Synthesis and cycloaddition reactions of [2-deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl]ethyne

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Dedicated to Fritz Sauter on the occasion of his 70th birthday
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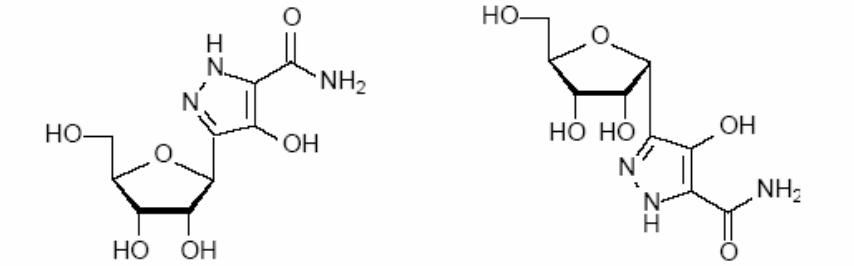
Abstract
The synthesis of [2-deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl]ethyne **5** by reaction of ethynylmagnesium bromide with 2-deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl chloride **2** is reported. The resulting *C*-glycoside precursor **5** undergoes [4+2]- as well as [3+2]-cycloaddition reactions to give 5- and 6-membered heterocyclic *C*-glycosides.

Keywords: 2-Deoxy-α-D-ribofuranosylethyne, [4+2]-cycloadditions, [3+2]-cycloadditions, pyridazine-*C*-glycosides, [1,2,3]triazole-*C*-glycosides

Introduction

Due to the pharmacological importance of some deoxynucleosides for example as inhibitors of HIV reverse transcriptase (e.g. AZT, 3'-azido-2',3'-dideoxythymidine,[1] ddI, 2′,3′-dideoxyinosine,[2] and the anti-cancer activity of some *C*-glycosides such as pseudocytidine[3]), we have now synthesized the first examples of 2-deoxy-*C*-glycosides which combine both structural properties. We used [4+2]- and [3+2]-cycloaddition reactions of suitable acetylenic carbohydrate derivatives. In the present case, the carbohydrate moiety is linked to the heterocyclic aglycone by a C-C bond. These compounds have the advantage of a higher stability against hydrolysis and do not show mutarotation like *N*-, *O*- or *S*-glycosides.[4]

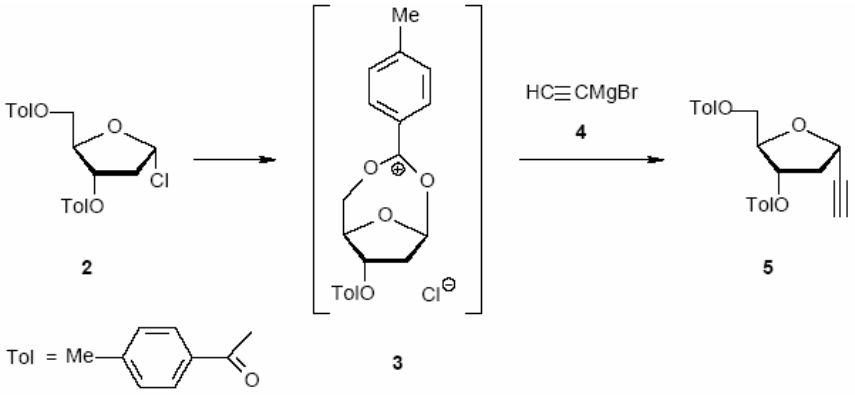
Although most naturally occurring *C*-glycosides are β-configured, some exist also as α-type. The antibiotic pyrazofurin anomer **1a** has been isolated from *Streptomyces candidus* in 1969 by Gerzon *et al*.[5] It has been suggested that pyrazofurin B (α-type) might be an artifact arising from acid-catalyzed isomerization.[6]



1a 1b

Results and Discussion

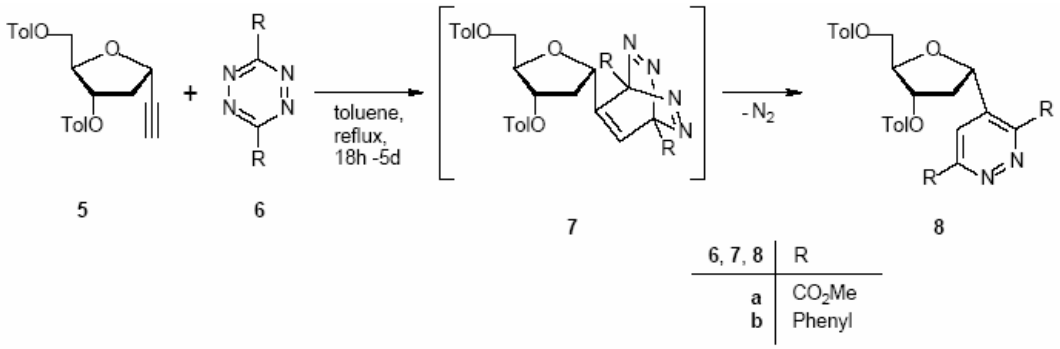
With this background we were in search of an efficient approach to a suitably substituted *C*-glycoside precursor. Based on the reactions of Grignard reagents with benzyl-protected ribose and ribose halides described by Buchanan *et al.*,[7] we transferred this procedure successfully to the deoxy carbohydrate series using 2-deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl chloride **(2)**. The application of a glycosyl halide is advantageous, because no further cyclization reaction is needed. In the case of the (protected) hemiacetal, the aldehyde reacts with the Grignard reagent to give two different diols which have to be cyclized in an additional reaction step.



Scheme 1

The nucleophilic displacement of the chloride anion in α-halide[8] **2** by ethynylmagnesium bromide **4** preferentially led to the α-deoxyribofuranosylethyne **5** (ratio α/β ≈ 3:1). Former investigations have revealed that the glycosylation of some pyrrolo[2,3-*d*]pyrimidines employing the chloride **2** under phase transfer conditions occurs stereospecifically by inversion of the configuration of the anomeric C-atom.[9] Our different observations may be explained by a neighbouring group effect of the 5'-toluoyl group as shown in the postulated intermediate **3** (Scheme 1). A similar effect has been observed in nucleophilic reactions of 2'-benzoyl- or 2'-acetyl-protected carbohydrate derivatives.[10] In this case, participation of the protecting group mainly leads to β-configured products.

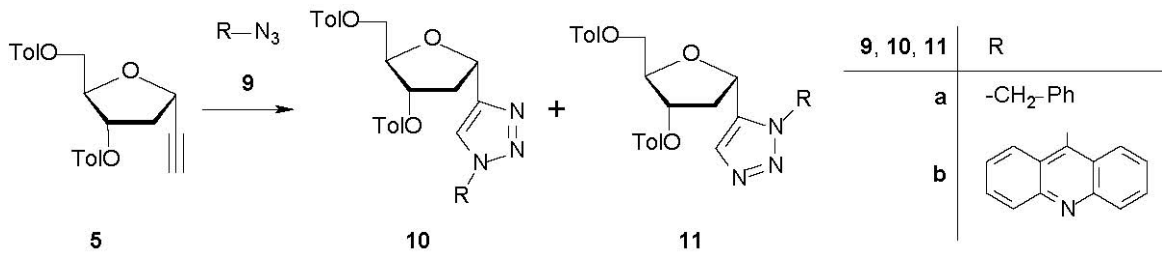
In general, the ethynyl *C*-glycoside **5** should be a suitable precursor for [4+2]-cyclo-addition reactions. However, since **5** did not undergo the Diels-Alder-reaction with one of the most reactive dienes, the Danishefsky diene,[11] we chose dimethyl [1,2,4,5]tetrazine-3,6-dicarboxylate[12] **6a** as one of the most activated electron-deficient heterocyclic diazadienes for [4+2]-cycloadditions with inverse electron demand. Reaction of **6a** with the precursor **5** resulted in a typical cycloaddition-extrusion sequence (Scheme 2). After extrusion of N_2 the pyridazine **8a** was formed. In turn, 3,6-diphenyltetrazine **6b** has been employed as well but turned out to be significantly less reactive. The reaction time increased from 18 h to 5 days while the yield decreased from 80% to 25%. The resulting *C*-glycosides **8** (Scheme 2) represent the first examples of 4-(2'-deoxyribo-furanosyl)pyridazines.[13]



Scheme 2

Since [4+2]-cycloadditions turned out to be smoothly applicable both ribose and deoxy-ribose derivatives, we also tried to representatively test the reactivity of the *C*-glycoside precursor **5** towards [3+2]-dipolar cycloaddition reactions, which were first employed in the carbohydrate field in 1957.[14]

Upon reaction of **5** with benzylazide **9a** (known as a promising powerful and stable 1,3-dipole[15]) at 100° C we obtained, after chromatographic work-up, the regioisomeric triazoles **10a** and **11a** in 62% total yield (Scheme 3). The separation of the two isomers by classical techniques failed, but with the aid of the NMR spectra, especially using NMR experiments such as NOE or COSY, some signals could be conclusively assigned to each isomers. The evaluation of the signal intensities [for example of the 5'-H of the triazole ring at δ 7.50 **(11a)** and 7.69 **(10a)** as well as the 2'-riboside-H at δ 2.30, 2.81 **(10a)** and δ 2.73, 2.94 **(11a)**, respectively] leads to the conclusion that formation of 11a predominates roughly in a 3:2 ratio. Considering steric effects, isomer **10a** is expected to be formed preferentially, but obviously, other factors such as polarities are involved as well. To confirm this type of 1,3-dipolar cycloaddition as a general approach to C-C linked 2-deoxyribofuranosyltriazoles we employed 9-azidoacridine[16] **9b** under similar conditions and isolated a mixture[17] of the novel *C*-glycosides **10b** and **11b** in 34% yield (Scheme **3**).



Scheme 3

Recently, [1,2,3]triazole nucleosides have been found to possess potent anti HIV-1 activity.[18]

Experimental Section

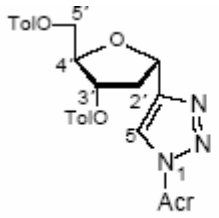
[2-Deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl]ethyne (5). 2-Deoxy-3,5-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl chloride **2** (16 g, 41 mmol) in dry THF (250 mL) was added drop-wise within 30 min at room temperature to ethynylmagnesium bromide (800 mL 0.5 M solution in THF, 40 mmol). The solution was stirred at room temperature for 5h and reduced to 1/3 of its volume *in vacuo*. Ether (500 mL) was added, and the solution was washed with 10% NH_4Cl_{aq} followed by water, and was dried ($MgSO_4$). After removal of the solvent *in vacuo* the residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate 3:1 as eluent) to give **5** as a pale yellow syrup (10.8 g, 28.4 mmol, 69%). MS (FAB, *m*-NBA): *m*/*z* 379.1 (MH^+); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (m, 1H, 2'-Hβ), 2.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.56 (d, 1H, *J* = 2.3 Hz, -C≡CH), 2.68 (dt, 1H, *J* = 13.5, 7.8 Hz, 2'-Hα), 4.50–4.60 (m, 2H, 5'-H), 4.62 (m, 1H, 4'-H), 5.00 (dt, 1H, *J* = 7.8, 2.3 Hz, 1'-H), 5.49 (m, 1H, 3'-H), 7.12–7.25 (m, 4H, ArH), 7.86–8.05 (m, 4H, ArH). Anal. calcd for $C_{23}H_{23}O_5$: C, 73.00; H, 5.86. Found: C, 72.93; H, 5.77.

Dimethyl 4-[2′-deoxy-3′,5′-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl]pyridazine-3,6-dicarboxylate (8a). Compound **5** (750 mg, 1.98 mmol) and dimethyl [1,2,4,5]tetrazine-3,6-dicarboxylate **6a** were dissolved in dry toluene (25 mL) and heated under reflux for 33 h. The solvent was removed *in vacuo*, and the residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate 1:2 as eluent) to give **8a** (870 mg, 1.59 mmol, 80%) as a pale yellow solid, mp 58–61 °C. MS (FAB, m-NBA): *m*/*z* 549.2 (MH^+); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.18 (d, 1H, *J* = 14.6 Hz, 2'-Hβ), 2.36 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.23 (ddd, 1H, *J* = 6.1, 5.8, 14.6 Hz, 2'-Hα), 4.03 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.50 (dd, 1H, *J* = 4.7, 8.3 Hz, 5'-H), 4.58 (dd, 1H, *J* = 4.7, 8.3 Hz, 5'-H), 4.88 (t, 1H, *J* = 4.7 Hz, 4'-H), 5.59 (d, 1H, *J* = 5.6 Hz, 3'-H), 5.97 (dd, 1H, *J* = 3.9, 9.0 Hz, 1'-H), 7.10 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.26 (s, 2H, Ar-H), 7.55 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.97 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.62 (s, 1H, pyridazine-H). Anal. calcd for $C_{29}H_{28}O_9N_2$: C, 63.50; H, 5.14; N, 5.11. Found: C, 63.08; H, 5.12; N, 5.62.

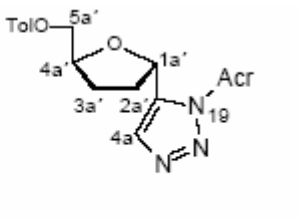
1-Benzyl-4-[2′-deoxy-3′,5′-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl][1,2,3]triazole (10a) and 1-benzyl-5-[2′-deoxy-3′,5′-bis[*O*-(*p*-toluoyl)]-α-D-ribofuranosyl][1,2,3] triazole (11a). Compound **5** (470 mg, 1.24 mmol) and benzylazide **9a** (1.2 g, 9.5 mmol) were heated under Ar

at 100 °C for 14 h. Purification by chromatography on silica gel (*n*-hexane/ethyl acetate 2:1 as eluent) afforded a mixture of **10a** and **11a** (390 mg, 62%) as a colorless syrup which crystallized on standing, mp 41–45 °C. MS (FAB, m-NBA): *m*/*z* 512.1 (MH^+); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (m, 1H, 2'-Hβ [**10a**]), 2.38 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.73 (m, 1H, 2'-Hβ [**11a**]), 2.81 (dt, 1H, *J* = 14.1, 7.4 Hz, 2'-Hα [**10a**]), 2.94 (dt, 1H, *J* = 13.8, 7.4 Hz, 2'-Hα [**11a**]), 4.42 (dd, 1H, *J* = 7.7, 4.3 Hz, 4'-H[**10a**]), 4.54–4.60 (m, 5H, 4'-H[**10a**], 5'-H[**10a**/**11a**]), 5.20 (dd, 1H, *J* = 7.8, 4.8 Hz, 3'-H[**10a**]), 5.47–5.60 (m, 5H, 3'-H[**11a**], CH_2Ph [**10a**/**11a**], 5.61 (d, 1H *J* = 15.3 Hz, 1'-H[**11a**]), 5.76 (d, 1H, *J* = 15.1 Hz, 1'-H[**10a**]), 7.18-7.37 (m, 18H, Ar-H), 7.50 (s, 1H, triazole-H [**11a**]), 7.69 (s, 1H, triazole-H [**10a**]), 7.74-7.97 (m, 8H, Ar-H). Anal. calcd for $C_{30}H_{29}O_5N_3$: C, 70.44; H, 5.71; N, 8.21. Found: C, 70.32; H, 5.77; N, 8.22.

1-(9-Acridino)-4-[2′-deoxy-3′,5′-bis[*O*-(p-toluoyl)-α-D-ribofuranosyl][1,2,3]triazole (10b) and 1-(9-acridino)-5-[2′-deoxy-3′,5′-bis[*O*-(p-toluoyl)]-α-D-ribofuranosyl][1,2,3] triazole (11b). Compound **9b** (2.6 g, 6.9 mmol) and 2'[deoxy-3',5'-bis[*O*-(*p*-toloyl)]-α-D-ribofuranosyl]ethyne **5** (1.1g, 5 mmol) were heated in abs. toluene (10 mL) to 60 °C for 3 days. After evaporation of the solvent and repeated column chromatography (silica gel, PE/diethyl ether 1:1) the mixture of regioisomers **10b** and **11b** (880 mg, 29.4%) was obtained as a slightly ochre solid, mp 82–85 °C. MS (FAB, m-NBA): *m*/*z* (%) 599.2 (M+1; 53.6) 307.1 (100); IR (KBr): [cm^{-1}] 3140, 3063, 2951, 2913, 1719, 1611, 1446, 1272; UV (CH_3CN): λ_{max} [nm] (log ε) 218 (4.32), 250 (4.88), 345 (3.67, 348 (3.67), 361 (3.84), 384 (3.55); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.26 (s, 3H, 11'-H), 2.29 (s, 3H, 11'-H), 2.39 (s, 3H, 11'-H), 2.67 (m, 1H, 2a'/2'-H), 2.87 (m, 1H, 2a'/2'-H), 2.97 (t, 1H, *J* = 3.6 Hz, 2a'/2'-H), 3.06 (m, 1H, 2a'/2'-H), 4.59 (m, 4H, 5a'/5'-H), 4.71 (m, 2H, 4a'/4'-H), 5.64 (dd, 1H, *J* = 6.2 Hz, 1a'/1'-H), 5.72 (m, 2H, 3a'/3'-H), 5.77 (dd, *J* = 7.8, 4.4 HZ, 1a'/1'-H), 6.98-7.65 (br, 18H, Ar-H), 7.72–8.02 (br, 10H, Ar-H), 8.04 (s, 1H, 4a/5-H), 8.12 (s, 1H, 4a/5-H), 8.31 (dd, *J* = 7.29, 2.44 Hz, Ar-H). Anal. calcd for $C_{36}H_{30}O_5N_4$: C, 72.23; H, 5.05. Found: C, 72.63, H, 5.02.



10b



11b

Acknowledgements

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