Chiral Cyclopentanoid Synthetic Intermediates via Asymmetric Microbial Reduction of Prochiral 2,2-Disubstituted Cyclopentanediones

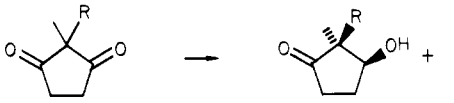
Summary: A prochiral distinction by microbial reduction of 2-propyl- (1), 2-allyl- (4), and 2-propynyl-2-methyl-1,3-cyclopentanedione (7) with bakers' yeast provides efficient access to several chiral cyclopentanoid synthetic intermediates. A short enantioselective synthesis of (*R*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione (17), a precursor to coriolin (18), from 5 is described.

Sir: Microbial-mediated reactions of synthetic substrates are useful means of preparing chiral intermediates for synthetic studies.[1] The asymmetric microbial reduction of the carbonyl functional group is a viable preparative method because of the variety and/or relaxed specificity of dehydrogenase enzymes available in microorganisms. Common bakers' yeast (*Saccharomyces cerevisiae*) is a particularly versatile and easy to use microorganism for this purpose.[2] We herein describe the efficient asymmetric reduction of one of two enantiotopic homomorphic[3] carbonyl groups (prochiral distinction) in 2,2-disubstituted 1,3-cyclopentanediones by bakers' yeast. In addition, the synthetic utility of these readily available chiral intermediates is demonstrated by the preparation of (*R*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione (17),[4] a key intermediate used in the total synthesis of coriolin (18) by Trost and Curran.[5]

The ability of certain enzymes to make prochiral distinctions is based on the formation of a preferred enzyme–substrate complex, which leads to a favored catalytic reaction for one of two enantiotopic homomorphic groups. Several 2,2-disubstituted 1,3-diones have been subjected to microbial reduction with a variety of microorganisms to provide chiral intermediates.[6] We chose to study the series 2-propyl- (1), 2-allyl- (4), and 2-propynyl-2-methyl-1,3-cyclopentanedione (7) using bakers' yeast. The allyl dione 4[7] and propynyl dione 7 were prepared by alkylation of 2-methyl-1,3-cyclopentanedione[8] (excess 3-bromopropene or 3-bromopropyne, 1 equiv of 1 N NaOH, 25 °C, 64 h, 70–85%). Catalytic hydrogenation of 4 (H_2, PtO_2 catalyst, 1 atm, 25 °C, 2 h, 98%) gave the propyl dione 1. The major products of the microbial reduction of 1, 4, and 7 were the corresponding ketols (see Table I). The reductions were carried out on a 1–20-g scale with consistent results. A typical procedure is described as follows: To a solution of 500 mL of pH 7 phosphate buffer, 150 g of D-glucose, and 4.0 g of yeast extract, warmed at 40 °C, was added 100 g of dry active bakers' yeast[9] and the mixture was stirred at 40 °C for 30 min, after which, 10 g of allyl dione 4 was added dropwise over 30 min. The mixture was stirred at room temperature 24 h and then continuously extracted with dichloromethane for 48 h to provide a crude product which was analyzed by gas chromatography (6 ft, 10% SE-30 on 80–100-mesh Chromosorb W) and found to consist of ketol 5 (70–80%), unreacted dione (4) (20–30%), and a small amount of diol[10] (<5%). The ketol 5 was readily purified by vacuum distillation [bp 75 °C (0.2 mm)]. The results of the microbial reductions are compared with the ketol products formed by reduction with 1 equiv of $NaBH_4$ in Table I. It is interesting to notice the similar trend of decreased stereoselectivity in both the microbial and $NaBH_4$ reductions in the series, propyl > allyl > propynyl and the greater sensitivity of the microbial system to substituent changes.

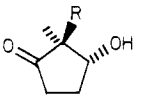
The enantiomeric composition of the chiral ketols was determined by analysis of the ^1H and ^{19}F NMR spectra of the corresponding (+)-α-(trifluoromethyl)benzeneacetic acid (MTBA) esters.[11] In all cases the microbial ketol products were better than 98% enantiomerically pure.[12]

Table I. Reduction of Prochiral 2,2-Disubstituted 1,3-Cyclopentanediones by Bakers' Yeast and $NaBH_4$



1, R = $CH_2CH_2CH_3$
4, R = $CH_2CH{=}CH_2$
7, R = $CH_2C{\equiv}CH$

2, R = $CH_2CH_2CH_3$
5, R = $CH_2CH{=}CH_2$
8, R = $CH_2C{\equiv}CH$



3, R = $CH_2CH_2CH_3$
6, R = $CH_2CH{=}CH_2$
9, R = $CH_2C{\equiv}CH$

entry	dione	rctn[a]	ketol products[b] (ratio)[c]	isolated yield[d] of ketol, %	recov[e] dione, %
1	1	A	2	60	30
2	1	B	2/3 (6:1), racemic	70	10
3	4	A	5/6 (10:1)	75	15
4	4	B	5/6 (3:1), racemic	75	5
5	7	A	8/9 (2:1)	60	25
6	7	B	8/9 (2:1), racemic	60	10

[a] Conditions A: yeast reduction (general procedure described in the text). Conditions B: dione, 0.1 M in ethanol, 1.0 equiv of $NaBH_4$, 0 °C, 3 h, add 1 N HCl to pH 2, evaporate in vacuum, aqueous workup with ether, vacuum distill or flash chromatography (silica gel, gradient 10–30% ethyl acetate in hexane). [b] The small amounts of diol products (<5%) formed were not fully characterized. [c] The ratio of ketol products was determined by ^1H NMR at 470 MHz with a control experiment establishing a practical limit of detection of 1.5% of isomer. [d] The yield reported is the average of three or more reactions and represents percentage conversion. [e] Longer reaction times led to complete consumption of dione but also greater amounts of diol products.

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(8) Available commercially from Aldrich Chemical Co. or readily prepared on a mole scale according to the procedure of Schick, H.; Lehmann, G.; Hilgetag, G. *Chem. Ber.* **1969**, *102*, 3238.

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(10) The structure of this diol is assigned as trans by analysis of its ^1H and ^{13}C NMR spectra.

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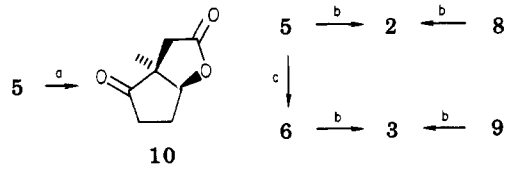
Scheme I.[a] Chemical Correlation of Chiral Products



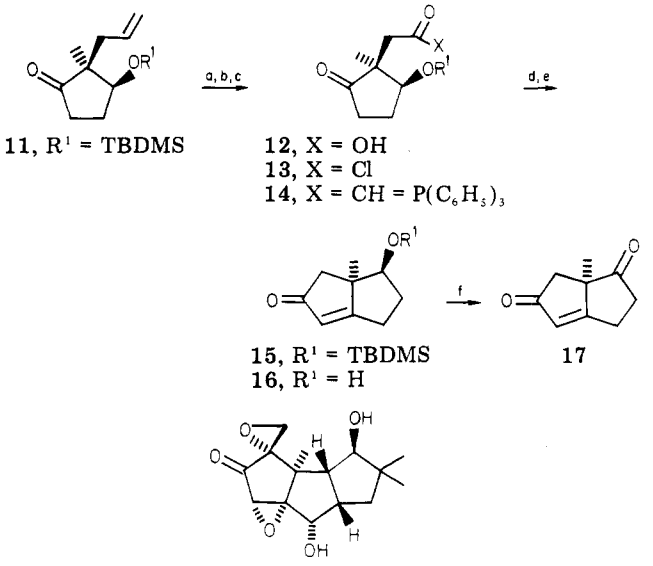
10

[a](a) **5**, 0.3 M in dichloromethane, 2.5 equiv of pyridine, −78 °C, excess O_3 (until solution turned blue), workup with cold 1 N HCl and dichloromethane, evaporate in vacuum, add acetone, 0.3 M, 0 °C, add Jones reagent (ref 15) dropwise, filter through Celite, evaporate in vacuum, workup with 1 N HCl and ethyl acetate, flash chromatography (silica gel, 40% ethyl acetate in hexane), crystallized (ether/hexane), mp 96 °C, 70%; (b) 0.01 equiv of PtO_2, ethanol (0.5 M), H_2, 25 °C, 2 h, filtered, evaporate in vacuum, 98%; (c) **5**, 0.1 M in dimethylformamide, 15 equiv of KNO_2, 85 °C, 36 h, evaporate in vacuum, added aqueous saturated NaCl (0.1 M), continuously extract with dichloromethane 24 h, evaporate in vacuum, bulb-to-bulb distill [70 °C (0.1 mm], 70%.

The absolute configuration of the chiral ketol **5**[13] was established by correlation with the known lactone **10**[14] by ozonolysis (excess O_3, pyridine, dichloromethane, −78 °C) followed directly by oxidation with Jones reagent[15] (acetone, 0 °C, 15 min) to give the lactone **10** in 70% yield. The allyl ketol **5** was reduced (PtO_2 catalyst, H_2, EtOH, 25 °C, 2 h, 98%), providing the ketol **2**. The propynyl ketol **8**[16] was reduced in a similar fashion to the ketol **2** for correlation. After several trials,[17] a suitable method was found to cleanly epimerize the hydroxyl group of the allyl ketol **5** involving treatment of the corresponding tosylate (*p*-toluenesulfonyl chloride, pyridine, 25 °C, 64 h, 85%) with potassium nitrite[18] (dimethylformamide, 85 °C, 35 h, 70%) to provide the (2*S*,3*R*)-allyl ketol **6**. Catalytic hydrogenation of **6** and **9** gave the same ketol **3**. An outline of the chemical correlation is shown in Scheme I.

To exemplify the utility of these readily available chiral intermediates in synthesis, we prepared (*R*)-5-methylbicyclo[3.3.0]oct-1-ene-3,6-dione **17** from ketol **5** (Scheme II). Protection of the hydroxyl group (*tert*-butyldimethylsilyl chloride, dimethylformamide, imidazole, 4-(dimethylamino)pyridine catalyst, 60 °C, 16 h, 90%) was followed by oxidative cleavage of the olefin **11**[19] ($KMnO_4$ catalyst, $NaIO_4$, 1:2 t-C_4H_9OH/H_2O, 25 °C, 16 h, 75%) to provide the carboxylic acid **12**. The acid chloride **13** was prepared in a routine fashion (oxalyl chloride, anhydrous toluene, 25 °C, 6 h). Two equivalents of a salt-free solution of methylenetriphenylphosphorane[20] in toluene was added slowly to the acid chloride **13** in toluene at −78 °C and after being stirred for 5 min the mixture was then refluxed for 6 h to accomplish an intramolecular Wittig reaction, providing, after chromatography (silica gel, 20% ethyl acetate in hexane), the enone **15** in 60% yield. The silyl ether group was cleaved (n-$Bu_4N^+F^-$, THF, 0 °C, 30 min, 85%) to provide the alcohol **16**. Oxidation of **16** (pyridinium chlorochromate, dichloromethane, 25 °C, 2 h, 85%) followed by chromatography (silica gel, 20% ethyl acetate in dichloromethane) gave enantiomerically pure enedione **17**.

Scheme II[a]



11, R^1 = TBDMS

12, X = OH
13, X = Cl
14, X = CH = $P(C_6H_5)_3$

15, R^1 = TBDMS
16, R^1 = H

17

18 (coriolin)

[a](a) **11**, 0.02 M in 1:2 *tert*-butyl alcohol, H_2O, 3 equiv of K_2CO_3, 4.0 equiv of $NaIO_4$, 0.01 equiv of $KMnO_4$, 25 °C, 16 h, add ethylene glycol to quench excess oxidant, filter, evaporate in vacuum, acidify residue to pH 4 with 1 N HCl, extract with ethyl acetate, 75%; (b) **12**, 0.5 M in toluene, 2 equiv of oxalyl chloride, 25 °C, 6 h, evaporate in vacuum; (c) preceding material, 0.1 M in toluene, −78 °C, add 2.2 equiv of methylenetriphenylphosphorane (0.3 M in toluene) dropwise; (d) preceding solution refluxed 6 h, workup with 1 N HCl and ether, flash chromatograph (fc; silica gel, 20% ethyl acetate in hexane), 60%; (e) **15**, 0.5 M in tetrahydrofuran, 0 °C, add 1.1 equiv of n-$Bu_4N^+F^-$ (1.0 M in tetrahydrofuran) dropwise, 30 min, workup with aqueous saturated $NH_4^+Cl^-$ and ether, 85%; (f) **16**, 0.5 M in dichloromethane, 1.5 equiv of pyridinium chlorochromate, 25 °C, 2 h, add ether, filter, evaporate in vacuum, fc (silica gel, 20% ethyl acetate in dichloromethane), 85%.

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Registry No. **1**, 25112-79-2; **2**, 80888-39-7; (±)-**2**, 81969-77-9; (±)-**3**, 81969-78-0; **3**, 81969-86-0; **4**, 26828-48-8; **5**, 72345-34-7; (±)-**5**, 81969-79-1; **6**, 81969-80-4; (±)-**6**, 81969-81-5; **7**, 68197-04-6; **8**, 77493-42-6; (±)-**8**, 81969-82-6; **9**, 81969-83-7; (±)-**9**, 81969-84-8; **10**, 71629-66-8; **11**, 81940-27-4; **12**, 81940-28-5; **13**, 81940-29-6; **15**, 81940-30-9; **16**, 81969-85-9; **17**, 74766-20-4; 2-methyl-1,3-cyclopentadione, 765-69-5; 3-bromopropene, 106-95-6; 3-bromopyropyne, 106-96-7.

Supplementary Material Available: A listing of spectral data, specific optical rotations, and combustion analysis for the chiral compounds described in this work (2 pages). Ordering information is given on any current masthead page.

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(12) A control experiment established a practical limit of detection of 1.5% of diastereomer in the ^1H NMR spectrum at 470 MHz.
(13) Spectral data, specific optical rotations, and combustion analysis data for the chiral compounds described in this paper are available as supplementary material (see the paragraph at the end of this paper).
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(16) The propynyl ketols **8** and **9** were separated by chromatography (silica gel, 10% ether, dichloromethane).
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