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Asymmetric synthesis of N-substituted *N*-hydroxyureas

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Abstract—Asymmetric synthesis of (*S*)-*N*-(1-arylethyl)-*N*-hydroxyureas, (*S*)-*N*-(6-methoxy)- and (*S*)-*N*-(6-benzyloxy-2,3-dihydrobenzofuran-3-yl)-*N*-hydroxyurea— lipoxygenase inhibitor, is described. Three approaches to the formation of the *N*-hydroxyurea moiety at the stereogenic center have been used. The first one, via the reaction of (*R*)-6-benzyloxy-2,3-dihydrobenzofuran-3-ol with *N*,*O*-bis(phenoxycarbonyl)hydroxylamine under Mitsunobu conditions, leads to a partially racemized product. Alternatively, the enantioselective reduction of oximes *O*-benzyl ethers of acetophenone, 4-methoxy- and 4-benzyloxyacetophenone, 6-methoxy- and 6-benzyloxy-2,3-dihydrobenzofuran-3-one with borane/oxazaborolidines can be controlled to produce either the corresponding hydroxylamine *O*-benzyl ethers or primary amines which have been transformed into N-substituted *N*-hydroxyureas in 57% to 99% ee.

1. Introduction

N-Hydroxyureas are inhibitors of various metal-containing hydrolytic and redox enzymes.[1–5] They also serve as donors of nitric oxide, a potent physiologically active compound.[6,7] Certain N-substituted *N*-hydroxyureas, derived from 2,3-dihydrobenzofuran, tetrahydrofuran, benzothiophene, and thiophene, are 5-lipoxygenase inhibitors exhibiting antiasthmatic, antiallergic, and antiinflammatory activities.[8–14] Syntheses of two such non-racemic inhibitors, (*R*)-*N*-1-(benzothiophen-2-yl)ethyl-*N*-hydroxyurea—an antiasthmatic drug Zileuton®, and (*S*)-*N*-(6-benzyloxy-2,3-dihydrobenzofuran-3-yl)-*N*-hydroxyurea **4**, using chiral pool precursors or chiral auxiliaries, have been reported.[15–18] Herein, we focused on the asymmetric synthesis of *N*-1-arylethyl- and *N*-(2,3-dihydrobenzofuran-3-yl)-*N*-hydroxyureas via enantioselective reduction of the corresponding ketones or their oximes *O*-ethers as a key transformation generating a stereogenic center.

2. Results and discussion

In the first approach, the reduction of 6-benzyloxy-2,3-dihydrobenzofuran-3-one **1** with borane/oxazaborolidine **5** generated from (1*R*,2*S*)-norephedrine produced (*R*)-6-benzyloxy-2,3-dihydrobenzofuran-3-ol **2** with an unexpectedly low enantioselectivity (Scheme 1). A moderate selectivity was achieved in the reduction of **1** with a modified sodium tetrahydridoborate catalyzed with β-ketoiminato cobalt(II) complex[19] **6**. Fortunately, oxazaborolidine **7**, generated from tributoxyborane and a terpene amino alcohol (1*R*,2*S*,3*R*,5*S*)-3-amino-bicyclo[3.1.1]heptan-2-ol,[20] was a more selective catalyst; the reduction of **1** in the presence of borane produced **2** in 87% ee.

In the next step, the reaction of a model (*S*)-1-phenylethanol, 93% ee, with *N*,*O*-bis(diphenoxycarbonyl)hydroxylamine[21] **8**, under Mitsunobu conditions, followed by a treatment with ammonia produced (*R*)-*N*-1-phenylethyl-*N*-hydroxyurea in 88% ee indicating a slight racemization. However, the transformation of **2**, 87% ee, carried out under the same conditions, proceeded with more extensive racemization producing **4** of 31% ee (Scheme 1). Changing the conditions of the reaction and substituting other phosphines for triphenylphosphine have not improved the enantiomeric excess of **4**. Apparently, the electron-donating effect of the 6-benzyloxy group favors the competing reaction path leading to partial racemization, which has also been observed in the Mitsunobu reaction of *ortho*- and *para*-alkoxybenzylic alcohols.[22,23]

In the second approach, 6-methoxy- and 6-benzyloxy-2,3-dihydrobenzofuran-3-one oximes, **9** and **15**, were converted

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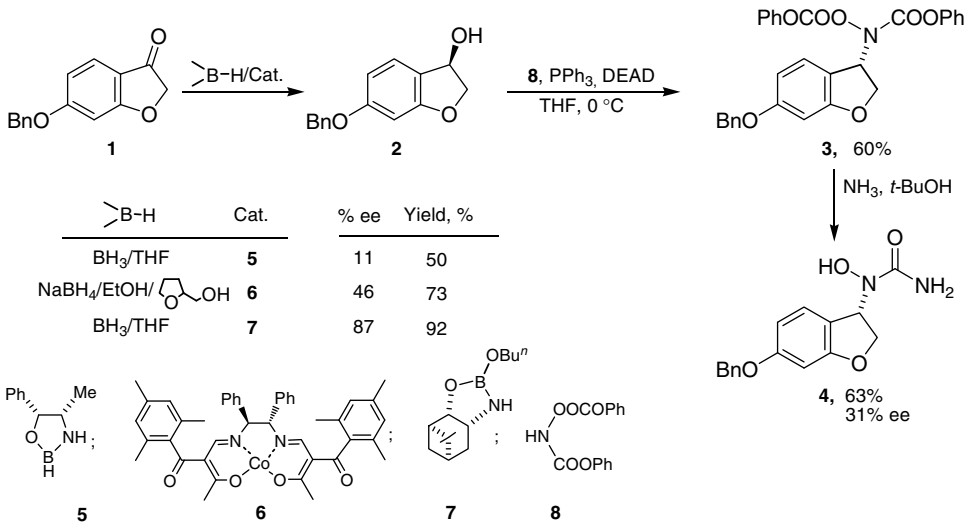
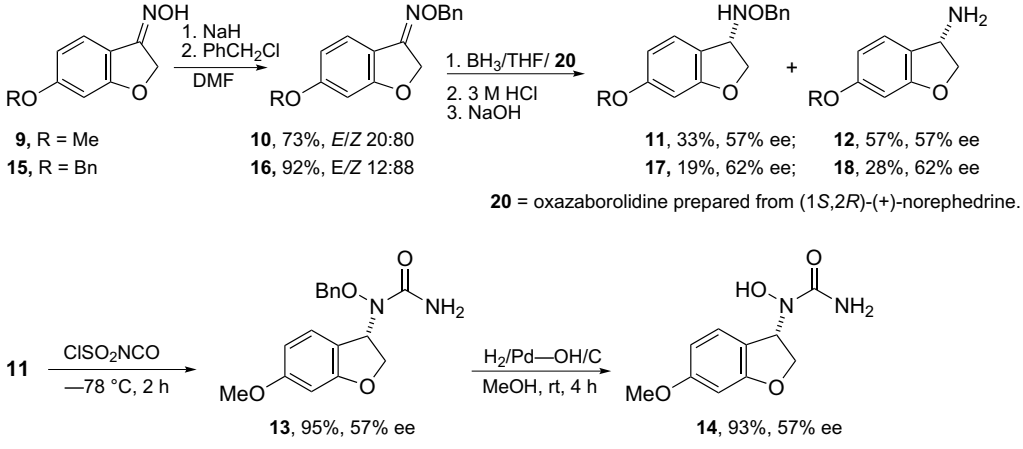


Scheme 1.

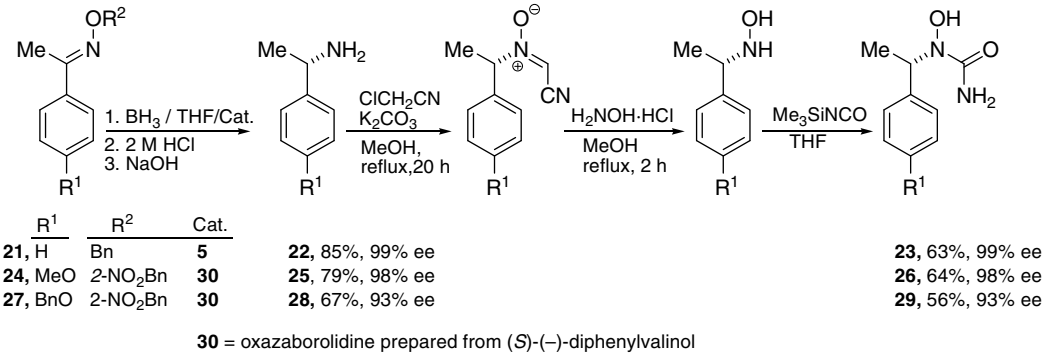
into their *O*-benzyl ethers **10** (*E*/*Z*, 20:80) and **16** (*E*/*Z* 12:88). The ethers were reduced with borane–tetrahydrofuran/oxazaborolidine **20** (1.0:1.5:1.5, 30 h at room temperature), and a mixture of N-substituted hydroxylamine *O*-benzyl ethers and primary amines **11**, **12** of 57% ee and **17**, **18**, of 62% ee, respectively, was obtained (Scheme 2). However, the selectivity of the reduction depends on the *E*/*Z* ratio and the reaction conditions. Thus, when **10**, enriched with *Z*-isomer (*E*/*Z* 8:92), was reduced with borane–tetrahydrofuran/**20** (1.0:1.3:1.3, 15 h at room temperature), **11** was obtained in 83.5% ee and 56% yield.

Hydroxylamine-*O*-benzyl ether **11** was separated as its hydrochloride, crystallizing during the acidic work-up of the reduction products, and free **11** was liberated by alkalization. Its debenzylation by hydrogenolysis on $Pd(OH)_2$/C resulted in the nitrogen–oxygen bond cleavage producing amine **12**. To circumvent the undesired reaction direction, **11** was transformed into *N*-benzyloxyurea derivative **13** which was readily debenzylated by hydrogenolysis on a Pd/C catalyst to give **14** in 57% ee. The same sequence of reactions applied to **17**, under the same conditions as used with **11**, to give the corresponding *N*-benzyloxyurea derivative. Unfortunately, its debenzylation resulted in the removal of both benzyl groups.

Consequently, in order to avoid the unselective debenzylation, and the separation of hydroxylamine ethers from amines, the approach was modified by adapting the amines as key intermediates leading to N-substituted *N*-hydroxyureas. Thus, in the phenyl series, acetophenone and 4-methoxyacetophenone (*E*)-oxime ethers, **21** and **24**, were reduced with borane/oxazaborolidines to amines **22**, 99% ee, and **25**, 98% ee, respectively (Scheme 3). Similarly, 4-benzyloxyacetophenone (*E*)-oxime ether **27** was reduced with borane/oxazaborolidine **30** to give **28**, 93% ee. The next step was the oxidation of these primary amines to the corresponding hydroxylamines. A few methods for such a conversion have been reported,[24–34] and we tested the most suitable procedures. Thus, the direct oxidation of **22** with hydrogen peroxide–urea complex, catalyzed by sodium tungstate, produced acetophenone oxime instead of the expected 1-phenylethylhydroxylamine.[24] This



Scheme 2.



Scheme 3.

sequence of transformations:[25] primary amine–*N*-cyanomethylamine–nitrone–N-substituted hydroxylamine, followed by its conversion into N-substituted *N*-hydroxyurea, worked well with amines **22**, **25**, and **28** (Scheme 3).

The enantiomeric excesses of the product *N*-hydroxyureas **23**, **26**, and **29** were the same as the starting amines, indicating that no racemization had occurred in the sequence of reactions. However, the sequence gave a mixture of products when applied to **18** prepared by the reduction of **16** (*E*/*Z* 12:88) with an excess of borane/oxazaborolidine **20**. Fortunately, **18** was transformed into hydroxylamine **31** using a modified method via an imine, oxaziridine, and then its acidic hydrolysis[26] (Scheme 4). Treatment of **31** with trimethylsilyl isocyanate produced **4** in 62% ee.

The enantiomeric excess of **4** was the same as the starting amine **18**. The amine in a higher enantiomeric excess can be prepared by the reduction of pure (*Z*)-benzyl or (*Z*)-2-nitrobenzyl ether of **15** with borane/oxazaborolidine **20**.

3. Conclusions

The reaction of (*R*)-6-benzyloxy-2,3-dihydroxybenzofuran-3-ol **2** with **8**, under Mitsunobu conditions, proceeded with extensive racemization preventing its use for the enantioselective formation of the hydroxylamine functionality at the 3-position. In the second approach, the enantioselective reduction of ketoxime *O*-benzyl ether **10** with borane/oxazaborolidine **20** produced a mixture of the corresponding hydroxylamine *O*-benzyl ether **11** and primary amine **12**. Separation of **11**, conversion into *N*-benzyloxyurea **13**, and deprotection by catalytic hydrogenolysis provided **14**. The route is applicable to ketoxime ethers lacking functionalities sensitive to palladium-catalyzed hydrogenation.

The third approach, via primary amines, avoids the separation and deprotection steps. Primary amines **22**, **25**, **28**, and **18** in 62–99% ee were obtained by the enantioselective reduction of ketoxime *O*-benzyl and 2-nitrobenzyl ethers with an excess of borane/oxazaborolidines. They were then oxidized to the corresponding hydroxylamines, and readily converted into *N*-hydroxyureas **23**, **26**, **29**, and **31**, with no racemization.

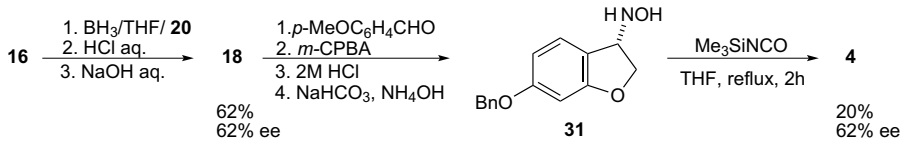
4. Experimental

4.1. General

Experiments with air and moisture sensitive materials were carried under a nitrogen atmosphere. Glassware was oven-dried for several hours, assembled hot, and cooled in a stream of nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 multinuclear instrument and on a Bruker AMX 300 MHz instrument. MS spectra were recorded on an AMD 604 spectrometer. Optical rotations were measured on a PolAAr 3000 automatic polarimeter. GC analyses were performed on a Perkin–Elmer AutoSystem XL chromatograph. HPLC analyses were performed on a Shimadzu LC-10AT chromatograph. Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were performed by Microanalysis Laboratory, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw.

4.2. Materials

Silica gel 60, E. Merck 230–400 mesh, was used for preparative column chromatography. Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV_{254} 0.2 mm plates. THF was freshly distilled from sodium benzophenone ketyl. 6-Hydroxy-2,3-dihydrobenzofuran-3-one,[35] its 6-benzyloxy derivative,[18] (1*R*,2*S*,3*R*,5*R*)-3-amino-6,6-dimethylbicyclo[3.1.1]heptan-3-ol,[20] 99% ee, *N*,*O*-bis(phenoxycarbonyl)-hydroxyamine,[21] (*S*)-(−)-diphenyl-



Scheme 4.

valinol,[36,37] 99% ee were prepared according to the literature procedures. Catalyst **6** (TCI) and (+)- and (−)-norephedrine (Aldrich) were commercial materials.

4.3. 6-Benzyloxy-2,3-dihydrobenzofuran-3-one 1

To a stirred mixture of 6-hydroxy-2,3-dihydrobenzofuran-3-one[35] (3.00 g, 20 mmol), dimethylformamide (50 mL), and anhydrous potassium carbonate, benzyl chloride (3.90 g, 31 mmol) was added dropwise over 30 min and the mixture was stirred for 24 h at rt. Water (75 mL) was added and the mixture was kept in a refrigerator for 3 h. The precipitate which was formed was filtered off and dried. After crystallization from cyclohexane in the presence of Darco G-60 active charcoal, the product was obtained: 4.20 g, 87%; mp 99–101 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.62 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.61 (d, $J = 2.1$ Hz, 1H, CH), 6.73 (dd, $J = 2.1$, 8.6 Hz, 1H, CH), 7.35–7.44 (m, 5H), 7.58 (d, $J = 8.6$ Hz, 1H, CH), lit.[7] ^{1}H NMR reported; ^{13}C NMR (50 MHz, $CDCl_3$) δ 70.53 (CH_2), 75.46 (CH_2), 97.37 (CH), 112.09 (CH), 125.08 (CH), 127.43 (CH), 128.38 (CH), 128.71 (CH), 114.51 (C), 135.50 (C), 167.14 (C), 176.31 (C), 197.40 (CO).

4.4. (*R*)-6-Benzyloxy-2,3-dihydrobenzofuran-3-ol 2

A solution of (1*R*,2*S*,3*R*,5*R*)-3-amino-6,6-dimethylbicyclo[3.1.1]heptan-3-ol[20] (16 mg, 0.1 mmol), tributoxyborane (28 mg, 0.12 mmol) in tetrahydrofuran (2 mL) was stirred for 1 h at rt under nitrogen atmosphere, and a solution of borane–dimethyl sulfide complex (10 M, 0.1 mL, 1 mmol) was added. After 15 min, a solution of **1** (0.24 g, 1 mmol) in tetrahydrofuran (1 mL) was added in 30 min, and the mixture was stirred for 1 h. Methanol (3 mL) was added and after 15 min the volatiles were removed under 0.5 mmHg at rt. The product was isolated by chromatography on a silica gel column (petroleum ether/ethyl acetate, 3:2): 0.22 g, 92%; mp 114–115 °C; $[\alpha]_D^{20} = -48.9$ (*c* 1.5, $CHCl_3$). HPLC analysis on a chiral column OD-H (*n*-hexane/isopropanol, 4:1), 87% ee, 0.6 mL/min, t_R 13.2*S*, 14.6*R*. The racemate was also analyzed. Configuration assignment is based on the correlation with *N*-hydroxyurea **4** of known configuration.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (dd, $J = 2.4$, 10.8 Hz, 1H, CH_2), 4.56 (dd, $J = 6.3$, 10.8 Hz, 1H, CH_2), 5.05 (s, 2H, CH_2), 5.30 (dd, $J = 2.4$, 6.3 Hz, 1H, CH), 6.51 (d, $J = 2.4$ Hz, 1H, CH), 6.57 (dd, $J = 2.4$, 8.4 Hz, 1H, CH), 7.30 (d, $J = 8.4$ Hz, 1H, CH), 7.32–7.44 (m, 5H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.25 (CH_2), 80.30 (CH_2), 71.87 (CH), 97.29 (CH), 108.38 (CH), 125.73 (CH), 127.40 (CH), 128.01 (CH), 128.59 (CH), 108.93 (C), 120.84 (C), 136.70 (C), 161.83 (C); Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.12; H, 5.98.

4.5. (*S*)-(+)-*N*-(6-Benzyloxy-2,3-dihydrobenzofuran-3-yl)-*N*-hydroxyurea 4

4.5.1. Method 1. To a solution of **2** (0.73 g, 3.0 mmol, 87% ee), **8** (1.23 g, 4.5 mmol), and triphenylphosphine (1.18 g, 4.5 mmol) in tetrahydrofuran (30 mL), a solution of diethyl azidodicarboxylate (0.78 g, 4.5 mmol) in tetrahydrofuran (5 mL) was slowly added at 0 °C, and the mixture was stirred in an ice-water bath for 4 h. Solvents were removed under vacuum and **3** was isolated by column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1): 0.90 g, 60%; mp 109–111 °C. To a solution of **3** (0.75 g, 1.5 mmol) in *tert*-butanol (3 mL) at −78 °C, liquid ammonia (2 mL) was added, the mixture was stirred in a glass pressure vessel for 3 h at rt, and then left overnight at 0 °C. After cooling to −78 °C, *n*-hexane (5 mL) was added and the volatiles were removed on a rotary evaporator. The product was isolated by column chromatography on silica gel, (methanol/dichloromethane, 5:95): 0.28 g, 62%; mp 172–174 °C; $[\alpha]_D^{20} = +30.0$ (*c* 1.0, DMSO), 31% ee. Lit.[18] $[\alpha]_D^{20} = +97.2$ (*c* 1.0, DMSO), 100% ee.

4.5.2. Method 2. To a solution of **18** (62% ee, 1.20 g, 5 mmol) in chloroform (10 mL) was added 4-methoxybenzaldehyde (0.68 g, 5 mmol) and the mixture was stirred for 20 h at rt. The solution was dried with anhydrous magnesium sulfate, and the solvent was removed under vacuum. Dichloromethane (20 mL) was added followed by 70% *m*-chloroperbenzoic acid (1.50 g, 6 mmol) at 0 °C, and the mixture was stirred for 3 h. Precipitated solid was filtered off and washed with dichloromethane (5 mL). The filtrate was washed with saturated sodium hydrogen carbonate solution (10 mL), water (10 mL), and saturated brine (10 mL), and then dried with magnesium sulfate. The solvent was removed, diethyl ether (10 mL) and 2 M hydrochloric acid (10 mL) were added, and the mixture was vigorously stirred for 20 h. The aqueous layer was separated, extracted with diethyl ether (2 × 10 mL), and basified with saturated sodium hydrogen carbonate solution (20 mL) and aqueous ammonia (10 mL). The mixture was extracted with ethyl acetate (2 × 20 mL), and the extract was dried with anhydrous magnesium sulfate, filtered, and concentrated to give crude **31**, 0.30 g. To this solution in tetrahydrofuran (5 mL) was added trimethylsilylisocyanate (0.10 g, 0.9 mmol) and the mixture was refluxed for 2 h. After cooling to rt, a saturated aqueous solution of ammonium chloride (5 mL) was added and the mixture was extracted with ethyl acetate (2 × 10 mL). The extract was washed with saturated brine (10 mL) and was dried with anhydrous magnesium sulfate. After filtration and concentration, the product was isolated by column chromatography on silica gel, (methanol/dichloromethane, 5:95): 0.20 g, 20%; mp 172–174 °C; $[\alpha]_D^{20} = +60.3$ (*c* 1.0, DMSO), 62% ee. Lit.[18] mp 174–176 °C. $[\alpha]_D^{20} = +97.2$ (*c* 1.0, DMSO), 99% ee. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.44 (dd, $J = 4.4$, 9.8 Hz, 1H, CH_2), 4.55 (dd, $J = 8.8$, 9.8 Hz, 1H, CH_2), 5.05 (s, 2H, CH_2), 5.77 (dd, $J = 4.4$, 8.8 Hz, 1H, CH), 6.45 (d, $J = 2.3$ Hz, 1H, CH), 6.48 (s, 2H, NH_2), 6.50 (dd, $J = 2.3$, 8.1 Hz, 1H, CH), 7.06 (d, $J = 8.1$ Hz, 1H, CH), 7.28–7.46 (m, 5H, CH), 9.12 (s, 1H, OH).

4.6. 6-Methoxy-2,3-dihydrobenzofuran-3-one

To a mixture of 6-hydroxy-2,3-dihydrobenzofuran-3-one[35] (9.13 g, 60 mmol), dimethylfomamide (100 mL), and anhydrous potassium carbonate (16.59 g, 120 mmol), methyl iodide (14.19 g, 100 mmol) was added and the mixture was stirred for 24 h at rt. Cold water (400 mL) was added, after which the mixture was kept in a refrigerator for 3 h,

and a solid product was filtered off and dried: 7.98 g, 81%. After crystallization from cyclohexane in the presence of Darco G-60 active charcoal: mp 122–124 °C. Lit.[38] mp 120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 6.55 (d, $J = 2.04$ Hz, 1H, CH), 6.65 (dd, $J = 2.0$, 8.5 Hz, 1H, CH), 7.57 (d, $J = 8.5$ Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.84 (CH_3), 75.46 (CH_2), 96.31 (CH), 111.65 (CH), 125.03 (CH), 114.34 (C), 168.17 (C), 176.50 (C), 197.45 (CO).

4.7. (*E*/*Z*)-6-Methoxy-2,3-dihydrobenzofuran-3-one oxime 9

Hydroxylamine hydrochloride (6.95 g, 100 mmol) was added to a mixture of 6-methoxy-2,3-dihydrobenzofuran-3-one (8.20 g, 50 mmol) and anhydrous sodium acetate (8.20 g, 100 mmol) in ethanol (100 mL). The mixture was refluxed for 5 h, cooled and then added to water (300 mL). The precipitated solid was filtered off, washed with water (50 mL), and dried: 5.91 g, 66%; mp 128–130 °C; (*E*) 24%, (*Z*) 76%. Lit.[39] solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 3H, CH_3), 5.05 (s, 2H, CH_2, 24%), 5.12 (s, 2H, CH_2, 76%), 6.52–6.60 (m, 2H, CH), 7.39 (d, $J = 8.4$ Hz, 1H, CH, 76%), 7.95 (d, $J = 8.4$ Hz, 1H, CH, 24%), 10.99 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ, the major isomer, 55.61 (CH_3), 71.50 (CH_2), 96.36 (CH), 108.95 (CH), 121.82 (CH), 112.71 (C), 154.78 (C), 163.08 (C), 166.43 (C).

4.8. (*E*/*Z*)-6-Methoxy-2,3-dihydrobenzofuran-3-one oxime *O*-benzyl ether 10

A solution of **9** (3.58 g, 20 mmol) in DMF (20 mL) was added to a mixture of sodium hydride (0.60 g, 25 mmol) and DMF (40 mL) at 0 °C and the mixture was stirred for 3 h at rt. A solution of benzyl chloride (3.16 g, 25 mmol) in DMF (20 mL) was then added and stirring was continued for 24 h at rt. Water (300 mL) was added and the mixture was kept in a refrigerator for 3 h. The precipitated solid was filtered off, washed with water (50 mL), and the product was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1): 3.93 g, 73%; mp 46–49 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.81 (s, 3H, CH_3), 5.04 (s, 2H, CH_2, 20%), 5.14 (s, 2H, CH_2, 80%), 5.18 (s, 2H, CH_2, 80%), 5.20 (s, 2H, CH_2, 20%), 6.46 (d, $J = 2.2$ Hz, 1H, CH), 6.56 (dd, $J = 2.2$, 8.6 Hz, 1H, CH), 7.25–7.45 (m, 5H, CH), 7.49 (d, $J = 8.6$ Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.47 (CH_3), 71.84 (CH_2), 76.36 (CH_2), 96.11 (CH), 109.20 (CH), 122.56 (CH), 127.82 (CH), 128.03 (2CH), 128.32 (2CH), 112.15 (C), 137.75 (CH), 156.77 (C), 163.94 (C), 167.34 (C). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.75; H, 5.74; N, 5.09.

4.9. (*S*)-(+)-*N*-6-Methoxy-2,3-dihydrobenzofuran-3-yl hydroxylamine *O*-benzyl ether 11

To a solution of (1*S*,2*R*)-(+)-norephedrine (4.54 g, 30 mmol) in tetrahydrofuran (30 mL) was added 1.5 M borane–tetrahydrofuran solution (40 mL, 60 mmol) at 0 °C and the mixture was stirred at this temperature for 5 h. A solution of **10** (5.39 g, 20 mmol) in tetrahydrofuran (50 mL) was added, and stirring was continued for 24 h at rt. Hydrochloric acid (3 M, 80 mL) was added at 0 °C and the mixture was stirred for 30 h at rt. The precipitated solid was filtered off and washed with diethyl ether (20 mL), after which water (20 mL) was added, and the mixture was basified with a solution of ammonia to pH ~ 10. The mixture was extracted with ethyl acetate (2 × 100 mL) and the extract was dried with anhydrous magnesium sulfate. Volatiles were removed under vacuum at rt and a pale yellow oil was obtained: 1.79 g, 33%; $[\alpha]_D^{20} = +21.5$ (*c* 1.7, $CHCl_3$). HPLC analysis on a chiral OD-H column (*n*-hexane/isopropanol, 98:2), 57% ee, 0.6 mL/min, t_R 20.28*S*, 21.99*R*. Racemate was also analyzed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.77 (s, 3H, CH_3), 4.49 (dd, $J = 7.0$, 10.0 Hz, 1H, CH_2), 4.58 (dd, $J = 3.0$, 10.0 Hz, 1H, CH_2), 4.70 (m, 1H, CH), 4.72 (s, 2H, CH_2), 5.45 (br s, 1H, NH), 6.41 (d, $J = 2.2$ Hz, 1H, CH), 6.44 (dd, $J = 2.4$, 8.0 Hz, 1H, CH), 7.21 (d, $J = 8.0$ Hz, 1H, CH), 7.30–7.40 (m, 5H, CH); ^{13}C NMR ($CDCl_3$) δ 55.49 (CH_3), 76.11 (CH_2), 76.54 (CH_2), 62.09 (CH), 96.32 (CH), 106.72 (CH), 126.02 (CH), 127.92 (CH), 128.40 (2CH), 128.48 (2CH), 117.16 (C), 137.63 (C), 161.96 (C), 162.31 (C). HRMS (*m*/*z*) calculated for $C_{16}H_{17}NO_3$: 271.12084. Found: 271.12195.

4.10. (*S*)-(+)-3-Amino-6-methoxy-2,3-dihydrobenzofuran 12

The acidic filtrate from the separation of the precipitated solid in the procedure described above was basified with 10% sodium hydroxide to pH ~ 12 and extracted with dichloromethane (3 × 30 mL). The combined extract was washed with water (10 mL) and dried with anhydrous magnesium sulfate. The solvent was removed and the product was isolated by column chromatography on silica gel (ethyl acetate/methanol/triethylamine, 70:30:1): 1.88 g, 57%; $[\alpha]_D^{20} = +12.5$ (*c* 1.8, $CHCl_3$). HPLC analysis of benzamide derivative on the OD-H chiral column (*n*-hexane/isopropanol, 9:1), 57% ee, 0.6 mL/min, t_R 30.20*R*, 32.76*S*. Racemate was also analyzed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62 (br s, 2H, NH_2), 3.77 (s, 3H, CH_3), 4.39 (dd, $J = 4.2$, 9.3 Hz, 1H, CH_2), 4.56 (dd, $J = 4.2$, 7.8 Hz, 1H, CH), 4.66 (dd, $J = 7.8$, 9.3 Hz, 1H, CH_2), 6.39 (d, $J = 2.2$ Hz, 1H, CH), 6.47 (dd, $J = 2.2$, 8.2 Hz, 1H, CH), 7.18 (d, $J = 8.2$ Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.25 (CH_3), 80.63 (CH_2), 53.26 (CH), 96.02 (CH), 106.61 (CH), 124.43 (CH), 123.03 (C), 160.85 (C), 161.08 (C). Hydrochloride, mp 162–163 °C (decomp.). Anal. Calcd for $C_9H_{12}ClNO_2$: C, 53.61; H, 6.00; N, 6.95. Found: C, 53.44; H, 5.98; N, 6.88.

4.11. (*S*)-(+)-*N*-(6-Methoxy-2,3-dihydrobenzofuran-3-yl)-*N*-benzyloxyurea 13

To a solution of **11** (1.09 g, 4 mmol) in dichloromethane (10 mL) under nitrogen was added chlorosulfonylisocyanate (0.82 g, 5.8 mmol) at −78 °C and the mixture was stirred for 2 h. Water (20 mL) was added and stirring was continued for 16 h. Dichloromethane (20 mL) was added, the organic layer was separated, washed with water (50 mL), saturated brine (20 mL), and dried with anhydrous magnesium sulfate. After filtration and concentration, the product was obtained: 1.20 g, 95%; mp 158–159 °C; $[\alpha]_D^{20} = +0.9$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (s, 3H, CH_3), 4.35 (d, $J = 10.0$ Hz, 1H,

CH_2), 4.53 (d, $J = 10.0$ Hz, 1H, CH_2), 4.55 (dd, $J = 8.0$, 10.0 Hz, 1H, CH_2), 4.63 (dd, $J = 4.0$, 10.0 Hz, 1H, CH_2), 5.28 (br s, 2H, NH_2), 5.93 (dd, $J = 4.0$, 8.0 Hz, 1H, CH), 6.50–6.60 (m, 2H, CH), 7.00–7.15 (m, 2H, CH), 7.20–7.40 (m, 4H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.51 (CH_3), 74.61 (CH_2), 79.27 (CH_2), 60.47 (CH), 96.14 (CH), 107.19 (CH), 126.34 (CH), 128.60 (2CH), 128.84 (CH), 129.18 (2CH), 115.98 (C), 134.56 (C), 161.22 (C), 162.24 (C), 163.03 (C). HRMS (*m*/*z*) calculated for $C_{17}H_{18}N_2O_4$: 314.12666. Found: 314.12757.

4.12. (*S*)-(+)-*N*-(6-Methoxy-2,3-dihydrobenzofuran-3-yl)-*N*-hydroxyurea 14

To a solution of **13** (0.88 g, 2.8 mmol) in methanol (40 mL), 20% $Pd(OH)_2$/C (0.10 g) was added and the mixture was vigorously stirred under hydrogen at 30 °C for 4 h. The catalyst was filtered off, the solvent was removed, and the product was obtained: 0.49 g, 93%; mp 158–160 °C; $[\alpha]_D^{20} = +72.6$ (*c* 1.5, DMSO), 57% ee. ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.70 (s, 3H, CH_3), 4.45 (dd, $J = 4.4$, 9.8 Hz, 1H, CH_2), 4.56 (dd, $J = 9.0$, 9.8 Hz, 1H, CH_2), 5.78 (dd, $J = 4.4$, 9.0 Hz, 1H, CH), 6.36 (d, $J = 2.2$ Hz, 1H, CH), 6.41 (dd, $J = 2.2$, 8.2 Hz, 1H, CH), 6.50 (s, 2H, NH_2), 7.08 (d, $J = 8.2$ Hz, 1H, CH), 9.12 (s, 1H, OH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 55.29 (CH_3), 73.17 (CH_2), 58.94 (CH), 95.51 (CH), 106.33 (CH), 125.53 (CH), 117.51 (C), 161.09 (C), 161.78 (C), 162.10 (C); MS (EI, 70 eV) *m*/*z* 224 (M^+, 0.3), 163 (10.46), 150 (15.39), 149 (100.00), 148 (53.88), 134 (15.07), 133 (37.60), 121 (82.78), 91 (10.92), 78 (11.02), 77 (25.48), 63 (11.22), 51 (14.12), 43 (14.46); Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.08; H, 5.53; N, 12.69. Found: C, 53.56; H, 5.39; N, 12.49.

4.13. (*E*/*Z*)-6-Benzyloxy-2,3-dihydrobenzofuran-3-one oxime 15

A mixture of **1** (12.01 g, 50 mmol), hydroxylamine hydrochloride (6.95 g, 100 mmol), sodium acetate (8.20 g, 100 mmol), and ethanol (200 mL) was refluxed for 3 h. After cooling, water (300 mL) was added, and the precipitated product was filtered off: 11.51 g, 90%; mp 159–160 °C (decomposition); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.05 (s, 2H, CH_2, 12% *E*), 5.12 (s, 2H, CH_2, 88% *Z*), 6.64 (dd, $J = 2.1$, 8.4 Hz, 1H, CH), 6.70 (d, $J = 2.1$ Hz, 1H, CH), 7.30–7.45 (m, 6H, CH), 11.00 (s, 1H, OH, 88% *Z*), 11.01 (s, 1H, OH, 12% *E*). Lit.[18] NMR reported. ^{13}C NMR (75 MHz, DMSO-d_6) the major isomer, δ 69.58 (CH_2), 71.47 (CH_2), 97.28 (CH), 109.63 (CH), 121.82 (CH), 127.72 (2CH), 127.92 (CH), 128.44 (2CH), 112.93 (C), 136.58 (C), 154.66 (C), 162.39 (C), 166.92 (C); Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.32; H, 5.13; N, 5.26.

4.14. (*E*/*Z*)-6-Benzyloxy-2,3-dihydrobenzofuran-3-one oxime *O*-benzyl ether 16

A solution of **15** (12.76 g, 50 mmol) in DMF (100 mL) was added to a mixture of sodium hydride (1.44 g, 60 mmol) and DMF (50 mL) at 0 °C. The mixture was stirred for 3 h at rt, and a solution of benzyl chloride (7.60 g, 60 mmol) in DMF (50 mL) was added and stirring was continued for 20 h at rt. Water (500 mL) was added and the mixture was kept in a refrigerator for 2 h. The precipitated product was filtered off, washed with water (50 mL), and dried. Crystallization from *n*-hexane gave 19.06 g, 92%; mp 102–104 °C; *E*/*Z* 12:88; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (s, 2H, CH_2, 12%), 5.07 (s, 2H, CH_2, 88%), 5.13 (s, 2H, CH_2), 5.19 (s, 2H, CH_2, 88%), 5.20 (s, 2H, CH_2, 12%), 6.53 (d, $J = 2.1$ Hz, 1H, CH), 6.63 (dd, $J = 2.1$, 8.7 Hz, 1H, CH), 7.30–7.45 (m, 10H, CH), 7.50 (d, $J = 8.7$ Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.26 (CH_2), 71.89 (CH_2), 76.49 (CH_2), 97.21 (CH), 109.93 (CH), 122.67 (CH), 127.42 (2CH), 127.88 (CH), 128.07 (2CH), 128.13 (CH), 128.36 (2CH), 128.62 (2CH), 112.44 (C), 136.24 (C), 137.73 (C), 156.79 (C), 163.05 (C), 167.28 (C); Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H 5.61; N, 4.05. Found: C, 76.26; H, 5.54; N, 4.07.

4.15. (*Z*)-6-Benzyloxy-2,3-dihydrobenzofuran-3-one oxime *O*-2-nitrobenzyl ether

Prepared from **15** (2.55 g, 10 mmol) and 2-nitrobenzyl bromide (2.38 g, 11 mmol) following the procedure described above. The product was crystallized from ethanol and then from 1-chlorobutane: 1.79 g, 46%; mp 105–107 °C (>99% *Z*); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.07 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 6.55 (d, $J = 2.0$ Hz, 1H, CH), 6.63 (dd, $J = 2.0$, 8.4 Hz, 1H, CH), 7.30–7.49 (m, 7H, CH), 7.60–7.65 (m, 2H, CH), 8.08 (d, $J = 8.0$ Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 70.30 (CH_2), 71.72 (CH_2), 72.92 (CH_2), 97.27 (CH), 110.13 (CH), 122.83 (CH), 124.70 (CH), 127.40 (2CH), 128.16 (2CH), 128.63 (2CH), 128.99 (CH), 133.43 (CH), 112.10 (C), 134.75 (C), 136.19 (C), 147.62 (C), 157.59 (C), 163.31 (C), 167.43 (C).

4.16. (*S*)-(+)-*N*-(6-Benzyloxy-2,3-dihydrobenzofuran-3-yl)hydroxylamine *O*-benzyl ether 17

A 1.5 M borane–tetrahydrofuran solution (40 mL, 60 mmol) was added to a solution of (1*S*,2*R*)-(+)-norephedrine (4.54 g, 30 mmol) in tetrahydrofuran (30 mL) at 0 °C and the mixture was stirred for 5 h. A solution of **16** (6.91 g, 20 mmol) in tetrahydrofuran (60 mL) was added, and the mixture was stirred for 20 h at rt. A 3 M hydrochloric acid (80 mL) was added and stirring was continued for 30 h. Tetrahydrofuran was removed on rotary evaporator and the remaining solution was alkalized to pH ~ 10 with 35% sodium hydroxide solution. The product was extracted with ethyl acetate (3 × 50 mL) and dried with anhydrous magnesium sulfate. The solvent was removed and the product isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1): 1.25 g, 19%; $[\alpha]_D^{20} = +12.1$ (*c* 1.1, $CHCl_3$). HPLC analysis on a chiral OD-H column (*n*-hexane/isopropanol, 95:5), 62% ee, 0.6 mL/min, t_R 30.03*S*, 35.82*R*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.49 (dd, $J = 7.2$, 10.0 Hz, 1H, CH_2), 4.58 (dd, $J = 3.2$, 10.0 Hz, 1H, CH_2), 4.69 (m, 1H, CH), 4.72 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.49 (br s, 1H, NH), 6.48 (d, $J = 2.2$ Hz, 1H, CH), 6.52 (dd, $J = 2.2$, 8.0 Hz, 1H, CH), 7.21 (d, $J = 8.0$ Hz, 1H, CH), 7.23–7.42 (m, 10H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 70.23 (CH_2), 76.08 (CH_2), 76.52

(CH_2), 62.10 (CH), 97.34 (CH), 107.60 (CH), 126.03 (CH), 127.39 (CH). HRMS (m/z) calculated for $C_{22}H_{21}NO_3$: 347.15214. Found: 347.15322. Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.13; H, 5.89; N, 4.05.

4.17. (*S*)-(+)-3-Amino-6-benzyloxy-2,3-dihydrobenzofuran 18

A 1.24 M borane–tetrahydrofuran solution (24.2 mL, 30 mmol) was added to a solution of (1*S*,2*R*)-(+)-norephedrine (2.27 g, 15 mmol) in tetrahydrofuran (20 mL) and the mixture was stirred for 4 h at 0 °C. A solution of **16** (2.42 g, 7 mmol) in tetrahydrofuran (10 mL) was added, and stirring was continued for 72 h at rt. A 2 M hydrochloric acid (90 mL) was added and the mixture was stirred for 24 h at rt. Tetrahydrofuran was removed under vacuum and the precipitated solid was filtered off, washed with diethyl ether (10 mL), and added to water (50 mL). The mixture was basified with solid sodium hydroxide to pH ~ 12. The mixture was extracted with diethyl ether (2 × 100 mL) and the extract dried with anhydrous magnesium sulfate, the solvent was removed, and the product was isolated by column chromatography on silica gel (ethyl acetate/methanol/triethylamine, 70:30:1): 1.06 g, 62%; mp 115–117 °C, $[\alpha]_D^{20} = +22.0$ (c 1.5, $CHCl_3$). HPLC analysis on a chiral OD-H column (*n*-hexane/isopropanol, 90:10), 62% ee, t_R 32.42*S*, 37.55*R*. The racemate was also analyzed. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00 (br s, 2H, NH_2), 4.02 (dd, $J = 4.8$, 8.4 Hz, 1H, CH), 4.49 (dd, $J = 4.80$, 8.0 Hz, 1H, CH_2), 4.56 (dd, $J = 8.0$, 8.4 Hz, 1H, CH_2), 5.04 (s, 2H, CH_2), 6.43 (d, $J = 2.1$ Hz, 1H, CH), 6.49 (dd, $J = 2.1$, 8.1 Hz, 1H, CH), 7.11 (d, $J = 8.1$ Hz, 1H, CH), 7.25–7.45 (m, 5H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 69.35 (CH_2), 80.24 (CH_2), 52.76 (CH), 96.48 (CH), 107.10 (CH), 125.03 (CH), 127.52 (2CH), 127,71 (CH), 128.00 (C), 128.37 (2CH), 137.16 (C), 159.41 (C), 160.65 (C); Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.80. Found: C, 74.50; H, 6.26; N, 5.67.

4.18. (*S*)-(−)-1-Phenylethylamine 22

4.18.1. Typical procedure. To a solution of (1*R*,2*S*)-(−)-norephedrine (4.54 g 30 mmol) in tetrahydrofuran (30 mL) was added 1.5 M borane–tetrahydrofuran solution (40.0 mL, 60 mmol) at 0 °C, and the mixture was stirred for 4 h. A solution of (*E*)-acetophenone oxime *O*-2-nitrobenzyl ether (7.75 g, 30 mmol) in tetrahydrofuran (90 mL) was added and stirring was continued for 20 h at rt. Next 2 M hydrochloric acid (120 mL) was added, and the mixture was stirred for 30 h at rt. Tetrahydrofuran was removed under vacuum and the remaining solution was alkalized with 20% aqueous sodium hydroxide solution to pH ~ 12. The mixture was extracted with ethyl acetate (4 × 100 mL). The extract was washed with saturated brine and dried with anhydrous magnesium sulfate. The product was isolated by column chromatography on silica gel, (chloroform/triethylamine 99:1): 3.40 g, 85%; $[\alpha]_D^{20} = -29.8$ (c 10, EtOH), 99% ee. Identified by comparison with an authentic sample (Aldrich), $[\alpha]_D^{20} = -30.0$ (c 10, EtOH).

4.19. (*S*)-(−)-1-(4-Methoxyphenyl)ethylamine 25

Prepared from (*E*)-4-methoxyacetophenone oxime *O*-2-nitrobenzyl ether by the reduction with borane/(*S*)-(−)-diphenylvalinol as described above: oil, 79%, $[\alpha]_D^{20} = -29.0$ (c 2.0, MeOH), 98.8% ee. Lit.[40] $[\alpha]_D^{20} = -28.8$ (c 2.0, MeOH), 98.1% ee.

4.20. (*S*)-(−)-1-(4-Benzyloxyphenyl)ethylamine 28

Prepared from 4-benzyloxyacetophenone oxime *O*-benzyl ether by the reduction with borane/(*S*)-(−)-diphenylvalinol as described above: 67%; mp 87–89 °C; $[\alpha]_D^{20} = -24.7$ (c 1.75, $CHCl_3$). HPLC analysis of trifluoroacetamide derivative on a chiral column OD-H (*n*-hexane/isopropanol, 9:1), 93% ee, 0.6 mL/min, t_R 8.32*S*, 8.91*R*. The racemate was also analyzed. The configuration assigned is based on the close similarity to **25** and the reduction of other 4-alkoxyacetophenone oxime ethers with (*S*)-(−)-diphenylvalinol.[37]

4.21. (*S*)-(−)-*N*-1-Phenylethyl-*N*-hydroxyurea 23

Prepared from **22**, 99% ee, following the reported methodology:[21,25] 63% yield; mp 132–134 °C; $[\alpha]_D^{20} = -50.6$ (c 1.25, EtOH). HPLC analysis on a chiral OJ column (*n*-hexane/ethanol, 95:5), 99% ee, 0.6 mL/min, t_R 29.89*S*, 37.48*R*. The configuration assigned is based on **22**. Racemate, mp 132–134 °C, was also analyzed. Lit.[21] mp 133–134 °C.

4.22. (*S*)-(−)-1-(4-Methoxyphenylethyl)-*N*-hydroxyurea 26

Prepared from **25**, 98% ee, following the reported methodology:[21,25] 78% ee; mp 130–131 °C; $[\alpha]_D^{20} = -41.1$ (c 1.2, DMSO), 98% ee. The configuration assigned is based on **25**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (d, $J = 7.2$ Hz, 3H, CH_3), 3.71 (s, 3H, CH_3), 5.22 (q, $J = 7.2$ Hz, 1H, CH), 6.23 (s, 2H, NH_2), 6.83 (d, $J = 8.7$ Hz, a half of AA′BB′ system, 2H, CH), 7.23 (d, $J = 8.7$ Hz, a half of AA′BB′ system, 2H, CH), 8.96 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.23 (CH_3), 54.36 (CH_3), 54.98 (CH), 113.19 (2CH), 128.65 (2CH), 133.99 (C), 158.09 (C), 161.44 (CO); MS: EI 70 eV, m/z 210 (M^+, 0.10), 136 (21.00), 135 (100.00), 134 (15.84), 105 (21.83), 91 (12.29), 77 (10.70).

4.23. (*S*)-(−)-1-(4-Benzyloxyphenylethyl)-*N*-hydroxyurea 29

Prepared from **28**, 93% ee, following the reported methodology:[21,25] 56% yield, mp 141–142 °C, $[\alpha]_D^{20} = -44.0$ (c 1.0, DMSO). HPLC analysis on a chiral OJ column (*n*-hexane/ethanol, 95:5), 93% ee, t_R 0.6 mL/min, 71.53*S*, 82.22*R*. The configuration assigned is based on **28**. Racemate, mp 140–142 °C, was also analyzed. Lit.[9] mp 140–141 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (d, $J = 6.9$ Hz, 3H, CH_3), 5.06 (s, 2H, CH_2), 5.22 (q, $J = 6.9$ Hz, 1H, CH), 6.23 (s, 2H, NH_2), 6.92 (d, $J = 8.7$ Hz, a half of AA′BB′ system; 2H, CH), 7.24 (d, $J = 8.7$ Hz, a half of AA′BB′ system, 2H, CH), 7.30–7.50 (m, 5H, CH), 8.97 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.18 (CH_3), 69.11 (CH_2), 54.37 (CH), 114.11 (2CH), 127.54 (2CH), 127.72 (CH), 128.39 (2CH), 128.56 (2CH), 134.25 (C), 137.24 (C), 157.18 (C), 161.43 (CO).

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