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Chemoenzymatic Synthesis of 2-Bromo-6-Hydroxy-3-Methoxy-2-Cyclohexen-1-one

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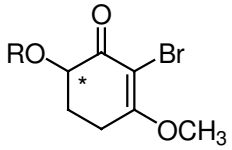
A chemoenzymatic synthesis of 2-bromo-6-hydroxy-3-methoxy-2-cyclohexen-1-one starting from cyclohexane-1,3-dione is reported. Manganese(III) acetate-mediated acetoxylation followed by the enzyme-mediated hydrolysis of α'-acetoxy enone affords hydroxy-enone **5** and acetoxy enone **4** with high enantiomeric excesses in good yields.

Key Words: Chemoenzymatic synthesis, cyclic polyoxo cyclohexenones, manganese(III) acetate, acetoxylation.

Introduction

The synthesis of optically active cyclic enones like **4** and **5** is of significant importance since they are important structural units in many biologically active compounds and are important synthons for the asymmetric synthesis of natural products.[1–7]



4, R=Ac
5, R=H

Several studies have been reported on the racemic and asymmetric synthesis of various hydroxy cyclic enones;[8–13] however, there is no work on the synthesis of 2-bromo-6-hydroxy-3-methoxy-2-cyclohexen-1-one to the best of our knowledge. We describe herein an efficient chemoenzymatic route to the 4-step synthesis of 2-bromo-6-hydroxy-3-methoxy-2-cyclohexen-1-one and 6-acetoxy-2-bromo-3-methoxy-2-cyclohexen-1-one, starting from cyclohexane-1,3-dione and using $Mn(OAc)_3$ methodology.

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In the literature, there are several papers about the $Mn(OAc)_3$ mediated direct acetoxylation and acyloxylation of enones and aromatic ketones followed by the enzymatic and fungus mediated resolution of acyloxy enones to obtain enantiomerically pure α-hydroxy ketones.[14−20] Since chiral 2-bromo-6-hydroxy-3-methoxy-2-cyclohexen-1-one has a multi-functional nature, it can take part in several stereoselective transformations and this led us to explore a chemoenzymatic method for obtaining it in its enantiomerically pure forms.

Experimental

All reagents were of commercial quality and reagent quality solvents were used without further purification. NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40-63 μm). Enantiomeric excesses were determined by HPLC analysis using a ThermoQuest (TSP) LC-MS equipped with an appropriate chiral column. GC/MS spectra were recorded on a ThermoQuest (TSP) Trace GC-2000 Series equipped with ThermoQuest Finnigan Multi Mass (EI, 70 eV).

Synthesis of 3-methoxy-2-cyclohexen-1-one (2). 1.0 M $TiCl_4$ solution in CH_2Cl_2 (0.50 mL, 0.50 mmol) was added at room temperature to a well-stirred solution of the cyclohexane-1,3-dione (2.0 g, 17.8 mmol) in methanol (35 mL). The reaction mixture was then stirred for an additional 30 min. After that, the mixture was filtered, concentrated and purified by flash column chromatography (3:1, EtOAc / *n*-Hexane) to afford the desired product as a yellow oily liquid (1.91 g, 15.1 mmol, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.97 (p, J = 6.39 Hz, 2H, CH_2), 2.31 (t, J = 6.47 Hz, 2H, CH_2), 2.39 (t, J = 6.22 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 5.33 (s, 1H, CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 28.7, 36.6, 55.4, 102.2, 178.2, 198.9. Spectroscopic data agree with the literature.[21]

Synthesis of 2-bromo-3-methoxy-2-cyclohexen-1-one (3). A solution of 3-methoxy-2-cyclohexen-1-one (1.9 g, 15.1 mmol) in dichloroethane (10 mL), maintained between 5 and 10 °C, was treated with NBS (2.7 g, 15.1 mmol) in portions over 0.5 h. After 0.5 h the mixture was filtered and the filtrate evaporated. The residue was dissolved in toluene (40 mL) and rapidly washed with cold water (2 x 20 mL). The organic layer was dried over $MgSO_4$ and evaporated to 5 mL, cooled to 0 °C and the product was filtered off as a white crystal (2.47 g, 12.1 mmol, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.06 (p, J = 6.43 Hz, 2H, CH_2), 2.52 (t, J = 6.42 Hz, 2H, CH_2), 2.71 (t, J = 5.97 Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 26.7, 36.6, 56.3, 102.9, 172.3, 190.6. Spectroscopic data agree with the literature.[22]

Synthesis of (±)-6-acetoxy-2-bromo-3-methoxy-2-cyclohexen-1-one (*rac*-4). A solution of 2-bromo-3-methoxy-2-cyclohexen-1-one (2.5 g, 12.1 mmol), $Mn(OAc)_3$ (9.7 g, 36.2 mmol) and benzene (120 mL) was heated under reflux for 52 h. After cooling, the reaction mixture was first filtered and then washed with sat. $NaHCO_3$ solution. The mixture was then dried over $MgSO_4$, concentrated and purified by flash column chromatography (1:1, EtOAc / *n*-Hexane) to yield the desired product as a red oily liquid (2.38 g, 9.03 mmol, 75%).

General procedure for the enzyme-catalyzed hydrolysis of (±)-6-acetoxy-2-bromo-3-methoxy-2-cyclohexen-1-one. Lipase (200-300 mg) was dissolved in 30 mL of potassium phosphate buffer (20 mM, pH 7.0) and added to a solution of the ***rac*-4** (1 mmol) in DMSO (3 mL) and the reaction mixture left to stir at room temperature. The reaction was monitored by TLC and when maximum conversion was reached the reaction was terminated by filtration. The unreacted acetate **4** and the product **5**

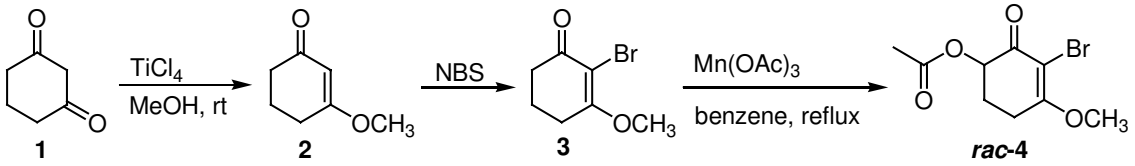
were separated by flash column chromatography (2:1, EtOAc / *n*-Hexane).

6-Acetoxy-2-bromo-3-methoxy-2-cyclohexen-1-one (4). Red oily liquid (118 mg, 0.45 mmol, 45%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.07 (m, 1H, H-5), 2.24 (m, 1H, H-5), 2.10 (s, 3H, CH_3), 2.68 (m, 1H, H-4), 2.82 (m, 1H, H-4), 3.90 (s, 3H, OCH_3), 5.25 (dd, J = 7.58, 4.97 Hz, 1H, H-6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.7, 24.8, 25.9, 56.4, 71.7, 101.2, 169.5, 171.3, 185.5; GC/MS (m/z) 264 (M^+), 220, 192, 183, 160, 141, 123, 111, 97, 80, 68, 52, 43, 42.

2-Bromo-6-hydroxy-3-methoxy-2-cyclohexen-1-one (5). White solid (90.6 mg, 0.41 mmol, 41%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.82 (ddd, J = 5.42, 5.36, 5.24 Hz, 1H, H-5), 2.39 (m, 1H, H-5), 2.62 (m, 1H, H-4), 2.80 (m, 1H, H-4), 3.63 (s, 1H, OH), 3.92 (s, 3H, OCH_3), 4.03 (dd, J = 5.45, 5.06 Hz, 1H, H-6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.2, 28.4, 56.3, 71.3, 99.2, 172.5, 192.1; GC/MS (m/z) 222 (M^+), 220, 179, 178, 175, 149, 97, 81, 69, 68, 67.

Results and Discussion

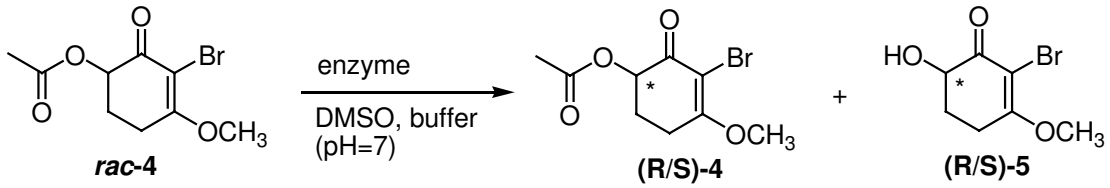
Commercially available cyclohexane-1,3-dione **(1)** was converted to the 3-methoxy-2-cyclohexen-1-one **(2)** and then to the 2-bromo-3-methoxy-2-cyclohexen-1-one **(3)** using procedures reported in the literature.[21,22] Then, oxidation of the enone **3** with 3 equivalents of manganese(III) acetate in benzene was performed to obtain the α'-acetoxy enone ***rac*-4** in 75% yield after purification by column chromatography (Scheme 1).



Scheme 1

Lipase type enzymes are used extensively for the synthesis of enantiomerically pure compounds via the resolution of racemic mixtures. The high stereoselectivity in organic media and their low cost make them very useful catalysts for enantioselective resolution.

In connection with published studies related to biocatalyst-mediated reactions, we tested several enzymes for screening the enantioselective hydrolysis of the acetoxy enone ***rac*-4** (Scheme 2). The hydrolysis of ***rac*-4** was investigated using 4 readily available enzymes: PLE (*Pig Liver Esterase*), *Amano* PS, CCL (*Candida Cylindracea Lipase*), and PPL (*Porcine Pancreatic Lipase*). Only *Amono* PS showed activity, with 50% conversion within 4 h. PLE, CCL and PPL did not show any activity toward the substrate. Careful monitoring of the reaction with TLC furnished the acetoxy enone (99% ee, 45% yield) and hydroxy enone (96% ee, 41% yield). Ee values were determined by HPLC analysis using a chiral column (Chiralcell OB column, UV detection at 254 nm, eluent: Hexane/2-propanol = 60:40, flow 0.5 mL.min^{-1} (Figures 1-3).



Scheme 2

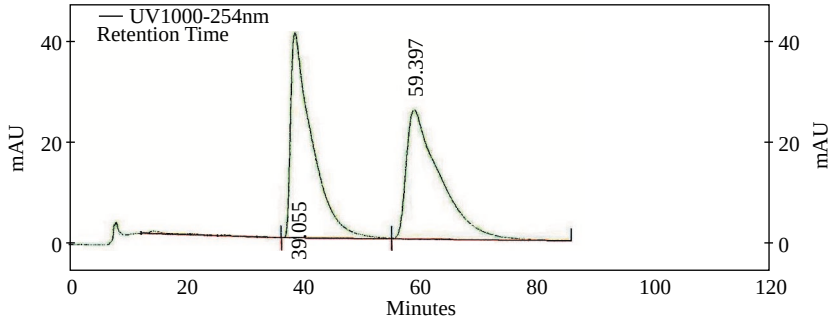


Figure 1. HPLC chromatogram of racemic α'-acetoxy-2-bromo-3-methoxy-2-cyclohexen-1-one.

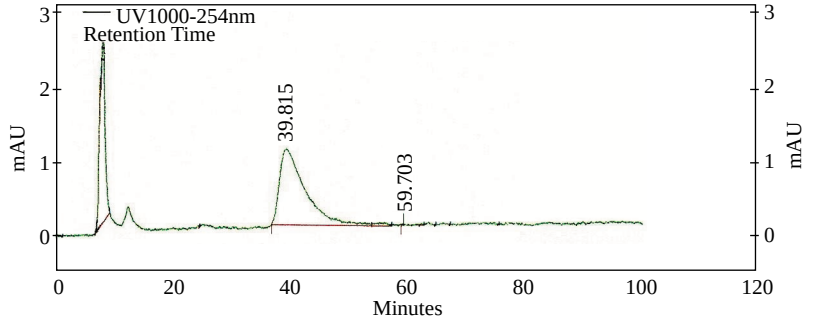


Figure 2. HPLC chromatogram of chiral α'-acetoxy-2-bromo-3-methoxy-2-cyclohexen-1-one.

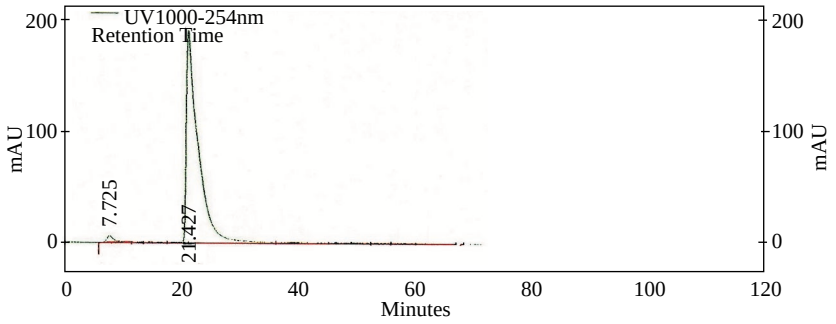


Figure 3. HPLC chromatogram of chiral α'-hydroxy-2-bromo-3-methoxy-2-cyclohexen-1-one.

In a typical experiment for enzymatic hydrolysis, the racemic acetoxy enone **4** was dissolved in DMSO, a phosphate buffer (pH 7.0) then added and the mixture stirred at room temperature in the presence of the enzyme. The reaction was monitored by TLC analysis. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to provide acetoxy enone **4** and hydroxy enone **5**.

The results show that manganese(III) acetate-mediated acetoxylation of an enone followed by enzyme-mediated hydrolysis of the acetoxy group provides hydroxy enone **5** and acetoxy enone **4** with high enantiomeric excesses in good chemical yields. Thus, highly functionalized, polyoxygenated chiral enones, **4** and **5**, with potential applications as synthetic intermediates have been successfully synthesized.

Acknowledgments

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