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A NEW PROTECTED FORM OF GLUCURONIC ACID FOR THE SYNTHESIS OF LABILE 1-O-ACYL-ß-D-GLUCURONIDES

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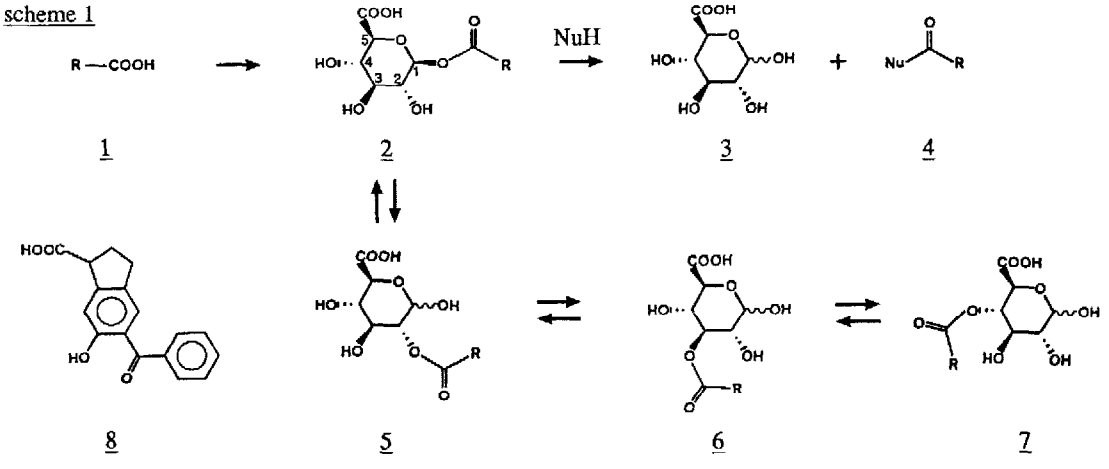
Summary: *A new approach to functionalized 1-O-acyl-ß-D-glucuronides is described. An essential element of this strategy is the use of the easily removable allyloxycarbonyl group for the protection of the hydroxylic functions of glucuronic acid.*

The formation of glucuronides is an important mechanism of conjugation of endogenous and exogenous compounds[1]. The 1-O-acyl-ß-D-glucuronides 2 are the metabolites of carboxylic acids 1 and of primary alcohols previously oxidized. These compounds 2 are sensitive towards electrophiles but are extremely labile towards nucleophiles, making their isolation from biological material very difficult [1,2]. The ester group in the anomeric position (in 2) is much more reactive towards nucleophiles (NuH) than a normal ester[1,3]. Therefore, the anomeric ester group migrates easily to C - (2) and is hydrolyzed very rapidly at pH > 8 (scheme 1). The 1-O-acyl glucuronides can also react with nucleophiles of the cell, a process which is claimed to have many biological implications [1,2,4].

scheme 1



1 2 3 4

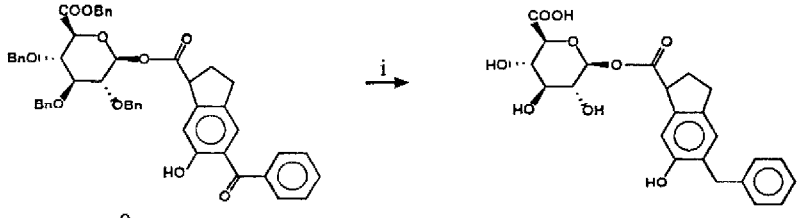
8 5 6 7

NuH = R'OH, R'SH, R'NH_2.

Due to their lability, the synthesis of 1-O-acyl glucuronides has proven to be a difficult task [1-3]. We report here a new approach to these compounds which can be performed on a multigram scale and under very mild conditions, and could, therefore, be of general use. This is illustrated by the synthesis of the acyl glucuronide of 8[5].

Initially we attempted the synthesis of 19 according to the conventional method of Keglevic [3b] using benzylic protection (scheme 2). Although this method proved to be useful in several cases, it is not always compatible with the functionalities present in the aglycone. This exactly was observed in the case of 9 where the deprotection was always accompagnied by reduction of the benzophenone moiety (--> 10, scheme 2). We found, however, that the benzylic ester can be cleaved selectively (scheme 3), but not the benzylic ethers. Therefore, another easily removable protective group for these hydroxylic functions was needed. The trichloroethylcarbonyl group was previously shown to be inadequate[3d]. The zinc complex of an acyl glucuronide was obtained which could not be displaced. Moreover, we found that the benzophenone moiety in 8 is reduced with zinc even at pH = 4 -6[6].

scheme 2



9 10 80%

i = Pd-c (5%), H_2 (1 atm), MeO-CH_2-CH_2-OH, RT, 24 hrs

We propose here the new protected form of glucuronic acid 16 which can be coupled stereoselectively with functionalized aglycons. The allyloxycarbonyl groups can be cleaved under neutral conditions with Pd $(PPh_3)_4$ in the presence of a Pd-π allyl complex scavenger [7,8]. The synthesis of 16 is outlined in scheme 3.

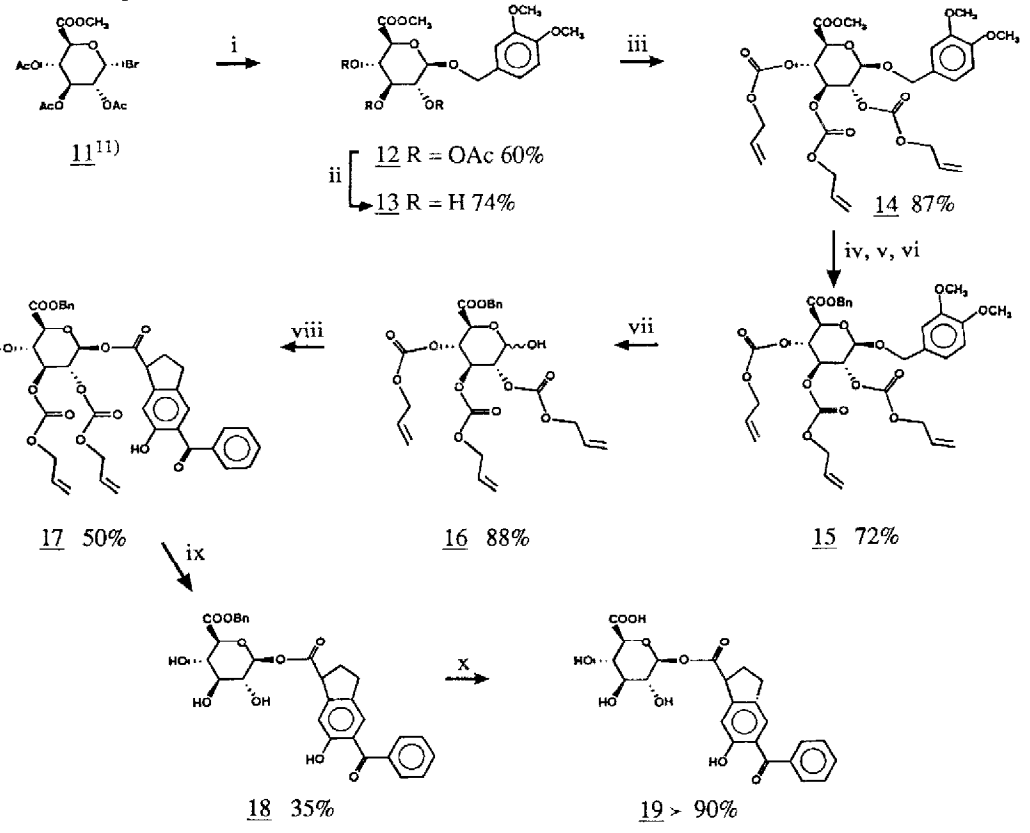
From preliminary experiments we concluded that an easily removable protection for the anomeric position is needed. For example a methyl ether in C -(1) cannot be cleaved in the presence of the allyloxycarbonyl groups [9]. We have chosen the 3,4-dimethoxybenzyl group which can be removed with DDQ [10]. The derivative 12 was obtained by a Koenigs -Knorr reaction with the bromide 11[11]. This reaction was scaled up; 500 g of 12 were isolated after one recrystallisation of the reaction mixture with MeOH[12]. After deacetylation, the allyloxycarbonyl groups were introduced very efficiently using a large excess of allyl chloroformate and pyridine at room temperature [13]. On trying to speed up the reaction with DMAP and NEt_3, a much lower yield of 14 was obtained, the major side product being the corresponding α, ß-unsaturated ester together with cyclic carbonates [14]. The exchange of the methyl ester to the benzylic ester (14 --> 15) was achieved in high overall yield by selective hydrolysis with NaOHaq., treatment with the 1-chloro-N,N,2-trimethylpropenylamine[16] followed by reaction with benzylic alcohol and pyridine. The crucial deprotection of the anomeric center was performed chemoselectively with DDQ.

The stereoselective coupling of 16 with 8 was achieved by a Mitsunobu reaction, in the presence of the free phenolic function, using triphenylphosphine and diisopropyl azodicarboxylate in THF at -50°C [16]. The major ß anomer 17 was isolated in 50% yield after chromatography [17]. The three allyloxycarbonyl groups were removed without affecting the ester function in C -(1) by treatment with $Pd(PPh_3)_4$ and acetylacetone as Pd - π allyl complex scavenger [18]. As juged by ^1H NMR (300 MHz) of the reaction mixture, the desired compound 18 was produced in more than 50% yield, together with some allylic ethers derivatives arising from the direct capture of the Pd - π allyl complex by the incipient alcoxide. The compound 18 can be isolated by recrystallisation, or more

efficiently, by preparative HPLC in 35% yield. When the purified product 18 was left at room temperature in a buffered solution at pH = 6.5, it underwent 80% of acyl migration (scheme 1, 2 --> 5, 6, 7) within 24 hours. This illustrates the lability of these acyl glucuronides [19] but it also underlines the mildness of the deprotection of the allyloxycarbonyl groups. The final cleavage of the benzylic ester was realized with hydrogen and Pd on charcoal as catalyst. Working in a mixture of AcOEt - MeOH (20 : 1), the acyl glucuronide 19 was isolated, on a gram scale, in high yield and did not require any purification [19]. No rearranged product and no reduction of the benzophenone moiety were detected by ^{1}H NMR (300 MHz).

The protected glucuronic acid 16 should find general use, in particular for the synthesis of other complex and labile acyl glucuronides and allow therefore fundamental studies concerning the biological properties of this important class of compounds.

scheme 3



i = 1.7 eq. Ag_2CO_3, 1.5 eq. 3,4-dimethoxybenzyl alcohol, PhH, RT, 72 hrs; ii = 0.1 eq. MeONa, MeOH, RT, 3 hrs; iii = 25 eq., allyl chloroformate, pyridine, RT, 60 hrs; iv = 1.05 eq. NaOH (0.1 N); THF - H_2O (1 : 1), RT, 18 hrs; V = 1.25 eq. Me_2C = C NMe_2Cl, CH_2Cl_2, RT, 1 hr; vi = 1.2 eq. $PhCH_2OH$, 1.2 eq. pyridine, CH_2Cl_2, RT, 24 hrs; vii = 2.6 eq. DDQ, CH_2Cl_2 - H_2O (10 : 1), RT, 24 hrs, 16 α/ß = 75/25 in $CDCl_3$; viii = 1.5 eq. PPh_3, 1.5 eq. i Prop-OOC-N=N-COO-iProp, THF, -50°C, 30 min, then 1 eq. 16, -50°C, 30 min, then 1.3 eq. 8, -50°C, 2 hrs --> RT, 3 hrs, ix = 0.2 eq. Pd $(PPh_3)_4$, 1.3 eq. PPh_3, 15 eq. acetylacetone, THF, RT, 6 hrs; x = Pd - C, H_2 (1 atm), AcOEt - MeOH (20 : 1), 14 hrs.

References and Notes

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5. 8 (Oxindanac) is an analgesic and antiphlogistic discovered in our laboratories: G. Haas, A. Rossi, Swiss Pat. CH 601190 (1974), Ciba-Geigy A.G. The acyl glucuronide 19 was isolated from biological material as one of the main metabolites of 8 : R. Spitzer, T. Winkler, F. Raschdorf, H. Stierlin, unpublished results.
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9. Either no reaction is observed (4 eq. H_2SO_4, Ac_2O, AcOH, RT, 30 hrs) or decomposition of the compound occurred under more drastic conditions.
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12. The major side product is the corresponding ortho ester which is soluble in MeOH.
13. The temperature should be maintained at 25° C during the addition of the allyl chloroformate in order to prevent the formation of the α, ß-unsaturated ester.
14. For the formation of trans cyclic carbonates see W.M. Doane, B.S. Shasha, E.I. Stout, C.R. Russell, C.E. Rist, Carbohydr. Res., 4, 445 (1967).
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17. After reaction α/ß = 18/22 for 17.
18. The excess of acetylacetone is conveniently removed under high vacuum at 25° C.
19. The products 18 and 19 can be stored in the solid state at -20° C.
20. Selected ^{1}H-NMR data (300 MHz, $CDCl_3$, δ(ppm), J(Hz); 15; 4.14 (H_5,d,$J_{4\text{-}5}$ = 9.5); 4.65 (H_1,d,$J_{1\text{-}2}$ = 7.5); 17 (major diastereomer); 4.35 (H_5,d,$J_{4\text{-}5}$ = 9.5); 5.88 (H_1,d,$J_{1\text{-}2}$ = 7.5); 19 (major diastereomer); 4.05 (H_5,d,$J_{4\text{-}5}$ = 5.68 (H_1,d,$J_{1\text{-}2}$ = 7.5).

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