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Asymmetric Synthesis of (R)-*N*-3-Butyn-2-yl-*N*-hydroxyurea, A Key Intermediate For 5-Lipoxygenase Inhibitors

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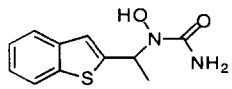
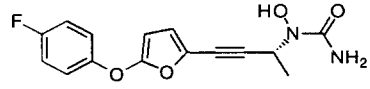
Abstract: An efficient asymmetric synthesis of (R)-*N*-3-butyn-2-yl-*N*-hydroxyurea from crotyl alcohol is described. The process involves asymmetric Sharpless epoxidation to establish the stereochemistry, formation of (S)-3-butynol and hydroxyl substitution with inversion by the masked *N*-hydroxyurea reagent *N,O*-bis(phenoxycarbonyl)hydroxylamine in a Mitsunobu reaction.

INTRODUCTION

Inhibitors of 5-lipoxygenase block the biosynthesis of leukotrienes which are known mediators of inflammatory and allergic disorders.[1] *N*-Hydroxyurea containing compounds like zileuton (**1**) were found to be effective 5-lipoxygenase inhibitors.[2] Zileuton has demonstrated promising therapeutic results in asthmatics.[3] Continued optimization of the inhibitory activity and duration of action of this series led to the discovery of *N*-(4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-yl)-*N*-hydroxyurea (A-78773) **2a,** a second generation 5-lipoxygenase inhibitor with improved potency and longer duration of action.[4] Resolution and evaluation of the enantiomers of **2a** revealed similar biochemical inhibitory activity. However upon oral administration the R-enantiomer (A-79175) **2b** had a much longer plasma half life due to greater resistance to glucuronidative metabolism and excretion.[5] The selection of the R-enantiomer **2b** for clinical evaluation prompted the investigation of an efficient asymmetric synthesis.



1 zileuton

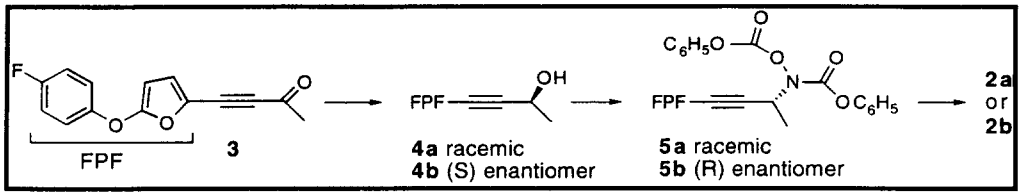


2a (A-78773) racemic
2b (A-79175) R+

RESULTS AND DISCUSSION

The synthesis of racemic 2**a** was accomplished from the alcohol intermediate **4a** utilizing a Mitsunobu reaction[6] with the masked *N*-hydroxyurea reagent, *N,O*-bis(phenoxycarbonyl)hydroxylamine.[7] The resulting urethane intermediate **5a** was demasked by aminolysis to provide the *N*-hydroxyurea **2a**. Our initial asymmetric synthetic approach targeted (S)- 4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-ol (**4b**) which could be transformed into the (R)-*N*-hydroxyurea precursor **5b** by inversion of configuration with the masked *N*-hydroxyurea variation of the Mitsunobu reaction (Scheme 1).

Scheme 1.

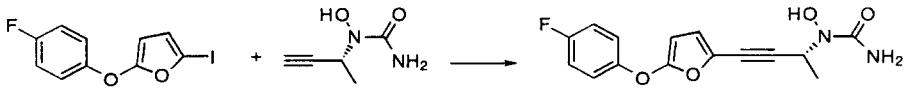


Two approaches to the asymmetric reduction of the acetylenic ketone **3** were investigated. The method of Midland et. al.[8] using (S)-Alpine-Borane complex produced alcohol **4b** in low chemical yield (~22%) and poor optical purity (56% ee). Enzymatic reduction using the alcohol dehydrogenase from *Thermoanaerobium brockii* (TBADH)[9,10] in the presence of NADPH provided an 18% conversion to **4b** with excellent optical purity (>99 % ee). The optical purity of **4b** was determined by esterification with (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid[11] and comparing the ^{1}H NMR spectra with that of the derivatized racemic alcohol **4a**.

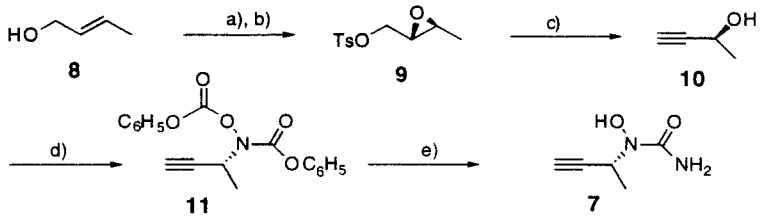
With **4b** of good optical purity from the enzymatic reduction in hand, we examined the substitution reaction of the hydroxyl group with *N,O*-bis(phenoxycarbonyl)hydroxylamine under the Mitsunobu conditions in order to validate the inversion of stereochemistry required to provide the (R)-urethane derivative **5b** (Scheme 1). The reaction proceeded to provide **5b** which was treated with concentrated NH_4OH in methanol at room temperature for 20 h to provide the *N*-hydroxyurea **2b** in 74% yield but only 33% ee. The stereochemical inversion normally observed in the Mitsunobu reaction is known to default using certain substrate/nucleophile couples[12]. The extensive racemization observed was likely due to a significant contibution from S_N1 mechanistic substitution resulting from both the phenoxysubstituted propargyl alcohol and the steric environment presented by the secondary center. The loss of optical purity in this reaction forced us to abandon this synthetic approach.

An alternative synthesis of **2b** was investigated involving a Heck coupling[13] of *N*-butynyl-2-yl derivatives with 5-(4-fluorophenoxy)-2-iodofuran **6** (Scheme 2).[14] The advantage of this convergent approach was that the desired optical purity was established in the key intermediate butyn-2-yl-*N*-hydroxyurea **7** before final assembly. The asymmetric synthesis of **7** involved a five step procedure as outline in Scheme 3.

Scheme 2.



Scheme 3.[a]

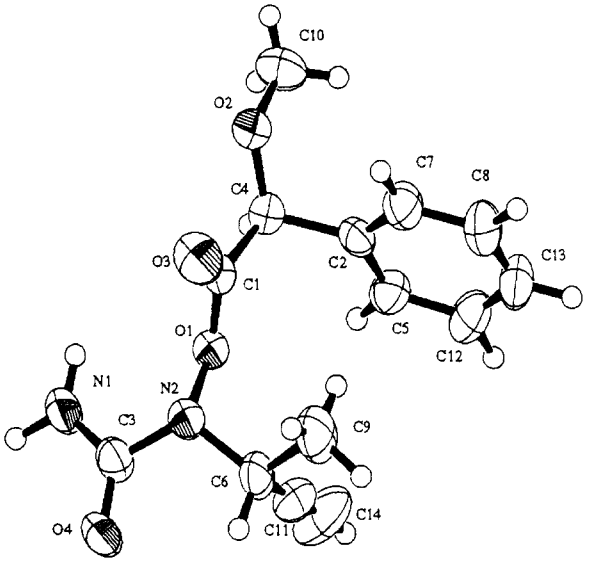


[a]reagents and conditions: a) L-(+)-DIPT, t-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, -20 °C; b) TsCl, Et_3N, -20 to -10 °C; c) n-BuLi, THF, -72 °C; then CH_3CO_2H, $NaHCO_3$; d) $C_6H_5O_2CNHOCO_2C_6H_5$, $(C_6H_5)_3P$, DEAD, THF; e) NH_4OH, MeOH, rt.

Sharpless epoxidation of crotyl alcohol (**8**) with t-butyl hydroperoxide in the presence of L-(+)-diisopropyl tartrate [L-(+)-DIPT] and titanium isopropoxide [Ti(i-PrO)4] gave (2S,3S)-2,3-epoxybutanol.[15] The alcohol was not isolated because of high water solubility but was immediately treated with triethylamine and *p*-toluenesulfonyl chloride to provide (2S-*trans*)-3-methyloxiranemethanol 4-methylbenzenesulfonate (**9**) in 22% overall yield without optimization. Exposure of the tosylate **9** to 6-fold excess of n-butyllithium provided the (S)-3-butyn-2-ol (**10**). To avoid complications of the high aqueous solubility of the product a non-aqueous workup was employed. The mixture of crude alcohol **10** was acidified with acetic acid to pH 5 and after stirring for 15 minutes the mixture was neutralized by adding solid $NaHCO_3$. The solids were removed by filtration through Celite and the filtrate was directly reacted with *N,O*-bis(phenoxycarbonyl) hydroxylamine under Mitsunobu conditions to afford *N,O*-bis(phenoxycarbonyl)-*N*-(S)-3-butyn-2-ylhydroxylamine (**11**). Treatment of urethane **11** with NH_4OH in methanol for 48 h gave (R)-*N*-hydroxy-*N*-(3-butyn-2-yl)urea (**7**) in 29% yield (in three steps from **9**) after purification by silica gel chromatography.

The (S)-*N*-hydroxy-N-(3-butyn-2-yl)urea was prepared in an analogous manner from crotyl alcohol by replacing [L-(+)-DIPT] with [D-(-)-DIPT] in 23% overall yield for the three steps from **9**.

The assignment of absolute configuration was originally based on the Sharpless epoxide assuming inversion of stereochemistry in the modified Mitsunobu urethane formation step. To confirm the absolute configuration of the final product, (R)-*N*-(3-butyn-2-yl)-*N*-hydroxyurea **7** was derivatized with (S)-α-methoxyphenylacetic acid using carbonyldiimidazole to provide (R)-*N*-(3-butyn-2-yl)-*N*-carbamoyl-O-(S)-α-methoxyphenylacetylhydroxylamine (**12**). X-ray crystallography confirmed the R absolute configuration for this *N*-hydroxyurea derivative by correlation of the relative stereochemistry to the asymmetric center of the derivatizing agent (Figure 1).



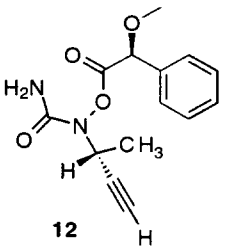


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Figure 1

An efficient synthesis of (R)- and (S)-*N*-3-butyn-2-yl-*N*-hydroxyurea from crotyl alcohol in good overall yield was achieved. The asymmetric 2-butynol starting material was prepared by application of the Sharpless epoxidation method. Substitution with a masked *N*-hydroxyurea reagent in a modified Mitsunobu reaction proceeded with inversion of stereochemistry to provide the desired *N*-3-butyn-2-yl-*N*-hydroxyurea. The absolute configuration of (R)-*N*-3-butyn-2-yl-*N*-hydroxyurea (**7**) was confirmed by derivatization and X-ray crystallography. (R)-*N*-3-butyn-2-yl-*N*-hydroxyurea (**7**) has proven to be a useful synthetic intermediate for the efficient synthesis of hundreds of enantiomerically pure acetylenic *N*-hydroxyureas by palladium catalyzed coupling with various aryl and heteroaryl systems for evaluation as pharmaceutically useful 5-lipoxgenase inhibitors.[16]

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Specific rotations were measured using Perkin Elmer 241 Polarimeter. ^{1}H NMR spectra were recorded using a Nicolet QE-300 (300 MHz) instrument. Mass spectra were obtained with Hewlett Packard HP5985 spectrometer. X-Ray crystallography was taken on a P4 Siemens apparatus with CCD detector. Microanalysis were performed by the Robertson Microlit Laboratories, Inc. in Madison, NJ. Reagents were obtained from Aldrich and Sigma chemical companies.

4-(5-(4-Fluorophenoxy)-2-furyl)-3-butyn-2-one (3).

A solution of (5-(4-fluorophenoxy)-2-furyl)acetylene (3.2 g, 15 mmol) in THF (50 mL) was treated with 2M LDA (8 mL, 16 mmol) at -70 to -50 °C and after 30 min *N*-methoxy-*N*-methylacetamide (2.1 g, 20 mmol) was added. The mixture was allowed to warm to 0 °C (~1 h) and then kept at -5 to +5 °C for the next 1.5 h. After 10% citric acid was added and the product was extracted with ethyl acetate. The organic layer was washed with water, brine, dried with anhydrous MgSO4 and concentrated *in vacuo*. The residue was chromatographed (silica gel, 6:1 hexane-ethyl acetate) to provide 1.9 g (52%) of the desired ketone, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 5.47 (d, J = 4 Hz, 1 H), 6.93 (d, J = 4 Hz, 1 H), 7.10 (m, 4 H).

(S)-4-(5-(4-fluorophenoxy-2-furyl)-3-butyn-2-ol (4b).

a) Reduction with (S)-Alpine-borane. To a solution of 0.5 M (S)-Alpine-borane (4 mL, 2 mmol) in THF (20 mL) at room temperature was added 4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-one **3** (244 mg, 1 mmol) in THF (10 mL). The mixture was stirred at room temperature for 58 h. Acetaldehyde (5 mL) was added and the mixture was stirred for additional 30 min. The THF was then removed *in vacuo* and the residue was dissolved in ethyl acetate. The acetate layer was washed with 10% citric acid, water, brine and dried with anhydrous $MgSO_4$. After removing ethyl acetate *in vacuo*, the residue was chromatographed (silica gel, 4:1 hexane-ethyl acetate) to obtain 55 mg (22%) of the desired alcohol: $[\alpha]_D^{23}$ = -10.0 (c = 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, J = 7 Hz, 3 H), 4.75 (q, J = 7 Hz, 1 H), 5.47 (d, J = 4 Hz, 1 H), 6.53 (d, J = 4 Hz, 1 H), 7.03 (d, J = 1 Hz, 2 H), 7.04 (s, 2 H). Starting ketone, 130 mg (53%), was also recovered.

b) Reduction with alcohol dehydrogenase from *Thermoanaerobium brockii* (TBADH) in phosphate buffer. A mixture of 4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-one **3** (61 mg, 0.25 mmol), TBADH (0.75 mg, 30 units), NADP (20 mg, 0.025 mmol) in isopropanol (4 mL) and 0.05 M phosphate buffer, pH 6.5 (10 mL) was treated with NADPH (17 mg, 0.02 mmol) at 36°C. The reaction was continued at 36 °C for 10 h and then TBADH (0.25 mg, 10 units) and NADPH (5 mg, 0.006 mmol) were added again. The reaction was continued for the next 18 h at 40 °C and then extracted with ethyl acetate. The acetate extract was washed with water, brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 4:1 hexane-ethyl acetate) to provide 11 mg (18%) of alcohol: $[\alpha]_D^{23}$ = -17.7 (c = 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) d 1.53 (d, J = 7 Hz, 3 H), 4.75 (q, J = 7 Hz, 1 H), 5.47 (d, J = 4 Hz, 1 H), 6.53 (d, J = 4 Hz, 1 H), 7.02 (d, J = 1 Hz, 2 H), 7.06 (s, 2 H) and 50 mg (81%) of recovered starting ketone.

c) reduction with TBADH in Trizma buffer. A mixture of ketone **3** (61 mg, 0.25 mmol), TBADH (0.75 mg, 30 units), NADP (20 mg, 0.025 mmol) and NADPH (17 mg, 0.02 mmol) in s-butanol (4 mL) and 0.05 M Trizma buffer, pH 6.7 (10 mL) was stirred at 37 °C for 20 h. After NADP (10 mg) and NADPH (8 mg) were added and the reaction was continued for the next 8 h. Work-up as in procedure c) gave 9.5 mg (15%) of alcohol: $[\alpha]_D^{23}$ = -17.7 (c = 0.48, $CHCl_3$) and 52 mg (85%) of recovered ketone.

4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-yl ester of (R)-α-methoxy-α-trifluoromethyl-phenylacetic acid.

To a solution of 4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-ol (**4a** or **4b**) (24.6 mg, 0.1 mmol), 1-hydroxybenzotriazole (13.5 mg, 0.1 mmol), (R)-α-methoxy-α-trifluoromethylphenylacetic acid (23.4 mg, 0.1 mmol) and dimethylaminopyridine (25 mg, 0.2 mmol) in THF (10 mL) was added dicylohexylcarbodiimide (20.6 mg, 0.1 mmol) and the resulting mixture was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The acetate solution was washed with 10% citric

acid, water, 10% solution of $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a short silica gel column (4:1hexane-ethyl acetate) to afford 41 mg (90%) of ester: ^1H NMR of ester of racemic alcohol **4a**: δ 1.59 and 1.66 (two d, 1:1, J = 7 Hz, 3 H), 3.56 and 3.59 (two d, 1:1, J = 1.5 Hz, 3 H), 5.46 (d, J = 4 Hz, 1 H), 5.87 (two q, 1:1, J = 7 Hz, 1 H), 6.57 (two d, 1:1 J = 4 Hz, 1 H), 7.05 (d-d, J = 1 and 6 Hz, 4 H), 7.40 (m, 5 H).

^1H NMR of ester of (S)-alcohol **4b** from the enzymatic reduction: δ 1.66 (d, J = 7 Hz, 3 H), 3.56 (d, J = 1.5 Hz, 3 H), 5.45 (d, J = 4 Hz, 1 H), 5.86 (q, J = 7 Hz, 1 H), 6.56 (d, J = 4 Hz, 1 H), 7.05 (d, J = 6 Hz, 4 H), 7.40 (m, 5 H).

***N*-(4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-yl)-*N*-hydroxyurea (2b).**

To a solution of 4-(5-(4-fluorophenoxy)-2-furyl)-3-butyn-2-ol **4b**, resulting from enzymatic reduction (60 mg, 0.24 mmol), *N,O*-bis(phenoxycarbonyl)hydroxylamine (72 mg, 0.25 mmol) and triphenylphosphine (66 mg, 0.25 mmol) in THF (10 mL) at room temperature under N_2 atmosphere was added dropwise a solution of DIAD (0.05 ml, 0.25 mmol) in THF (5 mL). The reaction was continued at room temperature for 3 h and then concentrated *in vacuo*. The residue was chromatographed (silica gel, 4:1 hexane-ethyl acetate) to afford 30 mg of *N,O*-bis(phenoxycarbonyl)-N-(4-(5-(4-fluoropohenoxy)-2-furyl)-3-butyn-2-yl)hydroxylamine **5b**.

Above hydroxylamine derivative was dissolved in methanol (15 mL) and treated with concentrated ammonium hydroxide (6 mL) for 20 h at ambient temperature. The mixture was then concentrated *in vacuo* and the residue was purified by chromatograhy (silica gel, 19:1 CH_2Cl_2-EtOAc) to afford 13 mg (74%) of the title product: mp 141-143 °C; $[\alpha]_D^{21}$ = + 16.7 (c = 0.15, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.34 (d, J = 7 Hz, 3 H), 5.12 (q, J = 7 Hz, 1 H), 5.76 (d, J = 4 Hz, 1 H), 6.56 (br. s, 2 H), 6.74 (d, J = 4 Hz, 1 H), 7.18 (m, 2 H), 7.26 (m, 2 H), 9.46 (s, 1 H); MS (DCI-NH_3) m/z 305 $(M + H)^+$, 322 $(M + NH_4)^+$

(2S, 3S)-2,3-epoxybutyl *p*-toluenesulfonate and (2R, 3R)-2,3-epoxybutyl *p*-toluenesulfonate (9).

The epoxidation of trans-crotyl alcohol and *p*-toluenesulfonylation of the hydroxyepoxide were performed according to the literature method of Sharpless et al.[15] After workup the crude products were purified by chromatography (silica gel, 99:1 CH_2Cl_2-EtOAc) and recrystallized from ethyl ether-pentane.

2S,3S-epoxide sulfonate **9**: mp 63-64 °C; $[\alpha]_D^{22}$ = -32.90 (c = 2.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6 Hz, 3 H), 2.46 (s, 3 H), 2.90 (m, 2 H), 4.00 (d-d, J = 6 and 10 Hz, 1 H), 4.18 (d-d, J = 4.5 and 10 Hz, 1 H), 7.37 (d, J = 9 Hz, 2 H), 7.80 (d, J = 9 Hz, 2 H).

2R,3R-epoxide sulfonate **9**: mp 59-60 °C; $[\alpha]_D^{22}$ = +32.93 (C = 3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6 Hz, 3 H), 2.46 (s, 3 H), 2.90 (m, 2 H), 4.00 (d-d, J = 6 and 10 Hz, 1 H), 4.18 (d-d, J = 4.5 and 10 Hz, 1 H), 7.36 (d, J = 9 Hz, 2 H), 7.81 (d, J = 9 Hz, 2 H); (lit.[15] mp 61-62 °C; $[\alpha]_D^{25}$ = +34.22 (c = 3.29, $CHCl_3$).

(R)-*N*-(3-butyn-2-yl)-*N*-hydroxyurea (7).

To a solution of (2S,3S)-2,3-epoxybutyl-*p*-toluenesulfonate **9** (484 mg, 2 mmol) in THF (20 mL) at -70 °C was added dropwise, under N_2, 1.6 M *n*-BuLi (3.8 mL, 6 mmol) and the reaction was allowed to stir at -70 to -60 °C for 50 min. The TLC showed disappearing of starting material but formation of an additional product beside desired alcohol. Additional *n*-BuLi (3.8 mL) was then added and after 20 min the TLC showed only only a single component corresponding to the desired alcohol. The glacial acetic acid was added to pH 5 followed after 15 min by finally powdered $NaHCO_3$. The mixture was stirred at 0 °C to room temperature for 3 h and then filtered. To the filtrate was added *N,O*-bis(phenoxycarbonyl)hydroxylamine (550 mg, 2 mmol),

Ph_3P (786 mg, 3 mmol) and dropwise a solution of diethylazodicarboxylate (DEAD, 0.5 ml, 3 mmol) in THF (5 mL). The mixture was stirred at room temperature for 16 h and then concentrated *in vacuo*. The residue was filtered through short silica gel pad (9:1 hexane-EtOAc) to afford crude *N,O*-bis(phenoxycarbonyl)-N-(3-butyn-2-yl)hydroxylamine, which was dissolved in methanol (15 mL) and treated with conc. NH_4OH (5 mL) for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by chromatography (silica gel, 9:1 CH_2Cl_2-EtOH) to provide 75 mg (29%) of the title compound: mp 127-128 °C; $[\alpha]_D^{24}$ = + 52.80 (c = 1.2, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 7 Hz, 3 H), 3.05 (d, J = 2.5 Hz, 1 H), 4.86 (d-q, J = 2.5 and 7 Hz, 1 H), 6.50 (br s, 2 H), 9.24 (s, 1 H); Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: 46.94; H, 6.28; N, 21.90.

(S)-*N*-(3-butyn-2-yl)-*N*-hydroxyurea.

The desired N-hydroxyurea was prepared with 23% overall yield according to the procedure described for R-isomer by using (2R, 3R)-2,3-epoxybutyl-*p*-toluenesulfonate as a starting material. mp 126-127 °C; $[\alpha]_D^{24}$ = -51.62 (c = 0.96, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 7 Hz, 3 H), 3.05 (d, J = 2.5 Hz, 1 H), 4.86 (d-q, J = 2.5 and 7 Hz, 1 H), 6.50 (br s, 2 H), 9.24 (s, 1 H).

(R)-*N*-(3-butyn-2-yl)-*N*-carbamoyl-O-(S)-α-methoxyphenylacetylhydroxylamine (12).

To a solution of (R)-*N*-(3-butyn-2-yl)-*N*-hydroxyurea (128 mg, 1 mmol) and (S)-α-methoxyphenylacetic acid (166 mg, 1 mmol) in anhydrous CH_2Cl_2 (20 mL) was added CDI (162 mg, 1 mmol) and the mixture was stirred at room temperature for 14 h. The raction was diluted with ethyl acetate (40 mL) and the resulting solution was washed with water, 10% citric acid, water, 10% solution of sodium bicarbonate, brine, dried with anhydrous $MgSO_4$ and concentrated in vacuo to obtain 270 mg of crude product. Crystallization from toluene gave crystals for X-ray crystallography: mp 144-145 °C; $[\alpha]_D^{20}$ = +7.3 (c = 0.11, THF); ^1H NMR (300 MHz, DMSO-d_6) δ 0.62 (m, 3 H), 3.12 (d, J = 2.5 Hz, 1 H), 3.33 (s, 3 H), 4.82 (d-q, J = 2.5 and 7 Hz, 1 H), 5.22 (s, 1 H), 7.03 (br s, 2 H), 7.41 (m, 5 H); MS (DCI-NH_3) m/z 277 $(M + H)^+$, 294 $(M + NH_4)^+$; Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83; N, 10.13. Found: C, 61.08; H, 5.83; N, 10.10.

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