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CHIRAL CYCLOHEXANOID SYNTHETIC PRECURSORS VIA ASYMMETRIC MICROBIAL REDUCTION OF PROCHIRAL CYCLOHEXANEDIONES

Dee W. Brooks*, Hormoz Mazdiyasni, and Sharmistha Chakrabarti
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Summary: Microbial reduction of various 2,2-disubstituted-1,3-cyclohexanediones with bakers' yeast provides efficient access to chiral cyclohexanoid synthetic precursors.

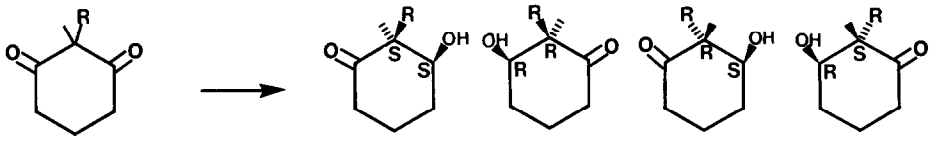
Asymmetric microbial reduction of the carbonyl functional group has been demonstrated to be a viable method to prepare chiral alcohols and common bakers' yeast (Saccharomyces cerevisiae) is a particularly easy microorganism to use for this purpose.[1,2] We have been interested in applying the concept of multiple prochiral distinctions by enzymes as a valuable element of synthetic strategy.[3,4] We wish to describe an extension of this theme to the preparation of chiral cyclohexanoids and outline a synthetic application to prepare a key chiral precursor (20b) for the diterpenoid zoapatanol (27), which illustrates the important point that this methodology not only provides chiral products resulting from the inherent asymmetric preference of the enzyme system, but by performing additional simple synthetic procedures on these microbial products all of the possible products containing two chiral centers can be obtained.

Treatment of 2-propyl-(1), 2-allyl-(6), and 2-propynyl-2-methyl-1,3-cyclohexanedione (11) [5] with actively fermenting bakers' yeast resulted in good yields of chiral monoreduced ketol products as shown in Table 1. The reductions were carried out on a 1- 10 g scale with consistent results.[6] The enantiomeric composition of the chiral ketols was determined by analysis and comparison of the ^{1}H and ^{19}F NMR spectra of the corresponding (+)-α - (trifluoromethyl)benzeneacetic acid (MTBA) esters [7] with those derived from the ketols prepared by $NaBH_4$ reduction (leq $NaBH_4$, 0.1M in ethanol, 0° C, 3h) . In each case the singlet of the 2-methyl group of each of the four possible +MTBA diastereomers derived from the racemic ketols was clearly observed in the ^{1}H NMR (470MHz) spectra. In all cases the microbial ketol products were found to have >98% enantiomeric excess.[8] Unlike the cyclopentanedione system,[3] these two reduction methods, enzymatic versus $NaBH_4$, proceeded with different stereoselectivity (major configuration for cyclopentanoids was [2S,3S] and cyclohexanoids [2R,3S]).

The assignment of structure and absolute configuration for the chiral cyclohexanoids was established as follows. Ring expansion of the cyclopentanoid mixture of 21,22

(67,33%) of known absolute configuration,[3] with diazomethane[9] (0.5M in ether, cat. $AlCl_3$, -40° C, add 2.1eq 0.5M CH_2N_2 in ether, 1h, silica gel chromatography, 65%) gave the corresponding cycloheptanoids 23,24 (67,33%). Similar ring expansion of the cyclohexanoid mixture 2a,4a (45,55%) with 1eq of CH_2N_2 gave 23,24 (42,58%). The allyl mixture 7a, 9a (45,55%) was correlated to 2a, 4a(45,55%) by catalytic hydrogenation (0.1 M in ethanol, 1atm H_2, PtO_2, 25° C, 3h). The propynyl mixture 12a, 14a (27,73%) was also correlated to 2a, 4a (25,75%) in this manner. It is interesting to recognize the asymmetric consistency of the microbial reduction of the carbonyl group in this series to provide only the S-hydroxy configuration.

Table 1.[a] Reduction of Prochiral 2,2-Disubstituted-1,3-Cyclohexanediones with Bakers' Yeast and $NaBH_4$

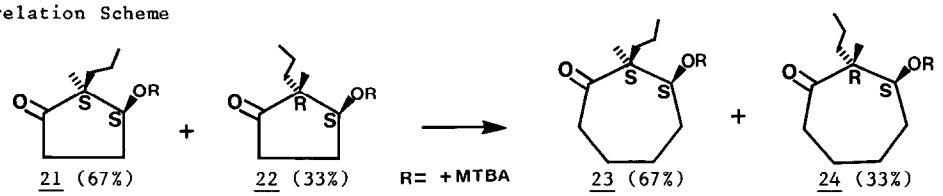


1 R=$CH_2CH_2CH_3$ — 2 — 3 — 4 — 5
6 R=$CH_2CH{=}CH_2$ — 7 — 8 — 9 — 10
11 R=$CH_2C{\equiv}CH$ — 12 — 13 — 14 — 15
16 R=$(CH_2)_3C(CH_3){=}CH_2$ — 17 — 18 — 19 — 20

entry	dione	reduction method	ketol products[b] (% composition)	isolated yield[c] of ketols %	recovered dione %
1	1	yeast	2,4 (22,78)	80	15
2	1	$NaBH_4$	2&3,4&5 (98,2)	70	10
3	6	yeast	7,9 (45,55)	80	15
4	6	$NaBH_4$	7&8,9&10 (83,16)	70	10
5	11	yeast	12,14 (27,73)	75	20
6	11	$NaBH_4$	12&13,14&15 (64,36)	70	15
7	16	yeast	17,19 (24,76)	75	10
8	16	$NaBH_4$	17&18,19&20 (95,5)	70	15

a) All compounds were characterized by ^1H and ^{13}C NMR, IR, and MS. b) 0a indicates the +MTBA ester of alcohol 0, 0b indicates the benzoate derivative of alcohol 0. c) The yield reported is the average of two or more reactions, see ref.6.

Correlation Scheme

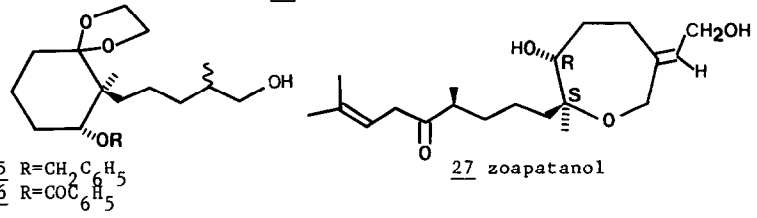


2,4a(45,55%) → 23 (42%) 24 (58%)

7,9a(45,55%) → 2,4a(46,54%) 12,14a(27,73%) → 2,4a(25,75%)

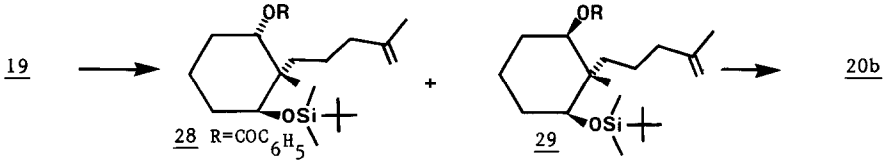
To further demonstrate the application of this methodology as a valuable element of synthetic design, we have prepared the chiral cyclohexanoid 26 which closely resembles a racemic intermediate 25 used in a total synthesis of the diterpenoid zoapatanol (27).[10] Treatment of 2-methyl-1,3-cyclohexanedione with leq $nBu_4N^+F^-$ followed by 5-iodo-2-methylpent-1-ene[11] (25°C, 64h) gave the C-alkylated dione 16 in 55% yield.[12] Reduction with yeast provided a mixture of two chiral ketols 17 and 19 (see Table 1). The absolute structures were assigned by comparison of the rotation and ^{13}C NMR spectra of the ketols 17 and 19 and the ^1H NMR spectra of the corresponding +MTBA esters 17a and 19a with those of the previously assigned cyclohexanoids.

Inspection of zoapatanol (27) reveals that the requisite cyclohexanoid precursor should have the [2S,3R] configuration. A series of standard chemical transformations were performed to convert the microbial products 17 and 19 to the [2S,3R] ketol 20. The chiral ketols 17 and 19 were readily separated by chromatography (silica gel, 0-20% ether in hexane). A hydroxyl inversion procedure[13] transformed ketol 17 to the desired configuration providing 20. Conversion of ketol 19 to its enantiomer 20 was accomplished by first protection of the hydroxy group as a silyl ether followed by reduction with $NaBH_4$ to give a mixture of diastereomers 28 and 29 (25,75%) which were separated by chromatography (silica gel, 0-20 % ether in hexane).[14] Conversion of 29 to the benzoate, desilylation (Bu_4NF) and oxidation (PCC) provided 20b. The optical rotation, $[\alpha]_D$ of 20b derived from 17 or 19 by the above chemical steps was -20.2° (c=3.5, $CHCl_3$) and -21.5° (c=1.5, $CHCl_3$) respectively. The optical rotation of the benzoate of 19 was +22.4° (c=3.4, $CHCl_3$). Inversion of the hydroxyl group in 19 followed by benzoate formation gave 18b, -51.2°(c=0.9, $CHCl_3$) which compared well with its enantiomer 17b, +52.6°(c=1.1, $CHCl_3$). Thus, by these procedures all of the chiral products [2S,3S], [2R,3R], [2R,3S], [2S,3R] could be obtained from prochiral starting materials such as 1, 6, and 11. Ketalization of 20b followed by hydroboration/oxidation provided 26, a compound similar to the intermediate 25 used in Kane's synthesis[10] of zoapatanol (27).



25 R=$CH_2C_6H_5$
26 R=COC_6H_5

27 zoapatanol



Further applications of this strategy to provide chiral intermediates for synthetic studies are being pursued.

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5) The allyl dione 6 and propynyl dione 11 were prepared by alkylation of 2-methyl-1,3-cyclohexanedione (excess 3-bromopropene or 3-bromopropyne, 1eq 1N NaOH, 25° C, 64h, 60-75%). Catalytic hydrogenation of 6 (H_2, PtO_2 catalyst, 1 atm, 25° C, 2h, 98%) gave the propyl dione 1.

6) The typical procedure is described as follows. To a solution of 1.0 L of distilled water, 150g of D-glucose, and 4.0g of yeast extract, warmed at 35°C, was added 100g of dry active bakers' yeast (Fleischmann's bakers' yeast produced by Standard Brands Inc.) and the mixture was stirred at 35°C for 30min, after which, 10g of the allyl dione 6 was added dropwise over 30min. The mixture was vigorously stirred at room temperature for 24h and then continuously extracted with dichloromethane for 48h providing a crude product consisting of ketol 7 and 9 (60-75%), unreacted dione 6 (20-30%), and a small amount of diol (<5%). The ketol mixture was readily purified by fractional distillation (bp 90-95°C at 0.3mm) or by chromatography on silica gel with 20-30% ethyl acetate in hexane.

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12) The corresponding O-alkylated product was formed in 35% yield and separated by chromatography (silica gel, 10% ethylacetate in hexane).

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14) The application of more stereoselective reducing agents have not been investigated in this demonstration example.

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