Me), 1.96 (C-8 Me), 2.70 (ABq, J = 6.4, H-14), 2.60 (s, H-5), 3.66 (OMe), 5.66 (br s, H-7); mass spectrum, m/e (relative intensity) 348 (M^+, 6), 333 (3), 320 (6), 275 (4), 224 (100), 192 (14), 164 (16), 150 (40), 123 (22), 109 (37), 95 (34), 69 (19).

Keto Ester 6 from 11. Basic alumina (500 mg) was added to a stirred solution of **11** (84.1 mg) in CH_2Cl_2 (15 mL). After 3 h of heating at reflux the mixture was filtered and the solvent evaporated. The residue (80.5 mg, 96.5%) was shown to be pure **6** by TLC analysis.

Methyl 6β-Hydroxygrindelate (7b). To a solution of **6** (163 mg, 0.47 mmol) in dry Et_2O (20 mL) was added an ethereal solution of $Zn(BH_4)_2$. The mixture was stirred for 4 days at room temperature and under N_2. After the addition of a HOAc (2 mL)–Et_2O (10 mL) solution and H_2O under ice cooling, the mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Chromatography of the residue (151 mg) over silica gel (10 g) with hexane and with mixtures of hexane and increasing amounts of EtOAc resulted in the recovery of starting material **6** (30.6 mg) and the isolation of **7b** (49 mg) and traces of **7a** (TLC). The oily hydroxy ester **7b**: $(\alpha)_D$ −136.7 (c 0.7 $CHCl_3$); IR ($CHCl_3$) 3690, 3615, 3000–2860, 1735, 1610, 1450, 1380, 1350, 1320, 1150, 1035, 1020, 980, 950, 880 cm^{-1}; ^1H NMR δ 1.07, 1.30, 1.32 (C-4, C-10 and C-13 Me), 1.83 (C-8 Me), 2.63 (ABq, J = 14.5, H-14), 3.65 (OMe), 4.37 (m, H-6), 5.50 (br dd, H-7); MS, m/e (relative intensity) 332 ($M^+ - H_2O$, 39), 317 (5), 299 (4), 247 (4), 200 (13), 197 (10), 187 (100), 171 (10), 145 (18), 105 (10), 91 (7); found for M^+, 350.2423 ($C_{21}H_{34}O_4$ requires 350.2457) and found for $M^+ - H_2O$, 332.2387 ($C_{21}H_{32}O_3$ requires 332.2351).

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Registry No. **1a**, 1438-57-9; **1b**, 1438-58-0; **2a**, 92471-20-0; **3a**, 79491-96-6; **4**, 79491-99-9; **5**, 92420-60-5; **6**, 80865-71-0; **7a**, 80931-20-0; **7b**, 80952-80-3; **8**, 92420-61-6; **10** (isomer 1), 92420-62-7; **10** (isomer 2), 92471-21-1; **11**, 92420-63-8; **12**, 92456-15-0.

A Novel Method for Stereoselective Glucuronidation

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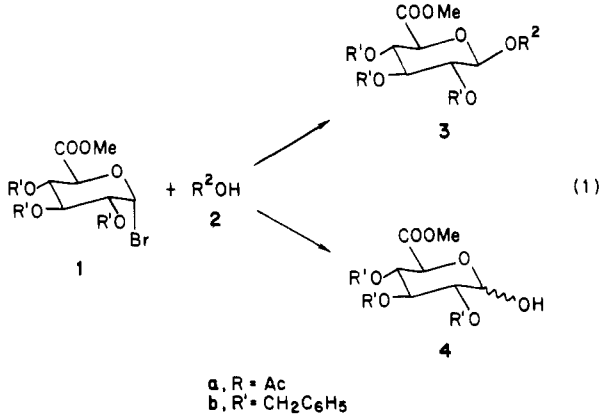
A variety of hydroxylic aglycones can be glucuronidated directly with methyl 2,3,4-tri-*O*-acetylglucopyranuronate (**4a**), activated with trimethylsilyl trifluoromethanesulfonate (Me_3Si–OTf). This reaction provides mostly β, and sometimes α, glucopyranosiduronic acid derivatives (referred to as glucuronides) rapidly and at low temperatures. The epimeric ratio depends on the relative aglycone nucleophilicity vs. its tendency to form a stabilized carbocation by the formal loss of –OH. Glucuronides of various aromatic and aliphatic aglycones as well as those of a number of cyanohydrins were prepared. The characteristic features of the ^1H NMR spectra of α and β derivatives which are presented are useful in the assignment of product stereochemistry and determination of epimeric ratios in those reactions where mixtures are obtained.

The synthesis of glucopyranosiduronic acid derivatives (referred to as glucuronides) is most frequently carried out via the Koenigs–Knorr reaction or its modifications (eq 1)[1] in which the electrophilic character of the anomeric bromide **1** is enhanced by a halophilic agent (such as silver carbonate, mercuric oxide, cadmium carbonate, etc.) that facilitates nucleophilic substitution by the aglycon **2**, leading to glucuronide **3**. The main drawbacks of these procedures are the instability of the bromo derivatives **1**[2] (which have a rather limited shelf life even at 0 °C), the need for elevated reaction temperatures and frequently prolonged reaction times, and the ubiquitous formation of hemiacetals **4** as hydrolysis side products of **1**. Some of these difficulties have been elegantly circumvented by modifying the leaving group. For example, the conversion of **4b** into the imidate **5b**, followed by activation with boron trifluoride allowed stereospecific reactions with various aglycones to give the corresponding β-glucuronides (eq 2).[3] However, this procedure also suffers from the necessity of preparing the reactive starting material, which has a limited stability and hydrolyzes quite readily to **4b**. Obviously, it would be highly desirable to carry out the glucuronidation directly on the stable free hydroxy derivatives **4**.



(1)

(1) (a) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957. (b) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243. (c) Keglevič, D. *Adv. Carbohydr. Chem. Biochem.* **1979**, *36*, 57.

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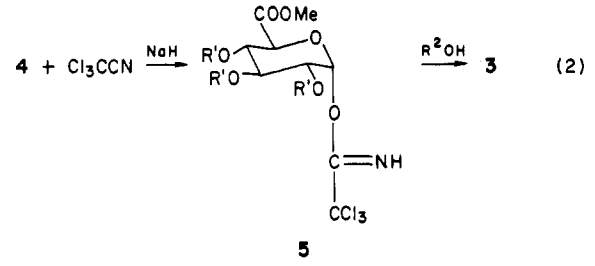

5

Surprisingly, although some glucosides have been prepared by direct coupling of aglycones to 1-hydroxy sugars in the presence of Lewis acids,[4] there has been nearly no interest in investigating the analogous approach for obtaining glucurondes. Since naturally occurring glucuronides are β derivatives,[5] the reticence in using **4a** as a starting material may have stemmed from a concern that the undesired α derivatives would probably be obtained, because an α stereochemistry has been generally assigned to **4a**.[6] Indeed, only one instace[6c] of the direct use of **4a** to synthesize a glucuronide has been reported, and the product obtained did have α stereochemistry.

We now report a facile, low temperature, rapid glucuronidation procedure starting from the stable hemiacetal **4a** that employs trimethylsilyl trifluoromethanesulfonate (Me_3Si–OTf) **6** as an activating agent (eq 3). This reaction

$$\mathbf{4a} + R^2OH + \underset{\mathbf{6}}{Me_3SiO\text{–}SO_2CF_3} \rightarrow \mathbf{3a} \qquad (3)$$

taken together with a simple synthesis of **4a** developed in our laboratories[6e] provides a very convenient general apparoach for glucuronide synthesis.

Results and Discussion

The general procedure for the glucuronidation involves addition of **6** to an equimolar solution of **4a** and the desired aglycon **2** in a nonpolar solvent. The reaction proceeds in the course of several hours at temperatures between −15 and 20 °C, and the products may be readily purified by flash chromatography. The wide applicability of the method is demonstrated by our preparation of a variety of glucuronides of aromatic and aliphatic aglycones including cyanohydrin derivatives (Table I). The ability to prepare cyanogenic glucuronides is a clear advantage of this approach since previous attempts to directly glucuronidate cyanohydrins by the standard Koenigs–Knorr approach failed. The cyanohydrins can not survive the reaction conditions and decompose to the carbonyl compound and hydrogen cyanide before glucuronidation takes place. This problem has recently been circumvented by a multistep procedure[7] in which the synthesis of compound **3r-β** was carried out via a Kenigs–Knorr glucuronidation of mandelamide, followed by dehydration of the amide to the corresponding nitrile. The examples given in Table I (entries 9–13) illustrate the mildness of our method, which

Table I. Glucuronide Derivatives 3

entry	aglycone R^2OH	reactn time	reactn temp, °C	product (% yield)	ratio of anomers, % α	% β	mp, °C	$[\alpha]^{25}_D$, deg ($HCCl_3$)	MS selected ions (70 eV) M + 43[a]	(M + 1)/(M + 29)	M − 59	analysis compd	calcd	found
1	Ph_2CHOH	30 min	−15	**3a** (91)	100		154	+145.6			441[b]	$C_{28}H_{28}O_{10}$	C, 62.39; H, 5.64	C, 62.05; H, 5.61
2	PhCHOHMe	30 min	0	**3b** (40)	86	14	oil							
3	$PhCH_2OH$	25 min	0	**3c** (57)		>98	137	*d*						
4	Br_3CCH_2OH	3 h	0	**3d** (22)		100	156	−17.81	600 (m + 1)[b]					
5	F_3CCH_2OH	3 h	0	**3e** (68)		100	147	−18.15	445 (m + 29)[b]		357[b]	$C_{15}H_{19}O_{10}F_3$	C, 43.27; H, 4.60	C, 43.44; H, 4.70
6	Me_2CHOH	3 h	0	**3f** (53)	~20	~80	137	*d*						
7	PhOH	2 h	25	**3g** (16)	26	74	115	*e*						
8	*p*-MeC_6H_4OH	1 h	0	**3h** (55)		100	138	*e*						
9	MeCHOHCN	2.5 h	0	**3i** (19)		100	138	−4.0	430[c]		328[c]	$C_{16}H_{21}NO_{10}$	C, 49.61; H, 5.42	C, 49.54; H, 5.45
10	$MeCH_2CHOHCN$	2.5 h	0	**3j** (16)		100	147	+21.66	444[c]		342[c]			
11	$Me_2CHCHOHCN$	2 h	0	**3k** (25)		100	127	−34.67	458[c]		356[c]	$C_{18}H_{25}NO_{10}$	C, 52.04; H, 6.02	C, 52.20; H, 6.19
12	Me_2COHCN	1 h	25	**3l** (25)		100	102	−31.27			342[c]	$C_{17}H_{23}NO_{10}$	C, 50.87; H, 5.78	C, 50.90; H, 5.88
13	PhCHOHCN	3 days	4	**3m** (21)		100	145.5	−44.40[f]	492[c]		390[c]			

[a] Characteristic M + 43 peak for polyacetylated sugars.[16] [b] Chemical-ionization spectra. [c] Electron ionization. [d] See ref 17. [e] See ref 2. [f] See ref 7; $[\alpha]^{25}_D$ −40.4° (CH_3OH).

(4) (a) Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1968**, *51*, 1631. (b) Koto, S.; Sato, T.; Morishima, N.; Zen, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1761. (c) Tsutsumi, H.; Ishido, Y. *Chem. Rev.* **1981**, *88*, 61. (d) Lacombe, J. M.; Pavia, A. A. *J. Org. Chem.* **1983**, *48*, 2557.

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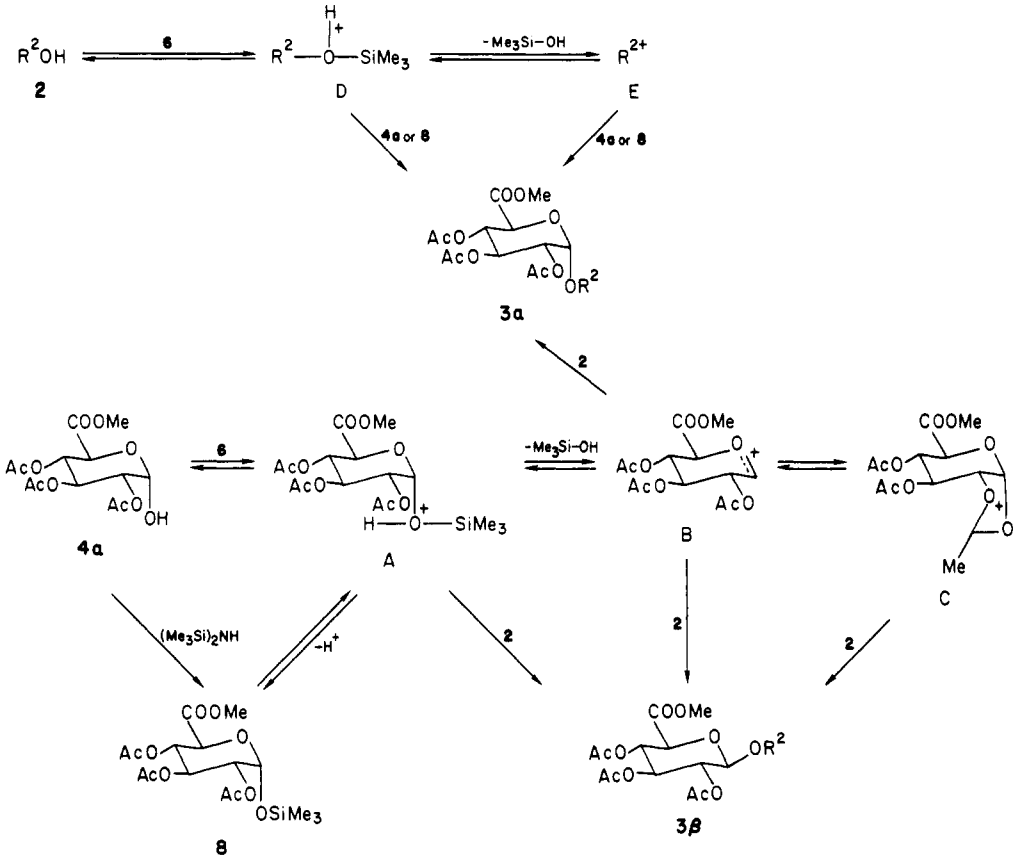
(6) (a) Ishidate, M.; Nakajima, T. *Chem. Pharm. Bull.* **1958**, *6*, 433. (b) Pravdić, N.; Keglević, D. *J. Chem. Soc.* **1964**, 4633. (c) Braun, H.; Weissler, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 400. (d) Compernolle, F. *Carbohydr. Res.* **1980**, *86*, 177. (e) Herzig, J.; Nudelman, A.; Fischer, B.; Keinan, E., unpublished results. Israel Patent Application pending. (f) From the 270-MHz NMR spectrum of **4a**, it can be clearly seen that this compound consists of ca. a 4:1 mixture of α/β epimers.

(7) Junghans, B. *Pharmazie* **1982**, *37*, 172.

Scheme I



enables direct formation of cyanohydrin glucuronides.

The results shown in Table I support a mechanism which is essentially an acid-catalyzed etherification. The ratio of the epimeric products (α and β anomers) produced (as estimated by ^{1}H NMR) depends largely on the aglycon used and reflects the net effect of two counteracting properties: (a) aglycon nucleophilicity and (b) its tendency to form a stabilized carbocation resulting from a formal loss of an -OH group. A likely reaction pathway is shown in Scheme I. Initial reaction of **4a** with the powerful silylating agent Me_3Si–OTf may give the oxonium ion A which can undergo rapid nucleophilic displacement of TMS-OH by the aglycon **2**, yielding the 3β-glucuronide. This is the case in most of the reactions carried out at -15–0 °C. However, with aglycones of lower nucleophilicity such as phenol (entry 7), where the reaction does not proceed below room temperature, A can undergo initial ionization to the oxo–stabilized cation B or to the anchimerically stabilized cation C.[8] Reaction of **2** with C will still give the β products, whereas nucleophilic attack of **2** on B may proceed nonstereospecifically to give a mixture of the two epimeric glucuronides 3α and 3β. Nucleophiles weaker than phenol (e.g., *m*- or *p*-nitrophenol) do not form glucuronides under these conditions. It appears that for phenolic compounds the limit of reactivity under the usual reaction conditions (i.e., between -15 and 0 °C) resides at a pKa of ca. 10 and above. Phenols with pKa's of ca. 9 however, are still reactive at 25 °C, but more acidic phenols fail to react even at room temperature.

Further support for a mechanism involving initial silylation of the anomeric hydroxyl rests on the isolation of the α-silylated glucuronide side product **8**, whose concentration increases as the nucleophilicity of the aglycon decreases. This side product is probably obtained via a proton loss from intermediate A. An authentic sample of **8** was prepared by direct silylation of **4a** with hexamethyldisilazane.[9,10] It has also been shown that an analogous silylated glucoside may serve as a starting material together with a silylated aglycon for a Me_3Si–OTf-catalyzed glycosidation.[11] An alternative pathway may be followed when the aglycon can form a stabilized cation such as D or E, as is the case with benzhydrol **2** and to a lesser extent with *sec*-phenethyl alcohol (**2b**) and 2-propanol (**2c**). Thus, the anomeric hydroxyl and the aglycon may switch roles of electrophile and nucleophile and the reaction may then proceed totally or in part by nucleophilic attack of **4a** or **8** on E, yielding the α-glucuronides. An analogous example of nucleophilic attack by a glucosidic hydroxyl on a stabilized carbocation was reported recently by Tietze.[12] Benzyl alcohol, which can form the corresponding cation E more readily than 2-propanol, did not, however, give detectable amounts of the expected α-glucuronide. The formation of a stereochemically pure β derivative may result from the greater nucleophilicity (due to lower steric demands) of benzyl alcohol as compared with secondary alcohols. Interestingly, although the hemiacetal **4a** exists as a mixture of the two anomers α and β in ca. a 4:1 ratio (as was evident from the proton NMR spectrum of **4a** or its silylated products 8-α and 8-β), a stereochemically pure β-glucuronide 3-β was produced when strong nucleophilic aglycones were employed. This may be attributed to possible rapid con-

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(10) The silyl derivatives 8-α and 8-β were unusually stable to hydrolytic conditions and were easily chromatographed on silica gel without undergoing decomposition.

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Table II. 270-MHz Proton NMR Data of Glucuronides 3[a]

compd	R^2O–	NMR data
3a-α	Ph_2CHO–	7.37–7.3 (m, 10 H, Ar), 5.72 (s, CH), 5.66 (dd, 9.68, 10.27, H-3), 5.20 (d, 3.8, H-1), 5.18 (dd, 9.68, 10.27, H-4), 4.92 (dd, 3.52, 10.27, H-2), 4.33 (d, 10.27, H-5), 3.72 (s, Me), 2.03 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 2.00 (s, 3 H, Ac)
3b-β[b]	PhMeCHO–	7.2 (m, 5 H, Ar), 4.80 (q, 6.54, CH), 4.07 (m, 10.27, H-5),[c] 3.78 (s, Me), 2.06 (s, 3 H, Ac), 2.02 (s, 6 H, Ac), 1.53 (d, 6.54, Me), 1.45 (d, 6.0, Me)
3b-α		7.2 (m, 5 H, Ar), 5.64 (dd, 9.68, 10.27, H-3), 5.18 (dd, 9.68, 10.27, H-4), 4.94 (d, 3.81, H-1), 4.83 (dd, 3.81, 10.27, H-2), 4.80 (q, 6.45, CH), 4.49 (d, 10.27, H-5), 3.78 (s, Me), 2.06 (s, 3 H, Ac), 2.02 (s, 6 H, Ac), 1.53 (d, 6.54, Me), 1.45 (d, 6.0, Me)
3c-β	$PhCH_2O$–	7.39–7.31 (m, 5 H, Ar), 5.26–5.19 (m, H-3, H-4), 5.09 (dd, 7.97, 9.99, H-2), 4.94 (d, 12.01, 1 H), 4.62 (d, 12.01, 1 H), 4.60 (d, 7.97, H-1), 4.03 (m, H-5),[c] 3.78 (s, Me), 2.04 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 2.01 (s, 3 H, Ac)
3d-β	Br_3CCH_2O–	5.4–5.2 (m, H-3, H-4), 5.1 (dm, H-2), 4.99 (d, 7.33, H-1), 4.64 (d, 12.3, 1 H), 4.32 (d, 12.3, 1 H), 4.10 (m, H-5),[c] 3.78 (s, Me), 2.08 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.04 (s, 3 H, Ac)
3e-β	F_3CCH_2O–	5.3–5.24 (m, H-3, H-4), 5.06 (dd, 7.33, 8.51, H-2),[d] 4.71 (d, 7.33, H-1), 4.21 (dq, 1 H), 4.13 (dq, 1 H), 4.08 (m, H-5),[c] 3.77 (s, Me), 2.06 (s, 3 H, Ac), 2.03 (s, 6 H, Ac)
3f-β	Me_2CHO–	5.2 (m, H-3, H-4), 4.97, 4.96 (dm, H-2), 4.94 (m, CH), 4.61 (d, 7.63, H-1), 4.02 (m, H-5),[c] 3.76 (s, Me), 2.04 (s, 3 H, Ac), 2.02 (s, 6 H, Ac), 1.14 (d, 6.16, Me), 1.23 (d, 6.45, Me)
3f-α		5.53 (dd, 9.4, 10.2, H-3), 5.27 (d, 3.7, H-1), 5.16 (dd, 9.4, 10.2, H-4), 4.82 (dd, 3.7, 10.2, H-2), 4.01 (d, 10.2, H-5), 3.90 (m, CH), 3.75 (s, Me), 2.046 (s, 3 H, Ac), 2.034 (s, 3 H, Ac), 2.029 (s, 3 H, Ac), 1.26 (d, 6.28, Me), 1.21 (d, 6.05, Me)
3g-β	PhO–	7.07–7.00 (m, 5 H, Ar), 5.46–5.25 (m, H-2, H-3, H-4), 5.15 (d, 7.04, H-1), 4.18 (m, H-5),[c] 3.73 (s, Me), 2.06 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.05 (s, 3 H, Ac)
3g-α		7.11–6.99 (m, 5 H, Ar), 5.81 (d, 3.86, H-1), 5.77 (t, 10.27, H-4), 5.26 (t, 10.27, H-3), 5.06 (dd, 3.8, 10.27, H-2), 4.45 (d, 10.27, H-5), 3.73 (s, Me), 2.06 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.05 (s, 3 H, Ac)
3h-β	p-MeC_6H_4O–	7.12 (d, 8.01, 2 H, Ar), 6.91 (d, 8.01, 2 H, Ar), 5.35–5.23 (m, H-2, H-3, H-4), 5.08 (d, 7.33, H-1), 4.15 (m, H-5),[c] 3.73 (s, Me), 2.30 (s, Me), 2.06 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.04 (s, 3 H, Ac)
3i-β	Me(CN)CHO–	5.30 (t, 9.09, H-3), 5.23 (dd, 9.68, 9.09, H-4), 5.04 (dd, 7.33, 9.09, H-2), 4.84 (d, 7.33, H-1), 4.77 (q, 5.57, CH), 4.11 (d, 9.68, H-5), 3.76 (s, Me), 2.10 (s, 3 H, Ac), 2.09 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 1.62 (d, 5.28, Me)
3j-β	Et(CN)CHO–	5.34–5.16 (m, H-3, H-4), 5.05 (t, 8.0, H-2), 4.83 (d, 7.2, H-1), 4.64 (t, 8.0, CH), 4.10 (d, 8.4, H-5), 3.75 (s, Me), 2.05 (s, 6 H, Ac), 2.09 (s, 3 H, Ac), 1.9 (m, 2 H), 1.06 (t, 7.2, Me)
3k-β	$Me_2CHCH(CN)O$–	5.3 (t, 8.01, H-3), 5.22 (t, 8.01, H-4), 5.06 (t, 8.01, H-2), 4.81 (d, 8.01, H-1), 4.50 (d, 4.4, CH), 4.11 (d, 8.01, H-5), 3.76 (s, Me), 2.09 (s, 3 H, Ac), 2.04 (s, 6 H, Ac), 1.6 (m, CH), 1.07 (d, 2.08, Me), 1.04 (d, 2.08, Me)
3l-β	$Me_2(CN)CO$–	5.32 (t, H-3),[f] 5.21 (t, H-4),[f] 5.04 (t, H-2),[f] 4.92 (d, 7.92, H-1), 4.10 (d, 9.68, H-5), 3.76 (s, Me), 2.08 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.66 (s, Me), 1.61 (s, Me)
3m-β	Ph(CN)CHO–	7.39 (m, 5 H, Ar), 5.76 (s, CH), 5.36–5.24 (m, H-3, H-4), 5.11 (t, H-2),[f] 5.02 (d, 7.23, H-1), 4.17 (m, H-5),[c] 3.75 (s, Me), 2.08 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.02 (s, 3 H, Ac)
5a-α	$Cl_3CC(=NH)O$–	8.76 (br s, NH), 6.63 (d, 3.5, H-1), 5.64 (dd, 9.3, 9.9, H-4), 5.26 (dd, 9.3, 9.9, H-3), 5.14 (dd, 3.5, 9.9, H-2), 4.49 (d, 9.9, H-5), 3.75 (s, Me), 2.05 (s, 6 H, Ac), 2.02 (s, 3 H)
8-β	Me_3SiO–	5.17 (m, H-3, H-4),[g] 4.86 (dm, H-2),[d] 4.75 (d, 7.3, H-1), 3.99 (m, H-5),[c] 3.69 (s, Me), 2.05 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 0.16 (s, 9 H)
8-α		5.53 (t, 9.97, H-4), 5.44 (d, 3.23, H-1), 5.16 (dd, 9.97, 10.27, H-3), 4.84 (dd, 3.23, 10.27, H-2), 4.45 (d, 9.97, H-5), 3.68 (s, Me), 2.05 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 0.17 (s, 9 H)

[a] Chemical shifts are given in δ values. Multiplicities, coupling constants (Hz), and proton assignments are given in parentheses. The relative integrations are indicated only in nonobvious cases. [b] Those signals which were not assigned could not be discerned due to overlap with other peaks. [c] Six-line splitting pattern (see text). [d] Doublet of non-first-order six-line pattern. [e] 300-MHz proton NMR spectrum. [f] Broad peaks from which J values could not be obtained. [g] Two superimposed six-line patterns.

version of the β-silylated cation (epimer of A) to C by an anchimeric displacement with the neighboring acetate group, which subsequently gave β derivatives. For those aglycones that reacted nonstereospecifically to give mixtures of α- and β-glucuronides, or for nitrophenols that did not react at all, Schmidt's procedure using **5a** was found to be the complementary method, giving stereochemically pure β derivatives (eq 2).

Proton Magnetic Resonance Analysis. In general, proton NMR spectra of α-glucuronides are invariably simpler than those of the corresponding β isomers, since at 270 MHz the signals assigned to H-2, H-3, and H-4 are frequently superimposed in the latter (Table II). However, in those cases where these signals are separated, H-2 appears at a higher field followed by H-4 and then H-3. In many cases, although the signals for protons H-2, H-3, and H-4 look like triplets, under careful analysis two distinct but similar coupling constants can be measured, indicating the expected presence of a doublet of doublets. This is most obvious for H-2, where $J_{1,2} = \sim 7.5$ Hz differs significantly from $J_{2,3} = \sim 9$ Hz. The spectra of analogous compounds (at 500 MHz) clearly showed all protons as a resolved doublet of doublets.[13]

For β-glucuronides, the signal for H-5 is found at higher field than the corresponding proton in the α epimers, in agreement with previous observations.[14a] It has also been stated that in the β derivatives the H-5 signal appears as a complex doublet,[14b] as a doublet of doublets, or as a multiplet[14c] due to long range coupling with H-3. We feel that this complex multiplicity does not stem from $^4J_{HH}$ long range coupling interactions. In our hands, many of the glucuronides showed a clearly defined, symmetrical six-line pattern for H-5. In addition, in the trifluoro derivative **3f**-β, extra lines forming a symmetrical pattern were also observed for protons H-2, H-3, and H-4, (Figure 1 part A). However, the H-1 signal always appeared as a plain doublet. It was further seen that upon irradiation of the H-5 signal partial decoupling of H-2 occurred and its pattern simplified, approaching that of a first-order spectrum. Similar changes in the H-5 signal were observed when H-2 was irradiated (Figure 1, part B). The unexpected multiplicity of H-5 (as well as that of H-2, H-3, and H-4) appears to be independent of the size of the aglycon residue, indicating that the observed spectral effects did not arise from conformational variations. It seems rather

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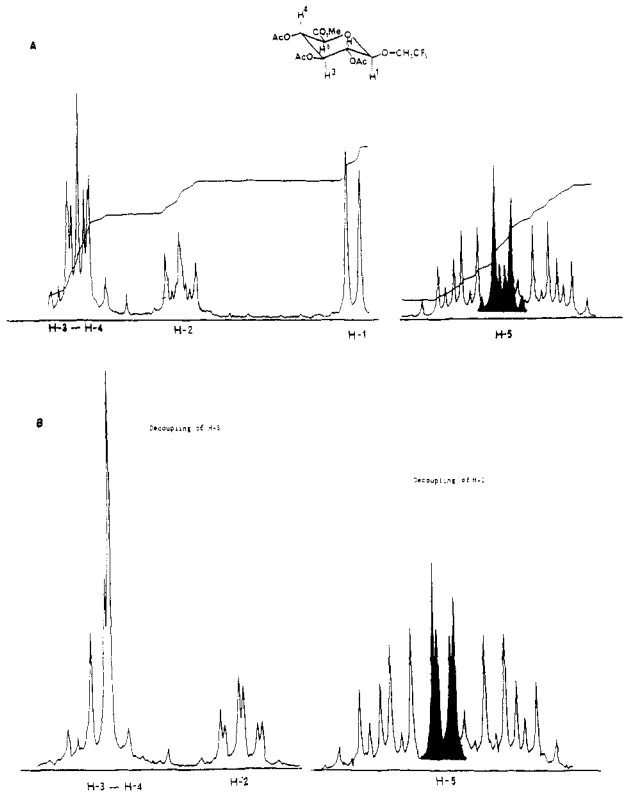

Figure 1. (A) NMR spectral pattern for the ring protons of compound **3e**-β. (B) NMR spectral pattern for protons H-2, H-3, H-4, and H-5 obtained upon decoupling of protons H-5 and H-2.

obvious that the absorption pattern of H-5 depends strongly on the chemical shift differences between H-3 and H-4. Thus, in compounds where these protons are clearly separated, a simple first-order spectrum os obtained. However, as the chemical shift difference decreases and these signals begin to appear as overlaping multiplets, second order interactions, commonly described as virtual coupling, come into play, reflecting themselves in the six-line pattern for H-5 and a more complex multiplet for H-2. These features of the experimental spectra can be reproduced in a computer simulation, taking into account only vicinal coupling constants (i.e., all $^4J_{HH} = 0$) (Figure 2). the correlation between the difference in the chemical shifts of protons H-3 and H-4 and the degree of complexity of the pattern of H-5 are shown in Figure 2. Thus, when the separation of these peaks exceeds 0.066 ppm, H-5 appears as a first-order doublet. But as that difference decreases, the complexity of the H-5 pattern increases. In conclusion, the more complex spectra reported for the β-glucuronides are due to second-order spectral effects rather than to conformationally controlled long-range coupling interactions.

In all spectra of glucuronides bearing aglycones with diastereotopic hydrogens (**3c**, **3d**, and **3e**) or methyl groups (**3f** and **3l**), a clear doubling was observed in the signals representing these groups. Proton NMR spectra of a number of glucuronides of aglycones having chiral centers (**3b**, **3i**, **3j**, **3k**, and **3m**) indicated that partial diastereomeric enrichment took place in the course of crystallization.

Experimental Section

General Remarks. Proton NMR spectra were recorded on a Bruker WH-270 spectrometer in $CDCl_3/Me_4Si$ and are reported in δ values from Me_4Si. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on a Varian Mat 731 spectrometer (CI = chemical ionization; EI = electron ionization). All reactions were carried out under anhydrous conditions in flame-dried glass apparatus under nitrogen in dry, freshly distilled solvents. The progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum sheets precoated with silica gel (Merck, Art.5554) and eluted with ethyl acetate/hexane mixtures; the developing agent was 1% sulfuric acid in methanol, followed by heat; flash column chromatography was carried out on silica gel (Merck, Art. 9385) eluted with ethyl acetate/hexane mixtures.

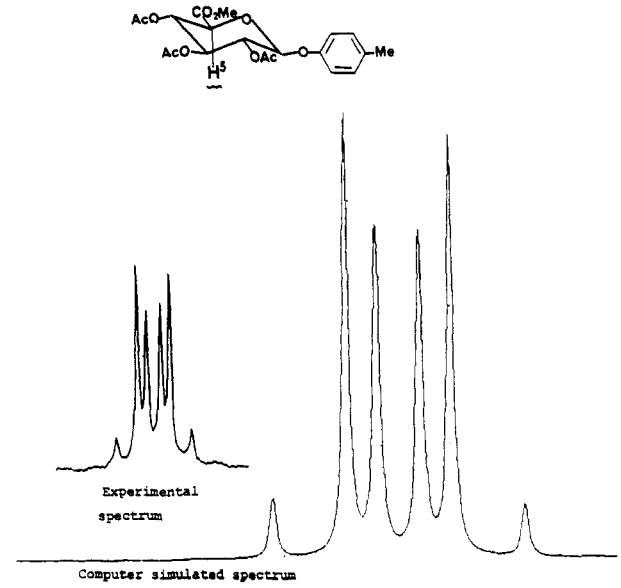

Figure 2. Computer simulated and experimental NMR patterns for the H-5 proton of **3h**-β.

General Procedure for the Preparation of Glucuronides 3. To a strictly anhydrous solution of **4a** (1 mmol) and an aglycon **2** (1 mmol) in 1,2-dichloroethane (10–20 mL) at the temperature indicated in Table I was added Me_3Si–OTf (1 mmol) in 1,2-dichloroethane (10–15 mL). Stirring was continued for 0.5–3 h and the reaction was monitored by TLC. When no further progress could be detected, the reaction was quenched by the addition of an equimolar amount of pyridine in 1,2-dichloroethane. The mixture was then washed with water, the organic phase was dried over magnesium sulfate and concentrated, and the residue was purified either by flash chromatography or by crystallization from a suitable alcohol (methanol, ethanol, or 2-propanol). The results are summarized in Table I.

Methyl 2,3,4-Tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranuronate (5a). The title compound **5a** was prepared by the same procedure as that described for **5b**.[3] The crystalline product was obtained in 55–60% yield from 2-propanol: mp 108 °C; $[\alpha]^{25}_D$ +91.6° (*c* 1.9, $CHCl_3$); mass spectrum (CI), *m/e* (relative intensity) 478 (M + 41) (3), 317 (M - 160) (23), 257 (M - 220) (52), 215 (M - 262) (12), 197 (M - 280) (24), 155 (M - 322) (100).

Methyl (*p*-Nitrophenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate. To an anhydrous solution of **5a** (0.478 g, 1 mmol) and 4-nitrophenol (0.139 g, 1 mmol) in dichloromethane, cooled to −15 °C under nitrogen, was added dropwise boron trifluoride etherate (0.025 g, 0.2 mmol) in 1 mL of dichloromethane. The mixture was stirred at −10 °C for 1 h and then quenched with aqueous sodium bicarbonate (up to pH 8). The organic phase was washed with water, dried, and concentrated. The residue was recrystallized from ethanol to give the title compound (0.35 g, 85% yield), mp 146 °C (lit.[15] 146 °C).

Methyl 2,3,4-Tri-*O*-acetyl-1-*O*-(trimethylsilyl)-α-D-glucopyranuronate (8). Silylation of compound **4a** was carried out by standard procedures[9] using hexamethyldisilazane and a catalytic amount of chlorotrimethylsilane. The product was

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obtained as a mixture of α and β epimers which upon subsequent chromatography on silica gel provided the pure α derivative and the β epimer containing small amounts of the α product; total yield, 49.4%. α derivative: mp 86 °C; $[a]^{25}_D$ + 108.9° (*c* 1.0, $CHCl_3$); MS (CI), *m/e* (relative intensity) 447 (M + 41) (2), 435 (M + 29) (32), 391 (M – Me) (38), 347 (M – OAc) (1), 317 (M – Me_3Si) (100).

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Registry No. **3a** (α-isomer), 92420-79-6; **3b** (β-isomer), 92420-80-9; **3b** (α-isomer), 92420-81-0; **3c** (β-isomer), 3080-47-5; **3d** (β-isomer), 92456-17-2; **3e** (β-isomer), 92420-82-1; **3f** (β-isomer), 92420-83-2; **3f** (α-isomer), 92420-84-3; **3g** (β-isomer), 4630-61-9; **3g** (α-isomer), 37797-57-2; **3h** (β-isomer), 92420-85-4; **3j** (β-isomer), 92420-93-4; **3i** (β-isomer), 92420-86-5; **3k** (β-isomer), 92420-87-6; **3l** (β-isomer), 92420-88-7; **3m** (β-isomer), 75410-50-3; **4a** (β-isomer), 3082-95-9; **5a** (α-isomer), 92420-89-8; **8** (β-isomer), 92420-90-1; **8** (α-isomer), 92420-91-2; Me_3SiOTF, 27607-77-8; Ph_2CHOH, 91-01-0; PhCH(Me)OH, 98-85-1; $PhCH_2OH$, 100-51-6; Br_3CCH_2OH, 75-80-9; Fe_3CCH_2OH, 75-89-8; Me_2CHOH, 67-63-0; PhOH, 108-95-2; MeC_6H_4OH, 106-44-5; MeCH(CN)OH, 78-97-7; $MeCH_2CH(CN)OH$, 4476-02-2; $Me_2CHCH(CN)OH$, 15344-34-0; $Me_2C(CN)OH$, 75-86-5; PhCH(CN)OH, 532-28-5; methyl (*p*-nitrophenyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate, 92420-92-3.

Notes

Chemical Ionization Mass Spectra of α-Hydroxy Carbonyl Derivatives. Formation of Stable Electron-Deficient Carbocations

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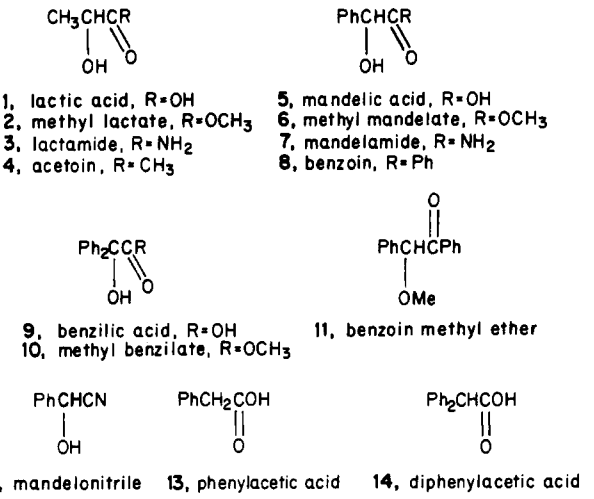
A number of recent studies have demonstrated clearly both the formation and the stability of so-called electron-deficient carbocations, i.e., carbocations substituted with potent electron-withdrawing substituents (groups or atoms).[1-4] Of particular interest to the present work is the surprising ease of generation during solvolysis of carbocations carrying an α-carbonyl moiety from secondary and tertiary benzylic, dialkyl acyclic, and tertiary cycloalkyl substrates.[5] In comparison, considerable structural reorganization occurs during the solvolysis of secondary cycloalkyl systems[6,7] while in the lone case of a secondary acyclic system reported so far solvolysis takes place via a k_Δ process involving methyl migration.[6] Further, with the (*S*-(+)-mesylate of methyl mandelate the observed high rate of racemization compared to solvolysis is compatible with an open-chain cation as against a cyclic oxirane structure which would result in retention of configuration.[5] On the other hand with the mesylate of acetoin (CH_3CH-(OMs)$COCH_3$) very little solvolysis was observed,[8] indicating that the phenyl group plays a stabilizing role in the secondary benzylic series. Several long-lived carbocations belonging to the secondary and tertiary benzylic type $Ar^+C(R)C(O)Ar$ (R = H or Ar) have been observed directly by ^{13}C NMR spectroscopy.[9-11]

Chart I



During the course of our investigations of the proton-transfer chemical ionization behavior of the α-hydroxy carbonyl derivatives **1–12**, we have observed results which closely parallel solution phase results. These are reported in the present paper. The predominant ionization reaction under chemical ionization conditions using CH_4 as the reagent gas is protonation of the substrate molecule by the gaseous Brønsted acids CH_5^+ and $C_2H_5^+$.[12] Since the proton affinities of the conjugate bases CH_4 and C_2H_4 are relatively low (130 and 164 kcal mol^{-1}, respectively[12]), the proton-transfer reaction is exothermic and fragmentation of the MH^+ ion formed from the substrate may occur. Normally the fragmentation reactions observed will be those of low critical energy, i.e., those forming stable ionic and neutral products, and the intensity of the fragment ions relative to the MH^+ ion can be taken as a measure of the stability of the product species formed.

The essential features of the CH_4 chemical ionization (CI) mass spectra of the 14 compounds studied (Chart I) are summarized in Table I. Lactic acid and its derivations (**1–4**) show abundant MH^+ ions, indicating the absence of

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