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Stereoselective synthesis of pinane-based β- and γ-amino acids via conjugate addition of lithium amides and nitromethane

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ABSTRACT

Michael addition of dibenzylamine to (−)- and (+)-*tert*-butyl myrtenate, (−)-**2** and (+)-**2**, derived from (−)- and (+)-myrtenal, furnished monoterpene-based β-amino acid derivatives in highly stereospecific reactions. The resultant amino esters (−)-**3** and (+)-**3** were transformed to unsubstituted, mono- and disubstituted and Fmoc-protected amino acids (−)-**6**-**11** and (+)-**6**-**11**, which are promising building blocks for the synthesis of β-peptides and 1,3-heterocycles. The microwave-assisted conjugate addition of nitromethane to α,β-unsaturated esters (−)-**12** and (+)-**12** likewise resulted in nitro esters (−)-**13** and (+)-**13** in highly stereospecific reactions. Compounds (−)-**13** and (+)-**13** were successfully transformed into γ-amino acids (−)-**16** and (+)-**16** in two steps.

1. Introduction

The discovery of the pharmacological importance of alicyclic β-amino acids increased the demand for the asymmetric syntheses of these versatile building blocks.[1] There are several well-known methods via which to obtain the alicyclic-type family of β-amino acids in homochiral form, including classical resolution and kinetic resolution, as well as a variety of asymmetric syntheses, for example, the enantioselective syntheses of β-lactams followed by ring opening, the selective reduction of enantiopure β-enaminoesters, the enantioselective desymmetrization of achiral anhydrides followed by Curtius degradation, or chiral ammonia equivalent TMS-SAMP addition to ω-halo-substituted enoates followed by further transformations.[2–6]

Besides the above-mentioned methods, the conjugate addition of amine nucleophiles to α,β-unsaturated carbonyl compounds is one of the most popular and useful procedures. Davies et al. recently published a comprehensive review of this field, covering the scope, limitations and synthetic applications of the use of enantiomerically pure lithium amides as homochiral ammonia equivalents in conjugate addition reactions.[1d] Most of these methods involve the use of chiral lithium amides, and only a few examples are to be found whereby chiral α,β-unsaturated esters are applied as the source of chirality in the conjugate addition of achiral amides.[7]

Besides their applications in β-amino acid synthesis, α,β-unsaturated esters are also excellent substrates for other types of conjugate addition, whereas nitroalkanes (e.g., nitromethane) can be used as nucleophiles, resulting in γ-amino acids, versatile building blocks for the syntheses of pharmacologically active natural compounds.[8]

We recently described the transformations of enantiomerically pure α-pinene, δ-pinene, 3-carene and apopinene to β-amino acid derivatives,[9] which proved to be excellent building blocks for the syntheses of monoterpene-fused saturated 1,3-heterocycles[9a–d] and stable H12 foldameric helices,[9g] and which were also applied in Ugi four-centre three-component reactions[9h] or as chiral catalysts in the enantioselective addition of Et_2Zn to aromatic aldehydes.[9d]

Further to their interest in organic syntheses, monoterpene-based amino acid derivatives have a wide range of pharmacological activities:[10] pinane-based amino esters possess marked anticonvulsant activity;[10a] their amides have been reported to be tyrosine kinase Axl inhibitors,[10b] and apopinane-based urea and thiourea derivatives exhibit a multidrug-resistance reversing effect on a mouse lymphoma cell line.[10c]

Our present aim was the preparation and transformations of a new family of monoterpene-based β- and γ-amino acid derivatives, starting from esters of (−)- and (+)-myrtenic acid derived from commercially available (−)-myrtenal and (+)-α-pinene. Our previous results relating to the preparation of amino acids[9f–h] suggested that these new chiral building blocks might serve as promising substrates for the synthesis of chiral catalysts, 1,3-heterocycles and foldamers.

2. Results and discussion

The Michael acceptor (−)-*tert*-butyl myrtenate (−)-**2** was synthesized from commercially available (−)-myrtenal (−)-**1** by a

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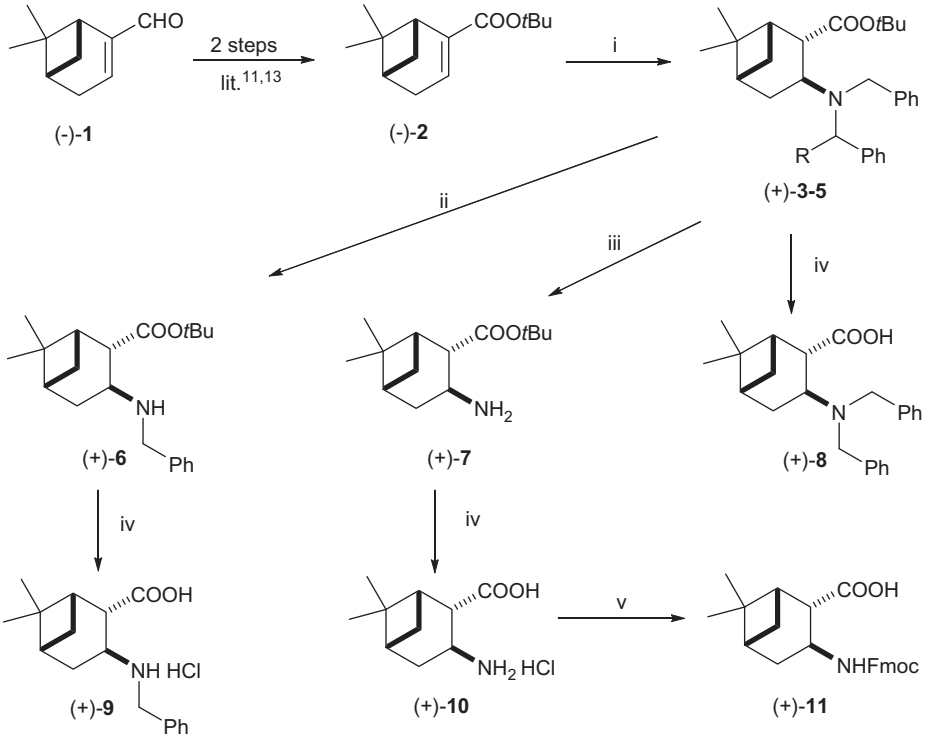


Scheme 1. Reagents and conditions: (i) 2.4 equiv of the appropriate lithium amide (**3**: lithium dibenzylamide, **4**: lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, **5**: lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide), dry THF, −78 °C, 6–8 h, then NH_4Cl(aq), 12–87%; (ii) 10% Pd/C, AcOH, 1 atm H_2, rt, 2 h, 89%; (iii) 10% Pd/C, AcOH, 1 atm H_2, rt, 12 h, 89%; (iv) 10% aq HCl/Et_2O, rt, 12 h, 71–89%; (v) 10% $NaHCO_3/H_2O$ to pH 8.0, MeCN, 0 °C, 1.0 equiv Fmoc-OSu, then 12 h, rt, 63%.

literature method in a two-step reaction: the oxidation of myrtenal to myrtenic acid, which was converted to the *tert*-butyl ester.[11] Since the (+) enantiomer of myrtenal is commercially unavailable, it was prepared from (+)-α-pinene according to a literature method by allylic oxidation with selenium dioxide.[12] The asymmetric Michael addition to compounds (−)-**2** and (+)-**2** followed a literature protocol, with the application of in situ generated achiral lithium dibenzylamide to exploit the effect of the chiral, conformationally constrained pinane ring system.[7c] NMR studies on the crude product proved that the addition was highly stereospecific (de >99%), resulting in *trans* dibenzylamino esters (−)-**3** and (+)-**3** as single products in excellent yields (Scheme 1). The configurations of the new chiral centres of (−)-**3** and (+)-**3** were determined in NOESY experiments, based on the observation of NOE effects between H–C-2 and H–C-7 and also between H–C-3 and Me–C-6.[†]

Since it has been reported that the conjugate addition of lithium dialkylamides to alicyclic α,β-unsaturated esters results in *cis* amino esters as main products,[1d] our aim was to study the effect of a more bulky substituent on the nitrogen with a view to shifting the regioselectivity towards *cis* products. The steric effect of the α-methyl substituent of (*S*)- and (*R*)-*N*-benzyl-*N*-α-methylbenzylamine on the reactivity and stereoselectivity was also investigated by preparing (+)-**4** and (+)-**5**. We observed similar *trans* stereoselectivity in each case, but the yield dropped from 87% to 45% when the (*S*)-amide (+)-**4** was used. When (*R*)-*N*-benzyl-*N*-α-methylbenzylamine was applied as ammonia equivalent, only a very low yield (12%) was achieved for (+)-**5** (Scheme 1).

It is likely that the addition proceeds via an enolate intermediate.[1d] Quantum chemical modelling of the possible intermediates with configurations (*R*)- and (*S*)-C3 revealed a stability difference of 4.75 kcal/mol in favour of (*S*)-C3 at the level of B3LYP/6-311G** (Figure 1, absolute configurations according to Scheme 1).[14] This suggests that the dibenzylamide approaches from the sterically less hindered side (opposite the methyl substituents), thereby furnishing (*S*)-C3 stereoselectivity. Inspection of the enolate intermediate suggests that the protonation of C2 in the second step again takes place on the sterically less shielded face, which eventually leads to the *trans* relative configuration. Since the steric effects play a crucial role in the course of the reaction and the surroundings of the reaction centre are tightly packed even at the less shielded face, α-methyl substituents could not modify the orienting effect of the Michael acceptor, but only caused decreased reactivity through the increased steric repulsion.

Hydrogenolysis of (−)-**3** and (+)-**3** over palladium on carbon (Pd/C) for 2 h resulted in the formation of monobenzyl derivatives (−)-**6** and (+)-**6** in acceptable yields. A longer reaction time led to primary amino esters (−)-**7** and (+)-**7** in excellent yields. Compounds (−)-**5**-**7** and (+)-**5**-**7** were successfully hydrolysed to amino acids (−)-**8**-**10** and (+)-**8**-**10** under acidic conditions. Starting from (−)-**10** and (+)-**10**, Fmoc-protected amino acids (−)-**11** and (+)-**11** were also prepared, as promising building blocks for peptide chemistry (Scheme 1).

When (−)-*tert*-butyl myrtenate was used in the Michael addition of nitromethane in order to obtain γ-amino acids, our first attempts under both conventional and microwave heating failed, probably due to the steric and electronic effects of the bulky *tert*-butyl group. Therefore, (−)- and (+)-methyl myrtenate (−)-**12** and (+)-**12** were prepared from (−)- and (+)-myrtenal (−)-**1** and (+)-**1** according to a literature process,[13] and were successfully applied in the conjugate addition. On the use of conventional heating (Method A), NMR studies on the crude product proved that the addition took place highly stereospecifically (de >99%), resulting in *trans* isomers (−)-**13** and (+)-**13** as single products, similarly as in the lithium amide reaction. The configurations of the new stereogenic centres in **13** were determined in NOESY experiments. The

[†] In the present experiments, all of the reactions were carried out on both enantiomers, although only one of them features in the Schemes.

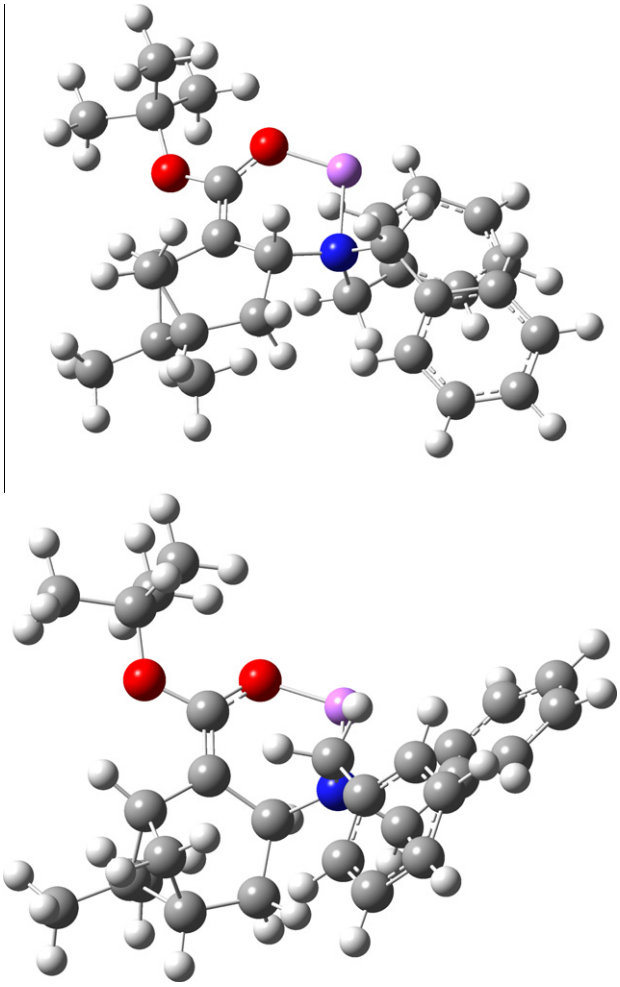


Figure 1. Geometries obtained at the B3LYP/6-311G** level for the (*R*)-C3 (top) and (*S*)-C3-enolate (bottom) intermediates.

disadvantage of this method is that, even after prolonged heating, the yield remains only moderate (<40%). However, when microwave irradiation was used, we obtained the desired nitro ester **13** in a short time (25 min) in high yield (73%). Moreover, under microwave conditions the *cis*-diastereomer **14** was also formed as a minor product and was isolated in 6% yield. In order to investigate the formation of the *cis* product, a control experiment was performed in which the major *trans* adduct was irradiated under identical microwave conditions in the presence of 1 equiv of DBU and 10 mol % of TBAB in nitromethane. Since the minor *cis* adduct could be detected in the crude reaction mixture together with a trace amount of **12**, we propose that the conjugate addition of nitromethane under the applied conditions is reversible and leads to equilibrium. Next, LiOH-mediated hydrolysis of nitro ester **13** furnished nitro acid **15** in an excellent yield, and the nitro moiety was subsequently reduced over Raney Ni to provide the target γ-amino acid **16** in good yield (Scheme 2).

3. Conclusions

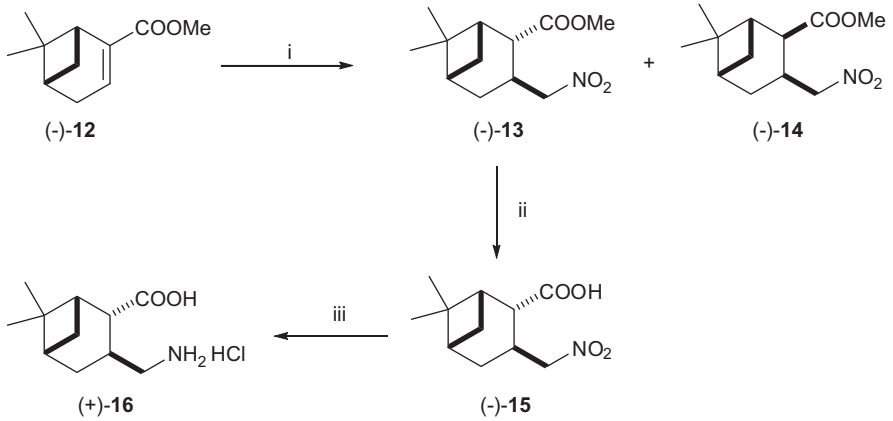
In conclusion, the highly stereospecific addition of lithium amides to *tert*-butyl 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carboxylate (+)-**2** and (−)-**2** proved to be an efficient method for the synthesis of a new family of pinane-based β-amino acids via a two-step transformation of the resulting *N*,*N*-dibenzyl β-aminoesters (+)-**3** and (−)-**3**. The microwave-assisted conjugate addition of nitromethane to the α,β-unsaturated methyl esters (−)-**12** and (+)-**12** resulted in highly stereospecifically nitro esters (−)-**13** and (+)-**13**, which were successfully transformed into γ-amino acids (−)-**16** and (+)-**16** in a two-step procedure.

4. Experimental

4.1. General experimental procedures

^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400.13 MHz (^{1}H) and 100.61 MHz (^{13}C) [$\delta = 0$ (TMS)] in $CDCl_3$, DMSO-d_6 or D_2O in a 5-mm tube. Chemical shifts are expressed in ppm (δ) relative to TMS as internal reference. *J* values are given in hertz (Hz). Microanalyses were performed on a Perkin–Elmer 2400 elemental analyser. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). Ab intio quantum chemical calculations were carried out by using GAUSSIAN 03 software at the B3LYP/6-311G** level with a default setup.

The enantiomeric purities of the compounds prepared were determined by means of GC measurements involving direct separation of the enantiomers on a CHIRASIL-DEX CB column (2500 × 0.25 mm ID), at 110 °C for (+)-**2** and (−)-**2** and at 110 °C for (+)-**7** and (−)-**7**. IR spectra were measured with an FT-IR spectrometer.



Scheme 2. Reagents and conditions: (i) Method A: 1 equiv DBU, 10 mol % TBAB, nitromethane, reflux, **13**: 39%; Method B: 1 equiv DBU, 10 mol % TBAB, nitromethane, 100 °C, MW, **13**: 73%, **14**: 6%; (ii) 2 equiv LiOH·H_2O, THF/water, reflux, 91%; (iii) 1 atm H_2, Raney Ni, MeOH, then 10% HCl/EtOH, 63%.

(−)-(1*S*,5*S*)-Myrtenal and (+)-(1*R*,5*R*)-α-pinene are commercially available. THF was dried over Na wire; all other chemicals and solvents were used as supplied. (−)-(1*R*,5*S*)- and (+)-(1*S*,5*R*)-*tert*-butyl and methyl 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carboxylates (+)-**2**, (+)-**3**, (−)-**2** and (−)-**3** were prepared by the literature methods, and were identical with those reported therein.[11,13]

4.2. General procedure for the lithium amide addition reactions

At first, 1.6 M *n*-BuLi solution was added dropwise to a stirred solution of secondary amine in dry THF at −78 °C under an argon atmosphere, followed by stirring for 30 min prior to the addition of a solution of the acceptor in THF at −78 °C. After the appropriate reaction time (6 h for **3**, 8 h for **4** and **5**), saturated aqueous NH_4Cl solution was added and the solution was warmed to room temperature, partitioned between Et_2O (3 × 200 mL) and brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography gave the desired product.

4.2.1. (1*S*,2*S*,3*S*,5*R*)-*tert*-Butyl 3-(dibenzylamino)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylate (+)-3

According to general procedure 4.2 8.90 g (45.1 mmol) of dibenzylamine in dry THF (100 mL), *n*-BuLi solution (27 mL of a 1.6 M solution in *n*-hexane) and 4.00 g (18.0 mmol) of (+)-**3** in dry THF (25 mL) gave the desired product after chromatographic purification on silica gel (*n*-hexane/Et_2O = 19:1). Isolated compound: 6.10 g (81%); an oil; $[\alpha]_D^{20} = +46.0$ (*c* 0.265, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84 (3H, s), 1.05 (1H, d, *J* = 9.9 Hz), 1.18 (3H, s), 1.42 (9H, s), 1.86–1.99 (2H, m), 2.14–2.26 (2H, m), 2.31–2.40 (1H, m), 2.89 (1H, dd, *J* = 1.6, 9.6 Hz), 3.59 (1H, d, *J* = 14.1 Hz), 3.73 (1H, d, *J* = 14.1 Hz), 4.04–4.11 (1H, m), 7.16–7.38 (10H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.3, 28.0, 28.4, 29.1, 33.0, 39.3, 41.9, 45.8, 51.1, 51.5, 54.6, 80.0, 127.0, 128.4, 129.0, 140.8, 174.7. IR = 2913, 1726, 1450, 1364, 1147, 739 cm^{-1}. Anal. Calcd for $C_{28}H_{37}NO_2$ (419.60): C, 80.15; H, 8.89; N, 3.34. Found: C, 80.27; H, 9.03; N, 3.17.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**3** was synthesized analogously to (+)-**3**, from (+)-(1*S*,5*R*)-*tert*-butyl 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carboxylate (+)-**2**; $[\alpha]_D^{20} = -49.0$ (*c* 0.265, MeOH); all the spectroscopic data were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{28}H_{37}NO_2$ (419.60): C, 80.15; H, 8.89; N, 3.34. Found: C, 80.30; H, 9.05; N, 3.08.

4.2.2. (1*S*,2*S*,3*S*,5*R*)-*tert*-Butyl 3-[benzyl((*S*)-1-phenylethyl) amino]-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylate (+)-4

Following general procedure 4.2 in a reaction time of 8 h, 1.91 g (9.0 mmol) of (*S*)-(−)-*N*-benzyl-α-methylbenzylamine in dry THF (20 mL), *n*-BuLi solution (5.4 mL of a 1.6 M solution in *n*-hexane) and 0.80 g (3.6 mmol) of (−)-**2** in dry THF (5 mL) gave the desired product (+)-**4** after chromatographic purification on silica gel (*n*-hexane/Et_2O = 19:1). Isolated compound: 0.70 g (45%); an oil; $[\alpha]_D^{20} = +86.0$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.91 (3H, s), 0.98 (1H, d, *J* = 9.9 Hz), 1.16 (3H, s), 1.38 (3H, d, *J* = 6.8 Hz), 1.43 (9H, s), 1.86–1.95 (2H, m), 2.08–2.17 (2H, m), 2.27–2.34 (1H, m), 2.79 (1H, dd, *J* = 1.7, 8.2 Hz), 3.76 (1H, d, *J* = 15.8 Hz), 3.90–4.00 (2H, m), 4.20–4.29 (1H, m), 7.10–7.36 (10H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 18.8, 23.3, 28.2, 28.6, 31.1, 33.3, 39.4, 42.2, 45.8, 50.5, 51.6, 53.2, 60.4, 79.8, 126.6, 126.9, 128.1, 128.2, 128.3, 128.4, 143.3, 145.5, 174.7. IR = 3250, 2927, 1728, 1367, 1147, 697 cm^{-1}. Anal. Calcd for $C_{29}H_{39}NO_2$ (433.63): C, 80.33; H, 9.07; N, 3.23. Found: C, 80.52; H, 9.25; N, 3.11.

4.2.3. (1*S*,2*S*,3*S*,5*R*)-*tert*-Butyl 3-[benzyl((*R*)-1-phenylethyl) amino]-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylate (+)-5

Following general procedure 4.2 in a reaction time of 8 h, 1.91 g (9.0 mmol) of (*R*)-(−)-*N*-benzyl-α-methylbenzylamine in dry THF (20 mL), *n*-BuLi solution (5.4 mL of a 1.6 M solution in *n*-hexane) and 0.80 g (3.6 mmol) of **2** in dry THF (5 mL) gave the desired product (+)-**5** after chromatographic purification on silica gel (*n*-hexane/Et_2O = 19:1). Isolated compound: 0.19 g (12%); an oil; $[\alpha]_D^{20} = +56.0$ (*c* 0.125, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, s), 1.14 (1H, d, *J* = 9.9 Hz), 1.13 (3H, s), 1.31 (3H, d, *J* = 6.9 Hz), 1.51 (9H, s), 1.75–1.81 (1H, m), 1.85–1.95 (1H, m), 2.17–2.11 (1H, m), 2.23–2.33 (1H, m), 2.75 (1H, d, *J* = 8.2 Hz), 3.72 (1H, d, *J* = 15.6 Hz), 3.75–3.81 (1H, m), 3.95 (1H, d, *J* = 15.4 Hz), 4.20–4.28 (1H, m), 7.10–7.50 (10H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.8, 23.3, 28.3, 29.1, 33.6, 39.6, 42.2, 45.9, 50.1, 51.1, 54.3, 59.4, 80.5, 126.9, 127.3, 128.2, 128.3, 128.4, 128.5, 143.8, 145.2, 176.0. IR = 3447, 2925, 1731, 1367, 1149, 700 cm^{-1}. Anal. Calcd for $C_{29}H_{39}NO_2$ (433.63): C, 80.33; H, 9.07; N, 3.23. Found: C, 80.50; H, 9.27; N, 3.01.

4.3. (1*S*,2*S*,3*S*,5*R*)-*tert*-Butyl 3-benzylamino-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylate (+)-6

To a suspension of 10% Pd/C (0.55 g) in glacial AcOH (50 mL), amino ester (+)-**3** (2.30 g, 5.5 mmol) in glacial AcOH (10 mL) was added, and the resulting mixture was stirred under H_2 (1 atm) at room temperature for 2 h. The solution was diluted with CH_2Cl_2 (100 mL) and filtered through a pad of Celite®, and the solvent was removed. The oily crude product obtained was dissolved in CH_2Cl_2 (200 mL) and was washed with 10% NaOH solution (50 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated in vacuo before purification via column chromatography (silica gel, toluene/EtOH = 9:1), affording a colourless oily product (+)-**6**. Isolated compound: 1.61 g (89%); an oil; $[\alpha]_D^{20} = +39.0$ (*c* 0.155, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84 (3H, s), 1.19 (1H, d, *J* = 10.3 Hz), 1.23 (3H, s), 1.42 (9H, s), 1.72 (1H, ddd, *J* = 3.1, 4.4, 13.4 Hz), 1.93–1.99 (1H, m), 2.30–2.46 (1H, m), 2.61 (1H, dd, *J* = 2.5, 5.3 Hz), 3.64–3.70 (1H, m), 3.73 (1H, d, *J* = 13.0 Hz), 3.84 (1H, d, *J* = 13.0 Hz), 7.21–7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.9, 27.4, 28.4, 31.1, 35.6, 38.4, 41.4, 43.9, 50.4, 52.3, 54.8, 80.5, 127.2, 128.6, 128.7, 140.7, 175.0. IR = 3467, 2923, 1710, 1455, 1064, 699 cm^{-1}. Anal. Calcd for $C_{21}H_{31}NO_2$ (329.48): C, 76.55; H, 9.48; N, 4.25. Found: C, 76.68; H, 9.69; N, 4.02.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**6** was synthesized analogously to (+)-**6**; $[\alpha]_D^{20} = -38.0$ (*c* 0.155, MeOH); all the spectroscopic data were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (+)-**6**. Anal. Calcd for $C_{21}H_{31}NO_2$ (329.48): C, 76.55; H, 9.48; N, 4.25; Found: C, 76.71; H, 9.63; N, 4.05.

4.4. (1*S*,2*S*,3*S*,5*R*)-*tert*-Butyl 3-amino-6,6-dimethylbicyclo [3.1.1]heptane-2-carboxylate (+)-7

To a suspension of 10% Pd/C (1.10 g) in glacial AcOH (100 mL), amino ester (+)-**3** (4.60 g, 11.0 mmol) in glacial AcOH (20 mL) was added, and the resulting mixture was stirred under H_2 (1 atm) at room temperature for 12 h. The solution was diluted with CH_2Cl_2 (200 mL) and filtered through a pad of Celite®, and the solvent was removed. The oily crude product obtained was dissolved in CH_2Cl_2 (200 mL) and was washed with 10% NaOH solution (50 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated in vacuo before purification via column chromatography (silica gel, toluene/EtOH = 4:1), affording colourless oily product (+)-**7**. Isolated compound: 2.36 g (90%); an oil; $[\alpha]_D^{20} = +20.0$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 (3H, s), 1.20 (1H, d, *J* = 9.8 Hz), 1.25 (3H, s), 1.48 (9H, s), 1.55 (1H, ddd, *J* = 2.8, 5.3, 13.7 Hz), 1.69 (2H, br s), 1.92–1.99 (1H, m), 2.34–2.55 (4H, m), 3.81–3.89 (1H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.9, 27.5, 28.5, 30.1, 32.1, 38.1, 41.5, 43.9, 44.8, 58.3, 80.6, 175.1. IR = 3367, 2924, 1725, 1367, 1160, 847 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_2$ (239.35): C, 70.25; H, 10.53; N, 5.85. Found: C, 70.40; H, 10.63; N, 5.69.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**7** was synthesized analogously to (+)-**7**; $[\alpha]_D^{20} = -22.0$ (*c* 0.25, MeOH); all the spectroscopic data were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{14}H_{25}NO_2$ (239.35): C, 70.25; H, 10.53; N, 5.85. Found: C, 70.37; H, 10.65; N, 5.70.

4.5. General procedure for the hydrolysis of amino esters

The appropriate amino ester (10 mmol) was dissolved in a mixture of Et_2O (15 mL) and 10% aqueous HCl solution (100 mL), which was followed by stirring at room temperature for 24 h. The mixture was then evaporated to dryness and the resulting white crystalline product was washed with Et_2O and filtered off.

4.5.1. (1*S*,2*S*,3*S*,5*R*)-3-(Dibenzylamino)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid hydrochloride (+)-8

Isolated compound: 2.84 g (71%); mp: 163–166 °C; $[\alpha]_D^{20} = +22.0$ (*c* 0.125, MeOH); ^{1}H NMR (DMSO-d_6, 51 °C) δ (ppm): 0.71 (3H, s), 1.24 (3H, s), 1.38 (1H, d, *J* = 10.4 Hz), 2.04–2.10 (1H, m), 2.31–2.49 (4H, m), 3.43–3.49 (1H, m), 4.19–4.41 (4H, m), 4.55–4.64 (1H, m), 7.37–7.62 (10H, m), 10.13 (1H, br s). ^{13}C NMR (DMSO-d_6, 51 °C) δ (ppm): 22.8, 26.3, 27.4, 30.5, 39.3, 40.9, 44.8, 46.8, 54.3, 54.9, 128.8, 129.1, 132.1, 133.3, 174.8. IR = 3386, 2936, 1721, 1457, 752, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{30}ClNO_2$ (399.95): C, 72.07; H, 7.56; N, 3.50. Found: C, 72.35; H, 7.69; N, 3.28.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**8** was synthesized analogously to (+)-**8**, from the 1*R*,2*R*,3*R*,5*S* enantiomer (−)-**3**; $[\alpha]_D^{20} = -24.0$ (*c* 0.125, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (+)-**8**. Anal. Calcd for $C_{24}H_{30}ClNO_2$ (399.95): C, 72.07; H, 7.56; N, 3.50. Found: C, 72.29; H, 7.70; N, 3.26.

4.5.2. (1*S*,2*S*,3*S*,5*R*)-3-Benzylamino-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid hydrochloride (+)-9

Isolated compound: 2.51 g (81%); mp: 217–219 °C; $[\alpha]_D^{20} = +28.0$ (*c* 0.125, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.73 (3H, s), 1.19 (3H, s), 1.67 (1H, d, *J* = 10.4 Hz), 1.93–1.99 (1H, m), 2.08 (1H, ddd, *J* = 2.5, 5.0, 16.6 Hz), 2.27–2.46 (3H, m), 3.13 (1H, dd, *J* = 1.9, 5.7 Hz), 4.14 (2H, dd, *J* = 13.1, 25.5 Hz), 4.17–4.25 (1H, m), 7.38–7.46 (3H, m), 7.59–7.66 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.8, 27.5, 30.7, 31.0, 39.0, 40.7, 44.3, 49.2, 49.4, 49.7, 129.4, 129.7, 131.1, 132.9, 175.3. IR = 3386, 2945, 1722, 1184, 695 cm^{-1}. Anal. Calcd for $C_{17}H_{24}ClNO_2$ (309.83): C, 65.90; H, 7.81; N, 4.52. Found: C, 65.73; H, 7.92; N, 4.65.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**9** was synthesized analogously to (+)-**9**, from the (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**6**; $[\alpha]_D^{20} = -30.0$ (*c* 0.125, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (+)-**9**. Anal. Calcd for $C_{17}H_{24}ClNO_2$ (309.83): C, 65.90; H, 7.81; N, 4.52. Found: C, 65.73; H, 7.92; N, 4.65.

4.5.3. (1*S*,2*S*,3*S*,5*R*)-3-Amino-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid hydrochloride (+)-10

Isolated compound: 1.96 g (89%); mp: 220–222 °C; $[\alpha]_D^{20} = +19.0$ (*c* 0.125, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.77 (3H, s), 1.20 (3H, s), 1.46 (1H, d, *J* = 10.1 Hz), 1.78–1.87 (1H, m), 1.91–1.96 (1H, m), 2.30–2.47 (4H, m), 2.85–2.89 (1H, m), 4.11–4.20 (1H, m), 8.27 (3H, br s), 12.74 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.7, 27.5, 30.9, 32.8, 38.6, 40.6, 42.8, 44.0, 50.5, 175.2. IR = 2923, 1719, 1220, 1195 cm^{-1}. Anal. Calcd for $C_{10}H_{18}ClNO_2$ (219.71): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.51; H, 8.11; N, 6.13.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**10** was synthesized analogously to (+)-**10**, from the (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**7**; $[\alpha]_D^{20} = -17.2$ (*c* 0.125, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (+)-**10**. Anal. Calcd for $C_{10}H_{18}ClNO_2$ (219.71): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.79; H, 8.35; N, 6.21.

4.6. (1*S*,2*S*,3*S*,5*R*)-3-[((9*H*-Fluoren-9-yl)methoxy)carbonylamino]-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid (+)-11

At first, 0.34 g (1.56 mmol) of (1*R*,2*R*,3*S*,5*R*)-amino acid (+)-**10** was dissolved in 6 mL of distilled water at 0 °C. 0.50 g (6 mmol) of $NaHCO_3$, 5 mL of MeCN and 0.51 g (1.5 mmol) of Fmoc-OSu were added to the solution at 0 °C. After stirring overnight at room temperature, the solution was acidified with 10% aqueous HCl solution and, after stirring for 1 h, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried (Na_2SO_4) and evaporated, and the crude product was purified by flash chromatography on a silica gel column (toluene/EtOH = 9:1), resulting in a white crystalline product. Isolated compound: 0.40 g (63%); mp: 90–92 °C; $[\alpha]_D^{20} = +21.0$ (*c* 0.125, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.80 (3H, s), 1.03 (1H, d, *J* = 10.5 Hz), 1.27 (3H, s), 1.57–1.63 (1H, m), 1.91–1.96 (1H, m), 2.37–2.45 (1H, m), 2.50–2.57 (1H, m), 2.59–2.72 (2H, m), 4.21 (1H, *t*, *J* = 5.9 Hz), 4.26 (1H, br s), 4.49–4.64 (2H, m), 4.98–5.06 (1H, m), 7.29–7.36 (2H, m), 7.37–7.44 (2H, m), 7.58 (2H, d, *J* = 7.7 Hz), 7.77 (2H, dd, *J* = 3.8, 7.5 Hz), 11.28 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 23.0, 26.7, 29.3, 35.6, 37.9, 39.9, 42.3, 43.7, 47.7, 55.3, 67.6, 120.4, 120.5, 125.4, 127.5, 128.2, 141.8, 157.2, 176.4. IR = 3345, 2945, 1730, 1543, 1268, 741 cm^{-1}. Anal. Calcd for $C_{25}H_{27}NO_4$ (405.49): C, 74.05; H, 6.71; N, 3.45. Found: C, 74.26; H, 6.89; N, 3.27.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**11** was synthesized analogously to (+)-**11**, from the (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**10**; $[\alpha]_D^{20} = -19.6$ (*c* 0.125, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (+)-**11**. Anal. Calcd. for $C_{25}H_{27}NO_4$ (405.49): C, 74.05; H, 6.71; N, 3.45. Found: C, 74.19; H, 6.85; N, 3.33.

4.7. Conjugate addition of nitromethane to (−)-12

Method A: A 10 mL round-bottomed flask containing 200 mg (1.11 mmol) of (1*R*,5*S*)-methyl myrtenate, 36.2 mg (10 mol %) of *n*-tetrabutylammonium bromide, 2 mL of nitromethane and 168 μL (1 equiv) of DBU was heated at reflux for 20 h. Next, the solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel; elution with 9:1 *n*-hexane/EtOAc gave (−)-**13**.

Method B: Microwave-assisted conjugate addition of nitromethane to (−)-**12** and (+)-**12**. A CEM Discover 10 mL vial containing 400 mg (2.22 mmol) of (1*R*,5*S*)-methyl myrtenate, 72.4 mg (10 mol %) of *n*-tetrabutylammonium bromide, 2 mL of nitromethane and 336 μL (1 equiv) of DBU and sealed with a Teflon cap was irradiated at 100 °C (250 W) for 25 min with a ramp time of 3 min under continuous cooling (Powermax). Next, the solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel; elution with 9:1 *n*-hexane/EtOAc gave the pure compounds **13** and **14**.

4.7.1. (1*S*,2*S*,3*S*,5*R*)-Methyl 6,6-dimethyl-3-(nitromethyl)bicyclo[3.1.1]heptane-2-carboxylate (−)-13

Isolated compound: 94 mg (39%, Method A) or 490 mg (73%, Method B); $[\alpha]_D^{20} = -0.4$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84 (1H, d, *J* = 10.6 Hz), 0.87 (3H, s), 1.24 (3H, s), 1.63–1.70 (1H, m), 1.96–2.01 (1H, m), 2.27–2.35 (1H, m), 2.38–2.45 (1H, m), 2.50–2.54 (1H, m), 2.70 (1H, dd, *J* = 2.6, 6.7 Hz), 3.37–3.47 (1H, m), 3,71 (3H, s), 4.36 (1H, dd, *J* = 8.6, 11.7 Hz), 4.52 (1H, dd, *J* = 5.8, 11.7 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.1, 27.3, 29.1, 31.0, 31.5, 38.6, 40.8, 43.4, 48.1, 52.5, 83.4, 174.6. IR = 2924,

1731, 1634, 1533, 1376, 1160 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81. Found: C, 59.62; H, 8.01; N, 5.76.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (+)-**13** was synthesized analogously to (−)-**13**, from (1*S*,5*R*)-methyl myrtenate; $[\alpha]_D^{20} = +0.4$ (*c* 0.25, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (−)-**13**. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81. Found: C, 59.59; H, 8.13; N, 5.68.

4.7.2. (1*S*,2*S*,3*R*,5*R*)-Methyl 6,6-dimethyl-3-(nitromethyl) bicyclo[3.1.1]heptane-2-carboxylate (−)-14

Isolated compound: 40 mg (6%, Method B); mp: 75–77 °C; $[\alpha]_D^{20} = -0.8$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.98 (3H, s), 1.26 (3H, s), 1.43 (1H, d, *J* = 10.7 Hz), 1.54–1.61 (1H, m), 1.95–2.00 (1H, m), 2.12–2.17 (1H, m), 2.18–2.31 (2H, m), 3.05–3.17 (1H, m), 3.34 (1H, d, *J* = 10.4 Hz), 3.62 (3H, s), 4.42 (1H, dd, *J* = 8.1, 13.6 Hz), 4.52 (1H, dd, *J* = 7.7, 13.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2, 26.5, 26.9, 27.6, 31.2, 39.3, 40.0, 43.9, 45.0, 52.0, 80.8, 174.8. IR = 2922, 1724, 1680, 1546, 1374, 1195, 1148 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81. Found: C, 59.66; H, 7.90; N, 5.87.

The (1*R*,2*R*,3*S*,5*S*)-enantiomer (+)-**14** was synthesized analogously to (−)-**14**, from (1*S*,5*R*)-methyl myrtenate; $[\alpha]_D^{20} = +0.7$ (*c* 0.25, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*R*,5*R*)-enantiomer (−)-**14**. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.13): C, 59.73; H, 7.94; N, 5.81. Found: C, 59.61; H, 8.02; N, 5.93.

4.8. (1*S*,2*S*,3*S*,5*R*)-6,6-Dimethyl-3-(nitromethyl)bicyclo[3.1.1] heptane-2-carboxylic acid (−)-15

A 25 mL round-bottomed flask containing 300 mg (1.24 mmol) of nitro ester (−)-**13** followed by 5 mL each of THF and water and 106 mg (2 equiv) of $LiOH{\cdot}H_2O$ was heated at reflux for 2 h. The solvent was evaporated off under reduced pressure and 10 mL of water was added to the residue, which was followed by extraction with EtOAc (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give nitro acid (−)-**15**. Isolated compound: 260 mg (91%); $[\alpha]_D^{20} = -0.6$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.86 (1H, d, *J* = 10.3 Hz), 0.92 (3H, s), 1.25 (3H, s), 1.64–1.71 (1H, m), 1.97–2.03 (1H, m), 2.28–2.37 (1H, m), 2.40–2.48 (1H, m), 2.52–2.57 (1H, m), 2.76 (1H, dd, *J* = 2.5, 6.6 Hz), 3.36–3.47 (1H, m), 4.37 (1H, dd, *J* = 8.7, 11.7 Hz), 4.53 (1H, dd, *J* = 6.0, 11.7 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 26.7, 28.4, 30.4, 31.0, 38.1, 40.2, 42.7, 47.3, 47.4, 82.8, 179.8. IR = 2947, 1701, 1551, 1380, 1286, 1156 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_4$ (227.12): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.12; H, 7.51; N, 6.10.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (+)-**15** was synthesized analogously to (−)-**15**, from (+)-**13**; $[\alpha]_D^{20} = +0.7$ (*c* 0.25, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (−)-**15**. Anal. Calcd for $C_{11}H_{17}NO_4$ (227.12): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.25; H, 7.42; N, 6.33.

4.9. (1*S*,2*S*,3*S*,5*R*)-3-(Aminomethyl)-6,6-dimethylbicyclo[3.1.1] heptane-2-carboxylic acid hydrochloride (+)-16

A 50 mL round-bottomed flask containing 200 mg (0.88 mmol) of nitro acid **15** was hydrogenated with H_2 gas at atmospheric pressure over Raney Ni in 15 mL of MeOH for 2 h. The mixture was then filtered and evaporated, and the product was purified by recrystallization as the hydrochloride, giving amino acid hydrochloride (−)-**16** as a white solid. Isolated compound: 130 mg (63%); mp: 196–198 °C; $[\alpha]_D^{20} = +1.4$ (*c* 0.25, MeOH); ^{1}H NMR (D_2O) δ (ppm): 0.86 (3H, s), 0.93 (1H, d, *J* = 9.8 Hz), 1.25 (3H, s), 1.55–1.65 (3H, s), 1.99–2.04 (1H, m), 2.31–2.38 (1H, m), 2.42–2.51 (2H, m), 2.75–2.78 (1H, m), 2.81–2.90 (1H, m), 3.04–3.16 (2H, m). ^{13}C NMR (D_2O) δ (ppm): 21.1, 26.0, 27.8, 30.1, 30.5, 37.3, 39.9, 42.8, 48.2, 48.7, 179.7. IR = 3434, 2943, 2906, 1711, 1613, 1498, 1385, 1200 cm^{-1}. Anal. Calcd for $C_{11}H_{20}ClNO_2$ (233.74): C, 56.52; H,8.62; N, 5.99. Found: C, 56.79; H, 8.47; N, 6.13.

The (1*R*,2*R*,3*R*,5*S*)-enantiomer (−)-**16** was synthesized analogously to (+)-**16**, from (+)-**15**; $[\alpha]_D^{20} = -1.5$ (*c* 0.25, MeOH); all the spectroscopic data and the mp were similar to those for the (1*S*,2*S*,3*S*,5*R*)-enantiomer (+)-**16** Anal. Calcd for $C_{11}H_{20}ClNO_2$ (233.74): C, 56.52; H,8.62; N, 5.99. Found: C, 56.83; H, 8.49; N, 6.25.

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