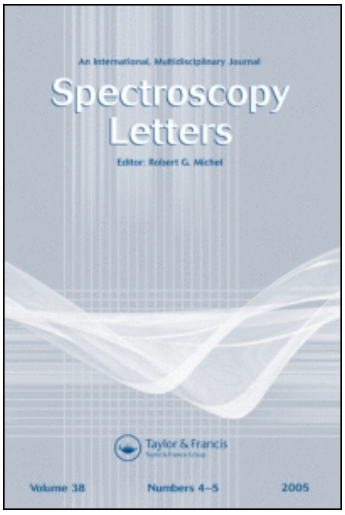

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Synthesis and NMR Spectroscopic Studies of Trichloroacetimidate Lactosyl Donor

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SYNTHESIS AND NMR SPECTROSCOPIC STUDIES OF TRICHLOROACETIMIDATE LACTOSYL DONOR

Key words: isomerization, temporary protecting-groups, trichloroacetimidate .

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ABSTRACT

Allyl 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside (**2**) was prepared from **1**, which was isomerized with palladium-charcoal to give 1-*O*-propenyl derivative **3** . On treatment of **3** with mercuric chloride and mercuric oxide afforded **4**, which was converted into the required α-trichloroacetimidate lactosyl donor **5** . This imidate carrying transient acetyl group at *O*-3 and 1,3-dioxolane ring, serve as a temporary protecting-groups that can be removed to unmask *O*-3, *O*-3' and *O*-4' in further extension .

A detailed NMR analysis [^{1}H, ^{13}C, and 2D ^{1}H-^{1}H correlation experiments (COSY)] was used for the structural elucidation of the building blocks, **2** and **5** .

INTRODUCTION

Protection of hydroxy functions of sugar derivatives by the allyl group has been shown to be a useful step[1] in the synthesis of oligosaccharides . Removal of the *O*-allyl group is achieved by a two-step process : isomerization of the allyl

ether to the 1-propenyl ether[2], and conversion of the propenyl ether into the free alcoholic group using acid[3], $HgCl_2/HgO$[4] or I_2/water[5].

Glycosyl trichloroacetimidates, introduced in 1980[6], are outstanding glycosyl donors[7-9] because of their stability, reactivity, diastereoselectivity, and general applicability.

The present paper describes the preparation of the lactosyl donor **5**. Full details of NMR analysis [^1H, ^{13}C and 2D ^1H-^1H correlation experiments (COSY)[10]] of the lactose derivatives **2** and **5** are now reported.

RESULTS AND DISCUSSION

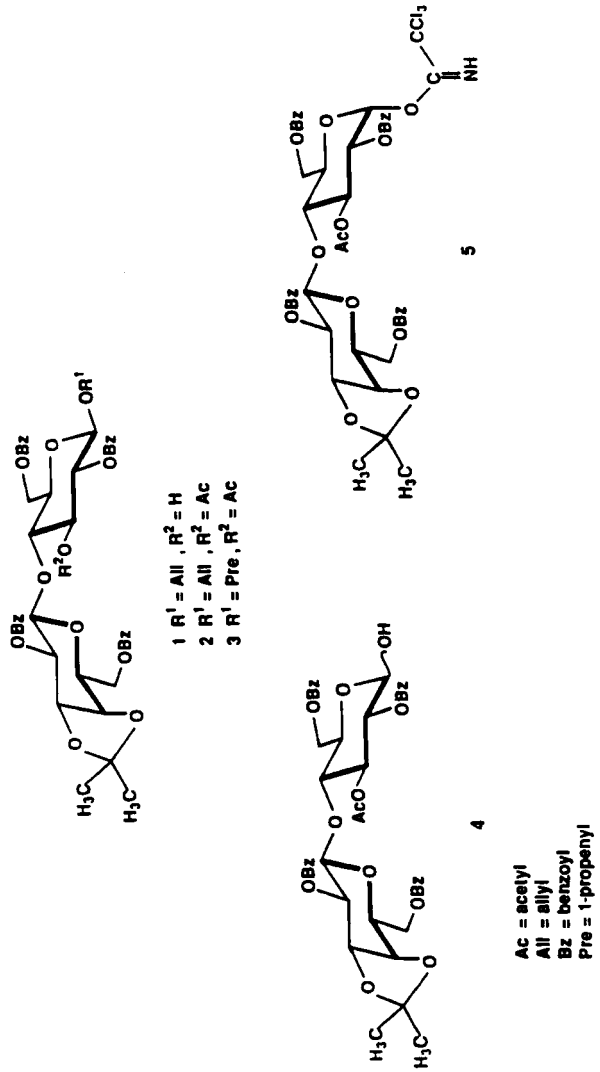
It was reported by Nashed and Musser[11], that the partial benzoylation of allyl-4-*O*-(3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside at low temperature yields, primarily, allyl 2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside (**1**), which has hydroxy group open at position 3. Acetylation of **1** with acetic anhydride in pyridine at ambient temperature gave allyl 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside (**2**).

The structure of **2** was proved through a study of the ^1H NMR, 2D ^1H-^1H correlation experiment (COSY), and ^{13}C NMR. The ability of high resolution NMR spectroscopy to provide information about the structural details is firmly established.

The ^1H NMR spectrum shown in Figure 1 is characterized by a multiplet at δ 8.20-7.25 corresponding to 20 aromatic protons, a multiplet in the region (δ 5.76-5.63) characteristic of the resonance of the vinyl proton (-C*H*=), a triplet centered at δ 5.46 (*J* 9.5 Hz) which is attributed to H-3, indicating a *trans* - diaxial disposition of H-2 and H-4. A multiplet at δ 5.31-5.02 equivalent to four protons, and a multiplet at δ 4.82-3.66 is attributed to the sugar ring protons and -OCH_2- of the allyl moiety. A singlet at δ 2.10 due to CH_3CO and two singlets at δ 1.65 and 1.35 correspond to $(CH_3)_2C$.

Complete assignment of the ^1H resonances of the sugar residues and allyl group was made from 2D ^1H-^1H correlation experiment (COSY) (Figure 2).

Allyl Residue .- Commencing from the resonance for the vinyl proton (-C*H*=), the chemical shifts of the CH_2= and -OCH_2- were established by tracing the



SCHEME

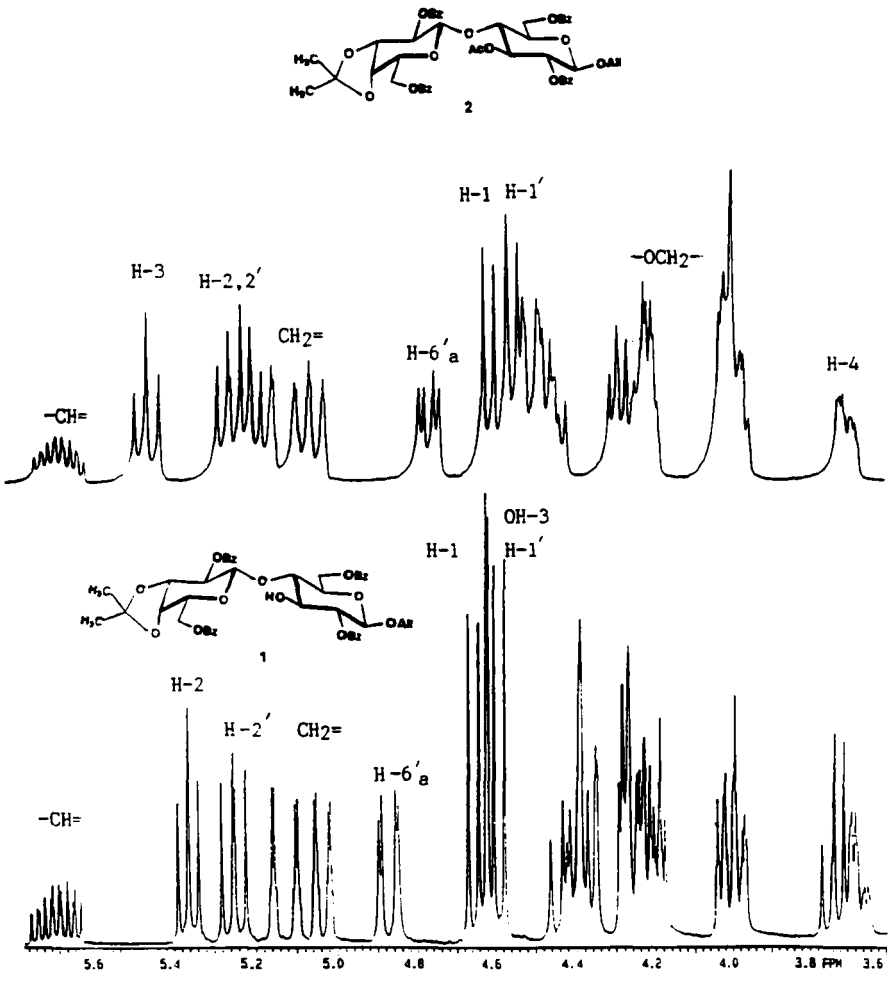
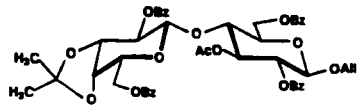


FIG. 1 A comparison of ^{1}H NMR spectra for compounds 1 and 2 .

connectivities *via* the cross-peaks . The signals at δ 5.16-5.03 is attributed to CH_2=, whereas the -OCH_2- resonance lies in the region (δ 4.24-4.18 and δ 4.06-3.94) . In addition, a weak CH_2=/-OCH_2- cross-peak was noted due to the long range coupling .

Glucose Residue .- The chemical shift for H-3 was traced easily on the ^{1}H NMR spectrum (Figure 1) . Connectivities from H-3, the ^{1}H resonances of glucose



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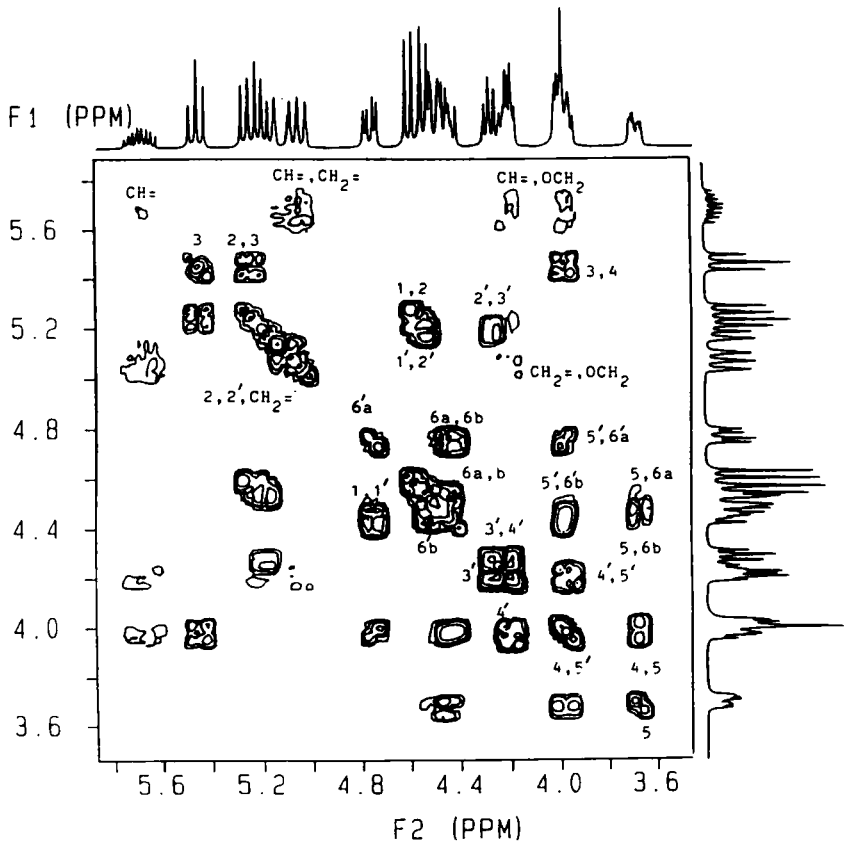

FIG. 2 COSY contour plot of the region δ 5.8-3.6 for compound 2 .

residue were established from the (COSY) spectrum (Figure 2), which showed a triplet at δ 5.26 due to H-2 . A doublet at δ 4.61 with large spacing ($J_{1,2}$ 7.9 Hz) corresponds to H-1 has a β-configuration . The signals for H-4, H-5, H-$6_{a,b}$ lie in the region (δ 4.06-3.94, 3.74-3.66, and 4.54-4.40) respectively .

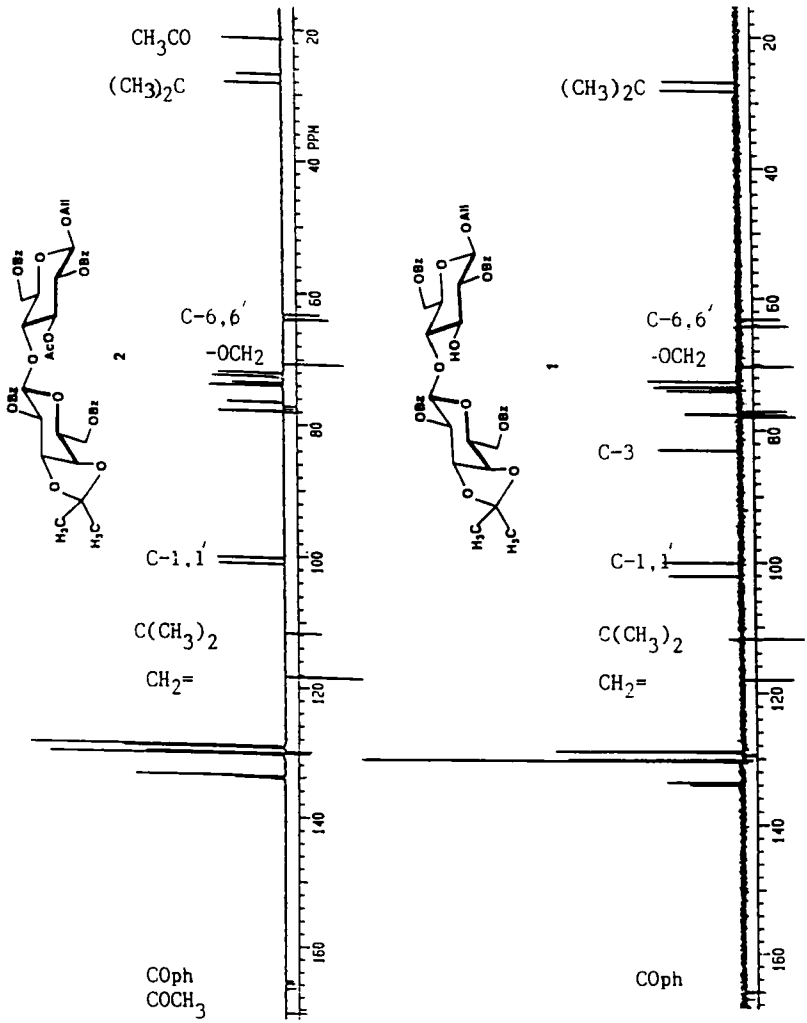

FIG. 3 A comparison of ^{13}C NMR spectra for compounds 1 and 2.

Galactose Residue .- Further inspection of the COSY spectrum (Figure 2) now identified the H-1' resonance (δ 4.55, $J_{1',2'}$ 8.1 Hz) and its cross-peak to H-2' (δ 5.21) . The chemical shifts for the H-3' to H-6'$_{a,b}$ resonances were distinguished by tracing the connectivities *via* cross-peaks .

A further elucidation of the structure of compound **2** is obtained through a study of the ^{13}C NMR and the attached proton test (APT) experiment (Figure 3) . The spectrum shows acetyl carbonyl group at δ 171.00, and a multiplet at δ 167.00-165.50 corresponds to the four benzoyl carbonyl groups . The aromatic and the vinyl carbons appeared at δ 134.00-128.50, the inverted peaks correspond to CH_2=CH- and the quaternary carbon atom in 1,3-dioxolane ring appeared at δ 118.28 and 111.66, respectively . The two signals at δ 101.15 and 100.17 are attributed to the two anomeric carbons having a β-configuration (C-1,1') . The inverted peak at δ 70.58 correspond to -OCH_2-, while the two signals at δ 63.88 and 63.21 are due to C-6,6' . The upright peaks at δ 77.85-72.07 correspond to the rest of the sugar ring methine carbons . The signals attributed to the dioxolane methyl groups appear at δ 28.13 and 26.81 . The small difference in the chemical shift is due to the flexibility of the 1,3-dioxolane ring[12,13] and the most probable conformation[14] of the 2,2-dimethyl-1,3-dioxolane ring is $^4T_5$ in which the two methyl groups are equivalent . Moreover, the high-field signal for the methyl acetyl group appear at δ 21.31 .

Boss and Scheffold[2] found that 10% palladium-activated charcoal is a particularly effective catalyst for isomerization of allyl ethers . The latter reagent was thus used for isomerization of **2** to 1-propenyl 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside (**3**) . The ^{13}C NMR chart of **3**, as compared with that of **2**, the inverted signals at δ 118.28 and 70.58 were disappeared . Moreover the intinsty of the peak at δ 28.00 was increased due to =CH-CH_3 .

Treatment of **3** with mercuric chloride and mercuric oxide in aqueous acetone[4] or iodine-water[5] afforded 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-**D**-glucopyranose (**4**) .

The structure of compound **4** was established on the basis of ^{13}C NMR spectrum, which showed the presence of α- and β-anomers with 2 : 1 ratio, respectively . The signals at δ 100.62 and 90.84 correspond to C-1',1 with α-configuration, while, the peaks of the anomeric carbons of the β-anomer appear at δ 100.80 and 96.35 . The 1-hydroxy compound **4** was then treated with

trichloroacetonitrile and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU)[15] to give 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-α-**D**-glucopyranosyl trichloroacetimidate (**5**) in an excellent yield .

The ^{1}H NMR spectrum of compound **5** (Figure 4) exhibited a singlet at δ 8.52 corresponding to N*H*, a multiplet at δ 8.14-7.23 due to the aromatic protons . The presence of the low-field doublet of the anomeric proton (δ 6.62, $J_{1,2}$ 3.7 Hz) indicates the presence of the glucose moiety in an α-configuration . A triplet centered at δ 5.82 (*J* 9.7 Hz) which is attributed to H-3, and a multiplet at δ 5.28-3.95 correspond to the rest of the sugar ring protons .

A further characterization of the structure of compound **5** is obtained through a study of the 2D ^{1}H-^{1}H correlation experiment (COSY) Figure 5 .

Glucose Moiety .- Commencing from the resonance for H-1, the chemical shifts for H-1 to H-4 were traced, which showed a doublet of doublets at δ 5.25 with small and large spacing ($J_{2,1}$ 3.8 and $J_{2,3}$ 10.1 Hz) due to H-2, and a multiplet at δ 4.10-4.00 correspond to H-4 .

Galactose Moiety .- As previously mentioned the interpretation of the (COSY) experiment chart requires knowing the exact position of at least one proton, which revealed a triplet at δ 5.22 due to H-2' with large splitting . A doublet at δ 4.64 ($J_{1',2'}$ 7.7 Hz) corresponding to H-1', a triplet at δ 4.34 ($J_{3',2'}$ 6.5 and $J_{3',4'}$ 5.8 Hz) is attributed to H-3', and a doublet of doublets at δ 4.26 ($J_{4',3'}$ 5.8 and $J_{4',5'}$ 2.0 Hz) is due to H-4' . It is evident, primarily from these *J* values that a major change from $^4C_1$ (**D**) conformation accompanies the formation of 1,3-dioxolane ring .

Moreover, characterization of compound **5** was based on its ^{13}C NMR and the attached proton test (APT) experiment (Figure 6), in which the signals of *C*=NH, C-1 with an α-configuration and *C*Cl$_3$ appeared at δ 160.60, 92.94 and 77.27, respectively .

These NMR studies have established unambiguously that the synthetic route employed here has led to the preparation of the lactosyl donor **5** having a temporary protecting-groups that can be removed to unmask *O*-3[16], *O*-3' and *O*-4' in further extension .

EXPERIMENTAL

General methods .- The instrumental and chromatographic procedures employed were given previously[17] . The following solvent combinations (v/v) were

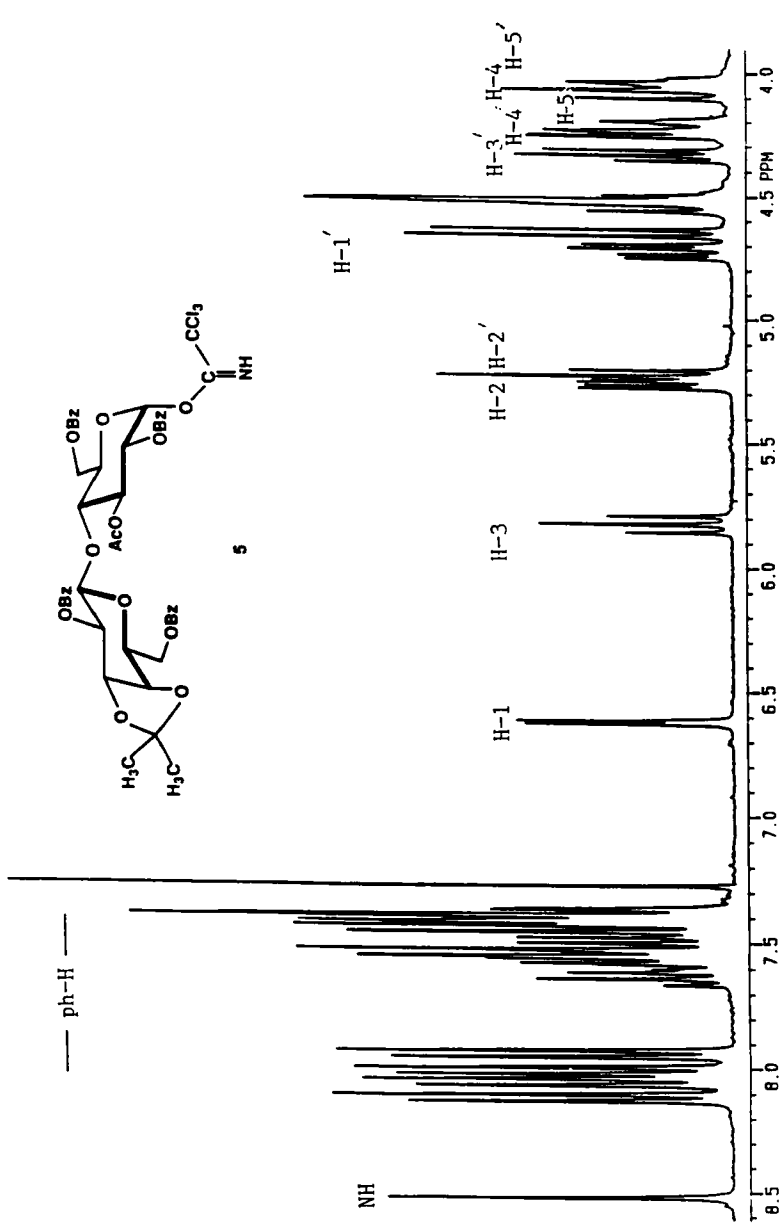

FIG. 4 ^{1}H NMR spectrum for compound **5**.

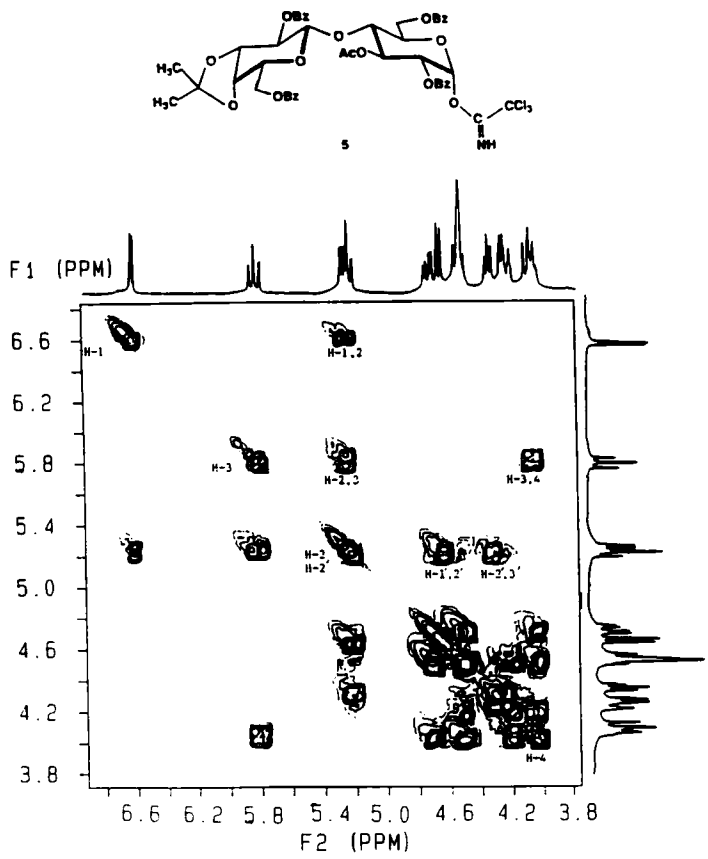

FIG. 5 COSY contour plot of the region δ 6.8-3.8 for compound 5 .

utilized for thin-layer and column chromatography : *A*, 19:1 chloroform-acetone; *B*, 8:2 toluene-ethylacetate; *C*, 9:1 toluene-ethylacetate; *D*, 29:1 chloroform-acetone .

*Allyl 3-O-acetyl-2,6-di-O-benzoyl-4-O-(2,6-di-O-benzoyl-3,4-O-isopropylidene-β-***D***-galactopyranosyl)-β-***D***-glucopyranoside* (**2**) .- To a solution of allyl 2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside (**1**) (2.1 g, 2.5 mmol) in dry pyridine (10 mL) acetic anhydride (5 mL) was added . The reaction mixture was stirred for 1 h at room

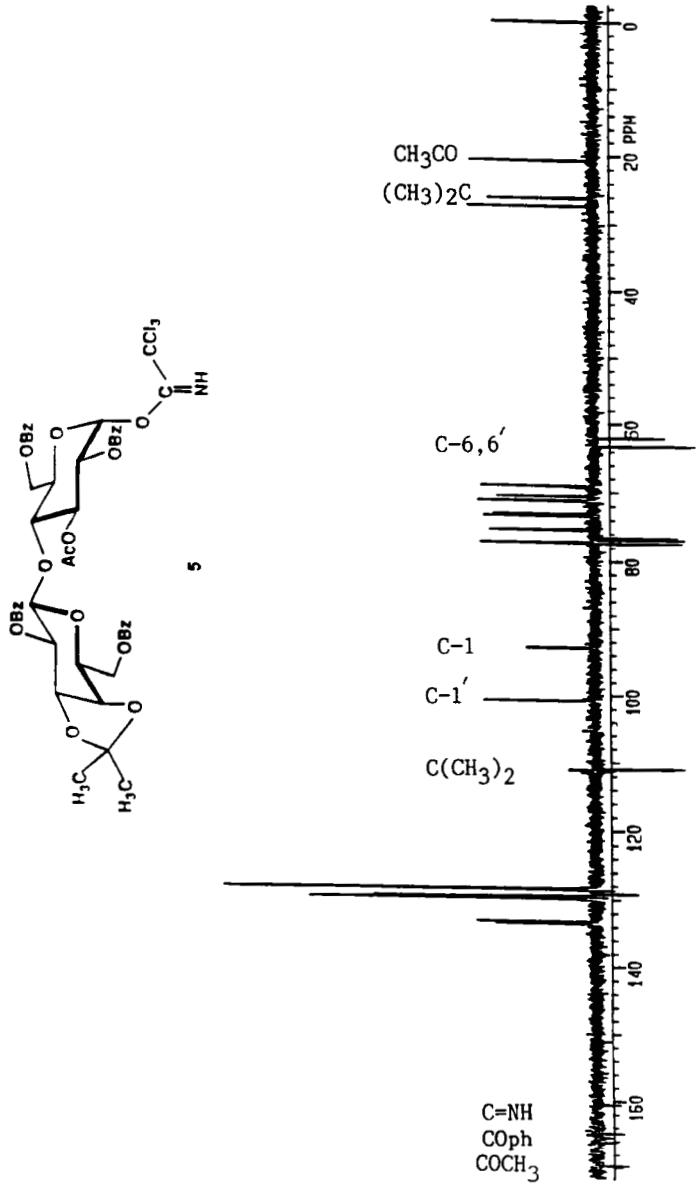

FIG. 6 ^{13}C NMR spectrum for compound 5.

temperature, when t.l.c. (solvent A) showed complete disappearance of the starting material . Methanol was added to the cooled solution to destroy excess acetic anhydride, the solvents were evaporated till dryness under reduced pressure . The residue was dissolved in dichloromethane, washed successively with aqueous hydrochloric acide (5%), water, sodium hydrogencarbonate solution (5%), water, dried over anhydrous sodium sulphate, and evaporated to dryness to give the title compound **2** as a syrup in almost quantitative yield . ^{1}H NMR ($CDCl_3$) : δ 8.20-7.25 (m, 20H, Ph-*H*), 5.76-5.63 (m, 1H, CH_2=C*H*-), 5.46 (t, 1H, *J* 9.5 Hz, *H*-3), 5.31-5.02 (m, 4H, H-2,2' and CH_2=CH-), 4.81-4.40 (m, 6H, *H*-1,1' and 2 CH_2), 4.32-4.18 (m, 3H, *H*-3',4' and 0.5 -OCH_2-), 4.06-3.94 (m, 3H, H-4,5' and 0.5 OCH_2-), 3.74-3.66 (m, 1H, *H*-5) 2.10 (s, 3H, CH_3CO), 1.65, 1.35 [2s, 6H, $(CH_3)_2$C]; ^{13}C NMR ($CDCl_3$) : δ 171.00 (*C*OCH_3), 167.00-165.50 (4 *C*OPh), 134.00-128.50 (aromatic and vinyl carbons), 118.28 (*C*H_2=CH), 111.66 [*C*$(CH_3)_2$], 101.15, 100.17 (C-1,1'), 70.58 (=CH-*C*H_2O-), 63.88, 63.21 (C-6,6'), 28.13, 26.81 [(*C*$H_3)_2$C], and 21.31 (*C*H_3CO) .

3-O-Acetyl-2,6-di-O-benzoyl-4-O-(2,6-di-O-benzoyl-3,4-O-isopropylidene-β-D-galactopyranosyl)-α-D-glucopyranosyl trichloroacetimidate (**5**) .- To a solution of **2** (1.5 g, 1.7 mmol) in methanol (27 mL) and water (3 mL) 10% palladium-activated charcoal (0.5 g) was added . The resulting suspension was boiled for 8 h under reflux with stirring . T.l.c. (solvent B) (after hydrolysis with mercuric chloride and mercuric oxide[4] or iodine in aqueous acetone[5]), then showed that isomerization was complete . The residue obtained by removal of the catalyst and evaporation of the solvents was chromatographed on a column of silica gel (solvent C) to afford 1-propenyl 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-β-**D**-glucopyranoside (**3**) as a glassy foam (1.13 g, 75%) . To a solution of **3** (0.8 g, 0.91 mmol) in acetone (15 mL) and water (2 mL), mercuric chloride (350 mg, 1.3 mmol) and mercuric oxide (193 mg, 0.90 mmol) were added . The resulting suspension was stirred for 30 min., at which time t.l.c. (solvent B) showed the reaction was complete . The mixture was then filtered through Celite, washed with acetone, and the combined filterates were evaporated . Chromatography of the residue on a column of silica gel (solvent C) gave 0.61 g (80%) of 3-*O*-acetyl-2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-**D**-galactopyranosyl)-**D**-glucopyranose (**4**) as a syrup . ^{13}C NMR ($CDCl_3$) : similar to that of **2** but showing δ 96.35

(C-1, β-configuration), 90.84 (C-1, α-configuration) and no signals for the allyl carbons .

To a solution of **4** (0.5 g, 0.60 mmol) in dry dichloromethane (5 mL), trichloroacetonitrile (0.5 mL) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) (80 μL, 0.53 mmol) were added . The reaction mixture was stirred for 30 min. at 0°C, at which time t.l.c. (solvent A) showed complete reaction . The reaction mixture was filtered through Celite, washed with dichloromethane, concentrated and purified on a short column of silica gel (solvent D), to give 430 mg (73%) of the title compound as an amorphous solid; $[\alpha]_D$ + 58.3°, $[\alpha]_{436}$ + 112.1° (*c* 2.3, dichloromethane); ^{1}H NMR ($CDCl_3$) : δ 8.52 (s, 1H, N*H*), 8.14-7.23 (m, 20H, Ph-*H*), 6.62 (d, 1H, $J_{1,2}$ 3.7 Hz, *H*-1), 5.82 (t, 1H, *J* 9.7 Hz, *H*-3), 5.28-5.14 (m, 2H, H-2,2'), 4.75-4.45 (m, 5H, H-1' and 2CH_2), 4.34 (t, 1H, $J_{3',2'}$ 6.5, $J_{3',4'}$ 5.8 Hz, H-3'), 4.26 (dd, $J_{4',3'}$ 5.8, $J_{4',5'}$ 2.0 Hz, H-4'), 4.22-4.15 and 4.10-3.95 (2m, 3H, H-4,5,5'), 2.05 (s, 3H, CH_3CO), 1.65, 1.35 [2s, 6H, (CH_3)$_2$C]; ^{13}C NMR ($CDCl_3$) : δ 169.70 (*C*OCH$_3$), 166.20-165.00 (4 *C*OPh), 160.60 (*C*=NH), 133.50-128.00 (aromatic carbons), 111.06 [*C*(CH$_3$)$_2$], 100.84 (C-1'), 92.94 (C-1), 77.27 (*C*Cl$_3$), 75.42, 73.49, 73.21, 71.38, 71.22, 70.63, 69.21, 63.32, 62.12 (C-6,6'), 27.45, 26.17 [(*C*H$_3$)$_2$C], 20.82 (*C*H$_3$CO); negative-ion LSIMS : *m/z* 985.0 (M-H$^+$)$^-$. *Anal.* Calc. for $C_{47}H_{44}Cl_3NO_{16}$ (985.2) : C, 57.30; H, 4.50; N, 1.42 . Found : C, 57.03; H, 4.49; N, 1.31 .

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