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Synthesis of chiral 4-pyrazolol derivatives starting from D-glucose

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Abstract. The condensation of protected and unprotected 3-ketoglucose (**1**) with hydrazines to 4-pyrazolols has been investigated. 3- (**5**) and 5-(D-*erythro*-1,2,3-trihydroxypropyl)-4-pyrazolol (**4**) were obtained from **1** in high yield, as a mixture of these two isomers. A regioselective route starting from protected **1** in two steps yielded a mixture of diastereomers as a result of epimerization in the side chain.

Introduction

The conversion of carbohydrates into chiral, heterocyclic compounds containing nitrogen has attracted considerable interest[1]. Recently, the synthesis of chiral hydroxyalkyl pyrazoles was reported from the reaction of sugar hydrazones with nitroalkenes[2,3] or hydrazones with sugar nitroalkenes[4]. A dipolar 1,3-cycloaddition of diazoalkanes with α,β-unsaturated sugar derivatives gave chiral pyrazolines, which could be converted by oxidation into their corresponding pyrazole derivatives[5]. Chiral pyrazolediones have been synthesized from 2,3-hexodiulosono-1,4-lactone[6]. Direct condensation of dicarbonyl sugars with hydrazine derivatives has been applied to the synthesis of 4(1*H*)-

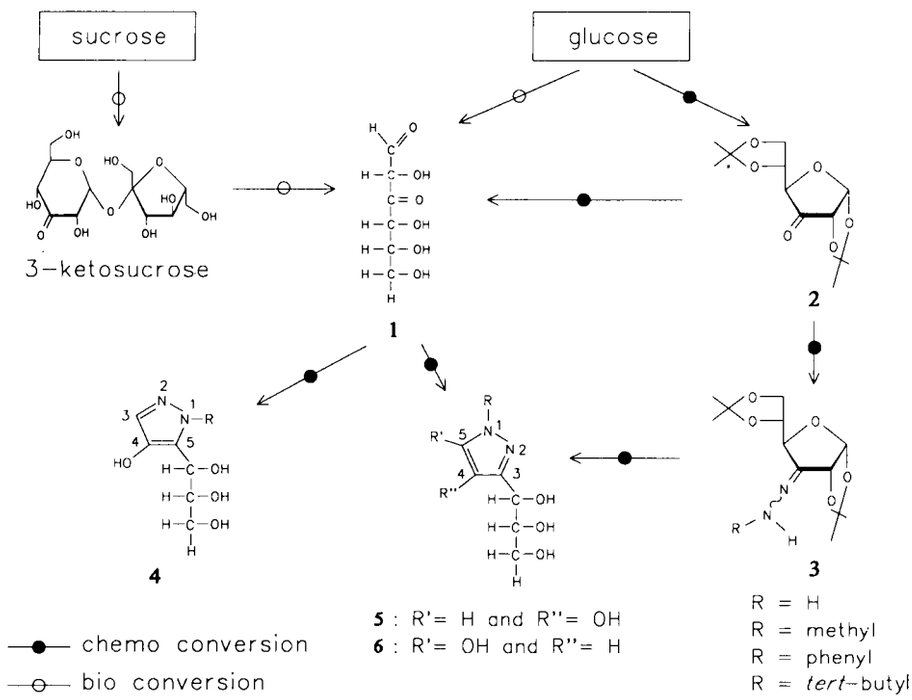

Figure 1. Synthesis of pyrazolols starting from sucrose or D*-glucose.*

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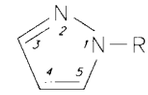
pyridazinones[7] and 3-(hydroxymethyl)-5-hydroxypyridazinium hydroxides[8]. A (trihydroxypropyl)pyrazole was synthesized starting from 1,2 : 5,6-di-*O*-isopropylidene-α-D--glucofuranoside[9].

We have used the 1,3-dicarbonyl sugar 3-ketoglucose (D-*ribo*-3-hexosulose) (**1**) as starting material for the synthesis of pyrazoles. Compound **1** can be obtained both from glucose by either chemical conversion[10,11] or fermentation[12], and from sucrose by fermentation followed by enzymatic hydrolysis[13]. The condensation of **1** with hydrazines is an attractive route to substituted pyrazolols (**4–6**), as depicted in Figure 1. We have studied the results of the direct synthesis of pyrazolols from **1** in comparison with those of the route via the hydrazone compound **3**[14].

Results and discussion

3-Ketoglucose (**1**) was prepared from diacetone–glucose (1,2 : 5,6-di-*O*-isopropylidene-α-D-glucose) by oxidation with the ruthenium/periodate system[10,11] into **2**, followed by acid hydrolysis using an ion-exchange resin in water. After filtering off the resin, the aqueous 3-ketoglucose solution was used without purification. Figure 1 shows that three isomeric pyrazolols (**4–6**) should be taken into account. Tautomerism of the pyrazolols to the corresponding pyrazolones further complicates identification of the products. The reaction of **1** with the hydrazine yielded two compounds (**4** and **5**) in the case of R ≠ H (methyl and phenyl) and one in the case of R = H. The phenyl derivatives of **4** and **5** were separated by preparative HPLC (column chromatography of the product mixture from methylhydrazine yielded only one of the isomers in pure form). Mass-spectroscopic analysis of these compounds gave the molar mass corresponding with **4–6** (R = H, methyl and phenyl, respectively), and the loss of $CH_2OH-CHOH^{\bullet}$ ($M^{\ddagger} - 61$). ^1H and ^{13}C NMR spectroscopy confirmed the formation of pyrazolols containing a C_3 carbohydrate chain.

NMR of the pyrazolol compound **5**, R = H (only one product formed, see above) showed that isomerization to the pyrazolone did not take place. Comparison of the ^{13}C NMR spectra (Table I) of this product and pyrazole (**7**, R = H)[15] shows a downfield shift of approximately 40 ppm for C-4, in accordance with a hydroxyl group at this position[16]. One signal is shifted upfield by 11 ppm, as is expected for the unsubstituted carbon, whereas the signal of the C atom bearing the triol side chain (C_3) remains in more or less the same position, because of the compensating effect of the neighbouring oxygen atoms.



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Similarly, NMR showed that both products with R = methyl bear the hydroxyl substituent at the C-4 position. The unsubstituted carbon atoms in structures **4** and **5** should be expected at 127 and 119 ppm, respectively; *i.e.*, shifted upfield by approximately 11 ppm compared with **7** (R = methyl)[15]. The structures of the phenyl-substituted products, one showing a signal for the unsubstituted C atom at 129.4 ppm, the other one at 112.6 ppm, have been assigned in the same manner. The downfield shift of the *ortho*-phenyl-carbon atom of **4** confirms the substitution of the phenyl group to be on the nitrogen atom α to the carbohydrate-substituted carbon atom C-5.

The ^{13}C NMR spectra showed single signals for the carbohydrate side chain. Thus, the configuration of the carbohydrate moiety is preserved, which means that we are dealing with the D-*erythro* configuration.

Table I ^{13}C *NMR data of 4-pyrazolol derivatives* **4–7** *obtained directly from* **1** *(δ in ppm).*

R	C-3	C-4	C-5	C-1′	C-2′	C-3′	CH_3	*ipso*	*ortho*	*meta*	*para*
7, H[a]	133.7	104.8	133.7								
4, H[b]	134.0	139.2	122.3	67.5	74.5	63.8					
7, methyl[a]	138.5	105.2	130.4				38.3				
4, methyl[b]	128.7	140.7	129.2	66.3	74.6	64.1	38.6				
5, methyl[b]	140.0[c]	139.6[c]	121.1	68.3	75.2	64.3	39.9				
7, phenyl[a]	141.0	107.8	127.4					139.9	118.5	129.4	126.1
4, phenyl[d]	129.4	140.5	126.6	65.5	74.4	63.0		140.2	125.2	128.8	127.4
5, phenyl[d]	141.4	142.5	112.6	68.6	74.9	63.2		140.1	117.4	129.1	125.2

[a] Ref. 15. [b] In D_2O with *tert*-butanol as internal reference. [c] These values may be interchanged. [d] In $CDCl_3$ with tetramethylsilane as internal reference.

Table II ^{13}C *NMR data of diastereomeric 4-pyrazolol derivatives* **5/8** *and* **9/10** *obtained via hydrazones* **2** *(δ in ppm).*

	R	C-3	C-4	C-5	C-1′	C-2′	C-3′	OCH_3	CH_3	$(CH_3)_3C$	Me_3C	*ipso*	*ortho*	*meta*	*para*
5/8	H	133.4	138.2	121.7	65.4	74.5	62.5								
		133.9	138.4	121.7	66.3	74.6	63.0								
9/10	H	–	139.6	–	75.2	73.1	62.4	55.8							
		–	139.7	–	75.8	73.8	62.8	56.1							
9/10	Me	137.1	141.2	119.1	77.8	74.8	63.8	56.6	39.1						
		137.8	141.2	119.2	78.4	75.4	64.1	56.8	39.1						
9/10	Ph	140.6	143.3	115.0	78.2	74.8	63.9	56.9				141.5	119.2	130.3	126.9
		141.3	143.4	115.0	78.9	75.5	64.2	57.1				141.5	119.2	130.3	126.9
9/10	*t*Bu	136.7	140.8	114.9	77.9	75.0	63.9	56.5		29.8	59.2				
		137.5	140.7	114.9	78.7	75.6	64.2	56.7		29.8	59.2				

Selective formation of **5** would be expected after deprotection and ring closure of the hydrazone derivatives **3** (R = H, methyl, phenyl, and *tert*-butyl, Figure 2). This reaction has been performed in anhydrous methanol with an ion-exchange resin in the H^+ form as catalyst. Surprisingly, each reaction product consisted of two compounds in an approximately 1:1 ratio according to ^1H NMR. The ^{13}C NMR data (Table II) are almost identical to those found for isomer **5**, except for the C-1′ carbon atom, which has been shifted downfield by approximately 10 ppm.

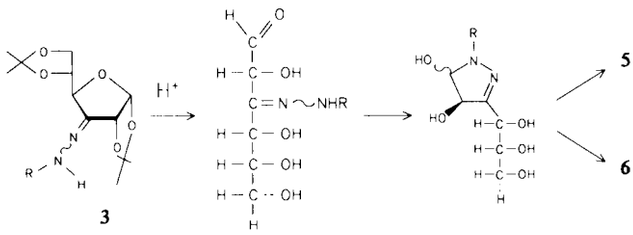
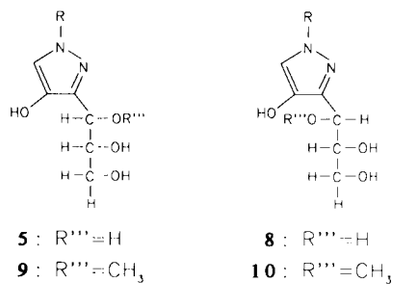


Figure 2. Acid hydrolysis followed by cyclization of hydrazones to pyrazolols. R = hydrogen, methyl, phenyl and tert*-butyl.*

Heating of the reaction product from **3** (R = *tert*-butyl) in $C_2D_2Cl_4$ to 100°C did not result in an equilibrium shift to one of the two isomers. In addition, a methoxy signal is present in both the ^1H and ^{13}C NMR spectra, in accordance with the mass spectrum which gave a molar mass corresponding with methylated **5** and loss of $CH_2OH-CHOH^{\bullet}$. On the basis of these analytical data, we concluded that the acid-catalyzed conversion of **3** in methanol results in a diastereomeric mixture of **9** and **10**, obtained from methoxylation at C-1′ with simultaneous epimerization.



5: R‴ = H **8**: R‴ = H

9: R‴ = CH_3 **10**: R‴ = CH_3

The work-up procedure involved ion-exchange chromatography with the resin in the H^+ form. The product with R = H was retained strongly on the resin; therefore, elution with water was necessary. Under these conditions, the methoxy groups of **9** and **10** were partly replaced by hydroxyl, resulting in **5** and **8**, as became apparent from ^1H and ^{13}C NMR spectroscopy and MS (M^+ of 188 and 174). In addition, a small portion of this pyrazolol was present as pyrazolone tautomers, as became clear from a signal at 207.3 ppm in the ^{13}C NMR spectrum. ^{13}C NMR showed that the methyl derivatives **5** and **8** were similarly tautomerized to their corresponding pyrazolone isomer to a small extent when eluted from the resin with water. Pyrazolone formation for **9** and **10** with R = methyl, phenyl, and *tert*-butyl was not observed when methanol was used. A mechanism which explains the results obtained is given in Figure 3. Protonation of C-1′-OH, probably via an intramolecular proton shift **11** → **12**, is followed by dehydration

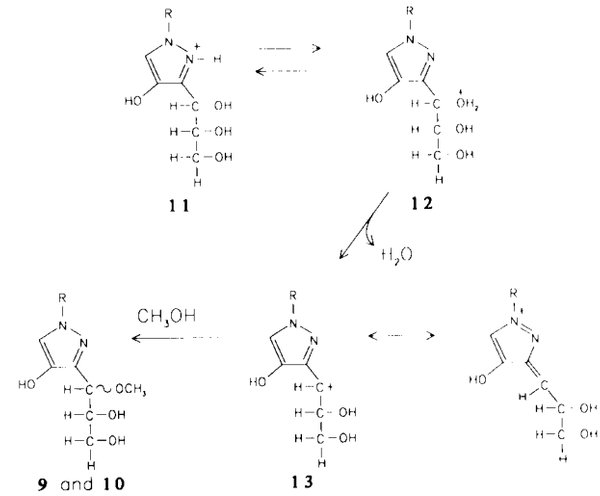


Figure 3. Reaction mechanism explaining methylation and epimerization at C-3′.

to the pyrazolol-stabilized carbenium ion **13**, which is methoxylated to **9** and **10**. A similar mechanism has been suggested to explain the α,β anomerization of furanosyl-substituted pyrazoles[17]. Alternatively, 1,4 elimination of water from **11** would lead to the azoniumalkene, *i.e.*, the resonance structure of **13**. A hetero-Michael addition would result in an epimeric mixture of **9** and **10**.

Conclusion

Condensation of 3-ketoglucose with hydrazines to form 4-pyrazolols occurs via selective dehydration. The hydroxyl function at C-1 of the original glucose moiety is selectively removed, assisted by the neighbouring nitrogen atom. The 4-pyrazolols can be prepared in high yield as a mixture of two isomers **4** and **5** in one step starting from **1**. Here, the chirality of the carbohydrate side chain is preserved. A regioselective route can be performed via the hydrazones **3** in a two-step synthesis. In this way, however, a mixture of D-*erythro* and D-*threo* isomers is obtained by epimerization in the carbohydrate side chain.

Experimental

^1H and ^{13}C NMR spectra were measured using a Nicolet NT-200 WB and a Varian VXR-400S spectrometer. The spectra were recorded either in $CDCl_3$ and CD_3OD as solvent, with tetramethylsilane, or in D_2O with *tert*-butanol as internal standard. Mass spectra were obtained using a VG 70-Se mass spectrometer. Optical rotations were measured using a Perkin-Elmer P 141 polarimeter. IR spectra were obtained from KBr discs using a Perkin-Elmer 1420 infrared spectrophotometer. Analytical HPLC was performed using a Waters M-6000 pump on a reversed-phase column (8 × 100 mm, Nucleosil C_{18}) at ambient temperature and an eluent flow of 1.0 ml/min. Preparative LC was performed using a Waters Ass. Prep LC 500 chromatograph equipped with two PrePak C18 cartridges.

General procedure for synthesis of 4-pyrazolols from 3-ketoglucose (**1**)

The appropriate hydrazine (3.5 mmol) was added to a solution of 3-ketoglucose (**1**) (600 mg, 3.4 mmol) in water (15 ml). TLC analysis showed complete conversion (silica, dichloromethane/methanol, 70/30, v/v) after 2 h. The reaction mixture was lyophilized and either a light-brown syrup or a solid was obtained.

*3-(D-*erythro-*1,2,3-Trihydroxypropyl)-4-pyrazolol* (**5**, *R = H)*

After lyophilization, the crude product was pure according to TLC (silica, dichloromethane/methanol, 70/30, v/v, R_f 0.28). Column chromatography (silica gel 60, dichloromethane/methanol, 70/30, v/v) gave **4** as a syrup in quantitative yield (590 mg). HPLC (aqueous 10 mM sodium 1-heptanesulfonate, set at pH 4 with phosphoric acid) showed one peak with retention time 5.4 min $[\alpha]_D^{20}$ + 138° (*c* 1, water). IR: ν_{max}^{KBr} 3375 cm^{-1} (OH), 1580 cm^{-1} (pyrazole C = N). ^1H NMR* (D_2O), δ (ppm): 3.55 [dd, 1H, H-3', *J*(3',3") 12.00 Hz, *J*(3',2') 6.80 Hz]; 3.71 [dd, 1H, H-3", *J*(3",2') 3.40 Hz]; 4.10 (m, 1H, H-2'); 4.79 [d, 1H, H-1', *J*(1',2') 6.40 Hz]; 7.29 (s, 1H, H-5). ^{13}C NMR, see Table I. MS: 174 (M^+, 8), 157(5), 139(3), 126(6), 113(100), 97(16). HR-MS: calculated for $C_6O_4H_{10}N_2$: 174.0641, measured: 174.0641.

*1-Methyl-3/5-(D-*erythro-*1,2,3-trihydroxypropyl)-4-pyrazolol (***4** *and* **5**, *R = methyl)*

A mixture of **4** and **5** (R = methyl) was obtained in quantitative yield (640 mg, 3.4 mmol). No by-products could be detected by TLC (dichloromethane/methanol, 70/30, v/v, R_f 0.42) and HPLC [aqueous 10 mM sodium 1-heptanesulfonate, set at pH 4 with phosphoric acid, retention time: 5.2 min (**4**) and 5.7 min (**5**)]. The ratio of **4**/**5** was 2:1. Isomer **4** could be isolated by column chromatography (silica gel 60, eluent dichloromethane/methanol, 70/30, v/v). IR: ν_{max}^{KBr} 3300 cm^{-1} (OH), 1590 cm^{-1} (pyrazole C = N).

4. ^1H NMR ($CDCl_3$/$(CD_3)_2SO$, 2/1, v/v), δ (ppm): 3.50 [dd, 1H, H-3', *J*(3',2') 5.86 Hz, *J*(3',3") 11.14 Hz]; 3.61 [dd, 1H, H-3", *J*(3",2') 6.03 Hz]; 3.78 (s, 1H, CH_3); 4.11 (m, 1H, H-2'); 4.82 [d, 1H, H-1', *J*(1',2') 5.19 Hz]; 6.99 (s, 1H, H-3);
5. ^1H NMR ($CDCl_3$/$(CD_3)_2SO$, 2/1, v/v), δ (ppm): 3.58–3.50 (2H, m, H-3' and H-3"); 3.74 (s, 1H, CH_3); 4.02 (m, 1H, H-2'); 4.75 (d, 1H, H-1', *J*(1',2') 4.88 Hz); 6.93 (s, 1H, H-5).
^{13}C NMR, see Table I. MS (of **4** and **5**): 188 (M^+, 6), 170 (10), 152 (6), 140 (22), 127 (94), 111 (100), 98 (19), 72 (50), 56 (27). HR-MS: calculated for $C_7O_4H_{12}N_2$: 188.0797, measured: 188.0806.

*1-Phenyl-3/5-(D-*erythro-*1,2,3-trihydroxypropyl)-4-pyrazolol (***4** *and* **5**, *R = phenyl)*

Upon reaction of **1** with phenylhydrazine, a brown oil was formed. After removal of the oil by extraction of the aqueous layer with chloroform followed by lyophilization of the aqueous solution, 688 mg (81%) of a mixture of **4** and **5** (R = phenyl) was obtained, TLC (silica, dichloromethane/methanol, 70/30, v/v); R_f 0.59. IR: ν_{max}^{KBr} 3375 cm^{-1} (OH), 1600 cm^{-1} (phenyl), 1580 cm^{-1} (pyrazole NH), 1502 cm^{-1} (phenyl).
The ratio of **4**/**5** was 3.7/1 according to analytical HPLC [water/methanol/trifluoroacetic acid, 70/30/0.1 v/v, retention times: 5.3 min (**4**) and 9.7 min (**5**)]. Preparative HPLC with the same eluent gave the trifluoroacetate of **4** with $[\alpha]_D^{20}$ + 3° (*c* 1, water) and the trifluoroacetate of **5** with $[\alpha]_D^{20}$ + 2° (*c* 1, water). NMR data for the 4-pyrazolol derivatives as free base.
4. ^1H NMR ($CDCl_3$), δ (ppm): 3.38 [dd, 1H, H-3', *J*(3',2') 5.31 Hz, *J*(3',3") 11.17 Hz]; 3.50 [dd, 1H, H-3", *J*(3",2') 6.59 Hz]; 4.16 (m, 1H, H-2'); 4.69 [d, 1H, H-1', *J*(1',2') 4.76 Hz]; 7.29 (s, 1H, H-3); 7.2–7.6 (H_{phenyl}).
5. ^1H NMR ($CDCl_3$), δ (ppm): 3.54 [dd, 1H, H-3', *J*(3',2') 6.59 Hz, *J*(3',3") 11.45 Hz] 3.60 [dd, 1H, H-3", *J*(3",2') 4.39 Hz]; 4.11 (m, 1H, H-2'); 4.87 [d, 1H, H-1', *J*(1',2') 4.87 Hz]; 7.60 (s, 1H, H-5); 7.2–7.6 (H_{phenyl}).
^{13}C NMR, see Table I. MS (of **4** and **5**): 250 (M^+, 5), 232(22), 214(7), 202(18), 189(43), 188(17), 174(23), 173(100), 160(42), 144(9), 118(32), 117(21), 106(13), 105(10), 104(53), 91(17), 78(18), 77(87), 51(39). HR-MS: calculated for $C_{12}O_4H_{14}N_2$: 250.0937, measured: 250.0954.

Ring closure of **3**, *R = H*

Compound **3** (R = H, 1.36 g, 5 mmol) was refluxed in anhydrous methanol (30 ml) with the ion-exchange resin Dowex 50 × 8–100 (4 g) for 2 h (monitored by TLC, dichloromethane/methanol, 96/4, v/v). Elution of the resin with water gave 490 mg (55%) of a mixture consisting of 80% of **5**/**8** and 20% of **9**/**10**. ^{13}C NMR: see Table II. MS/ 188 (M^+ of **9**/**10**, 2), 174 (M^+ of **5**/**8**, 5), 156(3), 127(**9**/**10**, 37), 114(24), 113(**5**/**8**, 100), 98(14), 97(27), 84(17), 70(**9**), 58(21).

Ring closure of **3**, *R = methyl*

Compound **3** (R = methyl, 2.00 g, 7 mmol) was refluxed in anhydrous methanol (30 ml) with the ion-exchange resin Dowex 50 × 8–100 (4 g) for 2 h (monitored by TLC, dichloromethane/methanol,96/4, v/v). Rinsing the resin with water gave 1.13 g (86%) of **5**/**8**, R = methyl. In contrast, eluting the resin with methanol yielded 530 mg (37%) of **9**/**10**, R = methyl.
^1H NMR of **9**/**10**, denoted by H and H', respectively, (CD_3OD), δ (ppm): 3.23 and 3.24 (6H, 2 × s, CH_3O and $CH_3'O$); 3.45 [2 × dd, 2H, H-3' and H'-3', *J*(3',3") 11.35 Hz, *J*(3',2') 6.77 Hz]; 3.55 [2 × dd, 2H, H-3" and H'-3", *J*(3",2') 4.58 Hz]; 3.75 (s, 6H, CH_3N and $CH_3'N$); 3.97 (m, 1H, H'-2'); 4.10 (m, 1H, H-2'); 4.29 [d, 1H, H'-1', *J*(1',2') 6.05 Hz]; 4.31 (d, 1H, H-1', *J*(1',2') 4.94 Hz]; 7.14 (s, 2H, H-5 and H'-5). ^{13}C NMR see Table II. MS of **9**/**10**: 202 (M^+, 9), 142(13), 141(100), 127(5), 111(9), 72(6).

*3-(D-*erythro/threo-*2,3-Dihydroxy-1'-methoxypropyl)-1-phenyl-4-pyrazolol (***9**/**10**, *R = phenyl)*

Compound **3**, (R = phenyl, 2.34 g, 6.7 mmol) was refluxed in anhydrous methanol (30 ml) with the ion-exchange resin Dowex 50 × 8–100 (4 g) for 2 h (monitored by TLC, dichloromethane/methanol, 96/4, v/v). Rinsing the resin with methanol yielded 1.55 g (88%) of **9**/**10**, R = phenyl). ^1H NMR of **9**/**10**, denoted by H/H' (CD_3OD), δ (ppm): 3.31 (2 × s, 6H, CH_3O and $CH_3'O$); 3.53 [2 × dd, 2H, H-3' and H'-3', *J*(3',3") 11.54 Hz, *J*(3',2') 7.59 Hz]; 3.64 [2 × dd, 2H, H-3" and H'-3", *J*(3",2') 4.86 Hz]; 4.07 (m, 1H, H'-2'); 4.19 (m, 1H, H-2'); 4.45 [d, 1H, H'-1', *J*(1',2') 4.21 Hz]; 4.46 [d, 1H, H-1', *J*(1',2') 3.66 Hz]; 7.20–7.68 (H_{phenyl}); 7.74 and 7.73 (2 × s, 2H, H-5 and H'-5). ^{13}C NMR see Table II. MS of **9**/**10**: 264 (M^+, 10), 204(15), 203(100), 104(35), 77(31).

*3-(D-*erythro/threo-*2,3-Dihydroxy-1-methoxypropyl)-1-*tert-*butyl-4-pyrazolol (***9**/**10**, *R =* tert-*butyl)*

Compound **3** (R = *tert*-butyl, 2.13 g, 6.5 mmol) was refluxed in anhydrous methanol (30 ml) with the ion-exchange resin Dowex 50 × 8–100 (4 g) for 2 h (monitored by TLC, dichloromethane/methanol, 96/4, v/v). Rinsing the resin with methanol yielded 1.00 g (67%) of **9**/**10**, R = *tert*-butyl. Subsequent washing the ion-exchange resin with 1M aqueous hydrogen chloride gave 548 mg (32%) of **5**/**8**, R = *tert*-butyl, as the hydrochloride salt. ^1H NMR of **9**/**10**, denoted by H and H' (CD_3OD), δ (ppm): 1.51 (2 × s, 18H, $(CH_3)_3C$ and $(CH_3')_3C$); 3.23 and 3.24 (2 × s, 6H, CH_3O and $CH_3'O$); 3.45 [2 × dd, 2H, H-3' and H'-3', *J*(3',3") 11.35 Hz, *J*(3',2') 6.59 Hz]; 3.56 [2 × dd, 2H, H-3" and H'-3", *J*(3",2') 4.85 Hz]; 3.99 (m, 1H, H'-2'); 4.13 (m, 1H, H-2'); 4.35 [d, 1H, H'-1', *J*(1',2') 5.49 Hz]; 4.37 [d, 1H, H-1', *J*(1',2') 4.21 Hz]; 7.26 and 7.27 (2 × s, 2H, H-5 and H'-5). ^{13}C NMR see Table II. MS of **9**/**10**: 244 (M^+, 11), 184(11), 183(71), 127(100), 97(9), 70(5), 57(20).

* Side chain locants have been primed and double-primed.

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