Asymmetric Synthesis of the (S)-1,1-dioxido-isothiazolidin-3-one ((S)-IZD) Phosphotyrosine Mimetic via Reduction of a Homochiral (R)-oxido-isothiazolidin-3-one

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Supporting Information

1- Experimentals
2- Chiral HPLC Purity Analysis
3- X-ray Crystallography Data
4- NMR Data
Experimentals:

All reagents and solvents were purchased at highest commercial quality and used without further purification. All microwave reactions were carried out in sealed tubes in an Emrys Optimizer microwave reactor (Biotage). NMR spectra were obtained using a Varian Mercury-400. Purifications by flash chromatography were performed on RediSep columns using an Isco CombiFlash SG100c. Preparative LCMS purifications were performed on a Waters FractionLynx system using mass directed fractionation and compound-specific method optimization [J. Comb. Chem. 2004, 6, 874-883]. The LC method utilized a Waters SunFire column (19 x 100 mm, 5 µM particle size), with a water/0.1% TFA and acetonitrile/0.1% TFA gradient at a flow rate of 30 mL/min over a total run time of 5 min.

The enantiomers of 9, 13, 14, 15 and 16 were each synthesized. The experimental for the (S)-IZD isomer, as assigned by the X-ray structure of 13, is reported herein. The \(^1\)H NMR, \(^13\)C NMR and MS were identical for each pair of enantiomers. The optical rotation, enantiomeric excess and chiral HPLC retention times are given for each enantiomer, except for 15 which was not resolvable by chiral HPLC and thus necessitated its SEM derivitization and inferred % ee analysis from 16 (Table 1).

8: 2-tert-butyl-5-chloroisothiazol-3(2H)-one-1-oxide. Racemic 8 was prepared according to our previously reported method in reference 8. The enantiomers 8A and 8B (35 mg/injection) were separated on a ChiralCel OD-H column (20 x 250 mm, 5 µM) run under isocratic conditions of 10% ethanol, 90% hexanes at a flow rate of 15 mL/min over a total run time of 10 minutes with UV monitoring at 220 nm and 254 nm.
9: **2-tert-butyl-5-phenylisothiazol-3(2H)-one-1-oxide.** 2-tert-butyl-5-chloroisothiazol-3(2H)-one-1-oxide (0.600 g, 2.89 mmol) and phenylboronic acid (0.37 g, 3.03 mmol) were dissolved in 1,4-dioxane (10 mL). To the solution was added cesium fluoride (2.18 g, 1.43 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (0.40 g, 0.49 mmol). The vessel was purged with nitrogen and then heated at 80 °C for 16 hours. The solids were removed by filtration and the crude material was purified by flash silica chromatography (hexane / ethyl acetate) to give 2-tert-butyl-5-phenylisothiazol-3(2H)-one-1-oxide as a viscous oil (625 mg, 87%).

^1^H NMR (400 MHz, CDCl₃): δ 7.66 - 7.69 (m, 2 H), 7.48 - 7.50 (m, 3 H), 6.66 (s, 1 H), 1.69 (s, 9 H). ^1^C NMR (100 MHz, CDCl₃): δ 168.0, 160.0, 131.9, 129.7, 128.2, 127.8, 121.8, 59.0, 29.4. LCMS calculated for C₁₃H₁₆NO₂S (M+H)^+: m/z = 250.1

13: **2-tert-butyl-5-phenylisothiazolidin-3-one-1-oxide:** A solution of 2-tert-butyl-5-phenylisothiazol-3(2H)-one-1-oxide (500 mg, 2.0 mmol) in methanol (7.0 mL) was chilled to 0 °C. To the solution was added sodium borohydride (75.9 mg, 2.0 mmol) as a solid and stirred for 15 min. The reaction was quenched with acetic acid and then purified by preparative LCMS to yield 2-tert-butyl-5-phenylisothiazolidin-3-one-1-oxide as a white solid (415 mg, 82%). ^1^H NMR (400 MHz, CD₃OD): δ 7.39 - 7.48 (m, 5 H), 4.63 (dd, J = 12.1, 7.2 Hz, 1 H), 3.51 (dd, J = 17.1, 12.1 Hz, 1 H), 3.05 (dd, J = 17.1, 7.3 Hz, 1 H), 1.60 (s, 9 H). ^1^C NMR (100 MHz, CD₃OD): δ 176.9, 131.2, 129.4, 129.1, 128.8, 60.2, 58.6, 34.1, 28.2. LCMS calculated for C₁₃H₁₈NO₂S (M+H)^+: m/z = 252.1
14: **2-tert-butyl-5-phenylisothiazolidin-3-one-1,1-dioxide.** *m*-Chloroperbenzoic acid (398 mg, 2.31 mmol) was added to a stirred solution of 2-tert-butyl-5-phenylisothiazolidin-3-one-1-oxide (290 mg, 1.15 mmol) in methylene chloride (14 mL) at 0 °C. The solution was stirred at room temperature for 18 hours and then concentrated *in vacuo*. The crude material was purified by preparative LCMS to yield 2-tert-butyl-5-phenylisothiazolidin-3-one-1,1-dioxide as a white solid (280 mg, 91%). 1H NMR (400 MHz, CD3OD): δ 7.43 - 7.47 (m, 5 H), 5.09 (t, J = 9.5 Hz, 1 H), 3.23 - 3.31 (m, 2 H), 1.64 (s, 9 H). 13C NMR (100 MHz, CD3OD): δ 167.9, 129.6, 129.3, 129.1, 128.9, 64.0, 61.0, 36.0, 26.9. LCMS calculated for C13H18NO3S (M+H)+: m/z = 268.1

15: **5-phenylisothiazolidin-3-one-1,1-dioxide.** 2-tert-butyl-5-phenylisothiazolidin-3-one-1,1-dioxide (57.4 mg, 0.215 mmol) was dissolved in trifluoroacetic acid (0.8 mL) and the reaction vessel was sealed and heated in a microwave reactor at 130 °C for 6 minutes. After cooling to ambient temperature, the solution was concentrated *in vacuo* and purified by preparative LCMS to yield 5-phenylisothiazolidin-3-one-1,1-dioxide as a white solid (31.2 mg, 69%). 1H NMR (400 MHz, CD3OD): δ 7.43 - 7.51 (m, 5 H), 5.16 (t, J = 8.8 Hz, 1 H), 3.27 - 3.42 (m, 2H). 13C NMR (100MHz, CD3OD): δ 169.1, 129.5, 129.4, 129.1, 128.9, 65.4, 37.5. LCMS calculated for C9H10NO3S (M+H)+: m/z = 212.0.

16: **5-phenyl-2-[[2-(trimethylsilyl)ethoxy]methyl]isothiazolidin-3-one 1,1-dioxide**

Samples of 15A (5.1 mg) and 15B (5.3 mg) were derivatized with excess Sem-Cl (~1.5
equiv.) in CH₂Cl₂ (0.5 mL) with DIEA (~10 equiv.) and stirred for 2 hours. The crude reaction was purified by preparative LCMS to afford the N-Sem protected heterocycles 16A (3 mg) and 16B (3 mg). The protected enantiomers, 16A and 16B, were resolved by chiral HPLC (Chiral Technologies ChiralCel OD-H, 4.6 x 250 mm column, 5 micron particle size, mobile phase 30% ethanol, 70% hexanes) and % ee’s determined. 'H NMR (400 MHz, CD₃OD): δ 7.53 - 7.43 (m, 5 H), 5.18 (t, J = 8.8 Hz, 1 H), 5.14 (d, J = 11 Hz, 1 H), 4.99 (d, J = 11 Hz, 1 H), 3.69 (t, J = 9 Hz, 2 H), 3.24 (dd, 1 H), 3.39 (dd, 1 H), 0.96 (t, 9 Hz, 2H), 0.05 (s, 9H). LCMS calculated for C₁₅H₂₃NO₄SSiNa (M+Na)^+: m/z = 365.5.

**Chiral HPLC Purity Analysis:**

HPLC purity was determined to be >98% ee for all final products, except 16A and 16B which were analyzed as described above in the experimental section, by the following the following chiral HPLC method (See Table 1); A Chiral Technologies ChiralPak IA column (4.6 x 250 mm, 5 µM) was run under isocratic conditions of 15% ethanol, 85% hexanes at a flow rate of 1 mL/min over a total run time of 60 minutes with UV monitoring at 220 nm and 254 nm. The specific rotation for each compound was measured with a Perkin-Elmer Model 341 polarimeter, ħ = 589 nm, 23 °C using a cell of path length of 10 cm.
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<th>Compd</th>
<th>Config. (C3)(^a)</th>
<th>Config. (Sulfur)(^a)</th>
<th>% ee</th>
<th>Specific Rot. (degrees)</th>
<th>Chiral HPLC (t_R) (min)</th>
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</table>

\(^a\)Stereochemical configurations of 8-16 were assigned based on the X-ray structure of compound 13.

X-ray Crystallography Data:

Data for C\(_{13}\)H\(_{17}\)NO\(_2\)S 13A were collected at –100 °C with a Bruker APEX-II CCD(MoK\(\alpha\) radiation) system using a colorless, irregular block data crystal of dimensions ~ 0.50 x 0.50 x 0.48mm. The data indexed with orthorhombic unit cell parameters, P2\(_1\)2\(_1\)2\(_1\), a = 5.7522(3) Å, b = 11.3813(6) Å, c = 19.5390(10) Å, Volume = 1279.17(12), Z=4, Formula weight = 251.34, Density = 1.305g/cm\(^3\), \(\mu\)(Mo) = 0.24mm\(^{-1}\). The SAINT integration yielded 47457 data, 4572 unique, within a 2\(\theta\) range of 4.14 to 65.14°, R(int-xl) = 0.0228. A SADABS correction was applied. The structure was solved using XS(Shelxtl), refined using shelxtl software package, refinement by full-matrix least squares on F\(^2\), scattering factors from Int. Tab. Vol C Tables 4.2.6.8 and 6.1.1.4, data/parameter ratio = 29.12, goodness-of-fit on F\(^2\) = 1.10, R indices[I>4sigma(I)] R1 = 0.0245, wR2 = 0.0682, R indices(all data) R1 = 0.0252, wR2 = 0.0688, max difference
peak and hole = 0.280 and -0.224 e/Å³. All of the hydrogen atoms were idealized using a riding model. The absolute configuration was determined with the R/S configuration at C3 is S and the sulfur configuration is R. The enantiomeric setting was based upon the refined flack parameter = 0.02(4) and an absolute configuration analysis (teXsan)¹,² which compares differences in Bijvoet pairs of reflection. The correct trend is observed especially for pairs with large significant differences (742 pairs correct vs. 72 pairs incorrect for significant differences between 1 and 2).

References:

1) TeXsan Structure Solution Software; Molecular Structure Corp.; 1985, 1992, The Woodlands, Texas

2) Shelxtl Software Suite, Version 5.1, G. Sheldrick, Bruker AXS Corp, Madison, Wisconsin