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Glycosylation of Acids under Phase Transfer Conditions. Partial Synthesis of Saponins.

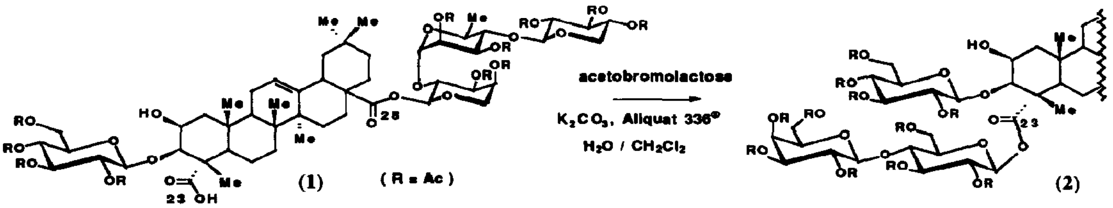
Christophe Bliard*, Georges Massiot and Serge Nazabadioko.

Laboratoire de Pharmacognosie, associé au CNRS, 51 Rue Cognacq-Jay, 51096 Reims, France.

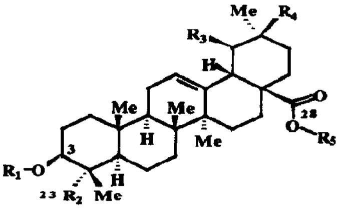
Abstract: β-D-glycosyl esters are prepared in high yields by reaction of various carboxylic acids and acetobromosugars. The reaction uses potassium carbonate under phase tranfer conditions. Deacetylation affords the β-D-glycosyl carboxylates.

As part of a program aiming at synthesizing natural and artificial saponins, we were faced with the problem of the glycosylation of hindered acid positions. One of the solutions in the literature consists of reacting the fragile silver salts of acids with the peracetate of 1-bromo sugars[1]. Yields are modest and reagents expensive. We wish to show that the reaction also proceeds, and with better yields, directly from acids and bromosugars under phase transfer conditions (PTC).

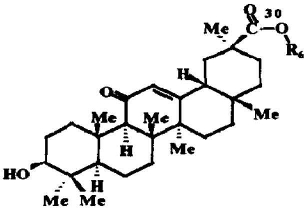
In a typical experiment, the undeca-acetate of medicoside J with a free carboxyl in position C-23 (**1**)[2] (18 mg) was dissolved in 0.2 ml CH_2Cl_2 in the presence of K_2CO_3 (4 mg), water (30 μl), Aliquat 336® (0.2 mg) and the vigorously stirred mixture was treated at room temperature with 10 mg of peracetobromolactose in several fractions. After 48 hours, the reaction was complete and the product (**2**) was isolated in 94% yield[3]. The new compound shows anomeric carbon signals at 100.9 (3C), 97.8 (2C), 92.2 and 92.1 ; the lactose anomeric protons appear at 5.68 and 4.43 ppm as doublets with J = 7 Hz showing that the glycosylation gives a β-D-derivative.



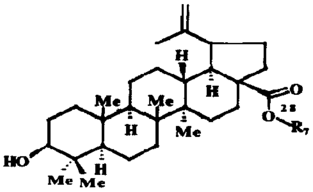
This reaction was extended to acetobromoglucose on different triterpenes bearing hindered acid functions at positions C-28 (α-hederin **4**→hederacoside **5**[4] (84%), oleanolic acid **6**→**7** (96%), ursolic acid **8**→**9** (95%) and betulinic acid **10**→**11** (92%)) and C-30 (glycyrrhizic acid derivatives **12**→**13** (97%). 1-Bromo derivatives of simple sugars (galactose W, gentiobiose X, lactose Y) and of more complex ones (**3**) gave good yields (84 to 95 %) of acyl glycosides on weights from 10 mg up to 2.5 g(**14** - **24**). The glycosyl conjugates were further deacetylated (Et_3N, MeOH, H_2O) without cleavage of the acyl glycoside function (70 to 98%)(**25** -**39**). As an example, glycosylation of oleanolic acid (**6**) with the peracetate of β-D-galactopyranosyl (1->4)-β-D-glucopyranosyl-(1->6)-β-D-glucopyranosyl-(1->6)-α-D-glucopyranosyl-1-bromide (**3**)[5] yielded the tetrasaccharide derivative (**17**, 84%) which was cleanly deacetylated to (**25**, 74%) with no loss of the sugar chain.



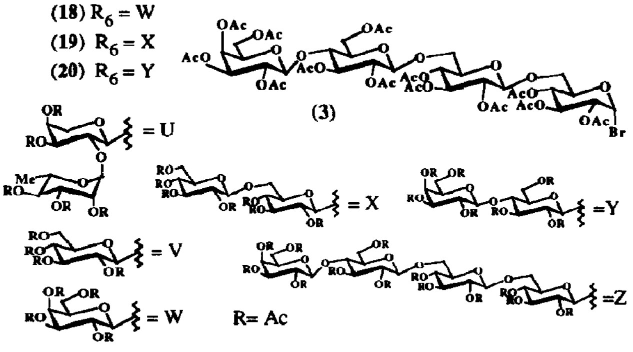
(4) $R_1 = U, R_2 = CH_2OH, R_3 = H, R_4 = CH_3, R_5 = H$
(5) $R_1 = U, R_2 = CH_2OH, R_3 = H, R_4 = CH_3, R_5 = V$
(6) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = H$
(7) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = V$
(8) $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H, R_5 = H$
(9) $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H, R_5 = V$
(14) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = W$
(15) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = X$
(16) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = Y$
(17) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = Z$
(21) $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H, R_5 = W$
(22) $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H, R_5 = X$
(23) $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H, R_5 = Y$
(24) $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H, R_5 = W$
(25) $R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = Z, R = H$



(12) $R_6 = H$
(13) $R_6 = V$
(18) $R_6 = W$
(19) $R_6 = X$
(20) $R_6 = Y$



(10) $R_7 = H$
(11) $R_7 = W$



(26 to 39) are (7), (9), (11), (13), (14-16), (18-20), (21-24) with R=H

Although reactions were run in two phase systems, their success depended on the solubility of the starting acid in the organic layer. Thus no coupling was obtained with partly water soluble acids such as proline, N-Boc-serine or 3 - indolyl acetic acid ; only decomposition of the bromosugar occurred. Excellent yields of glucosylation were obtained with simple aromatic acids (cinnamic acid, 93% ; 2,4,6-trimethoxy cinnamic acid, 94 % ; β-naphtoic acid, 96% ; O-acetyl salicylic acid, 80%) and with long chain acids (oleic acid, 96%; undecanedioic acid, 72%). In all examples β-D derivatives were obtained

The use of PTC in the synthesis of simple glycosides of phenols and in the esterification of acids with highly reactive halides has been reported previously[6]. It is shown here that this reaction is extendable to the glycosylation of complex acids on the gram scale, with high yields and no difficulties in obtaining the pure compounds.

References and notes:

1. Takabe, S. ; Takeda, T. ; Ogihara, Y. *Carbohydr. Res.*,1979, *76*, 101-108. Wulff, G. ; Krüger, W. ; Röhle, G. *Chem Ber.*, 1971, *104*, 1387-1399.
2. Massiot, G. ; Lavaud, C. ; Le Men-Olivier, L. ; Van Binst, G. ; Miller, S.P.F. ; Fales, H.M. *J. Chem. Soc. Perkin Trans I*, 1988, 3071-3079. Timbekova, A.E. ; Abubakirov, N.K. *Khim Prir Soedin.*,1987, 574-577.
3. All new compounds were fully characterized by ^1H and ^{13}C NMR, elemental analysis and mass spectrum of the acetylated (9) to (24) (and/or) deacetylated derivatives (26) to (39).
4. Kawai, H. ; Kuroyanagi, M. ; Umehara, K.; Ueno, A.; Satake, M. *Chem. Pharm. Bull.*, 1988, 4769-4775.
5. Prepared from amygdalin by tritylation, acetylation, coupling with 1-bromo peracetolactose and reaction with NBS according to Bliard, C. ; Massiot, G. ; Nazabadioko, S. *Tetrahedron Lett.*,1993, *34*, 5083-5084.
6. Des, D. ; Kleine, H.P. ; Weinberg, D.V. ; Kaufman, R. J. ; Sidhu, R. S. *Synthesis*, 1981, 883-885. Bocchi, V. ; Casnati, G. ; Dossena, A. ; Marchelli, R. ; *Synthesis*, 1979, 957-961.

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