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Synthesis of annelated pyranosides: a rapid and efficient entry to highly functionalized optically pure branched-pyrazoles

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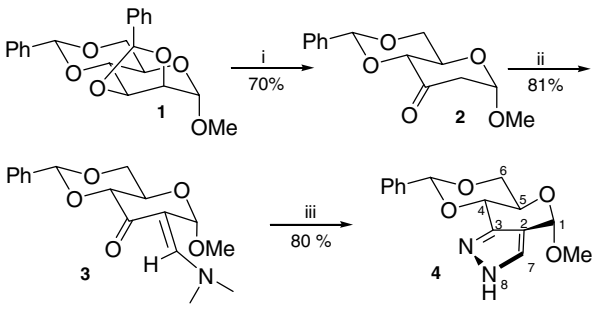
Abstract—Pyrazolo-pyranosides prepared from methyl-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside were functionalized to design new scaffolds suitable for peptidomimetic construction. Under certain acidic conditions, they undergo only pyranose ring-opening generating highly functionalized optically pure pyrazoles bearing an aldehyde function.

The use of scaffolds for the construction of biologically active compounds is now a well-accepted concept.[1] Chiral carbohydrate-based scaffolds are well suited for introducing stereodiversity in the final compounds.[2–4] Our preliminary results on the design of peptidomimetics based on sugar scaffolds led us to the conclusion that a challenge in this area is to construct platforms larger than a single pyranose ring.[5,6] In this regard pyranose-fused ring systems deserve some attention.[7,8] We have successfully used keto-sugars for pyranosidic homologation using hetero Diels–Alder reactions.[9–11] More recently, we became interested in the construction of nitrogen containing heterocycles fused to the pyranose ring and pyrazole has been chosen as the first target.

Pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic and sedative-hypnotic activities. Particularly, arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[12,13] The most common method to prepare pyrazole heterocycles involves the condensation of hydrazine derivatives with β-dicarbonyl compounds or with α,β-unsaturated carbonyl compounds.[14–16] However, the generality of this method is somewhat vitiated by the severe reaction conditions or the multistep sequence usually required to access the starting materials. Thus, continuing efforts have been made to develop efficient synthetic methods for preparing functionalized pyrazole derivatives. In this context, we report our preliminary results in the construction of pyrazolo-pyranose which lead to new scaffolds and afford a direct route to acyclo-pyrazole nucleosides.[17]

Starting from the known methyl 2,3:4,6-di-*O*-benzylidene α-D-mannopyranoside **1**, 2-deoxy-3-ulo derivative **2** was prepared by the action of BuLi on **1** as previously described.[9,10] The condensation of *N*,*N*-dimethylformamide dimethylacetal gave branched-chain ulose **3** in good yield. Pyrazole-annelated pyranoside**4** was prepared in 80% yield by the treatment of **3** with hydrazine hydrate (Scheme 1).[18]

In order to construct scaffolds for peptidomimetic design, the reactivity of compound **4** was explored



Scheme 1. Reagents and conditions: (i) **1**/BuLi/THF/−30 °C; **2**/NH_4Cl; (ii) $HCNMe_2(OMe)_2/CH_2Cl_2$; (iii) NH_2NH_2/MeOH.

Keywords: Pyrazoles; Pyranosides; Ring pyran opening; Scaffold.
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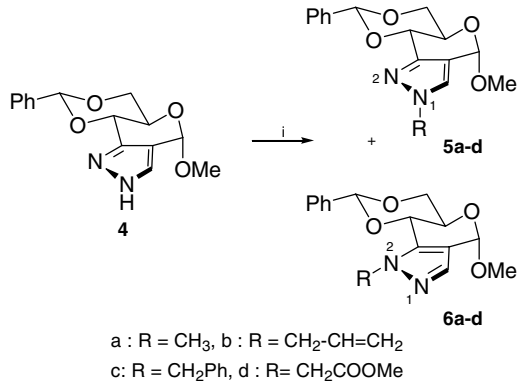


Scheme 2. Reagents and conditions: (i) method A: RX, NaH, THF; method B: RX, K_2CO_3, DMF; method C: RX, C_6H_6, NaOH, Bu_4NOH.

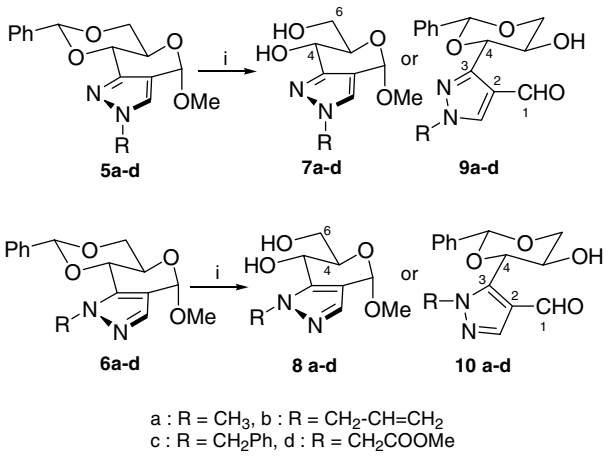
(Scheme 2). N-Alkylation of the pyrazole moiety with alkyl halides was investigated using three different methods A, B and C. In method A, NaH was used as the base and dry THF as the solvent. In method B, K_2CO_3 was used as the base and dry DMF as the solvent. Phase Transfer Catalysis (PCT) was used in method C, alkylation reactions being performed by stirring equimolar amounts of pyrazole and the appropriate alkyl halide in the presence of 40% aqueous sodium hydroxide and 40% aqueous tetrabutylammonium hydroxide in benzene. Different alkyl halides (MeI, BnBr, $BrCH_2$-COOMe and allylbromide) were selected as mimics of amino-acid side chains: methyl group for alanine, benzyl group for phenylalanine and methyl acetate for aspartic acid side chain. The chemical manipulation of the allyl group could serve for further functionalization.

Because of the two equivalent resonance forms of pyrazole **4** anion, a regioisomeric mixture of **5** and **6** is expected from N-alkylation, as described in the literature for unsymmetrical substituted pyrazoles.[19] Depending on the reaction conditions used, the three methods furnished two separable regioisomers **5** (N1-alkylated) and **6** (N2-alkylated) in different ratio (Table 1) except for allylbromide (entries 4–6) for which only regioisomer **5b** was obtained in good yield. Using method A, alkylation with methyl iodide gave mainly regioisomer **5a** (entry 1). This ratio is reversed using method B and C (entries 2 and 3). Alkylation with benzyl bromide using

Table 1. Alkylations of pyrazolo-pyranoside **4**

Entry	Alkyl halide	Method	Yield[a] (%)	**5/6** ratio
1	CH_3I	A	87	71:29
2	CH_3I	B	88	26:74
3	CH_3I	C	90	32:68
4	AllylBr	A	80	100:0
5	AllylBr	B	75	100:0
6	AllylBr	C	80	100:0
7	BnBr	A	56	100:0
8	BnBr	B	40	39:61
9	BnBr	C	79	56:44
10	$BrCH_2COOMe$	A	70	43:57
11	$BrCH_2COOMe$	B	71	59:41

[a] Yields refer to pure products after chromatography.



Scheme 3. Reagents and conditions: (i) for **7** and **8** formation: method A: PTSA (20%)/MeOH; for **9** and **10** formation: method B: PTSA (20%)/THF.

method A, provided only regioisomer **5c** (entry 7). The ratio of compound **6c** increased with both methods B and C (entries 8 and 9). Modest yields observed with methods A and B can be explained by the opening of the sugar ring forming aldehyde **9c** (Scheme 3). The introduction of ester functionality was achieved in good yield by alkylation with methyl bromoacetate. A mixture of regioisomers **5d** and **6d** in equal amounts was obtained with both methods A and B (entries 10 and 11).

The structures of regioisomers **5** and **6** have been established by 1D and 2D NMR (^1H, ^{13}C, COSY, HMBC, HMQC). Heteronuclear correlations (HMBC) between C7/H8 and C3/H8 strongly support the structure of substituted pyrazoles **5d** and **6d**, respectively (Fig. 1). Moreover, the chemical shift of H7 is upfield in regioisomer **6d** (7.46 ppm) as compared to regioisomer **5d** (7.75 ppm), whereas the chemical shift of C7 is downfield in regioisomer **6d** (136.8 ppm) versus regioisomer **5d** (131.5 ppm). These variations on chemical shifts were observed for all regioisomers and strongly support the structure of the substituted pyrazolo-pyranosides.

In order to develop the functionalization of the bicyclic scaffolds **5** and **6**, the cleavage of the benzylidene acetal of both compounds was considered.

Unexpectedly, acid hydrolysis using a catalytic amount of PTSA in methanol at room temperature for one hour gave a mixture of 4,6-diols **7** or **8** and pyrazoles **9** or **10**, respectively (Scheme 3). Prolonged stirring (12 h at

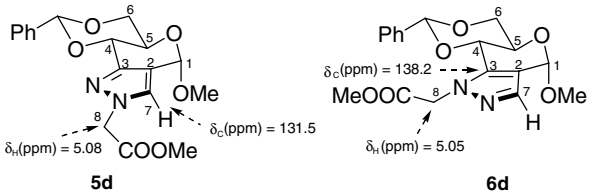


Figure 1. Heteronuclear correlations (HMBC) of substituted pyrazoles **5d** and **6d**, respectively.

Table 2. Hydrolysis of compounds **5** and **6**

Entry	R	4,6-Diol[a] (%)	Aldehyde[b] (%)
1	Me	**7a** (76)	**9a** (78)
2	Allyl	**7b** (75)	**9b** (66)
3	Bn	**7c** (72)	**9c** (68)
4	CH_2COOMe	**7d** (70)	**9d** (70)
5	Me	**8a** (78)	**10a** (63)
6	Bn	**8c** (73)	**10c** (63)
7	CH_2COOMe	**8d** (79)	**10d** (71)

[a] Yields refer to pure isolated compounds after chromatography (method A).
[b] Yields refer to pure isolated compounds after chromatography (method B).

room temperature) gave only diols **7** and **8** in good yield (Table 2).[20]

Polyhydroxylated pyrazoles are often considered as nucleoside acyclic analogues of biological interest.[17] Thus, we have developed optimized conditions for the formation of **9** and **10** in good yield. The replacement of methanol by THF in acidic hydrolysis allows the formation of only aldehydes **9** and **10** giving an efficient access to yet unknown optically active polyhydroxylated pyrazoles (Table 2) bearing an aldehyde function at the 4-position of the pyrazole ring.[21]

All these data suggest that acetal hydrolysis takes place first at the anomeric centre then at the benzylic centre. As soon as the six-membered benzylidene acetal is cleaved, glycosylation of the free sugar then occurs in methanol to provide compounds **7** or **8**. This unusual glycoside sensitivity towards acid hydrolysis could be explained by the strain induced by the tricyclic system and by the 2-deoxy nature of compounds **5** and **6**. In tetrahydrofuran, only the most sensitive glycosidic bond is cleaved giving aldehyde **9** or **10**.

In conclusion, we have described a rapid and efficient synthesis of enantiomerically pure highly functionalized pyrano-pyrazoles. From the two acetals present on these scaffolds, both can be selectively cleaved depending on the acidic hydrolysis conditions. Anomeric acetal hydrolysis is obtained in THF and gives access to new chiral pyrazoles functionalized at position 3 and 4 in good yields. Benzylidene acetal acidic hydrolysis of these pyrazolo-pyranosides occurs only in methanol yielding bicyclic scaffolds bearing hydroxyl functions at C4- and C6-position of the sugar ring. Further functionalization of these templates for the design peptidomimetics is under investigation.

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18. To a stirred methanolic solution of **3** (0.5 g, 1.56 mmol), hydrazine hydrate (0.2 mL, 6.24 mmol) was added. The reaction was monitored by TLC. After reaction completion, the solvent was evaporated and the solid was recrystallized from ethanol. Compound **4**: White powder, mp 221 °C, R_f (SiO_2, CH_2Cl_2/MeOH, 95:5) 0.5, $[\alpha]_D$ +88.3 (*c* 1.0, $CHCl_3$), IR *v* 3271 cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$): δ_H (ppm) 3.45 (s, 3H, *OMe*), 3.97 (td, 1H, H_5, $J_{5-6} = 9.9$ Hz, $J_{4-5} = 8.8$ Hz, $J_{5-6'} = 4.4$ Hz), 4.01 (t, 1H, H_6, $J_{5-6} = J_{6-6'} = 9.9$ Hz), 4.41 (dd, 1H, $H_{6'}$, $J_{5-6'} = 4.4$ Hz, $J_{6-6'} = 9.9$ Hz), 4.76 (d, 1H, H_4, $J_{4-5} = 8.8$ Hz), 5,64 (s, 1H, H_1), 5.89 (s, 1H, H benzylidene), 7.4–7.6 (m, 5H, aromatic), 7.75 (s, 1H, H_7), 12.95 (s, 1H, H_8); ^{13}C NMR (DMSO, 63 MHz): δ (ppm) 55.7 (*OMe*), 65.3 (C_5), 69.2 (C_6), 74.8 (C_4), 96.5 (C_1), 101.9 (C benzylidene), 115.7 (C_2), 127.3, 129.02 (C aromatic), 129.9 (C_7), 138.6 (C

aromatic), 146.0 (C_3). MS (ESI) m/z 312 $[M+H+Na]^+$, 311 $[M+Na]^+$.

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20. Representative procedure for diol formation: Compound **5** or **6** (0.5 mmol) was treated with PTSA (20 mol %) in MeOH (15 mL) at room temperature. The progress of the reaction was monitored by TLC and after completion, the reaction mixture was diluted with $NaHCO_3$ saturated aqueous solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel. Compound **7a**: R_f (SiO_2, CH_2Cl_2/MeOH, 9:1) 0.45, $[\alpha]_D$ +0.8 (*c* 1.02, $CHCl_3$); IR *v* 3378.15, 2924.36 cm^{-1}; ^1H NMR (DMSO, 250 MHz): δ_H (ppm) 3.39 (s, 3H, *Me*), 3.57–3.77 (m, 3H, H_6, $H_{6'}$, H_5), 3.82 (s, 3H, *OMe*), 4.37 (t, 1H, H_4, $J_{4\text{–}OH4} = 7.4$ Hz, $J_{4\text{–}5} = 9.1$ Hz), 4.77 (t, 1H, OH_6, $J_{5\text{–}OH6} = 5.8$ Hz), 5.41 (d, 1H, OH_4, $J_{OH4\text{–}5} = 7.4$ Hz), 5.49 (s, 1H, H_1), 7.61 (s, 1H, H_7); ^{13}C NMR (DMSO, 63 MHz): δ (ppm) 38.5 (*Me*), 54.3 (*OMe*), 60.7 (C_5), 62.2 (C_6), 73.9 (C_4), 94.1 (C_1), 115.5 (C_2), 127.4 (C_7), 149.7 (C_3). MS (ESI) m/z 238 $[M+H+Na]^+$, 237 $[M+Na]^+$.
21. Representative procedure: Compound **5** or **6** (0.5 mmol) was treated with PTSA (20 mol %) in THF (15 mL) at room temperature. The progress of the reaction was monitored by TLC and after completion, the reaction mixture was diluted with $NaHCO_3$ saturated aqueous solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel. Compound **9c**: R_f (SiO_2, hexane/EtOAc, 1:1) 0.25, $[\alpha]_D$ −29.3 (c 1.0, $CHCl_3$); IR *v* 2845, 1672 cm^{-1}; ^1H NMR (DMSO, 250 MHz): δ_H (ppm) 3.68 (t, 1H, H_6, $J_{6\text{–}6'} = J_{6\text{–}5} = 10.3$ Hz), 4.06 (td, 1H, H_5, $J_{5\text{–}6'} = 4.9$ Hz, $J_{5\text{–}6} = 10.3$ Hz, $J_{5\text{–}4} = 9.5$ Hz, $J_{5\text{-}OH} = 6.2$ Hz), 4.25 (dd, 1H, $H_{6'}$, $J_{6\text{–}6'} = 10.3$ Hz, $J_{5\text{–}6'} = 4.9$ Hz), 4.99 (d, 1H, H_4, $J_{4\text{–}5} = 9.5$ Hz), 5.29 (d, 1H, OH, $J_{OH\text{-}5} = 6.2$ Hz), 5.72 (s, 1H, H benzylidene), 7.37–7.40 (m, 10H aromatic), 8.57 (s, 1H, H_7), 10.02 (s, 1H, H_1); ^{13}C NMR (DMSO, 63 MHz): δ (ppm) 55.1 (C_8), 64.0 (C_5), 71.3 (C_6), 77.5 (C_4), 100.6 (C benzylidene), 121.6 (C_2), 126.2, 127.9, 128.0, 128.2, 128.6, 128.7 (C aromatic), 135.4, 136.2 (C aromatic), 137.8 (C_7), 150.8 (C_3), 184.8 (C_1). MS (ESI) m/z 388 $[M+H+Na]^+$, 387 $[M+Na]^+$.