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Asymmetric synthesis of *N*-1-(heteroaryl)ethyl-*N*-hydroxyureas

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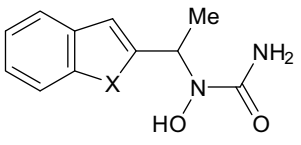
Dedicated to Professor Marian Mikołajczyk on the occasion of his 70th birthday

Abstract—The asymmetric synthesis of two 5-lipoxygenase inhibitors (*R*)-*N*-1-(benzofuran-2-yl)ethyl-*N*-hydroxyurea, 99% ee, and (*R*)-*N*-1-(benzo[*b*]thiophen-2-yl)ethyl-*N*-hydroxyurea, 95% ee, is described. The enantioselective reduction of 1-(benzofuran-2-yl)ethanone oxime *O*-benzyl ether and 1-(benzo[*b*]thiophen-2-yl)ethanone oxime *O*-benzyl ether with borane oxazaborolidine, generated from (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, was used for the formation of the stereogenic centres.

1. Introduction

Certain N-substituted *N*-hydroxyureas derived from arenes, furan, benzofuran, thiophene and benzo[*b*]thiophene, exhibit 5-lipoxygenase inhibiting activity.[1–4] 5-Lipoxygenase initiates the biosynthesis of leukotrienes, potent mediators of vascular inflammation and contraction of smooth muscles, involved in diseases such as allergy, asthma, psoriasis, inflammatory bowel disease and various cardiopulmonary diseases.[5–7] *N*-1-(Heteroaryl)ethyl-*N*-hydroxyureas **1** and **2** (Fig. 1) were the first 5-lipoxygenase inhibitors representing a new class of therapeutic agents containing the *N*-hydroxyurea functionality.[1–8] Zileuton® **2** has been introduced commercially as an anti-asthmatic and anti-inflammatory drug. Several syntheses of racemic **2**,[1,9–14] a resolution procedure[15] and three multistep syntheses of (*R*)-**2** using chiral pool precursors or chiral auxiliaries have also been reported.[16–18]



1, X = O
2, X = S, Zileuton® (Abbott Laboratories)

Figure 1.

Recently, we developed an asymmetric synthesis of (*S*)-*N*-1-(aryl)ethyl-*N*-hydroxyureas and (*S*)-*N*-(6-benzyloxy-2,3-dihydrobenzofuran-3-yl)-*N*-hydroxyurea.[19] Herein, we report on the asymmetric synthesis of (*R*)-**1** and (*R*)-**2** via the enantioselective reduction of 1-(benzofuran-2-yl)ethanone, its oxime ethers and 1-(benzo[*b*]thiophen-2-yl)ethanone oxime *O*-benzyl ether, respectively, as the key transformation generating stereogenic centres.

2. Results and discussion

1-(Benzofuran-2-yl)ethanone **3**, readily prepared from salicylic aldehyde and chloroacetone,[20] was reduced with borane/oxazaborolidine **4**, generated in situ from triisopropoxyborane and (1*S*,3*S*,4*R*,6*R*)-4-amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol,[21] producing (*S*)-1-(benzofuran-2-yl)ethanol **5**, 98% ee (Scheme 1). The reduction of **3** with borane/oxazaborolidines, generated from (1*S*,2*R*)-norephedrine or (*S*)-diphenylvalinol, resulted in a lower enantiomeric excess of **5**. In the next step, **5** was reacted with *N*,*O*-bis(diphenoxycarbonyl)hydroxylamine under Mitsunobu conditions.[22] The substitution product was treated with ammonia and (*R*)-**1**, 50% ee, was obtained in 76% yield.

The approach is short and convenient, but unfortunately, the substitution step results in partial racemization.

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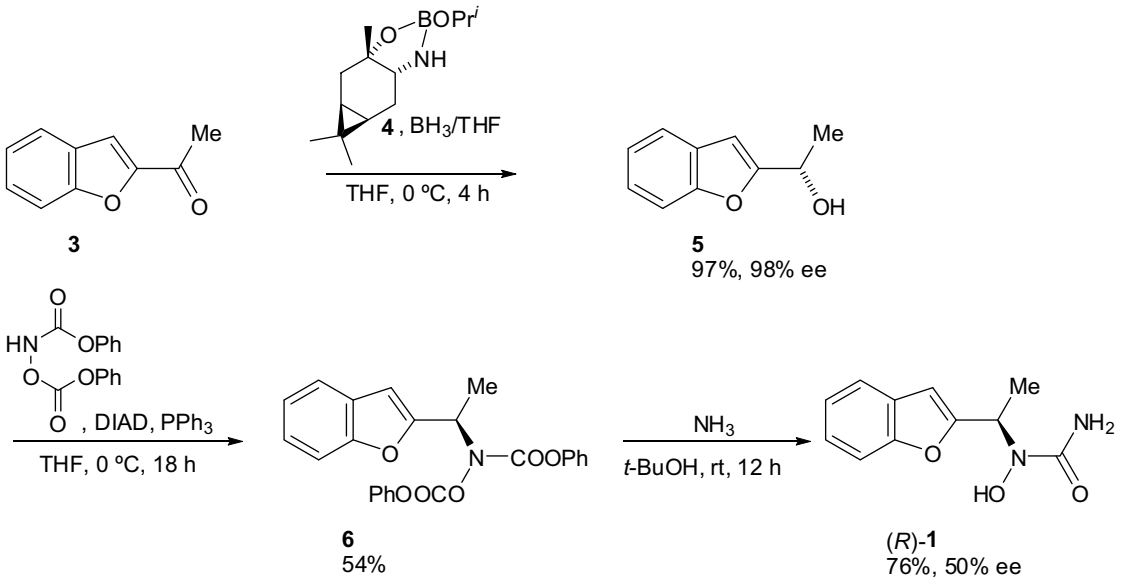
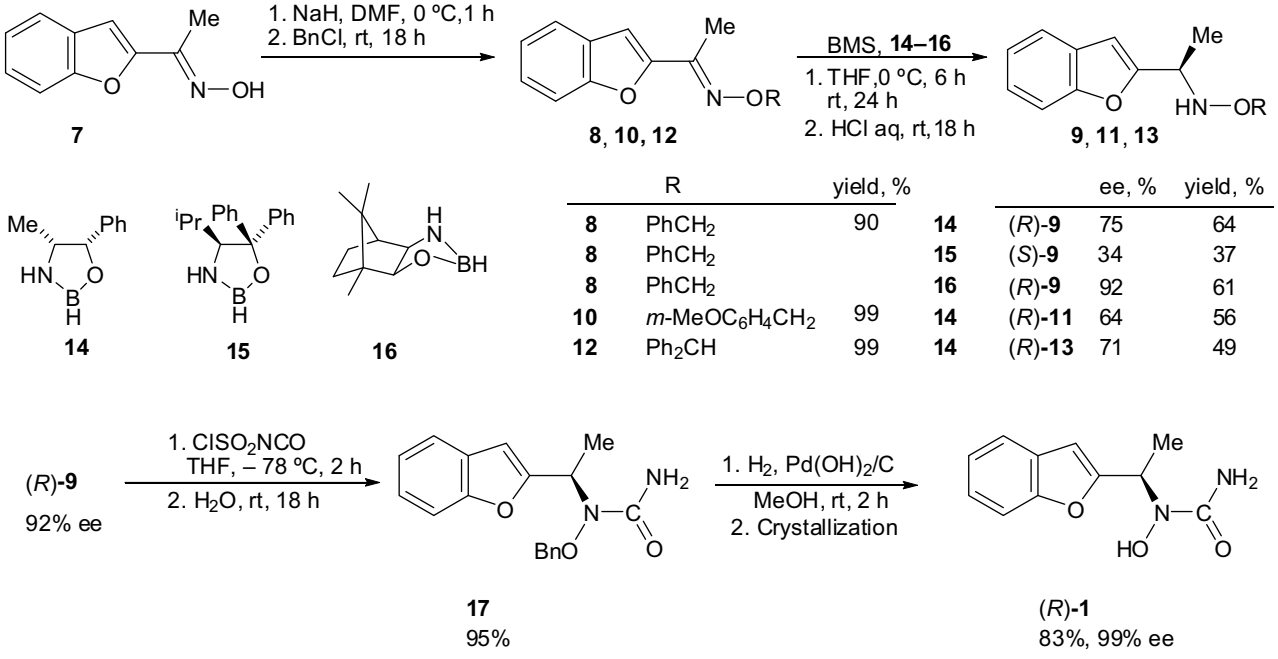


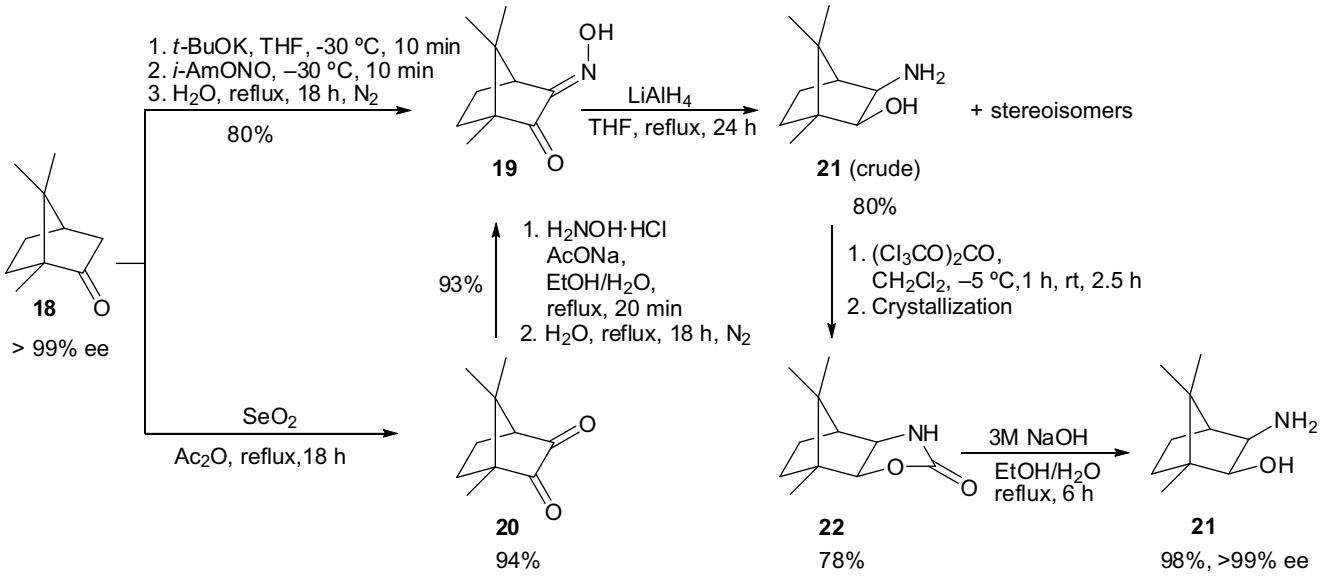
Scheme 1.

Apparently, the electron donating effect of the benzofuran-2-yl substituent at the reaction centre makes it prone to racemization, similar to secondary *ortho*- and *para*-alkoxybenzylic alcohols in the Mitsunobu reaction.[23,24]

In the second approach, **3** was converted into oxime **7**, and its *O*-benzyl ether **8** was reduced with borane/oxazaborolidine **14**, generated from (1*S*,2*R*)-norephedrine, to give (*R*)-**9**, 75% ee, in 64% yield (Scheme 2). Searching for higher enantioselectivity, *m*-methoxybenzyl and benzhydryl derivatives, **10** and **12**, were reduced with the same reagent. However, (*R*)-**11** and (*R*)-**13** were obtained in lower enantiomeric excesses, 64% and 71% ee, respectively. The reduction of **8** with borane/oxazaborolidine **15**, generated from (*S*)-diphenylvalinol, produced (*S*)-**9** in only 34% ee. In contrast, borane/oxazaborolidine **16**, generated from (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **21**, derived from (1*R*)-camphor **18** (Scheme 3), reduced **8** giving (*R*)-**9** in 92% ee (Scheme 2). Debenzylation of (*R*)-**9** by catalytic hydrogenolysis on Pd/C or Pd(OH)$_2$/C resulted in nitrogen–oxygen bond cleavage, while debenzylation with boron trichloride gave a mixture of products. Consequently, (*R*)-**9** was transformed into its *N*-benzyloxyurea derivative **17**, which was readily debenzylated by



Scheme 2.

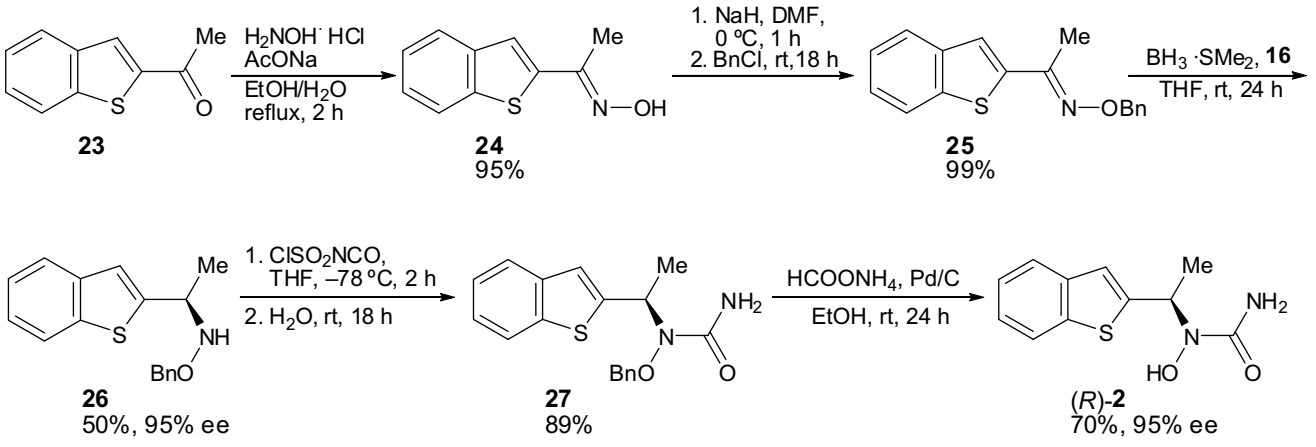


Scheme 3.

palladium catalyzed hydrogenolysis producing (*R*)-**1**, 92% ee, upgraded by crystallization to 99% ee (Scheme 2).

Although the synthesis of amino alcohol **21** (Scheme 3), via reduction of camphoroquinone monoxime with lithium tetrahydridoaluminate, has been reported several times,[25–34] the purification procedures resulted in low yields. We prepared camphoroquinone *E*-monoxime **19** by heating an *E*/*Z* mixture in refluxing water.[35] The mixture was obtained either by nitrosation of (1*R*)-camphor **18** or oximation of camphoroquinone **20** (Scheme 3). Oxime **19** was reduced with lithium tetrahydridoaluminate to give a crude amino alcohol **21**. The stepwise reduction of **19**, first with sodium tetrahydroborate, followed by lithium tetrahydridoaluminate,[34] leads to **21** containing less impurities as compared to the product of direct reduction with lithium tetrahydridoaluminate. All attempts to purify crude **21**, by crystallizing it or its salts with methanesulfonic, tartaric or oxalic acid, failed. The reaction with diethyl carbonate or 1,1′-carbonyldiimidazole (CDI) gave oxazolidone **22** in only 30–33% yield. Fortunately, treatment of crude **21** with triphosgene produced **22** in 78% yield, which was crystallized and then hydrolyzed to give pure **21**, as indicated by ^{1}H NMR spectrum lacking signals of impurities present in the spectrum of the crude product.

The approach via the reduction of an oxime ether was also applied to the asymmetric synthesis of (*R*)-**2**. Thus, 1-(benzo[*b*]thiophen-2-yl)ethanone **23**, readily prepared from thiosalicylic acid,[36] was converted into oxime **24** and its *O*-benzyl ether **25** (Scheme 4). The reduction of **25** with borane/oxazaborolidine **14** gave **26**, 80% ee, in 49% yield. A higher enantioselectivity was achieved in the reduction of **25** with borane/oxazaborolidine **16** producing **26**, 95% ee. Treatment of **26** with chlorosulfonyl isocyanate gave *N*-1-(benzo[*b*]thiophen-2-yl)ethyl-*N*-benzyloxyurea **27**. In contrast to **17,** debenzylation with hydrogen/palladium on carbon could not be achieved. Debenzylation with ammonium formate in the presence of Pd/C in ethanol, as reported earlier in the synthesis of (*R*)-**2** by a different



Scheme 4.

approach,[16] required a substantial load of 10% Pd/C and gave (*R*)-**2,** 95% ee, in 70% yield.

3. Conclusion

The highly enantioselective reduction of 1-(benzofuran-2-yl)ethanone with borane/oxazaborolidine, generated from (1*S*,3*S*,4*R*,6*R*)-4-amino-3,7,7-trimethylbicyclo[4.1.0]heptan-2-ol, gave (*S*)-1-(benzofuran-2-yl)ethanol in 98% ee. Its reaction with *N*,*O*-bis(diphenoxycarbonyl)hydroxylamine under Mitsunobu conditions, followed by reaction with ammonia resulted in partial racemization to produce (*R*)-**1** in 50% ee. Asymmetric synthesis of (*R*)-**1**, 99% ee and (*R*)-**2**, 95% ee, was achieved via the enantioselective reduction of 1-(benzofuran-2-yl)ethanone oxime *O*-benzyl ether and 1-(benzo[*b*]thiophen-2-yl)ethanone oxime *O*-benzyl ether with borane/oxazaborolidine **16**, respectively, as the key transformation generating the stereogenic centre. Our synthesis of (*R*)-**2** is the shortest described asymmetric approach to this compound.

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 an automatic polarimeter, PolAAr 3000, Optical Activity Ltd. GC analyses were performed on a Perkin–Elmer AutoSystem XL chromatograph, and HPLC analyses on a Shimadzu LC-10AT chromatograph. Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were performed by the Microanalysis Laboratory, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw.

4.2. Materials

Silica Gel 60, Merck 230–400 mesh, was used for preparative column flash 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. (1*S*,3*S*,4*R*,6*R*)-4-Amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol,[21] 1-(benzofuran-2-yl)ethanone,[20] *N*,*O*-bis(diphenoxycarbonyl)hydroxylamine[22] and 1-(benzo[*b*]thiophen-2-yl)ethanone[36] were prepared according to the literature.

4.3. (*S*)-(−)-1-(Benzofuran-2-yl)ethanol 5

A solution of (1*S*,3*S*,4*R*,6*R*)-4-amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (0.23 g, 1.5 mmol) and triisopropoxyborane (0.31 g, 1.65 mmol) in tetrahydrofuran (75 mL) was stirred for 1 h at room temperature, and 0.5 M borane–tetrahydrofuran (30 mL, 15 mmol) was added. The mixture was cooled to 0 °C and a solution of **3** (2.40 g, 15 mmol) in tetrahydrofuran (20 mL) was added with a syringe pump in 3 h, and then stirred for 1 h. Methanol (5 mL) was added and the mixture was stirred overnight at room temperature. Solvents were removed and the product was isolated by column chromatography on silica gel 80–200 mesh, petroleum ether–ethyl acetate (4:1), 2.36 g, 97%, $[\alpha]_D^{23} = -35.0$ (*c* 1.15, $CHCl_3$), 98% ee, by HPLC analysis on an OD-H chiral column, *n*-hexane–isopropanol, 9:1 (t_R 20.57 *S*; $f = 0.4$ mL/min; $T = 15$ °C; $p = 21$ kg f/cm^2). The racemate was also analyzed. Lit.[37] $[\alpha]_D^{20} = -33.3$, (*c* 10.17, $CHCl_3$), 91% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, $J = 6.6$ Hz, 3H, CH_3), 2.07 (d, $J = 4.8$ Hz, 1H, OH), 5.03 (dq, $J = 4.8$, 6.6 Hz, 1H, CH), 6.62 (t, $J = 1.0$ Hz, 1H, CH), 7.21 (td, $J = 7.5$, 1.2 Hz, 1H, CH), 7.27 (td, $J = 7.2$, 1.5 Hz, 1H, CH), 7.46 (ddd, $J = 7.8$, 1.0, 0.5 Hz, 1H, CH), 7.54 (ddd, $J = 7.9$, 1.2, 0.5 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.39 (CH_3), 64.17 (CH), 101.76 (CH), 111.18 (CH), 121.04 (CH), 122.75 (CH), 124.15 (CH), 128.10 (C), 154.75 (C), 160.17 (C).

4.4. 1-(Benzofuran-2-yl)ethanone oxime 7

A mixture of **3** (14.41 g, 90 mmol), hydroxylamine hydrochloride (12.50 g, 180 mmol), sodium acetate (20.50 g, 250 mmol), ethanol (75 mL) and water (90 mL) was stirred at reflux for 3 h. The mixture was cooled in a refrigerator, and the precipitated solid was filtered off, dried and crystallized from dichloromethane, 14.97 g, 95%, mp 153–154 °C. Lit.[38] 154–155 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.16 (s, 3H, CH_3), 7.20 (d, $J = 0.9$ Hz, 1H, CH), 7.24 (ddd, $J = 7.5$, 7.2, 1.0 Hz, 1H, CH), 7.325 (ddd, $J = 8.4$, 7.2, 1.5 Hz, 1H, CH), 7.56 (ddd, $J = 8.1$, 1.8, 0.9 Hz, 1H, CH), 7.64 (ddd, $J = 7.0$, 1.5, 0.6 Hz, 1H, CH), 11.62 (s, 1H, OH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 11.06 (CH_3), 105.53 (CH), 111.35 (CH), 121.40 (CH), 123.16 (CH), 125.24 (CH), 127.89 (C), 145.88 (C), 152.75 (C), 154.33 (C=N).

4.5. 1-(Benzofuran-2-yl)ethanone oxime *O*-benzyl ether 8

A 60% dispersion of sodium hydride in mineral oil (0.80 g, 20 mmol) was washed with *n*-hexane (2 × 10 mL), after which DMF (10 mL) was added and the mixture was cooled to 0 °C. A solution of **7** (3.07 g, 17.5 mmol) in DMF (20 mL) was added and the mixture was stirred for 1 h at room temperature. Benzyl chloride (2.53 g, 20 mmol) was added and the mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the product was extracted with diethyl ether (3 × 10 mL). Extracts were washed with saturated brine (40 mL) and dried with anhydrous magnesium sulfate. Ether was removed and the product 4.20 g, 90%, mp 81–83 °C was obtained. Lit.[39] mp 84 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 7.23–7.43 (m, 8H, CH), 7.60 (ddd, $J = 5.4$, 1.2, 0.6 Hz, 1H, CH), 7.66 (ddd, $J = 5.2$, 1.0, 0.4 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.01 (CH_3), 75.77 (CH_2), 107.64 (CH), 111.32 (CH), 121.65 (CH), 123.32 (CH), 125.82 (CH), 127.60 (C), 127.78 (CH), 127.84 (2CH),

128.32 (2CH), 137.69 (C), 147.12 (C), 151.30 (C), 154.46 (C=N). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.58; H, 5.61; N, 5.44.

4.6. (*R*)-(+)-*N*-(1-(Benzofuran-2-yl)ethyl)-*O*-benzylhydroxylamine 9

To a solution of (1*R*,2*S*,3*R*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (1.02 g, 6.0 mmol) in THF (30 mL) was added 10 M borane–dimethyl sulfide (1.2 mL, 12 mmol) and the mixture was stirred for 1 h at room temperature. A solution of **8** (1.32 g, 5.0 mmol) in THF (10 mL) was added over 1.5 h at room temperature and the mixture was stirred for 48 h. Then 3 M hydrochloric acid (20 mL, 60 mmol) was added at 0 °C and the mixture was stirred for 18 h. Tetrahydrofuran was removed under reduced pressure and the remaining mixture was basified with 10% aqueous sodium hydroxide to pH 12, stirred for 30 min, and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried with anhydrous magnesium sulfate, the solvent was removed and the product was isolated by flash chromatography on silica gel, *n*-hexane–ethyl acetate, 4:1, pale yellow oil, 0.82 g, 61%, bp 150–154 °C/0.1 mmHg, $[\alpha]_D^{20} = +46.6$ (*c* 1.77, $CHCl_3$), 92% ee, by HPLC analysis on a chiral OJ column, *n*-hexane–isopropanol 9:1 (t_R 22.40 *S*, 26.87 *R*; $f = 0.7$ mL/min; $T = 35$ °C; $p = 25$ kg f/cm^2). The racemate was also analyzed. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (d, $J = 6.6$ Hz, 3H, CH_3), 4.26 (quintet, $J = 6.6$ Hz, 1H, CH), 4.53 (d, $J = 11.7$ Hz, 1H, CH_2), 4.56 (d, $J = 11.7$ Hz, 1H, CH_2), 6.74 (s, 1H, CH), 6.93 (d, $J = 6.0$ Hz 1H, NH), 7.15–7.40 (m, 7H, CH), 7.52 (dm, $J = 7.5$ Hz, 1H, CH), 7.56 (dm, $J = 7.5$, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.67 (CH_3), 53.62 (CH), 75.64 (CH_2), 102.88 (CH), 110.92 (CH), 120.78 (CH), 122.64 (CH), 123.68 (CH), 127.43 (CH), 128.08 (4CH), 128.22 (C), 138.13 (C), 153.91 (C), 159.74 (C). MS: EI 70 eV *m*/*z*: 267 (M^+, 1.6), 235 (27.2), 208 (17.8), 146 (11.1), 145 (77.6), 92 (15.0), 91 (100.00). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.81; H, 6.48; N, 5.19.

4.7. (*R*)-(−)-*N*-1-(Benzofuran-2-yl)ethyl-*N*-benzyloxyurea 17

Chlorosulfonyl isocyanate (1.13 g, 8.0 mmol) was added dropwise to a solution of **9** (1.34 g, 5.0 mmol) at −78 °C and the mixture was stirred for 2 h at this temperature. Water (20 mL) was added, and stirring was continued for 24 h at room temperature. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 15 mL). The combined organic solutions were dried with anhydrous magnesium sulfate. The solvent was removed and the product was isolated by flash chromatography on silica gel, petroleum ether–ethyl acetate, 1:1, 1.50 g, 95%, mp 103–105 °C. $[\alpha]_D^{24} = -39.7$ (*c* 0.39, $CHCl_3$) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.67 (d, $J = 7.0$ Hz, 3H, CH_3), 4.48 (d, $J = 10.4$ Hz, 1H, CH_2), 4.66 (d, $J = 10.4$ Hz, 1H, CH_2), 5.37 (br s, 2H, NH_2), 5.66 (dq, $J = 7.0$, 1.0 Hz, 1H, CH), 6.73 (dd, $J = 1.4$, 1.0 Hz, 1H, CH), 7.20–7.60 (m, 9H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.40 (CH_3), 52.15 (CH), 78.74 (CH_2), 104.49 (CH), 111.25 (CH), 120.84 (CH), 122.67 (CH), 124.16 (CH), 128.11 (C), 128.55 (2CH), 128.73 (CH), 129.02 (2CH), 134.81 (C), 154.60 (C), 156.80 (C), 161.44 (C=O). MS (ESI) *m*/*z* 333.1 (M^++Na, 100). MS (EI, 70 eV) 235 (13.51), 208 (12.36), 203 (13.10), 160 (17.91), 146 (16.81), 145 (66.61), 144 (19.68), 117 (10.34), 115 (18.15), 108 (10.69), 91 (100.00), 79 (13.14), 77 (15.36). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.81; H, 5.78; N, 8.89.

4.8. (*R*)-(+)-*N*-1-(Benzofuran-2-yl)ethyl-*N*-hydroxyurea (*R*)-1

4.8.1. From 17 by hydrogenolysis. To a solution of **17** (0.50 g, 1,6 mmol) in methanol (15 mL) was added 20% $Pd(OH)_2$/C (0.1 g). The mixture was degassed and hydrogenated under 1.0 atm pressure for 2 h at room temperature. The catalyst was filtered off and volatiles were removed under reduced pressure, 0.29 g, 83%, 92% ee by HPLC analysis on a chiral OJ column, *n*-hexane–isopropanol 9:1 (t_R 21.00 *S*, 22.87 *R*; $f = 0.7$ mL/min; $T = 35$ °C; $p = 24$ kg f/cm^2). The product was crystallized from ethyl acetate–*n*-hexane 2:1, mp 147–148 °C, $[\alpha]_D^{22} = +14.4$ (*c* 0.42, DMSO), $[\alpha]_D^{22} = +52.9$ (*c* 0.44, MeOH), >99% ee by HPLC analysis on a chiral OJ column, *n*-hexane–isopropanol 9:1 (t_R 23.94 *R*; $f = 0.7$ mL/min; $T = 35$ °C; $p = 22$ kg f/cm^2). The racemate was also analyzed. ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.45 (d, $J = 7.0$ Hz, 3H, CH_3), 5.46 (qd, $J = 7.0$, 1.0 Hz, 1H, CH), 6.46 (s, 2H, NH_2), 6.71 (dd, $J = 1.0$, 0.8 Hz, 1H, CH), 7.18 (td, $J = 7.6$, 2.2 Hz, 1H, CH), 7.23 (td, $J = 7.6$, 2.2 Hz, 1H, CH), 7.49 (dm, $J = 8.0$, 1H, CH), 7.54 (dm, $J = 7.0$, 1H, CH), 9.16 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.86 (CH_3), 50.44 (CH), 103.48 (CH), 110.87 (CH), 120.72 (CH), 122.56 (CH), 123.74 (CH), 128.10 (C), 153.86 (C), 158.22 (C), 161.42 (C=O). MS (EI, 70 eV) *m*/*z* 220 (M^+, 3), 203 (30.14), 160 (22.98), 146 (19.55), 145 (100.00), 144 (22.20), 117 (16.41), 115 (21.16), 91 (12.03). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.79; H, 5.52; N, 12.75.

4.8.2. From 5 by substitution. To a solution of **5** (0.97 g, 6.0 mmol), *N*,*O*-bis(phenoxycarbonyl)hydroxylamine (1.80 g, 6.6 mmol) and triphenylphosphine (1.89 g, 7.2 mmol) in tetrahydrofuran (30 mL) was slowly added at 0 °C over 2 h a solution of diisopropyl azodicarboxylate (1.46 g, 7.2 mmol) in tetrahydrofuran (6 mL) and the mixture was left overnight at room temperature. The solvent was removed and the yellow oil (1.31 g), isolated by flash chromatography on silica gel, petroleum ether–ethyl acetate, 9:1, was added to a mixture of *tert*-butanol (8 mL) and liquid ammonia (8 mL) at −78 °C in a glass pressure vessel and was stirred overnight at room temperature. The vessel was cooled, opened and ammonia was evaporated at room temperature. Volatiles were removed under reduced pressure at room temperature and the product was isolated by flash chromatography on silica gel, dichloromethane–methanol 95:5, 0.55 g, 76%, mp 139–140 °C, $[\alpha]_D^{25} = +7.4$ (*c* 0.95, DMSO). ^{1}H and ^{13}C NMR spectra the same as described above. HPLC analysis on a chiral OJ column, *n*-hexane–ethanol 9:1 (t_R 21.00 *S*, 22.87 *R*;

$f = 0.7$ mL/min; $T = 35$ °C; $p = 24$ kg f/cm^2) showed 50% ee. The racemate was also analyzed.

4.9. 1-(Benzo[*b*]thiophen-2-yl)ethanone oxime 24

A mixture of 1-(benzo[*b*]thiophen-2-yl)ethanone **23** (15.86 g, 90 mmol), hydroxylamine hydrochloride (12.50 g, 180 mmol), sodium acetate (20.50 g, 250 mmol), ethanol (100 mL) and water (100 mL) was refluxed for 4 h, cooled and left overnight in a refrigerator. The crystalline product was filtered off, washed with cold water (10 mL) and dried, 16.43 g, 95%, mp 188–189 °C. Lit.[40] mp 183–184 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 7.32 (t, $J = 2.8$, 1H, CH), 7.35 (t, $J = 2.8$, 1H, CH), 7.68 (s, 1H, CH), 7.80 (m, 1H, CH), 7.86 (m, 1H, CH), 11.53 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.46 (CH_3), 122.22 (CH), 123.12 (CH), 123.91 (CH), 124.48 (CH), 125.40 (CH), 138.81 (C), 139.36 (C), 141.32 (C), 149.95 (C=N).

4.10. 1-(Benzo[*b*]thiophen-2-yl)ethanone oxime *O*-benzyl ether 25

A 60% dispersion of sodium hydride in mineral oil (2.40 g, 50 mmol) was washed with *n*-hexane (2 × 15 mL), after which DMF (70 mL) was added and the mixture was cooled to 0 °C. A solution of **24** (8.61 g, 45 mmol) in DMF (80 mL) was added dropwise, the mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. It was cooled to 0 °C, after which benzyl chloride (8.22 g, 50 mmol) was added, and stirring was continued for 18 h at room temperature. The solvent was removed under reduced pressure, water (150 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed and the product, 12.50 g, 98%, mp 92–94 °C, was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 7.30–7.48 (m, 8H, CH), 7.70–7.80 (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.55 (CH_3), 76.60 (CH_2), 122.16 (CH), 123.11 (CH), 123.78 (CH), 124.26 (CH), 125.35 (CH), 127.90 (CH), 128.34 (2CH), 128.38 (2CH), 137.51 (C), 139.34 (C), 139.95 (C), 140.75 (C), 151.10 (C=N). MS (EI, 70 eV) m/z 281 (M^+, 24.21), 91 (100.00). Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98; S, 11.40. Found: C, 72.47; H, 5.33; N, 4.96; S, 11.58.

4.11. (*R*)-(+)-*N*-(1-(Benzo[*b*]thiophen-2-yl)ethyl)-*O*-benzylhydroxylamine 26

A 9 M borane–dimethyl sulfide complex (1.33 mL, 12.0 mmol) was added to a solution of **21** (1.01 g, 6.0 mmol) in THF (10 mL) at room temperature and the mixture was stirred for 1 h. A solution of **25** (1.41 g, 5.0 mmol) in THF (15 mL) was slowly added in 2.5 h and the mixture was stirred for 40 h at room temperature. A 3 M hydrochloric acid (20 mL) was added at 0 °C and the mixture was stirred for 18 h at room temperature. Tetrahydrofuran was removed under reduced pressure, and the aqueous solution was alkalized with 10% aqueous sodium hydroxide to pH 11, stirred for 30 min and extracted with dichloromethane (3 × 20 mL). The extracts were combined and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the product was isolated by flash chromatography on silica gel, *n*-hexane–ethyl acetate, 9:1, 0.71 g, 50%, mp 58–60 °C, $[\alpha]_D^{20} = +34.7$ (*c* 1.70, $CHCl_3$). Lit.[16] $[\alpha]_D^{20} = +35.9$ (*c* 1.70, $CHCl_3$). HPLC analysis on a chiral OJ column, *n*-hexane–isopropanol 8:2 (t_R 23.71 *R*, 30.54 *S*; $f = 0.7$ mL/min; $T = 35$ °C; $p = 5$ kg f/cm^2) showed 95% ee. The racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, $J = 6.6$ Hz, 3H, CH_3), 4.51 (q, $J = 6.6$ Hz, 1H, CH), 4.72 (s, 2H, CH_2), 5.66 (br s, 1H, NH), 7.21–7.44 (m, 8H, CH), 7.70 (dm, $J = 6.5$ Hz, 1H, CH), 7.82 (dm, $J = 6.5$ Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ, 20.25 (CH_3), 56.75 (CH), 76.84 (CH_2), 120.82 (CH), 122.29 (CH), 123.19 (CH), 123.87 (CH), 124.03 (CH), 127.74 (CH), 128.26 (2CH), 128.45 (2CH), 137.66 (C), 139.48 (C), 139.49 (C), 147.71 (C). MS (EI, 70 eV) m/z 283 (M^+, 4.85), 251 (25.78), 250 (22.21), 224 (15.87), 162 (14.07), 161 (100.00), 160 (16.94), 128 (17.77), 91 (94.16). Anal Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94; S, 11.31. Found: C, 72.26; H, 6.00; N, 4.83; S, 11.40.

4.12. (*R*)-(−)-*N*-1-(Benzo[*b*]thiophen-2-yl)ethyl-*N*-benzyloxyurea 27

A solution of **26** (0.85 g, 3.0 mmol) in dichloromethane (8 mL) was cooled to −78 °C, after which chlorosulfonyl isocyanate (0.70 g, 4.8 mmol) was added and the mixture was stirred for 2 h at −78 °C. Water (15 mL) was added and stirring was continued for 18 h at room temperature. Dichloromethane (20 mL) was added, after which the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic solutions were dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was isolated by flash chromatography on silica gel, *n*-hexane–ethyl acetate, 2:1, 0.87 g, 89%, mp 134–136 °C, $[\alpha]_D^{25} = -63.3$ (*c* 1.33, EtOH); $[\alpha]_D^{25} = -39.1$ (*c* 1.00, $CHCl_3$). Lit.[16] $[\alpha]_D^{20} = -40.5$ (*c* 1.11, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, $J = 6.9$ Hz, 3H, CH_3), 4.68 (d, $J = 10.5$ Hz, 1H, CH_2), 4.79 (d, $J = 10.5$ Hz, 1H, CH_2), 5.22 (br s, 2H, NH_2), 5.75 (q, $J = 6.0$ Hz, 1H, CH), 7.26–7.38 (m, 8H, CH), 7.735 (dm, $J = 6.6$ Hz, 1H, CH), 7.40 (dm, $J = 6.6$ Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.35 (CH_3), 54.53 (CH), 79.11 (CH_2), 122.15 (CH), 122.24 (CH), 123.44 (CH), 124.10 (CH), 124.15 (CH), 128.60 (2CH), 128.72 (CH), 128.91 (2CH), 134.91 (C), 139.22 (C), 139.64 (C), 144.81 (C), 161.46 (C=O). MS (EI, 70 eV) m/z 236 (M^+), 219 (24.15), 176 (16.04), 175 (12.11), 162 (26.737), 161 (100.00), 160 (33.40), 134 (17.27), 128 (29.40), 115 (13.48), 89 (13.56), 43 (10.26).

4.13. (*R*)-(+)-*N*-1-(Benzo[*b*]thiophen-2-yl)ethyl-*N*-hydroxyurea (*R*)-2

To a degassed solution of **27** (0.17 g, 0.52 mmol) in ethanol (12 mL) were added ammonium formate (0.94 g, 15 mmol) and palladium catalyst (1.4 g, 10% Pd/C E101.NE/W + 50% H_2O), and the mixture was stirred for 4 h at

room temperature. The catalyst was filtered off through a pad of Celite. Ethanol was removed from the filtrate under reduced pressure. Water (20 mL) was added and the product was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was isolated by flash chromatography on silica gel, dichloromethane–methanol 95:5 and purified by preparative HPLC on C18 column, methanol–water 4:1, 0.087 g, 71%, mp 148–149 °C. $[\alpha]_D^{22} = +44.9$ (*c* 0.315, MeOH), 95% ee, by HPLC analysis on a chiral OJ column, *n*-hexane–isopropanol 8:2 (t_R 14.02 *S*, 16.47 *R*; $f = 0.7$ mL/min; $T = 35$ °C; $p = 25$ kg f/cm^2). Lit.[17] mp 148–149 °C, $[\alpha]_D^{24} = +47.0$ (*c* 1.1, MeOH), lit.[16] $[\alpha]_D = +50.3$ (*c* 0.35, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (d, $J = 6.9$ Hz, 3H, CH_3), 5.55 (qd, $J = 6.9$, 0.9 Hz, 1H, CH), 6.44 (s, 2H, NH_2), 7.25 (dd, $J = 1.0$, 0.9 Hz, 1H, CH), 7.28 (td, $J = 7.2$ Hz, 1H, CH), 7.32 (td, $J = 7.2$ Hz, 1H, CH), 7.76 (dm, $J = 6.6$ Hz, 1H, CH), 7.87 (dm, $J = 6.5$ Hz, 1H, CH), 9.22 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.86 (CH_3), 52.32 (CH), 121.26 (CH), 122.12 (CH), 123.19 (CH), 123.89 (CH), 124.06 (CH), 138.92 (C), 139.05 (C), 146.10 (C), 161.35 (C=O). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.87; S, 13.57. Found: C, 56.00; H, 5.32; N, 11.61; S, 13.45.

4.14. (*E*)-(1*R*)-(+)-3-Hydroxyimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 19

A solution of (1*R*)-(+)-camphor **18** (7.61 g, 50 mmol) in tetrahydrofuran (10 mL) was slowly added to a solution of potassium *tert*-butoxide (6.73 g, 60 mmol) in tetrahydrofuran (20 mL) at −30 °C, and the mixture was stirred for 10 min. Isoamyl nitrite (7.03 g, 60 mmol) was added over 20 min at −30 °C, the mixture was stirred for 10 min, and then left overnight at room temperature. Tetrahydrofuran was removed under reduced pressure, after which water (50 mL) was added, and the solution was extracted with diethyl ether (3 × 15 mL). The aqueous solution was diluted with water (150 mL) and acidified with acetic acid to pH 6. A pale yellow precipitate was filtered off, washed with water (10 mL) and dried, 7.80 g, 80%, mp 116–119 °C. ^{1}H NMR ($CDCl_3$) analysis showed a mixture of *E*/*Z* isomers, 26:74. Diagnostic signals in the spectrum: *Z*-isomer, 2.72 (d, $J = 4.2$ Hz, 1H, CH), *E*-isomer, 3.25 (d, $J = 4.5$ Hz, 1H, CH). A mixture of isomers (7.50 g) was refluxed with water (25 mL) for 18 h under nitrogen. After cooling to room temperature, the mixture was extracted with diethyl ether (2 × 25 mL), and the extract was dried with anhydrous magnesium sulfate. Ether was removed and a pale yellow product was obtained, 7.35 g, 98%, mp 150–151 °C, $[\alpha]_D^{26} = +199$ (*c* 1.41, $CHCl_3$). Lit.[39] mp 150 °C, $[\alpha]_D^{25} = +185$ (*c* 4.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.50–1.63 (m, 2H, CH_2), 1.70–1.84 (m, 1H, CH_2), 1.99–2.12 (m, 1H, CH_2), 3.25 (d, $J = 4.5$ Hz, 1H, CH), 8.50 (s, 1H, OH). The spectrum also contains a small doublet (3%) at 2.72 ppm (*Z*-isomer). ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.90 (CH_3), 17.60 (CH_3), 20.66 (CH_3), 23.75 (CH_2), 30.66 (CH_2), 44.89 (C), 46.62 (CH), 58.51 (C), 159.71 (C=N), 204.30 (C=O).

4.15. (1*R*,2*S*,6*R*,7*S*)-(−)-1,10,10-Trimethyl-3-oxa-5-azatricyclo[5.2.1.0^{2,6}]decan-4-one 22

A solution of **19** (7.25 g, 40 mmol) in diethyl ether (30 mL) was added dropwise to a solution of lithium tetrahydridoaluminate (4.55 g, 120 mmol) in diethyl ether (40 mL) and the mixture was refluxed for 24 h. It was cooled in an ice-water bath, after which ethyl acetate (4.6 mL) was added dropwise with stirring, followed after 5 min with 10% aqueous sodium hydroxide solution (4.6 mL), water (10 mL), diethyl ether (100 mL), and stirring was continued for 4 h at room temperature. The mixture was filtrated, washed with saturated brine (10 mL) and dried with anhydrous magnesium sulfate. Ether was removed and to the crude solid product **21** (6.42 g), dimethoxyethane (230 mL) and 6 M aqueous sodium hydroxide solution (22 mL, 130 mmol) were added. A solution of triphosgene (4.37 g, 14.7 mmol) in dichloromethane (90 mL) was added dropwise at −5 °C, stirring was continued for 1 h at this temperature, and for 2.5 h at room temperature. Water (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic solutions were washed with 10% acetic acid (100 mL), water (50 mL) and dried over anhydrous magnesium sulfate. Solvents were removed under reduced pressure and the product was isolated by flash chromatography on silica gel, petroleum ether–ethyl acetate (1:1), 5.29 g, 67%. After crystallization from *n*-hexane–ethyl acetate (2:1), mp 154–155 °C, $[\alpha]_D^{26} = -44.8$ (*c* 1.72, $CHCl_3$). Lit.[29] mp 156–158 °C, $[\alpha]_D^{22} = -43.4$ (*c* 2.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 0.95–1.07 (m, 2H, $2CH_2$), 1.48–1.60 (m, 1H, CH_2), 1.65–1.80 (m, 1H, CH_2), 1.85 (d, $J = 4.5$ Hz, 1H, CH), 3.76 (d, $J = 8.0$ Hz, $J = 1,2$ Hz, 1H, CH–N), 4.39 (d, $J = 8.0$ Hz, 1H, CH–O), 5.68 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.44 (CH_3), 23.26 ($2CH_3$), 24.76 (CH_2), 31.74 (CH_2), 46.36 (C), 48.18 (C), 48.68 (CH), 60.54 (CH), 88.40 (CH), 160.41 (C=O).

4.16. (1*R*,2*S*,3*R*,4*S*)-(−)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 21

A mixture of **22** (3.90 g, 20.0 mmol), sodium hydroxide (3.20 g, 80 mmol), ethanol (45 mL) and water (25 mL) was refluxed for 6 h. The solution was concentrated under vacuum to half of its volume, and extracted with diethyl ether (3 × 25 mL). The combined extract was dried with anhydrous magnesium sulfate, after which ether was removed, and a white crystalline product was obtained, 3.32 g, 98%, mp 211–212 °C, $[\alpha]_D^{22} = -8.2$ (*c* 1.15, MeOH). Lit.[29] mp 200 °C, $[\alpha]_D^{22} = -6.2$ (*c* 1.01, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.93–1.06 (m, 2H, $2CH_2$), 1.34–1.46 (m, 1H, CH_2), 1.53 (d, $J = 4.5$ Hz, 1H, CH), 1.59–1.73 (m, 1H, CH_2), 2.51 (br s, 3H, –OH, $–NH_2$), 3.02 (d, $J = 7.2$ Hz, 1H, CH–N), 3.35 (d, $J = 7.2$ Hz, 1H, CH–O). ^{13}C NMR (75 MHz $CDCl_3$) δ 11.35 (CH_3), 21.16 (CH_3), 21.88 (CH_3), 26.83 (CH_2), 33.07 (CH_2), 46.55 (C), 48.64 (C), 53.30 (CH), 57.28 (CH), 79.44 (CH). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.81; H, 11.32; N, 8.11.

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