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Asymmetric Synthesis of the (*S*)-1,1-Dioxido-isothiazolidin-3-one Phosphotyrosine Mimetic via Reduction of a Homochiral (*R*)-Oxido-isothiazolidin-3-one

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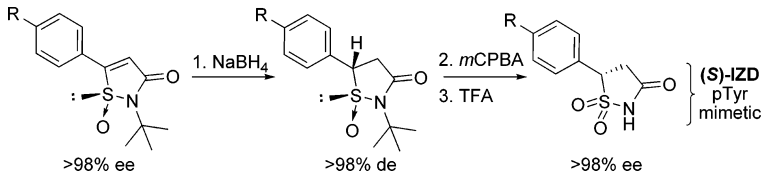
ABSTRACT



The first asymmetric synthesis of the (*S*)-1,1-dioxido-isothiazolidin-3-one ((*S*)-IZD) pTyr mimetic, which has been incorporated into the recently reported potent protein tyrosine phosphatase 1B (PTP1B) inhibitors, is presented herein. The key reaction is the reduction of the (*R*)-oxido-isothiazolidin-3-one heterocycle with excellent regiochemical and stereochemical control (>98% ee; 82% yield).

The discovery of potent cell-permeable phosphatase inhibitors has been a significant unmet medicinal chemistry challenge for over a decade. The search for protein tyrosine phosphatase 1B (PTP1B) is a particularly attractive drug target due to the extensive in vitro and in vivo biological data to support their use for the treatment of diabetes and obesity.[1−3] The deep active site of PTP1B that binds the phosphotyrosine (pTyr) portion of the peptide substrates has been the focus of most inhibitor design efforts to date. Several excellent pTyr mimetics have been identified, though nearly all contain a highly charged moiety, such as a carboxylic acid or phosphonate, that does not allow for adequate cell permeability.[4−7]

We recently reported the structure-based design of potent PTP1B inhibitors that incorporate a novel diffusely anionic 1,1-dioxido-isothiazolidin-3-one (IZD) pTyr mimetic (Table 1).[8−12] Of the two possible heterocyclic diastereomers, only the compounds, such as **2**, bearing the (*S*)-IZD isomer were

(1) Elchebly, M.; Payette, P.; Michaliszyn, E.; Cromlish, W.; Collins, S.; Loy, A. L.; Normandin, D.; Cheng, A.; Himms-Hagen, J.; Chan, C.-C.; Ramachandran, C.; Gresser, M. J.; Tremblay, M. L.; Kennedy, B. P. *Science* **1999**, *283*, 1544−1548.

(2) Klaman, L. D.; Boss, O.; Peroni, O. D.; Kim, J. K.; Martino, J. L.; Zabolotny, J. M.; Moghal, N.; Lubkin, M.; Kim, Y. B.; Sharpe, A. H.; Stricker-Krongrad, A.; Shulman, G. I.; Neel, B. G.; Kahn, B. B. *Mol. Cell. Biol.* **2000**, *20*, 5479−5489.

(3) Zinker, B. A.; Rondinone, C. M.; Trevillyan, J. M.; Gum, R. J.; Clampit, J. E.; Waring, J. F.; Xie, N.; Wilcox, D.; Jacobson, P.; Frost, L.; Kroeger, P. E.; Reilly, R. M.; Koterski, S.; Opgenorth, T. J.; Ulrich, R. G.; Crosby, S.; Butler, M.; Murray, S. F.; McKay, R. A.; Bhanot, S.; Monia, B. P.; Jirousek, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11357−11362.

(4) Bialy, L.; Waldmann, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3814−3839.

(5) Dewang, P. M.; Hsu, N.-M.; Peng, S.-Z.; Li, W.-R. *Curr. Med. Chem.* **2005**, *12*, 1−22.

(6) Johnson, T. O.; Ermolieff, J.; Jirousek, M. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 696−709.

(7) Moller, N. P. H.; Andersen, H. S.; Jeppesen, C. B.; Iversen, L. F. *Handb. Exp. Pharmacol.* **2005**, *167*, 215−262.

(8) Combs, A. P.; Yue, E. W.; Bower, M.; Ala, P. J.; Wayland, B.; Douty, B.; Takvorian, A.; Polam, P.; Wasserman, Z.; Zhu, W.; Crawley, M. L.; Pruitt, J.; Sparks, R.; Glass, B.; Modi, D.; McLaughlin, E.; Bostrom, L.; Li, M.; Galya, L.; Blom, K.; Hillman, M.; Gonneville, L.; Reid, B. G.; Wei, M.; Becker-Pasha, M.; Klabe, R.; Huber, R.; Li, Y.; Hollis, G.; Burn, T. C.; Wynn, R.; Liu, P.; Metcalf, B. *J. Med. Chem.* **2005**, *48*, 6544−6548.

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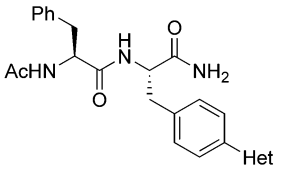
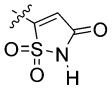
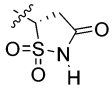
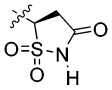
Table 1. (*S*)-IZD pTyr Mimetics Are Potent PTP1B Inhibitors



Entry	Acronym	Het	PTP1B IC_{50} (nM)
1	IZD		3000
2	(*S*)-IZD		190
3	(*R*)-IZD		16000

potent PTP1B inhibitors. Further studies demonstrated that the (*S*)-IZD is the most potent pTyr mimetic known to date and when incorporated in non-peptidic inhibitors can be caco-2 permeable and cellularly active.

We report herein a general approach to the stereoselective synthesis of the (*S*)-IZD pTyr mimetic via Suzuki coupling of the chiral chlorosulfinamide heterocycle **8** followed by a highly chemoselective (>99%) and stereoselective (>98% ee) reduction of the heterocyclic olefin. Oxidation to the heterocyclic sulfonamide **9** and deprotection afforded the desired (*S*)-IZD-containing compound **15** in good yields. A proposed mechanism is provided for this regioselective and stereoselective reduction consistent with our X-ray analyses and NMR studies.

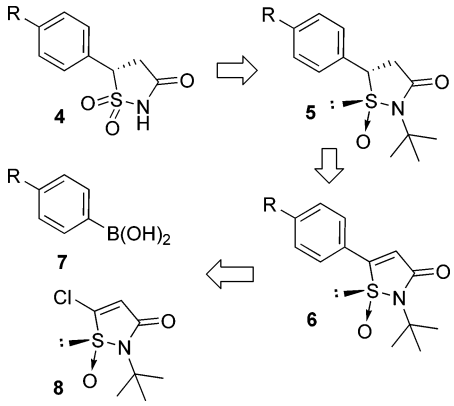
An asymmetric synthesis of the (*S*)-IZD was envisioned by several different synthetic processes. We initially attempted the catalytic asymmetric hydrogenation of unsaturated IZD-containing compounds, such as **1**, with various chiral ligands and metal catalysts. Although hydrogenation with Pd/C gave high yields of the desired products in our original research, none of the rhodium asymmetric reaction conditions attempted gave acceptable yields and/or selectivities to be synthetically useful.

We also considered the use of a chiral nitrogen protecting group on the (*S*)-IZD heterocycle, but reasoned this remote substituent may not afford suitable chiral induction. Also, recycling of the chiral auxiliary would not be possible and thus less economical than other routes.

Utilization of the homochiral heterocyclic sulfoxide **6** to control the stereochemistry of the desired (*S*)-IZD heterocycle was chosen for further investigation for two key reasons. Foremost, Ellman has demonstrated that chiral *N*-*tert*-butanesulfinyl imines are substrates for a variety of nucleophiles, providing excellent stereochemical control for these reactions.[13−15] We inferred that similar stereochemical control of the hydride delivery to the sulfamide heterocycle **6** could be expected due to the close proximity of olefin to the chiral sulfinamide center. Last, the resulting chiral sulfinamide can easily be converted to the biologically active IZD heterocycle **4** via an oxidation.

A retrosynthetic analysis identified the chiral chloro heterocycle **8** as the key source of chirality in this synthetic design. Coupling of **8** to an arylboronic acid would provide the unsaturated arylsulfinamide heterocycle **6**. The key transformation would rely on the stereocontrolled reduction of **6** induced by the adjacent chiral sulfinamide. The synthesis of the desired (*S*)-IZD **4** would be completed by oxidation of the sulfinide **5** and deprotection (Scheme 1).

Scheme 1. Retrosynthetic Analysis for (*S*)-IZD



The racemate of the chloro-sulfinamide heterocycle **8** is available in good yields and large quantities as previously described.[8] Initial studies demonstrated that the chlorosulfinamide heterocycle **8** was an excellent Suzuki coupling partner, affording the desired aryl heterocycle **9** in 90% yield under standard conditions (K_2CO_3, THF, 100 °C, 8 h) with phenylboronic acid **7**.

A variety of reduction conditions were attempted with racemic **9** (Table 2). Although hydrogenation conditions were again unsuccessful, hydride sources proved to be effective.

(9) Yue, E. W.; Wayland, B.; Douty, B.; Crawley, M. L.; McLaughlin, E.; Takvorian, A.; Wasserman, Z.; Bower, M. J.; Wei, M.; Li, Y.; Ala, P. J.; Gonneville, L.; Wynn, R.; Burn, T. C.; Liu, P. C. C.; Combs, A. P. *Bioorg. Med. Chem.* **2006**, *14*, 5833−5849.

(10) Ala, P. J.; Gonneville, L.; Hillman, M. C.; Becker-Pasha, M.; Wei, M.; Reid, B. G.; Klabe, R.; Yue, E. W.; Wayland, B.; Douty, B.; Polam, P.; Wasserman, Z.; Bower, M.; Combs, A. P.; Burn, T. C.; Hollis, G. F.; Wynn, R. *J. Biol. Chem.* **2006**, *281*, 32784−32795.

(11) Combs, A. P.; Zhu, W.; Crawley, M. L.; Glass, B.; Polam, P.; Sparks, R. B.; Modi, D.; Takvorian, A.; McLaughlin, E.; Yue, E. W.; Wasserman, Z.; Bower, M.; Wei, M.; Rupar, M.; Ala, P. J.; Reid, B. M.; Ellis, D.; Gonneville, L.; Emm, T.; Taylor, N.; Yeleswaram, S.; Li, Y.; Wynn, R.; Burn, T. C.; Hollis, G.; Liu, P. C. C.; Metcalf, B. *J. Med. Chem.* **2006**, *49*, 3774−3789.

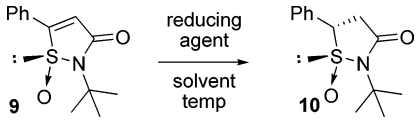
(12) Ala, P. J.; Gonneville, L.; Hillman, M.; Becker-Pasha, M.; Yue, E. W.; Douty, B.; Wayland, B.; Polam, P.; Crawley, M. L.; McLaughlin, E.; Sparks, R. B.; Glass, B.; Takvorian, A.; Combs, A. P.; Burn, T. C.; Hollis, G. F.; Wynn, R. *J. Biol. Chem.* **2006**, *281*, 38013−38021.

(13) Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709−6712.

(14) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995.

(15) Kochi, T.; Mukade, T.; Ellman, J. A. *Yuki Gosei Kagaku Kyokaishi* **2004**, *62*, 128−139.

Table 2. Optimization of Reduction Conditions[a]



entry	reducing agent	temp (°C)	solvent	yield[b] (%)	de[c] (%)
1	H_2/Pd/C	25	MeOH	0	n.d.
2	$NaBH_4$	0	THF	35	n.d.
3	$NaBH_4$	0	MeOH	82	>98
4	$NaBH_4$	0	1:1 THF/MeOH	63	>98
5	$NaBH_4$	25	1:1 THF/MeOH	67	>98
6	$LiBH_4$	0	1:1 THF/MeOH	80	>98
7	$LiBH_4$	25	1:1 THF/MeOH	76	>98

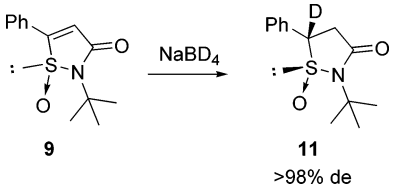
[a] Conditions: 1.0 equiv of reducing agent was added to a solution of the substrate at specified temperature. [b] Purified yields after chromatography. [c] Diastereomeric purity (% de) determined by chiral HPLC analysis with monitoring at 220 nm; n.d. = determined.

Reduction of **9** with either $NaBH_4$ or $LiBH_4$ at 0 °C in MeOH or a 1:1 MeOH/THF solution gave optimal yields of only one pair of enantiomers by ^{1}H NMR and HPLC, providing evidence that a high degree of stereochemical control was achieved.

To further establish the diastereoselectivity induced by the chiral sulfinamide, we required the individual enantiomers of **9**. Separation of the racemate of sulfinamide heterocycle **8** by preparative chiral HPLC proved to be facile and furnished multigram quantities of both enantiomers of **8** in >98% ee. Suzuki coupling of each individual enantiomer of sulfinamide heterocycle **8** to phenylboronic acid provided the desired enantiomerically pure *R*- and *S*-arylsulfinamides **9** (>98% ee). Reduction of each enantiomer of **9** provided only one unique diastereomer **13** for each, demonstrating unequivocally that the chiral induction from the sulfinamide was absolute (>98% de). We did not observe any of the other diastereomer by chiral HPLC or NMR.

The regioselectivity of the reduction was probed to deduce whether the hydride addition occurred α to the sulfinamide or α to the carbonyl of the unsaturated IZD heterocycle. Reduction of racemic **9** with $NaBD_4$ and NMR analysis of the reduced product **11** confirmed that the hydride addition occurs only α to the sulfinamide or the most substituted carbon (Scheme 2). The high degree of stereochemical control in the hydride delivery can thus be rationalized by the close proximity of the chiral sulfinamide to the newly formed chiral center.

Scheme 2. Regioselective and Stereoselective Reduction



An X-ray crystal structure of a single enantiomer of **13** (Chiral HPLC peak 1) provided the relative and absolute configuration of each stereocenter as as *S*- for C3 and *R*- for the sulfur atom. The enantiomeric setting was based upon the refined flack parameter of 0.02(4) and an absolute configuration analysis (teXsan), which compares differences in Bijvoet pairs of reflection (see Supporting Information for details). The ORTEP presentation of **13** clearly shows the hydrogen on the C3 carbon is on the opposite face of the heterocycle compared to that of the oxygen of the sulfinamide (Figure 1).

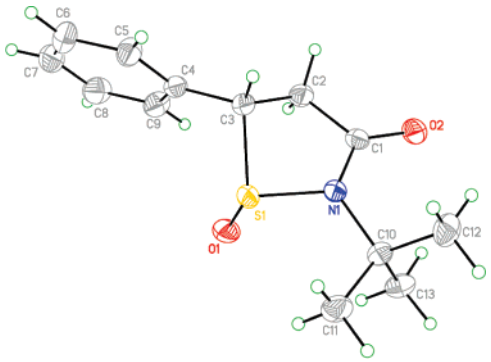
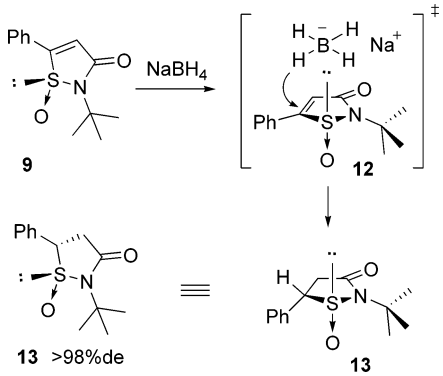


Figure 1. ORTEP presentation of **13**.

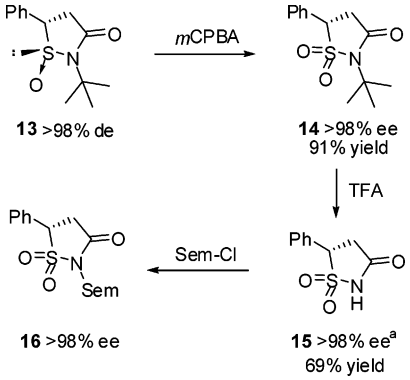
The proposed mechanism for the stereoselective reduction is depicted in Scheme 3, where the hydride attacks the

Scheme 3. Proposed Mechanism of Stereoselective Reduction



olefinic carbon adjacent to the sulfinamide from the opposite face of the heterocycle that bears the oxygen of the sulfinamide. This result is consistent with the hydride delivery from the less sterically and electronically disfavored face that bears only the lone pair of the sulfinamide. The absolute configuration obtained for **13** is *S* for the C3 carbon and *R* for the sulfur atom of the sulfinamide. Thus, the (*R*)-chlorosulfinamide heterocycle **8** is the key chiral intermediate required for the synthesis of the desired biologically active (*S*)-IZD heterocycle containing inhibitors.

Scheme 4. Sulfinamide Oxidation and Deprotection



[a] Percent ee inferred from derivatives **14** and **16**.

The asymmetric synthesis of the (*S*)-IZD **15** (Scheme 4) was completed in good yield by *m*CPBA oxidation of **13** to afford sulfonamide **14**, followed by cleavage of the *N*-*tert*-butyl protecting group from the (*S*)-IZD heterocycle using TFA and microwave irradiation for 60 seconds. Chiral HPLC analysis of **14** and its Sem-protected derivative **16**, since the acid **15** could not be completely resolved by chiral HPLC, confirmed there was no loss in stereochemical integrity during the final oxidation and deprotection steps.

In summary, a highly stereoselective asymmetric synthesis of the potent pTyr mimetic (*S*)-IZD has been established in an atom-efficient method. The key transformation is a regioselective and stereoselective additon of hydride to a (*R*)-sulfinamide heterocycle **9** in high yield and absolute stereochemical control (>98% de). The proposed mechanism for the stereocontrolled addition of the hydride to the heterocycle is consistent with the delivery of the hydride to C3 of the heterocycle from the face opposite to that of the sulfinamide oxygen as determined for the X-ray crystal structure of **13**. The use of this new methodology in the asymmetric synthesis of novel inhibitors of phosphatases, such as PTP1B, will be reported elsewhere.

Acknowledgment. The authors thank James Doughty of Incyte for chiral purity analysis. We also thank Will J. Marshall of the DuPont X-ray facility for solving the crystal structure of compound **13**.

Supporting Information Available: General experimental and analytical data for **4**−**16** and X-ray crystal structure data for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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