Syntheses of derivatives of *N*-acetyl-D-lactosamine from D-lactal hexaacetate. Hexa-*O*-acetyl-2-deoxy-2-phthalimido-β-D-lactosyl chloride

R. U. LEMIEUX, S. Z. ABBAS,[1] M. H. BURZYNSKA,[2] AND R. M. RATCLIFFE[3]

Department of Chemistry, University of Alberta, Edmonton, Alta., Canada T6G 2G2

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Two reaction routes are presented for the preparation of hexa-*O*-acetyl-2-deoxy-2-phthalimido-β-D-lactosyl chloride (**7**) from lactal hexaacetate (**1**). One route involves, in the first stage, reaction of **1** with nitrosyl chloride and proceeds by way of benzyl 2-amino-2-deoxy-α-D-lactoside (**4**) as an intermediate. The other route, which is considered more efficient, involves reaction of **1** with ceric ammonium nitrate and sodium azide and involves the β-anomer (**12**) of **4** as an intermediate. The preparation of **7** is of interest as a reagent for the preparation of 2-amino-2-deoxy-β-D-lactosides. The procedures offer routes for the preparation of D-lactosamine.

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On présente deux méthodes de préparation du chlorure d'hexa-*O*-acetyl-déoxy-2-phtalimido-2-β-D-lactosyle (**7**) à partir de l'hexaacétate de lactale (**1**). Une méthode fait intervenir, dans la première étape, la réaction du composé **1** avec le chlorure de nitrosyle et passe par un intermédiaire benzylamino-2-déoxy-2-α-D-lactoside (**4**). L'autre méthode, que l'on considère plus efficace, fait intervenir la réaction de **1** avec le nitrate d'ammonium cérique et l'azoture de sodium et implique comme intermédiaire l'anomère β (**12**) du composé **4**. L'intérêt de la préparation du composé **7** réside dans le fait qu'il est un moyen d'accès aux amino-2-déoxy-2-β-D-lactosides. Les méthodes ouvrent la voie à la préparation de la D-lactosamine.

[Traduit par le journal]

N-Acetyl-D-lactosamine (D-LacNAc) is of widespread occurrence as a component of the oligosaccharide portions of very many *N*- and *O*-linked glycoproteins and the oligosaccharides of milk (1). It is a building unit for the antigenic determinants of a number of certain Ii human blood group activities (2) as well as of the ABH Type 2 determinants (3).

In 1977[4] we announced our involvement in the chemical synthesis of oligosaccharide structures of possible interest to immunochemical investigations of the Ii determinants. On that occasion, the synthesis, amongst others, of βDLacNAc(1→6) and βDLacNAc(1→3) derivatives of both D-galactose and βDGalO$(CH_2)_8COOCH_3$ were reported. These syntheses are now reported in detail in an accompanying paper. The role that these products played in establishing the nature of the combining site of the monoclonal anti-I Ma myeloma protein have been reported in separate communications (5, 6). The synthesis of these β-glycosides of *N*-acetyl-D-lactosamine was accomplished by way of hexa-*O*-acetyl-2-deoxy-2-phthalimido-β-D-lactosyl chloride (**7**) using the silver triflate – collidine complex (7) to promote its condensation with the alcohol. The worth of this approach (the phthalimido-chloride method) for the establishment of β-glycosidic linkage from 2-amino-2-deoxy sugars (wherein the amino group is in equatorial orientation) was considered in an accompanying paper (4). We now wish to report details for the preparation of **7** from D-lactal hexaacetate (**1**) by two different routes. One process is based on the procedure for the preparation of 2-amino-2-deoxy-α-glycopyranoside which was developed in this laboratory (8) and which will be termed the nitroso-chloride route. The other process for the preparation of **7** is based on the azidonitration of glycals (9, 10) to form 2-azido-2-deoxy glycopyranosides and which will be designated as the azidonitrate route.

Ponpipom and co-workers (11, 12) have independently used the nitroso-chloride route for the preparation of the phthalimido-chloride **7**. Although full details have not been reported, these investigators used the same reaction sequences except for the conversion of **6** to **7**. Whereas we used the Vilsmeier reagent for this purpose (4), they chose to acetylate **6** for subsequent conversion to **7** using aluminum chloride. Dimitriev *et al.* (13) had previously prepared *N*-acetyl-D-lactosamine by way of a zinc reduction of the oximino-chloride **2**.

Very recently, Arnarp and Lönngren (14) published the use of the azidonitration route to achieve the bromide form of the chloride **7**. The reagent was used in the course of the preparation of hepta- and

[1]University of Alberta Postdoctoral Fellow 1975–1977. Present address: Chembiomed Ltd., W5-56 Chemistry Bldg., University of Alberta, Edmonton, Alta., Canada T6G 2G2.

[2]University of Alberta Postdoctoral Fellow 1978–1980.

[3]University of Alberta Postdoctoral Fellow (1975–1977) and Research Associate (1977–1979). Present address: Chembiomed Ltd., W5-56 Chemistry Bldg., University of Alberta, Edmonton, Alberta, Canada T6G 2G2.

[4]R. U. Lemieux, S. Z. Abbas, and B. Y. Chung. Abstr. Pap. Chem. Soc. Meeting, Norwich, England, April 8–10, 1977.

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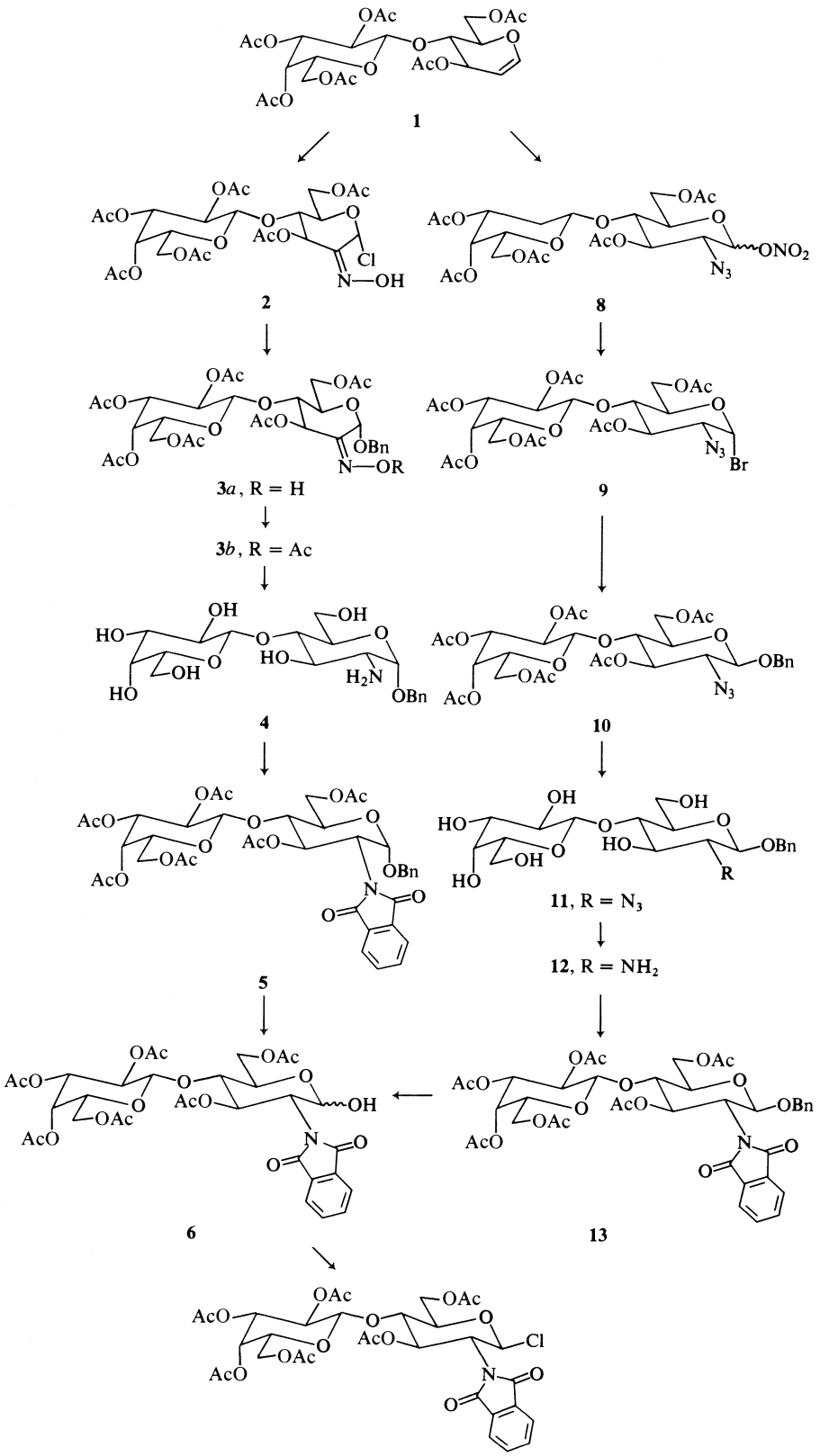

pentasaccharides which are building units of "complex type" aspargine-linked glycoproteins.

Although it was not possible to expend much effort toward the optimization of yields, it is noteworthy that the seven-stage process for converting D-lactal hexaacetate (**1**) to **6** by way of the azidonitration route proceeded in 23% overall yield whereas only near half this yield was obtained by way of the six-stage nitroso-chloride route. On the other hand, a number of transformations in the latter process proceeded in yields that likely can be substantially improved. At the time that this process was investigated, the relatively high reactivity of the phthalimido group in α-glycosides toward hydrolysis[5] was not recognized and this property likely had an influence on the low yields obtained in the preparation of compounds **5** (70%) and **6** (60%). Also, the relatively poor yields obtained in the reaction of the nitrosyl chloride adduct **2** with benzyl alcohol and for the diborane reduction of the oximinoacetate **3***b* appear unacceptable in view of our previous experiences (8) with these reactions. Nevertheless, we recommend the process by way of azidonitration as the more convenient and reliable laboratory preparation.

The synthetic sequences are straightforward and warrant little comment beyond the information contained in the experimental portion of this paper. It may be noted that the use (15) of a strongly basic resin for the removal of alkali-labile by-products in the preparation of **4** should prove generally useful for such preparations. The high resistance to hydrogenolysis displayed by the α-benzyl glycoside **5** as compared to its β-anomer **13** was to be expected (16) but was an important disadvantage in the formation of a product **6** which contains groups susceptible to solvolysis. The reduction of the azide **11** to the amine **12** using hydrogen sulfide (17) in the presence of amine proved highly convenient and essentially quantitative. The amine **4** was characterized both as its peracetate and as its *N*-acetyl derivative. The use of the Vilsmeier reagent for the conversion of **6** to **7** has been presented in a separate communication (4). The preparation of the azido-bromide **9** in 42% overall yield by way of the azidonitration of **1** has been reported (10).

Experimental

The general procedures and analytical methods were the same as previously described (4). The nmr measurements used either TMS (< 1%) as internal standard or 1:1 TMS–CCl_4 as external standard.

*Dimeric 3,6-di-*O*-acetyl-(4-*O*-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride (**2**)*

Nitrosyl chloride was added to a solution of D-lactal hexaacetate **1** (18) in dry ethyl acetate (280 mL) (19) to form **2**, mp 122–123°C, $[\alpha]_D^{20}$ +69.2° (*c* 1.0, $CHCl_3$), in 92% yield (lit. (13) mp 120–122°C, $[\alpha]_D^{20}$ +66.7° (*c*, 1.0, $CHCl_3$)).

*Benzyl 3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-oximino-α-D-*arabino*-hexopyranoside (**3**a)*

A solution of the nitrosyl chloride adduct (**2**) (60.0 g, 0.11 mol) and benzyl alcohol (14.0 g, 0.13 mol) in *N,N*-dimethylformamide (300 mL) was kept at room temperature for 2 days. The solvent was removed, the dark yellow residual oil was dissolved in diethyl ether (500 mL), and this solution was washed with water (3 × 200 mL). Work-up in the usual manner provided a solid foam which was chromatographed on a column of Silica Gel G (E. Merck A.G., Darmstadt) using ethyl acetate – hexane (1:1). The first and main fraction provided a solid (40.0 g, 59% yield), $[\alpha]_D^{24}$ +31.2° (*c* 1.3, $CHCl_3$), whose ^1H nmr spectrum was consistent with expectation for the title compound **3***a*. *Anal.* calcd. for $C_{31}H_{39}NO_{17}$: C 53.37, H 5.64, N 2.01; found: C 53.75, H 5.55, N 2.01.

*Benzyl 2-acetoximino-3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-*arabino*-hexopyranoside (**3**b)*

Treatment of the oxime **3***a* (27.0 g, 38 mmol) with pyridine – acetic anhydride (2:1) (150 mL) at 5°C for 12 h provided the title compound **3***b* (26.0 g, 90% yield) as a solid, $[\alpha]_D^{24}$ +31.0 (*c* 1, $CHCl_3$) (lit. (13) $[\alpha]_D^{25}$ +12° (*c* 1.45, $CHCl_3$)), with an ^1H nmr spectrum consistent with a high degree of purity. *Anal.* calcd. for $C_{33}H_{41}NO_{18}$: C 53.58, H 5.58, N 1.89; found: C 53.19, H 5.51, N 1.72.

*Benzyl 2-amino-2-deoxy-4-*O*-(β-D-galactopyranosyl)-α-D-glucopyranoside (**4**)*

A solution of the oximinoacetate **3***b* (25.0 g, 33.7 mmol) in tetrahydrofuran (200 mL) was added dropwise to a 1 *M* solution of diborane in tetrahydrofuran (800 mL) kept at −70°C in an atmosphere of nitrogen. After completion of the addition, the solution was allowed to warm to room temperature and kept for 24 h and then carefully poured into methanol (600 mL). Evaporation left an oil which was taken up in methanol, rendered acid with acetic acid, and evaporated to a solid residue. This residue was dissolved in methanol and the solution was applied to a column (2.5 × 50 cm) of a basic resin (15) (Dowex I-X8, 200–400 mesh, OH^- form). On elution with methanol and solvent removal, a crystalline solid (8.6 g, mp 138–142°C, 60% yield) was obtained. Recrystallization from ethanol raised the melting point to 164–168°C, $[\alpha]_D^{25}$ +64.6° (*c* 1, H_2O). The ^1H nmr was consistent with the structural assignment. *Anal.* calcd. for $C_{19}H_{29}NO_{10}\cdot H_2O$: C 49.77, H 7.03, N 3.05; found: C 50.76, H 6.95, N 3.11.

Acetylation of **4** provided benzyl 2-acetamido-3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside, mp 101–103°C; $[\alpha]_D$N +51° (*c* 0.4, $CHCl_3$) (lit. (12) mp 102–104°C, $[\alpha]_D^{25}$ +56.4 (*c* 1.56, $CHCl_3$)). De-*O*-acetylation readily provided crystalline benzyl 2-acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-α-D-glucopyranoside, mp 226–229°C, $[\alpha]_D^{25}$ +105.5° (*c* 0.85, H_2O).

*Benzyl 3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-α-D-glucopyranoside (**5**)*

Phthalic anhydride (1.2 g, 8 mmol) was added to a solution of the amine **4** (6.0 g, 13.9 mmol) in pyridine (25 mL). The solution was heated to 60–75°C for 20 min. Triethylamine (1.4 g, 13.9 mmol) and more phthalic anhydride (1.2 g, 8 mmol) were added and the heating was continued for 2 h. Methanol (50 mL) was added and the solution was evaporated to a dry residue which was taken up in 30 mL of a mixture of pyridine – acetic anhydride (2:1). After heating at 90°C for 3 h, the crude solid product was isolated in the usual manner and applied to a

[5]R. U. Lemieux and P. Hermentin, in preparation.

column (2.5 × 50 cm) of Silica Gel G for chromatography using ethyl acetate – hexane (2:1). The first fraction (7.88 g, 70% yield) was recrystallized from ethyl acetate – hexane, mp 177–180°C, $[\alpha]_D^{25}$ +86.1° (*c* 1.1, $CHCl_3$). The ^1H nmr was consistent with the structural assignment. The signals for C-1′ and C-1 occurred at 100.97 and 96.35 ppm, respectively. *Anal.* calcd. for $C_{39}H_{43}NO_{18}$: C 57.56, H 5.32, N 1.72; found: C 57.41, H 5.25, N 1.66.

*Benzyl 3,6-di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galacto-pyranosyl)-2-azido-2-deoxy-β-D-glucopyranoside (**10**)*

A solution of the azidobromide **9** (10), (20.5 g, 30 mmol), mp 156–157°C, $[\alpha]_D^{25}$ +87° (*c* 0.93, $CHCl_3$), in nitromethane (50 mL) was added dropwise to a stirred mixture of benzyl alcohol (10.0 g, 92 mmol), silver carbonate (30.0 g, 109 mmol), and Drierite (30.0 g) which was cooled to −22°C and protected from light and moisture. After stirring at this temperature for 18 h, the solids were removed by filtration and washed with dichloromethane. The combined filtrates were taken to dryness and the residue was dissolved in ethyl acetate – hexane (1:1) for passage through a short column of Silica Gel G. Solvent removal left an oily residue from which the title compound **10** crystallized on the addition of diethyl ether. After one recrystallization from diethyl ether (16.4 g, 77% yield), the melting point was 137–138°C, $[\alpha]_D^{25}$ −9.7° (*c* 2.3, $CHCl_3$). The ^1H- and ^{13}C nmr spectra in $CDCl_3$ were entirely consistent with the assigned structure; for example, in confirming the presence of the benzyl group, the six acetyl groups at 1.96, 2.03, 2.05, 2.11, 2 × 2.15 ppm and the two β-anomeric hydrogens at 4.45 (d, 8 Hz, H-1′) and 4.05 ppm (d, 8.5 Hz, H-1). The signals for C-1′ and C-1 were at 100.88 and 100.07 ppm, respectively. Absorption in the infrared (KBr) at 2110 cm^{-1} confirmed the presence of the azido group. *Anal.* calcd. for $C_{31}H_{39}O_{16}N_3$: C 52.47, H 5.54, N 5.92; found: C 52.22, H 5.64, N 5.68.

*Benzyl 2-azido-2-deoxy-4-O-(β-D-galactopyranosyl)-β-D-gluco-pyranoside (**11**)*

The acetate **10** (8.72 g, 12.3 mmol) was dissolved in 150 mL of 0.01 *N* sodium methoxide in methanol. Solvent removal provided crystals which were washed with a little cold methanol (5.01 g, 89% yield), mp 202–204°C, $[\alpha]_D^{25}$ −1.1° (*c* 0.4, CH_3OH). *Anal.* calcd. for $C_{19}H_{27}O_{10}N_3$: C 49.89, H 5.95, N 9.19; found: C 49.84, H 5.86, N 8.97.

*Benzyl 2-amino-2-deoxy-4-O-(β-D-galactopyranosyl)-β-D-glucopyranoside (**12**)*

A slow stream of hydrogen sulfide was bubbled through an ice-cold solution of the azide **11** (10.8 g, 23.5 mmol) in pyridine (210 mL) and triethylamine (60 mL) for 2.5 h. The solution was evaporated to dryness and the residue was extracted with a mixture of methanol–water (1:1). The extract was filtered through a bed of diatomaceous earth and evaporated. The residue (10.65 g) appeared to be the desired amine **12** as assessed by ^{13}C nmr and tlc. Although it was contaminated with traces of sulfur, it was used directly for the preparation of the phthalimido compound **13**. In order to remove the sulfur and obtain a sample for analysis, the compound was adsorbed on a cation-exchange resin (AG 50W-X2, 200–400 mesh, 40 g) in the H^+ form and, after washing, was desorbed with ammonium hydroxide. After solvent removal, the residue was taken up in water, the solution treated with charcoal and evaporated to a syrup which crystallized, mp 108–111°C, $[\alpha]_D^{25}$ −25.3° (*c* 2.4, H_2O); ^{13}C nmr (D_2O, external TMS): 136.68, 128.62, 128.53, 128.31, 102.95 (C-1′), 101.88 (C-1), 78.97 (C-4), 75.17, 74.76, 74.20, 72.53, 71.39, 70.86, 68.42, 60.81 and 60.27 (C-6 and C-6′), 56.02 (C-2). *Anal.* calcd. for $C_{19}H_{29}NO_{10}\cdot 0.5H_2O$: C 51.81, H 6.86, N 3.18; found: C 51.85, H 6.67, N 2.98.

*Benzyl 3,6-di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyrano-syl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (**13**)*

Treatment of the β-amine **12**, under the conditions described above for the conversion of the α-anomer **4** to **5**, provided the title compound **13** in 79% yield after recrystallization from ethyl acetate – hexane, mp 187–188°C, $[\alpha]_D^{25}$ −9.6° (*c* 2.5, $CHCl_3$). The ^1H- and ^{13}C nmr spectra ($CDCl_3$) were consistent with the structural assignment. The signals for the H-1 and H-1′ atoms were at 5.40 and 4.57 ppm each as doublets with spacings of 8.2 Hz. The low-field signal for H-1 is consistent with the deshielding expected by the vicinal phthalimido group. The signals for C-1′ and C-1 occurred at 101.06 and 97.1 ppm, respectively. *Anal.* calcd. for $C_{32}H_{37}NO_{18}$: C 57.57, H 5.33, N 1.73; found: C 57.57, H 5.44, N 1.72.

*3,6-Di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-α,β-D-glucopyranose (**6**)*

(a) *From the α-benzyl glycoside **5***

Hydrogenolysis of compound **5** (6.0 g, 7.3 mmol) dissolved in 5% solution of acetic acid in ethanol (100 mL) and using 5% palladium on charcoal (4.0 g) and 50 psi of hydrogen was incomplete after 24 h. The title compound was obtained in 60% yield by chromatography on Silica Gel G column (3 × 60 cm) and developing the column with ethyl acetate – hexane (2:1). It occurred as the second and main fraction, mp 116–120°C. The identity of the product was evident from a consideration of its ^1H nmr which, furthermore, was similar to that for the product obtained below. Moreover, both products could be converted to the phthalimido-chloride (**7**) in 82–85% yields.

(b) *From the β-benzyl glycoside **13***

Hydrogenolysis of compound **13** in ethanol – ethyl acetate (1:1) at 70 psi and room temperature using 10% palladium on charcoal proceeded readily to provide the title product, mp 132–140°C, in quantitative yield.

*3,6-Di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (**7**)*

The alcohol **6** (2.98 g, 4.13 mmol) was dissolved with *sym*-collidine (0.77 g, 6.4 mmol) in dichloromethane (20 mL). This solution was added dropwise to a suspension of *N*,*N*-dimethylchloroforminium chloride (Vilsmeier reagent) (1.70 g, 12.9 mmol) in dichloromethane (10 mL) kept at 0°C and in an atmosphere of dry nitrogen. The reaction mixture was allowed to warm to room temperature while being stirred for 3 h. Toluene (100 mL) was then added and the solution was washed with cold dilute aqueous hydrochloric acid (30 mL), then with aqueous sodium bicarbonate (30 mL), and finally with water (30 mL). After drying over anhydrous sodium sulfate, the solvent was removed to leave a residue which crystallized readily from dichloromethane – diethyl ether, mp 184–185°C, $[\alpha]_D^{25}$ +34.7° (*c* 1.8, $CHCl_3$) (lit. (12) mp 173–174°C; $[\alpha]_D^{25}$ +29.3° (*c* 1.5, $CHCl_3$)) (2.61 g, 85% yield). The compound was best characterized by its ^{13}C nmr spectrum ($CDCl_3$): 170.25, 170.07, 169.96, 169.09, 167.36, 134.54, 131.20, 123.80, 101.07 (C-1′), 85.55 (C-1), 78.60, 77.19, 76.44, 76.30, 75.77, 71.06, 70.96, 70.72, 69.12, 66.65, 62.03, 60.81, 67.91 (C-2), 20.82, 20.58, 20.46. *Anal.* calcd. for $C_{32}H_{36}NO_{17}Cl$: C 51.79, H 4.89, N 1.88, Cl 4.77; found: C 51.63, H 4.85, N 1.87, Cl 4.77.

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