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A Highly Enantioselective Conjugate Reduction of 3-Arylinden-1-ones Using Bakers' Yeast for the Preparation of (*S*)-3-Arylindan-1-ones†

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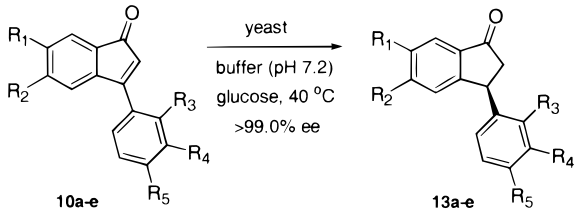
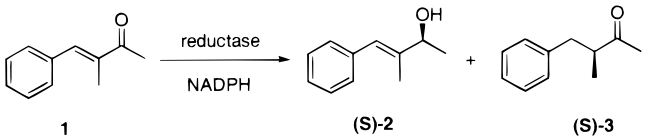
ABSTRACT



The bakers' yeast reduction of 3-(1,3-benzodioxol-5-yl)-6-propoxy-1*H*-inden-1-one 4 has been shown to give (*S*)-3-(1,3-benzodioxol-5-yl)-2,3-dihydro-6-propoxy-1*H*-indan-1-one 6 in 65% yield with high enantioselectivity (>99.0% ee), a key intermediate for the synthesis of the endothelin receptor antagonist SB 217242. In addition, the substituted 3-arylinden-1-ones 10a–e gave equally high enantioselectivity for the 3-arylindan-1-one products 13a–e. Mechanistic studies of the reaction indicate the operative pathway to be an asymmetric conjugate reduction, wherein the hydride transfer from NAD(P)H occurs from the *Re*-face of the indenone substrate.

The reduction of ketones or aldehydes employing microorganisms has been an area of active interest, and in this regard, bakers' yeast (*Saccharomyces cerevisiea*) has been the favored microbe on the basis of its ready availability, safety, and low cost.[1] Few investigations have been reported on the extension of these studies to α,β-unsaturated carbonyl compounds, and in this area some of the results have been controversial. For example, Fuganti[2] carried out a pioneering study on β-phenyl-substituted enones using bakers' yeast which resulted in the isolation of the (*S*)-allylic alcohol and only minor amounts of the saturated ketone. In subsequent work, they studied the reduction of 3-methyl-4-phenyl-buten-2-one **1**, and again the formation of allylic alcohol **(S)-2** was observed in 15% yield (Scheme 1).[3] Upon reexamination of the same reaction, first by Sakai[4] and later by Kawai,[5] each found that the reduction takes place at the α,β-unsaturated linkage, affording mostly the saturated ketone **(S)-3**. In

Scheme 1



† This paper is dedicated to the memory of Prof. Jack T. Edward of McGill University.

(1) (a) Servi, S. *Synthesis* **1990**, 1. (b) Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49.

(2) Fuganti, C.; Grasselli, P.; Servi, S.; Spreafico, F.; Zirotti, C.; Casati, P. J. *Chem. Res. Synop.* **1984**, 112.

(3) Fuganti, C.; Grasselli, P.; Servi, S.; Spreafico, F.; Zirotti, C.; Casati, P. J. *Chem. Res. Synop.* **1985**, 22.

(4) Sakai, T.; Matsumoto, S.; Hidaka, S.; Imajo, N.; Tsuboi, S.; Utaka, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3473.

(5) Kawai, Y.; Saitou, K.; Hida, K.; Hai-Dao, H.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2633.

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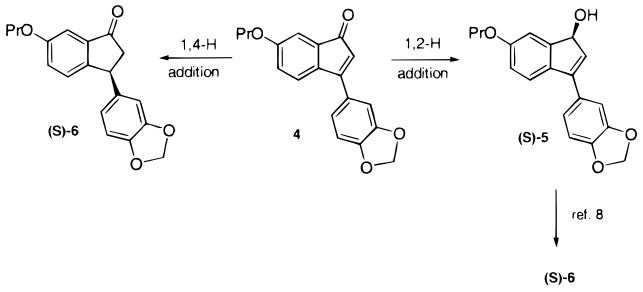
particular, Kawai has shown that a reductase isolated from bakers' yeast gives the saturated ketone **(S)-3** with good enantioselectivity and yield (80% ee, 71%).[6] In addition, Kawai showed through labeling studies that delivery of hydride at the β-position was derived from NAD(P)H with the hydrogen at the α-position presumably coming from water or a proton source within the reductase enzyme. Kawai also observed that the overall addition of hydrogen to the enone olefin occurred in a *trans* stereochemical fashion.

In our work, we required the chiral indanone **(S)-6** in connection with the synthesis of endothelin receptor antagonist SB 217242 currently in clinical development at Smith-Kline Beecham.[7] While the compound could be readily prepared by a catalytic hydride reduction using the Itsuno−Corey oxazoborolidine method to **(S)-5** followed by a formal 1,3-hydride rearrangement to yield **(S)-6**,[8] we became interested in the possibility of applying bakers' yeast as the reductant for this transformation (Scheme 2). It is well

Scheme 2

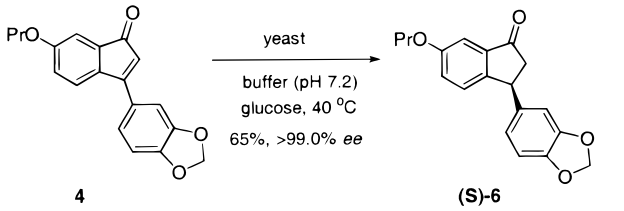


documented that bakers' yeast reductions of prochiral ketones typically deliver the (*S*)-alcohol often with high enantioselectivity, the absolute stereochemistry we desired for indenol **5**. In addition, we felt substrate **4** would offer an opportunity to investigate the bakers' yeast reduction of 3-arylinden-1-ones, which to date have not been studied in the literature in this manner, and also potentially address the issue of a 1,2- versus 1,4-reduction in this class of compounds.[9]

Initially we attempted the reduction of indenone **4** by dissolving the substrate (1.25 g) in EtOH (12.5 mL) and adding the solution to a mixture of bakers' yeast (6.0 g) and glucose (5.0 g) in deionized water (250 mL). The suspension was then stirred vigorously for 2 days at 40 °C with no control of pH. Interestingly, the yeast reduction afforded the indanone **(S)-6** with excellent enantioselectivity (>99.0% ee) and the desired absolute stereochemistry but not the expected alcohol product **(S)-5**. In addition, the yield was fairly low (25%) and further evaluation of the reaction mixture showed the remaining mass balance to be that of the starting enone.

Noting a significant drop in the pH (pH 7 → pH 4) during the course of the reaction, the reduction was repeated using a pH probe and automated titrant apparatus for the addition of 1 M NaOH. With the yeast mixture maintained at pH 7.2, the reduction afforded complete conversion of **4** after 24 h at 40 °C (Scheme 3). After purification by flash

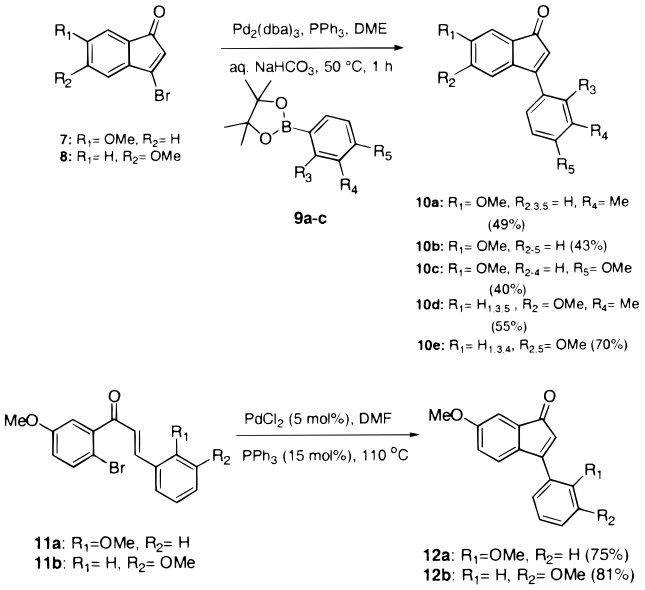
Scheme 3



chromatography, the indanone **(S)-6** was delivered in 65% yield with >99.0% ee! In comparison, the best enantioselectivity we observed for the oxazoborolidine approach was 94% ee for **(S)-6**.[8]

Due to the excellent results obtained for the bakers' yeast reduction of **4**, we decided to investigate the bakers' yeast reduction of other indenone substrates. Subsequently, two approaches were developed for the preparation of variously substituted 3-arylindenones (Scheme 4). In our initial approach, compounds **10a**−**e** were prepared by a Suzuki cross-coupling reaction of the respective pinacol boronate esters **9a**−**c**[10] with the 3-bromoinden-1-ones **7** and **8** which were prepared using conditions developed by Joullie.[11] Initially, the Suzuki coupling proved to be difficult due to the base

Scheme 4



(6) Kawai, Y.; Hayashi, M.; Inaba, Y.; Saitou, K.; Ohno, A. *Tetrahedron Lett.* **1998**, *39*, 5225.

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(8) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550.

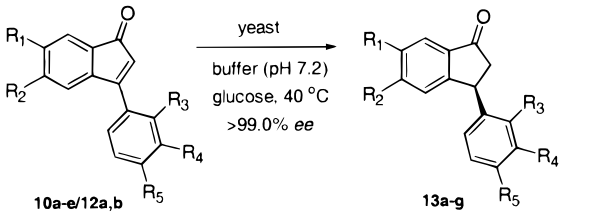
(9) This work was disclosed in part at Chiral USA 99, San Francisco, CA, May 2, 1999.

sensitivity of the bromide at elevated temperatures. Eventually we determined that the cross-coupling reaction progressed well when using aqueous $NaHCO_3$ with $Pd_2(dba)_3$/PPh_3 in DME at 50 °C to give yields of the 3-arylindenones in the 40−70% range.[12,13]

Attempts to prepare 3-arylindenones with electron-withdrawing groups (Cl, Br, NO_2) at the C(5)- or C(6)-position of the 3-bromoindenone using the Suzuki methodology failed to give appreciable amounts of the desired product. In the examples investigated, the base and thermal instability of the bromide and indenone product appeared to be responsible for the poor results. Similar results were observed when attempting to couple 2-furanboronic acid and 2-thiopheneboronic acid with bromides **7** and **8**. Consequently, the remaining indenone substrates **12a**,**b** were prepared using a previously reported procedure developed in our laboratories.[8]

The enantioselective conjugate reduction of 3-aryl-inden-1-ones using bakers' yeast appears to be a general transformation for this class of compounds (Scheme 5).[14] Using our

Scheme 5



(S)-13	R_1	R_2	R_3	R_4	R_5	Yield
a	OMe	H	H	OMe	H	81
b	OMe	H	H	Me	H	79
c	H	OMe	H	Me	H	61
d	OMe	H	OMe	H	H	84
e	OMe	H	H	H	H	70
f	OMe	H	H	H	OMe	52
g	H	OMe	H	H	OMe	50

standard conditions, all of our substrates gave high enantioselectivities (>99.0% ee) and good to excellent yields (50−84%) for the indanone products (**13a**−**g**).[15] Interestingly, changing the placement of the electron-donating groups on either aryl ring had little effect on the reaction outcome. For example, a significant electronic influence on enantioselectivity has been observed in numerous bakers' yeast reductions of prochiral substrates;[1,6] however, placement of a methoxy group at the C(5)- or C(6)-position did not change the stereoselectivity (**13f**, **13g**), nor did changing the substituents on the C(3)-phenyl ring.

A steric influence at the C(3)-position of the indenone substrate was also not observed. For example, a methoxy group in the ortho or meta positions of the C(3)-phenyl ring did not adversely affect the yield or enantioselectivity of the reduction, i.e., **13a** and **13d** were isolated in 81% and 84% yields, respectively.[16]

Realizing that an asymmetric conjugate reduction of indenone **4** was a viable reaction pathway, we wanted to determine the potential for rearrangement of **(S)-5** when subjected to the yeast reduction conditions. We reasoned that if a fast 1,3-hydrogen rearrangement occurred under these conditions, then only very low levels of **(S)-5** would be observed during the course of the reaction. On the other hand, if indenol **(S)-5** was stable to the yeast reaction conditions, then a conjugate hydride addition of the indenone system was most likely the operative mechanism.

To this end, the indenol **(S)-5** (94% ee) was subjected to the yeast reduction conditions at 40 °C. After 24 h, the indanone **(S)-6** was not observed by HPLC or TLC. In addition, **(S)-5** was completely recovered and the enantiomeric purity of **(S)-5** remained unchanged. In our subsequent experiment, racemic **5** was added to the yeast reduction of indenone **4** (5% added relative to **4**). After 20 h, complete consumption of **4** was achieved and the indanone **(S)-6**

(10) The pinacol boronate esters were prepared according to the procedure described by Tour: Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723.

(11) Heffner, R. J.; Joullie, M. M. *Synth. Commun.* **1991**, *21*, 2231.

(12) **General Procedure for the Preparation of 3-Arylinden-1-ones (10a−e)**: To a thoroughly degassed round-bottomed flask charged with DME (8.5 mL) were added triphenylphosphine (0.05 g, 0.189 mmol) and tris(dibenzylideneacetone)dipalladium (0.04 g, 0.042 mmol), and the resulting yellow solution was stirred under nitrogen for 1.5 h at room temperature. To this solution were added the β-bromoindenone (1.0 g, 4.2 mmol), aryl pinacol borate ester (4.6 mmol, 1.1 equiv), and a saturated $NaHCO_3$ solution (2.6 mL), and the mixture was heated to 50 °C for 1 h. The reaction mixture was then cooled to 25 °C, diluted with H_2O (25 mL), and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with a saturated NaCl solution (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to furnish **10a**−**e** after flash chromatography (SiO_2, 1:9 EtOAc/hexane).

(13) **Data for 10d**: mp 77−79 °C; ^{1}H NMR ($CDCl_3$) δ 7.46−7.25 (5 H, m), 6.88 (1H, d, J = 2.2 Hz), 6.65 (1H, dd, J = 2.2, 8.0 Hz), 5.96 (1H, s), 3.82 (3H, s), 2.41 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.72, 163.88, 160.78, 146.64, 138.70, 132.99, 131.10, 128.80, 127.93, 125.13, 124.54, 124.47, 124.39, 111.22, 110.23, 55.72, 21.43. Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.57; H, 5.63.

(14) **General Procedure for the Preparation of 3-Arylindan-1-ones Using Bakers' Yeast (13a−g)**: To a 250 mL round-bottomed flask charged with an aqueous phosphate buffer solution (70 mL, pH 7.2) warmed to 40 °C were added bakers' yeast (6.43 g) and α-D-glucose (5.14 g, 28.5 mmol). The 3-arylinden-1-one (1.0 g) was then dissolved in a minimum amount of hot EtOH (4−6 mL) and added to the reaction mixture. The reaction was stirred for 24 h, and a neutral pH was maintained through the addition of 1 mL aliquots of 1 M NaOH (10−15 mL). After 24 h, the reaction mixture was cooled to room temperature, EtOH (100 mL) added, the mixture filtered through Celite to remove the yeast, and the filtrate extracted with 2:1 EtOAc/acetone (4 × 150 mL). The organic layer was washed with H_2O (200 mL) and a saturated NaCl solution (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to furnish **13a**−**g** after flash chromatography (SiO_2, 1:9 EtOAc/hexane).

(15) The enantiomeric purity of **13a**−**g** was determined on a Chiralpak OD column, 9:1 hexane/IPA, 1 mL/min, 230 nm.

(16) **Data for 13c**: mp 115−116 °C; $[\alpha]_D$= −14.4°(c = 0.500, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.73 (1H, d, J = 7.8 Hz), 7.17 (1H, d, J = 7.6 Hz), 7.05 (1H, d, J = 7.6 Hz), 6.92 (3H, m), 6.65 (1H, d, J = 1.8 Hz), 4.45 (1H, dd, J = 3.7, 8.0 Hz), 3.77 (3H, s), 3.17 (1H, dd, J = 8.0, 19.0 Hz), 2.64 (1H, dd, J = 3.8, 19.0 Hz), 2.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 204.06, 165.59, 160.97, 143.64, 138.57, 130.23, 128.77, 128.29, 127.71, 125.04, 124.69, 115.93, 109.84, 55.63, 47.10, 44.42, 21.39. Anal. Cald for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.66; H, 6.42. **Data for 13g**: mp 91−93 °C; $[\alpha]_D$ = −26.7°(c = 0.375, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.72 (1 H, d, J = 8.5 Hz), 7.03 (2 H, d, J = 8.7 Hz), 6.92 (1 H, d, J = 8.5 Hz), 6.83 (2 H, d, J = 8.7 Hz), 6.63 (1 H, s), 4.44 (1 H, dd, J = 3.7, 8.0 Hz), 3.78 (3 H, s), 3.77 (3 H, s), 3.17 (1 H, dd, J = 8.1, 19.0 Hz), 2.61 (1 H, dd, J = 3.7, 19.0 Hz); ^{13}C NMR ($CDCl_3$) δ 204.06, 165.58, 161.18, 158.58, 135.74, 130.17, 128.57, 124.99, 115.91, 114.30, 109.72, 55.60, 55.26, 47.23, 43.69. Anal. Cald for $C_{17}H_{16}O_3$: C, 76.1; H, 6.01. Found: C, 75.83; H, 6.19.

obtained with >99.0% ee along with complete recovery of racemic **5**. Both of these experiments strongly suggest that indenol **(S)-5** is not an intermediate in the yeast reduction of **4**. Further confirmation was obtained when racemic **5** was treated with a phosphate buffer (pH 8.0) in EtOH and heated to 40 °C for 24 h. The indanone **6** was not observed by HPLC, confirming that neutral pH (or slightly higher) was not basic enough to promote the rearrangement of **(S)-5** to **(S)-6**.

From these experiments, we conclude the yeast reduction of **4** is a highly enantioselective conjugate reduction of the α,β-unsaturated indenone system. Reductases or dehydrogenases isolated from bakers' yeast have been shown to reduce prochiral ketones with high enantioselectivity.[5,6,17] The reductase enzyme requires a cofactor, NAD(P)H, which is the actual hydride source. In our simplified model, we propose the reductase enzyme complexes with the *Si* face of the indenone substrate allowing for *Re* face attack of NAD(P)H (Figure 1). We assume the overall hydrogen addition occurs with *trans* stereochemistry as observed by Kawai.[6]

In summary, a highly enantioselective transformation for the synthesis of indanone **(S)-6** has been accomplished using a bakers' yeast reduction. The method is an attractive alternative to the previously published procedure developed for the synthesis of the endothelin receptor antagonist SB 217242. In addition, the biotransformation is an effective method for the preparation of enantiomerically pure electron-rich (*S*)-3-arylindan-1-ones. Our current efforts are now focused on preparing 3-alkylinden-1-ones and studying their behavior under similar reaction conditions.

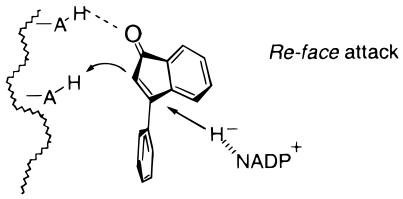


Figure 1.

Acknowledgment. We thank the Analytical Sciences department of SmithKline Beecham for the analytical support of this research and SB for the financial support of M.P. and A.K.

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