Synthesis of Trimethacarb Hydroxymethyl Metabolites and Corresponding Glucoside Derivatives

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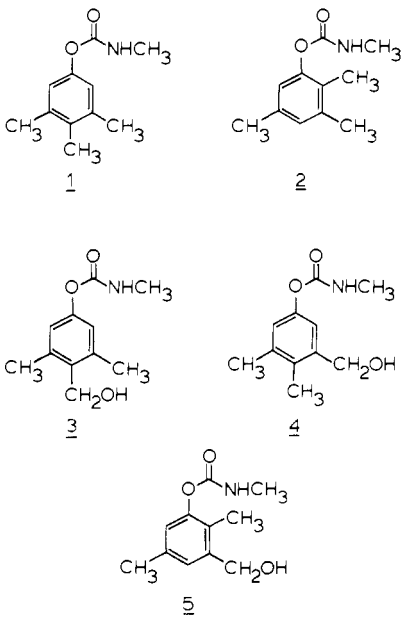
Improved syntheses are reported for 3,5-dimethyl-4-(hydroxymethyl)phenyl *N*-methylcarbamate (**3**), 4,5-dimethyl-3-(hydroxymethyl)phenyl *N*-methylcarbamate (**4**), and 2,5-dimethyl-3-(hydroxymethyl)-phenyl *N*-methylcarbamate (**5**), three metabolites of trimethacarb insecticide. The *O*-β-D-glucoside of **4** was prepared via coupling of the carbamoyl benzylic alcohol with acetobromo-α-D-glucose under Koenigs–Knorr conditions. This approach failed with **3**, necessitating a sequence of protection of the phenolic hydroxyl in 4-hydroxy-2,6-dimethylbenzyl alcohol as a benzyl ether, followed by glucosidation, selective debenzylation, and carbamoylation. The assignment of stereochemistry in the glucosides by carbon and high-field proton NMR is also discussed.

Broot brand of trimethacarb soil insecticide (Rhône-Poulenc Ag Co.) is a mixture (approximately 80:20) of two isomeric trimethylphenyl methylcarbamates (**1** and **2**). It

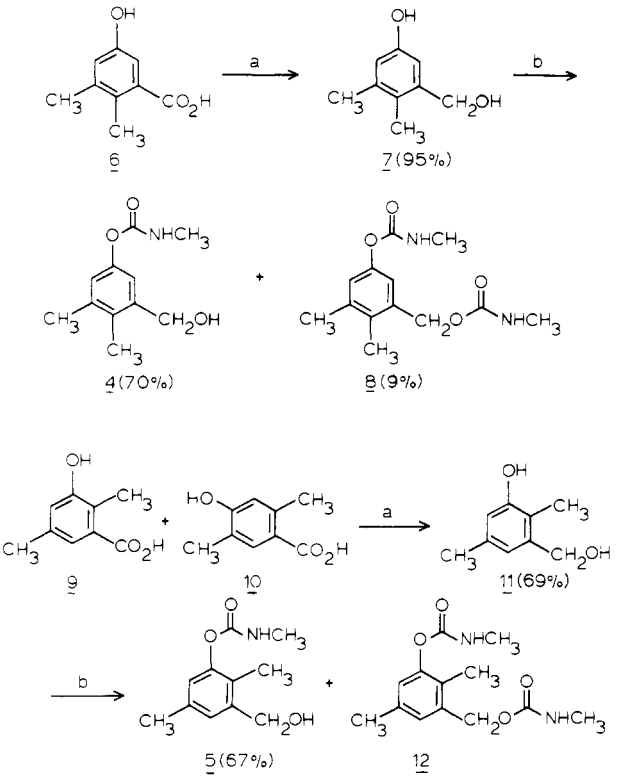


has been shown (Casida and Slade, 1970) that in the bean plant, the mouse, and the housefly the primary metabolic degradation of trimethacarb involves oxidation of one or more of the nuclear ring-methyl groups to a hydroxymethyl function. Further oxidation to the aldehyde or carboxylic acid was not observed in bean plants. This was interpreted as being a consequence of the rapid conjugation of the hydroxymethyl compounds to form glycosides. In connection with ongoing registration studies, high-purity samples of metabolites **3–5** were required. In addition, glucoside derivatives of at least one of the metabolites were desired as models of the conjugates. Herein is reported the synthesis of *O*-glucosides of **3** and **4** as well as improved syntheses of **3–5**.

RESULTS AND DISCUSSION

The hydroxymethyl metabolites **3–5** were prepared by Casida and Slade in their investigation of the metabolism of trimethacarb (1970). In the present work, their routes to **4** and **5** were followed with slight modifications. However, it was necessary to develop an entirely new synthesis of **3** to obtain the quantity of analytically pure material required.

Scheme I



[a] Conditions: (a) BH_3–THF; (b) MIC, NEt_3, CH_2Cl_2.

The preparations of **4** and **5** are shown in Scheme I. The benzoic acids **6**, **9**, and **10** were obtained according to literature methods (Charlesworth and Levene, 1963; Acton and Fujiwara, 1970). We found it more efficient to reduce these acids directly to the alcohols with borane–tetrahydrofuran complex (Brown et al., 1973) rather than to follow the esterfication lithium aluminum hydride sequence previously reported (Casida and Slade, 1970). This shortened the syntheses and gave considerably improved yields. In addition, the isolation procedure for **11** allowed the use of the mixture of phenolic acids produced in the sulfonation–caustic fusion of 2,5-dimethylbenzoic acid (Acton and Fujiwara, 1970) to obtain the alcohol **11** in pure form. The alcohols **7** and **11** were then carbamylated with methyl isocyanate in the presence of a catalytic amount of triethylamine. The crude carbamates **4** and **5** were

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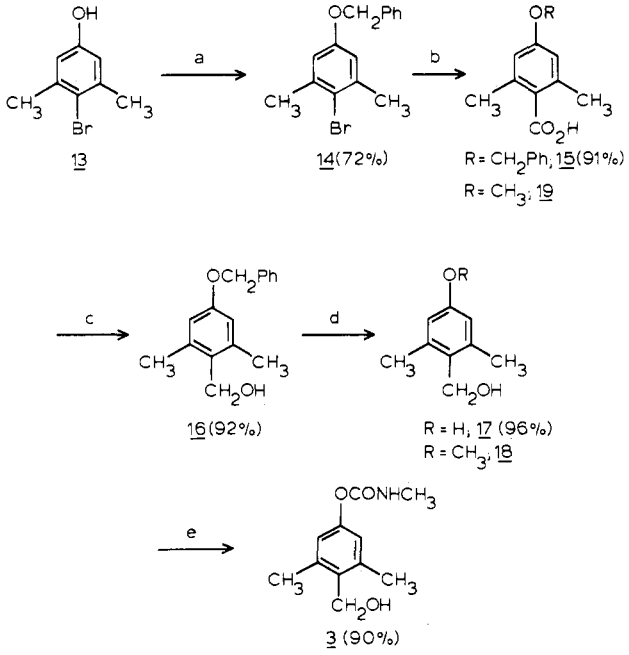
Scheme II



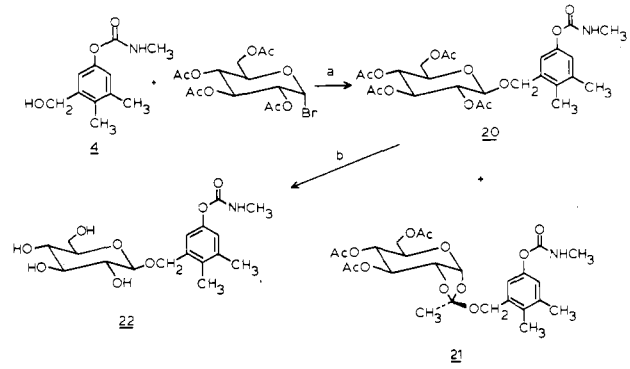
[a] Conditions: (a) $PhCH_2Cl$, NaI, DME, reflux; (b) Mg, CO_2; (c) $LiAlH_4$, THF; (d) 5% Pd/C, H_2, CH_3OH; (e) MIC, CH_2Cl_2, NEt_3.

found to be contaminated with biscarbamates **8** and **12**, respectively, and were purified by flash chromatography. Although the biscarbamates were not previously reported, we were unable to avoid their formation using the literature method (Casida and Slade, 1970) or a variety of other procedures.

The only published preparation of the phenol **17**, the immediate precursor of **3**, utilized the Lederer–Manasse reaction on 3,5-dimethylphenol (Auwers, 1907; Casida and Slade, 1970) to provide **17** in low (7.3%) yield, one of a number of products that is difficult to separate. The route developed involved introduction of the hydroxymethyl group via carbonation of the Grignard reagent derived from **14**, followed by reduction and debenzylation to give **17** in excellent yield (Scheme II). The use of a phenol protecting group, removable under nonacidic conditions, proved to be essential. The attempted cleavage of the methyl ether **18** with boron tribromide gave an intractable mixture in which no **17** could be detected. Treatment of **19** with hydriodic acid resulted in concomitant decarboxylation to give 3,5-dimethylphenol. The synthesis of **3** was completed by carbamylation under the same conditions as before. The biscarbamate formation that complicated the syntheses of **4** and **5** did not occur in this case, presumably due to the steric hindrance of the flanking methyl groups. The overall yield of **3** from **13** was 52%, compared to the 4% yield of the previous preparation (Casida and Slade, 1970).

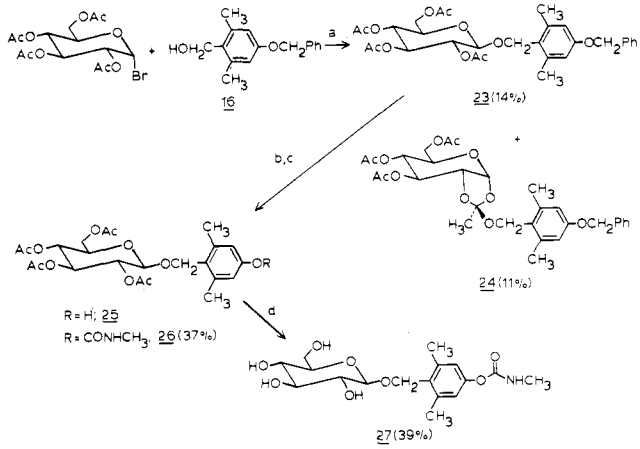
A major metabolic pathway for pesticides in plants involves an oxidation followed by conjugation as a glycoside (Kuhr, 1970). However, only a single report of the chemical synthesis of a glycoside of an oxidative metabolite of a carbamate insecticide has appeared. Cardona and Dorough (1973) synthesized the β-D-glucosides of carbaryl derivatives that had been hydroxylated at the 4- and 5-positions through the acid-catalyzed coupling of glucose pentaacetate with the hydroxy compounds. This approach did not appear promising for glucosidation of the trimethacarb metabolites, which contain acid-sensitive benzylic hydroxy groups. This concern was confirmed in a model study in which 2,6-dimethylbenzyl alcohol was treated with glucose

Scheme III



[a] Conditions: (a) Ag_2O, CH_2Cl_2; (b) $Ba(OCH_3)_2$, H^+.

Scheme IV



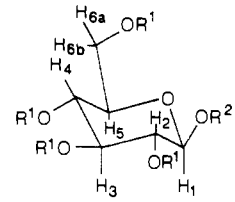
[a] Conditions: (a) Ag_2O, NaI, CH_2Cl_2; (b) 5% Pd/C, H_2; (c) MIC, NEt_3, CH_2Cl_2; (d) $Ba(OCH_3)_2$, H^+.

pentaacetate in the presence of *p*-toluenesulfonic acid and gave only the corresponding dibenzyl ether.

The classical Koenigs–Knorr reaction of acetobromo-α-D-glucose with **4** in the presence of silver(I) oxide (Scheme III) produced the desired tetraacetyl-β-D-glucoside **20** together with the orthoester **21**. Orthoester byproducts are common in Koenigs–Knorr reactions (Wulff and Rohle, 1974). The ratio of **20** to **21** was 1.0:.8, and the total isolated yield of the two products was 50% after separation by flash chromatography. The synthesis was completed through cleavage of the acetyl groups with barium methoxide. Scission of the carbamoyl group was minimized by the use of a significantly shorter reaction time than that reported for the carbaryl derivatives. A reaction time of 1 h gave a 95% yield of the glucoside; about 5% of the phenol resulted from carbamate cleavage as estimated by NMR integration. A reaction time of 4 h gave only a 53% yield of **20**. The isolated **20**, in this case, contained 10% of the carbamate cleavage product.

The direct glucosidation of the hydroxymethyl carbamate **3** gave a very complex mixture of products from which only the orthoester **29** could be isolated. The result is likely due to the presence of the labile carbamoyl moiety para to the hydroxymethyl group. Hydrolysis of the carbamoyl group under the slightly basic conditions of the Koenigs–Knorr coupling could lead to quinone methide derived products, a decomposition pathway established for the structurally similar natural product dhurrin (Mao and Anderson, 1965). The strategy of constructing the glucoside linkage prior to introduction of the carbamoyl function was thus adopted (Scheme IV). When the benzyl ether **16** was subjected to the Koenigs–Knorr conditions, the

Table I



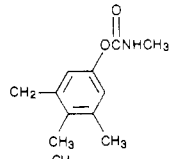
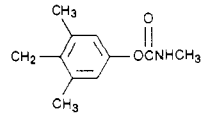
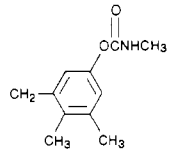
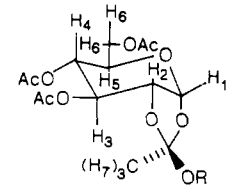
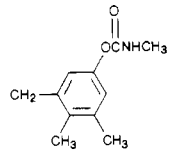
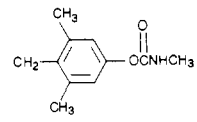
compd	R^1	R^2	chemical shifts, ppm H_1	H_2	H_3	H_4	H_5	H_{6a}	H_{6b}	coupling constants, Hz H_1–H_2	H_{6a}–H_5	H_{6b}–H_5	H_{6a}–H_{6b}
20	Ac		4.48		4.99–5.30		3.67	4.27	4.17	7.6	4.6	2.5	12.3
26	Ac		4.43		4.95–5.18		3.67	4.23	4.19	8.0	4.8	2.8	12.3
28	Ac	CH_2Ph	4.55		5.03–5.22		3.68	4.28	4.16	7.6	4.6	2.5	12.3
22	H		4.35		4.80–5.10		3.67	3.90	3.69	7.6	–	5.1	12.0

Table II



compd	R	chemical shifts, ppm H_1	H_2	H_3	H_4	H_5	H_6	H_7	coupling constants, Hz H_1–H_2	H_2–H_3	H_3–H_4	H_4–H_5	H_5–H_6
21		5.71	4.33	5.21	4.91	3.97	4.21	1.80	5.2	2.9	2.6	9.6	4.4
29		5.72	4.34	5.21	4.93	3.98	4.21	1.84	5.2	2.9	2.6	9.5	4.3

tetraacetylglucoside **23** and orthoester **24** were formed cleanly in modest yield. The lowered yield relative to the glucosidation of **4** was no doubt due to the steric hindrance of the ortho methyl groups in **16**. The glucoside **23** also was found to be unstable to silica gel, believed to be a consequence of the steric crowding about the glucoside linkage. In a similar case, Veibel and Hjorth (1952) attributed the rapid hydrolysis of mesityl-β-D-glucopyranoside to the steric strain introduced by the ortho methyl groups. A selective debenzylation followed by carbamylation furnished the carbamate **26** in 37% yield. Removal of the acetyl protecting groups as before gave **27**.

The assignment of β configuration to the glucosides prepared depends primarily on an analysis of the 250-MHz proton NMR data, presented in Table I. The 7.6–8.0-Hz values for the H_1–H_2 coupling constants are in the range expected for axial–axial couplings in β-D-glucopyranosides and are easily distinguished from the axial–equatorial couplings of 3.5–4.0 Hz seen in the corresponding α-anomers (Matsui and Okada, 1970). Spectral data from the known benzyltetraacetyl-β-D-glucoside **28** (Slotta and Heller, 1930) are included for comparative purposes. The chemical shifts of the anomeric protons fall between 4.35 and 4.48 ppm and support the stereochemical assignments. Matsui and Okada (1970) report shifts of 4.46–4.55 ppm for the anomeric protons in a series of related tetraacetyl-β-D-glucopyranosides, while the ^1H resonances in the corresponding α-anomers occur significantly downfield at 5.03–5.23 ppm.

The structural assignments of the orthoester products also resulted from an analysis of their carbon and proton NMR data (Table II). The ^{13}C spectra revealed the presence of three acetyl carbons and a quarternary orthoester carbon at 121.49 and 121.51 ppm in **21** and **24**, respectively. The occurrence of the ortho acetate methyl protons in the ^1H spectra at 1.80 and 1.84 ppm, 0.31 ppm

upfield from the acetyl methyl signals, was also diagnostic. The coupling constants and chemical shifts of the glucosyl ring protons were consistent with those reported for analogous orthoesters in which R is simple alkyl (Lemieux and Morgan, 1965). The exo stereochemistry of the benzyl carbamate moiety is assumed, based on the results of Lemieux and Morgan and literature precedent (Wulff and Rohle, 1974).

EXPERIMENTAL SECTION

Proton NMR spectra were obtained at 60 MHz on a Varian EM-360L or at 250 MHz on a Bruker WM-250 with tetramethylsilane as an internal standard. Carbon NMR spectra were obtained at 22.5 MHz on a JEOL FX-90Q. Infrared spectra were recorded on a Perkin-Elmer 299-B. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Flash chromatography was done according to the method of Still (1978) on Woelm silica (32–63 μm) or on Florisil (100–200 mesh). Tetrahydrofuran was distilled from sodium–benzophenone immediately prior to use. Melting points are uncorrected.

4,5-Dimethyl-3-(hydroxymethyl)phenol (7). A solution of 80.2 g (0.482 mol) of **6** in 500 mL of dry THF was cooled with an ice bath, and 723 mL of 1.0 M borane–THF complex was added dropwise, with stirring over a 1.5-h period so that the temperature was maintained below 10 °C. The reaction mixture was stirred at 10 °C for 1 h, during which time a large amount of white precipitate separated. The reaction mixture was treated with 150 mL of H_2O, followed by 300 mL of 3 N aqueous NaOH while being cooled in an ice bath. After the mixture was stirred for 15 min, the organic layer was separated and concentrated in vacuo. The residue was dissolved in the aqueous phase, cooled to 0 °C, and neutralized with acetic acid to approximately pH 6. The precipitate that separated on acidification was collected by filtration and dried to give 69.9 g (95%) of 4,6-dimethyl-3-(hydroxymethyl)phenol as a colorless solid, mp 136.0–141.5 °C [lit. mp 144–146 °C (Casida and Slade, 1970)].

2,5-Dimethyl-3-(hydroxymethyl)phenol (11). A 10.1-g sample of acid **9** contaminated with approximately 20% of isomer **10** was treated with 122 mL of 1.0 M borane–THF complex in the same way as for **7** to produce 6.4 g (69%) of 2,5-dimethyl-3-(hydroxymethyl)phenol (**11**) as a colorless solid, mp 136–139 °C [lit. mp 139–141 °C (Casida and Slade, 1970)]. Extraction of the acidified aqueous layer gave 1.7 g of a tan solid that contained additional **11** contaminated by the isomeric alcohol derived from **10** (TLC analysis).

4,5-Dimethyl-3-(hydroxymethyl)phenyl *N*-Methylcarbamate (4). A 2.5-g (16.4-mmol) portion of **7**, 0.1 mL (0.8 mmol) of triethylamine, 1.0 mL (16.4 mmol) of methyl isocyanate, and 100 mL of dichloromethane were stirred in a pressure bottle at 25 °C overnight. The reaction mixture was then filtered through Celite and concentrated in vacuo to give 3.6 g of a colorless semisolid. This residue was flash chromatographed with 95:5 (v/v) CH_2Cl_2–CH_3OH eluent. Early fractions contained 420 mg (10%) of biscarbamate **8** as a colorless solid. Recrystallization from EtOAc–hexane furnished 370 mg of **8** as colorless needles: mp 134.0–136.0 °C; ^1H NMR (acetone-d_6–Me_2SO-d_6) δ 2.18 (s, 3 H), 2.27 (s, 3 H), 2.66 (d, 3 H, J = 5.0 Hz), 2.69 (d, 3 H, J = 5.0 Hz), 5.03 (s, 2 H), 6.5–7.0 (br s, 1 H), 6.87 (s, 2 H), 7.0–7.5 (br s, 1 H); IR ($CHCl_3$) 3470, 1740 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.39; H, 6.84; N, 10.36.

Later fractions from the chromatography contained 2.60 g (76%) of 4,5-dimethyl-3-(hydroxymethyl)phenyl *N*-methylcarbamate (**4**) as a colorless solid. Recrystallization from ether–hexane gave 2.10 g of colorless platelets: mp 108.5–110.0 °C [lit. mp 104.0–106.5 °C (Casida and Slade, 1970)]; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 2.27 (s, 3 H), 2.4–2.9 (br s, 1 H, exchangeable with D_2O), 2.82 (d, 3 H, J = 5.0 Hz), 4.58 (d, 2 H, J = 4.0 Hz), 4.8–5.5 (br s, 1 H, exchangeable with D_2O), 6.83 (d, 1 H, J = 1.0 Hz), 6.98 (d, 1 H, J = 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.00, 20.32, 27.66, 63.28, 118.21, 122.00, 131.32, 138.12, 140.10, 148.60, 155.83; IR (KBr) 3300, 1715 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.91; H, 7.31, N, 6.83.

2,5-Dimethyl-3-(hydroxymethyl)phenyl *N*-Methylcarbamate (5). **11** (2.5 g, 16.4 mmol) was treated with 1.0 mL (16.4 mmol) of methyl isocyanate and 0.1 mL of triethylamine in 100 mL of CH_2Cl_2 in the same manner as was **7**. Flash chromatography with 95:5 (v/v) CH_2Cl_2–CH_3OH eluent separated 400 mg (9%) of biscarbamate **12** as an amorphous solid. Recrystallization from CH_2Cl_2–hexane furnished 320 mg of fine colorless needles: mp 143.0–146.0 °C; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.27 (s, 3 H), 2.73 (d, 3 H, J = 5.0 Hz), 2.81 (d, 3 H, J = 5.0 Hz), 5.07 (s, 2 H), 4.6–5.5 (br s, 2 H), 6.85 (br s, 1 H), 6.98 (br s, 1 H); IR ($CHCl_3$) 3470, 1730 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.40; H, 6.69; N, 10.21.

Further elution provided 2.4 g (70%) of a colorless liquid that slowly solidified on standing. Recrystallization from EtOAc–hexane gave 1.9 g (55%) of **5** as very fine white needles, mp 97.0–98.0 °C [lit. mp 105.0–106.0 °C (Casida and Slade, 1970)]. Additional recrystallization from ether–hexane and a low-temperature recrystallization from ether did not raise this melting point: ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.30 (s, 3 H), 2.81 (d, 3 H, J = 5.0 Hz with a s, 1 H which exchanged with D_2O), 4.50 (s, 2 H), 4.9–5.6 (br s, 1 H), 6.82 (br s, 1 H), 7.03 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.94, 20.88, 27.76, 63.28, 122.11, 125.52, 125.90, 136.25, 140.20, 149.39, 155.43; IR ($CHCl_3$) 3605, 2970, 1735 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14, H, 7.23; N, 6.69. Found: 63.20; H, 7.38; N, 6.73.

A large-scale preparation with 40.0 g (0.263 mol) of **11** and 15.5 mL (0.263 mol) of methyl isocyanate provided, after chromatography and recrystallization from EtOAc–hexane, 37.0 g (67%) of **5** as a colorless powder, mp 106.5–108.0 °C. No difference between the two samples could be detected by spectral or chromatographic means, though the melting points were significantly different. Different crystalline forms might account for this discrepancy. Anal.: C, 63.36; H, 7.12; N, 6.62.

4-Bromo-3,5-dimethylphenyl Benzyl Ether (14). A stirred mixture of 200 g (1.0 mol) of 4-bromo-3,5-dimethylphenol (**13**), 115 mL (1.0 mol) of benzyl chloride, 165.5 g (1.0 mol) of potassium iodide, 137.6 g (1.0 mol) of K_2CO_3, and 2.7 L of DME was heated to reflux under a nitrogen atmosphere for 7 days. The reaction mixture was evaporated and the residue purified by silica gel flash chromatography using 5% EtOAc in hexane to give 208 g (0.705 mol, 72% yield) of the desired ether **14** as a white solid: mp 46–48 °C; ^1H NMR ($CDCl_3$) δ 2.38 (s, 6 H), 5.03 (s, 2 H), 6.74 (s, 2 H), 7.41 (s, 5 H); IR (film) 2900, 1580, 1455, 1315, 1160 cm^{-1}. Anal. Calcd for $C_{15}H_{15}BrO$: C, 61.87; H, 5.19. Found: C, 61.85; H, 4.91.

4-(Benzyloxy)-2,6-dimethylbenzoic Acid (15). To 12.4 g (0.51 mol) of magnesium turnings in a round-bottomed flask was added a small amount of magnesium turnings freshly cleaned by MeI. A solution of 100 g (0.343 mol) of **14** in 400 mL of dry THF was added dropwise over 1 h. The mixture was heated to reflux for 40 min. The mixture was cooled to room temperature and transferred

into an addition funnel under a nitrogen atmosphere. This Grignard solution was added to a large excess of dry ice over 1 h. More dry ice was added and the mixture allowed to stand overnight. THF was evaporated and the residue partitioned between H_2O and hexane. The aqueous layer was acidified by 6 N HCl solution to pH 2 and extracted with CH_2Cl_2 (4 L). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give 81 g of the pure desired benzoic acid ether **15**: 0.316 mol (92% yield); mp 109–110 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 2.45 (s, 6 H), 5.08 (s, 2 H), 6.69 (s, 2 H), 7.40 (s, 5 H), 10.11 (br s, 1 H); IR (film) 3240–2000, 1690, 1605, 1315, 1290, 1180 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.94; H, 6.29; O, 18.73. Found: C, 74.97; H, 6.33; O, 18.70.

4-(Benzyloxy)-2,6-dimethylbenzyl Alcohol (16). To a suspension of 8.0 g of $LiAlH_4$ (0.211 mol) in 100 mL of dry THF was added a solution of 30 g (0.117 mol) of benzoic acid ether **15** dropwise at room temperature. The resulting mixture was heated to reflux under a nitrogen atmosphere for 3 h. The mixture was cooled to room temperature. The excess LAH was quenched with aqueous NH_4OH solution in an ice–H_2O bath. The suspension was filtered and the precipitate extracted with methylene chloride. The methylene chloride extract was combined with the filtrate. The combined mixture was partitioned between H_2O and methylene chloride. The organic layer was dried (Na_2SO_4) and evaporated to give 26 g (0.107 mol, 91.5% yield) of the desired benzyl alcohol ether **16**. This material was used in the following step without further purification. An analytical sample was obtained by recrystallization from CH_2Cl_2–hexane: mp 74–76 °C; ^1H NMR ($CDCl_3$) δ 2.38 (s, 6 H), 4.59 (s, 2 H), 4.98 (s, 2 H), 6.64 (s, 2 H), 7.38 (s, 5 H); IR (film) 3350, 2910, 1610, 1325, 1290, 1145 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49; O, 13.21. Found C, 79.08; H, 7.44, O, 13.78.

3,5-Dimethyl-4-(hydroxymethyl)phenol (17). A solution of 24.5 g (0.101 mol) of benzyl alcohol **16** in 200 mL of MeOH was hydrogenolyzed with 3.0 g of 5% Pd/C under a 45.5 psi hydrogen atmosphere for 5 h. The mixture was filtered through a pad of Celite and the filtrate evaporated to give 14.8 g (0.097 mol, 96% yield) of **17**, which was used without purification: ^1H NMR ($CDCl_3$–CD_3OD) δ 2.34 (s, 6 H), 4.58 (s, 2 H), 6.48 (s, 2 H).

3,5-Dimethyl-4-(hydroxymethyl)phenyl *N*-Methylcarbamate (3). A mixture of 14.8 g (0.097 mol) of (hydroxymethyl)phenol **17**, 150 mL of CH_2Cl_2, 0.5 mL of triethylamine, and 5.7 mL (0.097 mol) of methyl isocyanate in a sealed bottle was heated to 43 °C for $4^1/_2$ h. The mixture was cooled to room temperature and filtered to give 22 g of the pure desired (hydroxymethyl)phenyl carbamate **3**, which was recrystallized from hot CH_2Cl_2: mp 149–150 °C; 18.2 g (90% yield); ^1H NMR ($CDCl_3$) δ 1.31 (t, 1 H, J = 5 Hz), 2.40 (s, 6 H), 2.86 (d, 3 H, J = 5 Hz), 4.68 (d, 2 H, J = 5 Hz), 6.80 (s, 2 H); IR (KBr) 3600–2640, 1712, 1530, 1260, 1160 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.14; H, 7.64.

[2,3-Dimethyl-5-[(*N*-methylcarbamoyl)oxy]benzyl]tetra-*O*-acetyl-β-D-glucopyranoside (20) and Tri-*O*-acetyl-α-D-glucopyranose 1,2-[2,3-Dimethyl-5-[(*N*-methylcarbamoyl)oxy]benzyl orthoacetate] (21). A mixture of 1.66 g (7.17 mmol) of Ag_2O, 1.50 g (7.17 mmol) of **4**, and 25 mL of CH_2Cl_2 was cooled to 5 °C with an ice bath, and a solution of 2.95 g (7.17 mmol) of acetobromo-α-D-glucose in 10 mL of CH_2Cl_2 was added, dropwise and with stirring, in the dark. Stirring was continued at 5 °C for 1 h, and the mixture was allowed to warm to 25 °C over a 5-h period. The reaction mixture was filtered through Celite and concentrated in vacuo to give 4.1 g of a white amorphous solid that was flash chromatographed (9:1 (v/v) CH_2Cl_2–acetone). Early fractions contained 530 mg of the orthoacetate **21** as a colorless, glassy solid: mp 50–59 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.80 (s, 3 H), 2.11 (s, 9 H), 2.15 (s, 3 H), 2.26 (s, 3 H), 2.88 (d, 3 H, J = 4.9 Hz), 3.97 (dt, 1 H, J = 4.4, 9.6 Hz), 4.21 (d, 2 H, J = 4.4 Hz), 4.33 (dd, 1 H, J = 2.9, 5.2 Hz), 4.51 (d, 1 H, J = 11.6 Hz), 4.56 (d, 1 H, J = 11.6 Hz), 4.91 (dd, 1 H, J = 2.6, 9.6 Hz), 4.9–5.0 (br s, 1 H), 5.21 (dd, 1 H, J = 2.6, 2.9 Hz), 5.71 (d, 1 H, J = 5.2 Hz), 6.88 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.25, 20.42, 20.80 (3 C), 27.74, 63.14, 64.14, 67.07, 68.26, 70.05, 73.21, 97.05, 119.10, 121.49, 122.52, 131.73, 136.33, 139.23, 148.60, 155.53, 169.16, 169.67, 170.73; IR ($CHCl_3$) 3480, 3010, 1745 cm^{-1}. Anal. Calcd for $C_{25}H_{33}NO_{12}$: C, 55.66; H, 6.17; N, 2.60. Found: C, 55.31; H, 5.99; N, 2.73.

Intermediate fractions contained 820 mg of a 3:2 mixture of **20** and **21** as determined by NMR analysis.

Later fractions yielded 600 mg of the tetraacetylglucoside **20** as a colorless glass: mp 58.0–68.0 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 2.00 (s, 6 H), 2.02 (s, 3 H), 2.11 (s, 3 H), 2.14 (s, 3 H), 2.27 (s, 3 H), 2.88 (d, 3 H, J = 4.9 Hz), 3.67 (m, 1 H), 4.17 (dd, 1 H, J = 2.5, 12.3 Hz), 4.27 (dd, 1 H, J = 4.6, 12.3 Hz), 4.48 (d, 1 H, J = 7.6 Hz), 4.61 (d, 1 H, J = 12.2 Hz), 4.89 (d, 1 H, J = 12.2 Hz), 4.99–5.30 (m, 4 H), 6.90 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.21, 20.33, 20.52 (3 C), 20.69, 27.67, 61.91, 68.39, 69.09, 71.26, 71.69, 72.88, 98.56, 120.01, 122.91, 132.47, 135.05, 138.38, 148.40, 155.39, 169.26, 169.37, 170.20, 170.64; IR ($CHCl_3$) 3480, 3020, 1745 cm^{-1}. Anal. Calcd for $C_{25}H_{33}NO_{12}$: C, 55.66; H, 6.17; N, 2.60. Found: C, 55.39; H, 6.13, N, 2.48. The total yield of **20** was 1.09 g (28%), and the total yield of **21** was 860 mg (22%).

[2,3-Dimethyl-5-[(*N*-methylcarbamoyl)oxy]benzyl]-β-D-glucopyranoside (22). A solution of 2.0 g (3.71 mmol) of **20** in 100 mL of anhydrous CH_3OH was cooled to 4 °C with an ice bath and treated with 0.75 mL of a 1.60 N $Ba(OCH_3)_2$ in CH_3OH solution (Cardona and Dorough, 1973). After 1 h, the mixture was neutralized with 2.4 mL of standardized 0.500 N aqueous H_2SO_4. Decolorizing carbon was then added to aid in the filtration of the colloidal $BaSO_4$ that had separated. The filtrate was concentrated under reduced pressure to give a colorless liquid. Dilution of this residue with ether caused the precipitation of 1.3 g (94%) of **22** as a colorless, amorphous solid, mp 150–166 °C. An analytical sample was prepared by chromatographing on silica gel using an 88:12 (v/v) CH_2Cl_2–CH_3OH eluent: mp 171.0–174.0 °C; ^1H NMR (250 MHz, CD_3OD) δ 2.21 (s, 3 H), 2.27 (s, 3 H), 2.77 (s, 3 H), 3.69 (dd, 1 H, J = 5.1, 12.0 Hz with a m, 1 H), 3.90 (d, 1 H, J = 11.5 Hz), 4.35 (d, 1 H, J = 7.6 Hz), 4.65 (d, 1 H, J = 12.1 Hz), 4.8–5.1 (m, 9 H), 6.84 (d, 1 H, J = 2.0 Hz), 7.03 (d, 1 H, J = 2.0 Hz); ^{13}C NMR (Me_2SO-d_6) δ 13.90, 19.84, 27.04, 61.14, 68.02, 70.13, 73.44, 76.72, 76.93, 102.13, 119.16, 122.09, 131.16, 136.85, 137.20, 148.34, 155.11; HRMS Calcd for $C_{17}H_{25}NO_8$ m/e 371.1580, found 371.1581. Anal. Calcd for $C_{17}H_{25}NO_8 \cdot H_2O$: C, 52.44; H, 6.99; N, 3.60. Found: C, 52.78; H, 6.70; N, 3.39.

[4-(Benzyloxy)-2,6-dimethylbenzyl]tetra-*O*-acetyl-β-D-glucopyranoside (23) and Tri-*O*-acetyl-α-D-glucopyranose 1,2-[4-(Benzyloxy)-2,6-dimethylbenzyl orthoacetate] (24). A mixture of 5.0 g (0.0207 mol) of (hydroxymethyl)phenol ether **16**, 4.72 g of Ag_2O, 0.9 g of NaI, 8.32 g (0.020 mol) of α-D-acetobromoglucose, and 40 mL of CH_2Cl_2 was stirred at room temperature under a nitrogen atmosphere for 14 days. The mixture was filtered through a pad of Celite, and the solvent was evaporated. The residue was purified by flash column chromatography

on Florisil in 20% EtOAc in hexane to give 1.54 g (0.00270 mol, 13% yield) of glucoside **23** and 1.2 g (0.00210 mol, 10.1% yield) of orthoester **24**. Analytical data for glucoside **23**: ^{1}H NMR ($CDCl_3$) δ 1.90–2.08 (4 s, 12 H), 2.30 (s, 6 H), 4.08–4.52 (m, 4 H), 4.77 (s, 2 H), 4.90–5.21 (m, 5 H), 6.64 (s, 2 H), 7.36 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.72, 20.59, 20.72 (4 acetyl C), 62.25, 64.28, 68.64, 69.84, 71.29, 71.84 and 72.97 (5 C on glucosidyl moiety and 2-benzylic C), 97.76 (acetal C in β form), 114.42, 124.87, 127.50, 127.96, 128.62, 137.86, 148.87, 158.62 (12 aromatic C) 169.19, 169.40, 170.30 and 170.62 (4 C=O); CI mass spectrum (m + 1)/e 573. Analytical data for orthoester **24**: ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3 H), 2.02 (s, 3 H), 2.10 (s, 6 H), 2.32 (s, 6 H), 4.00–5.38 (m, 10 H), 5.72 (d, 1 H, J = 6 Hz), 6.66 (s, 2 H), 7.38 (s, 5 H).

(4-Hydroxy-2,6-dimethylbenzyl)tetra-*O*-acetyl-β-D-glucopyranoside (25). A mixture of 170 mg (0.3 mmol) of ether **23** in 10 mL of isopropyl alcohol and 10 mL of CH_2Cl_2 and 40 mg of 5% Pd on carbon was subjected to hydrogenolysis under 45.4 psi of H_2 for 17 h. The reaction mixture was filtered through a pad of Celite and the solvent evaporated. The residue (170 mg) was used in the following step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.94–2.10 (4 s, 12 H), 2.26 (s, 6 H), 4.00–4.50 (m, 4 H), 4.72 (s, 2 H), 4.80–5.20 (m, 3 H), 6.48 (s, 2 H).

[4-[(*N*-Methylcarbamoyl)oxy]-2,6-dimethylbenzyl]tetra-*O*-acetyl-β-D-glucopyranoside (26). A mixture of 170 mg of phenol **25**, 0.1 mL of methyl isocyanate, 0.05 mL of triethylamine, and 10 mL of CH_2Cl_2 was stirred at room temperature in a sealed bottle for 22 h. The reaction mixture was evaporated and the residue partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by Florisil flash column chromatography using 30% EtOAc in hexane to give 60 mg (0.11 mmol, 37% from ether **23**) of **26**: mp 157–159 °C (Et_2O–hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.97 (s, 3 H), 1.98 (s, 3 H), 2.02 (s, 3 H), 2.10 (s, 3 H), 2.34 (s, 6 H), 2.88 (d, 3 H, J = 4.8 Hz), 3.64–3.89 (m, 1 H), 4.16–4.29 (m, 2 H), 4.43 (d, 1 H, J = 8.0 Hz), 4.80 (AB q, 2 H, J = 11.7 Hz), 4.95–5.18 (m, 4 H), 6.81 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.58 (2 CH_3–Ph), 19.64, 20.56 and 20.67 (4 CH_3C=O), 27.71 (NCH_3), 52.85, 64.22, 68.72, 71.40, 71.92, 73.00 (5 C on glucosidyl moiety and benzylic carbon), 98.19 (acetal C in β form), 121.09, 129.40, 139.88, 158.82 (6 aromatic C), 155.20 (OC(O)N), 169.16, 169.40, 170.16 and 170.54 (4 acetyl C); IR (film) 3380, 2950, 1740, 1520, 1475, 1370, 1220, 1150, 1030 cm^{-1}; Anal. Calcd for $C_{25}H_{33}NO_{12}$: C, 55.78; H, 6.13; N, 2.60; O, 35.60. Found C, 55.72, H, 6.24; N, 2.58; O, 35.32.

[4-[(*N*-Methylcarbamoyl)oxy]-2,6-dimethylbenzyl]-β-D-glucopyranoside (27). To a solution of 780 mg (1.45 mmol) of carbamate acetate **26** in 91 mL of dry MeOH was added 0.316 mL of $Ba(OMe)_2$ solution at 4 °C under a nitrogen atmosphere. The resulting mixture was stirred at 4 °C for 1$^1/_2$ h when 0.146 mL of 1 N H_2SO_4 was added (to pH 7). After addition of 400 mg of activated charcoal the mixture was filtered through a pad of Celite and the filtrate was evaporated in vacuo. Ethyl ether (50 mL) was added to the residue. The resulting precipitate was filtered to give 210 mg (0.57 mmol, 39%) of the desired glucoside **27** as a white amorphous solid: ^{1}H NMR (acetone-d_6 and D_2O) δ 2.40 (s, 6 H), 2.77 (s, 3 H), 3.42–5.10 (m, 14 H), 6.79 (s, 2 H); ^{13}C NMR (acetone-d_6 and D_2O) δ 19.32, 61.46, 65.01, 70.30, 73.71, 76.58, 101.72, 114.99, 121.17, 130.84, 140.70, 150.93, 156.87; fast atom bombardment mass spectrum (argon gun, positive ions glycerol matrix) m/z (relative intensities) 372 (7) $(M + H)^+$, 192 (24) $(C_{11}H_{14}NO_2)^+$, 135 (100) $(C_9H_{10}O+H)^+$.

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