Abrusoside A: a New Type of Highly Sweet Triterpene Glycoside

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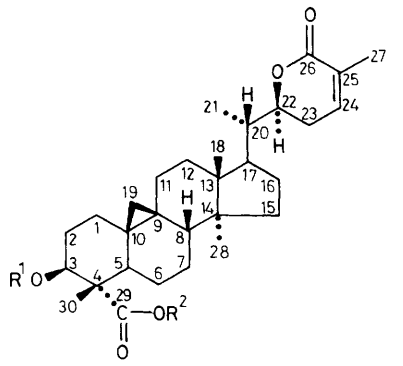
The structure and stereochemistry are reported for abrusoside A (**1**), an intensely sweet glycosidic constituent of *Abrus precatorius* leaves, based on the cycloartenol carbon skeleton.

There is a great deal of interest in the discovery of additional safe noncaloric and noncariogenic dietary sucrose substitutes. In the course of our continuing search for natural intense sweeteners,[1] we have isolated abrusoside A (**1**) from the leaves of *Abrus precatorius* L. (Leguminosae). This plant part was selected for further study when we were unable to confirm previous reports[2] that the oleanane-type triterpene glycoside, glycyrrhizin, was responsible for its sweetness.

Abrusoside A (**1**) (0.033% w/w dry weight) was isolated and purified from an 80% methanolic extract of *A. precatorius* leaves collected in Florida, after concentration into butan-1-ol, and fractionation into $CHCl_3$–MeOH (20 : 3) on chromatography over silica gel. Compound (**1**) crystallized from MeOH as needle-shaped crystals, m.p. 278—280 °C, $[\alpha]_D^{20}$ +11.2° (C_5H_5N, *c* 0.31), t.l.c. R_f 0.39 ($CHCl_3$–MeOH–H_2O, 13 : 7 : 2, lower layer). The elemental formula of (**1**) was established as $C_{36}H_{54}O_{10}$ by high-resolution fast-atom-bombardment mass spectrometry. Hydrolysis of (**1**) with 1 M HCl for 4 h at 100 °C afforded D-glucose and the aglycone, abrusogenin (**2**) {crystallized from MeOH, m.p. 278—280 °C, $[\alpha]_D^{20}$ +37° [$CHCl_3$–MeOH (1 : 1), *c* 0.1]}, which exhibited prominent bands at 3430 (OH) and 1707 cm^{-1} (C=O) in its i.r. spectrum (KBr). The ^1H n.m.r. spectrum (360 MHz, $CDCl_3$ + CD_3OD) of (**2**) indicated, among other resonances, the presence of two cyclopropyl methylene protons (δ 0.39, 0.61) and two low-field protons attached to carbons bearing oxygen (δ 4.09, 4.50). The presence of an α,β-unsaturated δ-lactone ring in the molecule of (**2**) was suggested by resonances at δ 167.13 (s), 140.29 (d), 127.96 (d), and 80.51 (d) in its ^{13}C n.m.r. spectrum (90.8 MHz, $CDCl_3$).[3] In selective induced polarization transfer (INEPT) n.m.r. experiments,[4] irradiation (Δ_1 and Δ_2 for J = 6 Hz) of H(22) (δ 4.50), H_a(23) (δ 2.58), and H(24) (δ 6.63) led, respectively, to three-bond enhancements of the C(17) (δ 47.54) and C(24) (δ 140.29), C(20) (δ 40.02) and C(25) (δ 127.96), and C(22) (δ 80.51) and C(26) (δ 167.13) carbons. The connectivity of the cyclopropyl ring to C(9) and C(10) was suggested by comparison of the ^{13}C n.m.r. and mass spectral data of (**2**) with those of model 9,19-cyclopropyl derivatives.[5] When separately methylated and acetylated under standard conditions, (**2**) afforded the methyl ester derivative (**3**) and the monoacetate (**4**).

Comparison of the ^{13}C n.m.r. spectra of (**1**) and (**2**) indicated that a D-glucopyranoside unit was affixed in the glycoside at C(3). In a further selective INEPT n.m.r. experiment, irradiation of the anomeric proton of (**1**) at δ 5.14 (Δ_1 and Δ_2 for J = 6 Hz) led to a three-bond enhancement at C(3) (δ 85.31). The resonance for the anomeric carbon (δ 105.50) and the ^1H n.m.r. coupling constant (J = 7.7 Hz) of the anomeric proton[6] permitted the configuration of sugar attachment in (**1**) to be assigned as β.

The complete structure and stereochemistry of the aglycone of (**1**) were confirmed by *X*-ray analysis of abrusogenin methyl ester (**3**).† (Figure 1). All the bond lengths and angles of compound (**3**) were normal, and the rings were found to be puckered, as expected. The absolute configuration of this molecule can be determined with reference to those chiral centres that correspond to the asymmetric carbons of cycloartenol.[7] In principle, only one known centre is needed, since



(**1**) R^1 = β-D-Glc; R^2 = H
(**2**) R^1 = R^2 = H
(**3**) R^1 = H; R^2 = Me
(**4**) R^1 = Ac; R^2 = H

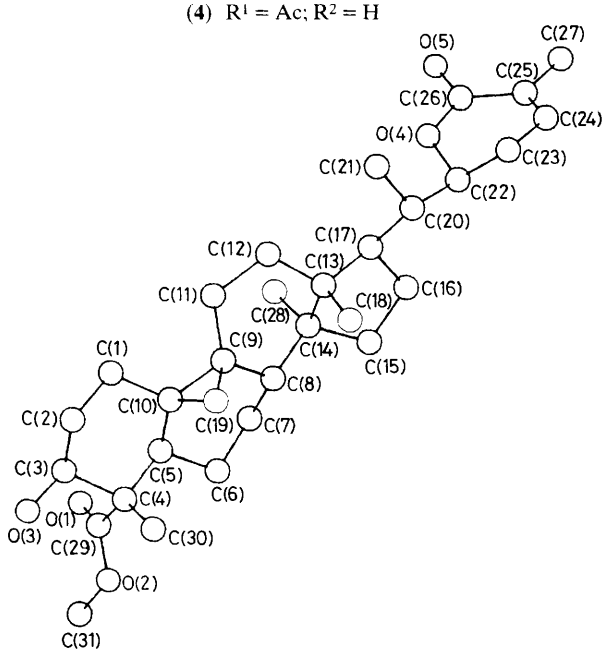


Figure 1. Crystal structure of abrusogenin methyl ester (**3**); hydrogen atoms have been omitted for clarity.

† Abrusogenin methyl ester (**3**) forms colourless prismatic crystals, monoclinic, space group $P2_1$, a = 11.728(3), b = 6.877(2), c = 17.962(4) Å, β = 75.68(39)°, V = 1403.7 Å^3, and Z = 2. The single-crystal *X*-ray diffraction data were collected using an Enraf-Nonius CAD4 diffractometer with Mo-K_α radiation. The structure determination (*via* direct methods) is based upon 1393 independent reflections ($2\theta \leq 50°$) with $I > 3\sigma(I)$. There are two molecules per unit cell and 36 independent atoms in one molecule. Anisotropic refinement for non-hydrogen atoms gave R = 0.073, R_w = 0.073. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

the relative chiralities of all asymmetric centres have been determined by *X*-ray analysis. Thus, since C(9) is known to be of *S* configuration, the other chiral centres in (**3**) were established as C(3) *S*, C(4) *S*, C(5) *R*, C(8) *S*, C(10) *R*, C(13) *R*, C(14) *S*, C(17) *R*, C(20) *S*, and C(22) *S*, respectively. The chiralities of all centres other than the additional asymmetric carbon, C(22), are in agreement with those of cycloartenol.[7]

Abrusoside A (**1**), the 3-β-D-glycopyranoside of (20*S*,-22*S*)-3β,22-dihydroxy-9,19-cycloanost-24-en-26,29-dioic acid δ-lactone, is the prototype member of a new class of triterpene glycoside sweetening agents. It has proven to be innocuous in preliminary acute toxicity tests in rodents and is not mutagenic. Further evaluation of this compound and some naturally occurring analogues is underway.

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