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Synthesis and transformation of novel cyclic β-amino acid derivatives from (+)-3-carene

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Abstract—The regio- and stereoselective addition of chlorosulfonyl isocyanate to (+)-3-carene **1** resulted in β-lactam **2**, which was converted to *N*-Boc-β-amino acid **4**, β-amino ester **7**, and carboxamide derivatives **18** and **20** via *N*-Boc activation and mild ring opening. The corresponding β-amino ester **7** was transformed to 2-thioxopyrimidin-4-one **11** and 2,4-pyrimidinedione **13**. LAH reduction of **5** and **7** resulted in amino alcohols **6** and **8**. The reaction of **8** with phenyl isothiocyanate, followed by cyclisation, furnished 1,3-oxazine **15**.

1. Introduction

The readily available homochiral terpenes and their derivatives are widely used as chiral auxiliaries in enantioselective transformations.[1] Various amino alcohol catalysts derived from monoterpenes such as (+)-pulegone,[2] β-pinene,[3] nopinone,[4] fenchone-camphor,[5] limonene[6] and recently (+)-3-carene[7] have been reported to have been used successfully in enantioselective syntheses. Derivatives of α-pinene such as 2-hydroxypinan-3-one[8] and the enantiomerically pure 3-amino-2-hydroxypinane[9] have also served as useful chiral reagents. Monoterpene-fused 1,3-oxazines have been applied as catalysts for enantioselective allylic substitutions.[10] In an earlier publication, we reported the transformations of enantiomerically pure α-pinene to β-amino acid derivatives and monoterpene-fused saturated 1,3-heterocycles.[11]

β-Amino acids and their derivatives, such as amino esters, amides or 1,3-amino alcohols, can serve for the synthesis of a wide range of saturated heterocycles.[12–14] Besides their chemical importance,[12] β-amino acids and their derivatives possess noteworthy pharmacological effects; for example, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin) and 2-aminocyclohexenecarboxylic acid (originally designed as a pyridoxal phosphate suicide inhibitor) have antifungal activity.[15,16] (1*R*,2*S*)-2-Amino-4-methylenecyclopentanecarboxylic acid (BAY 10-8888) possesses antifungal activity against *Candida albicans*, and clinical studies are in progress.[17,18] β-Amino acids can also be used as building blocks of modified analogues of pharmacologically active peptides.[19–23] Conformational studies of β-amino acid oligomers are currently at the focus of interest.[24–26]

Our present aim was the synthesis and transformation of homochiral β-amino acid derivatives prepared from (+)-3-carene, a commercially available homochiral source. The ring opening reactions of the corresponding β-lactam **3** to give novel homochiral β-amino acid derivatives were studied; and some cyclisation reactions of the resulting compounds were carried out to produce monoterpene-fused saturated 1,3-heterocycles.

2. Results and discussion

The synthetic route to the novel homochiral β-amino acid derivatives is shown in Scheme 1. The reaction of chlorosulfonyl isocyanate (CSI) with a cycloalkane is a well-known procedure for the synthesis of cycloalkane-fused β-lactams. There are several examples in the literature concerning the regio- and stereoselectivity of the cycloaddition, which proceeds in accordance with the Markovnikov orientation of CSI addition.[27]

Starting from commercially available (+)-3-carene **1**, the cycloaddition of CSI furnished the enantiomeric β-lac-

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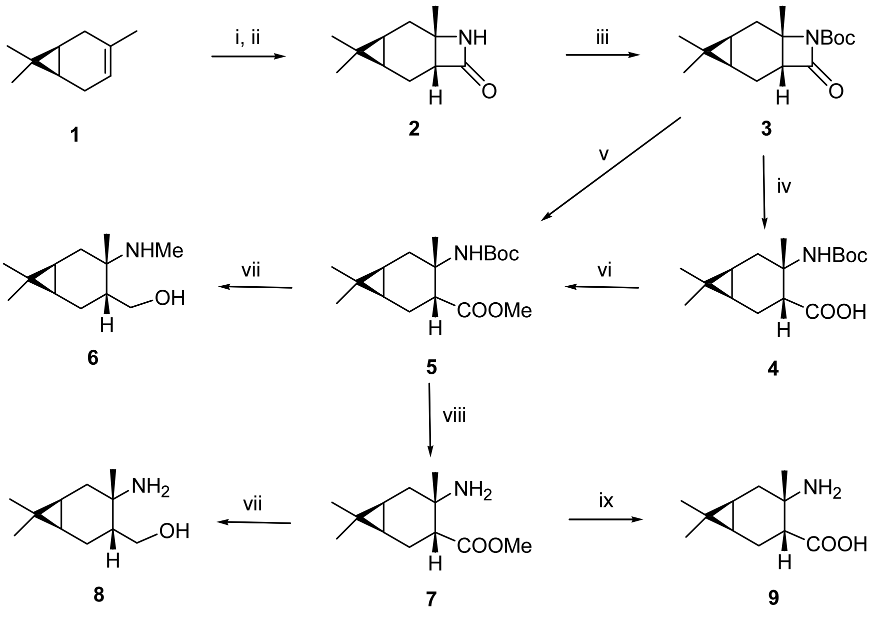
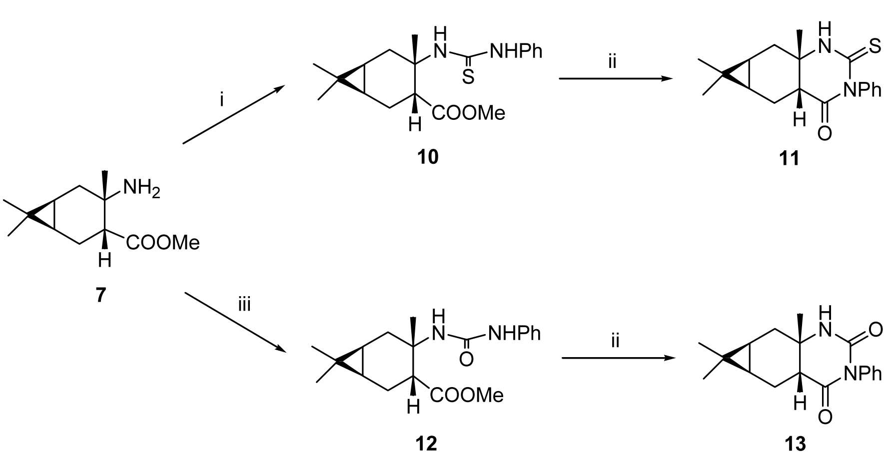


Scheme 1. *Reagents and conditions*: (i) CSI, Et_2O, 9 h, rt, 76%; (ii) Na_2SO_3, then KOH; (iii) Boc_2O, Et_3N, DMAP/THF, rt, 2 h, 82%; (iv) $LiOH/H_2O$, THF, rt, 7 h, 94%; (v) cat. NaOMe/MeOH, rt, 2 h, 89%; (vi) CH_2N_2/Et_2O, rt, 2 h, 98%; (vii) $LiAlH_4$/THF, rt, 2 h, **6**: 95%, **8**: 85%; (viii) TFA/CH_2Cl_2, rt, 2 h, 96%; (ix) dioxane/H_2O, reflux, 48 h, 88%.

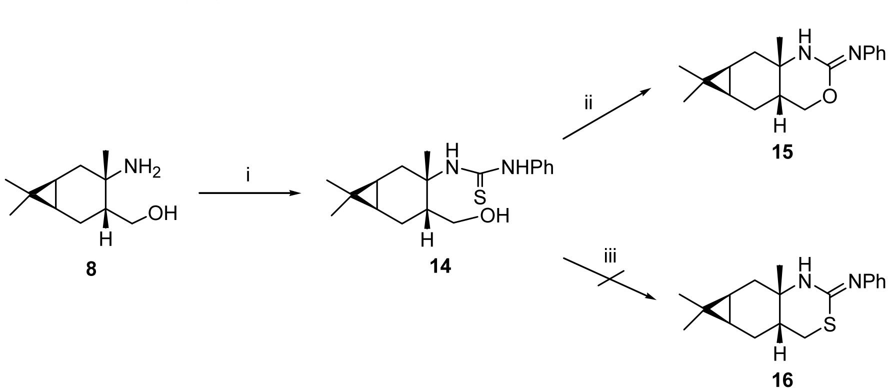
tam **2** in a regio- and stereoselective reaction. The *exo* stereoselectivity of the cycloaddition was earlier reported by Sasaki et al.[28] The CSI addition proceeded at room temperature in good yield (76%). There are several methods in the literature for the ring opening of azetidinones.[14,29,30] Our first attempt was the ring opening of **2** by refluxing with ethanol containing HCl to obtain the corresponding amino ester.[11] Hydrolysis of the β-lactam ring of **2** to the amino acid was also attempted with aqueous HCl.[31] None of the applied methods resulted in the expected compounds: only a mixture of several decomposed products was obtained under the given conditions. These results suggested that the strongly constrained carene ring system decomposes under highly acidic conditions. Activation of the carboxamide bond of azetidinone **2** therefore seemed necessary.

Treatment of the β-lactam **2** with di-*tert*-butyl dicarbonate resulted in *N*-Boc β-lactam **3**, which was readily opened under mild conditions. The reaction of **3** with aqueous LiOH in THF[32] gave homochiral *N*-Boc β-amino acid **4** in excellent yield (98%). The *N*-Boc amino ester was prepared in different ways. Either the ring opening of *N*-Boc β-lactam **3** in the presence of a catalytic amount of sodium methoxylate in dry methanol or the esterification of *N*-Boc β-amino acid **4** with diazomethane in dry diethyl ether gave **5** in excellent yield.

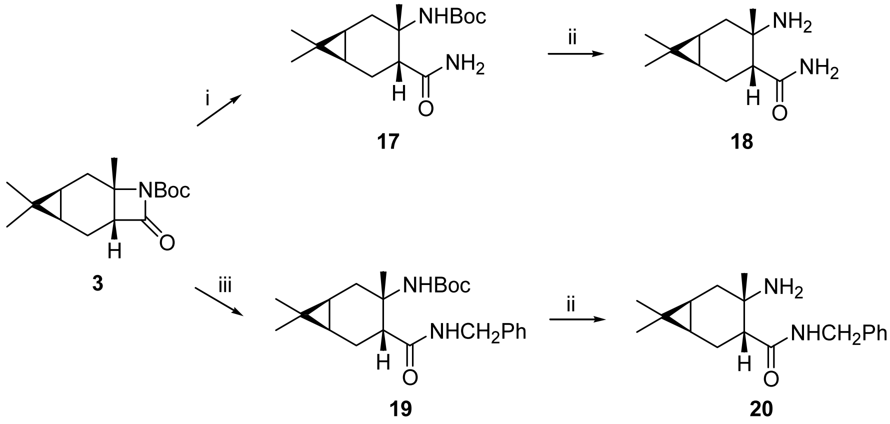
N-Boc amino ester **5** was reduced by lithium aluminium hydride to *N*-methyl amino alcohol **6**, and, after the deprotection of **5**, to the corresponding amino alcohol **8**. β-Amino ester **7** was transformed to β-amino acid **9** by refluxing in a dioxane:water = 1:1 mixture[33] for 2 days (Scheme 1).



Scheme 2. *Reagents and conditions*: (i) PhNCS/toluene, rt, 5 h, 91%; (ii) NH_3/MeOH, rt, **11**: 95%, **13**: 93%; (iii) PhNCO/toluene, rt, 5 h, 76%.



Scheme 3. *Reagents and conditions*: (i) PhNCS/toluene, rt, 5 h, 91%; (ii) MeI/MeOH, 15°C, 3 h, then KOH/MeOH, rt, 4 h, 90%; (iii) HCl/EtOH, reflux, 1 h.



Scheme 4. *Reagents and conditions*: (i) NH_3/MeOH, 4°C, 12 h, 60%; (ii) TFA/CH_2Cl_2, 0°C, 2 h, **18**: 77%, **20**: 65%; (iii) $PhCH_2NH_2$, KCN, DMF, 40°C, 24 h, 78%.

When β-amino ester **7** was reacted with phenyl isothiocyanate or phenyl isocyanate, the corresponding thiourea **10** or urea **12** was obtained. Compounds **10** and **12** were easily converted to 2-thioxo-4-pyrimidinone **11** and 2,4-pyrimidindione **13** by base-catalysed ring closure,[11] using methanol containing a catalytic amount of NH_3 (Scheme 2).

With phenyl isothiocyanate, amino alcohol **8** resulted in the thiourea adduct **14**, which was transformed to 2-phenylimino-1,3-oxazine **15**. Preparation of the corresponding thiazine **16** was not successful when HCl-containing ethanol was used;[34] only several decomposed products were observed (Scheme 3).

The nucleophilic ring opening of *N*-Boc-β-lactam **3** was also performed with amines such as NH_3 and benzylamine, resulting in *N*-Boc amides **17** and **19**. Both **17** and **19** were deprotected with trifluoroacetic acid[35] and gave the expected amides **18** and **20** (Scheme 4).

The compounds prepared have four stereogenic centres. Accordingly, the diastereomeric and hence the enantiomeric purity was proved by NMR spectroscopy and on a CHIRASIL-DEX CB column by GC. There was no sign of the presence of any other diastereomer in the spectra of the prepared compounds.

3. Conclusions

The regio- and stereoselective addition of CSI to (+)-3-carene resulted in enantiomerically pure β-lactam **2**, which was activated with a *tert*-butoxycarbonyl group. In contrast with β-lactam **2**, the *N*-Boc β-lactam was easily transformed to homochiral β-amino acid, amino ester, 1,3-amino alcohol and carboxamide derivatives. Starting from the amino ester, ring closure gave 2,4-pyrimidinedione and 2-thioxo-4-pyrimidinone. The use of 1,3-amino alcohol as starting material resulted in the saturated 1,3-oxazine.

The prepared β-amino acid derivatives may serve as chiral building blocks in the asymmetric synthesis of potential pharmacons, β-amino acid oligomers and modified analogues of natural peptides. They can also be used as chiral auxiliaries and catalysts in enantioselective syntheses.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz, $\delta = 0$ (TMS)), in $CDCl_3$, with the exceptions of compounds **9** and **20** (D_2O) and **18** (DMSO). Chemical shifts are expressed in ppm (δ) relative to TMS as internal reference. *J* values are given in Hz. FT-IR spectra were recorded on a Perkin–Elmer model 1000 spectrophotometer. Microanalyses were performed on a Perkin–Elmer 2400 elemental analyser. GC measurements were made on a Crompack CP-9002 system, consisting of a Flame Ionization Detector 901A and a Maestro II Chromatography data system (Chrompack International B.V., Middelburg, The Netherlands). The column used for direct separation was a CHIRASIL-DEX CB column (2500×0.25 mm I.D.) at 160°C, 80 kPa for **2**. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected.

4.1. (1*R*,3*R*,5*S*,7*S*)-4,4,7-Trimethyl-8-azatricyclo-[5.2.0.0^{3,5}]nonan-9-one 2

A mixture of 2.72 g (20.0 mmol) of (+)-(1*S*,6*R*)-3-carene **1** (Aldrich Chemical Co., 90% purity, 98% ee) and 2.84 g (20.0 mmol) of CSI was stirred in dry diethyl ether (50 mL) at room temperature for 9 h. Na_2SO_3 (3.78 g) in water (50 mL) was then cautiously added dropwise to the solution. The pH was held at 7–8 by the addition of 20% aqueous KOH. After separation of the organic phase, the aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic layer was dried (Na_2SO_4) and evaporated, and the resulting white crystalline product was recrystallized from hexane to give **2** (2.72 g, 76% yield); mp 108–111°C (lit.[17] 111–114°C); $[\alpha]_D^{20} = +56.9$ (*c* 1, MeOH); IR = 1769, 3233 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.66 (1H, dd, $J = 8.0$, 16.6 Hz, H-5), 0.76 (1H, dd, $J = 8.5$, 17.1 Hz, H-3), 0.97 (3H, s, Me-4), 1.04 (3H, s, Me-4), 1.00–1.11 (2H, m, H-6, H-2), 1.36 (3H, s, Me-7), 1.99 (1H, dd, $J = 8.0$, 15.6 Hz, H-6), 2.15 (1H, ddd, $J = 2.5$, 10.5, 15.6 Hz, H-2), 2.72 (1H, dd, $J = 2.5$, 4.5 Hz, H-1), 5.91 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 17.3, 24.2, 26.3, 28.9, 54.9, 58.9, 77.7, 83.1, 148.3. Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 74.05; H, 9.33; N, 7.96%.

4.2. (1*R*,3*R*,5*S*,7*S*)-*N*-*tert*-Butoxycarbonyl-4,4,7-trimethyl-8-azatricyclo[5.2.0.0^{3,5}]nonan-9-one 3

To a stirred solution of 2.0 g (11.2 mmol) of azetidinone **2** in dry THF (20 mL), triethylamine (0.32 mL, 22.4 mmol), di-*tert*-butyl dicarbonate (4.89 g, 22.4 mmol) and a catalytic amount of 4-dimethylaminopyridine were added. After stirring for 2 h at room temperature (the reaction was monitored by means of TLC), the mixture was evaporated to dryness. The oily residue obtained was purified by flash chromatography on a silica gel column (hexane:ethyl acetate = 9:1), resulting in a white crystalline product, **3** (2.56 g, 82% yield); mp 107–112°C; $[\alpha]_D^{20} = +29.7$ (*c* 1, MeOH); IR = 1708, 1792, 2936 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.53 (1H, dd, $J = 8.5$, 16.6 Hz, H-5), 0.72 (1H, dd, $J = 9.0$, 17.6 Hz, H-3), 0.89 (1H, q, $J = 9.0$ Hz, H-6), 0.95 (3H, s, Me-4), 1.01 (3H, s, Me-4), 1.05 (1H, m, $J = 4.5$, 9.1 Hz, H-2), 1.44 (3H, s, Me-7), 1.49 (9H, s, *tert*-butyl), 2.16 (1H, ddd, $J = 2.5$, 8.0, 15.1 Hz, H-2), 2.46 (1H, q, $J = 8.0$ Hz, H-6), 2.74 (1H, dd, $J = 2.5$, 4.5 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.6, 17.4, 17.9, 18.3, 18.4, 24.4, 26.2, 28.7, 28.8, 55.0, 58.8, 83.2, 148.3, 169.2. Anal. calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.56; H, 9.16; N, 5.13%.

4.3. (1*R*,3*R*,4*S*,6*S*)-4-*tert*-Butoxycarbonylamino-4,7,7-trimethylbicyclo[4.1.0]heptane-3-carboxylic acid 4

N-Boc-lactam **3** (2.0 g, 7.17 mmol) was dissolved in THF (50 mL) and treated with aq. LiOH (0.9 g in 20 mL of water) at room temperature. The mixture was stirred at room temperature for 7 h. The THF was removed in vacuo and, after the addition of water (10 mL), the solution was acidified to pH 3.5–4.0 with acetic acid and extracted with ethyl acetate (3×30 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to give a white crystalline product, **4** (2.0 g, 94% yield); mp 135–139°C; $[\alpha]_D^{20} = +31.3$ (*c* 1, MeOH); IR = 1686, 1729, 2977 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.58–0.75 (3H, m, H-6, H-1, H-5), 0.85 (3H, s, Me-7), 0.95 (3H, s, Me-7), 1.27 (3H, s, Me-3), 1.38 (9H, s, *tert*-butyl), 1.80 (1H, dd, $J = 7.1$, 14.1 Hz, H-2), 1.90 (1H, dd, $J = 6.6$, 11.6 Hz, H-5), 2.02–2.13 (1H, m, H-2), 2.96 (1H, dd, $J = 7.6$, 13.6 Hz, H-3), 5.37 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.8, 17.9, 18.1, 18.5, 21.0, 25.6, 29.1, 29.3, 30.8, 50.4, 51.8, 79.9, 156.0, 181.4. Anal. calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.45; H, 8.96; N, 3.96%.

4.4. Methyl (1*R*,3*R*,4*S*,6*S*)-4-*tert*-butoxycarbonylamino-4,7,7-trimethylbicyclo[4.1.0]heptane-3-carboxylate 5

Method A: To a stirred solution of *N*-Boc amino acid **4** (3.0 g, 10 mmol) in dry diethyl ether (30 mL), an ethereal solution of diazomethane was added dropwise at room temperature until the yellow colour remained. After stirring for 1 h, the diethyl ether was evaporated off and a yellow oil was obtained. The resulting crude product was used in the next step without further purification.

Method B: To a stirred solution of *N*-Boc lactam **3** (9.70 g, 35 mmol) in dry methanol (50 mL), NaOMe was added in catalytic amount at room temperature. After stirring for 2 h (the reaction was monitored by TLC), the solution was evaporated. Water (30 mL) was added to the oily residue, followed by extraction with $CHCl_3$ (3×30 mL). The organic phase was dried (Na_2SO_4) and evaporated. **5** was formed as a yellow oil (Method A: 3.10 g, 98% yield, method B: 9.57 g, 89% yield); $[\alpha]_D^{20} = -22.3$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.79–0.64 (3H, m, H-6, H-1, H-5), 0.91 (3H, s, Me-7), 1.00 (3H, s, Me-7), 1.24 (3H, s, Me-3), 1.44 (9H, s, *tert*-butyl), 1.79 (1H, dd, $J = 7.1$, 14.6 Hz, H-2), 1.95 (1H, dd, $J = 7.1$, 12.1 Hz, H-5), 2.11 (1H, ddd, $J = 8.06$, 14.6, 20.1 Hz, H-2), 3.12 (1H, t, $J = 10.6$ Hz, H-3), 3.70

(3H, s, COO-Me), 5.48 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.8, 17.9, 18.0, 18.6, 21.0, 25.6, 29.1, 29.2, 30.1, 50.2, 51.8, 52.4, 79.1, 156.9, 177.2. Anal. calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.34; H, 9.18; N, 4.64%.

4.5. (1*R*,3*R*,4*S*,6*S*)-(4,7,7-Trimethyl-4-methylamino-bicyclo[4.1.0]hept-3-yl)methanol 6

To a slurry of $LiAlH_4$ (0.36 g, 9.48 mmol) in dry THF (20 mL), amino ester **5** (1.0 g, 3.21 mmol) in THF (5 mL) was added dropwise at 0°C. After stirring for 2 h at room temperature (the reduction was monitored by means of TLC), the mixture was decomposed with water (1.0 mL) in THF (10 mL) under ice cooling. The inorganic material was filtered off and washed with THF (3×20 mL). Drying (Na_2SO_4) and evaporation gave **7** as a yellow oil (0.60 g, 95% yield); $[\alpha]_D^{20}=+11$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.52–0.59 (1H, m, H-6), 0.72 (1H, t, $J=8.1$ Hz, H-1), 0.78 (1H, dd, $J=5.0$, 15.1 Hz, H-5), 0.85–0.93 (1H, m, H-2), 0.91 (3H, s, Me-7), 1.03 (3H, s, Me-7), 1.15 (3H, s, Me-4), 1.58 (1H, dd, $J=7.05$, 15.11 Hz, H-5), 2.13–2.25 (2H, m, H-2, H-3), 2.26 (3H, s, NH-*Me*), 3.30 (1H, dd, $J=1.5$, 11.1 Hz, *CH₂*-OH), 4.13 (1H, dd, $J=2.5$, 10.6 Hz, CH_2-OH); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.5, 17.8, 18.1, 18.9, 19.1, 23.8, 28.0, 28.1, 29.5, 42.9, 54.1, 63.3. Anal. calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.15; H, 11.68; N, 6.90%.

4.6. Methyl (1*R*,3*R*,4*S*,6*S*)-4-amino-4,7,7-trimethyl-bicyclo[4.1.0]heptane-3-carboxylate 7

To a stirred solution of *N*-Boc amino ester **5** (0.20 g, 0.64 mmol) in dry CH_2Cl_2 (10 mL), trifluoroacetic acid (0.50 mL) was added at 0°C. After stirring for 2 h, the solution was neutralized with saturated aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (2×30 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to give **6** as a yellow oil product (0.13 g, 96% yield); $[\alpha]_D^{20}=-26.7$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm: 0.67–0.77 (2H, m, H-6, H-1), 0.93 (3H, s, Me-7), 1.02 (6H, s, Me-7, Me-4), 1.06 (1H, dd, $J=4.5$, 14.6 Hz, H-5), 1.85 (2H, ddd, $J=9.6$, 14.6, 24.1 Hz, H-2, H-5), 2.03 (1H, dd, $J=6.5$, 12.1 Hz, H-2), 2.14 (1H, ddd, $J=7.5$, 12.1, 19.6 Hz, H-3), 3.66 (3H, s, COO-Me); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.3, 17.8, 17.9, 18.3, 20.8, 28.6, 29.3, 33.5, 49.2, 50.2, 51.6, 177.1. Anal. calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.04; H, 9.82; N, 6.52%.

4.7. (1*R*,3*R*,4*S*,6*S*)-(4-Amino-4,7,7-trimethylbicyclo-[4.1.0]hept-3-yl)methanol 8

To a slurry of $LiAlH_4$ (0.36 g, 9.48 mmol) in dry THF (20 mL), amino ester **7** (1.0 g, 4.74 mmol) in THF (5 mL) was added dropwise at 0°C. After stirring for 2 h at room temperature (the reduction was monitored by means of TLC), the mixture was decomposed by the cautious addition of water (2.0 mL) dissolved in THF (10 mL) under ice cooling. The inorganic material was filtered off and washed with THF. Drying (Na_2SO_4) and evaporation of the solvent resulted in **8** as a yellow oil (0.73 g, 85% yield); $[\alpha]_D^{20}=+10.1$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.61–0.69 (1H, dd, $J=3.0$, 11.1 Hz, H-6), 0.77 (1H, t, $J=8.5$ Hz, H-1), 0.84–0.91 (1H, m, H-5), 0.90 (3H, s, Me-7), 1.03 (3H, s, Me-7), 1.20 (3H, s, Me-4), 1.23 (1H, d, $J=4.5$ Hz, H-2), 1.56–1.71 (2H, m, H-5, H-2), 2.28 (1H, ddd, $J=8.1$, 15.1, 20.6 Hz, H-3), 3.00 (2H, bs, NH_2), 3.34 (1H, dd, $J=2.0$, 11.1 Hz, CH_2-OH), 4.11 (1H, dd, $J=3.0$, 11.1 Hz, CH_2-OH); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.5, 18.1, 18.3, 19.4, 19.5, 27.7, 29.6, 37.9, 41.3, 51.2, 65.1. Anal. calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.95; H, 11.42; N, 7.53%.

4.8. (1*R*,3*R*,4*S*,6*S*)-4-Amino-4,7,7-trimethylbicyclo-[4.1.0]heptane-3-carboxylic acid 9

Amino ester **7** (0.55 g, 2.60 mmol) was dissolved in a mixture of dioxane and water (1:1, 10 mL). After stirring and refluxing for 2 days (the reaction was monitored by means of TLC), the mixture was evaporated to dryness and the resulting white crystalline product was filtered off and washed with acetone to furnish **9** (0.45 g, 88% yield); mp 273–275°C; $[\alpha]_D^{20}=+23$ (*c* 1, MeOH); ^{1}H NMR (D_2O) δ (ppm): 0.74–0.83 (2H, m, H-6, H-1), 0.97 (3H, s, Me-7), 1.03 (3H, s, Me-7), 1.31 (3H, s, Me-4), 1.36 (1H, d, $J=4.0$ Hz, H-5), 1.85–2.02 (2H, m, H-2, H-5), 2.08–2.20 (2H, m, H-2, H-3); ^{13}C NMR (D_2O) δ (ppm): 14.3; 15.9, 17.8, 18.0, 20.3, 23.9, 28.2, 29.9, 48.6, 52.6, 183.2. Anal. calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.75; H, 9.45; N, 6.85%.

4.9. Thiourea derivative 10

Phenyl isothiocyanate (0.60 g, 4.40 mmol) was added to a solution of 0.80 g (3.80 mmol) of amino ester **7** in dry toluene (30 mL). After stirring for 5 h at room temperature (the reaction was monitored by means of TLC), the solution was evaporated to dryness and the obtained white crystalline product was recrystallized from diisopropyl ether to give **10** (1.10 g, 84% yield); mp 142–145°C; $[\alpha]_D^{20}=-26.7$ (*c* 1, MeOH); IR = 1723, 2955, 3333 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.54 (1H, t, $J=8.6$ Hz, H-6), 0.72 (1H, dd, $J=5.6$, 15.1 Hz, H-1), 1.03 (3H, s, Me-7), 1.50 (3H, s, Me-7), 1.66 (3H, s, Me-4), 1.77 (2H, dd, $J=7.1$, 15.1 Hz, H-5, H-2), 1.95 (2H, dd, $J=7.6$, 12.1 Hz, H-5, H-2), 3.54 (3H, s, COO-*Me*), 4.20 (1H, dd, $J=9.6$, 15.1 Hz, H-3), 7.23-7.39 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.8, 17.7, 18.2, 18.7, 21.1, 24.1, 28.9, 29.1, 51.2, 52.5, 55.8, 126.5, 127.8, 130.4, 137.0, 176.7, 180.1. Anal. calcd for $C_{19}H_{26}N_2O_2S$: C, 65.86; H, 7.56; N, 8.08. Found: C, 65.75; H, 7.45; N, 7.85%.

4.10. (1a*R*,2a*R*,6a*S*,7a*S*)-1,1,6a-Trimethyl-4-phenyl-5-thioxodecahydro-4,6-diazacyclopropa[b]naphthalen-3-one 11

The appropriate thiourea derivative **10** (0.50 g, 1.45 mmol) was dissolved in methanol (10 mL). Five drops of methanol containing 25% NH_3 were added to the solution. After standing for 1 day at room temperature, the solution was evaporated to give **11** as a crystalline product (0.50 g, 95% yield); mp 293–296°C; $[\alpha]_D^{20}=+49.3$ (*c* 1, MeOH); IR = 1189, 1713, 2921, 3254 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ (ppm): 0.73–0.82 (1H, m, H-7a), 0.87 (1H, d, *J* = 8.1 Hz, H-1a), 0.91 (3H, s, Me-1), 1.06 (3H, s, Me-1), 1.24 (1H, dd, *J* = 4.0, 15.6 Hz, H-7), 1.41 (3H, s, Me-6a), 1.95–2.06 (1H, m, H-2), 2.10–2.21 (2H, m, H-2, H-7), 2.28 (1H, ddd, *J* = 1.5, 8.1, 10.1 Hz, H-2a), 7.15 (2H, d, *J* = 7.1 Hz, Ph), 7.39–7.50 (3H, m, Ph), 7.54 (1H, bs, NH); ^{13}C NMR (CDCl$_3$) δ (ppm): 15.8, 16.5, 18.6, 18.8, 20.4, 27.4, 28.9, 30.3, 45.3, 52.3, 129.3, 129.6, 129.8, 172.0, 182.6. Anal. calcd for $C_{18}H_{22}N_2OS$: C, 68.75; H, 7.05; N, 8.91. Found: C, 68.65; H, 6.96; N, 8.85%.

4.11. Urea derivative 12

Phenyl isocyanate (0.24 g, 2.04 mmol) was added to a solution of 0.40 g (1.89 mmol) amino ester **7** in toluene (30 mL). After stirring for 5 h at room temperature (the reaction was monitored by TLC), the solution was evaporated to dryness, resulting in **12** as a crystalline product (0.45 g, 76% yield); mp 179–182°C; $[\alpha]_D^{20}=+60.9$ (*c* 1, MeOH); IR = 1727, 3315, 3406 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ (ppm): 0.59–0.65 (1H, m, H-6), 0.75–0.87 (2H, m, H-1, H-2), 0.91 (3H, s, Me-7), 1.00 (3H, s, Me-7), 1.32 (3H, s, Me-4), 1.78–1.87 (1H, m, H-5), 1.92–2.06 (2H, m, H-2, H-5), 3.34 (1H, dd, *J* = 8.6, 13.6 Hz, H-3), 3.66 (3H, s, COO-*Me*), 5.71 (1H, bs, NH), 6.28 (1H, bs, NH), 7.02–7.09 (1H, m, Ph), 7.28–7.34 (4H, m, Ph); ^{13}C NMR (CDCl$_3$) δ (ppm): 15.8, 17.9, 18.1, 18.8, 21.2, 25.8, 29.2, 30.1, 50.1, 52.5, 52.6, 121.4, 124.0, 129.8, 139.7, 155.9, 177.7. Anal. calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.85; H, 7.96; N, 8.65%.

4.12. (1a*R*,2a*R*,6a*S*,7a*S*)-1,1,6a-Trimethyl-4-phenyloctahydro-4,6-diazacyclopropa[*b*]naphthalene-3,5-dione 13

The appropriate urea derivative **12** (0.50 g, 1.52 mmol) was dissolved in 20 mL of methanol. Five drops of methanol containing 25% NH$_3$ were added to the solution. After standing for 4 days at room temperature, the solution was evaporated and resulted in **13** as a white crystalline product (0.42 g, 93% yield); mp 191–196°C; $[\alpha]_D^{20}=+51.3$ (*c* 1, MeOH); IR = 1713, 2920, 3254 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ (ppm): 0.68–0.77 (1H, m, H-7a), 0.80–0.89 (1H, m, H-1a), 0.92 (3H, s, Me-1), 1.06 (3H, s, Me-1), 1.26 (1H, dd, *J* = 4.5, 16.1 Hz, H-7), 1.38 (3H, s, Me-6a), 1.97–2.17 (3H, m, 2×H-2, H-7), 2.20–2.28 (1H, m, H-2a), 5.25 (1H, bs, NH), 7.13–7.20 (2H, m, Ph), 7.35–7.50 (3H, m, Ph); ^{13}C NMR (CDCl$_3$) δ (ppm): 17.9, 18.1, 18.8, 21.4, 25.8, 29.2, 30.1, 50.5, 52.6, 52.8, 121.7, 124.3, 129.8, 139.4, 177.8. Anal. calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.35; H, 7.26; N, 9.25%.

4.13. (1*S*,3*S*,4*R*,6*R*)-1-(4-Hydroxymethyl-3,7,7-trimethylbicyclo[4.1.0]hept-3-yl)-3-phenylthiourea 14

Phenyl isothiocyanate (0.04 g, 0.29 mmol) was added to a solution of 0.10 g (0.54 mmol) of amino alcohol **8** in 10 mL of dry toluene. After stirring for 3 h at room temperature (the reaction was monitored by means of TLC), the solution was evaporated and resulted in **14** as a white crystalline product (0.16 g, 91% yield); mp 157–160°C; $[\alpha]_D^{20}=-80$ (*c* 1, MeOH); IR = 1551, 3236, 3399 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ (ppm): 0.73–0.83 (2H, m, H-6, H-1), 0.91 (3H, s, Me-7), 1.02 (3H, s, Me-7), 1.47 (2H, dd, *J* = 7.1, 15.1, H-5, H-2), 1.64 (3H, s, Me-4), 1.68–1.80 (2H, m, H-5, H-2), 3.32 (1H, dd, *J* = 3.0, 11.1 Hz, *CH*$_2$-OH), 3.81 (1H, dd, *J* = 11.1, 16.6 Hz, H-4), 3.91 (1H, dd, *J* = 3.0, 11.1 Hz, *CH*$_2$-OH), 7.12–7.53 (5H, m, Ph); ^{13}C NMR (CDCl$_3$) δ (ppm): 15.8, 18.2, 18.7, 19.2, 19.6, 24.2, 29.3, 31.4, 45.6, 57.4, 63.2, 126.8, 127.8, 130.4, 137.2, 180.1. Anal. calcd for $C_{18}H_{26}N_2OS$: C, 67.88; H, 8.23; N, 8.80. Found: C, 67.65; H, 8.16; N, 8.68%.

4.14. (1a*R*,2a*R*,6a*S*,7a*S*)-Phenyl-(1,1,6a-trimethyloctahydro-4-oxa-6-azacyclopropa[*b*]naphthalen-5-ylidene)-amine 15

To a stirred solution of 0.50 g (1.57 mmol) of thiourea derivative **14** in 15 mL of methanol, 0.54 mL (8.64 mmol) of iodomethane was added and the solution was stirred at 15°C for 3 h. After evaporation of the solvent, the residue was stirred in 15 mL of 2.5 N KOH in methanol for 4 h. The solution was then evaporated, and the residue was dissolved in water (30 mL) and extracted with chloroform (3×30 mL). After drying (Na$_2$SO$_4$) and evaporation of the organic layer, the crystalline product was recrystallized from hexane, which resulted in oxazine **15** (0.40 g, 90% yield); mp 132–134°C; $[\alpha]_D^{20}=+29.7$ (*c* 1, MeOH); IR = 1669, 2921 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ (ppm): 0.60–0.82 (2H, m, H-7a, H-1a), 0.92 (3H, s, Me-1), 0.95 (1H, m, H-7), 1.03 (3H, s, Me-1), 1.21 (3H, s, Me-6a), 1.26–1.38 (1H, m, H-2), 1.62–1.92 (3H, m, H-2a, H-2, H-7), 3.97 (1H, dd, *J* = 3.5, 10.1 Hz, H-3), 4.30 (1H, dd, *J* = 4.0, 10.6 Hz, H-3), 6.89–7.27 (5H, m, Ph); ^{13}C NMR (CDCl$_3$) δ (ppm): 15.3, 17.9, 18.1, 19.1, 19.4, 21.4, 25.9, 28.7, 31.9, 34.2, 70.5, 121.6, 122.6, 124.2, 129.4, 148.3. Anal. calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.95; H, 8.26; N, 9.75%.

4.15. *tert*-Butyl (1*R*,3*R*,4*S*,6*S*)-(3-aminocarbonyl-4,7,7-trimethylbicyclo[4.1.0]hept-4-yl)-carbamate 17

N-Boc-β-lactam **3** (2.0 g, 7.17 mmol) was dissolved in 20 mL of a 25% solution of NH$_3$ in dry methanol. The reaction mixture was allowed to stand at 4°C for 12 h. After evaporation (first at room temperature and then on a 60°C water bath), the white crystalline product was purified by flash chromatography on a silica gel column (hexane:ethyl acetate = 4:1) to give **17** (1.27 g; 60% yield); mp 81–85°C; $[\alpha]_D^{20}=+33$ (*c* 1, MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm): 0.64.0.79 (3H, m, H-6, H-1, H-5), 0.90 (3H, s, Me-7), 1.01 (3H, s, Me-7), 1.29 (3H, s, Me-4), 1.43 (9H, s, *tert*-butyl), 1.58–1.63 (1H, m, H-2), 1.75 (1H, dd, *J* = 7.1, 15.1 Hz, H-5), 2.10 (1H, dd, *J* = 9.6, 15.6 Hz, H-2), 3.15–3.21 (1H, m, H-3), 3.96 (1H, bs, NH); ^{13}C NMR (CDCl$_3$) δ (ppm): 16.1, 17.9, 18.1, 18.7, 21.4, 25.6, 29.2, 30.2, 30.3, 38.4, 51.0, 51.7, 79.1, 155.9, 178.9. Anal. calcd for $C_{16}H_{28}N_2O_3$: C, 64.83; H, 9.52; N, 9.45. Found: C, 64.76; H, 9.38; N, 9.27%.

4.16. (1*R*,3*R*,4*S*,6*S*)-4-Amino-4,7,7-trimethylbicyclo-[4.1.0]heptane-3-carboxamide 18

To a stirred solution of *N*-Boc carboxamide **17** (0.20 g, 0.67 mmol) in dry CH_2Cl_2 (10 mL), trifluoroacetic acid (0.50 mL) was added at 0°C. After stirring for 2 h, the trifluoroacetic acid was neutralized with saturated aqueous $NaHCO_3$, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to give **18** as a yellow oil product (0.10 g, 77% yield); $[\alpha]_D^{20}=+36.2$ (*c* 1, MeOH); ^{1}H NMR (DMSO) δ (ppm): 0.63 (1H, dd, $J=5.0$, 9.6 Hz, H-6), 0.74 (1H, d, $J=7.6$ Hz, H-1), 0.93 (3H, s, Me-7), 1.00 (3H, s, Me-7), 1.09 (1H, dd, $J=4.5$, 15.6 Hz, H-5), 1.18 (3H, s, Me-4), 1.82 (1H, dd, $J=6.0$, 13.6 Hz, H-2), 1.94–2.08 (2H, m, H-5, H-2), 2.12 (1H, dd, $J=9.6$, 15.6 Hz, H-3), 3.93 (2H, bs, NH_2); ^{13}C NMR (DMSO) δ (ppm): 14.8, 15.9, 17.6, 17.9, 19.6, 23.9, 28.6, 30.2, 44.4, 51.7, 176.6. Anal. calcd for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.27; N, 14.27. Found: C, 67.12; H, 10.09; N, 14.11%.

4.17. *tert*-Butyl (1*R*,3*R*,4*S*,6*S*)-(3-benzylaminocarbonyl-4,7,7-trimethylbicyclo[4.1.0]hept-4-yl)-carbamate 19

N-Boc-β-lactam **3** (0.28 g, 1.0 mmol) was dissolved in dry DMF (10 mL) under a N_2 atmosphere. Benzylamine (0.21 g, 2.0 mmol) and 0.05 g of KCN were added. After stirring for 24 h at 40°C (the reaction was monitored by means of TLC), diethyl ether (20 mL) was added to the solution and the mixture was washed in turn with brine (2×20 mL), 1N HCl (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). After drying (Na_2SO_4) and evaporation of the organic phase, the white crystalline product obtained was purified by flash chromatography on a silica gel column (hexane:ethyl acetate = 4:1) to give **19** (0.29 g, 78% yield); mp 182–184°C; $[\alpha]_D^{20}=+31.5$ (*c* 1, MeOH); IR = 1716, 2934, 3284 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.61–0.79 (4H, m, H-6, H-1, H-5, H-2), 0.87 (3H, s, Me-7), 1.25 (3H, s, Me-7), 1.43 (9H, s, *tert*-butyl), 1.52 (3H, s, Me-3), 1.72 (2H, dd, $J=7.1$, 15.1 Hz, *CH*$_2$-Ph), 2.25 (1H, ddd, $J=8.06$, 14.6, 19.6 Hz, H-2), 3.20 (1H, dd, $J=9.1$, 14.6 Hz, H-5), 4.43 (1H, d, $J=6.0$ Hz, H-3), 6.25 (1H, bs, NH), 7.22-7.38 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.1, 17.9, 18.2, 18.7, 21.7, 25.7, 26.3, 28.8, 29.2, 30.1, 44.3, 52.1, 79.0, 128.4, 128.5, 129.5, 138.4, 156.0, 176.2. Anal. calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.12; H, 8.59; N, 7.11%.

4.18. (1*R*,3*R*,4*S*,6*S*)-*N*-Benzyl-4-amino-4,7,7-trimethyl-bicyclo[4.1.0]heptane-3-carboxamide 20

The Boc group of the *N*-benzyl derivative of **19** (1.0 g, 2.59 mmol) was removed according to Section 4.17 to give benzylamide **20** as a yellow oil (0.48 g, 65% yield); $[\alpha]_D^{20}=+34.3$ (*c* 1, MeOH); ^{1}H NMR (D_2O) δ (ppm): 0.34–0.52 (2H, m, H-6, H-1), 0.70 (6H, s, Me-7, Me-7), 0.75 (3H, s, Me-4), 1.47 (2H, m, H-5, H-2), 1.62 (1H, dd, $J=6.0$, 11.6 Hz, H-5), 1.83 (2H, m, H-2, H-3), 4.03 (2H, s, *CH*$_2$-Ph), 6.95–7.19 (5H, m, Ph); ^{13}C NMR (D_2O) δ (ppm): 15.6, 18.0, 18.1, 18.7, 21.6, 29.3, 29.8, 35.2, 42.7, 49.1, 49.1, 127.6, 128.1, 129.1, 140.4, 176.3. Anal. calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.22; H, 8.99; N, 9.61%.

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References

1. Ho, T.-L. *Enantioselective Synthesis of Natural Products from Chiral Terpenes*; John Wiley: New York, 1992.
2. He, X. C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979–4987.
3. Posner, T.; Sears, P. T.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511–2513.
4. Goralski, C. T.; Chrisman, W.; Hasha, D. L.; Nicholson, L. W.; Rudolf, P. R.; Zakett, D.; Singaram, B. *Tetrahedron: Asymmetry* **1997**, *8*, 3863–3871.
5. Goldfuss, B.; Steigelman, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77–82.
6. Steiner, D.; Sethofer, S. D.; Goralski, C. T.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1477–1483.
7. Joshi, S. N.; Malhotra, S. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1763–1766.
8. Solladie-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 3240–3242.
9. Masui, M.; Shioiri, T. *Tetrahedron* **1995**, *51*, 8363–8370.
10. Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, *37*, 9143–9146.
11. Szakonyi, Z.; Martinek, T.; Hetényi, A.; Fülöp, F. *Tetrahedron: Asymmetry* **2000**, *11*, 4571–4579.
12. Juaristi, E. *Enantioselective Synthesis of β-Amino Acids*, New York, 1997.
13. Fülöp, F. *In Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, 2000; Vol. 22, pp. 273–306.
14. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204 and references cited therein.
15. Knapp, S. *Chem. Rev.* **1995**, *95*, 1859–1876 and references cited therein.
16. Kunisch, F.; Babczinski, P.; Arlt, D.; Plempel, M. Ger. Offen. DE 4,028,046; *Chem. Abstr.* **1992**, *117*, 20486a.
17. Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H.-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433–436.
18. Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K.-L. *Synthesis* **2003**, *1*, 136–140.
19. Bozó, B.; Fülöp, F.; Tóth, G. K.; Tóth, G.; Szucs, M. *Neuropeptides* **1997**, *31*, 367–372.
20. Porter, E. A.; Wang, X.; Lee, H.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
21. Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aquilar, M. I. *Curr. Med. Chem.* **2002**, *9*, 811–822.
22. Park, J. S.; Lee, H. S.; Lai, J. R.; Kim, B. M.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 8539–8545.
23. Langenhan, J. M.; Guzei, I. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2402–2405.
24. Gademann, K.; Hane, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534–1537.

25. Glatti, A.; Daura, X.; Seebach, D.; van Gunsteren, W. F. *J. Am. Chem. Soc.* **2002**, *124*, 12972–12978.
26. Martinek, T. A.; Tóth, G. K.; Vass, E.; Hollósi, M.; Fülöp, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 1718–1721.
27. Kamal, A.; Sattur, P. B. *Heterocycles* **1987**, *26*, 1051–1076.
28. Sasaki, T.; Eguchi, S.; Yamada, H. *J. Org. Chem.* **1973**, *38*, 679–686.
29. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, *12*, 1813–1826.
30. Parsons, P. J.; Camp, N. P.; Edwards, N.; Sumoreeah, L. R. *Tetrahedron* **2000**, *56*, 309–315.
31. Szakonyi, Z.; Fülöp, F.; Bernáth, G.; Evanics, F.; Riddell, F. G. *Tetrahedron* **1998**, *54*, 1013–1020.
32. Furet, P.; García-Ecchevería, C.; Gay, B.; Schoepfer, J.; Zeller, M.; Rahuel, J. *J. Med. Chem.* **1999**, *42*, 2358–2363.
33. Tamagnan, G.; Gao, Y.; Baldwin, R. M.; Zoghbi, S. S.; Neumeyer, J. L. *Tetrahedron Lett.* **1996**, *37*, 4353–4356.
34. Bernáth, G.; Szakonyi, Z.; Fülöp, F.; Sohár, P. *Heterocycles* **1994**, *37*, 1687–1694.
35. Csomós, P.; Bernáth, G.; Fülöp, F. *Monatsh. Chem.* **2002**, *133*, 1077–1084.