Enzymatic Resolution of a C_2 Symmetric Diol Derived from *p*-Benzoquinone: Synthesis of (+)- and (−)-Bromoxone

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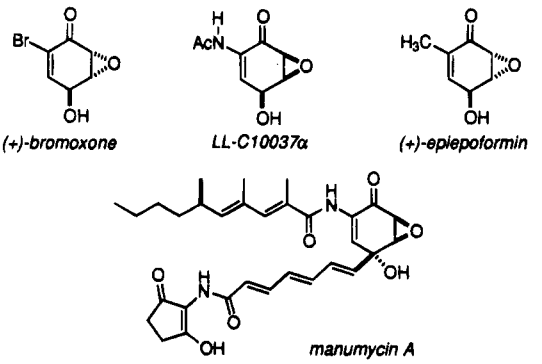
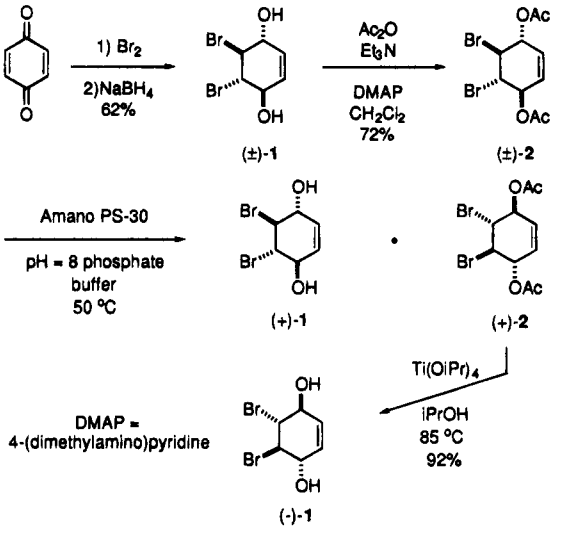
Our laboratory is engaged in a program of synthesis of enantiopure, densely-functionalized, bioactive targets.[1] Characteristics of our strategy are the use of simple achiral starting materials, such as cyclopentadiene, benzene, and cycloheptatriene, and the use of biocatalysis as a key step for the introduction of absolute stereochemistry.[2] In this context, the readily available, inexpensive *p*-benzoquinone and the bioactive natural products of the epoxyquinol class attracted our interest as starting material and targets, respectively. Epoxyquinol natural products, typified by (+)-bromoxone,[3a] LL-C10037α,[3b] (+)-epiepoformin,[3c] and the more complex manumycin A[3d] (Chart 1), exhibit antifungal and antitumor properties. (+)-Bromoxone and its acetate were isolated from marine acorn worms (*Phylum Hemichordata*, order Enteropneusta) by Higa and co-workers in 1987.[3a] The absolute and relative stereochemistry were determined via X-ray analysis of the acetate. The acetylated derivative displayed activity toward P388 cells (IC_{50} = 10 ng/mL). Only one synthesis of bromoxone has appreared, and that is in racemic form.[4] Herein we describe chemoenzymatic routes to both bromoxone enantiomers from *p*-benzoquinone.

The C_2 symmetric diol (±)-**1**, prepared via bromination/reduction of *p*-benzoquinone,[5] was converted into the known diacetate (±)-**2**.[6] The hydrolysis of (±)-**2** (7 g) with crude *Pseudomonas cepacia* lipase (Amano PS-30) (7 g) in pH 8 phosphate buffer at 50 °C over 16 h was found to be quite effective; the diacetate (+)-**2** (26%, ≥98% ee) and the diol (+)-**1** (47%, 90% ee) were obtained (Scheme 1).[7,8]

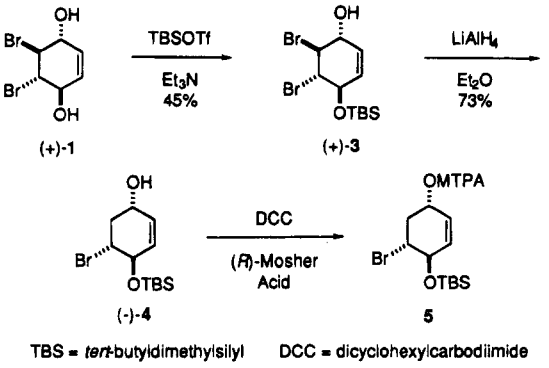
Chart 1 Epoxyquinol Natural Products



Scheme 1



Scheme 2



The enantiomeric excess of the diol (+)-**1** was determined by transformation to the Mosher ester derivative **5** as depicted in Scheme 2. The diol (+)-**1** was converted into the mono-TBS-protected diol (+)-**3** (TBSOTf/Et_3N), and the subsequent dibromo alcohol (+)-**3** was selectively debrominated to the monobromo alcohol (−)-**4** ($LiAlH_4$/Et_2O). Esterification of the alcohol (−)-**4** with the (*R*)-Mosher acid (DCC, DMAP, CH_2Cl_2) furnished the ester derivative **5** (Scheme 2). Analysis of the ester **5** derived from (±)-**1** and enantioenriched (+)-**1** indicated an enantiomeric excess of ≥90% (500 MHz, ^1H NMR) for the latter; one recrystallization from hexanes/acetone raised the enantiomeric excess to ≥98%. Similarly, the diacetate (+)-**2** was converted into the diol (−)-**1** using Seebach's transesterification method (Scheme 1),[9] and the diol (−)-**1** was converted into its Mosher ester as described for (+)-**1**. The optical purity of the diol (−)-**1** was

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(2) Enzymatic asymmetrization: Johnson, C. R.; Harikrishnan, L. S.; Golebiowski, A. *Tetrahedron Lett.* **1994**, *35*, 7735 and references therein. Enzymatic resolution: Johnson, C. R.; Sakaguchi, H. *SynLett* **1992**, 813. Sundram, H.; Golebiowski, A.; Johnson, C. R. *Tetrahedron Lett.* **1994**, *35*, 6975.

(3) (a) Higa, T.; Okuda, R. K.; Severns, R. M.; Scheuer, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063. (b) Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518. (c) Kamikubo, T.; Ogasawara, K. *Tetrahedon Lett.* **1995**, *36*, 1685. (d) Schröder, K.; Zeeck, A. *Tetrahedron Lett.* **1973**, 4995.

(4) Gautier, E. C. L.; Lewis, N. J. McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759.

(5) Altenbach, H.-J.; Stegelmeier, H.; Vogel, E. *Tetrahedron Lett.* **1978**, 3333.

(6) Seçen, H.; Maras, A.; Sütbeyaz, Y.; Balci, M. *Synth. Commun.* **1992**, *22*, 2613.

(7) Some monoacetate was also formed in this reaction. The configuration of the monoacetate corresponded with that of the diacetate (+)-**2**. This was a result of some hydrolysis of the slower reacting diacetate (+)-**2**.

(8) Similar conditions, but using less PS-30 lipase (1.4 g), gave the diacetate (+)-**2** (44%, 86% ee) and the diol (+)-**1** (40%, ≥98% ee). By varying the amount of enzyme used, either enantiomer of the diol, (+)-**1** or (−)-**1** (via deprotection of the diacetate (+)-**2**), could be obtained in optically pure form (≥98% ee) directly from the enzymatic hydrolysis reaction. (+)-**1**: mp 164–166 °C; $[\alpha]_D$ +45.8 (*c* 1.20, acetone). (−)-**1**: $[\alpha]_D$ −46.9 (*c* 1.40, acetone). (+)-**2**: mp 107–109 °C, $[\alpha]_D$ +11.7 (*c* 1.05, CH_2Cl_2).

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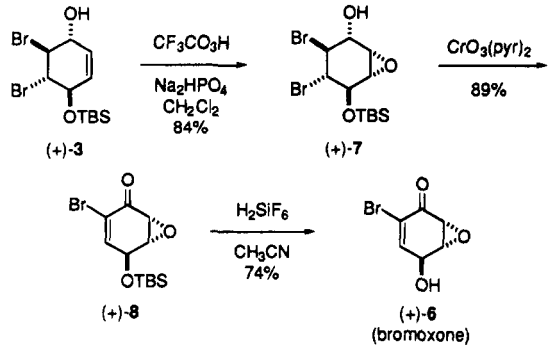
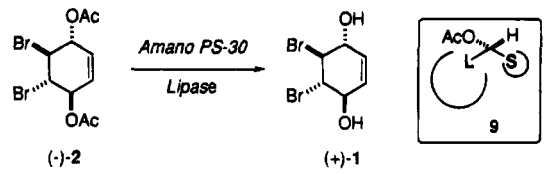
Scheme 3



found to be ≥98%. The same enantiomeric excess of the diacetate (+)-**2** was also determined via chiral shift analysis [(+)-Eu(hfc)$_3$, $CDCl_3$].

Alcohol (+)-**3** was subjected to buffered CF_3CO_3H (CH_2Cl_2/0 °C) which gave the *syn*-epoxide **7** as a single diastereomer in 84% yield (Scheme 3).[10] Oxidation/elimination of epoxide (+)-**7** to the bromoenone (+)-**8** proceeded cleanly in 89% yield with CrO_3(pyridine)$_2$.[11] Lastly, deprotection of the TBS ether in (+)-**8** was accomplished using DeShong's protocol (H_2SiF_6/CH_3CN),[12] which furnished (+)-bromoxone (**6**) in 74% yield.[13] The melting point of synthetic (+)-**6** was slightly higher than that reported for natural (+)-**6** (138–139 °C vs 123–127 °C);[3a] this difference is most likely due to slight impurities in the isolated material.[14] The $[\alpha]_D$ reported for natural (+)-bromoxone (**6**) was +220 (*c* 0.09, $CHCl_3$). We found

Scheme 4



that synthetic (+)-**6** was only sparingly soluble in $CHCl_3$; we recorded the rotation of our synthetic (+)-**6** in acetone and found $[\alpha]_D$ +193 (*c* 2.50, acetone). The optical purity of (+)-bromoxone (**6**) was determined to be ≥99% ee by chiral HPLC analysis.[15] In an analogous fashion, (−)-**3** was converted into (−)-bromoxone (**6**) (mp 137–139 °C; $[\alpha]_D$ −188 (*c* 1.85, acetone).

Since the absolute configuration of (+)-bromoxone (**6**) had been determined via X-ray analysis of its acetate, conversion of (+)- and (−)-**1** into (+)- and (−)-bromoxone (**6**), respectively, established which enantiomer of the diacetate (±)-**2** was hydrolyzed by the enzyme. The diacetate (−)-**2** with the configuration (1*R*,2*S*,3*S*,4*R*) was preferentially hydrolyzed (Scheme 4). This is consistent with the simple model **9** proposed for enzymatic action of *Pseudomonas cepacia* (Amano PS-30) toward secondary alcohols.[16]

Thus, (+)- and (−)-bromoxone (**6**) were synthesized in a very concise fashion from the enzymatically resolved diols (+)- and (−)-**1** in 25% and 29% overall yields, respectively. These diols should find use in the construction of more complex targets. Studies along these lines are in progress.

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Supporting Information Available: Experimental procedures and compound characterization data (20 pages).

JO9514883

(9) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.: Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(10) For *syn* selective epoxidations of 2-cyclohexen-1-ol with CF_3CO_3H see: McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

(11) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(12) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

(13) Synthetic (+)-**6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (dd, 1 H, *J* = 4.5, 9.0 Hz), 3.68 (dd, 1 H, *J* = 1.5, 3.5 Hz), 3.85 (ddd, 1 H, *J* = 1.5, 2.5, 3.5 Hz), 4.75 (dddd, 1 H, *J* = 1.5, 1.5, 5.5, 9.0 Hz), 7.14 (dd, 1 H, *J* = 2.5, 5.5 Hz); ^{13}C NMR (125 MHz, 10% $(CD_3)_2CO$ in $CDCl_3$) δ 53.40, 57.58, 64.43, 122.72, 144.69, 186.63; HRMS (EI) calcd for $C_6H_5BrO_3$ (M^+) 203.9422, found 203.9428.

(14) Only 0.6 mg of (+)-**6** was isolated (0.001% based on dry weight of marine worm).

(15) Chiralcel OB: elution with iPrOH/hexane (1/9); 0.5 mL/min; 260 nm; 27 min (+)-**6**; 40 min (−)-**6**.

(16) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656. Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597.