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COMMUNICATION

Sweet (hetero)aromatics: glycosylated templates for the construction of saccharide mimetics†‡

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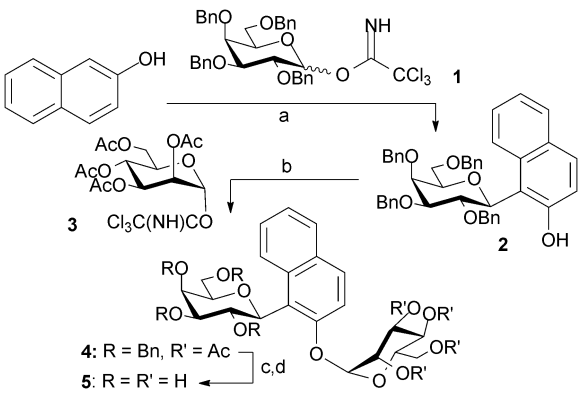
Mono- and diglycosylated aromatics and heteroaromatics may serve as building blocks for the construction of metabolically stable mimetics of oligosaccharides. Methods for their preparation from monosaccharidic precursors by direct *C*-glycosylation, dipolar cycloaddition or Larock cyclization are described.

Structurally defined oligosaccharides play an important role in the communication between cells in higher organisms.[1] Prominent examples are the blood group antigens which allow the differentiation between erythrocytes of different species and even different individuals or the sialyl Lewis^X tetrasaccharide which is involved in the recruitment of leukocytes within the inflammatory cascade.[2] While the recognition of cell surface oligosaccharides is a key process in numerous medical conditions, *e.g.* psoriasis,[3] asthma[4] or the reperfusion syndrome,[1d] their use as drugs is generally hampered by their poor pharmacokinetics.[5] To improve the metabolic stability and to retain or even increase the binding affinity to the target structure, various types of oligosaccharide mimetics have been developed.[5,6] In particular, *C*-glycosides possess a high stability against ubiquitous glycosidases and in this respect are privileged in the field of saccharide mimicry.[5,7]

Among the various methods used for the construction of *C*-glycosides, the reaction of suitable glycosyl donors with electron rich phenols[8] permits the straightforward synthesis of trisaccharide mimetics if the initial glycosylation of the *ortho*-position is followed by an *O*-glycosylation of the phenolic OH-group. As an example, 2-naphthol can be reacted with the benzylated galactosyl trichloroacetimidate **1**[9] in the presence of TMSOTf to furnish the thermodynamically preferred β-*C*-glycoside **2**.[8c,d,10] Subsequent reaction with the acetyl protected mannosyl trichloroacetimidate **3**[11] furnishes *O*,*C*-digylcoside **4**, albeit in only 28% yield (Scheme 1).[12] A similar glycosylation pattern is found in a natural product



Scheme 1 *Reagents and conditions*: (a) TMSOTf, CH_2Cl_2, molecular sieves 4 Å, 0 °C, 52%; (b) TMSOTf, CH_2Cl_2, molecular sieves 4 Å, 0 °C, 32%; (c) $Pd(OAc)_2$, MeOH, H_2 (1 bar), 25 °C, 43%; (d) NaOMe, MeOH, 25 °C, quant.

isolated from *Melaleucaquinquenervia*.[13] The high electron density makes the indole nucleus another suitable template for direct *C*-glycosylations.[14] 1-Glycosylindoles **6** can be prepared according to Mel'nik *et al.*[15] by reaction of hexoses with indoline followed by dehydrogenation with DDQ.[16] After peracetylation, BF_3-etherate promoted reaction with acetylated trichloroacetimidate donors furnishes 1,3-diglycosylindoles **8**, **9**, and **10** (Scheme 2). In the case of fucoside **10**, the produced anomeric mixture could not be separated by column chromatography.

The sterically more encumbered 2,3-diglycosylindoles may be viewed as mimetics of trisaccharides possessing a vicinal substitution pattern. These compounds can be obtained from 2-glycosylindoles like **14**,[17] the synthesis of which proceeds *via* *C*-glycosylacetylene **12**.[18] Reaction of the benzylated galactosyl acetate with tributyl[2-(trimethylsilyl)ethynyl]stannane in the presence of TMSOTf furnishes the TMS-acetylene, which can be desilylated with TBAF. Sonogashira-coupling with *N*-tosyl-2-iodoaniline and Cu(I)-catalyzed hydroamination yields the *N*-tosylatedindole **13**.[17a] Alkaline detosylation followed by $BF_3{\cdot}OEt_2$-promoted reaction of the resulting glycosylindole **14**[15] with acetylated trichloroacetimidates of D-mannose[19] furnishes the β-*C*-mannoside **15** (Scheme 3).

C-Fucosylation of **14** using donor **7**[20] gives significantly higher yields but results in the formation of both anomers in equal amounts (data not shown).

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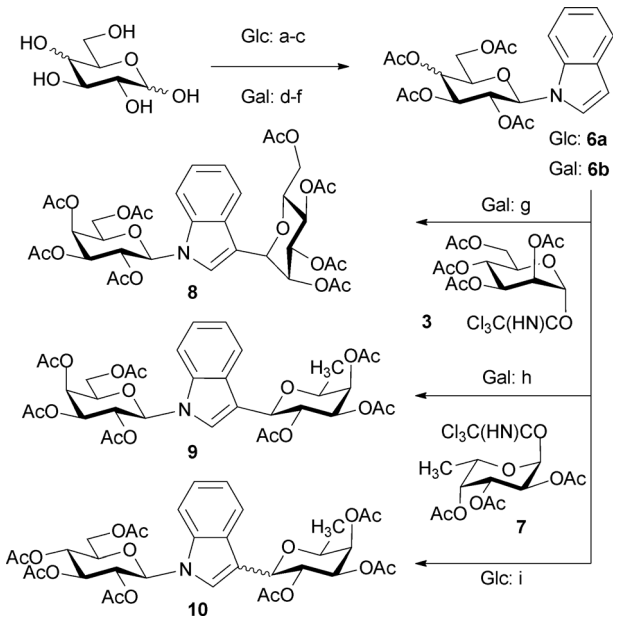
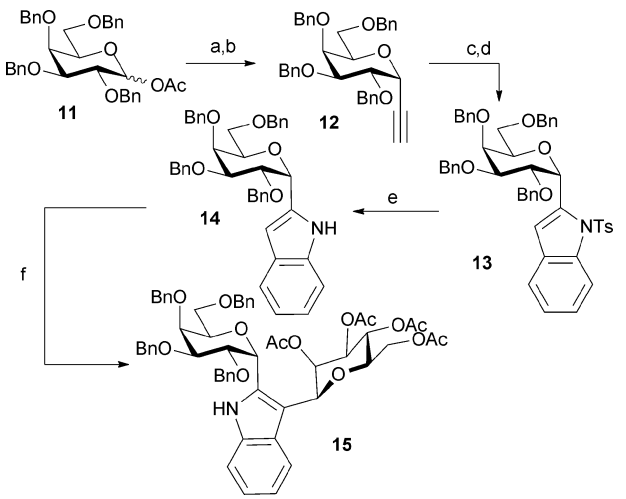
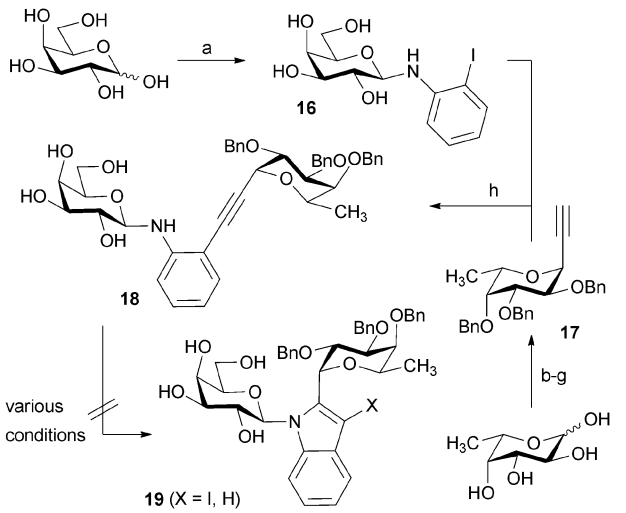


Scheme 2 *Reagents and conditions*: (a) indoline, EtOH, 40 °C, quant.; (b) Ac_2O, pyridine, 95%; (c) DDQ, dioxane, 25 °C, 94%; (d) indoline, EtOH, 40 °C, 82%; (e) DDQ, dioxane, 25 °C, 97%; (f) Ac_2O, pyridine, 25 °C, 92%; (g) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −60 °C → 0 °C, molecular sieves 4 Å, 55% (α); (h) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −60 °C → 0 °C, molecular sieves 4 Å, 33% (β); (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −15 °C → 8 °C, molecular sieves 4 Å, 44% (α/β = 1 : 1.7).



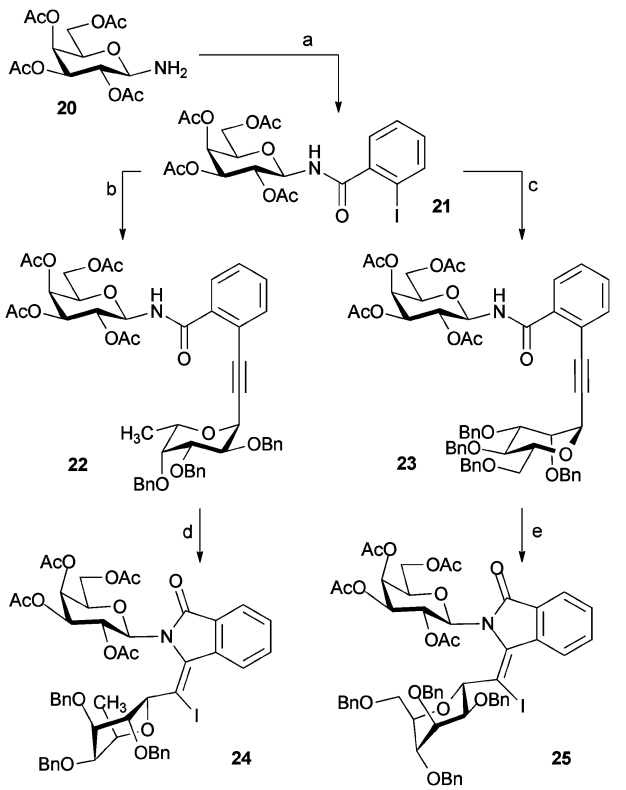
Scheme 3 *Reagents and conditions*: (a) $Bu_3SnC{\equiv}CSiMe_3$, TMSOTf, CH_2Cl_2, molecular sieves 4 Å; (b) TBAF, THF/H_2O, 25 °C, 32% over 2 steps; (c) *N*-tosyl-2-iodoaniline, $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 60 °C; (d) CuI, Et_3N, DMF, 60 °C, 78% over 2 steps; (e) KOH, MeOH, THF, 25 °C, 82%; (f) **3**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −15 °C → 25 °C, molecular sieves 4 Å, 23% (α).

In analogy to the synthesis of tosylindole **13**, the preparation of 1,2-diglycosylated indoles should be possible by coupling of alkynes of type **12** to *N*-glycosyl 2-iodoanilines.[21] Indeed, the Sonogashira reaction between these components provides ethynylanilines such as **18** in high yield which can already be viewed as trisaccharide mimetics. However, their cyclization to **19** with soft electrophiles or various coinage metal complexes has not been achieved so far (Scheme 4).[22]

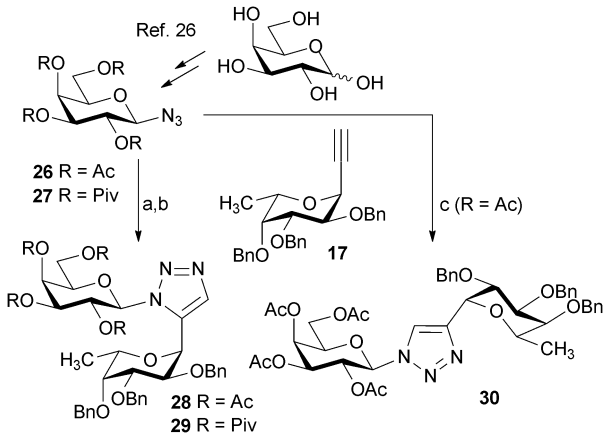


Scheme 4 *Reagents and conditions*: (a) 2-iodoaniline, AcOH, EtOH, 100 °C, 31%; (b) AllOH, AcCl, 70 °C → 40 °C; (c) BnBr, NaH, DMF; (d) $Ir(COD)(PPh_2CH_3)_2$, H_2, THF; (e) I_2, $NaHCO_3$, THF/H_2O (4 : 1); (f) Ac_2O, pyridine, DMAP, 49% over 5 steps; (g) $Bu_3SnC{\equiv}CSiMe_3$, TMSOTf, CH_2Cl_2, molecular sieves 4 Å; (h) $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 60 °C, 66%.

In contrast, extension of compounds of type **18** by one carbonyl group furnishes substrates for the Larock cyclization which turned out to proceed in high yield if iodine was used as the electrophile.[23] Reaction of glycosylamine **20** with



Scheme 5 *Reagents and conditions*: (a) 2-iodobenzoyl chloride, *N*-ethylmorpholine, THF, 0 °C, 90%; (b) **17**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 80 °C, 60%; (c) **12**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 60 °C, 76%; (d) I_2, $NaHCO_3$, CH_3CN, 25 °C, 76%; (e) I_2, $NaHCO_3$, CH_3CN, 25 °C 94%.



Scheme 6 *Reagents and conditions*: (a) Cp*Ru(COD)Cl, DMA, 100 °C, 120 W, 76%; (b) Cp*Ru(COD)Cl, DMA, 100 °C, 120 W, 60%; (c) CuI, DMF, EtN*i*Pr$_2$, 80 °C, 120 W, 75%.

2-iodobenzoyl chloride gives benzamide **21**, the Sonogashira reaction of which with glycosylacetylenes **12** and **17** yields alkynes **22** and **23**, respectively. Presumably due to the steric repulsion between both hexose residues, (alkylidene)isoindolinones **24** and **25** resulting from a 5-*exo*-dig cyclization are exclusively formed while the 6-*endo*-dig reaction with formation of 2,3-diglycosylated isoquinoline-1-ones was never observed (Scheme 5).[23,24]

As in other sterically demanding α-*C*-glycosides,[8d] the fucose residue in **24** and the mannose residue in **25** preferably adopt the respective ring-inverted conformation.

The Ru-catalyzed 1,3-dipolar cycloaddition of azides to terminal alkynes (RuAAC)[25] represents a straightforward possibility to produce heteroaromatics with a vicinal diglycosylation pattern. For example, fucosylacetylene **17** reacts with the pivaloylated and acetylated galactosylazides[26] **26** and **27** to the corresponding 1,5-diglycosylated 1,2,3-triazoles **28** and **29**. The regioisomeric 1,4-disubstituted products like **30** can be obtained from the same reactants using Cu(I) as the catalyst (CuAAC, Scheme 6).[27]

In summary, several general methods for the preparation of diglycosylated aromatic and heteroaromatic templates have been developed. Particular attention has been paid to the synthesis of products with two neighboring hexose residues as this pattern is frequently found in natural oligosaccharides. The presented compounds may serve as starting materials for the synthesis of functional glycomimetics with improved metabolic stability.

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