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Synthesis and transformations of enantiomeric 1,2-disubstituted monoterpene derivatives†

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Abstract

Regio- and stereospecific addition of chlorosulfonyl isocyanate to (+)- and (−)-α-pinene **1** resulted in enantiomerically pure β-lactams **2**, which were converted to enantiomeric β-amino esters **3** and 1,3-amino alcohols **4** and **6** with ee >99%. The resulting 1,3-difunctional compounds **3**, **4** and **6** were transformed to fused saturated 1,3-heterocycles such as tetrahydro-1,3-oxazines **7** and **9**, 2,4-pyrimidinedione **11** and 2-thioxopyrimidin-4-one **13** enantiomers.

1. Introduction

The readily available chiral terpenes and their derivatives are chiral auxiliary materials that are widely used in enantioselective transformations.[1] α-Pinene is a useful chiral source because both of its enantiomers are available commercially. Its derivatives, such as pinanediol,[2] 2-hydroxypinan-3-one[3] and *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane®),[4] have been widely utilized as chiral reagents in asymmetric syntheses. The preparation and some synthetic applications of enantiomerically pure 3-amino-2-hydroxypinane have also been reported by several authors.[5–7] As an example, the Eliel synthon (a 1,3-amino alcohol prepared from (+)-pulegone) has been successfully applied for the enantioselective synthesis of primary and secondary amines, α-hydroxy acids, isoxazolines, etc.[8–11]

Our aim was the preparation and some transformations of chiral β-lactams and β-amino acid derivatives, derived from chiral terpenes. Besides the chemical interest of β-amino acids,[12,13] some of them exert significant pharmacological effects, for example the antifungal antibiotic (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin).[14] They can be also used as building blocks for the preparation of modified analogues of pharmacologically active peptides.[15] Conformational studies of helix-forming β-amino acid oligomers are currently at the focus of interest.[16]

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† Dedicated to Professor Kalevi Pihlaja on the occasion of his 60th birthday.

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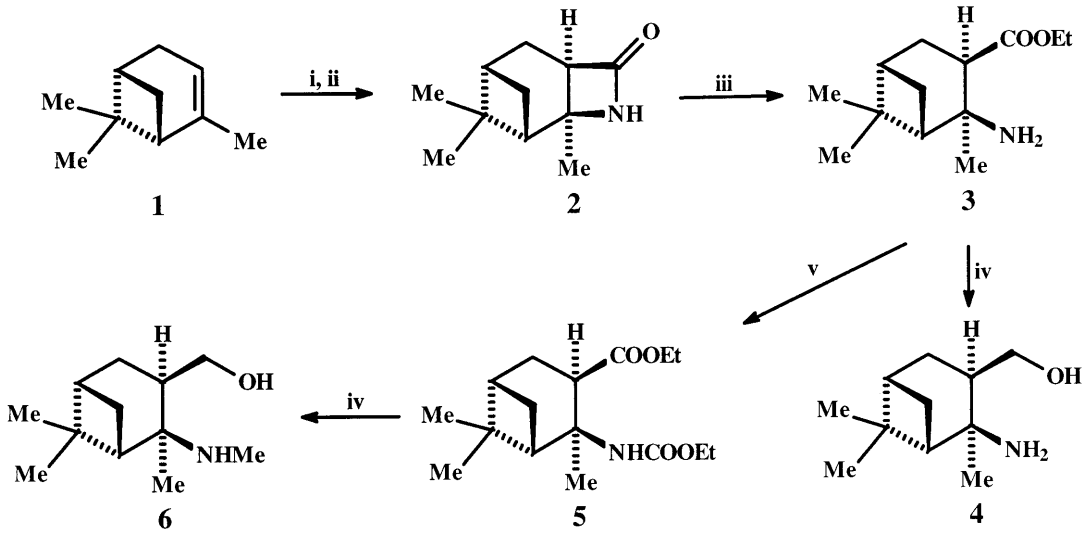
We additionally planned the synthesis and transformations of 1,3-amino alcohols, starting from (+)- and (−)-α-pinene to prepare cycloalkane-fused saturated 1,3-heterocycles.[12]

2. Results and discussion

The synthetic route for azetidinone **2** is shown in Scheme 1. Although both enantiomers were prepared, the scheme mentions only the compounds derived from (+)-α-pinene. The reaction of chlorosulfonyl isocyanate (CSI) with a cycloalkene is a well-known procedure for the synthesis of cycloalkane-fused β-lactams.[17–21] There are several examples in the literature concerning the regio- and stereospecificity of the cycloaddition, which proceeds in accordance with the Markovnikov orientation of CSI addition.[21–24]



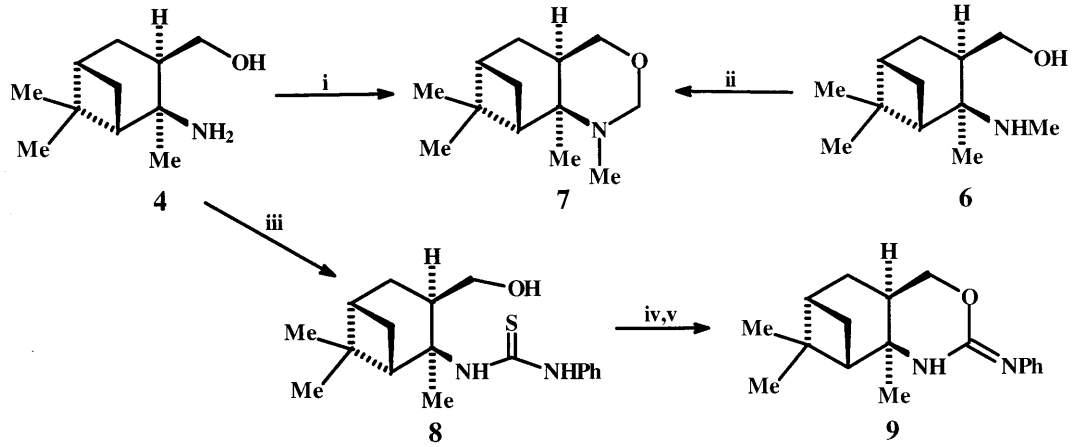
Scheme 1. (i) CSI, 1 h, rt, 76%; (ii) KOH, then Na_2SO_3; (iii) 22% HCl/EtOH, reflux, 60%; (iv) $LiAlH_4$/THF, reflux, **4**: 85%, **6**: 79%; (v) ClCOOEt, 10% NaOH/benzene, 81%

Starting from commercially available (+)- and (−)-α-pinene **1**, the cycloaddition of CSI furnished the enantiomeric β-lactam **2** in a regio- and stereospecific reaction. In contrast with the literature data (−60 to −73°C, 3 h, 40–52% overall yield, the enantiomer purity was not mentioned),[17–19] the cycloaddition proceeded with excellent yield (76%) at room temperature within 1 h (ee >99%). The *exo* stereoselectivity of the CSI cycloaddition was earlier proved through the application of $Eu(dpm)_3$, an NMR shift reagent, by Sasaki et al.[17]

The reaction of the azetidinone **2** with ethanol containing HCl resulted in β-amino ester **3**, which was converted to the corresponding amino alcohol **4** by lithium aluminium hydride (LAH) reduction. When amino ester **3** was treated with ethyl chloroformate, the *N*-ethoxycarbonyl derivative **5** was formed, which was reduced to the *N*-methyl amino alcohol **6** (Scheme 1).

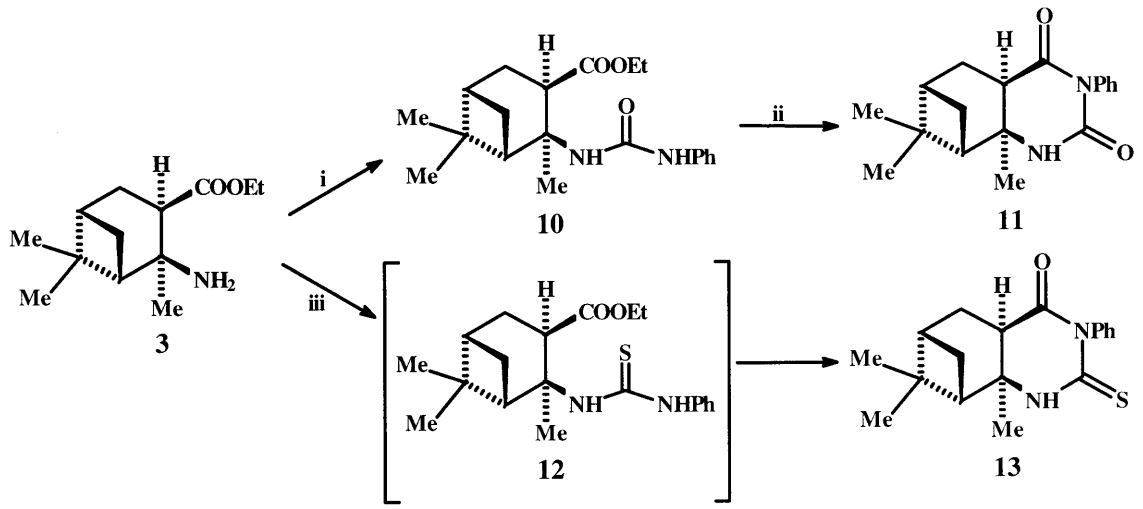
Starting from **4** and **6**, the *N*-methyl-1,3-oxazine **7** was prepared in two independent ways: from **6** with aqueous formaldehyde, or from **4** with a formaldehyde/formic acid mixture, when ring closure and *N*-methylation took place.[25]

With phenyl isothiocyanate, **4** gave the thiourea adduct **8**, which was transformed to the 2-phenylimino-1,3-oxazine **9** with methyl iodide, followed by alkaline methyl mercaptan elimination (Scheme 2).



Scheme 2. (i) HCOOH, CH_2O/H_2O, reflux, 51%; (ii) CH_2O/H_2O, rt, 65%; (iii) PhNCS/benzene, rt, 92%; (iv) MeI/MeOH, rt; (v) KOH/MeOH, rt, 60%

When amino ester **3** was reacted with phenyl isocyanate, urea derivative **10** was obtained, which was converted to the pyrimidinedione **11** by base-catalyzed ring closure (Scheme 3).



Scheme 3. (i) PhNCO/benzene, rt, 89%; (ii) NH_3/MeOH, rt, 87%; (iii) PhNCS/benzene, rt, 83%

The reaction of **3** and phenyl isothiocyanate resulted in the corresponding 2-thioxopyrimidin-4-one **13**: the thiourea intermediate **12** cyclized spontaneously even at room temperature (Scheme 3). All of the NMR signals of **2**, **7**, **9** and **13** were assigned. The relative configurations of the 1,2-disubstituted monoterpene derivatives were established on the basis of NOESY experiments, which revealed the *cis* relationship of Me-2 and H-7 (**7**, **9**, **13**) or H-5 (**2**). Conformational flexibility is possible in **7** and **9**. The ^3J(H-6, H-7) couplings reveal a predominantly gauche conformation for **9** (2.1, 9.1 Hz). The ^3J(H-6, H-7) couplings (6.0, 6.3 Hz) of **7** are indicative of considerable conformational flexibility of the heterocyclic ring.

The enantiomeric excesses were proved in **2**, **3** and **5** (ee >99%). There was no sign of the presence of any other diastereomer in the NMR spectra of the crude products **4** and **6**–**13**, consistent with a high enantiomeric excess of **4** and **6**–**13**.

3. Conclusions

Starting from (+)- and (−)-α-pinene, the regio- and stereoselective addition of CSI resulted in enantiomerically pure β-lactams, which were converted to chiral β-amino esters and 1,3-amino alcohols. The 1,3-difunctional compounds prepared were transformed to chiral fused saturated 1,3-heterocycles, such as 1,3-oxazines, 2,4-pyrimidinediones and 2-thioxo-4-pyrimidinones.

The resulting β-amino acid derivatives and 1,3-amino alcohols may serve as chiral building blocks for the synthesis of potential drugs, β-amino acid oligomers and modified analogues of natural peptides. They may also be used as chiral auxiliaries for further 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 $CDCl_3$). Chemical shifts are expressed in ppm (δ) relative to TMS as internal reference: J values are given in Hz.

GC measurements were performed on a Chrompack 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 130°C, 80 kPa for **2** and at 100°C, 80 kPa for **3** and **5**. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected.

4.1. (1S,2S,5R,7S)-2,8,8-Trimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one **2**‡

A mixture of 13.6 g (100.0 mmol) of (+)-(1*R*,5*R*)-α-pinene **1** and 14.30 g (101.2 mmol) of CSI was stirred in 300 ml of dry diethyl ether for 1 h. Sodium sulfite (20.4 g) in 140 ml water was then cautiously added dropwise to the solution. The pH was held at 7–8 by the addition of 20% aqueous potassium hydroxide. After separation of the organic phase, the aqueous layer was extracted with diethyl ether (2×100 ml). The combined organic layer was dried (Na_2SO_4) and evaporated, and the white crystalline product was recrystallized from isopropyl ether.

Compound **2** (13.6 g, 76%; mp: 144–147°C (lit.:[17–19] 146–148°C); $[\alpha]_D^{20} = +96.5$ ($c = 0.1$, MeOH); ee >99%). Analysis: calculated 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. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.91 (3H, *s*, Me-8), 1.32 (3H, *s*, Me-8), 1.47 (3H, *s*, Me-2), 1.53 (1H, *d*, H-9, $J = 11.08$ Hz), 1.83–1.93 (1H, *m*, H-6), 1.94–1.98 (1H, *m*, H-7), 2.09 (1H, *dd*, H-1, $J = 4.66$, 6.04 Hz), 2.12–2.21 (2H, *m*, H-6, H-9), 2.86 (1H, *d*, H-5, $J = 10.32$ Hz), 6.12 (1H, *s*, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.4, 25.1, 25.6, 25.7, 27.8, 42.3, 50.3, 50.4, 59.2, 173.8.

The (1*R*,2*R*,5*S*,7*R*)-enantiomer of **2** was prepared from (−)-(1*S*,5*S*)-α-pinene as described above; $[\alpha]_D^{20} = -96$ ($c = 0.1$, MeOH); ee >99%; the spectroscopic data and mp were similar to those for **2**. Analysis: found: C, 74.15; H, 9.26; N, 7.71.

‡ Although there is no change in the (1*R*,5*R*) configuration of (+)-α-pinene, the configuration of the corresponding atoms in the products **2**–**13** is (*S*,*S*), due to the changes in *CIP* priority.

4.2. Ethyl (1S,2S,3R,5S)-2-aminopinane-3-carboxylate **3**

Azetidinone **2** (13.5 g, 75.3 mmol) was dissolved in 80 ml of ethanol containing 10% hydrochloric acid. After refluxing for 12 h, the mixture was evaporated to dryness in vacuo. The residue was dissolved in water, basified with cold saturated sodium hydrogencarbonate solution and extracted with diethyl ether (3×50 ml). The combined organic phase was dried (Na_2SO_4), filtered and evaporated. The oily residue obtained was purified by flash chromatography on a silica gel column (toluene:ethanol = 9:1).

Compound **3** (10.2 g, 60%; $[\alpha]_D^{20} = -28$ ($c = 0.29$, EtOH); ee >99%). Analysis: calculated for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22; found: C, 69.43; H, 10.05; N, 6.47. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.02 (3H, *s*, Me-6), 1.22 (1H, *d*, H-4, $J = 10.58$ Hz), 1.26 (3H, *s*, Me-6), 1.31 (3H, *t*, CH_2-CH_3, $J = 7.05$ Hz), 1.36 (3H, *s*, Me-2), 1.78 (1H, *t*, H-1, $J = 5.29$ Hz), 1.89–2.00 (2H, *m*, H-4, H-5), 2.17–2. 26 (1H, *m*, H-7), 2.29–2.39 (1H, *m*, H-7), 3.01 (1H, *dd*, H-3, $J = 7.05$, 10.07 Hz), 4.19 (2H, *q*, CH_2-CH_3, $J = 7.05$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.8, 24.0, 28.4, 28.7, 29.3, 31.6, 39.7, 40.3, 47.0, 55.4, 56.4, 60.6, 175.6.

The (1*R*,2*R*,3*S*,5*R*)-enantiomer of **3** was prepared as described above; $[\alpha]_D^{20} = +26$ ($c = 0.29$, EtOH); ee >99%; the spectroscopic data and mp were similar to those for **3**. Analysis: found: C, 69.39; H, 10.35; N, 6.29.

4.3. (1S,2S,3R,5S)-2-Amino-3-hydroxymethylpinane **4**

To a slurry of $LiAlH_4$ (3.19 g, 15 mmol) in 150 ml of dry THF, amino ester **3** (10.14 g, 45.0 mmol) in 20 ml of THF was added dropwise at 0°C. After stirring and refluxing for 2 h (the reduction was monitored by means of TLC), the mixture was decomposed with 6.5 ml of water under ice cooling. The inorganic material was filtered off and washed with THF. After drying (Na_2SO_4) and evaporation, a pale-yellow oil was obtained. The prepared amino alcohol was purified as the hydrochloride. The base liberated for spectroscopic purposes was a viscous oil.

Compound **4** (7.0 g, 85%; $[\alpha]_D^{20} = -11$ ($c = 0.2$, MeOH)). Analysis: calculated for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64; found: C, 72.36; H, 11.52; N, 7.39. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.02 (3H, *s*, Me-6), 1.05 (1H, *d*, H-4, $J = 10.32$ Hz), 1.24 (3H, *s*, Me-6), 1.27 (3H, *s*, Me-2), 1.31–1.41 (1H, *m*, H-3), 1.65 (1H, *t*, H-1, $J = 5.79$ Hz), 1.85–1.97 (2H, *m*, H-5, H-7), 2.05–2.23 (2H, *m*, H-4, H-7), 3.47 (1H, *dd*, CH_2-OH, $J = 9.06$, 11.03 Hz), 3.62 (1H, *dd*, CH_2-OH, $J = 4.53$, 11.58 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.8, 28.0, 28.4, 28.8, 29.7, 38.8, 39.4, 40.4, 52.1, 63.0, 63.6.

The (1*R*,2*R*,3*S*,5*R*)-enantiomer of **4** was prepared as described above; $[\alpha]_D^{20} = +10$ ($c = 0.2$, MeOH); the spectroscopic data and mp were similar to those for **4**. Analysis found: C, 72.29; H, 11.50; N, 7.43.

4.4. Ethyl (1S,2S,3R,5S)-2-(ethoxycarbonylamino)pinane-3-carboxylate **5**

To a stirred solution of β-amino ester **3** (4.17 g, 18.8 mmol) and sodium hydrogencarbonate (1.59 g, 18.9 mmol) in 10 ml of water, ethyl chloroformate (1.99 ml, 20.9 mmol) was added dropwise at 0°C. The mixture was stirred for 1 h at 0°C. After standing overnight at room temperature, the precipitated oil was extracted with ethyl acetate (3×50 ml), and the organic phase was dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography on a silica gel column (toluene:ethanol = 19:1).

Compound **5** (4.5 g, 81%; $[\alpha]=-23$ ($c=0.17$, EtOH); ee >99%). Analysis: calculated for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71; found: C, 64.73; H, 9.35; N, 4.47. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.07 (3H, *s*, Me-6), 1.19 (3H, *t*, NHCOO-CH_2-*CH_3*, $J=7.05$ Hz), 1.29 (3H, *t*, CH_2-*CH_3*, $J=7.05$ Hz), 1.29 (3H, *s*, Me-6) 1.63 (3H, *s*, Me-2), 1.96–2.02 (1H, *m*, H-5), 2.07 (1H, *m*, H-4), 2.10–2.13 (1H, *m*, H-4), 2.20–2.28 (1H, *m*, H-7), 2.34–2.37 (1H, *m*, H-7), 2.65 (1H, *t*, H-1, $J=5.54$ Hz), 3.12 (1H, *t*, H-3, $J=9.57$ Hz), 3.98 (2H, *q*, NHCOO-*CH_2*-CH_3, $J=7.05$ Hz), 4.15–4.25 (2H, *m*, *CH_2*-CH_3), 5.91 (1H, *s*, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.6, 14.9, 23.8, 27.0, 29.2, 29.9, 31.2, 38.8, 40.5, 46.3, 51.9, 58.3, 60.4, 61.5, 155.3, 175.9.

The (1*R*,2*R*,3*S*,5*R*)-enantiomer of **5** was prepared as described above; $[\alpha]_D^{20}=+22$ ($c=0.17$, EtOH); ee >99%; the spectroscopic data and mp were similar to those for **5**. Analysis found: C, 64.50; H, 9.23; N, 4.41.

*4.5. (1*S,*2*S,*3*R,*5*S*)-2-Methylamino-3-hydroxymethylpinane* **6**

Amino ester **5** was reduced with LAH according to Section 4.3.

Compound **6** (6.7 g, 79%; $[\alpha]=-9$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10; found: C, 72.95; H, 11.52; N, 7.28. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.11 (3H, *s*, Me-6), 1.32 (3H, *s*, Me-6), 1.52–1.61 (4H, *m*, Me-2, H-4), 1.73 (1H, *dd*, H-1, $J=8.31$, 11.58 Hz), 1.92–2.05 (3H, *m*, H-3, H-5, H-7), 2.22–2.32 (1H, *m*, H-7), 2.52 (4H, *m*, N-Me, H-4), 3.94 (1H, *dd*, *CH_2*-OH, $J=4.03$, 11.58 Hz), 4.25 (1H, *dd*, *CH_2*-OH, $J=8.56$, 11.58 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.6, 25.2, 27.4, 27.9, 28.7, 29.7, 39.0, 39.9, 40.5, 49.4, 62.6, 66.5.

The (1*R*,2*R*,3*S*,5*R*)-enantiomer of **6** was prepared as described above; $[\alpha]_D^{20}=+8.2$ ($c=0.2$, MeOH); the spectroscopic data and mp were similar to those for **6**. Analysis: found: C, 73.34; H, 11.61; N, 7.33.

*4.6. (1*S,*2*S,*7*R,*9*S*)-2,3,10,10-Tetramethyl-5-oxa-3-azatricyclo[7.1.1.0^{2,7}]undecane* **7**

Method A: Amino alcohol **6** (0.48 g, 2.43 mmol) was stirred with 10 ml of 33% aqueous formaldehyde at room temperature for 1 h. The mixture was made alkaline with 10% aqueous potassium hydroxide and extracted with diethyl ether (3×30 ml). The combined organic phase was dried (Na_2SO_4) and evaporated to give an almost colorless oil, which was purified as the hydrochloride. The base liberated for spectroscopic purposes was a viscous oil.

Method B: Amino alcohol **4** (0.38 g, 2.07 mmol) was dissolved in a mixture of 5 ml of 33% aqueous formaldehyde and 5 ml of formic acid. After stirring and refluxing for 1 h, the solution was cooled, basified with 10% KOH solution and extracted with chloroform (3×30 ml). The combined organic phase was dried (Na_2SO_4) and evaporated to give an almost colorless oil, which was purified as the hydrochloride.

Compound **7** (Method A: 65%, Method B: 51%; mp: 147–150°C; $[\alpha]_D^{20}=-9$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{13}H_{24}ClNO$: C, 63.53; H, 9.84; N, 5.70; found: C, 63.92; H, 9.72; N, 5.96. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.05 (3H, *s*, Me-10), 1.06 (3H, s, Me-10), 1.29 (3H, *s*, Me-2), 1.50–1.60 (1H, *m*, H-8), 1.71 (1H, *d*, H-11, $J=9.32$ Hz), 1.86–1.98 (6H, *m*, H-1, N-Me, H-8, H-9), 1.99–2.10 (2H, *m*, H-7, H-11), 3.62 (1H, *dd*, H-6, $J=6.29$, 10.83 Hz), 3.73 (1H, *dd*, H-6, $J=6.04$, 10.83 Hz), 4.13 (1H, *d*, H-4, $J=6.04$ Hz), 4.23 (1H, *d*, H-4, $J=6.04$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 16.7, 24.5, 27.8, 30.2, 31.9, 32.0, 37.8, 38.9, 40.8, 52.3, 58.2, 69.2, 81.9.

The (1*R*,2*R*,7*S*,9*R*)-enantiomer of **7** was prepared as described above; $[\alpha]_D^{20}=+9$ ($c=0.2$, MeOH); the spectroscopic data and mp were similar to those for **7**. Analysis found: C, 63.97; H, 9.65; N, 5.61.

4.7. Thiourea derivative **8**

Phenyl isothiocyanate (0.48 g, 3.55 mmol) was added to a solution of 0.6 g (3.27 mmol) of amino alcohol **4** in 40 ml of toluene. After stirring for 3 h at room temperature (the reaction was monitored by means of TLC), the solution was evaporated and the pale-yellow crystalline product was recrystallized from isopropyl ether.

Compound **8** (1.04 g, 92%; mp: 119–121°C; $[\alpha]=-111$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{18}H_{26}N_2OS$: C, 67.88; H, 8.23; N, 8.80; found: C, 67.72; H, 8.39; N, 8.56. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.94 (1H, *d*, H-4, $J=10.83$ Hz), 1.05 (3H, *s*, Me-6), 1.29 (3H, *s*, Me-6), 1.66–1.89 (6H, *m*, H-1, Me-2, H-3, H-7), 1.89–1.97 (1H, *m*, H-5), 2.12–2.20 (1H, *m*, H-4), 2.20–2.39 (1H, *m*, H-7), 3.48 (1H, *dd*, CH_2-OH, $J=4.28$, 10.07 Hz), 3.69 (1H, *dd*, CH_2-OH, $J=2.01$, 11.08 Hz), 7.21–7.30 (2H, *m*, Ph), 7.38 (3H, *t*, Ph, $J=7.30$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.9, 29.2, 29.8, 30.0, 38.9, 40.4, 42.0, 62.1, 65.4, 127.5, 129.9, 180.6.

The (1*R*,2*R*,3*S*,5*R*)-enantiomer of **8** was prepared as described above; $[\alpha]_D^{20}=+105$ ($c=0.2$, MeOH); the spectroscopic data and mp were similar to those for **8**. Analysis: found: C, 67.97; H, 8.11; N, 8.72.

4.8. (1S,2S,7R,9S)-4-Phenylimino-2,10,10-trimethyl-5-oxa-3-azatricyclo[7.1.1.0^{2,7}]undecane **9**

To a stirred solution of 0.4 g (1.26 mmol) of thiourea derivative **8** in 15 ml of methanol, 0.43 ml (6.9 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 2.5N methanolic potassium hydroxide 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_2SO_4) and evaporation of the organic layer, the resulting oxazine was recrystallized from hexane.

Compound **9** (0.22 g, 60%; mp: 70–73°C; $[\alpha]_D^{20}=+245$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85; found: C, 76.33; H, 8.52; N, 9.61. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.04 (3H, *s*, Me-10), 1.13 (1H, *d*, H-11, $J=6.04$ Hz), 1.24–1.33 (6H, *m*, Me-2, Me-10), 1.69–1.72 (2H, *m*, H-1, H-8), 1.96 (1H, *s*, H-9), 2.08–2.18 (1H, *m*, H-8), 2.18–2.33 (2H, *m*, H-7, H-11), 3.86 (1H, *dd*, H-6, $J=2.27$, 10.58 Hz), 4.18 (1H, *d*, H-6, $J=8.31$ Hz), 6.96 (1H, *t*, Ph, $J=7.05$ Hz), 7.09 (1H, *s*, Ph), 7.20–7.29 (3H, *m*, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.2, 28.3, 28.7, 31.2, 32.0, 34.6, 40.4, 55.02, 57.8, 68.2, 109.7.

The (1*R*,2*R*,7*S*,9*R*)-enantiomer of **9** was prepared as described above; $[\alpha]_D^{20}=-250$ ($c=0.2$, MeOH); the spectroscopic data and mp were similar to those for **9**. Analysis: found: C, 76.27; H, 8.72; N, 9.93.

4.9. Urea derivatives **10**

Phenyl isocyanate (0.17 g, 1.42 mmol) was added to a solution of 0.3 g (1.33 mmol) of amino ester **4** in 30 ml of toluene. After stirring for 5 h at room temperature, the solution was evaporated and the crystalline product obtained was recrystallized from isopropyl ether.

Compound **10** (0.41 g, 89%; mp: 127–128°C; $[\alpha]_D^{20}=-23$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13; found: C, 69.89; H, 8.01; N, 8.35. ^{1}H NMR ($CDCl_3$)

δ (ppm): 1.07 (3H, s, Me-6), 1.21–1.31 (7H, *m*, H-5, Me-6, CH_2-CH_3), 1.72 (3H, *s*, Me-2), 1.95–2.01 (1H, *m*, H-7), 2.02–2.16 (2H, *m*, H-4, H-4), 2.22–2.32 (1H, *m*, H-7), 2.86 (1H, *t*, H-1, $J=5.79$ Hz), 3.14 (1H, *t*, H-3, $J=9.32$ Hz), 4.07–4.20 (2H, *m*, CH_2-CH_3), 5.96 (1H, *s*, C2-*NH*), 6.29 (1H, *s*, *NH*-Ph), 6.99–7.08 (1H, *m*, Ph), 7.24–7.30 (4H, *m*, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.6, 23.9, 27.5, 29.2, 30.2, 31.3, 38.9, 40.5, 46.6, 52.1, 59.3, 61.6, 121.2, 123.8, 129.4, 139.3, 154.9, 176.6.

The (1*R*,2*R*,3*S*,5*R*)-enantiomer of **10** was prepared as described above; $[\alpha]_D^{20}=+23$ ($c=0.2$, MeOH); the other physical, analytical and spectroscopic data and mp were similar to those for **10**. Analysis: found: C, 69.55; H, 8.13; N, 8.02.

*4.10. (1*S,*2*S,*7*R,*9*S*)-4,6-Dioxo-5-phenyl-2,10,10-trimethyl-3,5-diazatricyclo[7.1.1.0^{2,7}]-undecane* ***11***

The appropriate urea derivative **10** (0.4 g, 1.16 mmol) was dissolved in 20 ml of methanol. Five drops of methanol containing 25% ammonia were added to the solution and, after standing for 1 day at room temperature, the solution was evaporated and the crystalline product was recrystallized from isopropyl ether/ethyl acetate.

Compound **11** (0.3 g, 87%; mp: 205–207°C; $[\alpha]_D^{20}=-27$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39; found: C, 72.15; H, 7.59; N, 9.71. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.11 (3H, *s*, Me-10), 1.33 (3H, *s*, Me-10), 1.38 (1H, *d*, H-11, $J=10.83$ Hz), 1.46 (3H, *s*, Me-2), 1.91 (1H, *t*, H-1, $J=5.54$ Hz), 1.98 (1H, *ddd*, H-8, $J=2.01$, 8.31, 13.85 Hz), 2.08–2.14 (1H, *m*, H-9), 2.31–2.40 (1H, *m*, H-11), 2.59–2.69 (1H, *m*, H-8), 3.26 (1H, *dd*, H-7, $J=8.81$, 10.32 Hz), 5.39 (1H, *s*, H-3), 7.16–7.20 (2H, *m*, Ph), 7.36–7.41 (1H, *m*, Ph), 7.42–7.48 (2H, *m*, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.9, 28.8, 30.8, 32.1, 33.4, 38.9, 40.6, 41.0, 53.3, 55.8, 128.8, 129.2, 129.5, 135.5, 152.9, 173.2.

The (1*R*,2*R*,7*S*,9*R*)-enantiomer of **11** was prepared as described above; $[\alpha]_D^{20}=+26$ ($c=0.2$, MeOH); the spectroscopic data and mp were similar to those for **11**. Analysis found: C, 72.27; H, 7.31; N, 9.47.

*4.11. (1*S,*2*S,*7*R,*9*S*)-6-Oxo-5-phenyl-4-thioxo-2,10,10-trimethyl-3,5-diazatricyclo[7.1.1.0^{2,7}]-undecane* ***13***

Phenyl isothiocyanate (0.31 g, 2.3 mmol) was added to a solution of 0.5 g (2.2 mmol) of amino ester **3** in 40 ml of toluene. After stirring for 6 h at room temperature, the solution was evaporated and the crystalline product obtained was recrystallized from isopropyl ether/ethyl acetate.

Compound **13** (0.57 g, 83%; mp: 264–267°C; $[\alpha]_D^{20}=-8$ ($c=0.2$, MeOH)). Analysis: calculated for $C_{18}H_{22}N_2OS$: C, 68.76; H, 7.05; N, 8.91; found: C, 69.05; H, 7.26; N, 8.73. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.09 (3H, *s*, Me-10), 1.31–1.36 (4H, *m*, Me-10, H-11), 1.51 (3H, *s*, Me-2), 1.98 (1H, *ddd*, H-8, $J=2.01$, 8.31, 14.1 Hz), 2.04 (1H, *t*, H-1, $J=5.29$ Hz), 2.09–2.15 (1H, *m*, H-9), 2.37–2.45 (1H, *m*, H-11) 2.60–2.69 (1H, *m*, H-8), 3.34 (1H, *dd*, H-7, $J=9.57$ Hz), 7.15–7.23 (2H, *m*, NH, Ph), 7.39–7.50 (3H, *m*, Ph), 7.39–7.51 (1H, *m*, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.2, 28.8, 31.0, 31.2, 33.5, 39.1, 40.4, 40.8, 52.8, 60.1, 139.3, 169.9.

The (1*R*,2*R*,7*S*,9*R*)-enantiomer of **13** was prepared as described above; $[\alpha]_D^{20}=+7$ ($c=0.2$, MeOH); the spectroscopic data and mp were similar to those for **13**. Analysis found: C, 68.89; H, 7.31; N, 8.56.

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