COMMUNICATION

C-Glycoside formation *via* Lewis acid promoted reaction of *O*-glycosylimidates with pyrroles

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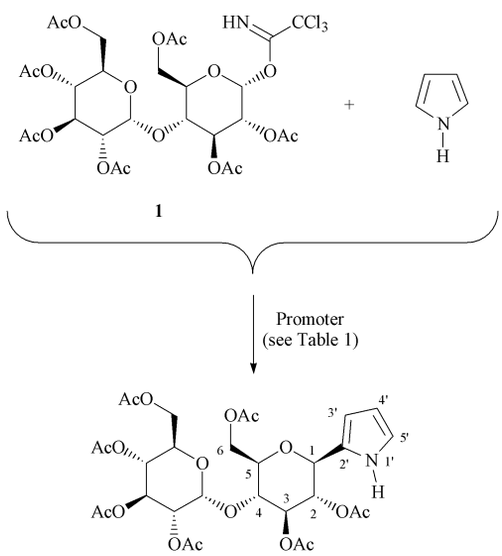
_O_-Glycosylimidates such as 1 react with pyrroles in the presence of $BF_3{\cdot}Et_2O$ to give _C_-glycosides, _e.g._ 2, that are readily elaborated to congeners such as 12 and 13.

The intimate involvement of carbohydrates in so many pivotal biological processes has prompted considerable interest in carbohydrate mimics as potential therapeutic agents.[1] In this connection, *C*-glycosides continue to attract significant attention because they are resistant to chemical and enzymatic hydrolysis of the glycosidic linkage whilst often retaining the capacity to interact with protein receptors in a similar manner to their more fragile *O*-linked counterparts.[2] As a consequence, manifold approaches to *C*-glycosides have been developed.[2–4] Whilst anomeric nucleophiles[3] and radicals[4] have been exploited in the generation of such compounds, the addition of a *C*-centred nucleophile to an activated and electrophilic *C*-glycosyl donor represents by far the most common approach.[2] In this context, pyrroles seem to have been overlooked[5,6] despite the fact that (i) they are very effective carbon-centred nucleophiles,[7] (ii) that electrophilic attack at C2 or C3 of this heterocycle can be controlled by appropriate substitution at the ring nitrogen[8] and, (iii), they are capable of manipulation in remarkably diverse ways.[9] As such, we now report that *O*-glycosyl trichloroacetimidates react with pyrroles in the presence of boron trifluoride to give, most often in high chemical yield, pyrrole *C*-glycosides. We also show that the pyrrole moiety within such products can be manipulated in various simple ways to generate a range of other potentially useful *C*-glycosides.

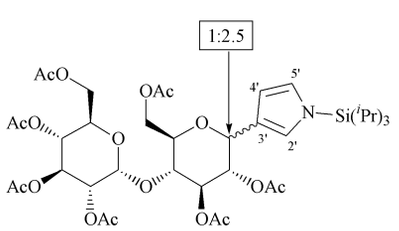
Preliminary investigations exploited the readily available peracetylated α-maltosyl trichloroacetimidate **1**[10] as an electrophilic glycosyl donor and pyrrole itself as the nucleophile (Scheme 1). A variety of reaction temperatures and Lewis acids [TMSOTf, $BF_3{\cdot}Et_2O$, and $Sc(OTf)_3$[11]] were examined in order to establish optimum conditions (Table 1) for formation of the anticipated *C*-glycoside **2**†. Such studies suggested that use of $BF_3{\cdot}Et_2O$ as promoter and a reaction temperature of −50 °C (Entry 6) represent close to the best conditions for this glycosylation process. Interestingly, reaction of the α-maltosyl bromide analogue[12] of **1** with pyrrole in the presence of silver carbonate–iodine[13] under various conditions failed to deliver any significant quantities of compound **2**. Further, although TMSOTf reputedly activates lactose octaacetate,[14] no reaction was observed, at −78 °C, between β-maltose octaacetate[15] and pyrrole in the presence of this promoter.

The optimum conditions defined above lead exclusively to the β-glycoside **2** with the stereochemistry of this material being readily established by ^{1}H NMR spectroscopic analysis. In particular, the resonance due to H1 in compound **2** appears as a doublet at δ 4.55 with J 10.0 Hz, thus implying a *trans*-diaxial relationship for H1/H2 and, thence, the illustrated β-configuration of the pyrrole ring at the anomeric centre. The location of the glycosyl moiety at C2′ on the heterocyclic ring follows from the ^{13}C NMR spectrum which shows that both the



Scheme 1

higher field resonances (at δ 108.5 and 107.6), due to the C3′ and C4′, derive from protonated carbons. Not surprisingly, substituents at nitrogen on the pyrrole ring can redirect attack of the glycosyl donor to C3′. Thus, reaction of compound **1** with *N*-methylpyrrole under the above-mentioned conditions afforded a *ca.* 2 : 1 mixture of the C2′ and C3′ glycosylated products, albeit in an unoptimised yield of 20%. In contrast, and in keeping with the outcome of the reaction of non-carbohydrate based electrophiles with *N*-(triisopropylsilyl)pyrrole,[8] treatment of this compound with trichloroacetimidate **1** in the presence of $BF_3{\cdot}Et_2O$ afforded the C3′-product **3** (31%) exclusively, although now as a *ca.* 1 : 2.5 mixture of α- and β-anomers.



Application of these sorts of reaction conditions to the glucopyranose-derived trichloroacetimidate **4**[10a] and the mannose-configured congener **5**[10a] lead to the *C*-glycosides **6**

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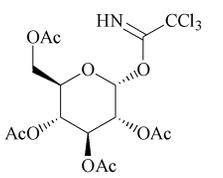
Table 1 Reaction of trichloroacetimidate **1** and pyrrole in the presence of various Lewis acid promoters[a]

Entry	Lewis acid[b]	Equiv. pyrrole	Temp. /°C,	Time/min	Yield **2**
1	TMSOTf	5	0	45	20%
2	TMSOTf	5	40	20	53%
3	TMSOTf	5	−50	20	54%
4	TMSOTf	5	−78	2	15%
5	$Sc(OTf)_3$	5	−50	20	0%
6	$BF_3{\cdot}Et_2O$	5	−50	20	84%
7	$BF_3{\cdot}Et_2O$	2	−50	20	56%

[a] Dichloromethane used as solvent in all cases. Powdered 4 Å molecular sieves were used in all cases. [b] In all the experiments listed *ca.* 2.5 mol equiv. of the relevant Lewis acid was employed.

(72%) and **7**‡ (83%), respectively. In the former conversion the β-anomer ($J_{1,2}$ 10.0 Hz) was the exclusive product of reaction whilst in the latter only the α-anomer was observed. Furanose-type trichloroacetimidates also readily engage in a $BF_3{\cdot}Et_2O$-catalysed reaction with pyrrole to produce *C*-glycosides. Thus, the ribose derivative **8**[16] affords product **9** (52% of a *ca.* 4 : 1 mixture of β- and α-anomers) whilst the mannose-derived trichloroacetimidate **10**[10a] affords *C*-glycoside **11** (100% of a *ca.* 2 : 3 mixture of α- and β-anomers).



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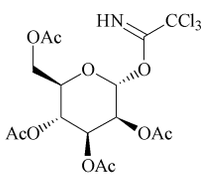

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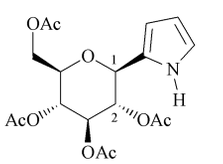

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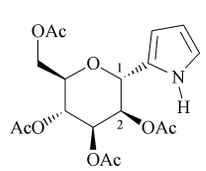

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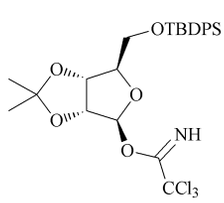

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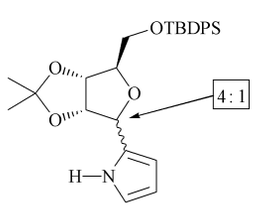

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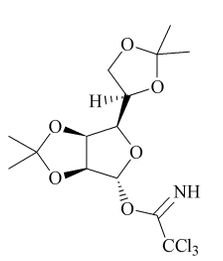

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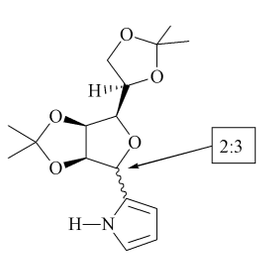

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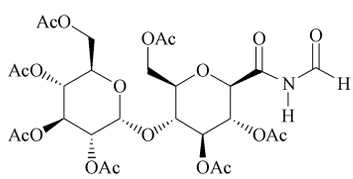
The capacity for manipulation of the pyrrole ring after it has been incorporated into a *C*-glycoside is highlighted by the observation that reaction of compound **2** with ozone[17] in DCM at −78 °C afforded, after reductive workup with thiourea in methanol, the formimide **12**§ (34%, mp 67–69 °C). Alternatively, the pyrrole ring within compound **2** can be hydrogenated under an atmosphere of dihydrogen in the presence of Adams' catalyst (PtO_2) to give the corresponding saturated system **13**§ (55%, mp 83–85 °C) as a single diastereoisomer of, as yet, undetermined configuration at C2′. The capacity of glycosylated pyrroles to engage in electrophilic aromatic substitution reactions was also examined. Interestingly, treatment of compound **2** with 2 equivalents of trichloroacetimidate **1** at −50 °C in the presence of $BF_3{\cdot}Et_2O$ did not give the hoped-for bis-*C*-glycoside **14** but, rather, the C4′-acylated product **15** (57%, mp 85–87.5 °C). Reaction of the same substrate (**2**) with one equivalent of *N*-bromosuccinimide in THF at −78 °C for 2 h then 20 °C for 1 h afforded the 4′,5′-dibromopyrrole **16** (86% based on NBS consumed). This last product represents an attractive scaffold because it should be capable of engaging in various Pd[0]-cross-coupling reactions[18] thus allowing access to many other 2-glycosylated-4,5-disubstituted pyrroles including systems attached to solid supports. Work aimed at exploring such possibilities is currently underway in these laboratories and will be reported upon in due course.



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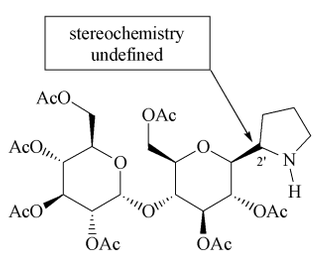

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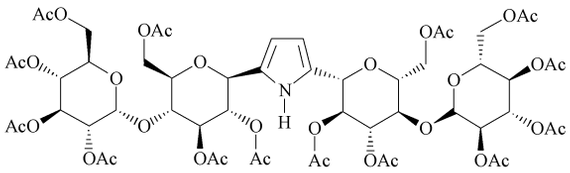
Experimental

Compound 2

A magnetically stirred mixture of trichloroacetimidate **1** (160 mg, 0.20 mmol) and powdered 4 Å molecular sieves (1.00 g) in anhydrous CH_2Cl_2 (15 mL) was maintained at 18 °C for 2 h then cooled to −50 °C. Pyrrole (70 mg, 1.00 mmol) and $BF_3{\cdot}Et_2O$ (70 mg, 0.50 mmol) were then added, the resulting mixture stirred at −50 °C for 20 minutes and then filtered through a pad of Celite™ which was washed with CH_2Cl_2 (20 mL). The combined filtrates were washed with $NaHCO_3$ (1 × 20 mL of a saturated aqueous solution), water (1 × 20 mL) and brine (1 × 20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light-yellow oil. This material was subject to flash chromatography (silica gel, 3 : 17 v/v acetone–toluene elution) and concentration of the appropriate fractions (R_f 0.2) afforded C-*glycoside* **2** (115 mg, 84%) as slightly light-sensitive and white microcrystalline masses, mp 75–77 °C, $[a]_D$ +51 (*c* 0.5, $CHCl_3$) (Found: C, 51.95; H, 5.77; N, 1.90%. $C_{30}H_{39}NO_{17}$ requires C, 52.55; H, 5.73; N, 2.04%); ν_{max} (NaCl)/



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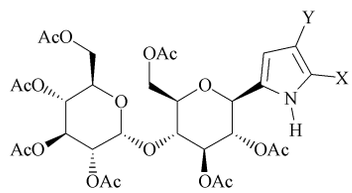

15 X = H, Y = Ac
16 X = Y = Br

cm^{-1} 3409, 1748, 1650, 1370, 1233, 1039, 899, 736, 602; δ_H ($CDCl_3$, 300 MHz) 8.42 (1H, broad s, NH), 6.74 (1H, ddd, *J* 2.6, 2.6 and 1.7, H5″), 6.09 (2H, m, H3″ and H4″), 5.45 (1H, d, *J* 4.0, H1′), 5.37 (2H, m), 5.06 (1H, t, *J* 10.2), 5.02 (1H, t, *J* 9.9), 4.87 (1H, dd, *J* 10.6 and 4.0), 4.55 (1H, d, *J* 10.0, H1), 4.46 (1H, dd, *J* 12.1 and 2.5), 4.27 (1H, t, *J* 3.4), 4.23 (1H, t, *J* 4.1), 4.05 (2H, m), 3.97 (1H, m), 3.79 (1H, ddd, *J* 9.6, 4.4 and 2.5), 2.12 (3H, s), 2.10 (3H, s), 2.05 (3H, s), 2.02 (3H, s), 2.00 (3H, s), 1.99 (3H, s), 1.88 (3H, s); δ_C ($CDCl_3$, 75 MHz) 170.6, 170.5, 170.2, 169.9, 169.6, 169.4, 167.7, 125.7, 118.6, 108.5, 107.6, 95.6, 76.1, 73.7, 72.8, 71.8, 69.9, 69.3, 68.5, 68.1, 67.9, 63.2, 61.4, 20.9(4), 20.8(6), 20.7, 20.6, 20.5; *m*/*z* (ESI) 707.7 [(M + Na)$^+$, 9%], 685.9 [(M + H)$^+$, 11], 589.0 (19), 457.0 (8), 414.0 (15), 396.1 (8), 380.1 (7), 330.8 (9), 283.9 (14), 191.9 (24), 173.9 (37), 84.1 (100), 71.1 (76), 60.0 (60).

Acknowledgements

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References

† All new and stable compounds had spectroscopic data [IR, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ Many of the pyrrole *C*-glycosides described here undergo facile anomerisation on dissolution in $CDCl_3$ containing traces of HCl. Such problems can be avoided by using $CDCl_3$ that has been stored over K_2CO_3.

§ *Selected spectral data for compound* **12**: ν_{max} (neat, NaCl plates)/cm^{-1} 1749, 1704, 1465, 1369, 1229, 1037, 901, 733, 601; δ_H (300 MHz, $CDCl_3$) 9.08 (1H, d, *J* 10.1), 8.82 (1H, d, *J* 9.5), 5.38 (1H, d, *J* 3.4), 5.35 (1H, dd, *J* 10.5 and 9.5), 5.26 (1H, dd, *J* 8.1 and 6.5), 5.08 (3H, m), 4.90 (1H, dd, *J* 10.1 and 4.1), 4.56 (1H, br d, *J* 12.1), 4.26 (1H, dd, *J* 12.8 and 4.3), 4.19 (1H, d, *J* 7.8, H1), 4.08 (1H, dd, *J* 12.4 and 2.2), 4.00 (1H, m), 3.88 (2H, m), 2.17 (3H, s), 2.11 (3H, s), 2.10 (3H, s), 2.07 (3H, s), 2.04 (3H, s), 2.02 (3H, s), 2.01 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.4, 170.2, 169.8, 169.6, 169.2, 167.8, 161.0, 96.0, 75.6, 75.2, 73.6, 72.8, 69.8, 69.2, 69.0, 68.6, 67.9, 62.7, 61.5, 20.9, 20.8, 20.7(5), 20.6(6); *m*/*z* (ESI) 691.9 [(M + H)$^+$, 22%], 618.9 (5), 439.1 (6), 383.0 (5), 330.9 (62), 270.9 (21), 168.9 (100), 108.9 (38).

Selected spectral data for compound **13**: ν_{max} (neat, NaCl plates)/cm^{-1} 3369, 1747, 1619, 1431, 1369, 1228, 1039, 910, 732, 602; δ_H (300 MHz, $CDCl_3$) 5.51 (1H, d, *J* 4.1), 5.33 (1H, t, *J* 9.7), 5.15 (1H, t, *J* 9.2), 4.86 (1H, dd, *J* 4.0 and 10.4), 4.50 (1H, dd, *J* 2.6 and 11.9), 4.40 (1H, d, *J* 8.4), 4.25 (1H, dd, *J* 3.4 and 12.2), 4.16 (1H, dd, *J* 4.1 and 12.0), 4.07 (1H, dd, *J* 2.2 and 12.5), 3.92 (1H, m), 3.85 (1H, t, *J* 9.4), 3.68 (1H, dd, *J* 3.2 and 10.1), 3.60 (1H, m), 3.45 (2H, m), 3.30 (1H, t, *J* 9.5), 2.12 (3H, s), 2.11 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 2.07 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 2.18–1.75 (5H, m); δ_C (75 MHz, CD_3Cl_3) 171.5, 170.7 (2), 170.6, 170.3, 169.9, 169.4, 95.3, 79.2, 78.4, 76.1, 75.8, 72.3, 71.8, 69.9, 69.4, 68.3, 68.1, 62.8, 61.4, 58.1, 24.9, 24.2, 21.3, 20.8, 20.7, 20.6; *m*/*z* (ESI) 711.9 [(M + Na)$^+$, 39%], 689.9 [(M + H)$^+$, 86], 589.0 (7), 458.0 (6), 380.0 (39), 359.8 (7), 330.8 (7), 285.9 (7), 284.0 (9), 236.0 (20), 191.9 (95), 173.9 (100), 155.9 (23), 116.0 (13), 97.9 (36). Found (HRMS): (M + H)$^+$ 690.2622. $C_{30}H_{43}NO_{17}H^+$ requires 690.2609.

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