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Stereoselective synthesis of carane-based chiral β- and γ-amino acid derivatives via conjugate addition

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ABSTRACT

Michael addition of dibenzylamine to (−)-*tert*-butyl isochaminate, prepared in three steps from (−)-perillaldehyde, furnished a carane-based β-amino acid derivative in a highly stereospecific reaction. The resulting amino ester was transformed to the bicyclic amino acid, a promising building block for the synthesis of 1,3-heterocycles and peptidomimetics. The conjugate addition of nitromethane to α,β-unsaturated methyl ester likewise resulted in nitro esters in stereospecific reactions. Catalytic reduction of the nitro group yielded a γ-amino ester. Under acidic conditions, the hydrolysis of the methyl ester resulted in an unexpected aminolactone-type product through rearrangement of the bicyclic carane system, whereas an alternative synthetic pathway through α,β-unsaturated benzyl ester furnished the desired γ-amino acid.

1. Introduction

In view of the importance of alicyclic and bicyclic chiral β-amino acids in the synthesis of 1,3-amino alcohol, 1,3-diamine or β-amino carboxamide chiral catalysts and building blocks of β-peptidic foldamers and saturated or partially saturated 1,3-heterocycles with promising pharmacological activities, increased attention is currently turning to the stereoselective synthesis of these chiral building blocks.[1–9]

Several powerful synthetic methodologies are available via which alicyclic or bicyclic β-amino acid enantiomers can be obtained, including enzyme-catalysed kinetic resolution,[10,11] and a variety of asymmetric syntheses, e.g. the enantioselective syntheses of β-lactams followed by ring opening,[12,13] or the enantioselective desymmetrization of achiral anhydrides followed by Curtius degradation.[14–16]

Besides the above methods, the conjugate addition of amine nucleophiles to α,β-unsaturated carbonyl compounds has recently become a powerful procedure to obtain alicyclic β-amino acids in enantiomerically pure form on a gram scale.[17,18] The principal strategy of these methods is the use of chiral lithium amides, and only a few examples are to be found where chiral α,β-unsaturated esters are applied as the source of chirality in the conjugate addition.[19–23]

Besides the synthesis of β-amino esters, α,β-unsaturated esters are excellent starting materials to obtain γ-amino acid derivatives via the conjugate addition of nitroalkanes, followed by catalytic reduction of the nitro group and hydrolysis of the ester function.[19,24–26] Because of their promising biological and therapeutic applications, the search for efficient and versatile synthetic strategies to gain access to a variety of γ-amino acids is a very active research field.[24,27]

Readily available optically active monoterpene derivatives, such as (+)- and (−)-pulegone, (+)- and (−)-verbenone, (+)-3-carene or (+)- and (−)-α-pinene, have often been considered as substrates for the synthesis of chiral reagents and as unique synthons in asymmetric syntheses of β-amino acids, 1,3-amino alcohols applied as chiral additives, catalysts or building blocks.[13,28–34] From this respect, the chiral, monoterpene-based α,β-unsaturated esters might be excellent starting materials, where the natural monoterpene skeleton may serve as the origin of the chirality for the stereoselective construction of the β- and γ-amino acid moiety.[19]

Our present aim was the preparation and some transformations of a new family of conformationally constrained carane-based chiral β- and γ-amino acid derivatives derived from commercially available (−)-perillaldehyde **1**. Our earlier results on pinane-based β-amino acid derivatives revealed that these bicyclic building

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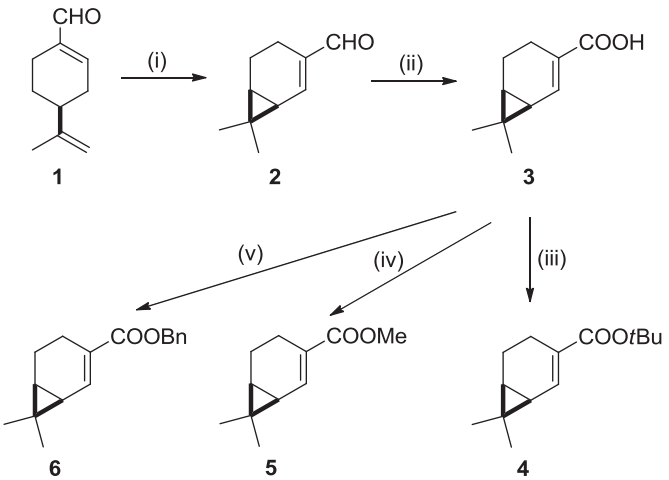
blocks with β- and γ-amino acid functions might serve as promising chiral substrates for the synthesis of chiral catalysts and foldamers.[4,7,19,35]

2. Results

For the synthesis of β-amino acid **9**, *tert*-butyl isochaminate **4** served as the key intermediate Michael acceptor, which was prepared from commercially available (−)-(4*S*)-perillaldehyde **1** by a combination of literature protocols in a three-step reaction: addition of HBr to **1**, followed by treatment with KO*t*Bu, yielded the bicyclic aldehyde **2**, which was then oxidized to (+)-isochaminic acid **3** by literature method,[36–39] which in turn was converted to the *tert*-butyl ester **4** (Scheme 1).[40] Besides **4**, benzyl and methyl esters **5** and **6** were also prepared.



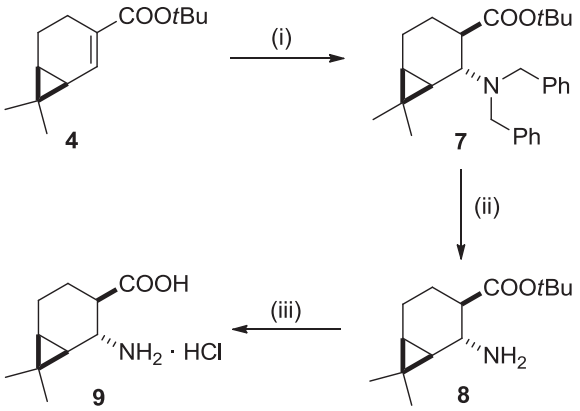
Scheme 1. (i) 33% HBr/AcOH, 0 °C, 0.5 h, 25 °C, 2 h, then 2-methylbutan-2-ol, *t*BuOK, 0 °C, 1 h, 25 °C, 2 h, 45%; (ii) 2-methyl-2-butene, *t*BuOH, $NaClO_2$ (aq), NaH_2PO_4 (aq), 60%; (iii) 2.7 equiv $(CF_3CO)_2O$, dry toluene, *t*BuOH, rt, 79%; (iv) $(COCl)_2$, DCM, 0–25 °C, 2 h, then dry MeOH, 2 h, 59%; (v) MeCN, 1.5 equiv DBU, 1 equiv BnBr, 0 °C to rt, 12 h, 53%.

Compound **3** has a known structure:[37,38] the compound reported in the publication by Jayasinghe et al.[38] is (−)-isochaminic acid, the enantiomer of **3**, but neither the source of chirality nor the enantiopurity of (−)-isochaminic acid is mentioned therein. We checked the optical rotation of **3** carefully under the same conditions (Lit. 38: −10°, *c*=1.3, diethyl ether) and found it to be +76°.

In the publication by Stumpf et al.,[37] the source of chirality was given as (+)-2-carene for (−)-isochaminic acid. As concerns the melting point of the substance, our value was 92–94 °C, in good agreement with the mp of 102–104 °C reported therein.

The asymmetric Michael addition to **4** followed a literature protocol,[19,39] with the application of in situ generated achiral lithium dibenzylamide to exploit the effect of the constrained carane ring system on the stereoselectivity of the addition (Scheme 2). NMR study of the crude product revealed the excellent stereoselectivity of the Michael addition, yielding **7** as a single diastereoisomer. Amino ester **7** was then transformed to the appropriate amino acid **9** in two steps. Hydrogenolysis of **7** over palladium on carbon (Pd/C) in MeOH resulted in primary amino ester **8** in excellent yield, which was successfully hydrolysed to amino acid **9** under acidic conditions.

The relative configuration of **9** was determined by X-ray crystallography (Fig. 1); the observed *exo* position of the amino substituent and the *endo* position of the carboxylic acid function correlated well with the results of NOESY experiments, where noteworthy NOE effects were observed between C2–H and C8–Me,



Scheme 2. (i) 2.4 equiv $LiNBn_2$, dry THF, −78 °C, 6 h, then NH_4Cl (aq), 81%; (ii) 5% Pd/C, *n*-hexane/EtOAc=1:1, 1 atm H_2, rt, 16 h, 90%; (iii) 10% HCl (aq), rt, 24 h, 45%.

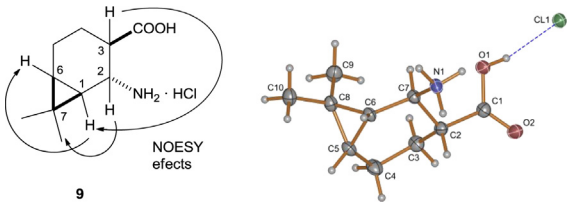


Fig. 1. NOESY effects and ORTEP plot of the configuration of **9**.

between C1–H and C6–H and between C1–H and C3–H (see Fig. 1 for numbering).

When *tert*-butyl isochaminate **4** was used in the Michael addition of nitromethane in order to obtain γ-amino acid **12**, our first attempts under either conventional or microwave heating failed. When methyl isochaminate **5** was applied in the conjugate addition with conventional heating, NMR studies of the crude product indicated that the addition took place stereospecifically, resulting in *trans* isomers **10a** and **10b** in a ratio of 90:10 (Scheme 3).

After separation of the isomers by column chromatography, the configurations of the new stereogenic centres were determined by NMR with NOESY experiments. It must be mentioned that, in contrast with our earlier results on the pinane ring system,[19] when the carane ring was subjected to microwave irradiation, a lower yield but similar stereoselectivity were observed as compared with conventional heating. Since the LiOH-mediated hydrolysis of nitro ester **10a** to obtain the corresponding nitro acid[19] was also unsuccessful (only a mixture of unknown compounds was detected), the next step was the reduction of **10a** over Raney Ni to provide amino ester **11** in good yield. Surprisingly, the hydrolysis of **11** under acidic conditions did not lead to the expected γ-amino acid **12**, but to the rearranged amino lactone **13** (Scheme 3). Besides the NOESY experiments, where considerable NOE effects were observed between C9–H and C4–Me and between C10–H and C6-H_{ax} (see Fig. 2 for numbering), the relative configuration of **9** was determined by X-ray crystallography (Fig. 2).

The proposed mechanism of the acid-catalysed rearrangement of **11** to **13** with formation of the favoured six-membered lactone ring is given in Fig. 3.[41] The synthesis of the desired γ-amino acid was finally accomplished by an alternative pathway, starting from benzyl ester **6** (Scheme 4).

Similarly as for methyl ester **5**, the conjugate addition of nitromethane to **6** resulted in two *trans* isomers, **14a** and **14b**, in a ratio of 90:10 (based on NMR measurements), but separation of the diastereoisomers failed both for the nitro esters **14a**,**b** and for the amino esters **15a**,**b** obtained by catalytic reduction. The mixture of amino esters **15a** and **15b** was therefore debenzylated with Pd/C as

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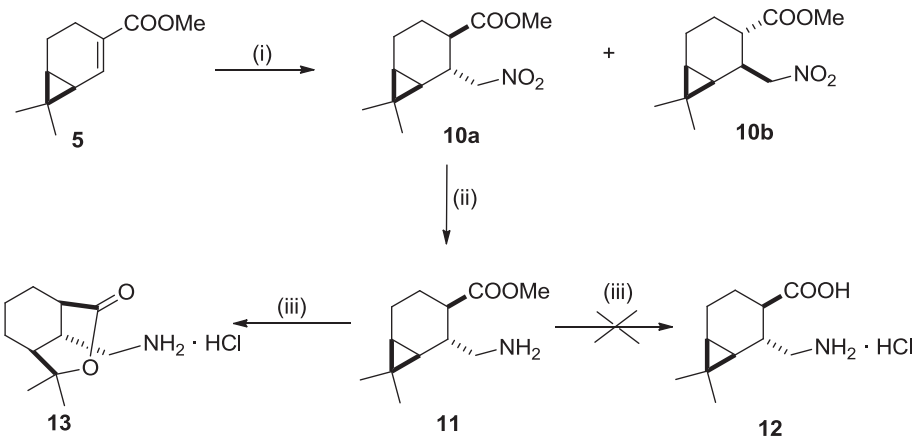


Scheme 3. (i) 1 equiv DBU, 0.1 equiv TBAB, $MeNO_2$, reflux, 12 h, **10a**: 74%, **10b**: 7%; (ii) 1 atm H_2, Raney-Ni, MeOH, rt, 2 h, 60%; (iii) 15% HCl (aq), rt, 24 h, 79%.

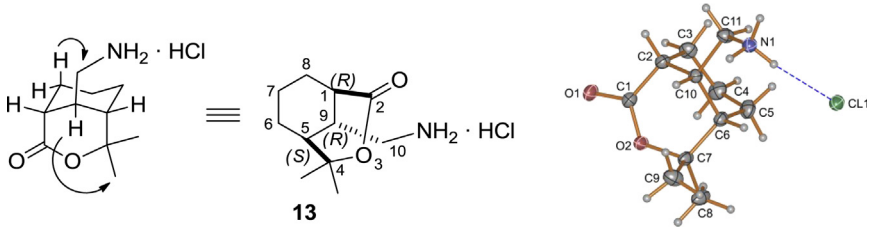


Fig. 2. ORTEP plot of the configuration of **13**.

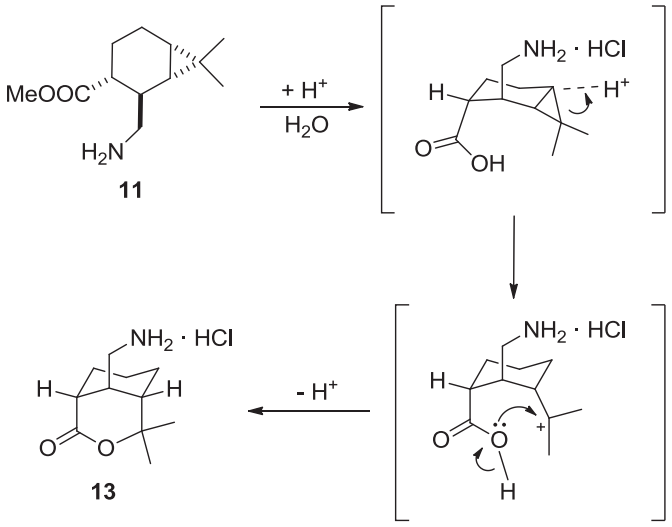


Fig. 3. Suggested mechanism for the rearrangement of **11**.

catalyst, and recrystallization of the crude product furnished major component γ-amino acid **16** in moderate yield (Scheme 4).

Similarly to **9**, the relative configuration of **16** was determined by NOESY experiments, where significant NOE effects were observed between C2–H and C7–Me, between C1–H and C6–H and between C1–H and C3–H.

3. Conclusions and outlook

The highly stereoselective addition of lithium amides to *tert*-butyl isochaminate **3** proved to be an efficient method for the synthesis of a new carane-based β-amino acid via three-step transformation of the resulting *N*,*N*-dibenzyl β-amino ester **7** on a gram scale. Conjugate addition of $MeNO_2$ to unsaturated esters **5** and **6** resulted in γ-nitro esters in stereoselective reactions. Acid-catalysed ring rearrangement of carane-based γ-amino ester **11** resulted in the unique bicyclic aminolactone **13**, while the originally desired γ-amino acid **16** was prepared via benzyl ester **15a**. We believe that incorporation of the resulting new β- and γ-amino acids in a β-peptide sequence will allow the formation of unique β-helix or β-sheet structures, thereby affording a novel route to promising β- and γ-peptides.

4. Experimental

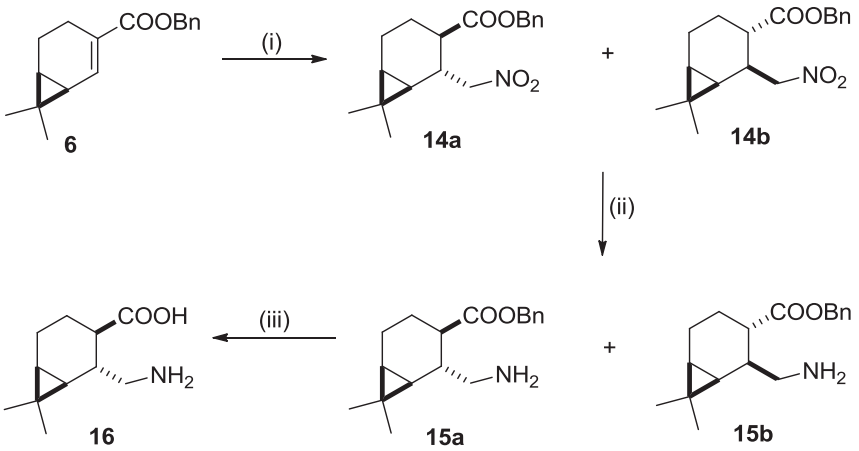
4.1. General

^1H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400.1 MHz (^1H) and 100.6 MHz (^{13}C) [δ=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 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. FTIR spectra were recorded in KBr pellets on an Avatar 300 FT-IR spectrometer (Thermo Nicolet, USA). 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).

(−)-(4*S*)-Perillaldehyde and dibenzylamine are available commercially. THF and toluene were dried over Na wire; all other chemicals and solvents were used as supplied.

4.2. (1*R*,6*S*)-7,7-Dimethylbicyclo[4.1.0]hept-2-ene-3-carboxylic acid (3)

To the solution of bicyclic aldehyde[2] **2** (10.0 g, 66.0 mmol) in MeCN (70.0 mL), solutions of NaH_2PO_4 (2.1 g, 105.1 mmol) in H_2O (30 mL), and 35% aqueous H_2O_2 (7.0 mL) were added at 10 °C. After 10 min, $NaClO_2$ (11.0 g, 121.6 mmol) in H_2O (95.0 mL) was added dropwise to the mixture, the solution was warmed to room temperature and was stirred for 12 h. Na_2SO_3 (1.6 g, 12.7 mmol) was



Scheme 4. (i) 1 equiv DBU, 0.1 equiv TBAB, $MeNO_2$, reflux, 20 h, 48%; (ii) 1 atm H_2, Raney-Ni, MeOH, rt, 4 h, 61%; (iii) 5% Pd/C, dry MeOH, 1 atm H_2, rt, 6 h, 36%.

then added to the mixture. After 30 min stirring at room temperature, the solution was basified with 10% aqueous KOH solution (pH 11) then the aqueous phase was extracted with *n*-hexane (3×100 mL). The aqueous phase was acidified with 10% aqueous HCl solution (pH 2) and extracted with DCM (3×200 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product obtained was purified by column chromatography on silica gel (R_f=0.42, *n*-hexane/EtOAc=4:1).

Compound **3**: white crystals; 4.9 g (45%); mp 92–94 °C;[37] $[\alpha]_D^{20}$=+86.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2906, 1683, 1425, 1290, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.16–1.21 (m, 1H), 1.17 (s, 3H), 1.27–1.33 (m, 1H), 1.71–1.85 (m, 1H), 1.85–1.98 (m, 2H), 2.40 (dd, *J*=8.3, 14.7 Hz, 1H), 7.40 (d, *J*=5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 17.2 (CH_2), 21.4 (CH_2), 24.6 (CH_3), 26.4 (CH), 29.4 (CH), 30.0 (C_q), 126.4 (C_q), 142.9 (CH), 172.8 (C_q). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.96; H, 8.19.

4.3. (1*R*,6*S*)-*tert*-Butyl 7,7-dimethylbicyclo[4.1.0]hept-2-ene-3-carboxylate (4)

To a solution of isochaminic acid (7.20 g, 43.3 mmol) **3** in dry toluene (60 mL), TFAA (16.4 mL, 24.47 g, 116.4 mmol) was added at room temperature. The resulting homogeneous solution was stirred for 40 min and then treated with *t*BuOH (52.0 g, 696 mmol) under ice-bath cooling. The solution was stirred for 4 h at room temperature, and the mixture was then diluted with toluene (200 mL) cooled to 0 °C and extracted first with 10% aqueous NaOH solution (100 mL), next with H_2O (100 mL) and finally with brine (100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (R_f=0.4, *n*-hexane/Et_2O=19:1), resulting in 7.60 g (79%) of compound **4** as a colourless oil.

Compound **4**: $[\alpha]_D^{20}$=+107.0 (*c*=0.25, MeOH); IR (KBr): ν_{max} 2931, 1698, 1637, 1367, 1280, 1169, 1053 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.07–1.13 (m, 1H), 1.14 (s, 3H), 1.18–1.25 (m, 1H), 1.47 (s, 9H), 1.69–1.81 (m, 1H), 1.81–1.93 (m, 2H), 2.27–2.41 (m, 1H), 7.13 (d, *J*=5.3 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.1 (CH_3), 17.4 (CH_2), 21.8 (CH_2), 24.1 (CH), 25.6 (CH), 28.4 (3×CH_3), 28.7 (C_q), 29.4 (CH_3), 79.8 (C_q), 128.9 (C_q), 138.4 (CH), 167.0 (C_q). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.34; H, 9.67.

4.4. (1*R*,6*S*)-Methyl 7,7-dimethylbicyclo[4.1.0]hept-2-ene-3-carboxylate (5)

To a solution of isochaminic acid **3** (1.00 g, 6.0 mmol) in dry DCM (50 mL) oxalyl chloride (0.57 mL, 6.7 mmol) was added in one portion. The mixture was stirred at room temperature for 2 h, then concentrated, and dry MeOH (50 mL) was added in one portion to the mixture. The solution was stirred for 15 min, concentrated in vacuo and the crude product obtained was purified via column chromatography on silica gel (R_f=0.35, *n*-hexane/Et_2O=9:1).

Compound **5**: a yellow oil; 0.56 g (60%); $[\alpha]_D^{20}$=+90.0 (*c* 0.25, MeOH);[42] IR (KBr): ν_{max} 2950, 1713, 1639, 1434, 1242, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.10–1.17 (m, 1H), 1.15 (s, 3H), 1.25 (dd, *J*=5.7, 7.4 Hz, 1H), 1.71–1.84 (m, 1H), 1.85–1.98 (m, 2H), 2.33–2.44 (m, 1H), 3.72 (s, 3H), 7.23 (d, *J*=5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 17.3 (CH_2), 21.8 (CH_2), 24.2 (CH_3), 25.9 (CH), 29.2 (CH), 29.3 (C_q), 51.6 (CH_3), 127.2 (C_q), 139.9 (CH), 168.0 (C_q). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.00; H, 8.65.

4.5. (1*R*,6*S*)-Benzyl 7,7-dimethylbicyclo[4.1.0]hept-2-ene-3-carboxylate (6)

To a solution of isochaminic acid **3** (1.00 g, 6.0 mmol) in 30 mL of MeCN at 0 °C, DBU (0.9 mL, 9.0 mmol) and benzyl bromide (0.72 mL, 6.0 mmol) were added and the resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 12 h. Saturated NaCl solution (50 mL) was next added and the resulting mixture was extracted with EtOAc (3×100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo before purification via column chromatography on silica gel (R_f=0.4, *n*-hexane/EtOAc=19:1).

Compound **6**: a colourless oil; 0.81 g (53%); $[\alpha]_D^{20}$=+72.0 (*c*=0.25, MeOH); IR (KBr): ν_{max} 2926, 1710, 1635, 1454, 1265, 1053, 744 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.13–1.19 (m, 1H), 1.17 (s, 3H), 1.25–1.31 (m, 1H), 1.73–1.85 (m, 1H), 1.87–1.92 (m, 1H), 1.98 (ddd, *J*=2.1, 8.5, 17.4 Hz, 1H), 2.39–2.49 (m, 1H), 5.19 (dd, *J*=12.8, 15.5 Hz, 2H), 7.29–7.41 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3 (CH_3), 17.5 (CH_2), 22.1 (CH_2), 24.5 (CH), 26.3 (CH), 27.6 (C_q), 29.6 (CH_3), 66.3 (CH_2), 127.4 (C_q), 128.4 (2×CH Ar), 128.9 (CH Ar), 137.0 (C_q). 140.7 (CH), 167.6 (C_q). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.37; H, 7.66.

4.6. (1*R*,2*R*,3*R*,6*S*)-*tert*-Butyl 2-dibenzylamino-7,7-dimethylbicyclo[4.1.0]heptane-3-carboxylate (7)

n-BuLi solution (27 mL of a 1.6 M solution in *n*-hexane) was added dropwise to a stirred solution of dibenzylamine (8.90 g, 45.1 mmol) in dry THF (100 mL) at −78 °C under an argon atmosphere, followed by stirring for 30 min prior to the addition of a solution of 4.00 g (18.0 mmol) of the acceptor **4** in dry THF (25 mL). After the appropriate reaction time (5 h), saturated aqueous NH_4Cl solution (100 mL) was added, the solution was

warmed to room temperature and partitioned between Et_2O (3×200 mL) and brine, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography on silica gel (R_f=0.6, *n*-hexane/Et_2O=19:1) gave 6.10 g (81%) of the desired product **7** as a colourless oil.

Compound **7**: $[\alpha]_D^{20}$=−5.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2937, 1724, 1454, 1365, 1149, 746, 698 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.61 (dd, *J*=7.3, 8.8 Hz, 1H), 0.71–0.77 (m, 1H), 0.74 (s, 3H), 1.05 (s, 3H), 1.09–1.21 (m, 1H), 1.44 (s, 9H), 1.58–1.78 (m, 3H), 2.31 (dt, *J*=3.6, 11.7 Hz, 1H), 2.76 (dd, *J*=4.0, 11.5 Hz, 1H), 3.42 (d, *J*=13.5 Hz, 2H), 3.91 (d, *J*=13.5 Hz, 2H), 7.17–7.39 (m, 10H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1 (CH), 17.2 (C_q), 18.9 (CH_2), 19.5 (CH_3), 20.2 (CH_3), 27.4 (CH_2), 28.3 (3×CH_3), 29.2 (CH_3), 45.9 (CH), 54.3 (CH_2), 54.9 (CH), 79.8 (C_q), 126.9 (CH Ar), 128.0 (CH Ar), 129.4 (CH Ar), 139.9 (C_q Ar), 175.5 (C_q). Anal. Calcd for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 79.84; H, 8.59; N, 3.01.

4.7. (1*R*,2*R*,3*R*,6*S*)-*tert*-Butyl 2-amino-7,7-dimethylbicyclo [4.1.0]heptane-3-carboxylate (8)

A solution of amino ester **7** (4.60 g, 11.0 mmol) in dry MeOH (20 mL) was added to a suspension of 10% Pd/C (1.10 g) in dry MeOH (100 mL) and the resulting mixture was stirred under H_2 (1 atm) at room temperature for 12 h. The solution was filtered through a pad of Celite, and the solvent was removed. The crude oily product obtained was dissolved in DCM (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 on silica gel (R_f=0.3, toluene/EtOH=4:1), affording 2.36 g (90%) of colourless oily product **8**.

Compound **8**: $[\alpha]_D^{20}$=−14.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2941, 1720, 1369, 1314, 1147 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.43 (dd, *J*=3.7, 9.2 Hz, 1H), 0.61 (t, *J*=8.3 Hz, 1H), 0.97 (s, 3H), 1.02 (s, 3H), 1.11–1.20 (m, 1H), 1.43 (s, 9H), 1.62–1.69 (m, 1H), 1.72–1.86 (m, 3H), 2.71 (dd, *J*=3.6, 11.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7 (CH_3), 17.5 (C_q), 18.5 (CH_2), 20.2 (CH), 26.6 (CH_2), 28.3 (3×CH_3), 29.2 (CH), 29.3 (CH_3), 47.6 (CH), 51.1 (CH), 80.4 (C_q), 176.1 (C_q). Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.74; H, 8.30; N, 4.51.

4.8. (1*R*,2*R*,3*R*,6*S*)-2-Amino-7,7-dimethylbicyclo[4.1.0]heptane-3-carboxylic acid hydrochloride (9)

Amino ester **8** (10 mmol) was dissolved in a mixture of Et_2O (15 mL) and 10% aqueous HCl solution (100 mL). The mixture was then stirred at room temperature for 24 h and subsequently evaporated to dryness, and the resulting white crystalline product **9** was washed with Et_2O, filtered off and purified by recrystallization from EtOH/Et_2O, resulting in 0.82 g (44%) product.

Compound **9**: white crystals; mp 214–216 °C; $[\alpha]_D^{20}$=−13.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2881, 1714, 1509, 1375, 1205 cm^{-1}. ^1H NMR (400.1 MHz, DMSO-d_6) δ 0.63–0.71 (m, 1H), 0.77 (t, *J*=7.5 Hz, 1H), 0.96 (s, 3H), 1.04 (s, 3H), 1.14–1.25 (m, 1H), 1.50–1.61 (m, 1H), 1.77–1.92 (m, 2H), 2.24–2.35 (m, 1H), 2.98 (dd, *J*=3.1, 10.5 Hz, 1H), 8.28 (br s, 3H), 12.85 (br s, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 15.8 (CH_3), 18.2 (C_q), 18.3 (CH_2), 20.5 (CH), 23.9 (CH), 26.4 (CH_2), 29.3 (CH_3), 43.6 (CH), 46.7 (CH), 175.9 (C_q). Anal. Calcd for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.34; H, 7.94; N, 6.08.

4.9. Conjugate addition of $MeNO_2$ to compound 5

A mixture of methyl isochaminate (**5**) (100 mg, 0.56 mmol), tetra-*n*-butylammonium bromide (TBAB) (18.1 mg, 0.1 equiv) and DBU (84 μL, 0.56 mmol) in 2 mL of $MeNO_2$ was heated under 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 (R_f=0.3 for **10a** and R_f=0.35 for **10b**, *n*-hexane/EtOAc=9:1), resulting in colourless oily products **10a** and **10b**.

4.9.1. (1*S*,2*R*,3*R*,6*S*)-Methyl 7,7-dimethyl-2-nitromethylbicyclo[4.1.0] heptane-3-carboxylate (**10a**).

Compound **10a**: a colourless oil; 100 mg (74%); $[\alpha]_D^{20}$=−2.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2953, 1735, 1154, 1377, 1166 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.48 (dd, *J*=5.0, 9.2 Hz, 1H), 0.66 (dt, *J*=2.6, 9.5 Hz, 1H), 0.99 (s, 3H), 1.00 (s, 3H), 1.27–1.42 (m, 1H), 1.65–1.73 (m, 1H), 1.78–1.88 (m, 2H), 2.07 (dt, *J*=3.8, 11.7 Hz, 1H), 2.18–2.29 (m, 1H), 3.68 (s, 3H), 4.38 (dd, *J*=8.9, 11.9 Hz, 1H), 4.52 (dd, *J*=4.2, 11.9 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.5 (CH), 18.1 (CH_2), 19.7 (CH_3), 23.3 (CH_3), 26.1 (C_q), 27.1 (CH_2), 28.9 (CH), 33.2 (CH), 42.4 (CH), 52.0 (CH_3), 80.2 (CH_2), 175.8 (C_q). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.43; H, 7.64; N, 5.51.

4.9.2. (1*S*,2*S*,3*S*,6*S*)-Methyl 7,7-dimethyl-2-nitromethylbicyclo[4.1.0] heptane-3-carboxylate (**10b**).

Compound **10b**: a colourless oil; 10 mg (7%); $[\alpha]_D^{20}$=−8.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2954, 1732, 1554, 1378, 1173 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.55 (dd, *J*=6.0, 9.4 Hz, 1H), 0.65 (dt, *J*=1.9, 8.6 Hz, 1H), 0.96 (s, 3H), 1.00 (s, 3H), 1.28–1.40 (m, 1H), 1.47–1.55 (m, 1H), 1.77–1.88 (m, 1H), 1.98–2.07 (m, 1H), 2.10–2.18 (m, 1H), 2.55 (q, *J*=4.3, 8.5 Hz, 1H), 3.70 (s, 3H), 4.72 (ddd, *J*=4.3, 8.2, 12.4 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1 (CH), 15.5 (CH_2), 19.4 (CH_3), 22.8 (CH_3), 26.2 (CH_2), 28.7 (CH_2), 29.9 (C_q), 33.6 (CH), 39.4 (CH), 51.7 (CH_3), 80.2 (C_q), 175.6 (C_q). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.43; H, 7.64; N, 5.51.

4.10. (1*S*,2*R*,3*R*,6*S*)-Methyl 2-aminomethyl-7,7-dimethylbicyclo[4.1.0]heptane-3-carboxylate hydrochloride (11)

Nitro ester **10a** (100 mg, 0.41 mmol) was dissolved in 15 mL of dry MeOH and hydrogenated with H_2 gas at atmospheric pressure over Raney Ni (80 mg) for 2 h. The mixture was then filtered, the filtrate was evaporated, and the product was purified by column chromatography (silica gel, R_f=0.5, toluene/EtOH=1:1), giving the amino ester, which was purified as hydrochloride **11** by recrystallization from EtOH/Et_2O.

Compound **11**: white crystals; 53 mg (52%); mp 198–201 °C; $[\alpha]_D^{20}$=−13.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2950, 1735, 1438, 1315, 1164 cm^{-1}. ^1H NMR (400.1 MHz, DMSO-d_6) δ 0.52–0.66 (m, 2H), 0.95 (s, 3H), 1.02 (s, 3H), 1.10–1.25 (m, 1H), 1.55–1.86 (m, 4H), 1.98 (dt, *J*=4.2, 11.6 Hz, 1H), 2.68–2.88 (m, 2H), 3.62 (s, 3H), 8.24 (br s, 3H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 15.4 (CH_3), 17.4 (C_q), 17.6 (CH_2), 18.8 (CH), 21.5 (CH), 26.1 (CH_2), 28.7 (CH_3), 31.7 (CH), 42.3 (CH), 42.9 (CH_2), 51.6 (CH_3), 175.7 (C_q). Anal. Calcd for $C_{12}H_{22}ClNO_2$: C, 58.17; H, 8.95; N, 5.65. Found: C, 57.87; H, 8.65; N, 5.35.

4.11. (1*R*,5*S*,9*R*)-9-Aminomethyl-4,4-dimethyl-3-oxabicyclo [3.3.1]nonan-2-one hydrochloride (13)

Amino ester **11** (100 mg, 0.47 mmol) was dissolved in a mixture of Et_2O (5 mL) and 15% aqueous HCl solution (15 mL). The mixture was stirred at room temperature for 12 h, and then evaporated to dryness, and the resulting white crystalline product **9** was washed with Et_2O, filtered off and purified by recrystallization from EtOH/Et_2O, resulting in 75 mg (79%) of amino lactone **13**.

Compound **13**: white crystals; mp 199–202 °C; $[\alpha]_D^{20}$=+10.0 (*c* 0.25, MeOH); IR (KBr): ν_{max} 2873, 1683, 1494, 1333, 1108 cm^{-1}. ^1H NMR (400.1 MHz, DMSO-d_6) δ 1.24–1.37 (m, 1H), 1.40 (s, 6H), 1.45–1.77 (m, 4H), 1.80–1.92 (m, 2H), 2.60–2.68 (m, 1H), 2.69–2.75 (m, 1H), 2.99–3.15 (m, 2H), 8.22 (br s, 3H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 19.5 (CH_2), 21.4 (CH_2), 24.2 (CH_2), 27.1 (CH_3), 30.4 (CH_3),

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32.3 (CH), 36.7 (CH), 38.5 (CH), 39.3 (CH_2), 85.8 (C_q), 173.7 (C_q). Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99. Found: C, 56.22; H, 8.32; N, 5.69.

4.12. (1*S*,2*R*,3*R*,6*S*)-Benzyl 7,7-dimethyl-2-nitromethylbicyclo[4.1.0]heptane-3-carboxylate (14a) and (1*S*,2*S*,3*S*,6*S*)-benzyl 7,7-dimethyl-2-nitromethylbicyclo[4.1.0]heptane-3-carboxylate (14b)

To a solution of **6** (0.6 g, 2.34 mmol) in 6 mL of $MeNO_2$ (76.0 mg, 0.23 mmol) of TBAB and 170 μL of DBU were added, and the mixture was heated under reflux for 20 h. Completion of the reaction was monitored by TLC. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel (R_f=0.5, *n*-hexane/EtOAc=9:1). The conjugate addition resulted in *trans* isomers **14a** and **14b** in a ratio of 90:10 (based on NMR measurements); separation of the diastereoisomers failed.

Compounds **14a**,**b**: a colourless oil; 0.36 g (48%); $[\alpha]_D^{20}=-3.0$ (*c* 0.25, MeOH); IR (KBr): ν_{max} 2950, 1733, 1552, 1377, 1161, 700 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.48 (dd, *J*=5.2, 9.2 Hz, 1H, major), 0.51–0.62 (m, 1H, minor), 0.66 (dt, *J*=1.5, 7.2 Hz, 1H, major), 0.93–0.96 (m, 1H, minor), 0.99 (s, 3H), 1.00 (s, 3H), 1.29–1.42 (m, 1H, major and minor), 1.45–1.53 (m, 1H, minor), 1.66–1.74 (m, 1H, major and minor), 1.80–1.90 (m, 2H, major and minor), 2.00–2.10 (m, 2H, minor) 2.11 (dt, *J*=3.9, 11.8 Hz, 1H), 2.21–2.30 (m, 1H), 2.53–2.60 (m, minor), 4.36 (dd, *J*=9.3, 12.1 Hz, 1H), 4.47 (dd, *J*=4.0, 11.9 Hz, 1H), 4.46–4.75 (m, minor), 5.13 (q, *J*=12.0, 18.3 Hz, 2H, major and minor), 7.31–7.39 (m, 5H, major and minor). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1 (CH_3, minor), 15.4 (CH_2, minor), 15.5 (CH, major), 18.1 (CH_2, major), 18.3 (CH_2, minor), 19.3 (CH_3, minor), 19.7 (CH_3, major), 22.9 (CH_3, minor), 23.3 (CH_3, major), 26.2 (C_q, major), 27.1 (CH_2, major), 28.7 (CH, minor), 28.9 (CH, major), 33.3 (CH, major), 33.6 (CH, minor), 39.5 (CH, minor), 42.4 (CH, major), 66.5 (CH_2, minor), 66.7 (CH_2, major), 80.0 (C_q, major), 80.1 (C_q, minor), 128.4 (CH Ar, major), 128.5 (CH Ar, minor), 128.6 (CH Ar, major), 128.7 (CH Ar, minor), 128.8 (CH Ar, major), 135.9 (C_q Ar, major), 175.2 (C_q, major). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.84; H, 7.02; N, 4.11.

4.13. (1*S*,2*R*,3*R*,6*S*)-Benzyl 2-aminomethyl-7,7-dimethylbicyclo[4.1.0]heptane-3-carboxylate (15a) and (1*S*,2*S*,3*S*,6*S*)-benzyl 2-aminomethyl-7,7-dimethylbicyclo[4.1.0]heptane-3-carboxylate (15b)

To a solution of mixture **14a**,**b** (300 mg, 0.94 mmol) in dry MeOH (20 mL), Raney Ni catalyst (100 mg) was added, and the resulting mixture was stirred under H_2 (1 atm) at room temperature for 4 h. The solution was filtered through a pad of Celite, and the solvent was removed in vacuo. The crude product was then purified by column chromatography on silica gel (R_f a,b=0.4, toluene/EtOH=1:1), resulting in a mixture of diastereoisomers **15a** (major) and **15b** (minor).

Compounds **15a**,**b**: a colourless oil; 164 mg (61%); $[\alpha]_D^{20}=-5.0$ (*c* 0.25, MeOH); IR (KBr): ν_{max} 2939, 1726, 1456, 1379, 1143, 761 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.42–0.51 (m, 1H, minor and major), 0.56 (t, *J*=7.3 Hz, 1H, major), 0.73 (dd, *J*=5.8, 9.1 Hz, 1H, minor), 0.88 (s, 3H, minor), 0.95 (s, 3H, minor overlapped with major), 1.00 (s, 3H, major), 1.15–1.34 (m, 1H, minor and major), 1.41–1.52 (m, 1H, minor), 1.54–2.03 (m, 6H, minor and major), 2.73 (br s, 1H, major), 2.91 (br s, 1H, major), 3.10 (t, *J*=9.2 Hz, 1H, minor), 3.43 (t, *J*=8.1 Hz, 1H, minor), 4.27 (br s, 2H), 5.04 (dd, *J*=12.3, 16.4 Hz, 2H, minor and major), 7.27 (m, 5H, minor and major). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (CH, major), 18.3 (CH_2, major), 19.1 (CH_3, minor), 19.6 (CH_3, major), 21.6 (C_q, major), 23.5 (CH_3, major), 24.9 (CH_3, minor), 26.9 (CH_2, major), 28.6 (CH, minor), 29.2 (CH, major), 38.3 (CH, major), 43.5 (CH, major), 47.4 (CH_2, major), 66.5 (CH_2, major), 128.4 (CH Ar, major), 128.7 (CH Ar, major), 136.1 (C_q Ar, major), 176.3 (C_q, major). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.92; H, 8.47; N, 4.51.

4.14. (1*S*,2*R*,3*R*,6*S*)-2-Aminomethyl-7,7-dimethylbicyclo[4.1.0]heptane-3-carboxylic acid (16)

A solution of amino esters **15a**,**b** (100 mg, 0.35 mmol) in dry MeOH (15 mL) was added to a suspension of 10% Pd/C (25 mg) in dry MeOH (15 mL), and the resulting mixture was stirred under H_2 (1 atm) at room temperature for 6 h. The solution was next filtered through a pad of Celite, the solvent was removed and the crude product **16** was purified by recrystallization (EtOH/Et_2O), resulting in 27 mg (36%) of amino acid **16**.

Compound **16**: white crystals; mp 186–188 °C; $[\alpha]_D^{20}=-18.0$ (*c* 0.25, MeOH); IR (KBr): ν_{max} 2915, 1652, 1558, 1402 cm^{-1}. ^1H NMR (400.1 MHz, D_2O) δ 0.44 (dd, *J*=4.9, 9.2 Hz, 1H), 0.65 (dt, *J*=1.5, 7.8 Hz, 1H), 1.07 (s, 3H), 1.08 (s, 3H), 1.24–1.39 (m, 1H), 1.61–1.92 (m, 5H), 2.90 (dd, *J*=7.9, 12.7 Hz, 1H), 3.10 (dd, *J*=4.7, 12.6 Hz, 1H), 3.30–3.35 (m, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 15.0 (CH), 17.9 (C_q), 18.5 (CH_2), 19.8 (CH_3), 24.2 (CH_3), 27.7 (CH_2), 28.4 (CH), 33.2 (CH), 45.4 (CH_2), 47.9 (CH). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.67; H, 9.41; N, 6.80.

4.15. X-ray structure determination

Crystals of **9** and **13** were immersed in cryo-oil, mounted in a MiTeGen loop, and measured at 120 K. The X-ray diffraction data were collected on an Agilent Technologies Supernova diffractometer, using Cu Kα radiation (λ=1.54184 Å). The *CrysAlisPro*[43] program package was used for cell refinements and data reductions. The structure was solved by a charge flipping method, using the *SUPERFLIP*[44] program. A multi-scan absorption correction based on equivalent reflections (*SADABS*)[45] was applied to the data. Structural refinement was carried out by using *SHELXL-2014*[46] with the *Olex2*[47] and *SHELXLE*[48] graphical user interfaces. In structure **9**, the NH and OH hydrogen atoms were located from the difference Fourier map and refined isotropically. Other hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms with C–H=0.98–1.00 Å, N–H=0.91 Å, and U_{iso}=1.2–1.5·U_{eq}(parent atom). The crystallographic details are summarized in Table S1 (see Supplementary data). Deposition numbers CCDC 1040500 and CCDC 1040501 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif].

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Supplementary data

^1H NMR and ^{13}C NMR copies of all compounds and X-ray crystallographic details are summarized in Table S1. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.019.

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