Bidirectional synthesis of di-t-butyl (2S,6S,8S)- and (2R,6R,8R)-1,7-diazaspiro[5.5]undecane-2,8-dicarboxylate and related spirodiamines

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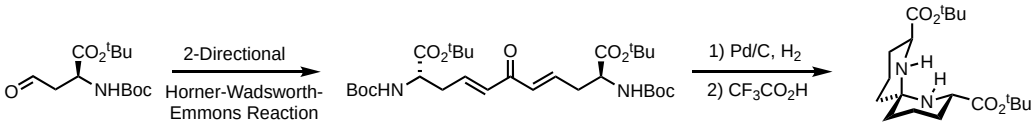
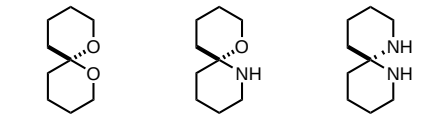


Abstract: Efficient syntheses of both enantiomers of a spirodiamine diester from (*L*)- and (*D*)-aspartic acid are described. The key transformation was the conversion of Boc-protected *t*-butyl aspartate into the derived aldehyde, two directional Horner-Wadsworth-Emmons olefination, hydrogenation and selective acid-catalyzed Boc-deprotection and spirocyclization. An alternative, two-directional approach to derivatives of 1,7-diazaspiro[5.5]undecane is described.

Modern approaches in medicinal chemistry are increasingly focused on sp^3-rich compounds for the discovery of novel classes of pharmacophores.[1] Spirocyclic compounds, in particular, have gained significant interest due to their complex three-dimensional shape and rigid conformation of the two rings which combine to generate a wide variety of novel and biologically relevant architectures.[2] Accordingly, there has been considerable interest in establishing methodology to synthesize and install these spirocyclic entities into a variety of molecules.[3,4] Spirodiamines including derivatives of 1,7-diazaspiro[5.5]undecane (**3**) are understudied compared with derivatives of 1,7-dioxaspiro[5.5]undecane (**1**) and 1,7-azaoxaspiro[5.5]undecane (**2**) (Figure 1) as well as other carbocyclic and heterocyclic spiro compounds.

Figure 1: (*O*,*O*), (*N*,*O*) and (*N*,*N*) spiro[5.5]undecane parent heterocycles.

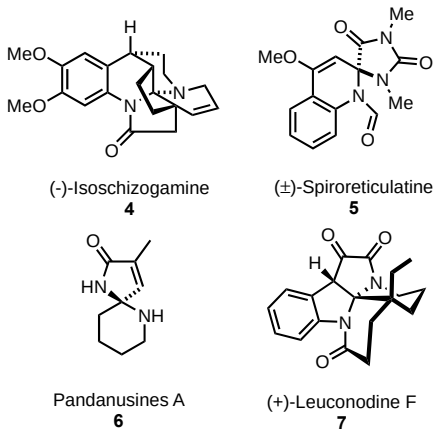


(*O*,*O*)-spiroketal **1** (*N*,*O*)-spiroketal "spirohemiaminal" **2** (*N*,*N*)-spiroketal "spirodiamine" **3**

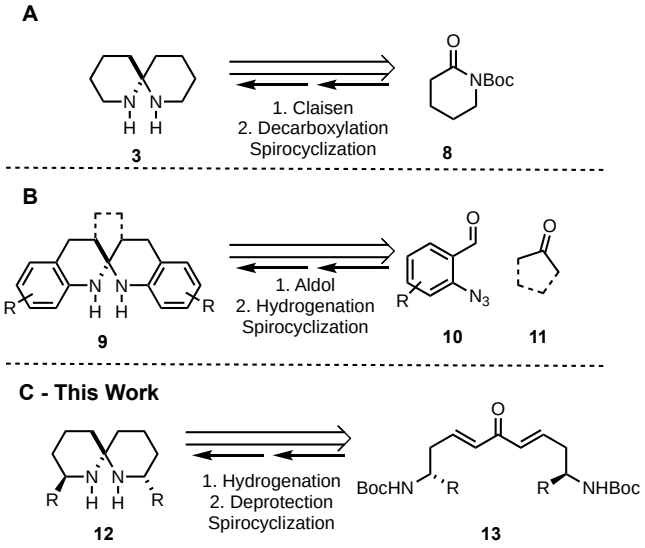
This lack of study is presumably due to the scarcity of the spirodiamine functionality in natural products, and the limited methods available for their synthesis. A selection of spirodiamine containing natural products are illustrated in Figure 2,[5–8]. Within our group we have reported the synthesis of both aliphatic and benzannulated spirodiamines alongside studies of their reactivity with organic and inorganic electrophiles.[9–11] Herein we report alternative methods for the synthesis of more

complex examples of spirodiamines utilizing bidirectional homologation strategies, which are concise but also ensure high enantiomeric purities with chiral derivatives as a result of the operation of the Horeau effect[12] (Scheme 1).

Figure 2: Spirodiamine containing natural products 4-7.

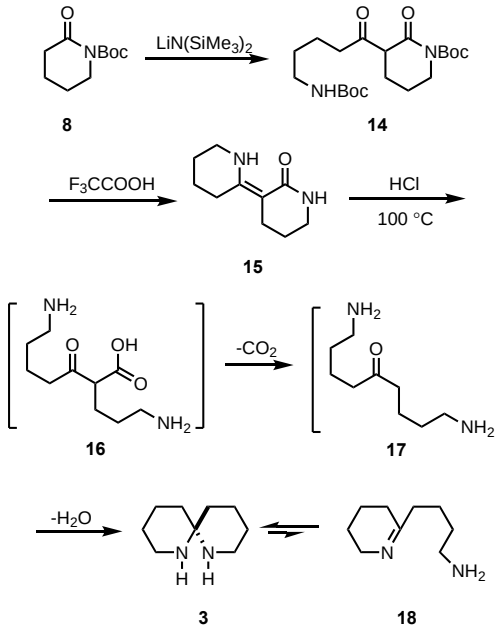


Scheme 1: Prior syntheses of (A) 1,7-diazaspiro[5.5]undecane (3) and (B) tetrahydrospirobiquinoline derivatives 9 and (C) the proposed synthesis of 2,8-disubstituted spirodiamines 12



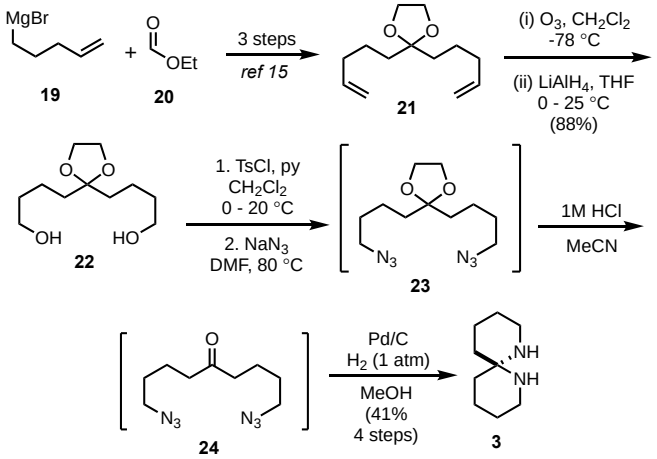
In an improvement of the early work of Büchel[13] and Kaupp,[14] our original approach to spiroaminal **3**, consisted of the self-Claisen condensation reaction of *N*-Boc-valerolactam (**8**) to produce lactam **14**, followed by two-step decarboxylative spirocyclization via intermediate **15**.[9] Since reporting this work, we were able to telescope the procedure further to a two-step process, with direct HCl catalyzed Boc-deprotection of intermediate **14**, decarboxylation and spirocyclization in the second step (Scheme 2).

Scheme 2: Prior synthesis of spirodiamine 3 and the proposed mechanism of the decarboxylation spirocyclization.



As an alternative and potentially highly flexible strategy, we envisaged that derivatives of the spirodiamine **3** should be available using a range of equivalent bidirectional homologation reactions strategically comparable to that used in our synthesis of tetrahydrospirobiquinolines **9.**[10] Thus following the work of Brasholz,[15] reaction of 4-pentenylmagnesium bromide (**19**) with ethyl formate (**20**) followed by oxidation and ketal protection gave the symmetrical diene **21**. Subsequent ozonolysis with a reductive work-up gave diol **22** (88%), which was sequentially allowed to react with 4-toluenesulfonyl chloride, sodium azide and methanolic hydrogen chloride to give diazidoketone **24**. Diazidoketone **24** was smoothly hydrogenated over palladium on carbon, which resulted in rapid spirocyclization to give spirodiamine **3** (41%) (Scheme 3).

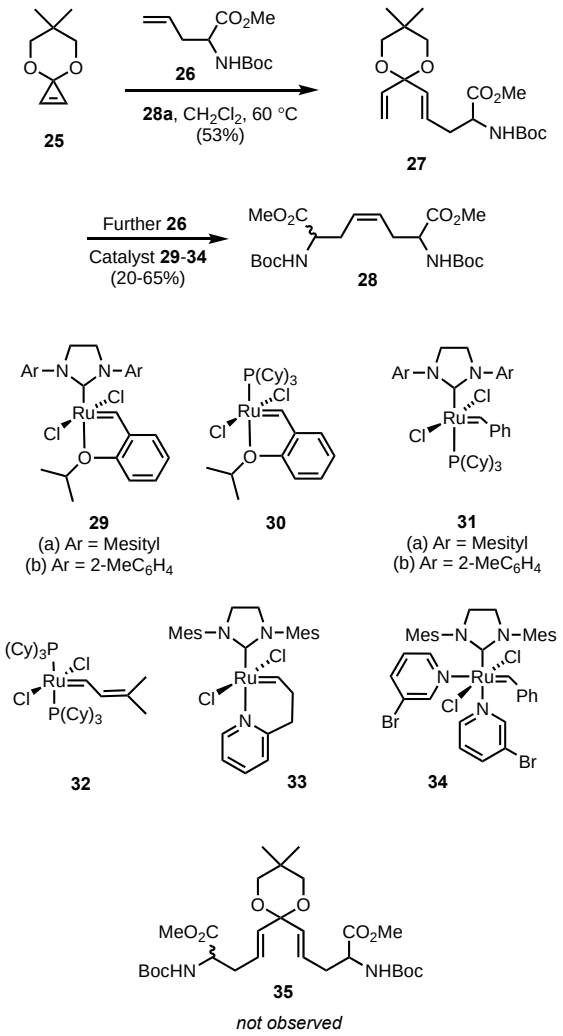
Scheme 3: The bidirectional Grignard reagent approach to spirodiamine 3.



Whilst the transformations in Scheme 3 showed that a bidirectional strategy was valid, the synthetic sequence involved the use of diazides **23** and **24**, which could prove hazardous on any scale up synthesis. We therefore sought to establish a

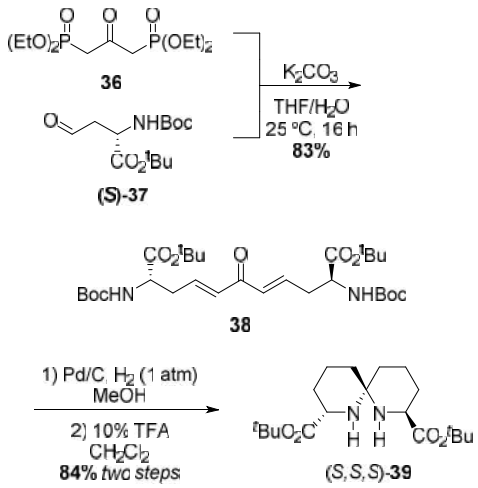
shorter bidirectional route that avoided any use of azides. In consequence, we examined the two-directional alkene metathesis reactions of cyclopropene **25**.[16] However, it soon became apparent that, whilst the initial ring opening-cross metathesis to produce alkenes such as **27** was successful, the subsequent second cross metathesis reaction of vinyl ketal **27** with the allyl glycine derivative **26** was impractically slow and reactions resulted only in the formation of the homo cross metathesis product **28** and none of the required double homologated product **35** even with myriad ruthenium based catalysts **29** to **34** in toluene or dichloromethane solution from room temperature to 120 °C (Scheme 4).[17]

Scheme 4: The attempted olefin metathesis approach to spirodiamines.



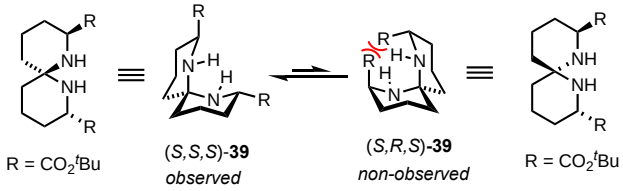
In view of these failures, we examined the double Horner-Wadsworth-Emmons reaction of diphosphonate **36** with aldehyde **37**, which is based on the work of Chen,[18] and our initial target was spirodiamine diester **39**. Thus condensation of (*S*)-aldehyde **37**[19] with diphosphonate **36** in the presence of potassium carbonate gave dienone **38** (83%). Subsequent double hydrogenation over palladium on carbon and deprotection-spirocyclization catalyzed by trifluoroacetic acid gave the spirodiamine **39** {$[\alpha]_D$ = +5.5}(Scheme 5). The relative stereochemistry of the spirodiamine **39**, which is effectively a double α-amino-ester, was confirmed by an X-ray crystal structure determination. Its absolute (*S*,*S*,*S*)-stereochemistry was assumed based on the stereochemistry of the (*S*)-aspartic acid precursor of aldehyde (*S*)-**37**.

Scheme 5: The synthesis of spirodiamine 39 via double Horner-Wadsworth-Emmons coupling reaction of phosphonate 36 and aldehyde 37.



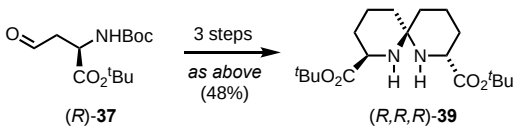
It is noteworthy that the stereochemistry of the resultant spirane center is controlled by the absolute stereochemistry of the ring substituents together with the double anomeric effect as observed with derivatives of 1,7-dioxaspiro[5.5]undecane (**1**).[11] In our work, spirodiamine **39** was only observed as a single diastereoisomer and showed no spirane center epimerization on even on storage in chloroform solution over 48 hours or over 6 months as a solid sample (Figure 3).

Figure 3: The observed structural conformation of spirodiamine (*S,S,S*)-39.



The double Horner-Wadsworth-Emmons homologation process was also applied for the conversion of the enantiomeric (*R*)-aldehyde **37**[19] into the enantiomeric (*R,R,R*)-spirodiamine **39** (48%) {$[\alpha]_D$ = -5.5} (Scheme 6).

Scheme 6: The synthesis of opposing enantiomeric spirodiamine ester (*R,R,R*)-39



The facile synthesis of enantiopure 2,8-disubstituted spirodiamine diesters utilizing a double Horner-Wadsworth-Emmons is reported. We believe these novel di-α-amino-esters will have useful applications for the synthesis of novel peptides, macrocyclic compounds and in the elaboration of novel pharmacophores in medicinal chemistry. Further syntheses and applications of such spirodiamines will be reported in due course.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware under atmospheric conditions, using commercially supplied solvents and reagents unless otherwise stated. Large-scale hydrogenations were carried out in a Parr® hydrogenator. Column chromatography was carried out on silica gel, using flash techniques unless otherwise stated (eluents are given in parentheses). Analytical TLC was performed on pre-coated silica gel F254 aluminum plates with visualization under UV light and/or by staining with either aqueous potassium permanganate solution, acidic vanillin solution or phosphomolybdic acid solution. Melting points were obtained using a hot stage apparatus and are uncorrected. IR spectra were recorded on neat films. Optical rotations were recorded in a cell with a path length of 0.5 dm with concentrations (c) quoted in g/mL. ^{1}H NMR and ^{13}C NMR spectra were recorded respectively at 400 MHz and 101 MHz with chemical shifts (δ) quoted in ppm, relative to $CHCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm). Analytical and preparative chiral HPLC was carried out on a Chiralpak® IA column using 10% *iso*-propanol in hexane as the mobile phase.

Safety Note. Whilst low molecular weight azides are potentially hazardous, we have had no issues with any of the intermediates in terms of their thermal stability or uncontrolled decomposition. It is advised however to handle these compounds carefully behind a blast shield. When carrying out reactions with sodium azide, it is advised to keep the reaction with constant nitrogen or argon sparging to prevent the accumulation of HN_3 in the headspace.[20]

2,2,Di-(4-hydroxybutyl)-1,3-dioxolane (22). Ozone was bubbled through diene **21**[15] (2.1 g, 10 mmol) in CH_2Cl_2 (50 mL) at -78 °C until a blue color persisted. The solution was sparged with argon until the color had faded, the solvent was evaporated in *vacuo* and the residue re-dissolved in THF (30 mL). The solution was cooled to 0 °C, and $LiAlH_4$ (1.9 g, 50 mmol, 5.0 equiv) was added in several portions with stirring. The ice bath was removed and, after 4 h, the suspension was cooled to 0 °C and MeOH (12 mL), 2 M NaOH (12 mL) and H_2O (12 mL) were added sequentially in a dropwise manner with stirring. The resultant white precipitate was filtered off and washed with EtOAc. The layers were separated, the organic layer was dried ($MgSO_4$), filtered and solvent evaporated in *vacuo* to yield the crude diol **22** (1.9 g, 88%) as a colorless liquid. This product could be carried on to the next step crude, but an analytically pure sample was isolated by chromatography (EtOAc). The data for this sample of the diol **22** were consistent with the values reported in the literature:[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 4H), 3.65 (t, *J* = 6.4 Hz, 4H), 1.68 – 1.60 (m, 4H), 1.60 – 1.54 (m, 4H), 1.50 – 1.39 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 111.7, 65.1 (2C), 62.9 (2C), 36.9 (2C), 33.0 (2C), 20.1 (2C); HRMS (EI) *m/z* calcd for $C_{11}H_{22}O_4$ ($M^{\cdot+}$): 218.1518, found: 218.1520.

1,7-Diazaspiro[5.5]undecane (3). *p*-TsCl (3.5 g, 18.3 mmol, 4.0 equiv) was added in a single portion with stirring to diol **22** (1.0 g, 4.6 mmol, 1.0 equiv) in pyridine (10 mL) at -10 °C. After 1 h, reaction was quenched with H_2O (50 mL) and the mixture was extracted with CH_3Cl (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield the crude di-4-toluenesulfonate ester as a yellow oil. This residue was dissolved in DMF (12.5 mL) with NaN_3 (1.3 g, 20.5 mmol, 4.5 equiv) and heated at 80 °C for 1 h. After cooling to room temperature, reaction was quenched with H_2O (50 mL). The mixture was extracted with CH_3Cl (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent removed by rotary evaporation. The crude diazide **23** was dissolved in MeCN (5 mL) and 1 M HCl (1 mL) was added dropwise with stirring at room temperature. After 3 h, the mixture was diluted with saturated aqueous $NaHCO_3$ (1 x 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$)

and the solvent removed by rotary evaporation. The crude keto-diazide **23** was dissolved in MeOH (20 mL) and flushed with argon, when 10 wt.% Pd/C (100 mg) was added and the suspension was stirred under an atmosphere of hydrogen (1 atm) for 4 h. The catalyst was filtered off, and the filtrate rotary evaporated. The crude spirodiamine **3** (289 mg, 41%) was obtained as a colorless liquid and was >95% pure. Alternatively, purification by Kugelrohr distillation (125 ^{0}C, 9 x 10^{-2} mbar) gave spirodiamine **3** as a colorless oil with data consistent with those reported in the literature:[9] ^{1}H NMR (400 MHz, $CDCl_3$,) δ 2.62 (bs 4H), 1.77 (bs, 2H), 1.43-1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.6, 40.1 (2C), 36.8 (2C), 26.1 (2C), 20.0 (2C); HRMS (ESI) *m/z* calcd for $C_9H_{19}N_2$ ($M + H^+$): 155.1548, found: 155.1546.

5,5-Dimethyl-2-ethenyl-2-(4-*tert*-butyloxycarbonylamino-5-methoxy-5-oxo-1*E*-pentenyl)-1,3-dioxane (27). Hoveyda–Grubbs™ 2nd generation catalyst **29a** (8 mg, 14 µmol, 10 mol%) was added with stirring to the *DL*-allylglycine derivative **26**[22] (65 mg, 0.28 mmol, 2.0 equiv) and the cyclopropene **25**[23] (20 mg, 0.14 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) under N_2 at 60 ^{0}C. After 4 h, evaporation under reduced pressure and chromatography on silica (gradient EtOAc : pentane 0 : 1 to 2 : 8) gave the mono-adduct **27** as yellow oil (27 mg, 52%): IR ν_{max} 1749, 1714, 1590, 1484, 1260, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.65 – 5.52 (m, 2H), 5.50 – 5.36 (m, 2H), 5.29 (dd, *J* = 10.7, 1.3 Hz, 1H), 4.30 (m, 1H), 3.75 (s, 3H), 3.61 – 3.48 (m, 4H), 2.77 – 2.63 (m, 2H), 1.46 (s, 9H), 1.03 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 155.4, 137.6, 133.1, 128.8, 116.7, 98.8, 79.7, 71.5, 71.4, 52.9, 52.3, 30.7, 30.1, 28.4 (3C), 22.5 (2C); HRMS (ESI) *m/z* calcd for $C_{19}H_{31}NO_6$ ($M + Na^+$): 392.2049, found 392.2056.

Di-*tert*-butyl (*2S,4E,7E,10S*)-2,10-di-((*tert*-butoxycarbonyl)amino)-6-oxoundeca-4,7-dienedioate [(*S,S*)-38]. Tetraethyl (2-oxopropane-1,3-diyl)-bis-phosphonate (**36**)[19] (134 mg, 0.41 mmol, 1.0 equiv) and K_2CO_3 (169 mg, 1.22 mmol, 3.0 equiv) were dissolved in THF and H_2O (4 mL, 1 : 1). (*S*)-Aldehyde (*S*)-**37**[18] (200 mg, 0.73 mmol, 1.8 equiv) was added with stirring at room temperature. After 16 h, reaction was quenched with brine (10 mL) and the mixture extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation. The residue was chromatographed on silica (gradient EtOAc : pentane 0 : 1 to 1 : 4) to give the dienone (*S,S*)-**38** (174 mg, 83%) as colorless oil: $[\alpha]_D^{20}$ +78.9 (*c*, 0.10, $CHCl_3$); IR ν_{max} 3381, 1717, 1505, 1367, 1154, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.69 (m, 2H), 6.32 (d, *J* = 14.7 Hz, 2H), 5.45 (d, *J* = 7.7 Hz, 1H), 4.48 – 4.34 (m, 2H), 2.71 (ddd, *J* = 46.0, 14.7, 7.7 Hz, 4H), 1.48 (s, 18H), 1.46 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 170.5 (2C), 155.1 (2C), 142.0 (2C), 131.4 (2C), 82.6 (2C), 79.9 (2C), 53.0 (2C), 36.3 (2C), 28.3 (6C), 28.0 (6C); HRMS (ESI) *m/z* calcd for $C_{29}H_{49}N_2O_9$ ($M + H^+$): 569.3438, found: 569.3441.

Di-*tert*-butyl (*2R,4E,7E,10R*)-2,10-di-((*tert*-butoxycarbonyl)amino)-6-oxoundeca-4,7-dienedioate [(*R,R*)-38]. Using the same procedure as previously described for (*S,S*)-**37** with aldehyde (*R*)-**37** (500 mg, 1.83 mmol) gave diene (*R,R,R*)-**38** (426 mg, 75%) as a colorless oil. The analytical data were identical to the data of the (*S,S*)-**38** enantiomer apart from the specific rotation: $[\alpha]_D^{20}$ -75.6 (*c*, 0.10, $CHCl_3$).

Di-*tert*-butyl (*2S,6S,8S*)-1,7-diazaspiro[5.5]undecane-2,8-dicarboxylate [(*S,S,S*)-39]. Dienone **(*S,S*)-38** (50 mg, 0.09 mmol) was dissolved in EtOH (2 mL) and 10% Pd/C (10 wt%; 5 mg) was added. The mixture was stirred under a hydrogen atmosphere (1 atm) for 16 h, when the catalyst was filtered off, and the filtrate rotary evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and trifluoroacetic acid (2 mL) was added dropwise with stirring. After 2 h before, the mixture was washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3 x 10

mL) and all the combined organic extracts were washed with brine (1 x 30mL) and dried ($MgSO_4$). The mixture was filtered and the filtrate rotary evaporated to give the spirodiamine (*S*,*S*,*S*)-**39** (22 mg, 70%) as white solid: mp 114.0-115.4°C ($CHCl_3$); $[\alpha]_D^{20}$ +5.5 (*c*, 0.10, $CHCl_3$); IR ν_{max} 1727, 1453, 1367, 1157, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (d, *J* = 11.8, 2H), 2.00 – 1.90 (m, 2H), 1.80 – 1.40 (m, 30H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (2C), 80.9 (2C), 65.0, 52.3 (2C), 37.9 (2C), 29.4 (2C), 28.1 (6C), 19.6 (2C); HRMS (ESI) *m/z* calcd for $C_{19}H_{34}N_2O_4$ ($M + H^+$): 355.2597, found: 355.2599.

Di-*tert*-butyl (*2R,6R,8R*)-1,7-diazaspiro[5.5]undecane-2,8-dicarboxylate [(*R,R,R*)-39]. The hydrogenation and spirocyclization as described previously for (*S*,*S*,*S*)-**39** using diene **(***R*,*R*)-**38** (150 mg, 0.26 mmol) gave spirodiamine (*R*,*R*,*R*)-**39** (59 mg, 64%) as a white solid. The analytical data were identical to the data of (*S*,*S*,*S*)-**39** enantiomer apart from the specific rotation: mp 113.4-114.0 °C (CH_2Cl_2); $[\alpha]_D^{20}$ - 5.5 (*c*, 0.10, $CHCl_3$).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publication website at DOI:

X-Ray crystallographic determination of spirodiamine (*S*,*S*,*S*)-**39**; copies of ^1H and ^{13}C NMR spectra for all new compounds and copies of chiral HPLC traces for spirodiamines (*S*,*S*,*S*)-**39** and (*R*,*R*,*R*)-**39** (PDF).

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Notes

The authors declare no competing financial interest.

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