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THE REGIOSELECTIVITY OF DIBUTYLSTANNYLENE-MEDIATED OXIDATION OF METHYL 3',4'-*O*-ISOPROPYLIDENE-α- AND β-LACTOSIDE. A NEW SYNTHESIS OF *N*-ACETYLLACTOSAMINE§

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Abstract - The dibutylstannylene-mediated oxidation of methyl 3',4'-*O*-isopropylidene-α-lactoside (**1**) under different conditions using bromine as oxidizing agent has been investigated. The regioselectivity of this reaction strongly depends on the solvent and the nature of the added base. The 2-keto derivative, isolated as the corresponding methyloximino (**10**) or benzyloximino (**13**) derivatives, is the only oxidation product when acetonitrile is used as solvent and tributyltin methoxide as base. The oxidation of methyl 3',4'-*O*-isopropylidene-β-lactoside (**5**) under the same conditions results in regioselective oxidation at C-3. The simple regioselective oxidation of the α-anomer (**1**) leads, after hydrogenation of the oximes (**10** and **13**) derived from the resulting 2-keto derivative, to lactosamine derivatives in a simple and convenient manner.

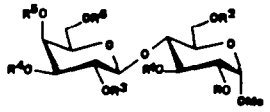
Regioselective oxidation of diols, triols, and other polyhydroxy derivatives have been reported,[1-17] although the latter usually gives the desired polyhydroxy ketones in low yield.[16,17] These reactions are of importance in synthetic organic chemistry and particularly in carbohydrate chemistry, where the regioselective oxidation of an easily available starting material may afford a polyhydroxy ketone which could be converted, through standard reactions, into a valuable product in very few steps. The advantages of this synthetic approach in comparison to multistep procedures are obvious and its main difficulty consists in achieving good selectivity and reasonable yield in the key oxidation step.

We now report the results of a study of the di-*n*-butylstannylene-mediated regioselective oxidation of methyl 3',4'-*O*-isopropylidene-α-(**1**) and -β-(**5**)-lactoside. This study has permited a direct and simple synthesis of the biologically important disaccharide *N*-acetyllactosamine (**2**) in reasonable yield. *N*-Acetyllactosamine (**2**) is a constituent of glycoproteins,[18,19] blood group substances,[18] and human milk oligosaccharides[20] and has been previously synthesized.[21-30] The regioselective oxidation of carbohydrate derivatives through di-*n*-butylstannylenes is well documented[6,15,35] although the direct oxidation of a pentahydroxy derivative such as **1** or **5** has never been reported.

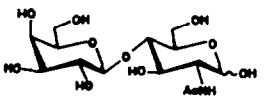
RESULTS AND DISCUSSION

Compound **1** was prepared from methyl-hepta-*O*-acetyl-β-lactoside (**6**)[40] by anomerization with titanium tetrachloride to give a mixture of **6** and methyl-hepta-*O*-acetyl-α-lactoside (**7**) from which **7** was isolated by crystallization in 60 % yield. Deacetylation of **7** followed by acetalation with 2,2-dimethoxypropane gave **1** in 62 % yield. Two other acetalated derivatives could be isolated in low yield (13 %) from the acetalation mixture, probably[31,32] **8** and **9** [signals at δ 27.9 and 26.2 for the 3',4'-*O*-isopropylidene group and δ 48.6 and 24.0 (double intensity) in the ^{13}C-n.m.r. spectra.] Compound **1** possesses only a *vic*-

§ *Dedicated to Professor José M. Fernández-Bolaños on occasion of his 65th birthday.*



1 R = R^1 = R^2 = R^3 = R^6 = H ; R^4 R^5 = CMe_2



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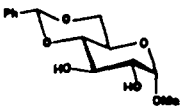
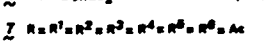


3

4 R = R^1 = $SnBu_2$ R^2 = R^3 = R^6 = H ; R^4, R^5 = CMe_2

7 R = R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Ac



8 R = R^1 = R^3 = R^6 = H ; R^2 = CMe_2OMe R^4 , R^5 = CMe_2

9 R = R^1 = R^2 = R^3 = H ; R^6 = CMe_2OMe , R^4, R^5 = CMe_2

5 R = H ; R^1 , R^2 = CMe_2

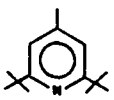
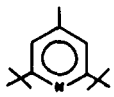
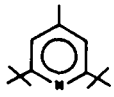
6 R = R^1 = R^3 = Ac

diol system which, according to reported results[6] using methyl 4,6-benzylidene-α-D-glucopyranoside (**3**), may undergo regioselective oxidation on C-2 *via* the corresponding 2,3-*O*-di-*n*-butylstannylene (**4**).

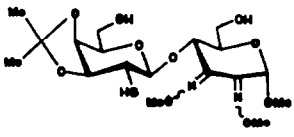
No reaction was observed when **1** was treated in the conditions reported for the regioselective oxidation of **3** (di-*n*-butyltin oxide, benzene, then bromine as oxidizing agent). Several reaction conditions were then investigated using different solvents and adding different bases to neutralize hydrobromic acid.[13] The oxidation mixtures were directly reacted with *O*-methyl-hydroxylamine and the resulting ketones were thus isolated as the corresponding oximes. The results are shown in Table 1. Other minor products not included in the table were also formed (t.l.c.) but not isolated. The best results were obtained when acetonitrile was used as solvent and tributyltin methoxide as base (entry 5). In these conditions methyl 4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2-(*O*-methyloximino)-α-D-arabino-hexopyranoside (**10**) could be isolated as the only product in 34% yield (64% on the basis of **1** transformed). The ^{1}H-n.m.r. spectra of **10** showed a singlet for H-1 at δ 5.72 ppm, a doublet ($J_{3,4}$ = 8.9 Hz) for H-3 at δ 4.58 ppm and a singlet for the *O*-methyloximino group at δ 3.93 ppm. It is interesting to note that when the oxidation step was performed in the presence of 2,6-di-*tert*-butyl-4-methyl-pyridine as a base (entries 2 and 3) the 2,3-dioximinoderivative **11** was also formed. The ^{1}H-n.m.r. spectrum of **11** showed a singlet for H-1 at δ 5.45 ppm, a doublet for H-4 at δ 5.05 ppm (J = 9.0 Hz) and two singlets for the methyloximino groups at δ 4.10 and 4.05 ppm.

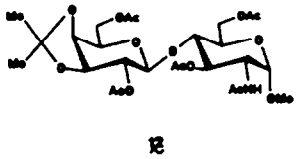
TABLE 1

Experimental conditions of the dibutylstannylene-mediated bromine oxidation of compound **1**.
Yields correspond to isolated methyloximino derivatives.

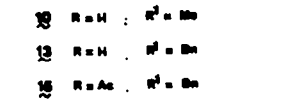
Entry	Base (equiv.)		Solvent	Yield (%)		
				1	**10**	**11**
1		(1.2)	benzene	100	-	-
2		(1.2)	THF	72	9	12
3		(1.2)	MeCN	66	10	18
4	$(Bu_3Sn)_2O$	(1.2)	MeCN	65	22	-
5	Bu_3SnOMe	(1.5)	MeCN	47	34	-

Treatment of **10** with hydrogen in the presence of palladium on charcoal and hydrazine[34] afforded, after 60 h, a mixture which was acetylated to give methyl *N*-acetyl-3,6,2',6'-tetra-*O*-acetyl-3',4',-*O*-isopropylidene α-lactosaminide (**12**) in moderate yield (39%). In an attempt to improve the yield and to decrease the hydrogenation time, the





11 12



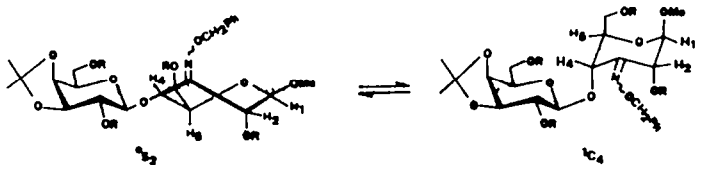
10 R = H : R' = Me
13 R = H . R' = Bn
16 R = Ac . R' = Bn

14 R = H : R' = Bn
15 R = Ac : R' = Bn

mixture of oxidation products obtained in the conditions indicated in entry 5 of table 1, was treated with *O*-benzylhydroxylamine hydrochloride since the expected 2-benzyloximino derivative **13** was thought to be more readily hydrogenated. A minor product (**14**) accompaning **13** (2:1 ratio **13**:**14**) could be detected (t.l.c.) in the oximation mixture. After acetylation and chromatographic separation of this mixture, **15** and the acetylated 3-benzyloximino derivative **16** were obtained. Compound **16** was isolated as a mixture of *E*/*Z* isomers, the ^{1}H-n.m.r. spectra of which showed the signals assigned to H-2 as two doublets ($J \simeq 5.5$ Hz) shifted at low field (δ 5.70 and 5.32), and the signal assigned to H-4 of the *E* isomer also shifted at low field (δ 4.72).

Hydrogenation of the mixture of oximes (**13** and **14**) in the above conditions was complete in 24 h (t.l.c.). After acetylation of the reaction mixture **12** was isolated in 48% yield (based on starting **13**).

The oxidation of methyl 3',4'-*O*-isopropylidene-β-lactoside (**5**) in the conditions described above for the α-anomer gave, after treatment of the oxidation mixture with *O*-benzylhydroxylamine, 3-(*O*-benzyloximino)-4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-ribo-hexopyranoside (**17**) in 50% yield as a 5:1 mixture of *Z*/*E* isomers. Acetylation of **17** gave, after chromatography,



17 R = H
18 R = Ac *Z* isomer ($^0S_2 > {}^1C_4$)
19 R = Ac *E* isomer ($^0S_2 \simeq {}^1C_4$)

the pure isomers **18** and **19**. The ^{1}H-n.m.r. spectra of the *Z*-oxime (**18**) showed vicinal coupling constant values which could not be accommodated in a structure with the glucopyranoid moiety in the $^4C_1$ conformation ($J_{1,2} = 3.6$, $J_{4,5} = 3.0$ Hz). These values could be accounted for assuming a conformational equilibrium $^0S_2 \rightleftharpoons {}^1C_4$ of this ring. The observed long range coupling $^4J_{2,4} = 0.9$ Hz is also in agreement with this conformational equilibrium. The value $^3J_{C1,H5} = 3.9$ Hz was also in between those expected for $^1C_4$ ($J_{C1,H5} = 6.2$ Hz) and $^0S_2$ ($J_{C1,H5} = 2.8$ Hz). Compound **19** spontaneously transformed into **18**. The ^{1}H-n.m.r. of **19** also showed vicinal and long-range couplings which could be interpreted as indicative of an $^0S_2 \rightleftharpoons {}^1C_4$ conformation of the glucopyranoid ring ($J_{1,2} = 1.7$, $J_{4,5} = 3.7$ and $J_{2,4} = 1.2$ Hz).[42]

The observed different regioselectivity of the oxidation reaction depending on the anomeric configuration of the starting lactoside can not be easily rationalized. Steric repulsions of the substituent at the anomeric position and the approaching oxidazing agent may be invoked, although favoured pentacoordination of tin with the anomeric oxygen could also explain the preferred oxidation at position 2 of the α-anomer.

It could be concluded from the above results that polyhydroxy derivatives can be oxidized with reasonable regioselectivity depending on the structure of the starting material. Compound **12** is a useful intermediate for the synthesis of biologically important *N*-acetyllactosamine containing oligosaccharides[36-38] and its preparation in only two steps using the oxidation procedure reported in this paper constitutes a further example of the potentiality of regioselective organotin derivatives activation in carbohydrate chemistry.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. T.l.c. was performed on silica gel GF_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on silica gel Merck (70-230). ^{1}H-N.m.r. spectra were recorded using a Varian XL-300 (300 MHz) spectrometer. Carbon-proton coupling constants were measured through selective decoupling[39] and first order analysis of the resulting partially coupled ^{13}C-n.m.r. spectrum. Routine ^{13}C-n.m.r. spectra were recorded on a Bruker WP-80 (20 MHz) spectrometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Methyl hepta-*O*-acetyl-α-lactoside (7)

Methyl hepta-*O*-acetyl-β-lactoside[40] (6, 35 g, 53.8 mmol) in absolute chloroform (525 mL), was treated with a solution of titanium tetrachloride (10.5 g, 55 mmol) in absolute chloroform (90 mL) and refluxed with stirring for 5 h. The mixture was then cooled, washed successively with ice-water, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and filtered through charcoal. The filtrate was evaporated to give a syrup (33 g) which crystallized from ethanol. Compound 7 (21 g, 60%) was obtained as a solid, mp 158-160° C, $[\alpha]_D^{20}$ + 68° (c 0.8, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 5.47 (t, 1H, $J_{2,3}$ = 9.9, $J_{3,4}$ = 9.1 Hz, H-3), 5.35 (d, 1H, $J_{3',4'}$ = 3.5 Hz, H-4'), 5.12 (dd, 1H, $J_{1',2'}$ = 7.9, $J_{2',3'}$ = 10.5 Hz, H-2'), 4.95 (dd, 1H, $J_{2',3'}$ 10.5, $J_{3',4'}$ 3.5 Hz, H-3'), 4.86 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.82 (dd, 1H, $J_{1,2}$ = 3.7, $J_{2,3}$ = 9.9 Hz, H-2), 4.48 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 4.46 (dd, 1H, $J_{5,6a}$ = 2.2, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.12 (m, 3H, H-6b, H-6a' and H-6b'), 3.90 (m, 2H, H-5 and H-5'), 3.75 (t, $J_{3,4} \simeq J_{4,5}$ = 9.1 Hz, H-4), 3.39 (s, 3H, OMe), 2.16, 2.14, 2.07, 2.06, 2.05, 2.04 and 1.97 (7s, each 3H, 7Ac). (Found: C, 49.60; H, 5.60. Calcd. for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.89).

Methyl 3',4'-*O*-isopropylidene-α-lactoside (1)

Compound 7 (10 g, 15.4 mmol) was added with stirring at room temperature to a solution of sodium (0.2 g) in methanol (100 mL). When t.l.c. (2:1 chloroform-methanol) revealed the presence of only a product, the reaction mixture was neutralized (Amberlite IR-120) and evaporated to give a syrup (5.7 g) which was treated with acetone (250 mL), N,N'-dimethylformamide (9 mL), 2,2'-dimethoxypropane (9 mL) and concentrated sulfuric acid (0.9 mL). The mixture was refluxed for 2 h, and then neutralized (Na_2CO_3) and concentrated to give a residue which was chromatographed (ethyl acetate-methanol 5:1) affording 1 (3.7 g, 60%) as a solid, mp 114-116°C, $[\alpha]_D^{20}$ + 109° (c 0.51, methanol). N.m.r. data (D_2O): ^{13}C, δ 112.2 (CMe_2), 103.2 (C-1'), 100.1 (C-1), 80.0, 79.8, 74.9, 74.6, 74.0, 72.9, 72.1, 71.4, 67.8, 62.0, 61.2, 56.4 (OMe), 28.4 and 26.7 (2Me). (Found: C, 48.34; H, 7.12. Calcd. for $C_{16}H_{28}O_{11}$: C, 48.48; H, 7.12).

Oxidation of methyl 3',4'-*O*-isopropylidene-α-lactoside (1)

A mixture of 1 (0.5 g, 1.26 mmol), acetonitrile (20 mL), molecular sieve 4 Å and dibutyltin oxide (0.36 g, 1.45 mmol), was stirred at 90°C for 16 h. After cooling at room temperature, tributyltin methoxide (0.6 g, 1.8 mmol) was added and a solution of bromine (0.30 g, 1.9 mmol) in dichloromethane (1.3 mL) dropped for 2 h. The molecular sieve was filtered and washed with warm chloroform, and the combined filtrate and washings were concentrated. The residue was dissolved in pyridine (5 mL) and treated with *O*-benzylhydroxylamine hydrochloride (0.5 g, 3.1 mmol) at 50°C for 30 min. The solution was concentrated and the residue stirred with hexane (≃ 15 mL) and kept overnight at -10°C. The hexane layer was decanted and column chromatography (15:1 chloroform-methanol) of the syrupy residue gave a mixture (0.31 g, 50%) of methyl 2-(*O*-benzyloximine)-4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-α-D-*arabino*-hexopyranoside (13) and methyl 3-(benzyloximine)-4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-α-D-*ribo*-hexopyranoside (14, mixture E/Z) in a ratio ≃ 2:1, respectively. Further elution of the column gave 1 (0.23 g).

Conventional acetylation of the mixture gave, after column chromatography (3:2 hexane-ethyl acetate), methyl 3,6-di-*O*-acetyl-4-*O*-(2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2-*O*-benzyloximine)-α-D-*arabino*-hexopyranoside (15) contaminated with traces of regioisomers. ^{1}H-N.m.r. data of 15 ($CDCl_3$): δ 5.75 (s, 1H, H-1), 5.72 (d, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 5.10 and 5.04 (2d, each 1H, J = 11.9 Hz, CH-Ph), 4.91 (dd, 1H, $J_{1',2'}$ = 7.7 Hz, $J_{2',3'}$ = 6.4 Hz, H-2'), 4.44 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1'), 4.41 (dd, 1H, $J_{5,6a}$ = 2.1, $J_{6a,6b}$ = 11.9 Hz, H-6a), 4.32 (d, 2H, $J_{5',6'}$ = 6.2 Hz, H-6'a,b), 3.94 (dt, 1H, $J_{4,5}$ = 1.8, $J_{5',6'}$ = 6.2 Hz, H-5'), 3.85 (dd, 1H, $J_{3,4}$ = 9.2, $J_{4,5}$ = 9.8 Hz, H-4), 3.39 (s, 3H, OMe), 2.10 (s, 3H, Ac), 2.09 (s, 9H, 3Ac, 1.54 and 1.32 (2s, each 3H, 2Me). The fraction eluted next was 16 (*E*-isomer) contaminated with the Z-isomer. ^{1}H-N.m.r. data ($CDCl_3$) of 16 (*E*): δ 5.70 (dd, 1H, $J_{1,2}$ = 5.4, $J_{2,4}$ = 0.9 Hz, H-2), 5.20 (s, 2H, CH_2Ph), 4.83 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 4.82 (t,1H, $J_{1',2'} \simeq J_{2',3'}$ = 8.0 Hz, H-2'), 4.72 (dd, 1H, $J_{4,5}$ = 8.7, $J_{2,4}$ = 0.9 Hz, H-4), 4.58 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 3.65 (m, 1H, H-5'), 3.43 (s, 3H, OMe), 2.14, 2.11, 2.09 and 2.07 (4s, each 3H, 4Ac), 1.51 and 1.30 (2s, each 3H, 2 Me).

Methyl 2-acetamido-3,6-di-*O*-acetyl-4-*O*-(2,6-di-*O*-acetyl-3',4'-*O*-isopropylidene-β-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside [methyl *N*-acetyl-3,6,2',6'-tetra-*O*-acetyl-3',4'-*O*-isopropylidene-α-D-lactosaminide] (12)

A solution of the mixture of 13 and 14 (ratio 2:1) (0.3 g, 0.6 mmol) and hydrazine (0.3 mL) in ethanol 90% (17 mL) was hydrogenated over 10% Pd/C (0.45 g) at 50 p.s.i. for 28 h. The catalyst was collected on Celite and washed with warm ethanol, and the combined filtrate and washings were concentrated. The residue was acetylated in the usual conditions and after column chromatography compound 12 (0.115 g, 48% based on the amount of 13 present in the starting mixture), was obtained as a solid, mp 81-83°C, $[\alpha]_D^{20}$ = + 86° (c 0.5, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, 5.78 (d, 1H, $J_{2,4}$ = 9.7 Hz, NH), 5.19 (dd, 1H, $J_{2,3}$ = 10.6, $J_{3,4}$ = 8.9 Hz, H-3), 4.67 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.36 (d, 1H, $J_{1',2'}$ = 7.7 Hz,

H-1'), 4.24 (m, 1H, $J_{1,2}$ = 3.7, $J_{2,3}$ = 10.6 Hz, H-2), 3.72 (dd, 1H, $J_{3,4}$ = 8.9, $J_{4,5}$ = 10.0 Hz, H-4), 3.37 (s, 3H, OMe), 2.13, 2.12, 2.10 and 2.07 (4s, each 3H, 4AcO), 1.95 (1s, 3H, AcN), 1.53 and 1.32 (2s, each 3H, 2Me); ^{13}C, δ 171.3, 170.7, 170.5, 170.1 and 169.3 (CO), 110.9 (CMe_2), 100.7 and 98.2 (C-1 and C-1'), 76.9, 76.2, 73.2, 72.9, 71.3, 70.9, 68.7, 63.1, 62.3, 55.3, 52.2, 27.3 and 26.2 (2Me), 23.2 (Me-CON), 20.8 (Ac). (Found: C, 51.54; H, 6.80; N, 2.56. Calcd. for $C_{26}H_{39}O_{15}N$: C, 51.57; H, 6.49; N, 2.31).

Oxidation of methyl 3',4'-*O*-isopropylidene-β-lactoside (5)

Compound 5[41] (1 g) was oxidized as described above for **1**. After treatment with *O*-benzylhydroxylamine hydrochloride and subsequent column chromatography (20:1 chloroform-methanol), methyl 3-(*O*-benzyloximino)-4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-*ribo*-hexapyranosides (**17**, 0.61 g, 50%) was obtained. Conventional acetylation and column chromatography (3:2 hexane-ethyl acetate) gave methyl 2,6-di-*O*-acetyl-4-*O*-(2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl) 3-*Z*-(*O*-benzyloximine)-β-D-ribopyranoside (**18**, 0.55 g) and the *E*-isomer **19** (0.12 g).

Compound **18** was a syrup. N.m.r. data ($CDCl_3$): ^{1}H, δ 7.20-7.40 (m, SH, 1Ph), 5.98 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-2), 5.17 (s, 2H, CH_2Ph), 4.98 (dd, 1H, $J_{1',2'}$ = 8.1, $J_{2',3'}$ = 6.6 Hz, H-2'), 4.78 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 4.38 (d, 1H, $J_{1',2'}$ = 8.1 Hz, H-1'), 3.44 (s, 3H, OMe), 2.09, 2.07, 2.04 and 2.01 (4s, each 3H, 4Ac), 1.54 and 1.32 (2s, each 3H, 2Me); ^{13}C, δ 148.3 (C=N-O), 137.3 (c-*ipso*), 110.6 (CMe_2), 100.7 and 99.4 (C-1, C-1'), 56.3 (OMe), 21.9, 20.8 and 20.6 (4Ac). (Found: C, 55.31; H, 6.16; N, 2.52. Calcd for $C_{31}H_{41}O_{15}N$: C, 55.77; H, 6.19; N, 2.10).

Compound **19** spontaneously transformed into **18**. N.m.r. data ($CDCl_3$): ^{1}H, δ 7.2-7.3 (m, 5H, 1Ph), 5.26 (t, 1H, $J_{1,2}$ = 1.2 Hz, H-2), 5.15 (s, 2H, CH_3Ph), 4.84 (s, 1H, H-4), 4.81 (dd, 1H, $J_{1',2'}$ = 8.4, $J_{2',3'}$ = 7.3 Hz, H-2'), 4.73 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1), 4.42 (d, 1H, $J_{1',2'}$ = 8.4 Hz, H-1'), 3.39 (s, 3H, OMe), 2.06, 2.04, 2.01 and 1.96 (4s, each 3H, 4Ac), 1.44 and 1.24 (2s, each 3H, 2Me); ^{13}C, δ 147.9 (C=N-O), 136.8 (C-*ipso*), 110.7 (CMe_2), 102.5 and 100.7 (C-1, C-1'), 56.4 (OMe), 21.0, 20.8 and 20.7 (4Ac).

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