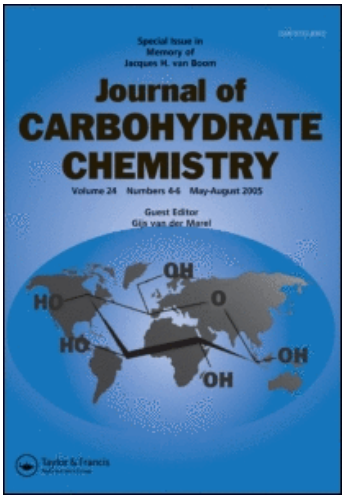

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Stereoselective Synthesis of 3-*C*-Branched-Chain Sugars by Aldol Reaction of Furanos-3-Uloses with Acetone

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STEREOSELECTIVE SYNTHESIS OF 3-C-BRANCHED-CHAIN SUGARS BY ALDOL REACTION OF FURANOS-3-ULOSES WITH ACETONE.

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ABSTRACT

Aldol reaction of 1,2-O-isopropylidene-5-O-tertbutyl-dimethylsilyl-α-D-erythro-pentofuranos-3-ulose (**1**) with acetone in the presence of aqueous K_2CO_3 afforded 3-C-acetonyl-1,2-O-isopropylidene-5-O-tertbutyl-dimethylsilyl-α-D-ribofuranose(**2**). Similar reaction of 1,2:5,6-di-O-isopropylidene- α-D-ribo-hexofuranos-3-ulose (**3**) afforded 3-C-acetonyl-1,2:5,6-di-O-isopropylidene- α-D-allofuranose (**4**) and (1R, 3R, 7R, 8S, 10R)-perhydro-8-hydroxy-5,5,10-trimethyl-2,4,6,11,14-pentaoxatetracyclo [8,3,1,$0^{1,8}$,$0^{3,7}$] tetradecane. The stereochemistry of the new chiral centers were determined by ^{1}H NOE experiments.

INTRODUCTION

Branched-chain sugars are widely spread naturally occurring products.[1,2] They are also useful chiral synthons for the total synthesis of other naturally occurring non carbohydrate compounds.[3,4] Some of the most used methods for the formation of new C-C bonds at the branching point take advantage of the reactivity of the carbonyl group of uloses. For example, the addition of diazomethane,[5] the wittig reaction,[6] and the addition of carbon nucleophiles, such as, organometallic reagents (Mg,[7] Li,[8] Zn,[9] Si[10]), hydrogen

cyanide,[12] and nitromethane,[5,13] received considerable attention. However, the aldol reaction[14] has been little studied. The scarce reports include the reaction of formaldehyde with reducing sugars to give 2-C-hydroxymethyl carbohydrates[15] and the reaction of malonic-type enolates with the keto group of uloses.[16]

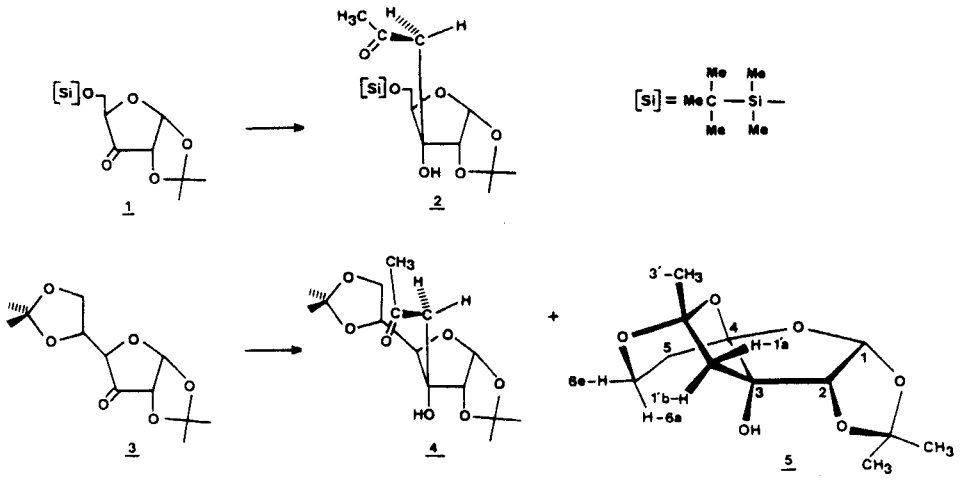
Here we report the stereoselective synthesis of 3-C-branched furanoses by aldol reaction of furanos-3-uloses with acetone.

RESULTS AND DISCUSSION

Reaction of 1,2-O-isopropylidene-5-O-tert-butyldimethylsilyl-α-D-*erythro*-pentofuranos-3-ulose[17] (**1**) with refluxing acetone in the presence of aqueous K_2CO_3 afforded the 3-C-acetonyl-ribofuranose **2** in 58% yield. The use of other bases, such as 1,5-diazabicyclo[5.4.0]undecene-5 (DBU), or NaOH in methanol afforded complex mixtures. The reaction of **1** with other active methylene compounds, such as 2-butanone, acetaldehyde, ethyl acetate, and acetonitrile, in the presence of a variety of bases, such as K_2CO_3, DBU and Et_3N, also afforded complex reaction mixtures. Particularly, the reaction of **1** with 2-butanone in the presence of aqueous K_2CO_3 gave a mixture, which could not be separated by chromatography, the NMR spectrum of which revealed that it contained at least three aldol reaction products.

A similar reaction of 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[18] (**3**) with acetone and aqueous K_2CO_3 afforded the 3-C-acetonyl hexofuranose **4**, in 15% yield, and the polycyclic derivative **5**, in 56% yield. A rapid work up of the latter reaction allowed the spectroscopic identification of a third, unstable compound **6**, which could not be obtained pure. This compound, on standing in solution and during the workup was spontaneously transformed into **5**. Compound **4** is not an intermediate for the formation of **5**, since treatment of the former under the above mentioned aldol reaction conditions did not afford **5**.

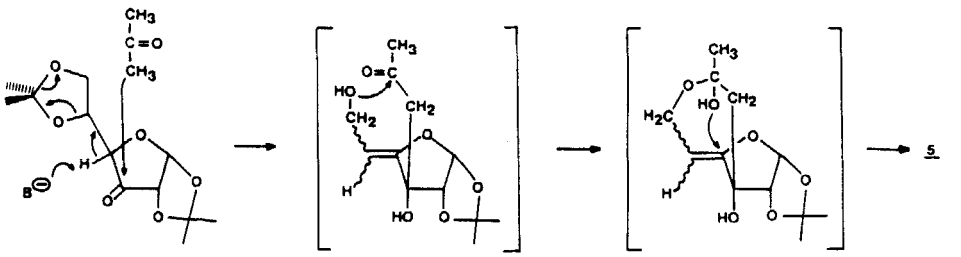
Accordingly a possible pathway to rationalize the formation of **5** could be that shown in Scheme 2. Removal of



SCHEME 1

the 5,6-O-isopropylidene group followed by aldol reaction with acetone would afford **6**. Although cyclic acetals are easily hydrolyzed under acidic catalysis,[19,20,21] it is known that their removal is promoted by the generation of a carbanion on the carbon atom adjacent to the dioxolane ring. The final products of this process are γ-hydroxy enol ethers,[19] such as **6**. Formation of a carbanion by abstraction of the acidic 4-H,[22] followed by intramolecular reaction of the 6-CH_2OH of **6** with the 3-C-acetonyl C=O group would give intermediate **7**. The hemiacetal OH group of the latter would react, also intra-molecularly, with the enol ether double bond to afford **5**. Although the transformation **6** --> **7** is usually acid catalized, the synthesis of cyclic acetals of sugars[19] can also be carried out under basic conditions.[23]

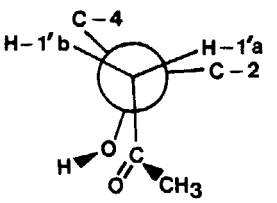
The stereochemistry of the C-3 carbon atom of **2** and **4** was inferred from nuclear Overhauser effect (NOE) experiments[24] (Table 1). Proton H-1'a induced a NOE to H-1 (1.2-4.5%) and H-2 (2.7-6.6%), and H-1'b induced a NOE to H-4 (1.3-4.7%) and H-5(1.1-4.6%). Irradiation of H-1'a and H-1'b did not induce a NOE to the isopropylidene Me(endo) group. These data suggest that there is a preferred rotamer, such as **8**, around the C_3-$C_{1'}$ bond and that the 3'-C-acetonyl group is trans-oriented with respect to the 1,2-O-isopropylidene group.[18]



3 6 7 5

SCHEME 2

The structure suggested for **6** is based on spectroscopic data. The IR spectrum showed a band at 1650 cm^{-1} characteristic of vinyl ethers. The ^1H NMR spectrum showed the absence of H-4 and the presence of a triplet at δ 4.97 ppm, assigned to H-5, and a doublet at δ 4.22, assigned to H-6. These signals are in agreement with the exocyclic double bond.



8

The IR spectrum of **5** showed the absence of carbonyl and olefinic bands. The ^1H NMR spectrum of **5** showed the upfield chemical shift of the 1'-CH_2 and 3'-CH_3 signals, with respect to the same signals of **6**, in agreement with the transformation $CH_3-\overset{O}{\overset{\|}{C}}-CH_2-$ ---> $CH_3-\overset{O\ O}{\overset{\diagdown\ \diagup}{C}}-CH_2-$ undergone by the 3-C-branch. The ^1H NMR spectrum of **5** also showed the absence of H-4 and the presence of an ABXY system, assigned to H-5e (δ 1.91), H-5a (δ 2.17), H-6e (δ 4.00) and H-6a (δ 4.38). The magnetic parameters of this ABXY systems are in agreement with the indicated structure.

TABLE 1. NOE values for 2 and 4

Compd	Proton Irradiated	NOEs observed at the indicated protons H-1	H-2	H-4	H-5	H-1'a	H-1'b	CH_3 (endo)	CH_3 (exo)
2	H-1	-88.6	6.1	-	-	0.9	-	-	-
	H-2	6.7	-84	-	-	-	-	-	-
	H-5	0.9	-	-	-89	1.4	4.0	-	-
	H-1'a	1.2	2.7	-	-	-60	15.9	-	-
	H-1'b	-	-	1.3	1.1	-	-59	-	-
	CH_3(endo)	-	1.1	4.1	-	-	-	-94	-
	CH_3(exo)	2.2	4.5	-	-	-	-	-	-96
4	H-1	-91	6.7	-	-	-	-	-	-
	H-2	5.6	-86	-	-	2.2	-	-	-
	H-1'a	4.5	6.6	-	-	-80	19	-	-
	H-1'b	-	1	4.7	4.6	22.7	-85	-	-
	CH_3(endo)	-	-	3.9	-	-	-	-90	-
	CH_3(exo)	2.0	3.2	-	-	-	-	-	-65

TABLE 2. NOE values for 5

Proton Irradited	NOEs observed at the indicated protons[a] H-1	H-2	H-5a	H-5e	H-6a	H-6e	H-1'a	H-1'b	3'-CH_3
H-1	-82	4.0	-	-	-	-	-	-	-
H-2	6.2	-76	-	-	-	-	4.2	-	-
H-5a	-	-	-63	13.5	-	2.1	-	-	-
H-5e	-	-	15.4	-60	3.4	1.0	-	-	-
H-6a	-	-	-	-	-71	17.5	-	2.6	-
H-6e	-	-	2.9	1.2	17.9	-73	-	-	-
H-1'a	-	8.4	-	-	-	-	-75	-	2.5
H-1'b	-	1	-	-	4.0	-	-	-90	0.6
3'-CH_3	-	-	-	-	-	-	1.6	0.8	-95

[a] No NOE was observed at the two isopropylidene CH_3 (endo) and CH_3 (exo) bands upon irradiation of the indicated protons. The only exception was a NOE of 1% observed at the CH_3 (exo) band upon irradiation of H-2.

The trans orientation of the 3-C-branch of **5** with respect to the 1,2-O-isopropylidene group was demostrated by the high magnitude of NOE induced to H-2 (8.4%) upon irradiation of H-1'a and the absence of NOE induced to the isopropylidene Me (endo) group upon irradiation of H-1'a and H-1'b (Table 2).

The stereochemistry at C-4 of **5** was suggested by the facile, spontaneous ketalization, **6**--->**5**, which is in agreement with the disposition of the 4-O and 3-C-branch on the same side of the furanose ring of **5**. Furthermore, the stereochemistry at C-4 of **5** was demonstrated by NOE experiments (Table 2). Irradiation of H-1'a induces a NOE to H-2 (8.4%) and to 3'-CH_3 (2.5%), while irradiation of H-1'b induces a NOE to H-6a (4%). As determined from the corresponding molecular models, these values are only compatible with the structure shown for **5** in which the dioxane ring is in the chair form.

In conclusion, the aldol reaction can be a useful procedure for the stereoselective synthesis of branched chain sugars. In the present case the stereochemistry of the new chiral center is controlled by the 1,2-O-isopropylidene group, which directs the approach of the acetone from the sterically less hindered β-face of the molecule. However, under the basic reaction conditions needed other reactions may occur, which can afford unexpected products.

EXPERIMENTAL

General Procedures. ^1H NMR spectra were recorded with a Bruker AM-200 or a Varian EM-390 spectrometers using Me_4Si as internal standard. Mass spectra were recorded with a Vacuum Generators VG 12-250 spectrometer. IR spectra were obtained using a Shimadzu IR-435 spectrometer. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck), and preparative thin layer chromatography was performed on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). Flash column chromatography was performed with silica gel 60 230-400 mesh (Merck).

3-C-Acetonyl-1,2-O-isopropylidene-5-tert-butyldimethylsilyl-α-D-ribo-furanose (2). To a solution of compound 1[16] (2g, 6.4 mmol) in acetone (30 mL) K_2CO_3 (0.83 g) and water (5 mL) were added. The reaction mixture was boiled under reflux for 3 h and then concentrated to dryness under reduced pressure. The residue thus obtained was treated with chloroform (20 mL) washed with water (3 x 20 mL), and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed on a Flash-silica gel column using ethyl acetate-hexane (1:6) as the eluent to give compound (2) (1.38 g, 58%) as a white foam: $[\alpha]_D$+ 47° (c 1, $CHCl_3$); IR (film) 3480 (OH), 1710 cm^{-1} (ketone C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 9H, t-Bu), 1.26 (s, 3H, isopropylidene exo-Me), 1.49 (s, 3H, isopropylidene endo-Me), 2.16 (s, 3H, CH_3CO), 2.30 (d, 1H, $J_{1'a,1'b}$= 15.4 Hz, H-1'a), 2.85(d, 1H, H-1'b), 3.33 (bs, 1H, 3-OH), 3.72 (m, 2H, H-5), 3.82 (dd, 1H, H-4), 4.43 (d, 1H, $J_{1,2}$= 4Hz, H-2), 5.69 (d, 1H, H-1); m/z: 361 (M^++ 1, 0.3%), 345 (M^+-15, 2), 280 (16), 245 (M^+-$tBuMe_2Si$, 87).

Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.66; H, 8.88. Found: C, 56.58; H, 8.93

Reaction of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (3) with acetone. To a solution of compound 3[17] (1g, 3.6 mmol) in acetone (20 mL) K_2CO_3 (0.83 g) and water (5 mL) were added. The reaction mixture was boiled under reflux for 4 h and then concentrated to dryness under reduced pressure. The residue thus obtained was treated with chloroform (20 mL), washed with water (3 x 20 mL), and dried over anhydrous sodium sulphate. The solvent was evaporated to give a syrup which was purified by preparative TLC using ethyl acetate-hexane (1:1) as the eluent. The plates were developed three times. The faster moving band (Rf= 0.4) gave **3-C-Acetonyl-1,2 : 5,6-di-O-isopropylidene-α-D-allo-furanose (4).** (0.170 g, 15% yield) as a syrup; $[\alpha]_D$ + 66° (c 1, $CHCl_3$); IR (Film) 3400 (OH), 1700 cm^{-1} (ketone C=O); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (s, 3H, 1,2-O-isopropylidene exo-Me), 1.38, 1.46 (2s, 6H, 5.6-di-O-isopropylidene-Me), 1.58 (s, 3H, 1,2-O-isopropylidene endo-Me), 2.30 (s, 3H, CH_3CO), 2.38 (d, 1H, $J_{1'a,1'b}$= 15.1 Hz, H-1'a), 3.11 (d, 1H, H-1'b), 3.15 (bs, 1H, 3-OH), 3.80 (d, 1H, $J_{4,5}$ = 4 Hz, H-4), 3.90-4.12 (m, 3H, H-5,

H-6), 4.59 (d, 1H, $J_{1,2}$ = 2 Hz, H-2), 5.74 (d, 1H, H-1); m/z: 316 (M^+, 2%), 301 (M^+-15, 50).

Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.96; H, 7.59. Found: C, 56.70; H, 7.70.

The slower moving band (Rf = 0.1) gave a (4:1) mixture of **6** and **5** as a syrup (0.56 g, 56%). Spectroscopic data of **3-C-Acetonyl-5-deoxy-1,2-O-isopropylidene- α -D-erythrohex-4-enofuranose (6)**: IR (Nujol) 3470 (OH), 1700 (ketone C=O), 1650 cm^{-1} (C=C-O); ^1H NMR ($CDCl_3$, 90 MHz) δ1.40, 1.47 (2s, 6H, isopropylidene), 2.23 (s, 3H, 3'-CH_3), 2.63, 2.90 (AB system, 2 H, $J_{1'a,1'b}$= 15 Hz, H-1'a, H-1'b), 4.20 (d, 2H, $J_{5,6}$= 7 Hz, H-6), 4.63 (d, 1H, $J_{1,2}$= 3.5 Hz, H-2), 4.96 (t, 1H, H-5), 5.98 (d, 1H, H-1).

When the workup was not carried out rapidly the slower moving band (Rf = 0.1) gave (1R, 3R, 7R, 8S, 10R)-perhydro-8-hydroxy-5,5,10-trimethyl-2,4,6,11,14-pentaoxatetracyclo-[8,3,$1,0^{1,8},0^{3,7}$] tetradecane **5** (0.56 g, 56%) as the only product as a white foam: $[\alpha]_D$ - 146° (c 1, $CHCl_3$); IR (Nujol) 3450 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 1,41 (s, 3H, 3'-CH_3), 1.47 (s, 3H, isopropylidene exo-Me), 1.59 (s, 3H, isopropylidene endo-Me), 1.91 (ddd, 1H, $J_{5e,6e}$= 0.8, $J_{5e,6a}$= 4.1, $J_{5e,5a}$= 12.4 Hz, H-5e), 2.17 (dt, 1H, $J_{5a,6e}$= 6.7, $J_{5a,6a}$= 12.1 Hz, H-5a), 2.35 (d, 1H, $J_{1'a,1'b}$= 14.6 Hz, H-1'a), 2.44 (d, 1H, H-1'b), 3.37 (s, 1H, 3-OH), 4.00 (ddd, 1H, $J_{6a,6e}$= 11.6 Hz, H-6e), 4.38 (dt, 1H, H-6a), 4.52 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-2), 6.03 (d, 1H, H-1); m/z: 259 (M^++ 1, 10%), 258 (M^+, 1), 257 (6), 243 (2), 241 (18), 201 (3), 200 (2.5), 185 (7), 183 (26).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 6.98. Found: C, 55.82; H, 6.82.

Nuclear Overhauser effect experiments.- ^1H NMR steady-state NOE difference spectroscopy experiments were carried out on compounds **2**, **4** and **5** with a Brucker AM 200 spectrometer operating in the pulse mode. The standard Brucker microprogram library was used to perform sequential multiplet line irradiation.[25] Each irradiation multiplet frequency was cycled 20 times before acquisition. A total irradiation time of 2s and an acquisition time of 2s was used. Solutions ($CDCl_3$+Me_4Si) were measured at 30°C and a 90° read pulse was used in all cases. The coupling power was

adjusted in order to obtain maximum saturation (80-90%) compatible with minimun frequency spillover to neighbouring multiplets. FID were weighted with a 2 Hz exponential line-broadening factor, substracted and Fourier transformed. NOE values were calculated from integrals of the difference and control irradiation spectra.

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