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Baker's Yeast Mediated Bioreduction of Prochiral Ketones Having 6-(4-Oxo-1,3-dioxinyl) Group[1)]

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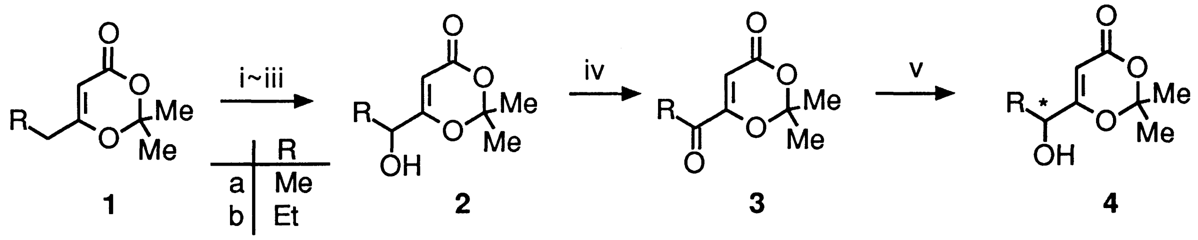
Prochiral ketones having 6-(4-oxo-1,3-dioxinyl) group as one terminal unit by fermenting baker's yeast gave chiral alcohols, which could be convertible to optically active hydroxyesters, β-ketoesters, and lactones.

Use of microorganisms is one of the effective methods for the preparation of chiral compounds. Among them, baker's yeast (Saccharomyces cerevisiae) is especially useful, because it is readily available and simple to handle. Since the enantioselectivity of this method is dependent upon the difference of bulkiness of two groups attached to the carbonyl group,[2)] it is desirable to explore new functions which not only display marked steric requirement, but also can be manipulatable after the reduction.

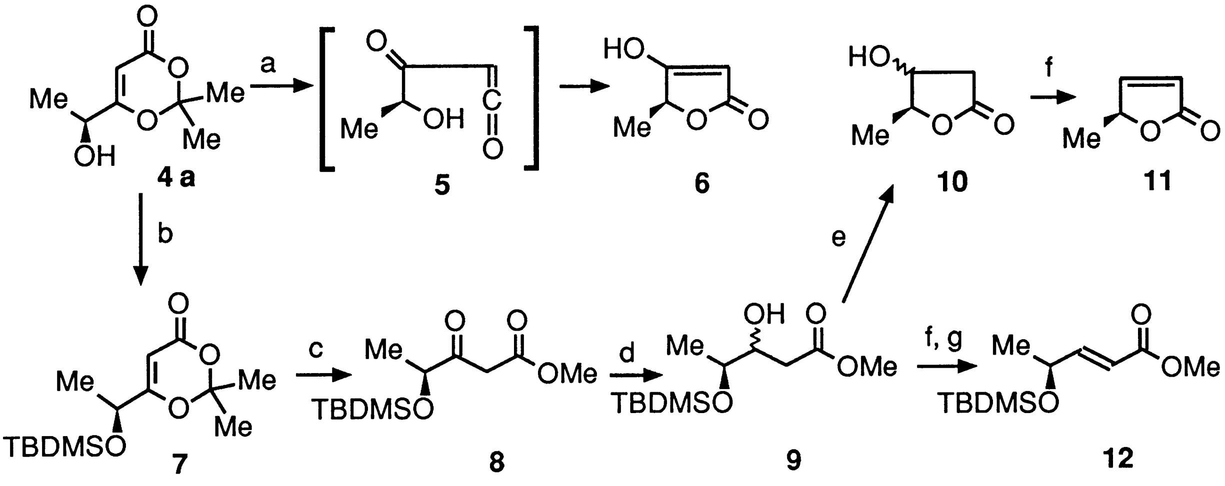
In this paper, we will report the baker's yeast reduction of prochiral ketones having 6-(4-oxo-1,3-dioxinyl) group as one terminal unit. Since the dioxinones are known as versatile synthons,[3)] it is obvious that the corresponding alcohols would be useful for a variety of organic syntheses.

At first, the bioreduction of dioxinones (**3**) having an acyl group at the 6-position was examined. The simplest ketone (**3a**) in this series was synthesized by PCC oxidation of 6-(1'-hydroxyethyl)dioxinone (**2a**) readily obtainable from the 6-ethyl derivative (**1a**) according to the three-step procedure developed recently in our laboratory.[4)]



Scheme 1. Reagents and conditions: i) NBS/CCl_4, hν (>300 nm)/AIBN; ii) NaOAc/DMF; iii) K_2CO_3/MeOH-H_2O; iv) PCC; v) baker's yeast reduction

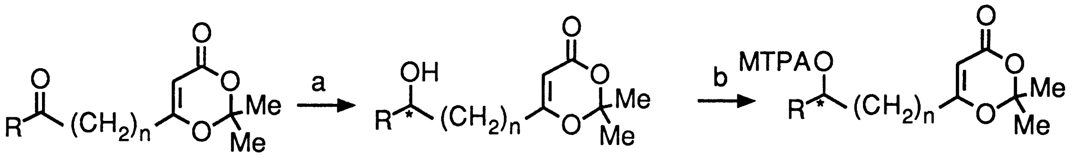
When **3a** was treated with fermenting baker's yeast,$^{5)}$ the alcohol (**4a**) was obtained in satisfactory chemical yield (90%) with high e.e. (91%). The chiral dioxinonealcohol (**4a**) thus obtained was refluxed in toluene to give (S)-(+)-γ-methyltetronic acid [**6**: mp 110-112 °C, $[\alpha]_D^{20}$ +12.9° (c 0.59, H_2O)] in 88% yield.$^{6)}$ This reaction proceeded via intramolecular ketene trapping (see, **5**) as demonstrated in our recent work.$^{4)}$ Another use of **4a** was its conversion to chiral β-angelica lactone (**11**).$^{7)}$ Thus, the protected alcohol (**7**) derived from **4a** was reacted with methanol in refluxing toluene to give chiral γ-hydroxy-β-ketoester [**8**: oil, $[\alpha]_D^{26}$ -0.38° (c 3.14, $CHCl_3$)], which afforded the lactone [**11**: oil, $[\alpha]_D^{22}$ +90.9° (c 2.60, $CHCl_3$)] via reduction to vic-alcohol (**9**), fluoride-mediated deprotection of the silyl group to **10**, followed by mesylation. It is noted that **9** could also be converted stereoselectively to (E,S)-γ-hydroxy-α,β-unsaturated ester [**12**: oil, $[\alpha]_D^{25}$ +4.7° (c 1.14, $CHCl_3$)].



Scheme 2. Reagents and conditions: a) toluene, reflux; b) TBDMSCl-imidazole/DMF; c) toluene-MeOH, reflux; d) $NaBH_4$/MeOH; e) n-$Bu_4N^+F^-$/THF; f) MsCl-Et_3N, 0 °C; g) DBU/benzene, reflux

6-(1-Oxopropyl)dioxinone (**3b**) was prepared from the corresponding 6-propyldioxinone (**1b**), and treated with fermenting yeast to give the corresponding alcohol (**4b**) only in low chemical and optical yields. Therefore, we examined the bioreduction of the dioxinones having a 2'-oxo- or 3'-oxoalkyl group at the 6-position. The substrates were synthesized from 2,2,6-trimethyl-1,3-dioxin-4-one by the following procedures. While **13a** was prepared by base-mediated acylation with acetyl chloride, **13b** was synthesized via bromination, base-mediated condensation with benzyl acetoacetate, followed by deprotection of the benzyl group by catalytic hydrogenation. In the last step, the primary product (a β-ketoacid) decarboxylated spontaneously. The bioreduction of both compounds afforded the corresponding alcohols (**14**) of high e.e., irrespective of the number of homologation. The results are summarized in Table 1.

Table 1. Bioreduction of 6-Oxoalkyl-1,3-dioxin-4-ones with Fermenting Yeast



3: n=0
13 : n≠0

4: n=0
14: n≠0

15

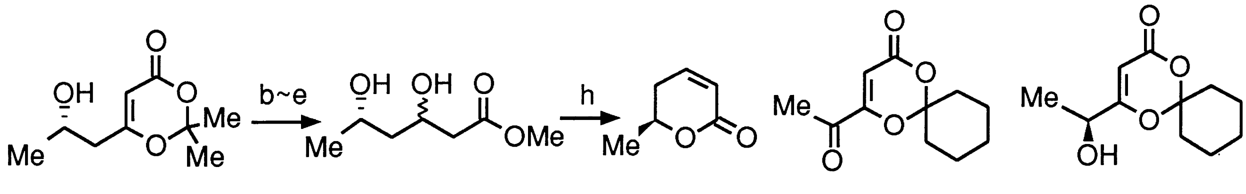
a: fermenting baker's yeast, 32 °C; b: MTPA-OH, DCC, DMAP, CH_2Cl_2

Entry	R	n	Reaction time/d	Yield/(%)	$[\alpha]_D$/° ($CHCl_3$)	ee[a] /(%)	Absolute Config.
3a	Me	0	1	90	-5.4	91	S
3b	Et	0	1	53	+7.5	43	-[b]
13a	Me	1	2	44(55)[c]	+25.2	90	S
13b	Me	2	2	23(33)[c]	+16.8	>98[d]	-[b]

a) Determined by 500 MHz ^{1}H-NMR of the MTPA esters (**15**).
b) Undetermined.
c) Yields in parenthesis are based on the consumed ketones.
d) No other enantiomer could be detected.

Though the absolute configuration of **4b** and **14b** have not been determined yet, S-structure of **4a** is obvious by its conversion to **6** and 11 (vide supra). The same S-structure for **14a** was also verified by conversion to (S)-(+)-parasorbic acid [**17**: $[\alpha]_D^{26}$ +150.8° (c 0.52, EtOH)].[8]

It should be noted that the spiro derivative (**18**) was also reduced by baker's yeast to give the corresponding alcohol (**19**) in almost 100% e.e., whose absolute structure was determined by its conversion to **6**. This fact shows that an introduction of bulkier substituents at the 2-position of the dioxinone would enhance enantioselectivity of this reduction.



14a **16** **17** **18** **19**

Scheme 3. Reagents and conditions: b-e) the same as Scheme 2; h) TsOH/benzene, reflux

In conclusion, 6-oxoalkyl-1,3-dioxin-4-ones were found to be reduced by fermenting baker's yeast in high enantioselectivities. Chiral alcohols containing dioxinone ring at the terminal would serve as synthons for enantiomerically pure compounds in two ways: 1) synthesis of chiral lactones and 2) synthesis of chiral alcohols containing a variety of heterocyclic rings. Since synthesis of the lactones has already been accomplished in the present study, our efforts are now being made for synthesizing a variety of heterocycles having chiral alcoholic side chain.[9,10]

References

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9) Dioxinones could be readily transformed either to six- or five-membered heterocycles, such as pyridines, pyrimidines, isoxazolines, 2-pyrazolines, as demonstrated in our earlier study. See reference 3.
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