8, H-4), 9.67 (1H, s, H-8). *Anal.* Calcd. for $C_{12}H_{17}ClO_3$: C, 58.90; H, 7.00%. Found: C, 58.66; H, 6.93%.

To a solution of the aldehyde (0.46 g, 1.88 mmol), 2-methyl-2-butene (2.0 ml, 18.8 mmol) and KH_2PO_4 (0.89 g, 6.58 mmol) in H_2O–*t*-BuOH (1:5, 15 ml) was added 85% $NaClO_2$ (0.7 g, 6.58 mmol) with ice cooling. After stirring for 30 min at r.t., the mixture was acidified to pH 3 with 1 N HCl aq. and extracted with $CHCl_3$. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (*n*-Hexane:EtOAc=8:1 +1% AcOH) to give 0.37 g (76%) of **13** as slightly yellow oil. IR ν_{max} (film) cm^{-1}: 3700–3470 (br.m), 2979 (s), 2440–2780 (br.m), 1747 (s), 1712 (s), 1455 (m), 1415 (m), 1371 (m), 1308 (m), 1170 (s), 971 (m), 790 (m). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.20 (3H, d, J=6.8, CH_3-2), 1.78 (3H, s, CH_3-7), 2.31 (1H, ddd, J=7.0 and 13.9, H-3a), 2.47–2.61 (2H, m, H-3b and H-2), 4.09 (2H, s, H-8), 4.62 (2H, s, $ClCH_2C(O)$), 5.71 (1H, dt, J=7.3 and 14.6, H-4), 6.06 (1H, d, J=11.0, H-6), 6.29 (1H, dd, J=11.0 and 14.6, H-5).

(R,4E,6E)-8-Acetoxy-2,7-dimethyl-4,6-octadienoic acid (6). To a solution of **5** (0.1 g, 4.71 mmol) in CH_2Cl_2 (30 ml) was added Dess-Martin perindinane (0.4 g, 0.943 mmol) while ice cooling. After stirring for 15 min, the reaction mixture was poured into 5% $Na_2S_2O_3$ aq. and extracted with $CHCl_3$. The organic layer was successively washed with sat. $NaHCO_3$ aq. and sat. NaCl aq., dried with $MgSO_4$ and concentrated *in vacuo*.

The residue was purified by neutral silica gel chromatography (*n*-Hexane:EtOAc=15:1) to give 0.075 g (76%) of an aldehyde as a colorless oil. IR ν_{max} (film) cm^{-1}: 3035 (m), 2973 (m), 2933 (m), 2717 (m), 1731 (S), 1455 (m), 1374 (m), 1229 (s), 1022 (m), 969 (m), 877 (m). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.11 (3H, d, J=6.8, CH_3-7), 1.77 (3H, s, CH_3-2), 2.08 (3H, s, $CH_3C(O)$), 2.23 (1H, ddd, J=7.3 and 14.6, H-6a), 2.45 (1H, m, H-7), 2.54 (1H, ddd, J=7.3 and 13.8, H-6b), 4.50 (2H, s, H-1), 5.67 (1H, dt, J=7.1 and 14.0, H-5), 6.03 (1H, d, J=10.1, H-3), 6.29 (1H, dd, J=10.1 and 14.0, H=4), 9.65 (1H, s, H=8).

To a solution of this aldehyde (0.075 g, 0.357 mmol) obtained from **5**, 2-methyl-2-butene (0.33 ml, 3.21 mmol) and KH_2PO_4 (0.048 g, 3.57 mmol) in H_2O–*t*-BuOH (1:5, 30 ml) was added 85% $NaClO_2$ (0.131 g, 12.5 mmol) while ice-cooling. After stirring for 12 h, the reaction mixture was acidified to pH 3 with 1 N HCl aq. and extracted with $CHCl_3$. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (*n*-Hexane:EtOAc=10:1 +1% AcOH) to give 0.0578 g (71%) of **6** as a slightly yellow oil. IR ν_{max} (film) cm^{-1}: 3680–3100 (br.m), 2780–2440 (br.m), 2977 (S), 1731 (S), 1456 (m), 1377 (m), 1233 (s), 1023 (m), 970 (m). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.25 (3H, d, J=6.8, CH_3-2), 1.82 (3H, s, CH_3-7), 2.13 (3H, s, $CH_3C(O)$), 2.33 (1H, ddd, J=7.3 and 14.6, H-3a), 2.54 (1H, ddd, J=7.3 and 13.8, H-3b), 2.61 (1H, m, H-2), 4.55 (2H, s, H-8), 5.73 (1H, dt, J=7.5 and 15.0, H-4), 6.08 (1H, d, J=10.9, H-6), 6.35 (1H, dd, J=10.9 and 15.0, H-5).

2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyl (R,4E,6E)-8-acetoxy-2,7-dimethyl-4,6-octadienoate (8). To the suspension of **6** (0.021 g, 0.0928 mmol) and MS AW 300 molecular sieves (ca. 0.01 g) in CH_2Cl_2 (1.0 ml) were successively added **7** (0.117 g, 0.237 mmol) and TMSOTf (2.52 ml, 13.92 mmol) at −78°C. After stirring for 100 min, sat. $NaHCO_3$ aq. was added, and the reaction mixture was allowed to stand at ambient temperature. The mixture was extracted with CH_2Cl_2. The organic layer was washed with sat. NaCl aq., dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by neutral silica gel chromatography (*n*-Hexane:EtOAc=15:1) to give 0.0169 g (32.7%) of **8** as a colorless oil. ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.14 (3H, d, J=6.8, CH_3-2), 1.77 (3H, s, CH_3-7), 2.02, 2.03, 2.04, 2.078, 2.084 (15H, 5s, $CH_3C(O)$), 2.26 (1H, ddd, J=7.3 and 14.6, H-3a), 2.46 (1H, ddd, J=7.3 and 13.8, H-3b), 2.58 (1H, m, H-2), 3.85 (1H, m, H-5′), 4.11 (1H, dd, J=2.2 and 16.9, H-6′a), 4.31 (1H, dd, J=3.8 and 16.9, H-6′b), 4.49 (2H, s, H-8), 5.05–5.31 (3H, m, H=2′, 3′, 4′), 5.57 (1H, dt, J=7.1 and 15.8, H-5), 5.71 (1H, d, J=8.3, H-1′), 6.00 (1H, d, J=9.0, H-3), 6.28 (1H, dd, J=9.0 and 15.8, H=4).

2′,3′,4′,6′-Tetra-O-chloroacetyl-β-D-glucopyranosyl (R,4E,6E)-8-chloroacetoxy-2,7-dimethyl-4,6-octadienoate (16). To a suspension of **13** (0.085 g, 0.328 mmol) and **17** (0.18 g, 0.328 mmol) and MS AW 300 molecular sieves (ca. 0.01 g) in CH_3CN (3.0 ml) was added Ag_2CO_3 (0.055 g, 0.197 mmol). After stirring for 2d at r.t. in the dark, the reaction mixture was filtered, and the filtrate poured into water. The mixture was extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*.

The residue was purified by neutral silica gel chromatography (*n*-Hexane–EtOAc = 7:1) and then treated with Biobead® to give 0.0978 g (41.0%) of **β-16** as a colorless oil. IR ν_{max} (film) cm^{-1}: 3030 (m), 2957 (S), 1768 (s), 1496 (w), 1458 (m), 1411 (m), 1375 (m), 1310 (s), 1157 (S), 1076 (s), 1004 (m), 964 (m), 794 (m), 759 (s), 697 (m). ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.16 (3H, d, J = 6.9, CH_3-2), 1.78 (3H, s, CH_3-7), 2.26 (1H, ddd, J = 7.5 and 15.0, H-3a), 2.47 (1H, ddd, J = 7.5 and 15.0, H-3b), 2.59 (1H, m, H-2), 3.76 (1H, t, H-5′), 3.97, 4.01, 4.03, 4.09, 4.12 (10H, 5s, $ClCH_2C(O)$), 4.30 (1H, dd, J = 3.8 and 15.0, H-6′a), 4.40 (1H, dd, J = 4.1 and 15.0, H-6′b), 4.62 (2H, s, H-8), 5.25 (2H, m, H-2′ and H-3′), 5.40 (1H, t, J = 9.5, H-4′), 5.58 (1H, dt, J = 7.5 and 15.0, H-4), 5.78 (1H, d, J = 8.3, H-1′), 6.05 (1H, d, J = 12.8, H-6), 6.39 (1H, dd, J = 12.8 and 15.0, H-5).

β-D-Glucopyranosyl (R,4E,6E)-8-hydroxy-2,7-dimethyl-4,6-octadienoate (1). To a solution of β-16 (0.06 g, 0.0826 mmol) in CH_2Cl_2–MeOH (3:1, 9 ml) was added thiourea derivative **18** (0.12 g, 0.826 mmol) at r.t. After stirring for 20 h at r.t., the reaction mixture was concentrated *in vacuo* and purified by neutral silica gel chromatography ($CHCl_3$:MeOH = 10:1) in a Sephadex® LH-20 column to give 0.0226 g (79%) of **1** as a colorless oil. $[\alpha]_D^{29}$ +4.59° (*c* 0.165, MeOH). IR ν_{max} (film) cm^{-1}: 3389 (br.s), 2925 (m), 1739 (s), 1633 (m), 1455 (m), 1169 (m), 1075 (s), 705 (w). ^{1}H-NMR δ (MeOH-d_4, 300 MHz): 1.04 (3H, d, J = 6.9, CH_3-2), 1.63 (3H, s, CH_3-7), 2.26 (1H, ddd, J = 7.5 and 15.0, H-3a), 2.39 (1H, ddd, J = 7.5 and 15.0, H-3b), 2.45 (1H, m, H-2), 3.18–3.90 (6H, H-2′, H-3′, H-4′, H-5′, H-6a′b′), 3.84 (2H, s, H-8), 5.34 (1H, d, J = 7.9, H-1′), 5.52 (1H, dt, J = 7.5 and 15.0, H-4), 5.90 (1H, d, J = 10.7 and 15.0, H-6), 6.24 (1H, dd, J = 10.7, H-5). HRFABMS m/z 345.1547 (calcd. for $C_{16}H_{25}O_8$, 345.1549).

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