Baker's yeast mediated synthesis of natural products

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Abstract – Baker's yeast converts α,β-unsaturated aldehydes (1) into a set
of materials, including the methyl diols (3), formed by acyloin-type
condensation of a pyruvate derived C_2 unit, followed by reduction, the
diol (12), formed by hydration-reduction and the saturated alcohol (14),
all useful for the preparation of chiral natural products belonging to
quite different structural classes.

INTRODUCTION

Organic chemists recognized the ability of baker's yeast to transform unconventional
substrates stereoselectively since a long time ago, as one can judge from the considerable
amount of work in this area reported in the early literature.[1] However, there has been a
recent revival of interest for the use of baker's yeast in organic synthesis, in the more
general context of a preparative approach to enantiomerically pure forms of biologically
active natural products and drugs based on the use, as starting materials, of readily
available natural products.[2] These materials, however, usually are available in only one
enantiomeric form, a circumstance which represents a major drawback when both enantiomers of
the target molecule are needed, or when the absolute configuration of the final product
cannot be obtained from the starting material. Furthermore, the types of chirality present
amongst this set of compounds are rather limited; they are particularly abundant in the
R,R^1CHX structure (X = oxygen or nitrogen functions) and sparse in the R,R^1,R^2CH and
$R,R^1,R^2C(OR^3)$ moieties. These observations stimulated a search for new, relatively small,
highly functionalized chiral materials complementary or alternative to those already present,
and it was thought that this need could be satisfied at least in part by compounds available
by enzymic transformations of non-conventional substrates using either isolated enzymes or
microorganisms.[3] Organic chemists, who are not generally keen in growing cultures, began
using baker's yeast which is readily available and cheap, using it like a common shelf
reagent in reactions very similar to the natural transformations that it catalyzes. Most of
the current applications of baker's yeast involve stereospecific reduction of compounds
containing carbonyl groups and wide substrate acceptance is shown.[4] However, in some
instances, the synthetic significance of these transformations is diminished by the limited
reaction stereospecificity, perhaps because several enzymatically active principles are
acting on the same substrate with opposing stereobiases.

For some years now[5] we have been involved in the preparation of synthetically useful
optically active materials through a series of new baker's yeast mediated transformations of
non conventional substrates, most of which not involving the simple reduction of the
carbonyl function and without equivalent in classical organic chemistry.

(2S, 3R) METHYL DIOLS VIA REDUCTION OF THE (R) α-HYDROXY-METHYLKETONE FORMED ON DECARBOXYLATIVE INCORPORATION OF PYRUVATE INTO α,β-UNSATURATED ALDEHYDES

The (2S,3R) diols (3) are obtained from the α,β-unsaturated aldehydes (1) on baker's yeast
treatment in up to 25% yield. The asymmetric C-C bond forming process is identical to the
one reported by Neuberg[6] wherein benzaldehyde is transformed into (R) acetylphenylcarbinol,
a key intermediate in the manufacture of (-)-ephedrine, in fermenting baker's yeast and
involves addition of a C_2 unit equivalent of acetaldehyde onto the si face of the carbonyl
carbon to form the (R) α-hydroxyketone (2), that is subsequently reduced onto the re face to

give product (3), actually isolated. Pyruvate is the C_2 donor and as yeast pyruvate decarboxylase (E.C. 4.1.1.1) accepts as substrates α-oxo acids higher than pyruvate, on incubating (1) with α-oxobutanoate with baker's yeast that had been washed with water (4R) (2 d-f) are obtained, subsequently reduced by yeast in the presence of D-glucose to the corresponding anti diols. It should be noted that the latter chiral educts are formed by coupling two reagents (aldehyde and α-oxoacid) that have been added to the reaction mixture. This reaction, which would be often desirable, is seldom observed in the enzymic catalysis.
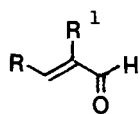
1 a R= Ph; R^1= H
 b R= Ph; R^1= Me
  c R= CO_2Et; R^1= Me
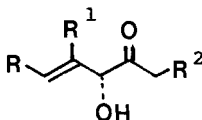
2 a R= Ph; R^1=R^2= H
  b R= Ph; R^1= Me; R^2=H
  c R= CO_2Et; R^1= Me; R^2= H
  d R= Ph; R^1= H; R^2= Me
  e R= Ph; R^1=R^2= Me
  f R= CO_2Et; R^1=R^2= Me
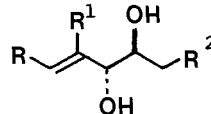
3 a R= Ph; R^1=R^2= H
  b R= Ph; R^1= Me; R^2= H
  c R= CO_2Et; R^1= Me; R^2= H
  d R= Ph; R^1= H; R^2= Me
  e R= Ph; R^1=R^2= Me
  f R= CO_2Et; R^1=R^2= Me

The diols (3) are particularly suited for the preparation of small molecules that contain relatively few chiral carbon atoms in their framework and whose chirality is due to oxygen substitution. From the isopropylidene derivatives of (3) it is possible to extrude, by ozonolysis, the C_4, C_5 and C_6 carbonyl compounds (4), that are convertible into the epimers (5) by base treatment. From (4) and (5) a variety of optically active natural products
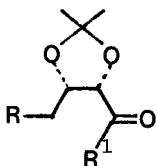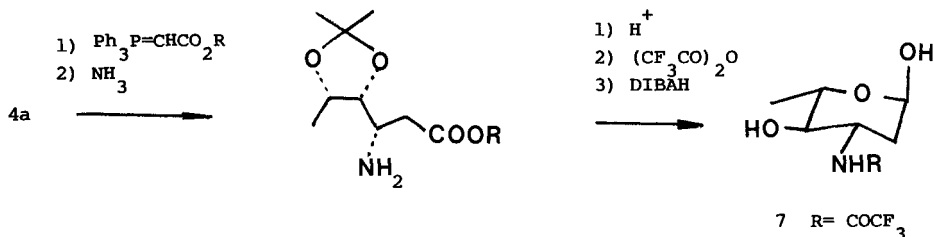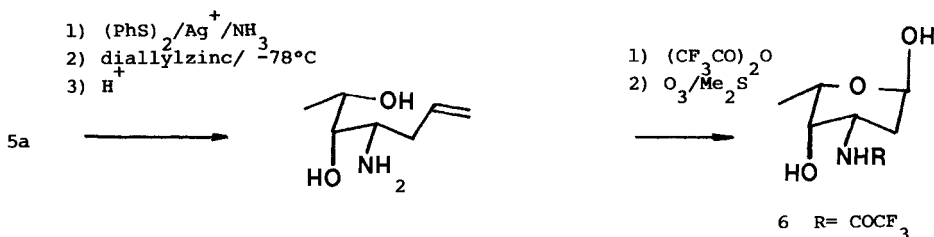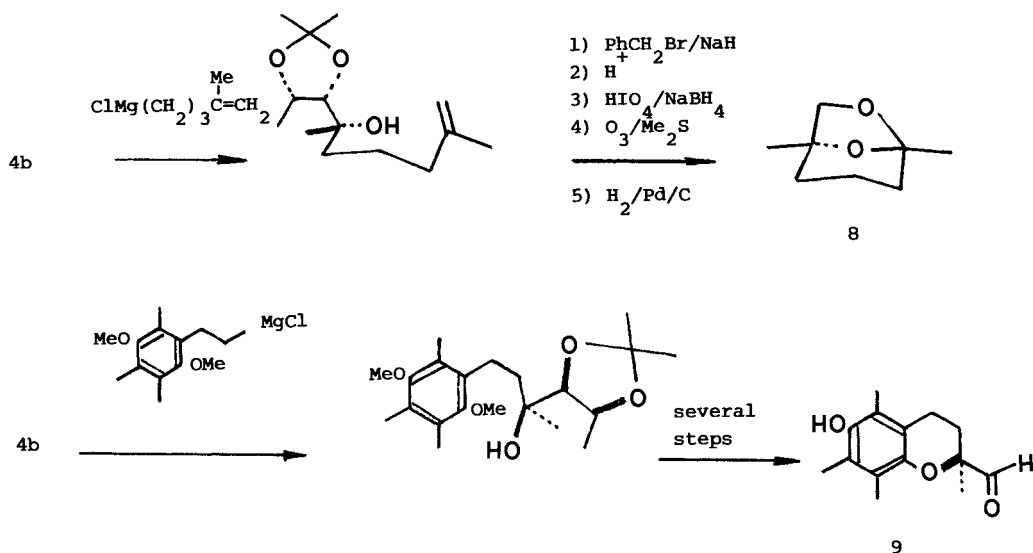

4 a R=R^1= H
  b R= H; R^1= Me
  c R= Me; R^1= H
  d R=R^1= Me
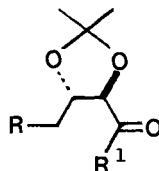
5 a R=R^1= H
  b R= H; R^1= Me
  c R= Me; R^1= H
  d R=R^1= Me

belonging to quite different structural classes has been obtained.[8,9] These include, amongst others, deoxyamino sugars components of the anthracycline glycosides such as L-daunosamine (6)[10] and L-acosamine (7),[11] pheromones such as (-)-frontalin (8)[12] and the C_{14} chromanyl moiety of natural α-tocopherol (9).[13]

1) (PhS)$_2$/Ag$^+$/NH$_3$
2) diallylzinc/ -78°C
3) H$^+$

5a

1) (CF$_3$CO)$_2$O
2) O$_3$/Me$_2$S

6 R= COCF$_3$

1) Ph$_3$P=CHCO$_2$R
2) NH$_3$

4a

1) H$^+$
2) (CF$_3$CO)$_2$O
3) DIBAH

7 R= COCF$_3$

1-PROTECTED (2*R*) 1,2,4-BUTANETRIOLS BY HYDRATION–REDUCTION OF 4-OXYGEN SUBSTITUTED CROTONALDEHYDE

γ-oxygen substituted crotonaldehyde (10), on yeast treatment, is not undergoing the acyloin-type condensation reported above, but is transformed, in ca. 25% yield, into the (2R) diol (12) of over 95% ee.[14] This transformation is expected to be the consequence of two chemical changes involving water addition across the double bond, followed by reduction of the intermediate 3-hydroxybutyraldehyde. Surprisingly enough, there is a dramatic difference in activity on subtle substrate structural changes. Indeed, product (11), as the consequence of the additional α-methyl group, is undergoing the acyloin-type condensation leading eventually to a product like (3). The synthetic significance of product (12) is due to the fact that its absolute configuration matches that of unnatural malic acid.[15]


10 a   R= COC$_6$H$_5$; R^1= H
   b   R= CH$_2$C$_6$H$_5$
11   R= COC$_6$H$_5$; R^1= Me

12 a   R= COC$_6$H$_5$
   b   R= CH$_2$C$_6$H$_5$
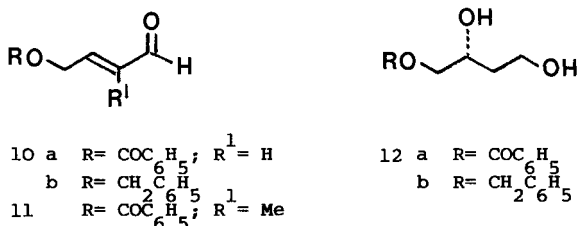
(*S*) 3(2-FURYL)-2-METHYLPROPAN-1-OL FROM REDUCTION OF α-METHYL-β-(2-FURYL)ACROLEIN

The high yield (72%) yeast conversion of (13) into (14)[16] affords a synthetically useful chiral material, due to the fact that it contains, in masked form, the C$_5$ structural unit present in natural isoprenoid compounds. This can be revealed by ozonolysis, as shown by the conversion into (S) (-)-3-methyl-γ-butyrolactone (15). Product (14) is a bifunctional chiral intermediate which does not need protective manipulation in that the furan ring can be seen as a carbonyl protecting group and selectively removed permitting elongation at both ends of the molecule. The functionalities of (14) can be used in different order. Either direct ozonization with oxidative work up should lead to (15). Alternatively, the alcohol functional group could be used to modify the side chain and the furan ring ozonized at a later stage. Taking advantage of the above mentioned properties, product (14) has been used for the preparation of (4R,8R) 4,8-dimethyldecanal (16), a pheromone component isolated

from <u>Tribolium castaneum</u>. Thus, the synthesis of (16) is achieved by coupling two furylmethyl propanol units and adding two C_1 at each end.

    13   14   15   16
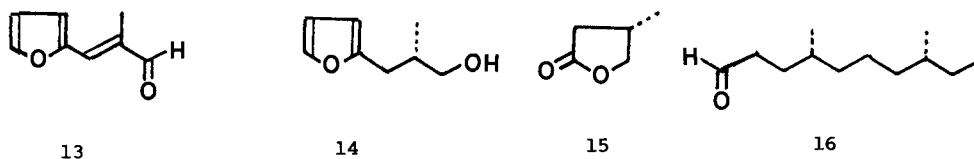
Similarly, from two molecules of (14), the C_{15} terpenoid side chain (17) of natural α-tocopherol (18) has been obtained. By coupling (9) and a suitable derivative of (17), in a convergent synthesis, the C_{29} framework of optically active (18) is constructed.[17] The two chiral synthons required for the preparation of (9) and (17) are obtained in a single baker's yeast mediated transformation of the aldehyde (13), which affords, close to (14), a (2<u>S</u>,3<u>R</u>) methyl diol of type (3), from which (4 b) is obtained.

    9   +

        17

                    18
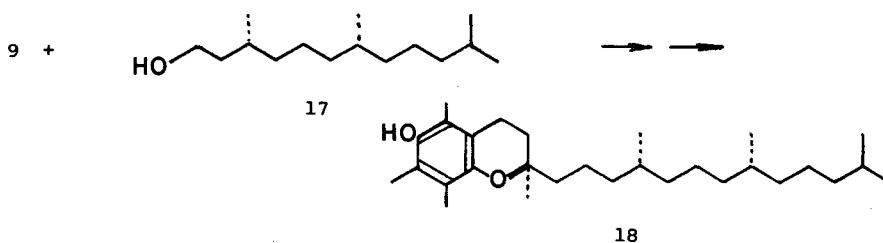
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