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BAKER'S YEAST MEDIATED SYNTHESIS OF EPIMERIC 2,3-DIDEOXY-2-C-METHYL D-GLUCOSE DERIVATIVES

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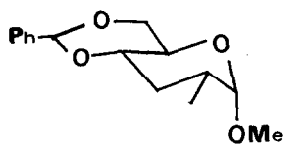
The 2-C-methyl-2,3-dideoxy-D-glucose derivatives (15) and (17) are obtained through a sequence involving as key step the enantioselective baker's yeast conversion of (2RS,5RS) (5) into (2R,4S,5R) (7).

The epimeric 2,3-dideoxy-2-C-methyl-D-glucose derivatives (1) and (2), accessible from D-glucose in 8 and 7 steps, respectively, have been recently used as starting materials in the synthesis of the mycotoxin (+)-dipladiatoxin[1] and of the pheromone (-)-α-multistriatin.[2] Key intermediates in the above procedures are the acyclic products (3) and (4), available, in turn, in multistep sequences from (1) and (2).

In our interest[3] in microbially-aided preparations of carbohydrate-like chiral synthons which can be used as alternative to natural carbohydrates in the synthesis of natural products we thought that the baker's yeast reduction of racemic (2RS,5RS) and (2SR,5RS) α-acetoxy ketones (5) and (6) could lead to carbinols straightforwardly convertible either into cyclic (1) and (2) or into (3) and (4), and we now report on the results obtained.

To this end, the oily (2RS,5RS) α-acetoxy ketone (5) and its (2SR,5RS) diastereoisomer (6), mp 112-114 °C (methanol), separated by crystallization and chromatography,[4] were submitted to the yeast treatment.[5] However, (2SR,5RS) (6) was not reduced under the conditions in which the (2RS,5RS) diastereoisomer (5) afforded the (2R,4S,5R) carbinol (7), $[\alpha]_D^{20}$ -35° (c 1, $CHCl_3$) (30% yield), close to 50% unreacted material, showing $[\alpha]_D^{20}$ +30° (c 2, $CHCl_3$). Relative and absolute stereochemistry of (7) was assigned as follows. Basic hydrolysis of (7) yielded quantitatively the diol (8), $[\alpha]_D^{20}$ +7.6° (c 1, $CHCl_3$), with 4,5 anti stereochemistry,[6] as indicated by ^1H NMR studies onto the derivative (9), $[\alpha]_D^{20}$ +12.8° (c 1, $CHCl_3$), whereas acid methanolysis of (7) afforded the methyl furanoside (10), with syn relationship[7] between the C-2 methyl group and H-4. Finally, the diol (8), on HIO_4 oxidation in THF, afforded the (3R) aldehyde (11), $[\alpha]_D^{20}$ +7.5° (c 1, $CHCl_3$).[8]

The α-acetoxy ketone recovered after the production of (7) was submitted to the yeast treatment in two subsequent runs to give more (7) in yields of about 10% and 5% respectively.



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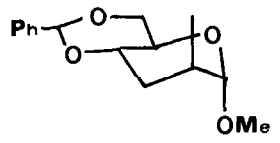

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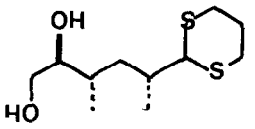

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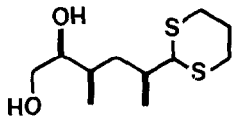

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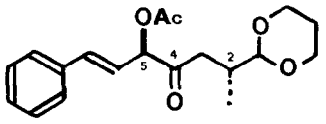

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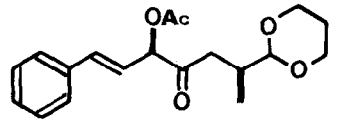

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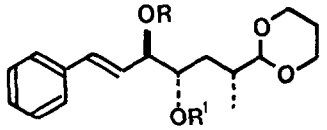
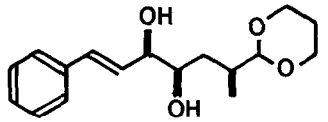
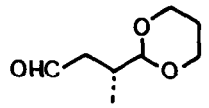


(7) R= Ac; R^1 = H
(8) R= R^1 = H
(9) R,R^1 = >C=O



(12)



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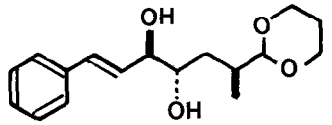

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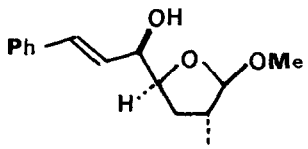

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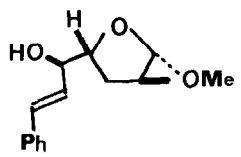
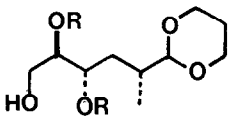


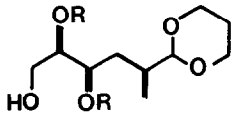
(14)

The unreacted α-acetoxy ketone recovered at the end of this series of experiments was α-epimerized (0.5% Et_3N in MeOH/23 °C/24 h) to (2S,5R) (6), $[\alpha]_D^{20}$ -91° (c 2, $CHCl_3$). Two successive crystallizations from methanol raised the α value to -106°, whereas ^1H NMR studies in the presence of tris [3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium (III) indicated it to contain a single enantiomer. Indeed, (2S,5R) (6), obtained in ca. 55% overall yield from the material recovered from the yeast treatment, on $NaBH_4$ reduction in MeOH at -40 °C and basic hydrolysis afforded (2S,4R,5R) (12), $[\alpha]_D^{20}$ -4.3° (c 1, $CHCl_3$) and the (2S,4S,5R) diastereoisomer (13), in 4:1 ratio and 75% overall yield. The assignement of the 4,5 syn and 4,5 anti stereochemistry to the latter products is based on ^1H NMR studies onto the isopropylidene derivatives.[6] Furthermore, product (12) afforded, on HIO_4 oxidation, as above, the enantiomer of (11), $[\alpha]_D^{20}$ -7.2° (c 1, $CHCl_3$), and, on acid methanolysis, the methyl glycoside (14), with syn relationship between the C-2 methyl group and H-4.[7] Using $Zn(BH_4)_2$ as reducing agent, from (2S,5R) (6) the anti diol (13) was eventually obtained as almost exclusive product.

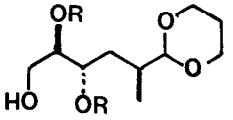
In order to complete the synthetic work, the diols (8), (12) and (13) were converted in two steps [1) Ac_2O/pyridine/23 °C/24 h, 2) O_3 in MeOH at -40 °C, then $NaBH_4$] (70-75% yield) into the epimeric 2-C-methyl-2,3-dideoxy-D-glucose derivatives (15) and (17) and into the D-galacto diastereoisomer (16), conceivably convertible into (3) and (4).



(15) R= Ac



(16) R= Ac



(17) R= Ac

As far as the stereochemical aspects of the above biotransformation are concerned, it appears that the yeast enzyme(s) involved in the reduction of racemic diastereoisomeric (5) and (6) are quite sensitive to the β' stereochemistry. Hydrogen addition onto the C-4 carbonyl group occurs from the re face of the (5R) enantiomer, but, of the two diastereoisomers, the one with a (2R) methyl group is reduced at much higher rate. From a practical point of view, this fact allows the obtainment by yeast treatment, out of the mixture of diastereoisomeric α-acetoxy ketones (5) and (6), of carbinol (7), with three chiral centres, in enantiomerically pure form. Also, using (2RS,5RS) (5) as substrate, as the result of the kinetic enzymic resolution, the survived α-acetoxy ketone is enriched in the (2S,5S) enantiomer, subsequently converted by epimerization into the (2S,5R) diastereoisomer (6).

The conversion of the (2R,4S) 2-C-methyl methylfuranoside (10) into the (2R,4S), C_{12} 2-C-methyl γ-lactone marmelo lactone A[9] is in progress.

REFERENCES AND FOOTNOTES

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3. G.Fronza, C.Fuganti, P.Grasselli and S.Servi, Tetrahedron Letters,1985,26,4961

4. Products (5) and (6) were obtained in ca. 1:1 mixture from $\overbrace{S(CH_2)_3SCHCH_2CH(CH_3)}\overbrace{CHO(CH_2)_3O}$ on sequential treatment with: a) 1 mol eq n-BuLi/THF/-40 °C, b) $C_6H_5CH=CHCHO$, c) Ac_2O/pyr., d) $HgO/BF_3.Et_2O/THF-H_2O$, in 45% yield.

5. Typically, 20 g of α-acetoxyketone in 40 ml EtOH are added within 30 min to 1 kg of baker's yeast in 4 l tap water, containing 0.5 kg of D-glucose, under stirring at 25-30 °C. After 4-5 h, ethyl acetate extraction of the filtered (Celite) reaction mixture afforded the required products, separated by SiO_2 column chromatography.

6. The relative configuration of carbons 4 and 5 for compounds (7), (12) and (13) has been established on the basis of the chemical shifts of the ring protons of the carbonate or isopropylidene derivatives. It is known (M.Anteunis and D.Danneels, Org.Magn.Reson., 1975,7,345) that in a five-membered ring a proton is shifted upfield when a vicinal substituent changes from the anti to the syn position. This effect ranges in magnitude from about 0.1 to 0.5 ppm. In the present case protons H-4 and H-5 are shifted upfield by 0.4-0.5 ppm going from the (4S,5R) to the (4R,5R) configuration. Relevant NMR data (300 MHz, $CDCl_3$): (9)(4,5-erythro) δ: 5.25 (H-5, J(4,5) 7.9 Hz), 5.02 (H-4). 4-epi (9)(4,5-threo) δ: 4.81 (H-5, J(4,5) 7.5 Hz), 4.60 (H-4). Isopropylidene derivative of (12)(4,5-threo) δ: 4.14 (H-5, J(4,5) 7.4 Hz), 3.89 (H-4). Isopropylidene derivative of (13)(4,5-erythro) δ: 4.68 (H-5, J(4,5) 6.0 Hz), 4.33 (H-4).

7. The relative configuration of the ring chiral carbons have been established through a set of n.O.e. experiments. The most significant experiment was the irradiation of Me-2 group which caused the enhancement of H-4 (4%), H-1 (6%) and H-3e (2%) protons and no enhancement of H-5 and OMe-1 signals. In addition, the small values of the vicinal coupling constants J(1,2) and J(2,3e) suggest that the Me-2 and OMe-1 groups are trans pseudoaxially oriented and allow the assignement of the pseudoaxial and pseudoequatorial methylene protons. ^1H NMR data (300 MHz, $CDCl_3$). 5-O-Me derivative of (10), δ: 6.64 (H-7, J(6,7) 16.0, J(5,7) 1.0 Hz), 5.97 (H-6, J(5,6) 8.1 Hz), 4.65 (H-1, J(1,2)< 0.5 Hz), 4.23 (H-4, J(4,5) 8.1, J(3pe,4) 6.9, J(3pa,4) 9.0 Hz), 3.65 (H-5), 3.41 (OMe-5), 3.37 (OMe-1), 2.25 (H-2, J(2,3pe) 1.5, J(2,3pa) 7.2, J(2,Me) 7.3 Hz), 1.93 (H-3pa, J(3pe,3pa) 12.4 Hz), 1.52 (H-3pe), 0.92 (Me-2). (14), δ: 6.69 (H-7, J(6,7) 16.1, J(5,7) 1.4 Hz), 6.19 (H-6, J(5,6) 7.5 Hz), 4.64 (H-1, J(1,2)<0.5 Hz), 4.29 (H-4, J(4,5) 5.5, J(4,3pa) 7.2, J(4,3pe) 7.0 Hz), 4.10 (H-5), 3.40 (OMe), 3.00(OH), 2.35 (H-2, J(2,3pa) 7.2, J(2,3pe) 2.1, J(2,Me) 7.2 Hz), 2.15 (H-3pa, J(3pa,3pe) 12.2 Hz), 1.02 (Me-2), 1.62 (H-3pe).

8. Prepared from (2R) $C_6H_5CH=CHCH_2CH(Me)COOH$ (C.Fuganti and P.Grasselli, J.C.S.Chem.Comm.1979, 995) through unexceptional steps: $[\alpha]_D^{20}$ +7.6°

9. Y.Nishida, H.Ohrui and H.Meguro, Agric.Biol.Chem.,1984,48,1211

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