Pergamon

Baker's yeast-mediated reduction of cyclohexanones containing a nitro or a sulfonyl group at C-3

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Abstract: Baker's yeast-mediated reduction of 3-(nitromethyl)-, 3-(phenylsulfonyl)-, and 3-[(phenylsulfonyl)methyl]-cyclohexanones **1a,c,d** led to the delivery of a hydride to the *re*-face of the prochiral ketones to provide cyclohexanols (1*S*,3*S*)- and (1*S*,3*R*)-**2a,c,d** with high enantioselectivities in good yields. The remote nitro and sulfonyl groups, in contrast to alkyl and sulfenyl groups, may play an important role in binding to an enzyme. © 1997 Elsevier Science Ltd

Introduction

Baker's yeast (BY)-mediated asymmetric reduction of ketones has been widely used to obtain chiral building blocks, because it is cheap, versatile, and easy to perform.[1] Although the reduction with BY is undertaken by a complex set of dehydrogenases that individually afford *S*- and *R*-alcohols in an enantioselective manner,[2] the stereoselectivity is generally predicted by the Prelog rule,[3] that is, a hydride is transferred to the *re*-face of the prochiral ketone.

On the other hand, the stereochemistry of the reduction by hydride-transfer reagents has been studied most thoroughly with conformationally biased cyclohexanone derivatives. Axial alcohols are likely to be formed under kinetic control when the reducing agent is a sterically hindered hydride-donor, because the equatorial direction of approach is more open and is preferred by a bulky reagent.[4]

The enantiomerically pure cyclohexane ring system is a common feature in a wide variety of natural products, and a number of methods are available for its construction. Although a few examples of the BY reduction of C-2-substituted cyclohexanones have been described,[5] there is no report on the reduction of cyclohexanones **1** containing a functional group at C-3. On treatment of **1** with BY the Prelog rule predicts the predominant formation of cyclohexanols (1*S*,3*S*)-**2** and (1*S*,3*R*)-**2**, while in the kinetic-controlled reaction the use of a bulky hydride-transfer reagent seems to afford cyclohexanols (1*S*,3*S*)-**2** and (1*R*,3*R*)-**2** (Scheme 1).
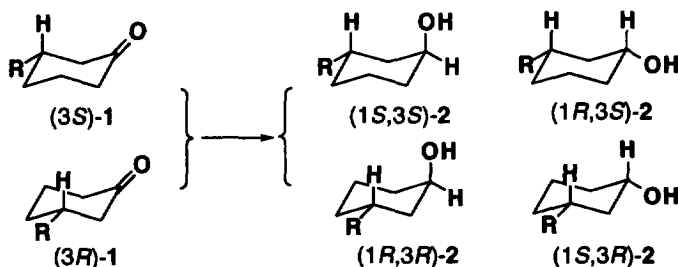
Scheme 1. Reduction of **1**.

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Table 1. Baker's yeast reduction of cyclohexanones 1a–e

Substrate	R	Product	% e.e.^{a} (% yield^b)	
			(1S,3S)-2	(1S,3R)-2
1a	CH₂NO₂	2a	>99 (46)	>99 (43)
1b	SPh	2b	6 (5)	9 (6)
1c	SO₂Ph	2c	>99 (45)	>99 (40)
1d	CH₂SO₂Ph	2d	90 (41)	95 (38)
1e	n-C₄H₉	2e	— (0)	— (0)

^{a} Determined by HPLC analysis of the corresponding Mosher esters. ^{b} Isolated yield.

The objective of the present work is to elucidate the stereochemistry of BY-mediated reduction of 1, and in addition, to clarify the participation of remote nitrogen and sulfur functional groups, because nitrogen and sulfur based reagents have become an essential part of the armoury of synthetic chemists.

Results and discussion

Treatment of nitromethane with 2-cyclohexenone in the presence of a base readily gave 3-(nitromethyl)-cyclohexanone 1a. In a similar fashion 3-(phenylthio)cyclohexanone 1b was prepared from benzenethiol and 2-cyclohexenone, and the subsequent oxidation of 1b gave 3-(phenylsulfonyl)cyclohexanone 1c. On the other hand, 3-[(phenylsulfonyl)methyl]cyclohexanone 1d was prepared efficiently by 1,4-addition of methyl (phenylsulfonyl)acetate to 2-cyclohexenone, followed by demethoxycarbonylation with NaCl in dimethylsulfoxide.[6]

The reduction of 1a, 1c and 1d with BY (Table 1) afforded a mixture of two diastereoisomeric cyclohexanols in high enantiomeric excess (e.e.), but 3-butylcyclohexanone 1e was found to be unreactive towards BY. The e.e. of the products was determined by HPLC analysis of the corresponding Mosher esters.

Since calculation (MM-2) for cyclohexanones 1a–e and cyclohexanols 2a–e suggests that the conformations having a group R equatorial are more stable than the axial one, four diastereoisomeric and enantioisomeric cyclohexanols are assumed to be obtained as shown in Scheme 1. However, the high e.e. of 2a, 2c and 2d reveals the formation of only two of them.

The conformations of the two isomers of 2a were determined by NMR as follows. H-C COSY measurement of (1S,3S)-2a and (1S,3R)-2a revealed that chemical shifts δ_H 2.58–2.71 and 2.17–2.33 were based on H_γ at C-3, and 4.13–4.17 and 3.60–3.71 were on H_α at C-1. NOE between H_α and H_γ was not observed in (1S,3S)-2a, but found in (1S,3R)-2a. These findings mean that H_α in (1S,3S)-2a was located at the equatorial position and H_α in (1S,3R)-2a in the axial position.

Asymmetric 1,4-addition of nitromethane to 2-cyclohexenone catalyzed by the rubidium salt of L-proline yielded (3R)-3-(nitromethyl)cyclohexanone (3R)-1a,[7] and the subsequent reduction with NaBH₄ gave a mixture of diastereoisomeric (1R,3R)-3-(nitromethyl)cyclohexanol (1R,3R)-2a' (71% e.e., $[\alpha]_D^{22}$ +3.76) and (1S,3R)-3-(nitromethyl)cyclohexanol (1S,3R)-2a' (71% e.e., $[\alpha]_D^{22}$ +3.40) (Scheme 2). By comparison of their NMR and CD spectra with those of (1S,3S)-2a (>99% e.e., $[\alpha]_D^{22}$ −5.30) and (1S,3R)-2a (>99% e.e., $[\alpha]_D^{22}$ +4.80), the absolute configurations of two isomeric products 2a in the BY-mediated reductions were confirmed.

Similarly (1R,3R)-3-(phenylsulfonyl)cyclohexanol (1R,3R)-2c' (6% e.e., $[\alpha]_D^{22}$ +0.39) and (1S,3R)-
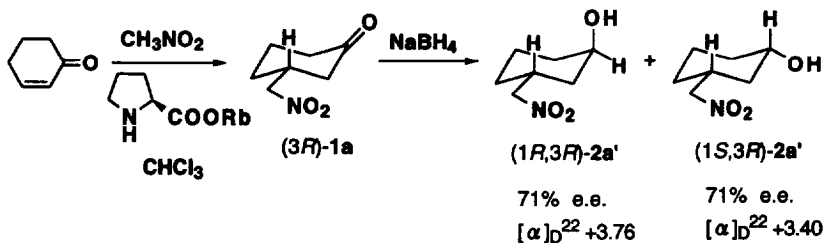
Scheme 2. Asymmetric synthesis of (1R,3R)-2a′ and (1S,3R)-2a′ by use of L-prolin Rb salt.

3-(phenylsulfonyl)cyclohexanol (1S,3R)-2c′ (6% e.e., $[\alpha]_D^{22}$ +0.12) were prepared by asymmetric 1,4-addition of benzenethiol to 2-cyclohexenone, followed by oxidation. The absolute configurations of 2b and 2c were determined by comparison of the physical data of (1R,3R)-2c′ and (1S,3R)-2c′ as described above, and furthermore, that of 2d was established from analogy with CD spectra of 2a and 2c.

The high enantioselectivity in the BY reduction means that a hydride is transferred predominantly to the re-face of the carbonyl group of 1a, 1c and 1d. The similarity of the e.e.s in (1S,3S)-2 and (1S,3R)-2 suggests that if a group R occupied the equatorial position also in the transition state, many differences between the equatorial and axial directions of approach of NADH were not detected. These results are different from those using a bulky hydride-transfer reagent. For example, on treatment with L-Selectride 1d underwent reduction to give a mixture of axial and equatorial alcohols, i.e., (1S*,3S*)-2d and (1S*,3R*)-2d in 96/4 ratio. However, at present we cannot exclude the reaction mechanisms that different enzymes may serve in the formation of (1S,3S)-2 and (1S,3R)-2, or that the kinetic resolution may arise from differentiation at the C-3 position.

In spite of the resemblance of chemical shifts of a carbonyl group in ^{13}C NMR spectra (1a–e; δ_C 208, 209, 206, 209, and 210 ppm, respectively), the stereoselectivity in the reduction of 1a–e with BY were much influenced by the remote functional group such as a nitro or a sulfonyl group, whose polarity is assumed to play an important role in binding to an enzyme. On the other hand, similar treatment of 5-phenylsulfonyl-2-pentanone with BY gave (2S)-5-phenylsulfonyl-2-pentanol 2f in 45% e.e. By comparison of e.e.s of 2d and 2f a cyclic compound may be bound to an enzyme. Interestingly, quite different results have been obtained in the lipase-catalyzed resolution of cyclohexanols containing a variety of substituents at C-3. Details on these will be reported in the near future.

Experimental

NMR spectra were recorded with a JEOL JNM-A-400 (400 MHz) or a Bruker AC-300 (300 MHz) using tetramethylsilane as an internal standard and CDCl$_3$ as a solvent. IR spectra were taken on a Shimadzu FT-IR-8600 instrument. Optical rotations were determined with a JASCO DIP-370 polarimeter, and CD spectra were obtained with a JASCO J-720W spectropolarimeter. HPLC analyses were carried out with a Shimadzu LC-6A machine equipped with a ODS, a PYE, or a chiral cellulose column (Daicel CHIRALPAX OB-H). Column chromatography was performed with Wakogel 200 silica gel, and TLC with Merck silica gel 60 F$_{254}$. Baker's yeast was obtained from the Oriental Yeast Co.

3-(Nitromethyl)cyclohexanone 1a and 3-(phenylthio)cyclohexanone 1b were readily prepared by the base-catalyzed reactions of 2-cyclohexenone with nitromethane and benzenethiol, respectively, and 3-(phenylsulfonyl)cyclohexanone 1c was obtained from 1b in a quantitative yield by oxidation with m-chloroperbenzoic acid (MCPBA).

3-[(Phenylsulfonyl)methyl]cyclohexanone 1d

To a solution of 2-cyclohexenone (1.92 g, 20 mmol) and methyl phenylsulfonylacetate (5.14 g, 24 mmol) in benzene (20 ml) was added triethylamine (0.20 g, 2 mmol) at room temperature, and

the resulting solution was refluxed for 8 h and then allowed to cool to room temperature. After the reaction was quenched with water (50 ml), the aqueous layer was separated and washed with ethyl acetate (2×80 ml). The combined organic phase were washed with brine, dried (MgSO$_4$), filtered, and evaporated to dryness. The crude product was purified by column chromatography [silica gel, eluent hexane–ethyl acetate (3:1)] to afford 3-[(methoxycarbonyl)(phenylsulfonyl)methyl]cyclohexanone **3d** (5.15 g, 83%) as a pale yellow liquid. IR v_{max} (neat/cm^{-1}) 1740, 1713 and 1305; ^{1}H NMR (CDCl$_3$) δ 1.56–2.88 (m, 9 H), 3.52 & 3.58 (s, 1 H), 3.99 & 3.92 (d, *J*=8.3 & 7.7 Hz, 1 H) and 7.57–7.91 (m, 5 H).

A suspension of **3d** (3.10 g, 10 mmol), NaCl (1.17 g, 20 mmol), and water (0.18 g, 10 mmol) in dimethylsulfoxide (50 ml) was refluxed for 8 h[6] after which it was cooled and diluted with water (200 ml). The resultant mixture was extracted with ethyl acetate (3×100 ml), and the combined extracts were washed with brine, dried (MgSO$_4$), and filtered. After removal of the solvent, purification by column chromatography [silica gel, eluent hexane–ethyl acetate (3:1)] provided **1d** (1.59 g, 63%) as a yellow solid. Mp 143°C; v_{max} (Nujol/cm^{-1}) 1709 and 1300; ^{1}H NMR (CDCl$_3$) δ 1.51–1.57 (m, 3 H), 2.01–2,59 (m, 6 H), 3.02–3.17 (m, 2 H) and 7.57–7.93 (m, 5 H). Anal. calcd for C$_{13}$H$_{16}$O$_3$S: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.93; H, 6.30; S, 12.50.

Reduction of *1a–d* with Baker's yeast (BY)

General procedure

A suspension of 3-(nitromethyl)cyclohexanone **1a** (1.57 g, 10 mmol), BY (60 g) and sucrose (15 g) in water (300 ml) was stirred at 30°C for 4 days, and then filtered. The filtrate was extracted with ethyl acetate (3×100 ml), and the combined extracts were washed with brine, dried (MgSO$_4$), filtered, and freed of solvent *in vacuo*. Column chromatography [silica gel; eluent hexane–ethyl acetate (3:1)] of the residue gave (1*S*,3*S*)-3-(nitromethyl)cyclohexanol (1*S*,3*S*)-**2a** (0.74 g, 46%) and (1*S*,3*R*)-3-(nitromethyl)cyclohexanol (1*S*,3*R*)-**2a** (0.68 g, 43%). (1*S*,3*S*)-**2a**: a pale yellow liquid; [α]$_D^{22}$ −5.30 (c=1.02, MeOH); e.e.>99%; IR v_{max} (neat/cm^{-1}) 3388 and 1552; ^{1}H NMR (CDCl$_3$) δ 1.04–1.84 (m, 8 H), 2.04 (s, 1 H), 2.58–2.71 (m, 1 H), 4.13–4.17 (m, 1 H) and 4.25–4.28 (m, 2 H). (1*S*,3*R*)-**2a**: a pale yellow liquid; [α]$_D^{22}$ +4.80 (c=1.00, MeOH); e.e.>99%; IR v_{max} (neat/cm^{-1}) 3384 and 1550; ^{1}H NMR (CDCl$_3$) δ 0.91–2.85 (m, 8 H), 2.17–2.33 (m, 1 H), 2.50 (s, 1 H), 3.60–3.71 (m, 1 H) and 4.28–4.31 (m, 2 H).

The physical data for **2b–d** obtained from **1b–d** are summarized below.

(1S,3S)-3-(Phenylthio)cyclohexanol (1S,3S)-2b

Yield 5%, a pale yellow viscous liquid, [α]$_D^{22}$ +0.48 (c=0.52, MeOH); e.e. 6%; IR v_{max} (neat/cm^{-1}) 3498; ^{1}H NMR (CDCl$_3$) δ 1.36–2.06 (m, 10 H), 4.23–4.27 (m, 1 H) and 7.53–7.88 (m, 5 H).

(1S,3R)-3-(Phenylthio)cyclohexanol (1S,3R)-2b

Yield 6%; a pale yellow viscous liquid, [α]$_D^{22}$ +1.12 (c=1.21, MeOH); e.e. 9%; IR v_{max} (neat/cm^{-1}) 3460; ^{1}H NMR (CDCl$_3$) δ 1.42–2.18 (m, 10 H), 3.35–3.48 (m, 1 H) and 7.52–7.80 (m, 5 H).

(1S,3S)-3-(Phenylsulfonyl)cyclohexanol (1S,3S)-2c

Yield 45%; a white solid, mp 75°C; [α]$_D^{22}$ −6.27 (c=1.28, MeOH); e.e.>99%; IR v_{max} (Nujol/cm^{-1}) 3508 and 1300; ^{1}H NMR (CDCl$_3$) δ 1.42–1.76 (m, 7 H), 2.00–2.14 (m, 2 H), 3.35–3.46 (s, 1 H), 4.25–4.29 (m, 1 H) and 7.54–7.89 (m, 5 H).

(1S,3R)-3-(Phenylsulfonyl)cyclohexanol (1S,3R)-2c

Yield 40%; a white solid; mp 85°C; [α]$_D^{22}$ +1.95 (c=1.02, MeOH); e.e.>99%; IR v_{max} (Nujol/cm^{-1}) 3445 and 1305; ^{1}H NMR (CDCl$_3$) δ 1.11–1.43 (m, 4 H), 1.88–2.06 (m, 4 H), 2.19–2.30 (m, 1 H), 2.39–3.00 (s, 1 H), 3.53–3.61 (m, 1 H) and 7.27–7.89 (m, 5 H).

(1S,3S)-3-[(Phenylsulfonyl)methyl]cyclohexanol (1S,3S)-2d

Yield 41%; a pale yellow solid; $[\alpha]_D^{22}$ −1.42 (c=1.00, MeOH); e.e. 90%; IR ν_{max} (Nujol/cm^{-1}) 3425 and 1300; ^{1}H NMR (CDCl$_3$) δ 1.11–1.26 (m, 2 H), 1.37–1.94 (m, 7 H), 2.41–2,52 (s, 1 H), 2.96–3.06 (m, 2 H), 4.03–4.05 (m, 1 H) and 7.55–7.96 (m, 5 H). Anal. calcd for C$_{13}$H$_{18}$O$_3$S: C, 61.39; H, 7.13; S, 12.61. Found: C, 61.63; H, 7.20; S, 12.60.

(1S,3R)-3-[(Phenylsulfonyl)methyl]cyclohexanol (1S,3R)-2d

Yield 38%; a pale yellow solid; $[\alpha]_D^{22}$ +1.25 (c=1.06, MeOH); e.e. 95%; IR ν_{max} (Nujol/cm^{-1}) 3327 and 1300; ^{1}H NMR (CDCl$_3$) δ 0.92–1.36 (m, 4 H), 1.74–2.19 (m, 6 H), 3.04 (d, J=6.1 Hz, 2 H), 3.47–3.63 (m, 1 H) and 7.55–7.93 (m, 5 H).

Synthesis of (1R,3R)-3-(nitromethyl)cyclohexanol (1R,3R)-2a′ and (1S, 3R)-3-(nitromethyl)cyclohexanol (1S,3R)-2a′

According to literature procedures,[6] (3R)-3-(nitromethyl)cyclohexanone (3R)-1a was prepared from 2-cyclohexenone and nitromethane in the presence of the Rb salt of L-proline. To a stirred solution of (3R)-1a (0.78 g, 5 mmol) in ethanol (25 ml) was added NaBH$_4$ (0.08 g, 2 mmol) at room temperature and the resulting mixture was stirred for 6 h. After it had been treated with saturated aqueous NaCl (100 ml), the aqueous phase was extracted with ethyl acetate (2×100 ml), and the combined organic phase was washed with brine, dried (MgSO$_4$), filtered and concentrated. Subsequent column chromatography [silica gel, eluent hexane–ethyl acetate (3:1)] provided (1R,3R)-2a′ (0.15 g, 19%) and (1S,3R)-2a′ (0.62 g, 78%). (1R,3R)-2a: a pale yellow liquid; $[\alpha]_D^{22}$ +3.76 (c=1.02, MeOH); e.e. 71%; the same IR and ^{1}H NMR data as those of (1S,3S)-2a. (1S,3R)-2a′: a pale yellow liquid; $[\alpha]_D^{22}$ +3.40 (c=1.02, MeOH); e.e. 71%; the same IR and ^{1}H NMR data as those of (1S,3R)-2a.

Synthesis of (1R,3R)-3-(phenylsulfonyl)cyclohexanol (1R,3R)-2c′ and (1S,3R)-3-(phenylsulfonyl) cyclohexanol (1S,3R)-2c′

(3R)-3-(Phenylthio)cyclohexanone (3R)-1b was synthesized from 2-cyclohexenone and benzenethiol in a similar fashion to that described above. To a stirred solution of (3R)-1b (0.82 g, 4 mmol) in dichloromethane (50 ml) was added MCPBA (80% purity, 1.94 g, 9 mmol) at room temperature and the resulting mixture was stirred for 10 h before being quenched with water (100 ml). The aqueous phase was separated and extracted with dichloromethane (80 ml). The combined organic phase was washed with saturated aqueous NaHCO$_3$, brine, dried (MgSO$_4$), filtered and concentrated. Crude (3R)-3-(phenylsulfonyl)cyclohexanone (3R)-1c (0.95 g) was used without further purification.

Treatment of (3R)-1c (0.95 g, 4 mmol) with NaBH$_4$ in a similar fashion to that described above gave a mixture of (1R,3R)-2c′ (0.15 g, 16%) and (1S,3R)-2c′ (0.70 g, 74%). (1R,3R)-2c′: $[\alpha]_D^{22}$ +0.39 (c=1.56, MeOH); e.e. 6%; the same IR and ^{1}H NMR data as those of (1S,3S)-2c. (1S,3R)-2c′: $[\alpha]_D^{22}$ +0.12 (c=1.32, MeOH); e.e. 6%; the same IR and ^{1}H NMR data as those of (1S,3R)-2c.

Determination of the enantiomeric excess (e.e.)

Treatment of the alcohol 2a–d with (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA chloride) and 4-dimethylaminopyridine in the customary manner gave the corresponding MTPA esters in quantitative yields. The enantiomeric excesses of the alcohols were determined by HPLC measurements of the MTPA esters.

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