First Isolation of Disubstituted *cis*-5,6-Dihydro-1,10-phenanthrolines. Lipase-Mediated Resolution of *cis*- and *trans*-Phenoxy Alcohol Isomers and Assignment of Absolute Stereochemistry via CD and NMR Spectroscopy

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ABSTRACT 5,6-Dihydro-1,10-phenanthrolines can display axial and central chirality. In conjunction with the ligating properties of the diimino moiety, this class of compounds is of great interest to applications in supramolecular chemistry. We report the first preparation of *cis*-5,6-dihydro-1,10-phenanthroline derivatives by reacting triphenyl borate with the corresponding epoxide precursor. We found that solvent and temperature choice determined the stereoselectivity of the epoxide opening giving rise to the *cis* (14:1 dr) or *trans* (99:1 dr) product. Racemates of each stereoisomeric mixture, *cis*- and *trans*-phenoxy alcohol, were separated via highly enantioselective transesterifications with lipase PSCI from *Burkholderia cepacia* (97% *ee*, $E >$ 200). Stereochemical assignments were carried out using CD and X-ray analyses in conjunction with NMR studies of α-methoxy-α-(trifluoromethyl)phenylacetic acid and α-methoxyphenylacetic acid esters. *Chirality 24:245–251, 2012.*

KEY WORDS: axial chirality; epoxide opening; triphenyl borate; solvent effect; enzymatic resolution; transesterification; Mosher ester

INTRODUCTION

Epoxides are important building blocks because they readily react with numerous nucleophiles. Most reactions proceed with *anti*-selectivity while only few reports describe *syn*-selective openings. Examples include the direct reaction of epoxides with nitric oxide,[1,2] the hydrofluorination of aryl epoxides using $BF_3{\cdot}OEt_2$,[3] the epoxide opening with aryl borates,[4,5] the aluminum-, boron-, or zinc-mediated opening of glycal and 2,3-dihydrofuran epoxides,[6–9] and the tin-mediated palladium catalyzed etherification of vinyl epoxides.[10] *syn*-Adducts are isolated indirectly by inverting the alcohol of the *anti* product. Methods include the Mitsunobu reaction[11–19] and the substitution of sulfonates.[20–24] The preparation of *cis*-1-amino-2-indanol is a notable industrial example and was carried out independently by researchers at Merck and Sepracor. Each synthesis entailed the conversion of indene oxide to its *cis* amino alcohol but involved either a Ritter reaction or a benzoxazole intermediate to control the stereochemistry.[25–27]

1,10-Phenanthroline derivatives have found use in organic, inorganic, medicinal, and biochemistry[28–30] including their application in chiral catalysis,[31–33] bioaffinity assays,[34] medicine[35–40] and as sensors.[41–44] B-ring-modified 5,6-dihydro-1,10-phenanthrolines have unique structural properties and can display axial chirality and/or central chirality; the latter typically referring to the presence of one or more stereogenic centers in the absence of an axis or plane.[45–47] A few derivatives were recently prepared via epoxide-opening with oxygen- and nitrogen nucleophiles,[48–51] and via intramolecular Ullmann coupling of two ethyl-bridged pyridine rings.[52] Until now no optically active *cis*-5,6-dihydro derivatives that contain axial and central chirality have been reported.

EXPERIMENTAL SECTION

Commercial chemicals and reagents in 98+ purity were used without further purification. Amano lipases were purchased from Aldrich. Solvents were acquired as reagent grade for reactions and as high-performance liquid chromatography (HPLC) grade for analytical measurements. 1,10-Phenanthroline-5,6-epoxide was synthesized according to the literature.[53–56] Melting points were determined in open capillaries using a Thomas-Hoover Unimelt instrument. NMR spectra were recorded using a 400 MHz Jeol Eclipse nuclear magnetic resonance instrument. IR spectra were obtained from Bruker Equinox 55 and Perkin–Elmer 1710 Fourier Transform Infrared Spectrometers. Elemental analyses were carried out by Numega Resonance Labs, San Diego, CA. HPLC data were collected using a Shimadzu instrument consisting of a column (Chiralcel® OD-H), solvent delivery system (LC-20AT), detector (SPD-20A), autosampler (SIL-20A), and degasser (DGU-20A5). CD spectra were recorded in spectroscopy grade methanol with a Jasco J-815 CD Spectrometer using a 0.1-cm path cell at 20°C.

Determination of Enantiomeric Excess and E-Values

The enantiomerically enriched alcohols and acetates were chromatographically separated (SiO_2; $CHCl_3$/1% MeOH) and analyzed by chiral

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HPLC using a 70:30 mixture of isopropanol and hexane as eluent at a 0.5 ml/min flow rate and UV–vis detection at 266 nm. Enantiomeric excess was obtained by comparing the area percentage of each enantiomer. *E*-values were calculated from the enantiomeric excess of the substrate (ee_S) and the product (ee_P).[57]

Preparation of (±)-trans-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-ol ((±)-trans-5,6-Dihydro-5-hydroxy-6-phenoxy-1,10-phenanthroline) [(±)-trans-Alcohol 2]

To a solution of 1,10-phenanthrolin-5,6-epoxide (1.00 g, 5.10 mmol) in acetonitrile (1 ml) was added a solution of triphenyl borate (2.96 g, 10.19 mmol) in acetonitrile (1 ml) under an argon atmosphere. The reaction mixture was stirred at room temperature for 3 days after which aqueous NaOH (10%, 10 ml) and chloroform (100 ml) were added, the organic layer was separated and the aqueous layer extracted twice with chloroform (50 ml). The combined organic layer was washed twice with aqueous NaOH (10%, 10 ml), dried with Na_2SO_4, filtered, and concentrated. The product was isolated after column chromatography (SiO_2; chloroform/1% methanol) in 58–74% yield (0.86–1.10 g) (*trans*:*cis* ratio = >99:1). M.p. 215°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.76–8.73 (2H, m), 8.09 (1H, app d, J = 7.7 Hz), 7.75 (1H, app d, J = 7.7 Hz), 7.37 (1H, dd, J = 4.8 Hz, J = 7.7 Hz), 7.34–7.24 (3H, m), 7.06–7.01 (3H, m), 5.53 (1H, d, J = 10.6 Hz), 5.26 (1H, d, J = 10.3 Hz), 3.29 (1H, br s); ^{1}H-NMR (400 MHz, CD_3OD) δ: 8.69–8.67 (2H, m), 8.07 (1H, app d, J = 7.7 Hz), 7.87 (1H, app d, J = 7.3 Hz), 7.49 (1H, dd, J = 4.8 Hz, J = 7.7 Hz), 7.41 (1H, dd, J = 4.9 Hz, J = 7.9 Hz), 7.31–7.26 (2H, m), 7.08 (2H, app d, J = 7.7 Hz), 6.99 (1H, app t, J = 7.3 Hz), 5.56 (1H, d, J = 8.0 Hz), 5.11 (1H, d, J = 8.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.0, 150.4, 150.4, 150.2, 149.7, 134.0, 133.8, 132.9, 131.5, 130.1, 124.4, 124.0, 122.4, 115.6, 80.0, 71.3; FTIR (KBr, pellet) ν/cm^{-1}: 3131, 3063, 2889, 1595, 1584, 1565, 1492, 1433, 1420, 1232, 1172, 1123, 1057, 1036, 1008, 854, 795, 751, 714, 691; analysis calculated for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65 Found: C, 74.52; H, 4.51; N, 9.45.

Preparation of (±)-cis-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-ol ((±)-cis-5,6-Dihydro-5-hydroxy-6-phenoxy-1,10-phenanthroline) [(±)-cis-Alcohol 3]

To a solution of 1,10-phenanthrolin-5,6-epoxide (1.00 g, 5.10 mmol) in dimethylformamide (DMF) (5 ml) was added a solution of triphenyl borate (1.77 g, 6.12 mmol) in DMF (5 ml) under argon atmosphere. The reaction mixture was stirred at 80°C for 3 days after which the solvent was evaporated and aqueous NaOH (10%, 10 ml) and chloroform (150 ml) were added. After stirring the mixture for 1 h at room temperature the organic layer was separated and the aqueous layer extracted twice with chloroform (50 ml). The combined organic layer was washed with aqueous NaOH (10%, 10 ml), dried with Na_2SO_4, filtered, and concentrated. The product was isolated via column chromatography (SiO_2; chloroform/1% methanol) in 35% yield (520 mg) (*cis*:*trans* ratio = 14:1). M.p. 222°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.85–8.80 (2H, m), 7.99 (1H, app d, J = 7.7 Hz), 7.64 (1H, app d, J = 7.7 Hz), 7.40 (1H, dd, J = 4.8 Hz, J = 7.7 Hz), 7.32–7.23 (3H, m), 7.05 (1H, app t, J = 7.3 Hz), 6.95 (2H, app d, J = 7.7 Hz), 5.46 (1H, d, J = 4.0 Hz), 5.15 (1H, d, 3.3 Hz), 2.74 (1H, br s); ^{1}H-NMR (400 MHz, CD_3OD) δ: 8.71–8.66 (2H, m), 8.05 (1H, app d, J = 7.7 Hz), 7.87 (1H, app d, J = 7.7 Hz), 7.50 (1H, dd, J = 4.8 Hz, J = 7.7 Hz), 7.38 (1H, dd, J = 4.8 Hz, J = 7.7 Hz), 7.29–7.24 (2H, m), 7.03 (2H, app d, J = 7.7 Hz), 6.98 (1H, app t, J = 7.3 Hz), 5.62 (1H, d, J = 3.7 Hz), 5.14 (1H, d, J = 3.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.2, 151.0, 150.4, 150.3, 149.8, 136.5, 136.1, 132.9, 130.0, 129.7, 124.6, 123.9, 123.3, 118.2, 78.3, 69.0; FTIR (KBr, pellet) ν/cm^{-1} 3145, 2911, 2848, 1590, 1563, 1487, 1423, 1341, 1212, 1160, 1132, 1104, 1089, 1069, 1035, 970, 948, 873, 822, 773, 756, 727, 697; analysis calculated for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65 Found: C, 74.39; H, 5.20; N, 9.63.

General Procedure for Lipase Catalyzed Kinetic Resolution of Racemic Phenoxy Alcohols

A solution of racemic phenoxy alcohol (100 mg) in acetonitrile (5 ml) and vinyl acetate (20 ml) was placed in a 50-ml round bottomed flask. Amano lipase PSCI (500 mg) was added and the flask was closed with a glass stopper and sealed with Parafilm®. The suspension was stirred at 50°C. After 50% substrate conversion (monitored by ^{1}H-NMR) the reaction mixture was filtered through Celite, the solvent removed in vacuo and the residue purified by column chromatography (SiO_2; chloroform/1% methanol).

Characterization of Enantiomerically Enriched Phenoxy Alcohols

(*S,S*)-*trans*-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-ol ((*S,S*)-*trans*-5,6-dihydro-5-hydroxy-6-phenoxy-1,10-phenanthroline) [(+)-(*S,S*)-*trans*-alcohol 2]. Forty-six milligrams (46%) yield; *ee* = 97%; $[\alpha]_D^{25}$ = +74.5° (*c* 1, methanol); chiral HPLC analysis: t_R = 13.0 min ((*S,S*)-enantiomer) and t_R = 10.8 min ((*R,R*)-enantiomer); CD: (*c* = 3.44 ×·10^{-4} mol/l).

(5*S*,6*R*)-*cis*-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-ol((5*S*,6*R*)-*cis*-5,6-dihydro-5-hydroxy-6-phenoxy-1, 10-phenanthroline) [(−)-(5*S*,6*R*)-*cis*-alcohol 3]. Forty-eight milligrams (48%) yield; *ee* = 97%; $[\alpha]_D^{25}$ = −82.2° (*c* 1, methanol); chiral HPLC analysis: t_R = 19.1 min ((5*S*,6*R*)-enantiomer) and t_R = 16.2 min ((5*R*,6*S*)-enantiomer); CD: (*c* = 6.89·× 10^{-4} mol/l).

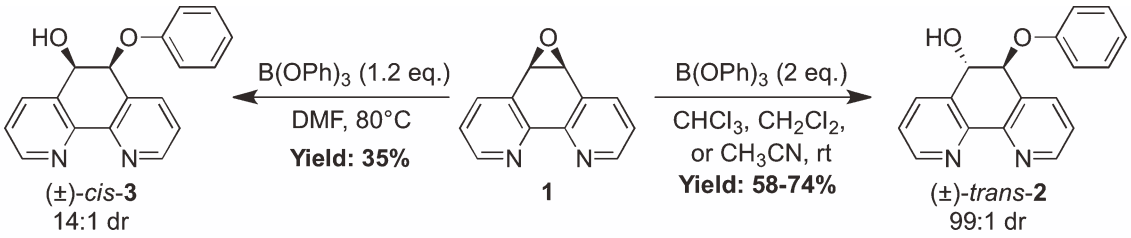
Hydrolysis of (−)-(5*R*,6*S*)-*cis*-acetate **5** using NH_4OH/MeOH afforded (+)-(5*R*,6*S*)-*cis*-alcohol **3** in quantitative yield. *ee* = 97%, $[\alpha]_D^{25}$ = +84.3° (*c* 1, methanol).

Characterization of Enantiomerically Enriched Phenoxy Acetates

(*R,R*)-*trans*-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-yl acetate ((*R,R*)-*trans*-5,6-dihydro-5-acetoxy-6-phenoxy-1,10-phenanthroline) [(−)-(*R,R*)-*trans*-alcohol 4]. Fifty-five milligrams (48%) yield, *ee* = 97%; $[\alpha]_D^{25}$ = −232.9° (*c* 1, methanol); m.p. 124°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.85–8.83 (2H, m), 7.79 (1H, app d, J = 7.7 Hz), 7.69 (1H, app d, J = 7.7 Hz), 7.36–7.29 (4H, m), 7.06–6.99 (3H, m), 6.46 (1H, d, J = 7.7 Hz), 5.61 (1H, d, J = 7.7 Hz), 2.01 (3H, s); ^{1}H-NMR (400 MHz, CD_3OD) δ: 8.75–8.73 (2H, m), 7.92 (1H, app d, J = 7.7 Hz), 7.87 (1H, app d, J = 7.7 Hz), 7.49–7.44 (2H, m), 7.32–7.27 (2H, m), 7.06–6.99 (3H, m), 6.37 (1H, d, J = 6.2 Hz), 5.80 (1H, d, J = 6.6 Hz), 1.96 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.4, 158.1, 151.1, 151.0, 150.7, 150.4, 135.8, 135.7, 130.2, 129.9, 129.4, 124.3, 124.2, 122.5, 116.4, 76.6, 71.2, 20.9; FTIR (KBr, pellet) ν/cm^{-1} 3054, 3001, 2962, 2924, 2852, 1726, 1583, 1488, 1455, 1428, 1372, 1344, 1292, 1242, 1172, 1127, 1079, 1019, 967, 890, 753, 715, 697; analysis calculated for $C_{20}H_{16}N_2O_3$·1/4$CHCl_3$: C, 67.15; H, 4.52; N, 7.73 Found: C, 66.78; H, 4.81; N, 7.59; chiral HPLC analysis: t_R = 14.1 min ((*S,S*)-enantiomer) and t_R = 41.3 min ((*R,R*)-enantiomer). CD: (*c* = 3.01·× 10^{-4} mol/l).

(5*R*,6*S*)-*cis*-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-yl acetate ((5*R*,6*S*)-*cis*-5,6-dihydro-5-acetoxy-6-phenoxy-1,10-phenanthroline) [(−)-(5*R*,6*S*)-*cis*-acetate 5]. Fiftysix milligrams (49%) yield, *ee* = 97%; $[\alpha]_D^{25}$ = −103.8° (*c* 1, methanol); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.89–8.84 (2H, m), 7.95–7.91 (2H, m), 7.41–7.30 (4H, m), 7.06 (1H, app t, J = 7.3 Hz), 7.00 (2H, app d, J = 7.7 Hz), 6.23 (1H, d, J = 3.7 Hz), 5.67 (1H, d, J = 3.6 Hz), 1.99 (3H, s); ^{1}H-NMR (400 MHz, CD_3OD) δ: 8.76–8.70 (2H, m), 8.02–7.96 (2H, m), 7.50–7.45 (2H, m), 7.33–7.28 (2H, m), 7.06 (2H, app d, J = 7.7 Hz); 7.01 (1H, app t, J = 7.3 Hz), 6.31 (1H, d, J = 3.6 Hz), 5.90 (1H, d, J = 3.6 Hz), 1.96 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.7, 157.7, 151.6, 151.2, 150.5, 150.1, 137.5, 134.7, 130.7, 130.0, 128.8, 124.3, 124.2, 122.9, 117.1, 75.3, 69.5, 21.0; FTIR (KBr, pellet) ν/cm^{-1} 3062, 2961, 2926, 2854, 1748, 1587, 1568, 1491, 1422, 1372, 1234, 1039, 796, 753, 694; analysis calculated for $C_{20}H_{16}N_2O_3$·1/5$CHCl_3$: C, 68.11; H, 4.58; N, 7.86 Found: C, 67.81; H, 4.72; N, 7.57; chiral HPLC analysis: t_R = 17.6 min ((5*S*,6*R*)-enantiomer) and t_R = 30.6 min ((5*R*,6*S*)-enantiomer); CD: (*c* = 4.42·× 10^{-4} mol/l).

Acetylation of (−)-(5*S*,6*R*)-*cis*-alcohol **3** using $Mg(ClO_4)_2$ (0.1 eq.) and acetic anhydride (1.2 eq.) afforded (+)-(5*S*,6*R*)-*cis*-acetate **5** in quantitative yield. *ee* = 97%, $[\alpha]_D^{25}$ = +101.3° (*c* 1, methanol).



Scheme 1. Opening of epoxide **1** with triphenyl borate.

Single-Crystal Structure Analysis

Monocrystals of (±)-*cis*-alcohol **3** were obtained via recrystallization from methanol. X-ray quality crystals of (±)-*trans*-acetate **4** were grown in chloroform via slow solvent evaporation. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 721749 [(±)-*trans*-acetate **4**] and CCDC 796394 [(±)-*cis*-alcohol **3**]. Copies of the data can be obtained, free of charge, upon request to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac. Uk].

RESULTS AND DISCUSSION

Preparation of Racemic cis- and trans-5,6-Dihydro-6-phenoxy-1,10-phenanthrolin-5-ol

We previously found that magnesium perchlorate and alumina catalyzed the ring-opening of epoxide **1** with nitrogen nucleophiles, whereas oxygen nucleophiles required a stronger Lewis acid, ytterbium(III) triflate.[48,51] Reactions proceeded with a variety of alcohols in 81–99% yield but attempts to use phenol were unsuccessful. We herewith report the first isolation of phenoxy alcohol derivatives, which was accomplished through the conversion of substrate **1** with triphenyl borate. Moreover, our findings revealed that the stereoselectivity was highly temperature and solvent dependent. Optimized conditions required the use of two equivalents of triphenyl borate in acetonitrile at room temperature to afford the *trans*-product in 58–74% yield and 99:1 dr. A high *cis*-selectivity (14:1) was observed when 1.2 eq. of reagent were employed in DMF at 80°C (Scheme 1).

Control experiments were carried out by heating a solution of (±)-*trans*-phenoxy alcohol **2** in DMF or acetonitrile at 80°C for 2 days. No isomerization to (±)-*cis*-alcohol **3** was observed leading to the conclusion that the products are thermodynamically stable.

Lipase-Catalyzed Resolution

Recent reports have focused on the enzymatic resolution of a variety of *trans*-5,6-dihydro-1,10-phenanthroline derivatives using two commercially available lipases, *Pseudomonas fluorescens* (AK) and *Burkholderia cepacia* (PSCI).[49–51] Our previous studies showed that PSCI provides 4–5 times faster conversion rates with similar enantioselectivities in comparison to lipase AK.[51] Therefore, lipase PSCI was our first choice for the kinetic resolution of *trans*- and *cis*-phenoxy alcohols **2** and **3** (Schemes 2 and 3).

Schemes 2 and 3 illustrate that PSCI promotes the resolution of both diastereomers with excellent enantioselectivities ($E > 200$), giving rise to all compounds in 97% *ee*.

Conformational Analysis and Assignment of Absolute Configuration

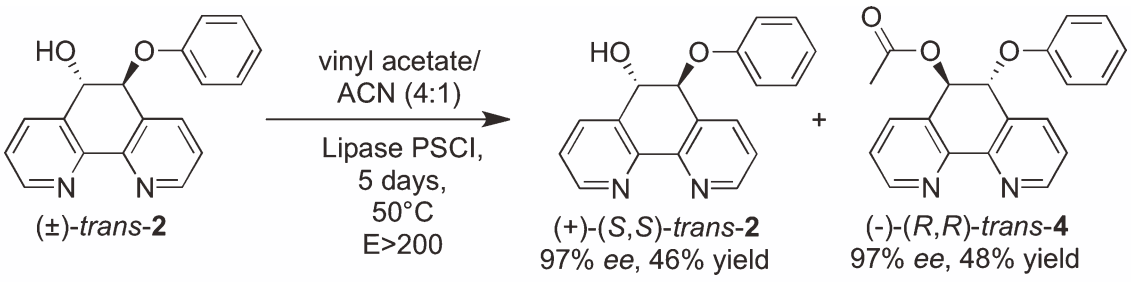
The stereochemistry of all synthesized products was assigned by a combination of X-ray crystallography, ^{1}H-NMR, and CD spectroscopy.

We observed that mainly two CD bands are important for the stereochemical assignment of 5,6-dihydro-1,10-phenanthrolines. The 230–280 nm region is associated with the helicity of the cyclohexadiene moiety (B-ring, Fig. 1), whereas the 210–235 nm region correlates with the helicity of the biaryl chromophore (Fig. 2). A positive cotton effect (*P*) is expected for a right-handed twist and a negative cotton effect (*M*) for a left-handed twist (Fig. 2).

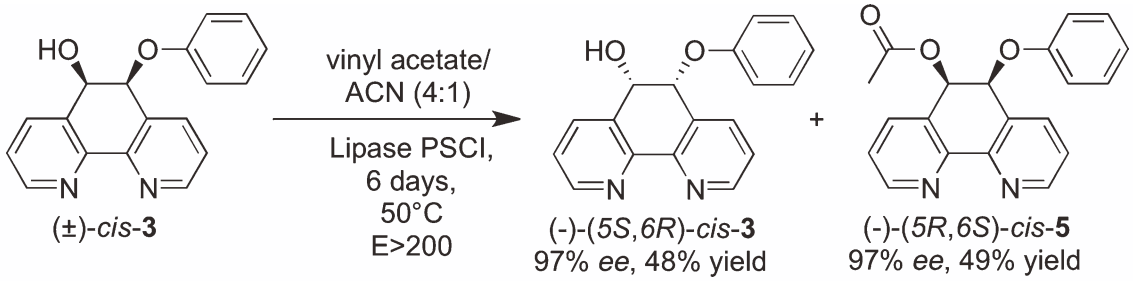
The coupling constants of the benzylic hydrogens, *J*(5H,6H), of the (+)-*trans*-alcohol **2** and (−)-*trans*-acetate **4** were used to identify the preferred conformation as diequatorial (*J*(5H,6H) = 8.1 Hz) and diaxial (*J*(5H,6H) = 6.4 Hz), respectively (Table 1). X-ray analysis of acetate **4** corroborated our NMR spectroscopy findings for the solid state (Fig. 3).

The CD spectrum of (−)-*trans*-acetate **4** is dominated by the negative band at 217 nm, which correlates with the *M*-helicity of the bipyridyl chromophore, and the 251 nm band that is indicative of the *M*-helicity in the *cis*-diene moiety (Fig. 3). These results clearly support a (5*R*,6*R*) configuration.

The absolute configuration of (+)-*trans*-alcohol **2** should be exactly the opposite of (−)-*trans*-acetate **4**. The (5*S*,6*S*) assignment for compound **2** was confirmed by a negative



Scheme 2. Enzymatic kinetic resolution of (±)-*trans*-phenoxy alcohol **2**.



Scheme 3. Enzymatic kinetic resolution of (±)-*cis*-phenoxy alcohol **3**.

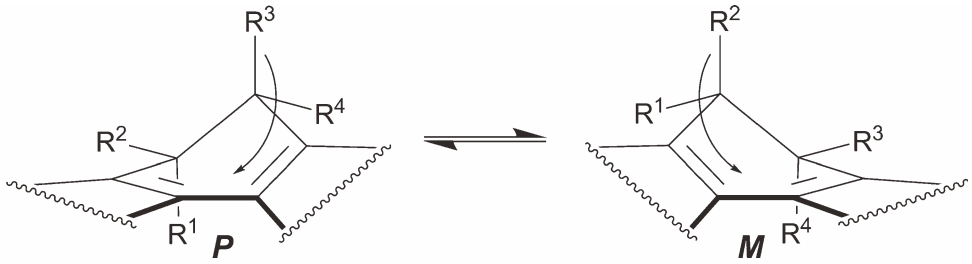


Fig. 1. Helical chirality of the cyclohexadiene moiety.

band in the 210–230 nm region after taking into account a preferential diequatorial conformation of both B-ring substituents. Furthermore, the positive band at 247 nm showed the opposite sign of the 251 nm band of (−)-*trans*-acetate **4** (Fig. 3). It is known that the low energy CD band of compounds with two axial hydrogens can have opposite sign CD bands and disagree with the helicity of the diene moiety.[60,61] Our findings are supported by studies on related *trans*-9,10-dihydrophenanthrenes by Gawroński *et al.* who utilized CD analyses to deduce both the absolute configuration and the conformation of molecules. The authors found that *trans*-9,10-dihydrophenanthrenes displayed a positive band in the 230–280 nm region and assigned the (*S*,*S*)-configuration.[59]

^{1}H-NMR spectroscopy failed to reveal the conformational preferences of (−)-*cis*-alcohol **3** and (−)-*cis*-acetate **5** (Table 1), but the crystal structure of the former showed that the smaller hydroxyl group assumes the pseudo-equatorial position while the bigger phenoxy group occupies the pseudo-axial position to avoid allylic strain with H7 (Fig. 4). The CD spectrum of (−)-*cis*-alcohol **3** showed two negative bands (*M*) in the 210–230 nm and 230–280 nm region, which is in excellent agreement with the (5*S*,6*R*)-configuration. Our results correlate well with CD studies of the structurally related (+)-(*R*)-5-methyl-5,6-dihydro-1,10-phenathroline.[62]

The CD spectrum of (−)-*cis*-acetate **5** also exhibited a negative band at 210–230 nm indicating *M*-helicity of the bipyridyl moiety. This can be explained by the interconversion of the phenoxy and acetyl group between the pseudo-axial and the pseudo-equatorial positions, which have similar *A*-values (Fig. 4).

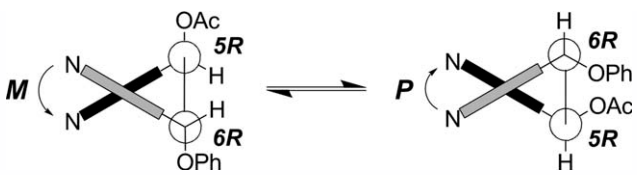


Fig. 2. Helicity of (*R*,*R*)-*trans*-5,6-dihydro-6-phenoxy-1,10-phenanthrolin-5-yl acetate.

Assignment of Absolute Configuration Using NMR Spectroscopy of MTPA and MPA Esters

In order to confirm the absolute configuration of (+)-*trans*-alcohol **2** and (−)-*cis*-alcohol **3** after enzymatic resolution, we prepared the α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) and α-methoxyphenylacetic acid (MPA) esters,[63] assigned the proton signals by a combination of ^{1}H, NOE, and COSY NMR experiments and applied the Mosher correlation model that was recently reviewed by Riguera and coworkers.[64] For both the *cis*- and *trans*-phenoxy-esters, we found that the positive and negative $\Delta\delta(^1H)$ values are regularly dispersed on the left and the right side of the MTPA and MPA plane, respectively (see Supporting Information). Negative Δδ values were calculated for the protons in C2, C3, and C4 position whereas positive values were determined for the C6, C7, C8, and C9 position in addition to the phenoxy group. Only the C9 proton of the *cis*-phenoxy MTPA esters has with −0.01 a slightly negative $\Delta\delta^{SR}(^1H)$ value. Since this value is so close to zero and this proton is far away from the chiral center and the shielding effect of the MTPA

TABLE 1. Summary of stereochemical assignment[a]

Compound	(+)-*trans*-**2**	(−)-*trans*-**4**	(−)-*cis*-**3**	(−)-*cis*-**5**
CD Band (230–280 nm)	*M*	*M*	*M*	N/A
CD Band (210–230 nm)	*P*	*M*	*M*	*M*
J(5H,6H)/Hz in CD_3OD	8.1	6.4	3.5	3.6
Absolute configuration/ conformation	(5*S*,6*S*) diequatorial	(5*R*,6*R*) diaxial	(5*S*,6*R*)	(5*R*,6*S*)

[a] J(5H,6H) ∼ 7 Hz for an equal population of the diaxal and diequatorial conformations; J(5H,6H) < 7 for a preference for the diaxial conformation; J(5H,6H) > 7 for dominant diequatorial conformation.[58,59]

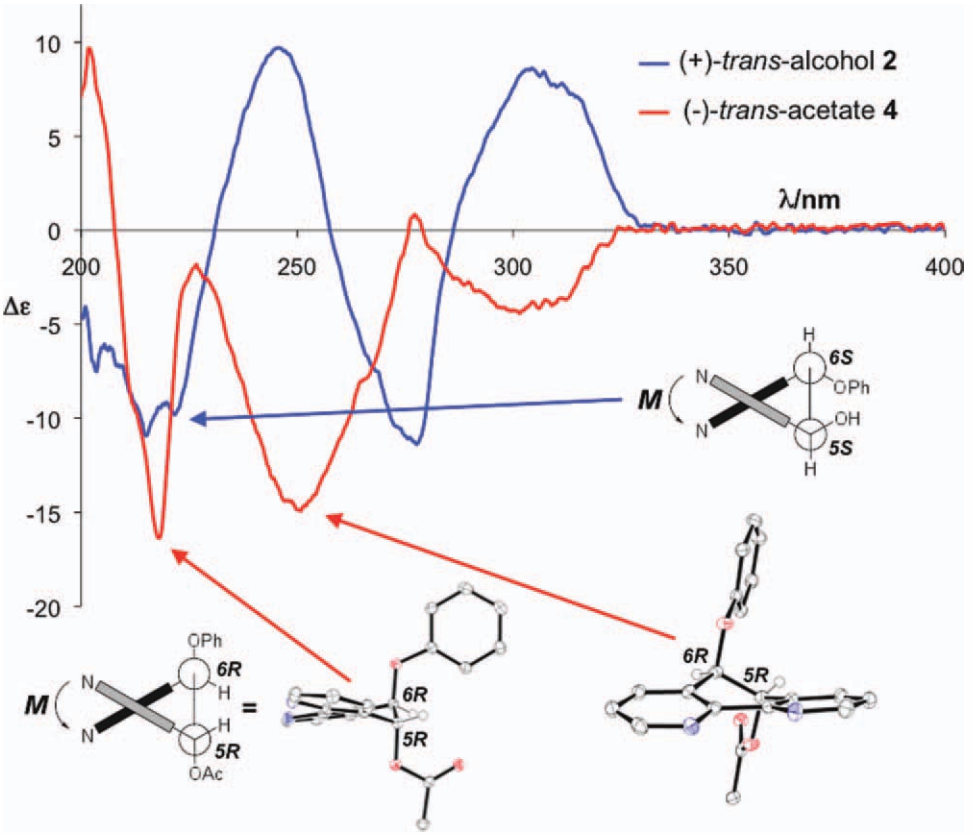


Fig. 3. CD spectra of (+)-*trans*-alcohol **2** (blue) and (−)-*trans*-acetate **4** (red). Two stereoviews of the solid-state structure of (±)-*trans*-acetate **4** showing 50% probability ellipsoids. The chloroform molecule has been omitted for clarity.

phenyl ring it appears to be less relevant for the assignment. Furthermore, the $\Delta\delta^{SR}(^{19}F)$ values calculated for the *cis*- and *trans*-phenoxy MTPA ester resonances are both positive. Based on ^{1}H- and ^{19}F-NMR analyses the stereogenic center of each alcohol, (−)-*cis*-**3** and (+)-*trans*-**2**, has the *S*-configuration.

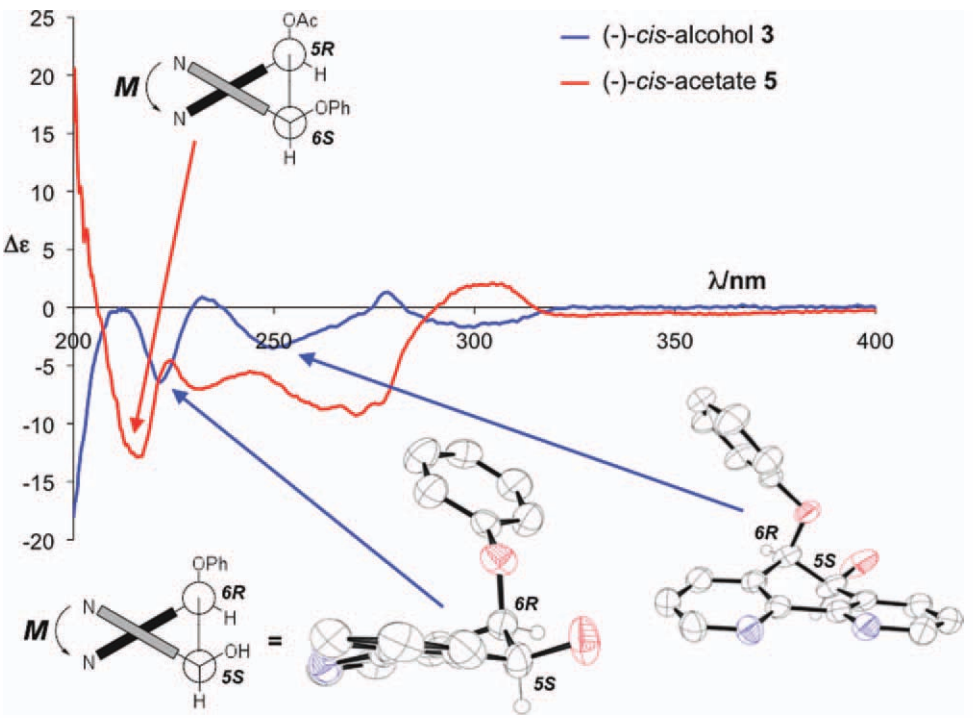


Fig. 4. CD spectra of (−)-*cis*-alcohol **3** (blue) and (−)-*cis*-acetate **5** (red). Two stereoviews of the solid-state structure of (±)-*cis*-alcohol **3** showing 50% probability ellipsoids.

CONCLUSION

We have developed an effective method for the stereoselective ring opening of 1,10-phenanthrolin-5,6-epoxide with triphenyl borate giving rise to the first *cis* and *trans* isomers of 5,6-dihydro-6-phenoxy-1,10-phenanthrolin-5-ol. The stereoselectivity was influenced by the choice of solvent and temperature. Reactions at higher temperature in DMF favored the *cis* product (14:1 dr for *cis*-**3**), whereas those at lower temperatures in dichloromethane, chloroform, or acetonitrile afforded predominantly the *trans* derivative (>99:1 dr for *trans*-**2**). We identified lipase PSCI from *Burkholderia cepacia* as an effective catalyst for the transesterification of racemic *cis*- and *trans*-phenoxy alcohol stereoisomers (97% *ee*, $E >$ 200). This is the first report for the enzymatic resolution of a *cis*-5,6-dihydro-1,10-phenanthroline derivative. The absolute configuration of all products was corroborated by both CD and NMR studies. Our results indicate a preference of lipase PSCI to acetylate the (*R*)-hydroxyl group. We also report the first X-ray crystal structures of *cis*- and *trans*-5,6-disubstituted-5,6-dihydro-1,10-phenanthroline derivatives.

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