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Semisynthesis of Abrusoside A Methyl Ester

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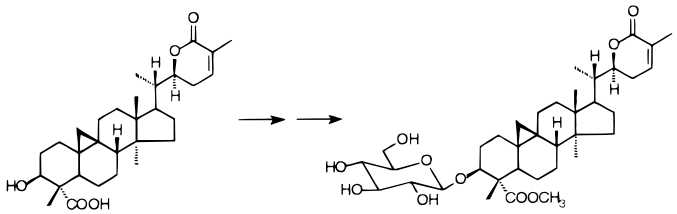
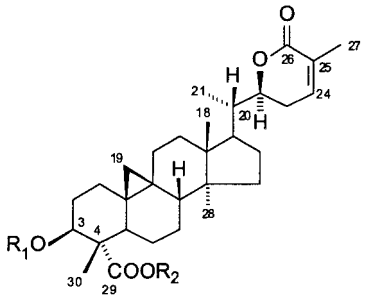
ABSTRACT



Abrusoside A methyl ester (6) was prepared from abrusogenin (1) through methylation (CH_2N_2) and a subsequent coupling reaction with 1-chloro-2,3,4,6-tetra-*O*-acetylglucopyranose (3) in the presence of AgOTf and TMU in CH_2Cl_2, followed by deacetylation using K_2CO_3 in MeOH–H_2O.

Abrusosides A−E have been isolated from the leaves of *Abrus precatorius* L. (Leguminosae) as novel cycloartane-type triterpene glycoside sweet principles.[1−3] The structure and relative stereochemistry of the common aglycon of these compounds, abrusogenin (**1**), were confirmed by single-crystal X-ray crystallography of its methyl ester (**2**) (Figure 1).[1] The sweetness intensity of the abrusoside sweeteners varies from marginally sweet to about 100× sweeter than 2% w/v sucrose, depending on the number and type of saccharide units affixed to C-3 and methylation of the carboxylic acid units of glucuronic acid substituents, when present.[2,3] Therefore, modified glycosylation of abrusosides A−E may increase the sweetness potency of these natural products. To achieve this goal, glucosylation of the hydroxyl group at the C-3 position of abrusogenin (**1**) was attempted using a number of glycosylation methods (Table 1).[4−8] Herein, we report the first successful glucosylation of the sterically hindered hydroxyl group at the C-3 position in ring A of a cycloartane-type triterpene such as abrusogenin methyl



	R_1	R_2
1	H	H
2	H	CH_3
4	2′,3′,4′,6′-tetra-*O*-acetylglucopyranose	CH_3
5	Ac	CH_3
6	D-glucopyranose	CH_3

Figure 1. Structures of abrusogenin analogues and glycosides.

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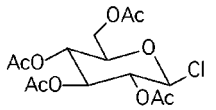
Table 1. Glycosylation of Abrusogenin Methyl Ester (**2**)



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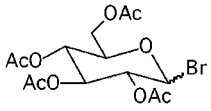

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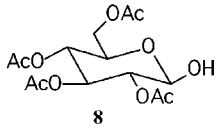

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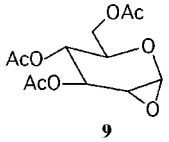

9

saccharide	reagents	conditions	product (yield, %)
3	AgOTf, TMU, THF	rt, 24 h	NR[a]
3	AgOTf, TMU, CH_2Cl_2[4]	rt, 15 h	**4** (52)
7	Ag_2CO_3, toluene	rt, 4 h	NR
8	PPh_3, DIAD, THF[5]	rt, 15 h	NR
9	$ZnBr_2$, THF[6]	−78 °C then rt, 13 h	NR
9	$ZnCl_2$, THF[7]	−78 °C then rt, 13 h	NR
9	AgOTf, TMU, CH_2Cl_2	rt, 168 h	NR
9	AgOTf, TMU, THF	rt, 72 h	NR
9	$AgBF_4$, THF[8]	rt, 72 h	NR

[a] NR: no reaction.

ester (**2**). Apparently, steric hindrance resulting from the presence of a carboxylic acid methyl ester (C-29) and a methyl group at the C-4 position makes the required glycosylation unexpectedly difficult. Due to this steric hindrance, glucosylation was found to be only successful in the present investigation with 1-chloro-2,3,4,6-tetra-*O*-acetylglucopyranose (**3**) in the presence of AgOTf and TMU in CH_2Cl_2. Other glycosylation methods gave no reaction, resulting in full recovery of the starting material.

Abrusogenin (**1**), isolated from *A. precatorius* leaves, was methylated with CH_2N_2 to obtain abrusogenin methyl ester (**2**) in order to protect the C-4 carboxylic acid group. Without the protecting carboxylic acid functionality, glucosylation occurred exclusively at this carboxylic acid position. 1-Chloro-2,3,4,6-tetra-*O*-acetylglucopyranose (**3**) was prepared by the reaction of penta-*O*-acetylglucopyranose (1 g) with $AlCl_3$ (325 mg) in 5 mL of CH_2Cl_2. After stirring the reaction mixture overnight at room temperature, the solvent was removed in vacuo and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was evaporated in vacuo, and the residue was chromatographed over silica gel using petroleum ether−EtOAc (3:1) to afford **3** in 67% yield. To a CH_2Cl_2 solution (2 mL) of abrusogenin methyl ester (**2**, 20 mg) were added 150 mg of **3** in 0.5 mL of CH_2Cl_2 and TMU (60 mg). AgOTf (100 mg) was slowly added to the reaction mixture, and the solution was stirred overnight at room temperature under N_2. The solvent was removed in vacuo, and the residue was partitioned between EtOAc and H_2O. Purification of the dried organic residue by silica gel column chromatography, using petroleum ether−EtOAc (3:1), gave abrusogenin methyl ester 2′,3′,4′,6′-tetra-*O*-acetylglucopyranoside (**4**, 52%)[9] and abrusogenin methyl ester 3-*O*-β-acetate (**5**, 30%). A solvent effect was observed, since glucosylation was successful only when CH_2Cl_2 was used as solvent. When THF was employed in this manner, there was no reaction (Table 1). Treatment of **4** with saturated K_2CO_3 in MeOH−H_2O (10:1) gave deacetylated abrusoside A methyl ester (**6**, 95%).[10] The β-stereochemistry of the substituent at the C-3 position of **6** was confirmed by ^{1}H NMR (J = 13.5 and 4.6 Hz). The stereochemistry of the anomeric proton of the glucopyranosyl group was also assigned as β by ^{1}H NMR (J = 8.3 Hz).

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(9) Mp 286−288 °C; $[\alpha]_D$ +20.5° (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 234 (3.1), 283 (2.9) nm; IR (film) ν_{max} 3421, 2883, 1653, 1418, 1250, 1066, 790 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (1H, d, J = 6.2 Hz, H-24), 5.15 (1H, t, J = 9.6 Hz, H-2′), 5.02 (1H, t, J = 9.7 Hz, H-3′), 4.94 (1H, dd, J = 9.8 and 8.0 Hz, H-4′), 4.49 (1H, dd, J = 11.0 and 2.8 Hz, H-22), 4.47 (1H, d, J = 7.9 Hz, H-1′), 4.25 (1H, dd, J = 12.0 and 5.0 Hz, H-6a′), 4.12 (1H, dd, J = 12.0 and 2.2 Hz, H-5′), 4.06 (1H, dd, J = 12.0 and 4.5 Hz, H-3), 3.70 (3H, s, $COOCH_3$), 2.57 (1H, br t, J = 15.8 Hz, H-23), 2.08, 2.05, 2.02, 1.99 (12H, s, $OCOCH_3$), 1.91 (3H, br s, CH_3-27), 1.26 (3H, s, CH_3-30), 0.99 (3H, d, J = 6.7 Hz, CH_3-21), 0.95 (3H, s, CH_3-18), 0.92 (3H, s, CH_3-28), 0.59, 0.38 (2H, d, J = 4.2 Hz, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8 (C-29), 170.7, 170.3, 169.5, 169.4 ($OCOCH_3$), 166.7 (C-26), 139.7 (C-24), 128.2 (C-25), 102.0 (C-1′), 85.3 (C-3), 80.2 (C-22), 72.7 (C-5′), 71.5 (C-3′), 71.0 (C-2′), 68.7 (C-4′), 62.1 (C-6′), 54.3 (C-4), 51.7 ($COOCH_3$), 48.8 (C-14), 47.6 (C-8), 47.4 (C-17), 45.2 (C-13), 44.9 (C-5), 40.1 (C-20), 35.4 (C-12), 32.6 (C-15), 31.4 (C-1), 29.7 (C-19), 29.6 (C-2), 28.5 (C-23), 27.9 (C-7), 27.5 (C-11), 26.3 (C-16), 25.3 (C-10), 24.9 (C-6), 22.7 (C-9), 20.8, 20.64, 20.63, 20.61 ($OCOCH_3$), 19.3 (C-28), 17.8 (C-18), 17.2 (C-27), 12.8 (C-21), 9.8 (C-30); ESMS (negative-ion mode) *m*/*z* 828 [M]$^-$, 614, 347.

(10) Mp 176−178 °C; $[\alpha]_D$ +3.3° (*c* 0.3, MeOH); UV λ_{max} (log ϵ) 231 (3.1), 279 (2.8) nm; IR (film) ν_{max} 3450, 2921, 2851, 2333, 1699, 1323, 1072 cm^{-1}; ^{1}H NMR (500 MHz, C_5D_5N) δ 6.65 (1H, d, J = 4.7 Hz, H-24), 4.94 (1H, d, J = 8.3 Hz, H-1′), 4.59 (1H, m, H-22), 4.57 (1H, dd, J = 13.5 and 4.6 Hz, H-3), 4.52 (1H, dd, J = 11.4 and 4.0 Hz, H-6a′), 4.43 (1H, dd, J = 12.2 and 5.8 Hz, H-6b′), 4.22 (2H, m, H-3′ and H-4′), 3.95 (2H, m, H-2′ and H-5′), 3.91 (3H, s, $COOCH_3$), 2.45 (1H, m, H-23), 1.94 (3H, br s, CH_3-27), 1.52 (3H, s, CH_3-30), 1.01 (3H, d, J = 6.6 Hz, CH_3-21), 0.93 (3H, s, CH_3-18), 0.82 (3H, s, CH_3-28), 0.53, 0.26 (2H, d, J = 3.8 Hz, H-19); ^{13}C NMR (125 MHz, C_5D_5N) δ 177.4 (C-29), 166.2 (C-26), 140.4 (C-24), 127.8 (C-25), 106.2 (C−1′), 85.6 (C-3), 80.3 (C-22), 78.6 (C-5′), 78.4 (C-3′), 75.2 (C-2′), 71.6 (C-4′), 62.9 (C-6′), 54.6 (C-4), 51.9 ($COOCH_3$), 49.0 (C-14), 48.1 (C-8), 47.8 (C-17), 45.3 (C-13), 44.9 (C-5), 40.1 (C-20), 35.5 (C-12), 32.9 (C-15), 32.1 (C-1), 30.0 (C-9), 29.7 (C-2), 27.9 (C-23), 27.5 (C-7), 26.4 (C-11), 25.7 (C-16), 25.3 (C-10), 23.0 (C-6), 20.1 (C-9), 19.5 (C-28), 18.0 (C-18), 17.3 (C-27), 13.1 (C-21), 10.7 (C-30); ESMS (negative-ion mode) *m*/*z* 659 [M−1]$^-$, 484, 423, 233, 212.