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BAKER'S YEAST MEDIATED PREPARATION OF CARBOHYDRATE-LIKE CHIRAL SYNTHONS

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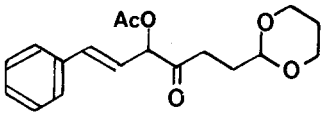
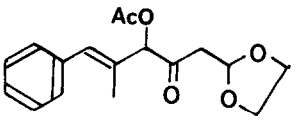
Summary: Baker's yeast mediated reduction of the α-acetoxy ketones (1)-(3) proceeds with high enantio- and stereoselectivity to give the anti carbinols (4)-(6), easily converted into the masked chiral deoxy sugars (12)-(14), from which D- and L-deoxysugars have been obtained.

Carbohydrates are now being used as starting materials in the synthesis of enantiomerically pure forms of natural products and drugs belonging to quite different structural classes.[1] In most instances, the incorporation of natural hexoses and pentoses in the carbon framework of elaborated chiral molecules involves regioselective removal of oxygen function(s) and/or chain elongation at either end of the sugar moiety. It thus follows that actual starting materials in the carbohydrate-based syntheses must be regarded the members of a defined set of suitably protected (deoxy)sugar derivatives prepared from natural carbohydrates, sometimes in multistep, low-yield sequences.[2] In this context, we now report on a non-carbohydrate-based preparation of synthetically useful masked deoxysugars of the D and L-series, and on their subsequent conversion into the deoxysugar derivatives (15), (16), (17) and (21), through a sequence involving, as the relevant step, the enantio- and stereoselective baker's yeast mediated reduction of the α-acetoxy ketones (1)-(3).

Thus, the α-acetoxy ketones (1)-(3), bearing two masked carbonyl functions (being the two carbonyl moieties revealable chemoselectively with different reagents) in 1,6 and 1,5 relationship, respectively, on treatment with baker's yeast,[3] afforded, as major transformation products, the chiral anti carbinols (4), (5) and (6) in 20, 35 and 30% yield, respectively, and 30-40% unreacted starting materials. The (4S,5R) carbohydrate-like carbinol (4) was shown to be enantiomerically pure because of its conversion through oily intermediates (Scheme) into the optically pure α-methylglycoside (15a), $[\alpha]_D^{20}$ +46° (c 3.5, CCl_4), and into the β-anomer (15b), $[\alpha]_D^{20}$ -29° (c 3.5, CCl_4), in 1:2 ratio, being the optical properties well in agreement with the lit.[4] values. The acetate obtained upon yeast reduction of (2) was shown to be a 75:25 mixture of two enantiomers by ^1H NMR studies onto the (+)-MTPA ester[5] of the methyl



(1)



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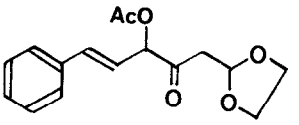

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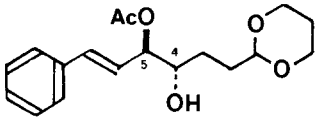

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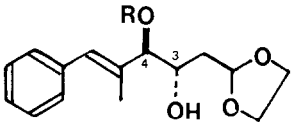
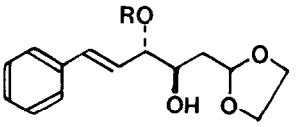
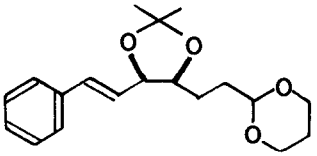


(5) R= Ac
(6) R= H



(7) R= Ac
(8) R= H



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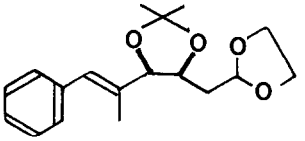

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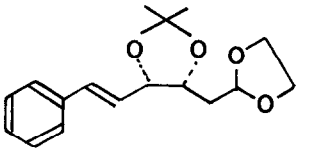

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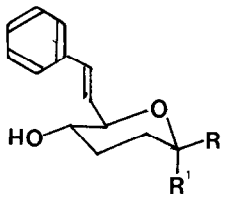
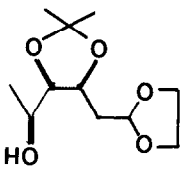


(12) R,R^1 = H,OMe



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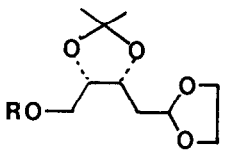
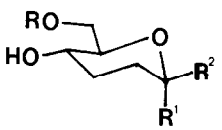
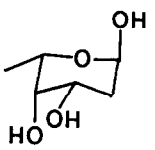


(14) R= Ph_2Bu^tSi



(15a) R= Ph_2Bu^tSi; R^1= OMe; R^2= H
(15b) R= Ph_2Bu^tSi; R^1= H; R^2= OMe



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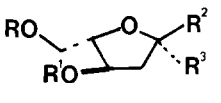


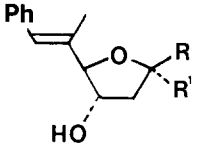
(17a) R= R^1= COPh; R^2= H; R^3= OMe
(17b) R= R^1= COPh; R^2= OMe; R^3=H
(17c) R= Ph_2Bu^tSi; R^1=R^3=H; R^2=OMe
(17d) R= Ph_2Bu^tSi; R^1=R^3=H; R^2=OMe

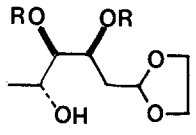
SCHEME

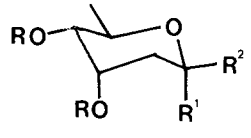
(4)→(9): (1) K_2CO_3/MeOH/23°C/24 h, (2) $Me_2C(OMe)_2$PTSA/23°C/16 h (80%). (9): $[\alpha]_D^{20}$ -12° (c 1, $CHCl_3$)
(9)→(12): 1% HCl in MeOH/23°C/12 h (70%). (12): $[\alpha]_D^{20}$ +25° (c 1, $CHCl_3$)
(12)→(15): (1) O_3 in MeOH/-78°C, then $NaBH_4$, (2) 1.2 mol eq Ph_2Bu^tSiCl/pyridine/23°C (65%)
(6)→(10): $Me_2C(OMe)_2$/PTSA/23°C/24 h (90%)
(10)→(13): (1) O_3/CH_2Cl_2/-78°C, then 1 mol eq Ph_3P, (2) DIBAL/Et_2O/-78°C (75%). (13): $[\alpha]_D^{20}$ -26° (c 1, $CHCl_3$)
(13)→(16): 1% H_2SO_4/60°C/4 h, then $BaCO_3$ (73%)

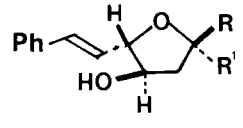
glycoside (18a), $[\alpha]_D^{20}$ +63° (c 1, $CHCl_3$) and of its anomer (18b), $[\alpha]_D^{20}$ -32° (c 1, $CHCl_3$), obtained from the crude acetate in two steps [(1) K_2CO_3/MeOH/23°C/24 h, (2) 1% HCl in MeOH/23°C/8 h] in 1:0.7 ratio and 65% overall yield. The most abundant enantiomer was assigned the (3S,4R) absolute configuration depicted in (5) on the basis of the following evidence. The crude diol fraction obtained upon basic deacetylation gave in 50% yield on recrystallization from hexane-ethyl acetate (3S,4R) (6), m.p. 90-91°C, $[\alpha]_D^{20}$-22.7° (c 1, $CHCl_3$), shown to be enantiomerically pure by the above method applied onto the derived methyl glycoside (18a), $[\alpha]_D^{20}$+120°. Product (6) was converted (Scheme) into 2,6-dideoxy-L-lyxohexose (16), m.p. 101-103°C, $[\alpha]_D^{20}$-55° (c 1, H_2O, equilibrium).[6] Conversely, when the crystalline diol (6) was coverted into the dibenzoate and the latter was ozonised in methanol at -78°C, $NaBH_4$ reduction afforded highly protected (3S,4R,5R) (19), in 4:1 ratio with the (3S,4R,5S) diastereoisomer. Compound (19) by treatment with 1% HCl in methanol gave rise to methyl 2,6-dideoxy-D-ribohexopyranoside (20) (85%), subsequently converted by debenzoylation and hydrolysis into optically pure D-digitoxose (21), $[\alpha]_D^{20}$+46° (c 1, H_2O, equilibrium).[7]

At variance with the α-acetoxy ketones (1) and (2), reduced by yeast with (R) enantioselectivity, product (3) affords, on bioreduction, a monoacetate containing 65-70% excess of the (3R,4S) enantiomer (7). This has been demonstrated by ^1H NMR studies onto the (+)-MTPA ester of the methylglycosides (22a) and (22b) prepared from (7) [(1) K_2CO_3/MeOH/23°C/24 h, (2) 1% HCl in MeOH/23°C/24 h] and by obtainment from the latter, in three steps [(1) C_6H_5COCl/pyridine/23°C/24 h, (2) O_3 in MeOH/-78°C, then $NaBH_4$, (3) C_6H_5COCl/pyridine/23°C/3 h] of the methyl glycoside (17a), $[\alpha]_D^{20}$-32° (c 1, $CHCl_3$) and of the anomer (17b), $[\alpha]_D^{20}$+7° (c 1, $CHCl_3$) in 1:1 ratio and 38% overall yield from (7). Authentic samples of the enantiomers of (17a) and (17b), prepared from methyl 2-deoxy-D-ribofuranoside[8] showed $[\alpha]_D^{20}$+88° and -19.8°, respectively. Moreover, the diol obtained upon basic hydrolysis of the crude monoacetate gave, on recrystallization from hexane-AcOEt, a crystalline material, m.p. 96-97°C, in 35% yield, shown by the above ^1H NMR method, to contain over 90% of the (3R,4S) enantiomer (8). The latter, in three steps [(1) $Me_2C(OMe)_2$/PTSA/23°C/24 h, (2) O_3 in MeOH/-78°C, then $NaBH_4$, (3) Ph_2Bu^tSiCl/pyridine/23°C/24 h], gave rise to the fully protected (3R,4S) 2-deoxypentose (14),









(18a) R= H; R^1= OMe (18b) R= OMe; R^1= H (19) R= COPh (20) R= COPh; R^1,R^2= H,OMe (21) R= H; R^1,R^2= H,OH (22a) R= OMe; R^1= H (22b) R= H; R^1= OMe

$[\alpha]_D^{20}$ +3.3° (c 1, $CHCl_3$) in 45% overall yield. Product (14), with 1% HCl in methanol at 0°C afforded the methyl glycoside (17c), $[\alpha]_D^{20}$ -48° (c 1, $CHCl_3$) and the anomer (17d), $[\alpha]_D^{20}$ +46° (c 0.9, $CHCl_3$). The corresponding derivatives prepared from 2-deoxy-D-ribose[9] showed α +51° and -47°, respectively. The significance of the present experiments is further enhanced from the fact that the α-acetoxy ketones recovered from the yeast treatment leading to (4S,5R) (4) and (3S,4R) (5) showed $[\alpha]_D^{20}$ +132° and +120° (c 1, $CHCl_3$), respectively. These materials were shown by ^1H NMR studies with tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium (III) to contain ca. 90 and 80% respectively, of a single enantiomer, which holds, as a consequence of a kinetic enzymic resolution, the (5S) and (4S) configuration. Indeed, the latter material, on DIBAL reduction (Et_2O/-78°C) afforded a mixture of anti and syn diols in 85:15 ratio, which separated in 35% yield the enantiomer of (6), m.p. 90°C, $[\alpha]_D^{20}$ +21.3° (c 1, $CHCl_3$), in 85% overall yield. With $LiAlH_4$, from the above acetoxy ketone, the anti and syn diols were obtained in 55:45 ratio (90%). From the latter mixture, once converted into the isopropylidene derivatives, the (3R,4S) enantiomer of (10), $[\alpha]_D^{20}$+24° (c 1, $CHCl_3$) and the (3S,4S) diastereoisomer, $[\alpha]_D^{20}$-28° (c 1, $CHCl_3$) were obtained by chromatography (85%). From the latter materials, the L and D enantiomers of the lyxo and ribo deoxysugars (16) and (21), and the L-arabino and D-xylo isomers should be accessible through the above methods. Similarly, from the (5S) α-acetoxy ketone survived to the yeast reduction of (1), by the above procedures, the L enantiomer of the 2,3-dideoxyglucose derivative (15) was obtained.

Considerations on the steric aspects (i.e.: the change from (R) to (S) enantioselectivity in the yeast reduction on going from (1) and (2) to (3)) of the whole-cells enzymic transformations reported above are outside the purposes of the present preparative work. There are recent examples[10] of changes of stereochemistry in the yeast reduction of carbonyl compounds even on subtle substrate structural modifications, explained by admitting the participation, within the bioconversion, of several enzymes acting with opposite stereochemistry. We are now investigating these aspects.

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