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A SIMPLE STEREOSELECTIVE SYNTHESIS OF C_2-BRANCHED 2-DEOXY-PENTITOLS.

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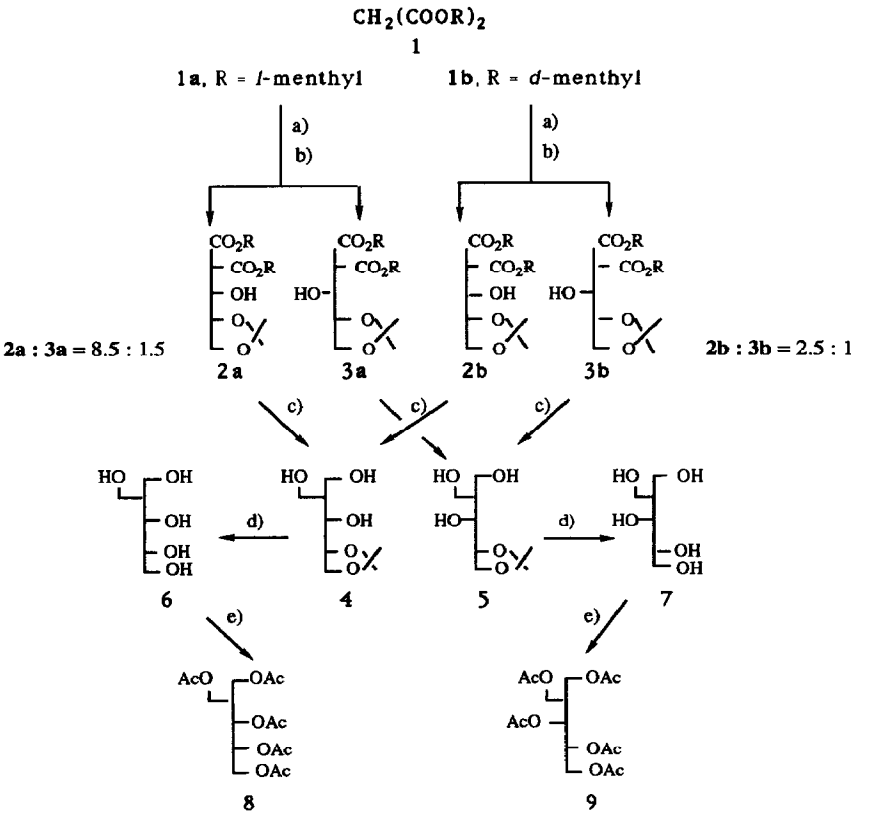
Abstract: 2,3-O-isopropylidene-D(+)-glyceraldehyde reacts with di-*l*-menthyl-malonate to give the penturonates **2a**, and **3a** in an *erythro-threo* 8.5:1 ratio. The C_2-branched sugars 2-deoxy-2-hydroxymethyl-3,4-*erythro*-pentitol **6** and 2-deoxy-2-hydroxymethyl-3,4-*threo*-pentitol **7** were obtained by submitting **2a** and **3a** to routine procedures. The same reaction, performed with di-*d*-menthylmalonate, resulted in a decreased diastereoselectivity, providing a 2.5:1 mixture of *erythro* and *threo* diastereomers.

In the field of carbohydrates and other polihydroxylated materials the interest for branched chain sugars[1] is growing which are found to be part of complex macrocyclic tetraether lipids[2] and can serve as chiral synthons for the synthesis of some important macrolide antibiotics such as erythromycin[3], streptovaricin[4], and the glycosidic components of nucleoside antibiotics such as amipurymicin[5]. A useful synthetic strategy for this class of compounds arises from addition of organometallics to suitable chiral carbonyl derivatives.

Reported herein is a new type of C_2-branched 2-deoxy-pentitols which can be readily prepared according to the following simple procedure. *l*-Menthyl(2-deoxy-2-carboxy-*l*-menthyl)-4,5-O-isopropylidene-3,4-*erythro*-penturonate **2a** and the corresponding *l*-menthyl-*threo* diester **3a**, were obtained in good yield, by addition of 2,3-O-isopropylidene-D-(+)-glyceraldehyde to di-*l*-mentylmalonate in the presence of LDA and TMSCl in ether at -82°C followed by cautious aqueous quenching of the reaction mixture at the same temperature. The diasteroisomers **2a** and **3a**, obtained in 8.5:1.5 ratio, were easy recovered in pure state by flash chromatography (silica gel, hexane : EtOAc 95:5) and converted to 2-deoxy-2-hydroxymethyl-3,4-*erythro*-pentitol **6**, and 2-deoxy-2-hydroxymethyl-3,4-*threo*-pentitol **7**, by $LiAlH_4$ reduction *via* the 4,5-O-isopropylidene-2-deoxy-2-hydroxymethyl-pentitols **4** and **5**, respectively (Scheme).

When the same aldehyde was treated with di-*d*-menthylmalonate according the above procedure, a lowering of steroselectivity was observed, and a 2.5:1 mixture of *erythro* and *threo* penturonates **2b** and **3b** was obtained, which were converted to pentitols **6** and **7**, after their chromatographic separation, by the above convergent sequence.

Scheme



a): LDA, TMSCl (1.1 mol equiv., to **1**) in Et_2O, -82°C, 15 min. b): 2,3-O-isopropylidene-D-(+)-glyceraldehyde (2 mol equiv., to **1**), -82°C, 30 min, aqueous quenching at -82°C. (81%); c) $LiAlH_4$ (5 mol equiv, to **2** and **3**), in Et_2O, rfx, 30 min, (75%); d): CF_3COOH/H_2O 2:1 v/v, room temperature, 6h, (96%); e): Ac_2O, Py, rfx, 6h, (91%).

The configuration at C-3 was assigned on the basis of ^1H NMR and literature data. In particular the greater values of the coupling constants ($J_{3,4}$) observed for the major product and its derivatives are in conformity with the already reported examples of the prevalent anti-addition to protected D-glyceraldehyde[6] which is in accordance with the Felkin-Ahn rule.

This synthetic approach fits in the field of the double asymmetric syntheses (the chiral substrate and chiral reagent interaction) with mached and mismached cases[7]. In order to evaluate the degree of 1,2-asymmetric induction of the chiral substrate which could dictate the stereochemical course of the reaction, the dicyclohexylmalonate was selected as achiral reagent model and treated with 2,3-O-isopropylidene-D-(+)-glyceraldehyde according to the above protocol. Surprisingly, in this case a completely different course of the reaction was observed, compromising the model requirements[8].

Considering the easy preparation of the reagents[9], the complete recovery of the chiral auxiliaries, together with the possibility of obtention of both stereoisomers, the present synthetic approach promise to be completely respondent to the requirements of a valuable synthesis of sugars[10,11].

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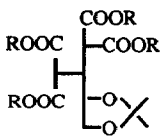
8 The hyperbranched compound A was obtained in 55% yield, probably arising from a Knoevenagel-type condensation of glyceraldehyde and subsequent Michael addition of a second molecule of dicyclohexylmalonate to the activated double bond. The same corresponding branched uronate B was recovered, albeit in very poor yield, when the reaction was perfomed with diethylmalonate.



A : R = Cyclohexyl

B : R = Ethyl

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11 All the compounds reported in this paper show spectral data in accordance with the proposed structure. Selected ^{1}H NMR data:
2-Deoxy-2-hydroxymethyl-3,4-*erythro*-pentitol pentaacetate, **8**: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ: 5.32 (1H, dd, J=6.3 and 5.3 Hz, H_3); 5.24 (1H, dt J=6.3 and 3.1 Hz, H_4); 4.32 (1H, dd, J=3.1 and 9.2 Hz, H_5); 4.23-4.06 (5H, m); 2.39 (1H, dq, J=5.3 and 2.2 Hz, H_2); 2.08 (3H, s); 2.07 (3H, s); 2.06 (3H, s); 2.05 (3H, s); 2.03 (3H,s).
2-Deoxy-2-hydroxymethyl-3,4-*threo*-pentitol pentaacetate, **9**: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ: 5.31 (1H, dd, J=4.1 and 4.9 Hz, H_3); 5.26 (1H, dt J=4.1 and 4.4 Hz, H_4); 4.23 (1H, dd, J=4.4 and 12.1 Hz, H_5); 4.18-3.98 (5H,m); 2.31 (1H, dq, J=4.9 and 5.8 Hz); 2.13-2.06 (15H, m).