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PREPARATION OF LACTONE DERIVATIVES ON GLYCOSIDATION OF OLEANOLIC ACID UNDER TRIFLIC CATALYSIS

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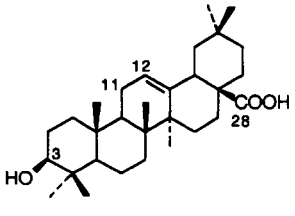
ABSTRACT.—Glycosidation of oleanolic acid, using triflic acid derivatives resulted in the lactonization of the triterpenoid acid.

The triterpenoid saponins form a large group of naturally occurring substances which are widely distributed throughout the plant kingdom (1–3). This rapidly growing class of compounds has attracted increasing interest attributable to its broad spectrum of biological activities. Various saponin derivatives have shown antitumor (4), antifungal (5,6), leishmanicidal (7), and cytotoxic (8) activities.

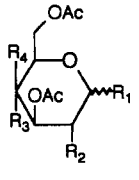
The chemical synthesis of such compounds has not been extensively investigated due to their structural complexity. Two methods have been applied to the glycosidation of triterpenoids: the Koenig-Knorr method (9–13) and the orthoester method (14). These methods give undesirable by-products, require stringent reaction conditions, and use toxic heavy metal salts as catalysts.

Our interest in this field is devoted to the development of new synthetic routes for these compounds. Thus, we have recently reported a new glycosidation reaction of oleanolic and ursolic acid by employing enzymatic catalysis (15). In the present paper, we report our results on the glycosidation of oleanolic acid [**1**], using the 1-*O*-acetyl glycosyl donors **2** or **3** catalyzed by trifluoromethanesulfonic (triflic) derivatives.

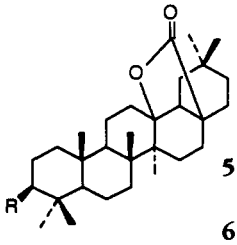
Following the original work on the glycosidation of simple alcohols by 1-*O*-acetyl sugars in the presence of $ZnCl_2$ (16), several Lewis acids have been used as



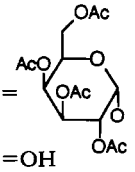
1



2 $R_1=R_2=R_4=OAc$, $R_3=H$
3 $R_1=R_3=OAc$, $R_2=OH$, $R_4=H$
4 $R_1=OH$, $R_2=R_3=OAc$, $R_4=H$



5 R=



6 R=OH

TABLE 1. Glycosylation Conditions for Oleanolic Acid [**1**].

Entry	Glycosyl donor	Catalyst	Temperature	Products, yield (%)
1	**2β**	Tf_2O	−33→25°	**5** (65)
2	**3**	TfOAg	0→20°	**4** (59), **6** (38)

effective promoters of glycosidation, especially for the preparation of disaccharides (17–19). Along these lines, Nakanishi *et al.* (20) reported that the catalytic use of trimethylsilyl triflate (TMSOTf) promoted the galactosidation of the hindered α-hydroxyl (C-7) of cholic acid methyl ester by β-pentaacetylgalactoside.

To our knowledge, the above methods have not been reported in the synthesis of triterpenoid saponins.

We attempted to prepare saponin derivatives of oleanolic acid using 1-*O*-acetyl glycosyl and triflic derivatives. Our results are summarized in Table 1. Thus, treatment of oleanolic acid **1** with β-pentaacetylgalactoside [**2β**] in the presence of triflic anhydride (Tf_2O), at low temperature (−33°) afforded glycoside lactone **5** (Table 1, entry 1).

The structure elucidation of the synthetic lactone **5**, described here for the first time, was accomplished on the basis of spectral properties. The carbonyl stretching region in the ir spectrum (KBr), clearly showed a typical γ-lactone band at 1759 cm^{-1}. The ^{13}C-nmr spectrum of **5** showed signals for one galactoside moiety with an α-configuration (anomeric carbon δ C-1′ 96.2 ppm) (21,22), attached to the C-3 position of the aglycone (δ C-3 89.5 ppm). A signal at δ 178.9 ppm (C-28) indicated an ester linkage (23), confirming the ir interpretation.

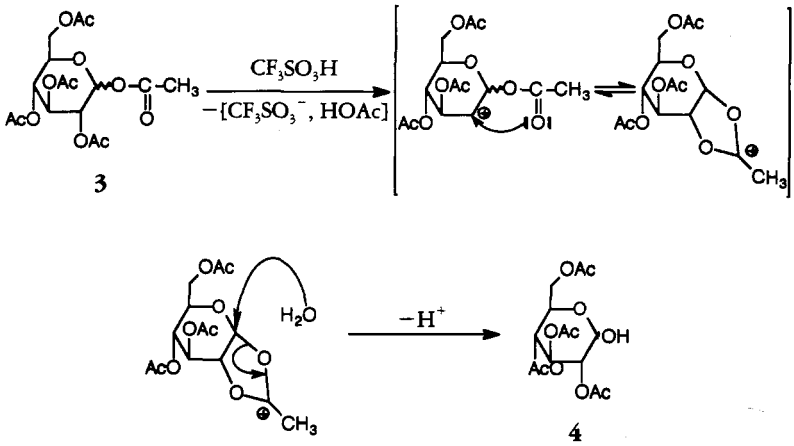
The probable mechanism for the transformation begins with the protonation of the C-12–C-13 double bond of oleanolic acid by triflic acid. The tertiary carbocation obtained would be stabilized by lactonization (24,26) giving the oleanolic lactone **6**. Next, interaction of triflic acid with the anomeric acetyl of **2β** would give a pyranoxonium trifluoromethanesulfonate intermediate which would preferentially accept the nucleophile **6** from the α (axial) side (27), leading to the glycoside lactone **5**.

The result obtained with 1,3,4,6-tetra-*O*-acetyl-D-glucopyranose **3** (Table 1, entry 2) shows that the use of a glycosyl donor without an acyloxy group with electron-withdrawing properties at the C-2′ position ["disarmed sugar" (28,29)], does not give the desired triterpenoid glucoside. We obtained only the triterpenoid lactone **6** (38%) and the transesterified sugar **4** (59%). The ^1H-nmr spectrum of **6** does not show any signals due to olefinic protons; furthermore, under eims (70 eV) the ion at *m/z* 278, characteristic of a retro-Diels-Alder fragmentation of a triterpene unsaturated C-ring, was not observed. On the basis of these spectral data and by comparison with physical data for the lactone isolated from *Hyptis albida* (30), **6** was characterized as 3β-hydroxyolean-28,13-β-olide.

The formation of the oleanolic lactone **6** was probably due to the interaction of the catalyst (TfOAg) with the aglycone to form a complex between a silver cation (Ag^+) and the double bond of oleanolic acid (31), which was stabilized by lactonization to **6**.

The glucosidation of **6** does not take place, because the transesterification of the sugar **3** (Scheme 1) proceeds faster than glucosidation.

Our results agree with those of Oganesyan (32) who has shown that, in H_2SO_4, triterpenoid compounds with a Δ^{12} double bond are protonated at the double bond with the formation of a carbocation, in accordance with the



SCHEME 1. 1,2-Transesterification of the glucosyl donor **3**.

Markovnikov's rule, and when a carboxy group is present at C-28, subsequent lactonization takes place.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All reactions were performed under N_2. The uncorrected mps were determined on a Büchi melting point apparatus. Nmr spectra were recorded with a Bruker AM 200 spectrometer, ^{1}H-nmr spectra at 200 MHz, ^{13}C-nmr spectra at 50.32 MHz ($CDCl_3$, TMS as internal standard). Ir spectra were run as KBr disc pellets with a Nicolet 20 SX spectrophotometer and optical rotations were measured with a Perkin-Elmer 241 polarimeter. Cc was performed on Merck Si gel 60 (230–400 mesh). Merck Kieselgel 60 F_{254} was used for tlc.

The glucosyl donor 1,3,4,6-tetra-*O*-acetyl-D-glucopyranose [**3**] was prepared according to Chittenden's procedure (33). Oleanolic acid [**1**] was isolated from olive leaves (*Olea europaea*) harvested from the area of Marseille, France, in June 1988.

FORMATION OF SAPONIN LACTONE **5**.—Triflic anhydride (Tf_2O) (0.9 ml, 5.3 mmol) was slowly injected to a stirred solution (−33°) of β-D-pentaacetylgalactose **2** (1.4 g, 3.5 mmol) in dry CH_2Cl_2 (15 ml), containing molecular sieves (4 Å). After a few min, a solution of oleanolic acid **1** (500 mg, 1.1 mmol) in dry CH_2Cl_2 (50 ml) was added slowly into the above solution which was stirred at −33° for 4 h. The temperature of the mixture was slowly raised to 25°, and stirring continued for 3 h. Cold H_2O (50 ml) was added, and the mixture was then extracted with CH_2Cl_2. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, and then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on a Si gel column, with $CHCl_3$-Me_2CO (50:3) to give **5** (560 mg, 65%), mp 258–263° (dec); $[\alpha]^{20}D$ +45.3° (*c*=0.5, $CHCl_3$); ir ν max 2946, 1759, and 1226 cm^{-1}; ^{13}C nmr ($CDCl_3$/TMS) δ 96.2, 66.4, 67.9, 64.2, 68.4, 61.9 (C-1′, C-2′, C-3′, C-4′, C-5′, C-6′), 19.6 (C-11), 36.9 (C-12), 90.6 (C-13), 89.5 (C-3), 178.9 (C-28).

FORMATION OF **4** AND **6**.—A solution of oleanolic acid [**1**] (500 mg, 1.1 mmol) in dry CH_2Cl_2 (40 ml) was slowly added to a mixture of 1,3,4,6-tetra-*O*-acetyl-D-glucopyranose [**3**] (51.2 g, 3.5 mmol), silver triflate (TfOAg) (1.3 g, 5 mmol), and molecular sieves (4 Å) in dry CH_2Cl_2 (20 ml), and stirred at 0° for 4 h. After stirring at 20° for 8 h, the mixture was washed with saturated aqueous sodium thiosulfate and H_2O, then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The brown residue obtained was purified by chromatography on a Si gel column, using $CHCl_3$-Me_2CO (50:3), to give **6** as a white solid (190 mg, 38%), mp 274° [lit. (30), 278°], and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose [**4**] as a syrup (710 mg, 59%), $[\alpha]^{20}D$ +71° (*c*=0.8, $CHCl_3$) {lit. (33), $[\alpha]^{21}D$ +67°; lit. (34), $[\alpha]^{20}D$ +75° (*c*=1, $CHCl_3$)}.

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