6-Spiro-1,4-diazepane-2,5-diones by Head-to-Tail N1/C2 Amide Bond Formation

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The synthesis of a series of 6-spiro-1,4-diazepane-2,5-diones containing an arylpropylamide moiety via head-to-tail cyclisation of a terminal amine and a terminal carboxylate ester is described. To induce ring closure of the dipeptide precursor, both lactamisation of the N4/C5 amide bond and N1/C2 amide bond were investigated. Whereas ring closure of the N4/C5 amide bond proved unsuccessful, ring closure of the N1/C2 amide bond was more viable. Furthermore, it was discovered that incorporation of a *N*,*N*-disubstituted amide bond in the peptide sequence was essential for cyclisation to occur.

Introduction

The exploration of privileged structures in drug discovery has gained significant popularity and relevance in recent years.[1] An important example of these privileged structures, the 1,4-benzodiazepine-2,5-diones, have been reported to possess a wide range of pharmacological activities.[2] Whereas many reports describe the synthesis of 1,4-benzodiazepine-2,5-diones,[3] few describe the synthesis of 1,4-diazepane-2,5-diones.[4,5]

Usually, 1,4-diazepane-2,5-diones are synthesized through head-to-tail cyclisation of the terminal amine and carboxylic acid of a linear dipeptide, consisting of an α- and a β-amino acid, using a carboxylate activating reagent. Unfortunately, the cyclisation reaction is sometimes accompanied with dimerisation of the dipeptide precursor and usually proceeds in low or moderate yields. Recently, Van Maarseveen and co-workers succeeded to improve the yield of 1,4-diazepane-2,5-dione formation using an intramolecular Staudinger ligation reaction.[4b] Remarkably, scarce examples have been reported in which diazepane formation was accomplished by direct lactamisation of the terminal ester and amine functional groups without conversion of the ester to an activated carboxylic acid followed by ring closure.[5]

As continuation of our research on the application of nitro- and cyanoalkenes in cycloaddition reactions leading to rigid arylethyl/propylamines and derivatives thereof,[6] we set out to study the preparation of compounds in which an arylpropylamide moiety is fixed within a 6-spiro-1,4-diazepane-2,5-dione **I** (Figure 1). These 6-spiro-1,4-diazepane-2,5-diones **I** were envisioned to arise from the linear dipeptides **II** or **III** via lactamisation of the N4/C5 or the N1/C2 amide bond (pathways A and B, Figure 1). In turn, precursor **II** and **III** can be obtained from the cyclic masked β-amino ester **IV** which can be prepared from 3-aryl-2-cyanoprop-2-enoates **V** using a [4+2] cycloaddition reaction. In this paper the structural requirements for a head-to-tail cyclisation reaction via pathway A or B to give 6-spiro-1,4-benzodiazepane-2,5-diones containing an arylpropylamide moiety are described.

Results/Discussion

Pathway A

To prepare 6-spiro-1,4-diazepane-2,5-diones according to the strategy outlined in Figure 1, methyl (*E*)-2-cyano-3-phenylprop-2-enoate (**1**) was reacted with an excess of 2,3-dimethylbuta-1,3-diene to give the cycloadduct **2** in quantitative yield (Scheme 1). Although compound **1** can be converted to a variety of five- or six-membered (hetero)cycles,[7] in this paper the reactivity of cycloadduct **2** was studied, because of a) the robustness of the resulting cycloadduct, b) the ease of purification, and c) the ease of characterization. The nitrile **2** was reduced using Raney nickel and hydrogen to give the amine **3** in quantitative yield.[8]

Fmoc-Gly-OH was coupled with the amine **3** using 1,3-diisopropylcarbodiimide and a catalytic amount of *N*-hydroxybenzotriazole to obtain the amide **4** in 98%. The Fmoc group was removed using THF/MeOH/sodium hydroxide to obtain the amine **6** in a yield of 80%.

Since the rate of cyclisation reactions is enhanced by the *gem*-dialkyl effect,[9] compound **7** was synthesized (Scheme 1). Compound **7** was obtained in a yield of 84% by coupling of the amine **3** with Fmoc-Aib-OH using 1,3-

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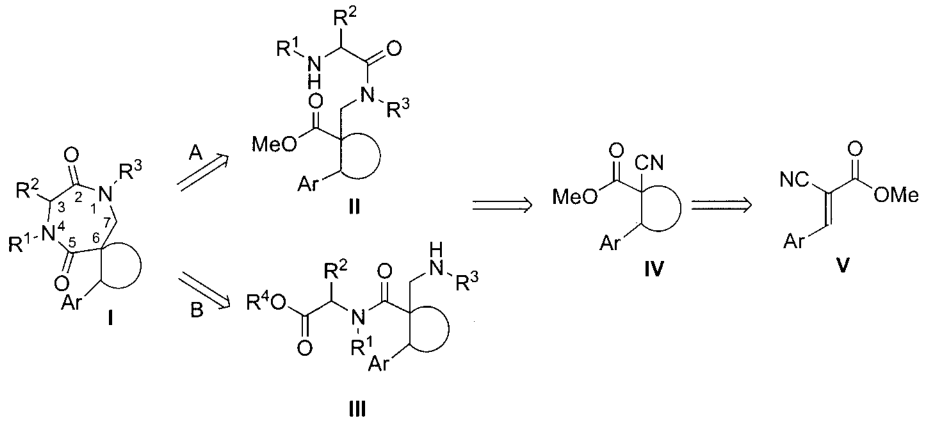
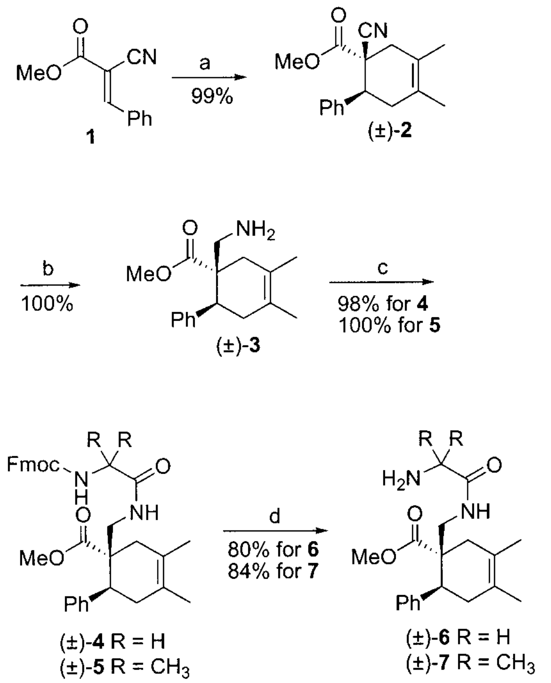


Figure 1. General synthetic strategy towards 6-spiro-fused 1,4-diazepane-2,5-diones



Scheme 1. Synthesis of amines **6** and **7**. Reagents and conditions: (a) 2,3-dimethylbuta-1,3-diene, reflux, 40 h; (b) Raney nickel, 1 bar H_2, 1 M NH_3/MeOH, room temp., 9 h; (c) Fmoc-Gly-OH, DIPC, HOBt, 0 °C, 15 min then room temp., 17 h; or Fmoc-Aib-OH, DIPC, HOBt, 0 °C, 15 min then room temp., 24 h (d) THF/MeOH/1 M NaOH, 10:2:1.5, room temp., 1 h; or piperidine, THF, room temp., 1 h

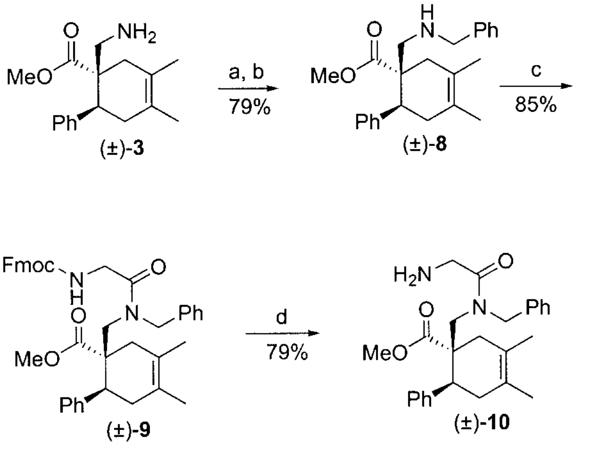
diisopropylcarbodiimide followed by removal of the Fmoc group under basic conditions.

A series of initial reactions was conducted in order to-synthesise 6-spiro-1,4-diazepane-2,5-diones. Unfortunately, reaction of neither the amine **6** nor **7** under thermal, acidic, basic, nor high-pressure conditions resulted in 6-spiro-1,4-diazepane-2,5-dione formation.

The failure of the amines **6** and **7** to react via head-to-tail cyclisation, might be caused by the preferred *trans* conformation of the *N*-monosubstituted amide bond which prevents the terminal amine group and ester group to come in close proximity.[10] To solve this problem a conformationally unbiased *N*,*N*-disubstituted amide bond was incorporated in the peptide sequence.[11] For this purpose, substitution of the amide bond with a benzyl group appeared to be the most versatile option since it has been demonstrated that, if desired, the benzyl group can be removed using several different procedures.[12]

To test this concept, the linear precursor **10** was synthesized according to the route depicted in Scheme 2. The amino ester **8** was obtained in a yield of 79% by reaction of the amine **3** with benzaldehyde, followed by reduction with sodium borohydride. The amino ester **8** was coupled with Fmoc-Gly-OH to obtain the protected amine **9**. The protecting group was removed using sodium hydroxide to obtain the amine **10** in a yield of 79%. Interestingly, NMR assignment of the compounds **9** and **10** was hampered by presence of two conformers in solution, which is indicative for a conformationally unbiased amide bond in the peptide sequence. Disappointingly, the cyclisation of compound **10** was not possible when using thermal conditions, basic conditions or high pressure conditions.

The chemical inertness, with respect to diazepane formation, of the compounds **6**, **7**, or **10**, is probably caused by

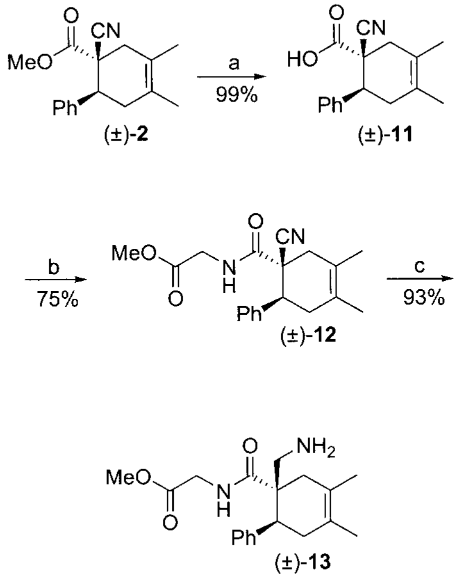


Scheme 2. Synthesis of amino ester **10**. Reagents and conditions: (a) benzaldehyde, $MgSO_4$, Et_2O, room temp., 1 h; (b) $NaBH_4$, MeOH, 0 °C then room temp., 14 h; (c) Fmoc-Gly-OH, DIPC, HOBt, 15 min, 0 °C, then **8**, room temp., 17 h; (d) THF/MeOH/1 M NaOH, 6:1:1, room temp., 1 h.

the lack of reactivity of the hindered carboxylate ester.[13] However, this problem can be circumvented by following pathway B, which involves lactamisation of an unhindered amine and ester group (Figure 1).

Pathway B

Hydrolysis of the ester **2** gave the acid **11** in nearly quantitative yield (Scheme 3). Upon coupling of **11** with glycine methyl ester hydrochloride using 1,3-diisopropylcarbodiimide, the amide **12** was obtained in 75%. After reduction of compound **12** with Raney nickel to obtain the amino ester **13**, a series of cyclisation reactions were attempted. However, again no cyclisation could be induced.



Scheme 3. Synthesis of amino ester **13**. Reagents and conditions: (a) THF/MeOH/LiOH, 2:1:1, room temp., 1 h; (b) DIPC, HOBt, THF, 0 °C, 15 min, then Et_3N, H-Gly-OMe·HCl, room temp., 48 h; (c) Raney nickel, 1 bar H_2, 1 м NH_3/MeOH, 4 h.

To favour the diazepane formation, a *N*,*N*-disubstituted amide bond was incorporated in the dipeptide sequence (Scheme 4). For this reason, the acid **11** was coupled with *N*-benzylglycine methyl ester. Instead of using 1,3-diisopropylcarbodiimide as coupling reagent, the acid **11** was treated with oxalyl chloride to obtain the corresponding acid chloride.[14] The acid chloride was coupled with *N*-benzylglycine methyl ester in the presence of an excess of triethylamine to yield the desired amide **14** in 77%.

Unexpectedly, treatment of compound **14** with Raney nickel and hydrogen in ammonia/methanol did not yield the desired amine **15**, but in stead compound **16** was formed. Further research revealed that compound **16** was also formed in the absence of Raney nickel by basic treatment of the nitrile **14**. When it was attempted to crystallise enamine **16** by slow evaporation of a solution of **16** in dichloromethane/heptane, compound **17** was obtained in a yield of 63%.[15] The structure of compound **17** was determined with X-ray crystallography (Figure 2).[16]

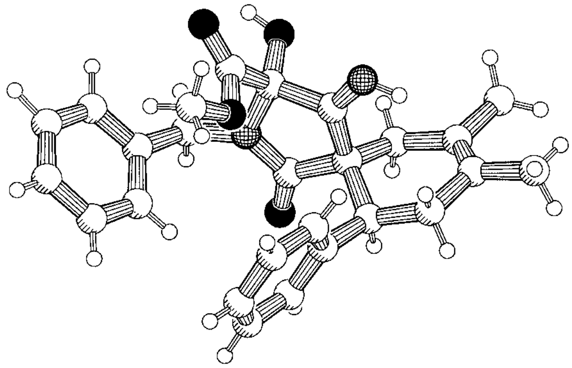
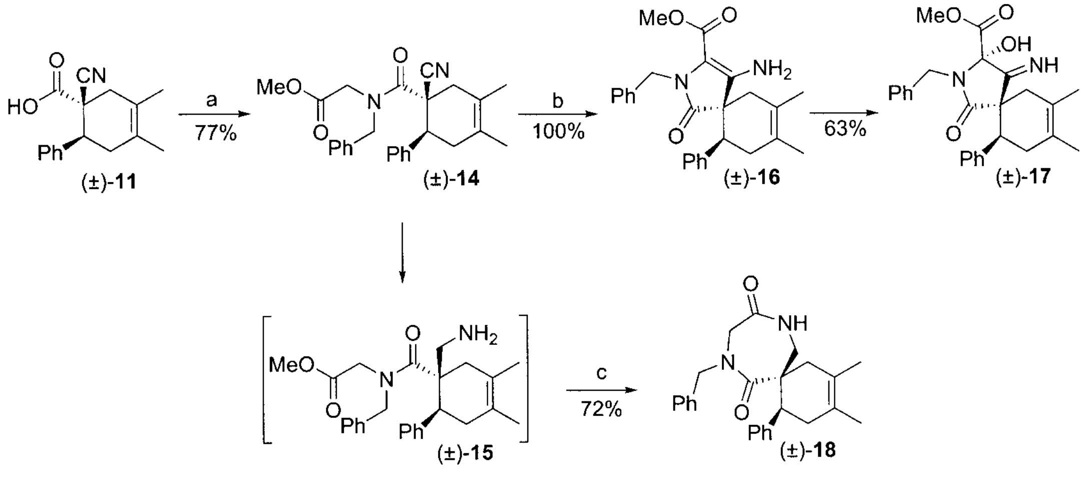


Figure 2. X-ray structure of compound **17**[17]

To prevent the formation of compound **16**, the reduction of the nitrile **14** was performed under nonbasic reaction conditions. Surprisingly, reaction of the nitrile **14** with Raney nickel under 50 bar of hydrogen at 80 °C, did not

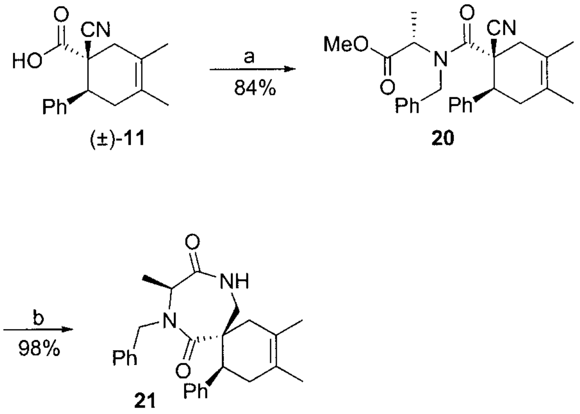


Scheme 4. Reagents and conditions: (a) $(COCl)_2$, DMF, THF, 0 °C, 2 h, then Et_3N, Bn-Gly-OMe, CH_2Cl_2, room temp., 20 h; (b) Et_3N, MeOH, room temp., 20 h; (c) Raney nickel, 50 bar H_2, 80 °C, 17 h.

yield the amine **15** but instead spontaneous cyclisation occurred to give the diazepane **18** in a yield of 72%.

Stimulated by these results, we were interested to investigate diazepane formation for a more hindered precursor. For this purpose, the acid **11** was coupled with *N*-benzylalanine methyl ester (**19**) using oxalyl chloride to yield the compound **20** as a mixture of two diastereoisomers (Scheme 5). Upon reduction of the nitrile group spontaneous cyclisation occurred leading to the diazepane **21** as a mixture of two diastereoisomers in a yield of 98%.

Next, H-Pro-O*t*Bu was coupled with the acid **11** to give the diastereoisomers **22a** and **22b** in a yield of 93% (Scheme 6). Then the nitrile of diastereoisomers **22a** and **22b** was hydrogenated using Raney nickel. Whereas the reduction of diastereoisomer **22a** gave in good yield the diazepane (–)-**23a**, diastereoisomer **22b** yielded in 85% the amine **24**.[18] To obtain the diazepane **23b**, the amine **24** was heated in the presence of triethylamine in methanol. After 3 days the reaction was finished and the products (+)-**23b** and (+)-**23a** were formed in a ratio of 3.5:1, respectively. To prevent epimerization of the α-proton of proline and thus formation of diazepane (+)-**23a**, the cyclisation of amine **24** was attempted under nonbasic conditions. Refluxing a solution of amine **24** in toluene for 5 days gave the diazepane (+)-**23b** in a yield of 88%. The crystal structures of both the diazepanes (–)-**23a** and (+)-**23b** were determined by X-ray structure analysis.[15]



Scheme 5. Only the diastereoisomers resulting from reaction of (1*R*,6*S*)-**11** with alanine are shown. Reagents and conditions: (a) $(COCl)_2$, DMF, THF, 0 °C, 2 h, then Et_3N, Bn-Ala-OMe, CH_2Cl_2, room temp., 20 h; (b) Raney nickel, 20 bar H_2, 1 M NH_3/MeOH, room temp., 22 h

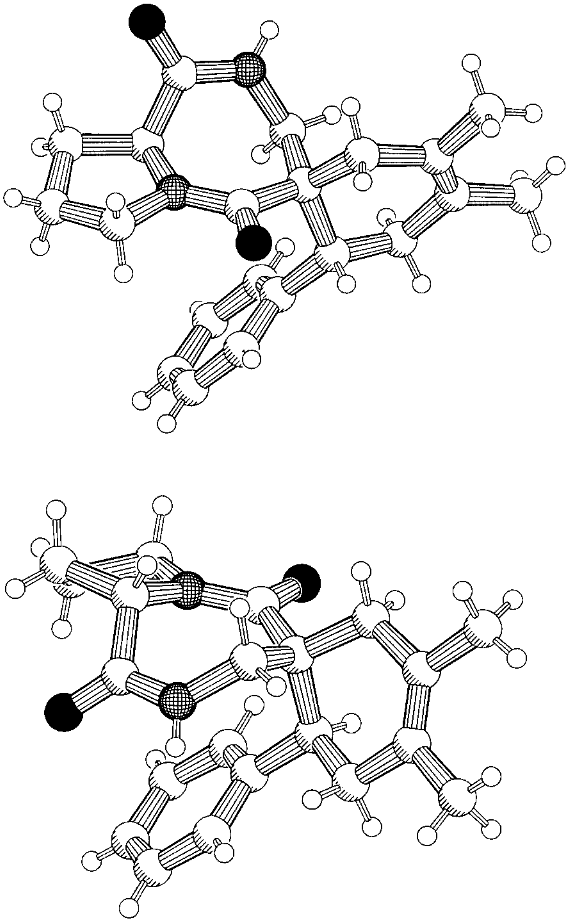
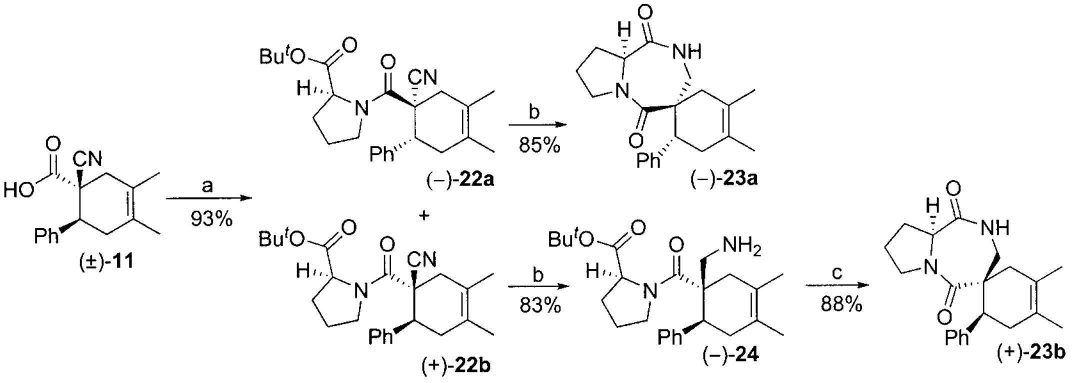


Figure 3. X-ray structure of (–)-**23a** and (+)-**23b**[16]

Conclusions

The present study has established an efficient synthesis of spiro-1,4-diazepane-2,5-diones via a head-to-tail lac-



Scheme 6. Reagents and conditions: (a) $(COCl)_2$, DMF, THF, 0 °C, 2 h, then Et_3N, H-Pro-O*t*Bu, CH_2Cl_2, room temp., 17 h; (b) Raney nickel, 40 bar H_2, 1 M NH_3/MeOH, room temp., 17 h; (c) toluene, reflux, 5 d.

tamisation of the terminal NH_2 and the terminal carboxylate ester of a dipeptide consisting of a cyclic β-amino acid and an α-amino acid. Whereas ring closure of N4/C5 amide bond (pathway A) proved unsuccessful, ring closure of the N1/C2 amide bond (pathway B) was more viable (Figure 1). In addition, it was observed that for cyclisation to occur, it is essential that a conformationally unbiased *N*,*N*-disubstituted amide bond is incorporated in the linear dipeptide sequence. Currently research is in progress to translate the approach outlined in this paper to the solid phase.

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DMX-300 spectrometer. Chemical shifts are reported in parts per million downfield relative to tetramethylsilane (δ = 0.00 ppm) for ^{1}H NMR and relative to $CDCl_3$ (δ = 77.16 ppm) for ^{13}C NMR spectra. Optical rotations were measured with a Perkin–Elmer 241 polarimeter, using concentrations (*c*) in g/100 mL. Mass spectra were recorded with a VG7070E double-focusing mass spectrometer using EI and CI modes. IR spectra were recorded with an Anadis Thermo Mattson IR300 spectrometer. Elemental analysis was carried out with a Carlo Erba Instruments CHNSO EA 1108 element analyzer. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-254 plates. Spots were visualised with UV or by dipping the TLC plate into a 6.2% aqueous sulfuric acid solution containing ammonium molybdate (42 g/L) and ceric ammonium sulfate (3.6 g/L) followed by charring. Column chromatography was carried out with Acros silica gel (0.035–0.070mm). Solid-phase extractions were performed using isolute® SCX-2 columns which were purchased from Argonaut. Melting points were determined with a Buchi B-545 melting point apparatus and are uncorrected. When necessary, reactions were performed under standard Schlenk conditions. Ethyl acetate and heptane were distilled prior to use. Tetrahydrofuran was dried by distillation from sodium and benzophenone. Raney® 2800 nickel was purchased from Aldrich and was extensively washed with methanol prior to use.

Literature Preparations: Methyl (*E*)-2-cyano-3-phenylprop-2-enoate (**1**) was prepared by condensation of benzaldehyde with methyl cyanoacetate in the presence of piperidine in ethanol solution.[19] *N*-benzylglycine methyl ester and *N*-benzylalanine methyl ester{$[\alpha]_D^{20}$ = −40.6 (*c* = 1.0, methanol), ref.[20] $[\alpha]_D^{21}$ = –41.0 (*c* = 1.8, methanol)} were prepared by reductive amination of the corresponding amino acid methyl ester hydrochloride.[21]

(±)-Methyl (1*R*,6*S*)-1-Cyano-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (2): A mixture of cyanoalkene **1** (11.9 g, 63.6 mmol) and 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide (100 mg) was heated to reflux in 2,3-dimethylbuta-1,3-diene (25.0 mL, 221 mmol). After 40 h the reaction mixture was evaporated to dryness in vacuo. The crude product was crystallised from a small amount of hot ethanol to give the cycloadduct **2** (15.6 g, 90%) as white crystals. A second crop (1.60 g, 9%) was obtained by concentration of the filtrate and crystallisation from hot ethanol. Analytical data were in agreement with literature.[23]

(±)-Methyl (1*R*,6*S*)-1-(Aminomethyl)-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (3): Cycloadduct **2** (870 mg, 3.23 mmol) was dissolved in 1 M ammonia/methanol (20 mL). Raney nickel (spoontip) was added and the reaction mixture was stirred under hydrogen (1 bar) for 9 h at room temperature. The reaction mixture was filtered through Celite® and the filtrate was concentrated to dryness to yield the amine **3** (882 mg, 100%). The crude product was sufficiently pure for further reactions and was used as such. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (br. s, 2 H), 1.66 (s, 3 H), 1.72 (s, 3 H), 1.69 (br. d, *J* = 18.3 Hz, 1 H), 1.98 (br. d, *J* = 17.1 Hz, 1 H), 2.37–2.56 (m, 2 H), 2.46 (d, *J* = 12.9 Hz, 1 H), 2.78 (d, *J* = 12.9 Hz, 1 H), 3.43 (dd, *J* = 5.4 Hz, 5.4 Hz, 1 H), 3.64 (s, 3 H), 7.15–7.28 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 19.1, 34.2, 35.8, 43.4, 46.1, 51.7, 52.2, 124.2, 124.7, 126.7, 128.2, 128.6, 142.5, 176.2 ppm. HRMS calcd. for $[M]^+$ ($C_{17}H_{23}N_1O_2$): 273.1729; found 273.1726. IR (film): ṽ = 2907, 1727, 1455, 1433, 1200, 703 cm^{-1}.

(±)-Methyl (1*R*,6*S*)-1-{[(2-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}acetyl)amino]methyl}-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (4): Fmoc-Gly-OH (1.26 g, 4.23 mmol) was dissolved in tetrahydrofuran (10 mL) and the solution was cooled to 0 °C. The solution was stirred and 1,3-diisopropylcarbodiimide (691 µL, 4.41 mmol) and *N*-hydroxybenzotriazole (10.0 mg) were added. After 15 minutes, a solution of the amine **3** (1.05 g, 3.84 mmol) in tetrahydrofuran (6 mL) was added dropwise to the reaction mixture. After addition of the amine, the reaction mixture was slowly warmed to room temperature. After 17 h the solvents were evaporated and the dry residue was dissolved in dichloromethane. The organic layer was washed once with both saturated sodium hydrogen carbonate and 0.5 N potassium hydrogen sulfate. The organic layer was dried (sodium sulfate), filtered and the solvents were evaporated to dryness. The crude product was purified using column chromatography (CH_2Cl_2/MeOH, 50:1) to give the amide **4** (2.10 g, 98%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 3 H), 1.68 (s, 3 H), 1.93 (d, *J* = 17.1 Hz, 1 H), 2.24 (dd, *J* = 6.0 Hz, 18.0 Hz, 1 H), 2.39 (dd, *J* = 8.4 Hz, 18.0 Hz, 1 H), 2.56 (d, *J* = 17.1 Hz, 1 H), 3.25 (dd, *J* = 4.5 Hz, 13.2 Hz, 1 H), 3.41 (dd, *J* = 6.0 Hz, 8.4 Hz, 1 H), 3.56 (s, 3 H), 3.61 (dd, *J* = 7.8 Hz, 13.2 Hz, 1 H), 3.71–3.79 (m, 2 H), 4.19 (t, *J* = 6.9 Hz, 2 H), 4.37 (d, *J* = 6.9 Hz, 1 H), 5.33 (br. s, 1 H), 6.16 (br. s, 1 H), 7.10–7.40 (m, 7 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.54 (d, *J* = 7.2 Hz, 2 H), 7.72 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.3, 34.9, 36.2, 40.3, 44.9, 47.3, 51.1, 52.2, 67.4, 120.0, 123.5, 124.1, 125.0, 127.0, 127.1, 127.7, 128.3, 128.5, 141.0, 141.2, 143.6, 168.5, 175.7. MS (EI): *m/z* (%) = 552 (7) $[M]^+$, 330 (27) $[M - Fmoc]^+$, 178 (100). HRMS calcd. for $[M]^+$ ($C_{34}H_{36}N_2O_5$): 552.2624; found 552.2628. IR (film): ṽ = 2910, 1718, 1671, 1519, 1446, 1230, 906, 759, 728, 707 cm^{-1}.

(±)-Methyl (1*R*,6*S*)-1-{[(2-Aminoacetyl)amino]methyl}-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (6): The protected amine **4** (272 mg, 494 µmol) was dissolved in a mixture of tetrahydrofuran (10 mL), methanol (2 mL) and 1 M NaOH/H_2O (1.5 mL). The reaction mixture was stirred at room temperature for 1 hour and the reaction was quenched with acetic acid (90 µL). The reaction was concentrated to dryness in vacuo and the residue was dissolved in dichloromethane. The organic layer was washed with saturated sodium hydrogen carbonate. The organic layer was dried (sodium sulfate), filtered and the solvents evaporated in vacuo. The crude product was subjected to solid-phase extraction using an isolute® SCX-2 column. The crude product was loaded on the column dissolved in dimethylformamide. The product was eluted from the column using first methanol and then 1 M ammonia/methanol. The amine **6** (130 mg, 80%) was obtained as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (br. s, 2 H), 1.68 (s, 6 H), 1.93 (d, *J* = 16.7 Hz, 1 H), 2.27–2.39 (m, 2 H), 2.56 (d, *J* = 16.7 Hz, 1 H), 3.23 (dd, *J* = 4.8 Hz, 13.2 Hz, 1 H), 3.23 (dd, *J* = 5.0 Hz, 13.0 Hz, 1 H), 3.26 (s, 2 H), 3.42–3.52 (m, 2 H), 3.61 (s, 3 H), 7.10–7.28 (m, 5 H), 7.37 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.3, 35.3, 35.7, 41.0, 44.4, 44.9, 51.0, 52.1, 123.7, 124.2, 126.9, 128.2, 128.5, 141.4, 172.3, 175.5 ppm. HRMS calcd. for $[M]^+$ ($C_{19}H_{26}N_2O_3$): 330.1942; found 330.1944. IR (film): $\tilde{\nu}$ = 2907, 1722, 1666, 1524, 1433, 1225, 1204, 1126, 1100, 728, 703 cm^{-1}.

(±)-Methyl (1*R*,6*S*)-1-{[(2-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-2-methylpropanoyl)amino]methyl}-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (5): To a solution of 2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-methylpropanoic acid (Fmoc-Aib-OH) (292 mg, 897 µmol) in tetrahydrofuran (1 mL) at 0 °C was added 1,3-diisopropylcarbodiimide (147 µL, 937 µmol) and *N*-hydroxybenzotriazole (10.0 mg). The mixture was stirred for 15 minutes before a solution of the amine **3** (223 mg, 816 µmol) in tetrahydrofuran (3 mL) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 24 h. After evaporation of the solvent, the residue was dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate and 0.5 N potassium hydrogen sulfate. The organic layer was dried with sodium sulfate, filtered, and the solvents evaporated in vacuo. The crude product was purified using column chromatography (EtOAc/heptane, 2:5). The product **5** (474 mg, 100%) was obtained as a white foam. R_f (EtOAc/heptane, 2:5) = 0.12. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 1.47 (s, 3 H), 1.66 (s, 3 H), 1.68 (s, 3 H), 1.99 (d, *J* = 16.8 Hz, 1 H), 2.24 (dd, *J* = 6.0 Hz, 17.7 Hz, 1 H), 2.37 (dd, *J* = 8.1 Hz, 17.7 Hz, 1 H), 2.51 (br. d, *J* = 16.8 Hz, 1 H), 3.17 (dd, *J* = 4.2 Hz, 13.5 Hz, 1 H), 3.42 (dd, *J* = 6.0 Hz, 8.1 Hz, 1 H), 3.51 (s, 3 H), 3.66 (dd, *J* = 8.1 Hz, 13.5 Hz, 1 H), 4.16 (t, *J* = 6.6 Hz, 1 H), 4.34 (d, *J* = 6.6 Hz, 2 H), 5.33 (br. s, 1 H), 6.46 (br. s, 1 H), 7.12–7.39 (m, 7 H), 7.32–7.38 (m, 2 H), 7.53–7.56 (m, 2 H), 7.72 (d, *J* = 7.5 Hz, 2 H) ppm. MS (EI): *m/z* (%) = 580 (8) $[M]^+$, 549 (1) $[M - OCH_3]^+$, 520 (1) $[M - COOCH_3]^+$, 384 (29), 178 (69) [9-methylfluor-9-ylium]$^+$, 165 (100). HRMS calcd. for $[M]^+$ ($C_{36}H_{40}N_2O_5$): 580.2937; found 580.2936. IR (film): $\tilde{\nu}$ = 2907, 1718, 1662, 1519, 1446, 1247, 1087, 906, 737 cm^{-1}.

(±)-Methyl (1*R*,6*S*)-1-{[(2-Amino-2-methylpropanoyl)amino]methyl}-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (7): The protected amine **5** (439 mg, 756 µmol) was dissolved in tetrahydrofuran/piperidine, 4:1 (5 mL) and the reaction mixture was stirred at room temperature. After 1 hour the reaction mixture was evaporated to dryness and the crude product was subjected to solid-phase extraction using an isolute® SCX-2 column. The desired amine **7** (229 mg, 84%) was obtained as a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 6 H), 1.67 (s, 6 H), 1.90 (d, *J* = 16.5 Hz, 1 H), 2.28–2.35 (m, 2 H), 2.53 (br. d, *J* = 16.5 Hz, 1 H), 3.13 (dd, *J* = 4.8 Hz, 13.5 Hz, 1 H), 3.44 (d, *J* = 8.1 Hz, 1 H), 3.48 (d, *J* = 8.1 Hz, 1 H), 3.60 (s, 3 H), 7.13–7.27 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.4, 29.5, 29.6, 35.3, 35.5, 41.3, 44.4, 51.0, 52.1, 55.0, 123.8, 124.2, 126.9, 128.2, 128.6, 141.5, 175.5, 177.2 ppm. HRMS calcd. for $[M]^+$ ($C_{21}H_{30}N_2O_3$): 358.2257; found 358.2257. IR (film): $\tilde{\nu}$ = 2911, 1722, 1662, 1511, 1433, 1217, 1096, 914, 733, 703 cm^{-1}.

(±)-Methyl (1*R*,6*S*)-1-[(Benzylamino)methyl]-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (8): The amine **3** (1.29 g, 4.70 mmol) and benzaldehyde (549 mg, 5.17 mmol) were dissolved in diethyl ether (2 mL). Magnesium sulfate (1.0 g) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered to remove the magnesium sulfate and the filtrate was evaporated to dryness. The crude imine was dissolved in methanol (5 mL). The solution was stirred at 0 °C and sodium borohydride (190 mg, 5.02 mmol) was added in small portions to the reaction mixture to prevent excess foaming of the reaction mixture. After addition of all sodium borohydride the reaction mixture was allowed to reach room temperature and was stirred for 14 h. The reaction was quenched with acetic acid (300 µL) and the reaction mixture was concentrated in vacuo. The product was dissolved in dichloromethane and the organic layer was washed once with saturated sodium hydrogen carbonate. The water layer was then extracted twice more with dichloromethane. The combined organic layers were dried (magnesium sulfate), filtered, and the solvent was removed under vacuo. The crude product was purified using column chromatography (EtOAc/heptane, 1:7) to give the secondary amine **8** (1.36 g, 79%) as a clear oil that solified upon storage in the fridge. M.p. (heptane) 63 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 1 H), 1.63 (s, 3 H), 1.68 (s, 3 H), 1.99–2.18 (m, 2 H), 2.33–2.54 (m, 2 H), 2.36 (d, *J* = 11.4 Hz, 1 H), 2.63 (d, *J* = 11.4 Hz, 1 H), 3.45 (dd, *J* = 4.8 Hz, 6.6 Hz, 1 H), 3.47 (s, 3 H), 3.64 (s, 2 H), 7.12–7.28 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.5, 35.3, 36.1, 43.7, 51.2, 52.0, 53.2, 54.4, 124.39, 124.43, 126.6, 126.7, 127.9, 128.0, 128.1, 128.7, 140.5, 142.7, 176.2 ppm. MS (EI): *m/z* (%) = 363 (39) $[M]^+$, 332 (1) $[M - OCH_3]^+$, 304 (1) $[M - CH_3OOC]^+$, 197 (22) $[M - CH_3OOC - NH_2CH_2Ph]^+$, 120 (100) $[CH_2NHCH_2Ph]^+$, 91 (93) [tropylium]$^+$. HRMS calcd. for $[M]^+$ ($C_{24}H_{29}NO_2$): 363.2198; found 363.2198. IR (film): $\tilde{\nu}$ = 2911, 1722, 1493, 1455, 1195, 1126, 1100, 737, 703 cm^{-1}. $C_{24}H_{29}NO_2$ (363.5): calcd. C 79.30, H 8.04, N 3.85, found C 79.25, H 8.16, N 3.92.

(±)-Methyl (1*R*,6*S*)-1-{[Benzyl(2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino)acetyl)amino]methyl}-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (9): Fmoc-Gly-OH (930 mg, 3.13 mmol) was dissolved in tetrahydrofuran (5 mL). The solution was cooled and 1,3-diisopropylcarbodiimide (513 µL, 3.28 mmol) and *N*-hydroxybenzotriazole (10.0 mg) were added to the reaction mixture. After 15 minutes, a solution of the amine **8** (1.08 g, 2.98 mmol) in tetrahydrofuran (5 mL) was added dropwise to the reaction mixture. The reaction was allowed to reach room temperature. After 17 h the solvent was removed, and the residue was dissolved in dichloromethane. The organic layer was washed with saturated sodium hydrogen carbonate and 0.5 N potassium hydrogen sulfate. The organic layer was dried (sodium sulfate), filtered, and the solvents evaporated to dryness. The crude product was purified using column chromatography (EtOAc/heptane, 1:3) to give the protected amine **9** (1.71 g, 85%) as a white solid. Compound **9** is present as a mixture of two conformers (a/b) in a ratio of 0.8:0.2 respectively in $CDCl_3$. Selected signals[24] ^1H NMR (300 MHz, $CDCl_3$): δ (a/b) = 1.65 (s, 3 H, 3 H), 1.74 (s, 3 H, 3 H), 1.92−2.27 (m, 2 H, 2 H), 2.33−2.72 (m, 2 H, 2 H), 3.15 (d, *J* = 15.9 Hz, 1 H), 3.26−3.47 (m, 2 H, 1 H), 4.10−4.40 (m, 5 H, 4 H), 4.80 (d, *J* = 15.3 Hz, 1 H), 6.85−7.77 (m, 18 H, 18 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ (a) = 19.1, 19.8, 33.8, 36.6, 43.2, 44.2, 47.4, 50.8, 51.6, 52.6, 53.3, 67.2, 119.9, 124.2, 125.1, 125.9, 127.0, 127.6, 127.7, 128.4, 128.9, 129.0, 135.5, 141.2, 142.2, 143.75, 143.82, 155.8, 169.3, 175.6 ppm. MS (EI): *m/z* (%) = 642 (0.2) $[M]^+$, 420 (10) $[M - Fmoc]^+$, 390 (54) $[M - Fmoc - NH_2CH_2]^+$, 91 (100). HRMS calcd. for $[M]^+$ ($C_{41}H_{42}N_2O_5$): 642.3094; found 642.3095. IR (film): $\tilde{\nu}$ = 3062, 2898, 1722, 1658, 1495, 1450, 1265, 1210, 1048, 759, 735, 703 cm^{-1}.

(±)-Methyl (1*R*,6*S*)-1-{[(2-Aminoacetyl)(benzyl)amino]methyl}-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylate (10): The protected amine **9** (1.68 g, 2.61 mmol) was dissolved in a mixture of tetrahydrofuran (30 mL), methanol (5 mL) and 1 M NaOH/H_2O (5 mL). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and the residue was partitioned between a solution of saturated sodium hydrogen carbonate and dichloromethane. The organic layer was isolated and the water layer was extracted twice with dichloromethane. The combined organic layers were dried (magnesium sulfate), filtered, and the solvents evaporated to dryness. The crude product was purified using column chromatography (CH_2Cl_2/MeOH, 9:1) to yield the amino ester **10** (870 mg, 79%) as a white foam. Compound **10** is present as a mixture of two conformers (a/b) in a ratio of 0.8:0.2 respectively in $CDCl_3$. Selected signals[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ (a/b) = 1.64 (s, 3 H), 1.74 (s, 3 H), 1.86–2.20 (m, 2 H, 2 H), 2.32–2.59 (m, 2 H, 2 H), 3.97 (d, J = 15.0 Hz, 1 H), 4.27 (s, 2 H), 4.96 (d, J = 15.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = (a) 19.3, 19.9, 34.0, 36.8, 43.9, 44.3, 51.0, 51.8, 52.7, 53.9, 124.3, 125.4, 125.9, 127.0, 127.6, 128.5, 129.1, 136.5, 142.5, 174.3, 175.8 ppm. MS (EI): m/z (%) = 420 (40) $[M]^+$, 390 (47) $[M - NHCH_2]^+$, 362 (9) $[M - Gly]^+$, 91 (100). HRMS calcd. for $[M]^+$ ($C_{26}H_{32}N_2O_3$): 420.2413; found 420.2412. IR (film): $\tilde{\nu}$ = 2909, 1727, 1657, 1494, 1433, 1087, 735, 703 cm^{-1}.

(±)-(1*R*,6*S*)-1-Cyano-3,4-dimethyl-6-phenylcyclohex-3-ene-1-carboxylic Acid (11): The ester **2** (2.08 g, g7.74 mmol) was stirred in tetrahydrofuran (20 mL), methanol (10 mL), and 1.25 M LiOH/H_2O (10 mL) at room temperature. After one hour the reaction was quenched with acetic acid (750 µL). The reaction mixture was concentrated in vacuo. The residue was diluted with 0.5 N potassium hydrogen sulfate and the resulting solution was extracted three times with diethyl ether. The combined organic layers were dried (magnesium sulfate), filtered, and the solvents evaporated to dryness to obtain the acid **11** (1.95 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 6 H), 2.25 (dd, J = 5.1 Hz, 17.3 Hz, 1 H), 2.49 (d, J = 16.8 Hz, 1 H), 2.62–2.76 (m, 1 H), 2.84 (d, J = 16.8 Hz, 1 H), 3.21 (dd, J = 5.1 Hz, 12.0 Hz, 1 H), 7.22–7.36 (m, 5 H), 8.88 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.3, 36.8, 41.3, 46.0, 50.9, 118.0, 120.7, 126.7, 128.1, 128.8, 138.7, 174.1 ppm. HRMS calcd. for $[M]^+$ ($C_{16}H_{17}NO_2$): 255.1259; found 255.1259. IR (film): $\tilde{\nu}$ = 2910, 2254, 1718, 906, 733, 703 cm^{-1}.

(±)-Methyl 2-({[(1*R*,6*S*)-1-Cyano-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}amino)acetate (12): The acid **11** (1.00 g, 3.71 mmol) and *N*-hydroxybenzotriazole (10.0 mg) were dissolved in tetrahydrofuran (5 mL). While stirring at 0 °C, 1,3-diisopropylcarbodiimide (640 µL, 4.09 mmol) was added. After 15 minutes, triethylamine (432 mg, 4.27 mmol) was added to the reaction mixture. Next, glycine methyl ester hydrogenchloride (512 mg, 4.09 mmol) was added in small portions to the reaction mixture. After 3 h the reaction mixture was slowly warmed to room temperature. After 48 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane and the organic layer was washed once with saturated sodium hydrogen carbonate and once with 0.5 N potassium hydrogen sulfate. The water layers were extracted two times with dichloromethane. The combined organic layers were dried (magnesium sulfate), filtered, and the solvents evaporated to dryness. The crude product was purified using column chromatography (EtOAc/heptane, 1:4) to obtain the amide **12** (903 mg, 75%). R_f (EtOAc/heptane, 1:4) = 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 6 H), 2.24 (dd, J = 5.1 Hz, 18.6 Hz, 1 H), 2.38 (d, J = 17.3 Hz, 1 H), 2.68–2.79 (m, 1 H), 3.02 (d, J = 17.3 Hz, 1 H), 3.28 (dd, J = 5.1 Hz, 12.3 Hz, 1 H), 3.50 (dd, J = 4.8 Hz, 18.0 Hz, 1 H), 3.63 (s, 3 H), 3.86 (dd, J = 5.4 Hz, 18.0 Hz, 1 H), 6.44 (br. s, 1 H), 7.18–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 19.2, 36.3, 40.9, 41.9, 45.8, 51.2, 52.7, 120.2, 121.5, 125.9, 127.9, 128.1, 128.6, 139.1, 167.0, 168.8 ppm. HRMS calcd. for $[M]^+$ ($C_{19}H_{22}N_2O_3$): 326.1631; found 326.1630. IR (film): $\tilde{\nu}$ = 3382, 1748, 1679, 1524, 1433, 1368, 1208, 703 cm^{-1}.

(±)-Methyl 2-({[(1*R*,6*S*)-1-(Aminomethyl)-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}amino)acetate (13): The nitrile **12** (111 mg, 340 µmol) was dissolved in 1 M NH_3/MeOH (7 mL). After addition of a catalytic amount of Raney nickel it was stirred at room temperature under hydrogen (1 bar) for 4 h and then filtered through Celite®. The filtrate was evaporated to dryness. The crude product was subjected to solid-phase extraction using an isolute® SCX-2 column to obtain the desired amine **13** (105 mg, 93%) as an oil. R_f (CH_2Cl_2/MeOH, 9:1) = 0.26. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 2 H), 1.69 (s, 3 H), 1.78 (s, 3 H), 1.97 (d, J = 17.7 Hz, 1 H), 2.13 (d, J = 17.7 Hz, 1 H), 2.35 (d, J = 12.8 Hz, 1 H), 2.38–2.54 (m, 2 H), 2.88 (d, J = 12.8 Hz, 1 H), 3.39 (dd, J = 3.9, J = 6.9 Hz, 1 H), 3.71 (s, 3 H), 3.87 (dd, J = 4.8, J = 18.0 Hz, 1 H), 4.10 (dd, J = 6.0 Hz, 18.0 Hz, 1 H), 7.12–7.28 (m, 5 H), 7.61 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 19.6, 35.3, 36.4, 41.9, 44.1, 47.6, 50.4, 52.6, 123.7, 126.7, 128.3, 128.9, 142.9, 170.7, 176.8 ppm. HRMS calcd. for $[M]^+$ ($C_{19}H_{26}N_2O_3$): 330.1944; found 330.1942. IR (film): $\tilde{\nu}$ = 707, 728, 910, 1208, 1364, 1437, 1524, 1645, 1740, 2910 cm^{-1}

(±)-Methyl 2-(Benzyl-{[(1*R*,6*S*)-1-cyano-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}amino)acetate (14): The acid **11** (457 mg, 1.79 mmol) was dissolved in tetrahydrofuran (4 mL). A few drops of dimethylformamide were added and the reaction mixture was cooled to 0 °C. Oxalyl chloride (312 µL, 3.58 mmol) in tetrahydrofuran (1.5 mL) was added dropwise and the reaction mixture was stirred for 1 hour. The reaction mixture was evaporated to dryness in vacuo and the residue was dissolved in dichloromethane (5 mL). The solution was cooled to 0 °C and triethylamine (498 µL, 3.58 mmol) in dichloromethane (2 mL) was added dropwise. Next, *N*-benzylglycine methyl ester (337 mg, 1.88 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was allowed to reach room temperature. After 3 h the reaction mixture was diluted with dichloromethane and the organic layer was washed with saturated sodium hydrogen carbonate and 1 M ammonium chloride. The water layers were extracted twice more with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered, and the solvents evaporated to dryness. The crude product was purified using column chromatography (EtOAc/heptane, 1:4) to give the amide **14** (573 mg, 77%) as an oil. The amide is present as a mixture of conformers a/b in a ratio of 0.53:0.47 respectively in $CDCl_3$. Selected signals[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ = (a/b) 1.74 (s, 6 H, 6 H), 2.18–2.39 (m, 1 H, 1 H), 2.43–2.85 (m, 3 H, 3 H), 3.02 (br. s, J = 16.1 Hz, 1 H), 3.18–3.77 (m, 5 H, 6 H), 3.80–4.03 (m, 1 H, 1 H), 4.25 (br. d, J = 18.2 Hz, 1 H), 4.62 (br. d, J = 15.5 Hz, 1 H), 4.85–5.14 (m, 1 H, 1 H). 6.75–7.56 (m, 10 H, 10 H). MS (EI): m/z (%) = 416 (36) $[M]^+$, 385 (2) $[M - OMe]^+$, 357 (5) $[M - COOMe]^+$, 325 (21) $[M - benzyl]^+$, 210 (46), 91 (100). HRMS calcd. for $[M]^+$ ($C_{26}H_{28}N_2O_3$): 416.2100; found 416.2101. IR (film): $\tilde{\nu}$ = 2907, 2252, 1754, 1647, 1496, 1433, 1365, 1208, 959, 912, 770, 737, 702, 648 cm^{-1}.

Preparation of Compounds 16 and17: The nitrile **14** (28.9 mg, 69.4 µmol) was dissolved in 1 M triethylamine/methanol (1 mL) and stirred at room temperature. After 20 h the reaction mixture was concentrated to dryness to obtain the compound **16** (28.9 mg, 100%) as a white solid. Upon attempted crystallization of compound **16** from dichloromethane/heptane, compound **17** (18.1 mg, 63%) was obtained.

(±)-Methyl (5*R*,10*S*)-4-Amino-2-benzyl-7,8-dimethyl-1-oxo-10-phenyl-2-azaspiro[4.5]deca-3,7-diene-3-carboxylate (16): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 6 H), 2.08 (d, J = 17.1 Hz, 1 H), 2.38 (dd, J = 6.3 Hz, 18.9 Hz, 1 H), 2.65–2.83 (m, 1 H), 2.91 (d, J = 17.1 Hz, 1 H), 3.46 (dd, J = 6.3 Hz, 12.0 Hz, 1 H), 3.49 (s, 3 H), 4.43 (d, J = 15.3 Hz, 1 H), 4.85 (d, J = 15.3 Hz, 1 H), 5.85 (s, 2 H), 6.24–6.33 (m, 2 H), 6.93–7.08 (m, 3 H), 7.16–7.32 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.2, 36.5, 39.8, 45.2, 45.9, 50.6, 53.5, 103.2, 124.3, 126.0, 126.2, 126.2, 127.3, 127.9, 128.3, 128.6, 137.9, 139.7, 153.1, 162.0, 173.4 ppm. HRMS calcd.

for $[M]^+$ ($C_{26}H_{28}N_2O_3$): 416.2100; found 416.2097. IR (film): ṽ = 2947, 1727, 1612, 1491, 1451, 1273, 1241, 1193, 1149, 910, 731, 699 cm^{-1}.

(±)-Methyl (3*S*,5*R*,10*S*)-2-Benzyl-3-hydroxy-4-imino-7,8-dimethyl-1-oxo-10-phenyl-2-azaspiro[4.5]dec-7-ene-3-carboxylate (17): M.p. (CH_2Cl_2/heptane) 185 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 3 H), 1.78 (s, 3 H), 2.13 (d, J = 16.8 Hz, 1 H), 2.34–2.50 (m, 1 H), 2.67–2.93 (m, 2 H), 2.76 (s, 3 H), 3.52 (dd, J = 6.3 Hz, 11.7 Hz, 1 H), 3.85 (d, J = 15.3 Hz, 1 H), 4.91 (d, J = 15.3 Hz, 1 H), 6.67–6.78 (m, 2 H), 6.97–7.13 (m, 3 H), 7.14–7.30 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.2, 35.1, 41.5, 42.6, 43.9, 50.8, 53.1, 86.5, 125.7, 127.0, 127.1, 127.7, 127.9, 128.4, 129.7, 135.1, 139.7, 169.5, 175.3, 175.3 ppm. HRMS calcd. for $[M]^+$ ($C_{26}H_{28}N_2O_4$): 432.2049; found 432.2051. IR (film): ṽ = 1753, 1714, 1670, 1453, 1436, 1391, 1351, 1263, 1138, 911, 734, 699 cm^{-1}. $C_{26}H_{28}N_2O_4$ (432.5): calcd. C 72.20, H 6.53, N 6.48; found C 71.80, H 6.33, N 6.16.

(±)-(5*S*,6*R*)-8-Benzyl-2,3-dimethyl-5-phenyl-8,11-diazaspiro[5.6]dodec-2-ene-7,10-dione (18): The nitrile **14** (120 mg, 288 μmol) was dissolved in methanol (5 mL) in an autoclave. To the solution was added a catalytic amount of Raney nickel followed by hydrogenation at 50 bar H_2 and 80 °C. After 17 h the reaction was stopped and the reaction mixture was filtered through Celite®. The filtrate was evaporated to dryness and the crude product was subjected to column chromatography (EtOAc/heptane, 1:1). After the column the diazepane **18** (80.7 mg, 72%) was obtained as a white solid. R_f (EtOAc/heptane, 1:1) = 0.34. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 3 H), 1.61 (s, 3 H), 1.98–2.17 (m, 2 H), 2.25–2.36 (m, 1 H), 2.87 (d, J = 17.7 Hz, 1 H), 3.02 (dd, J = 1.5 Hz, 13.2 Hz, 1 H), 3.21 (dd, J = 6.9 Hz, 15.0 Hz, 1 H), 3.53–3.64 (m, 2 H), 3.76 (dd, J = 5.1 Hz, 14.7 Hz, 1 H), 4.00 (d, J = 14.9 Hz, 1 H), 4.98 (d, J = 14.9 Hz, 1 H), 6.46 (br. s, 1 H), 6.54–6.71 (m, 2 H), 7.00–7.26 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.3, 34.3, 40.1, 40.4, 46.5, 50.8, 52.5, 53.9, 123.0, 124.2, 127.0, 127.2, 127.6, 128.38, 128.39, 129.5, 136.1, 140.3, 171.6, 174.0 ppm. HRMS calcd. for $[M]^+$ ($C_{25}H_{28}N_2O_2$): 338.2151; found 388.2150. IR (film): ṽ = 2912, 1691, 1624, 1494, 1472, 1454, 1403, 1359, 1224, 911, 733, 703 cm^{-1}.

Methyl (2*S*)-2-(Benzyl-{[(1*RS*,6*SR*)-1-cyano-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}amino)propanoate (20): The acid **11** (1.15 g, 4.51 mmol) was dissolved in tetrahydrofuran (5 mL). A few drops of dimethylformamide were added and the reaction mixture was cooled to 0 °C. Oxalyl chloride (745 μL, 1.9 equiv.) in tetrahydrofuran (2 mL) was added dropwise to the reaction mixture. After 2 h the reaction mixture was evaporated to dryness in vacuo. The crude acid chloride was dissolved in dichloromethane (6 mL) and the solution was cooled to 0 °C. Triethylamine (1.19 mL, 1.9 equiv.) in dichloromethane was added dropwise to the reaction mixture. Next, *N*-benzylalanine methyl ester (867 mg, 1.0 equiv.) in dichloromethane (3 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at 0 °C for 1 hour and then 20 h at room temperature. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate and 1 M ammonium chloride. The water layers were extracted twice with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered and the solvents evaporated to dryness. The crude product was purified using column chromatography (EtOAc/heptane, 1:4) to yield the amide **20** (1.63 g, 84%) as a white solid. The amide is formed as a mixture of two diastereoisomers which are both present in solution as a mixture of conformers. Selected signals[24] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02–1.34 (m, CH_3-Ala), 1.71 (s, CH_3-ring), 2.20–2.36 (m, CH-ring), 2.42–2.56 (m, CH-ring), 2.58–2.86 (m, CH-ring), 2.88–3.14 (m, CH-ring), 3.39 (s, OCH_3), 3.44–3.57 (m, CH-Ala), 3.67 (s, OCH_3), 4.25–4.73 (m, CH_2-benzyl), 7.00–7.54 (m, aromats) ppm. MS (EI): *m*/*z* (%) = 430 (50) $[M]^+$, 371 (11) $[M - COOMe]^+$, 339 (27) $[M - benzyl]^+$, 210 (65), 91 (100). HRMS calcd. for $[M]^+$ ($C_{27}H_{30}N_2O_3$): 430.2257; found 430.2255. IR (film): ṽ = 2902, 1744, 1648, 1496, 1454, 1432, 1330, 1219, 1115, 770, 737, 701 cm^{-1}.

(5*SR*,6*RS*,9*S*)-8-Benzyl-2,3,9-trimethyl-5-phenyl-8,11-diazaspiro[5.6]dodec-2-ene-7,10-dione (21): The amide **20** (511 mg, 1.19 mmol) was dissolved in 1 M NH_3/MeOH (5 mL) in an autoclave. A catalytic amount of Raney nickel was added and the reaction mixture was hydrogenated under 20 bar of hydrogen at room temperature. After 22 h the reaction mixture was filtered through Celite® and the filtrate was evaporated to dryness. To remove minor impurities, the crude product was purified over a small silica column (EtOAc/heptane, 1:1) to obtain the desired diazepane **21** (467 mg, 98%) as a white foam. According to NMR analysis the diazepane was present as a mixture of diastereoisomers in a ratio of 0.56:0.44. R_f (EtOAc/heptane, 1:1) = 0.33. ^1H NMR (300 MHz, $CDCl_3$): δ = (major/minor) 0.77 (d, J = 7.5 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 1.65 (br. s, 3 H, 3 H), 1.69 (s, 3 H, 3 H), 2.04–2.18 (m, 2 H, 1 H), 2.26 (d, J = 17.4 Hz, 1 H), 2.33–2.53 (m, 1 H, 1 H), 2.85 (br. d, J = 16.8 Hz, 1 H), 3.07 (d, J = 17.5 Hz, 1 H), 3.13 (dd, J = 7.2 Hz, 15.0 Hz, 1 H), 3.26 (dd, J = 6.6 Hz, 15 Hz, 1 H), 3.56 (dd, J = 5.4 Hz, 12.9 Hz, 1 H), 3.67–3.83 (m, 3 H), 3.84–3.94 (m, 2 H), 4.30 (d, J = 15.0 Hz, 1 H), 4.41 (d, J = 15.9 Hz, 1 H), 4.62 (d, J = 15.9 Hz, 1 H), 4.78 (d, J = 15.0 Hz, 1 H), 6.74 (br. s, 1 H, 1 H), 6.85–7.46 (m, 10 H, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 17.5, 19.0, 19.08, 19.18, 19.24, 33.7, 33.8, 37.6, 39.7, 40.5, 42.1, 46.0, 46.3, 47.7, 49.7, 53.4, 52.7, 53.1, 60.7, 122.9, 123.3, 123.6, 124.0, 126.4, 126.5, 126.9, 127.1, 127.2, 127.6, 128.0, 128.1, 128.3, 128.4, 129.3, 129.4, 136.7, 138.7, 140.1, 140,2, 173.2, 173.7, 175.0, 175.3 ppm. HRMS calcd. for $[M]^+$ ($C_{26}H_{30}N_2O_2$): 402.2307; found 402.2307. IR (film): ṽ = 1687, 1616, 1494, 1450, 1388, 1358, 1273, 766, 734, 702 cm^{-1}.

Preparation of Compounds 22a and 22b: The acid **11** (2.00 g, 7.83 mmol) was dissolved in tetrahydrofuran (10 mL). A few drops of dimethylformamide were added and the reaction mixture was cooled to 0 °C. Oxalyl chloride (1.30 mL, 1.9 equiv.) in tetrahydrofuran (2 mL) was added dropwise to the reaction mixture. After 2 h the reaction mixture was evaporated to dryness in vacuo. The crude acid chloride was dissolved in dichloromethane (10 mL) and the solution was cooled to 0 °C. Triethylamine (3.0 mL, 2.8 equiv.) in dichloromethane (3 mL) was added dropwise to the reaction mixture. Next, H-Pro-O*t*Bu (1.34 g, 1.0 equiv.) in dichloromethane (4 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to reach room temperature. After 17 h, the reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate and 1 M ammonium chloride. The water layers were extracted twice with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered and the solvents evaporated to dryness. The crude product was purified using column chromatography (EtOAc/heptane, 1:7) to yield the amides **22a** (1.51 g, 47%) and **22b** (1.47 g, 46%) as a white solids.

(–)-*tert*-Butyl (2*S*)-1-{[(1*S*,6*R*)-1-Cyano-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}tetrahydro-1*H*-pyrrole-2-carboxylate (22a): $[\alpha]_D^{20}$ = –113 (c = 1.03, CH_2Cl_2). R_f (EtOAc/heptane, 1:4) = 0.27. The amide is present as a mixture of conformers a/b in $CDCl_3$ in a ratio of 0.59:0.41. Selected signals[24] ^1H NMR (300 MHz, $CDCl_3$): δ (a/b) = 1.28 (s, CH_3), 1.43 (s, CH_3), 1.70 (s, *t*Bu), 2.14–2.33 (m, 1 H, 1 H), 2.35–2.47 (m, 1 H, 1 H), 2.59–2.94 (m, 1 H, 2 H), 3.17–3.22 (m, 1 H), 3.26–3.40 (m, 2 H), 3.42–3.58 (m, 1 H, 2 H), 3.77 (ddd,

J = 6.6 Hz, 6.6 Hz, 10.2 Hz, 1 H), 4.20 (dd, J = 5.1 Hz, 8.4 Hz, 1 H), 4.31 (dd, J = 1.8 Hz, 8.1 Hz, 1 H), 7.15–7.47 (m, 5 H, 5 H) ppm. MS (EI): m/z (%) = 408 (34) [M]$^+$, 352 (89) [M – tBu]$^+$, 335 (14) [M − OtBu]$^+$, 307 (88) [M – COOtBu]$^+$, 210 (74) [M − Boc − Pro]$^+$, 91 (93), 70 (100). HRMS calcd. for [M]$^+$ ($C_{25}H_{32}N_2O_3$): 408.2413; found 408.2414. IR (film): ṽ = 2976, 2911, 1735, 1632, 1398, 1364, 1152, 910, 698 cm^{-1}.

(+)-*tert*-Butyl (2*S*)-1-{[(1*R*,6*S*)-1-Cyano-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}tetrahydro-1*H*-pyrrole-2-carboxylate (22b): [α]$^{20}_{D}$ = +14.7 (c = 0.99, CH_2Cl_2). R_f (EtOAc/heptane, 1:4) = 0.34. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.30 (m, 1 H), 1.43 (s, 9 H), 1.60–1.87 (m, 3 H), 1.71 (s, 3 H), 1.73 (s, 3 H), 2.21 (dd, J = 4.8 Hz, 17.7 Hz, 1 H), 2.44 (d, J = 17.4 Hz, 1 H), 2.74–2.90 (m, 1 H), 3.09–3.23 (m, 2 H), 3.35 (dd, J = 5.1 Hz, 12.3 Hz, 1 H), 3.62 (ddd, J = 6.9 Hz, 6.9 Hz, 10.2 Hz, 1 H), 4.09 (dd, J = 5.7 Hz, 7.8 Hz, 1 H), 7.17–7.32 (m, 3 H), 7.35–7.44 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.0, 25.6, 28.17, 28.23, 35.4, 42.1, 46.1, 48.5, 48.6, 62.0, 81.2, 119.8, 121.2, 125.2, 127.6, 128.2, 128.3, 139.5, 165.1, 170.4 ppm. MS (EI): m/z (%) = 408 (4) [M]$^+$, 352 (79) [M – tBu]$^+$, 335 (14) [M − OtBu]$^+$, 307 (38) [M – COOtBu]$^+$, 210 (40) [M − Boc − Pro]$^+$, 91 (79), 70 (100). HRMS calcd. for [M]$^+$ ($C_{25}H_{32}N_2O_3$): 408.2413; found 408.2401. IR (film): ṽ = 2976, 2911, 1735, 1636, 1398, 1368, 1148, 910, 728, 698 cm^{-1}.

(–)-*tert*-Butyl (2*S*)-1-{[(1*R*,6*S*)-1-(Aminomethyl)-3,4-dimethyl-6-phenylcyclohex-3-enyl]carbonyl}pyrrolidine-2-carboxylate (24): Compound **22b** (530 mg, 1.30 mmol) was dissolved in 1 M ammonia/methanol (7 mL) in an autoclave. A catalytic amount of Raney nickel was added and the reaction mixture was stirred under hydrogen (40 bar). After 17 h the reaction mixture was filtered through Celite® and the filtrate was concentrated to dryness in vacuo. The crude product was purified using column chromatography (CH_2Cl_2/MeOH, 24:1) to yield the amine **24** (444 mg, 83%). [α]$^{20}_{D}$ = –43.9 (c = 1.08, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.52 (s, 2 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 1.70–2.07 (m, 5 H), 2.15 (d, J = 17.6 Hz, 1 H), 2.28 (d, J = 13.8 Hz, 1 H), 2.33–2.46 (m, 1 H), 2.79 (d, J = 17.6 Hz, 1 H), 3.12 (d, J = 13.8 Hz, 1 H), 3.37–3.49 (m, 1 H), 3.52 (dd, J = 4.5 Hz, 5.1 Hz, 1 H), 3.77–3.88 (m, 1 H), 4.40–4.53 (m, 1 H), 7.12–7.27 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.4, 26.3, 27.8, 28.3, 36.0, 36.2, 43.0, 46.8, 48.1, 53.1, 62.5, 81.1, 123.6, 125.5, 126.7, 128.1, 128.8, 142.5, 171.9, 173.3 ppm. HRMS calcd. for [M]$^+$ ($C_{25}H_{36}N_2O_3$): 412.2726 found 412.2725. IR (film): ṽ = 2976, 1733, 1612, 1451, 1390, 1366, 1222, 1153, 767, 737, 704 cm^{-1}.

(–)-3,4-Dimethyl-6-phenyl-2′,3′,7′,8′,9′,9a′-hexahydro-1′*H*,5′*H*-spiro[cyclohex-3-ene-1,4′-pyrrolo[1,2-*a*][1,4]diazepine-1,5-dione] (23a): Compound **22a** (168 mg, 411 µmol) was dissolved in 1 M ammonia/methanol (5 mL) in an autoclave. A catalytic amount of Raney nickel was added and the reaction mixture was stirred under 40 bar H_2. After 17 h the reaction mixture was filtered through Celite® and the filtrate was concentrated to dryness in vacuo. The crude product was purified using column chromatography (CH_2Cl_2/MeOH, 20:1) to give the diazepane **23a** (118 mg, 85%). An analytical sample was obtained by crystallisation of the product from CH_2Cl_2/heptane. [α]$^{20}_{D}$ = –66.7 (c = 1.23, CH_2Cl_2). M.p. (CH_2Cl_2/heptane) 229 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.41 (m, 1 H, H-8), 1.46–1.60 (m, 1 H, H-7), 1.61–1.73 (m, 1 H, H-8), 1.66 (s, 3 H, H-11), 1.69 (s, 3 H, H-10), 2.01–2.16 (m, 2 H, H-1, H-2), 2.19–2.32 (m, 1 H, H-7), 2.36–2.53 (m, 1 H, H-2), 3.00 (d, J = 17.4 Hz, 1 H, H-1), 3.13–3.28 (m, 2 H, H-4, H-9), 3.40–3.62 (m, 3 H, H-3, H-6, H-9), 3.71–3.83 (m, 1 H, H-4), 6.73 (dd, J = 6.0 Hz, 6.0 Hz, NH), 7.16–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.2, 22.3, 27.6, 32.9, 39.35, 39.37, 46.1, 48.6, 51.5, 55.2, 123.2, 123.7, 126.7, 127.0, 127.9, 128.8, 139.9, 172.3, 172.5 ppm. HRMS calcd. for [M]$^+$ ($C_{21}H_{26}N_2O_2$): 338.1994; found 388.1996. IR (film): ṽ = 2915, 1689, 1616, 1410, 1268, 768, 740, 703 cm^{-1}.

(+)-3,4-Dimethyl-6-phenyl-2′,3′,7′,8′,9′,9a′-hexahydro-1′*H*,5′*H*-spiro[cyclohex-3-ene-1,4′-pyrrolo[1,2-*a*][1,4]diazepine-1,5-dione] (23b): The

Table 1. Crystallographic data and parameters for the compounds **17**, **23a**, and **23b**

Compound	**17**	**23a**	**23b**
Emperical formula	$C_{26}H_{28}N_2O_4$	$C_{21}H_{26}N_2O_2$	$C_{21}H_{26}N_2O_2$
Molecular mass	432.50	338.44	338.44
Temperature [K]	208(2)	293(2)	208(2)
Wavelength [Å]	0.71073	0.71073	0.71073
Crystal system	monoclinic	orthorhombic	orthorhombic
Space group	$P2_1/n$	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimension [Å, °]			
a	16.0418(12)	9.4452(5)	7.01380(10)
b	7.5508(5)	13.6480(13)	12.3349(7)
c	19.0123(7)	29.921(3)	20.6112(11)
α	90	90	90
β	98.032(5)	90	90
γ	90	90	90
Volume [^{3}]	2280.3(2)	3857.1(5)	1783.17
Z	4	8	4
Density, calculated [mg/m^3]	1.260	1.166	1.261
µ [mm^{-1}]	0.085	0.075	0.081
F(000)	920	1456	728
Crystal size [mm]	0.46 × 0.31 × 0.22	0.26 × 0.18 × 0.13	0.29 × 0.20 × 0.18
θ range [°]	2.16−27.50	3.06−27.50	3.06−27.50
Reflections collected	45674	43704	61751
Independent reflections [R_{int}]	5236 [0.0506]	8833 [0.0513]	4092 [0.0433]
Refinement method	full-matrix least-squares on F^2		
Data/restraint/parameters	5236/0/401	8833/0/465	4092/0/330
Goodness-of-fit on F^2	1.041	1.000	1.075
R_1, wR_2 indices [$I > 2\sigma(I)$]	0.0552, 0.1078	0.0628, 0.1235	0.0405, 0.0851
R_1, wR_2 indices (all data)	0.0887, 0.1194	0.1729, 0.1576	0.0499, 0.0887
Largest diff. peak and hole [e·$^{-3}$]	0.290 and –0.249	0.227 and –0.159	0.224 and –0.218

amine **24** (104 mg, 252 µmol) was dissolved in toluene (3 mL) and heated at reflux. The progress of the reaction was monitored using TLC and NMR spectroscopy. After 5 days the reaction was finished and the reaction mixture was evaporated to dryness. The crude product was purified using column chromatography (CH_2Cl_2/MeOH, 20:1) to obtain the desired diazepane **23b** (75.1 mg, 88%) as a light yellow oil. An analytical sample was obtained by crystallisation from EtOAc/heptane to give small sugar-like crystals. $[\alpha]_D^{20} = +52$ ($c = 0.08$, CH_2Cl_2). M.p. (EtOAc/heptane) 195 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.65$ (s, 3 H), 1.71 (s, 3 H), 1.64–1.96 (m, 4 H), 2.24–2.38 (m, 2 H), 2.52–2.67 (m, 1 H), 2.95–3.07 (m, 1 H), 3.43–3.74 (m, 5 H), 4.33 (dd, $J = 6.9$ Hz, 6.9 Hz, 1 H), 5.36 (dd, $J = 6.9$ Hz, 6.9 Hz, 1 H), 7.10–7.33 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 19.05, 19.07, 22.2, 28.4, 33.5, 42.8, 43.0, 44.2, 49.4, 51.6, 56.3, 122.9, 123.9, 126.6, 128.0, 128.2, 141.2, 170.4, 173.2 ppm. HRMS calcd. for $[M]^+$ ($C_{21}H_{26}N_2O_2$): 338.1994; found 388.1995. IR (film): $\tilde{\nu} = 2911$, 1687, 1599, 1402, 1153, 911, 733, 702, 647 cm^{-1}. $C_{21}H_{26}N_2O_2$ (338.5): calcd. C 74.53, H 7.74, N 8.28; found C 74.35, H 7.54, N 8.11.

Crystal Structure Determinations:[16] Crystals suitable for X-ray diffraction studies were grown by slow evaporation from CH_2Cl_2/heptane for **17** and **23a**, and EtOAc/heptane for **23b**. Single crystals were mounted in air on glass fibres. Intensity data were collected at room temperature for **23a** and at −65 °C for **17** and **23b**. A Nonius Kappa CCD single-crystal diffractometer was used (φ and ω scan mode), using graphite-monochromated Mo-K_α radiation. The structures were solved by the program CRUNCH[25] and were refined with standard methods using SHELXL97[26] with anisotropic parameters for the non-hydrogen atoms. For **23a** all hydrogens were placed at calculated positions and were refined riding on the parent atoms. For **17** and **23b** the hydrogens were initially placed at calculated positions and were freely refined subsequently. Crystallographic data and parameters of the refinements are listed in Table 1.

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[15] Upon standing in $CDCl_3$ for 22 h the same reaction was observed. The conversion of **16** to **17** probably involves molecular oxygen. The details of the reaction mechanism are currently under investigation.

[16] Crystallographic data for the structures **17**, **23a** and **23b** have been deposited with the Cambridge Crystallography Data Centre as supplementary publication numbers CCDC-252852, -252850 and -252851 contain the supplementary crystallographic data for

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