Stereoselective synthesis of 5-(1-aminoalkyl)-2-pyrrolidones and 1,7-diazaspiro[4.5]decane-2,8-diones from chiral *N-tert*-butanesulfinyl imines and ethyl 4-nitrobutanoate

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GRAPHICAL ABSTRACT

Stereoselective Synthesis of 5-(1-Aminoalkyl)-2-pyrrolidones and 1,7-Diazaspiro[4.5]decane-2,8-diones from Chiral *N*-*tert*-Butanesulfinyl Imines and Ethyl 4-Nitrobutanoate

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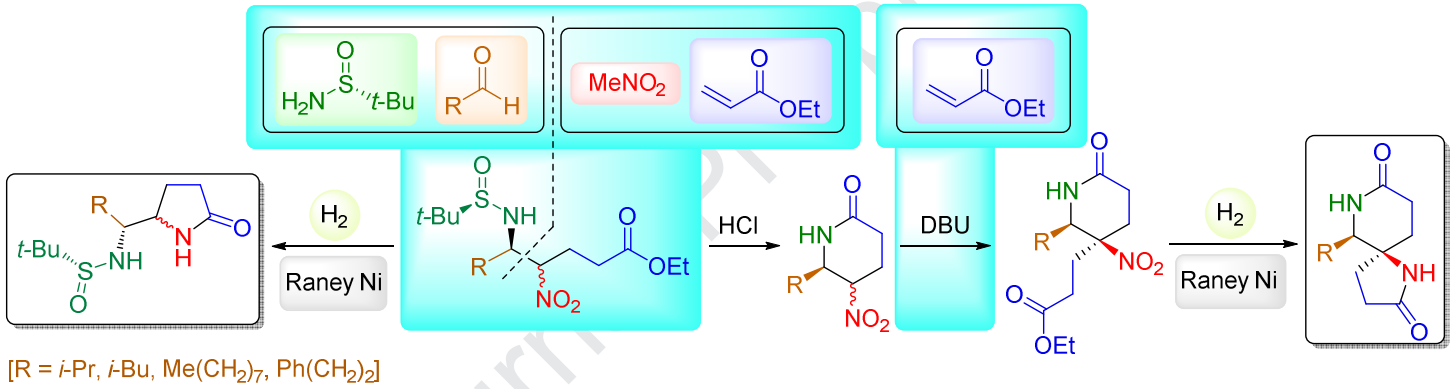

Stereoselective Synthesis of 5-(1-Aminoalkyl)-2-pyrrolidones and 1,7-Diazaspiro[4.5]decane-2,8-diones from Chiral *N-tert*-Butanesulfinyl Imines and Ethyl 4-Nitrobutanoate

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Dedicated to Professor Stephen G. Davies

Abstract
The reaction of *N-tert*-butanesulfinyl imines with ethyl 4-nitrobutanoate under basic conditions produced nitro amine derivatives. The resulting β-nitroamine derivatives, isolated as a 1:1 mixture of epimers, were easily transformed into 5-(1-aminoalkyl)-2-pyrrolidones, upon reduction of the nitro group with concomitant γ-lactam formation. On the other hand, selective removal of the sulfinyl group in the β-nitroamine derivatives led to 5-nitropiperidin-2-ones in reasonable yields. From these compounds, and following a two-step process, involving conjugative addition to ethyl acrylate and final reduction of the nitro group, 1,7-diazaspiro[4.5]decane-2,8-diones were accessed in a highly stereoselective fashion.

Keywords: Aza-Henry reaction; Chiral sulfinyl imines; 2-Pyrrolidones; Diazaspiro compounds; Intramolecular cyclizations

1. Introduction

The development of methodologies, which allow access to compounds with linear chains bearing contiguous stereogenic centers in a stereoselective fashion from relatively simple molecules, is one of the most important targets faced by synthetic organic chemists,[1] something which is achieved in Nature with high efficiency by the influence of enzymes.[2] Among these methodologies, the reaction of imines with nitro compounds, the so called nitro-Mannich or aza-Henry reaction, has emerged as an important tool in the last decade to produce β-nitroamine derivatives.[3] The interest in this molecular array lies in the presence of two vicinal nitrogen-containing functional groups with the nitrogen atoms in different oxidation states. The stereoselective version of this reaction has been achieved under the influence of both metal-based and organic catalysts (Scheme 1),[4] and also working with stoichiometric amounts of chiral reagents,[5,6] namely chiral imines, which are responsible for transferring the chiral information. Among chiral imines, *N-tert*-butanesulfinyl derivatives are of great relevance in synthesis as electrophiles, both enantiomers being accessible in large-scale processes.[7] Importantly, the *tert*-butanesulfinyl group is easily removed under acidic conditions leading to free amines, and in addition, the recycling of this chiral auxiliary can be performed maintaining the chiral integrity of the precursor in reasonable yields.[8]

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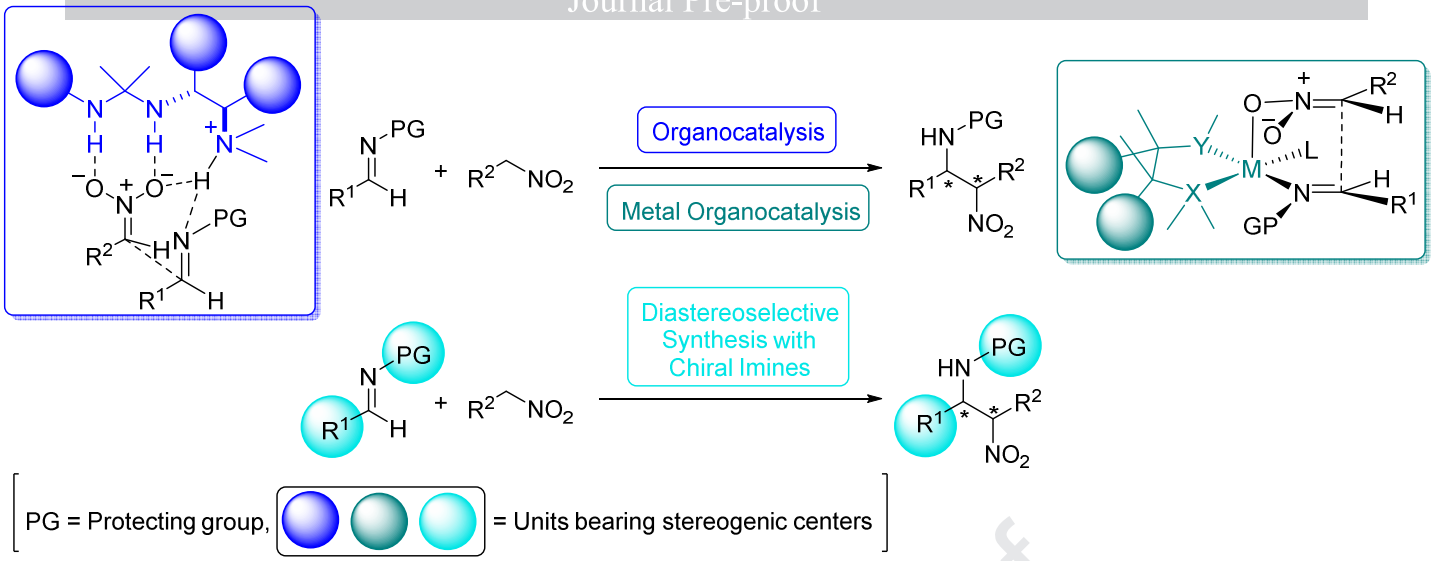
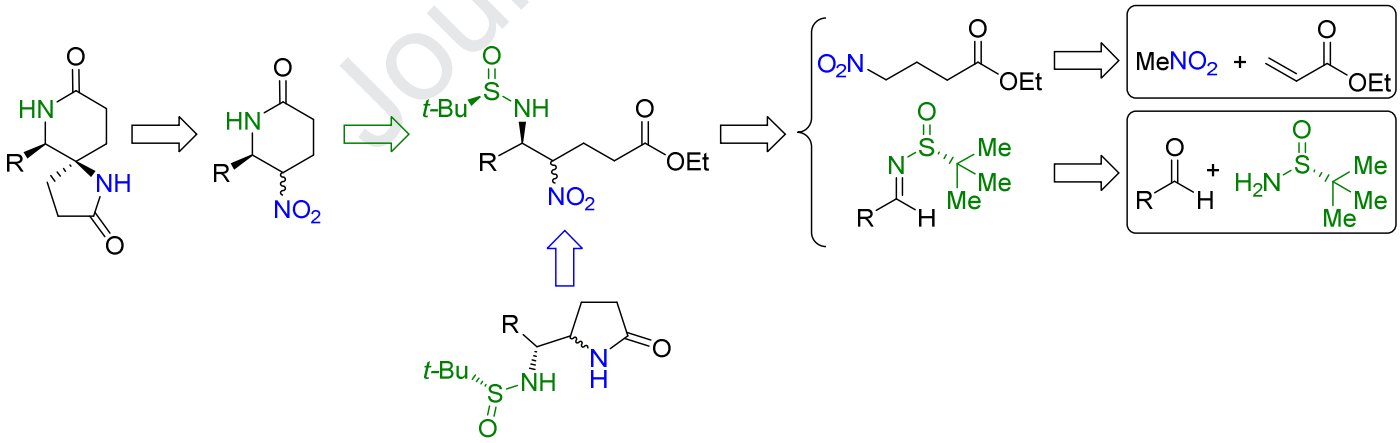


Scheme 1. Strategies for the stereoselective aza-Henry reaction.

On the other hand, and apart from the indium-promoted allylation and propargylation of these imines,[9] and also the reaction with enolates and enolate-surrogates,[10] we have also studied the reaction with different nitro compounds under basic conditions,[11] paying special attention to the stereochemical pathways of these nucleophilic additions. What we observed is that the attack of the nucleophile always occurred on the *Si*-face of the chiral imines with R_S configuration. Many of the resulting enantioenriched functionalized amine derivatives have been used as precursors in the synthesis of natural alkaloids,[12] and other nitrogen containing heterocycles.[13] Continuing our interest in this topic, we report herein the synthesis of 5-(1-aminoalkyl)-2-pyrrolidones and 1,7-diazaspiro[4.5]decane-2,8-diones from a common precursor obtained by reaction of *N*-*tert*-butanesulfinyl aldimines and ethyl 4-nitrobutanoate, taking advantage of the possibility of performing a selective intramolecular cyclization involving the ester functionality and the nitrogen atoms of the nitro and the sulfinamide groups (Scheme 2).

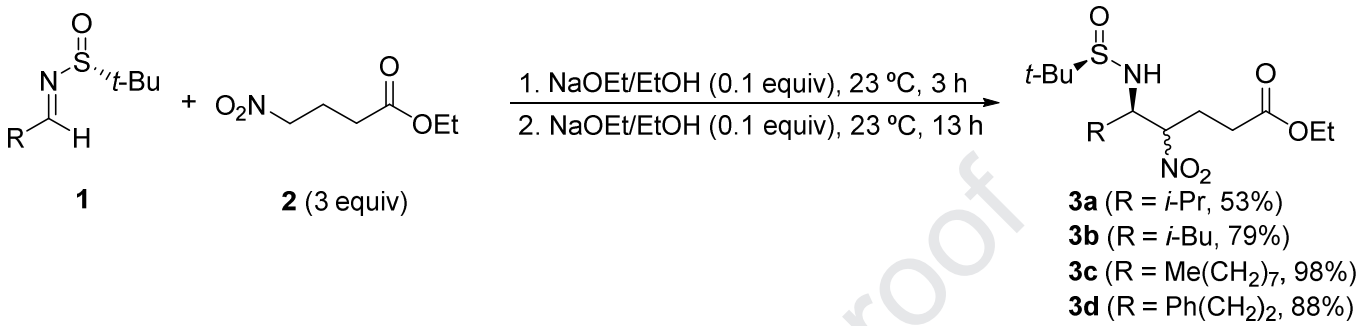


Scheme 2. Proposed retrosynthesis of 2-pyrrolidones and diazaspiro[4.5]decane-2,8-diones from *N*-*tert*-butanesulfinyl aldimines and ethyl 4-nitrobutanoate

2. Results and Discussion

Our approach to the synthesis of the target heterocycles started with the diastereoselective aza-Henry reaction of *N*-*tert*-butanesulfinyl aldimines **1** with ethyl 4-nitrobutanoate (**2**). Chiral aldimines **1** were obtained by coupling commercially available (*R*)-*tert*-butanesulfinamide with the corresponding aldehyde,[14] meanwhile nitrobutanoate **2** was prepared from ethyl acrylate and nitromethane through a conjugate addition under basic conditions. We have already reported that compounds **3** were obtained in relatively high yields when the aza-

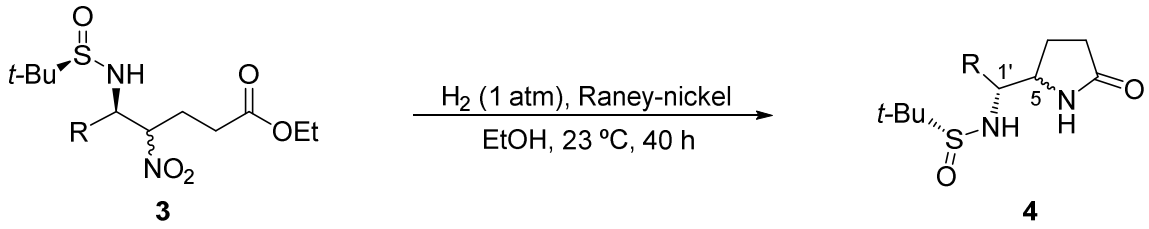
Henry reaction was carried out in the presence of 0.1 equivalents of sodium ethoxide at room temperature for 3 hours, followed by subsequent addition of another 0.1 equivalents of the same base to the reaction mixture (Scheme 3).[15] Nitro amino derivatives **3** were isolated in yields ranging from 53 to 98%. A serious drawback of this method is that aromatic aldimines performed poorly relative to the aliphatic ones, with a retro aza-Henry reaction taking place to a large extent under the basic reaction conditions, and also in the purification process with silica gel column chromatography. These reactions proceeded with almost total facial diastereoselectivity, and the nucleophilic nitronate attacked from the *Si*-face of the (R_S)-sulfinyl imine. However, compounds **3** were always isolated as a 1:1 mixture of epimers due to the acidic character of the proton bonded to the carbon bearing the nitro group.



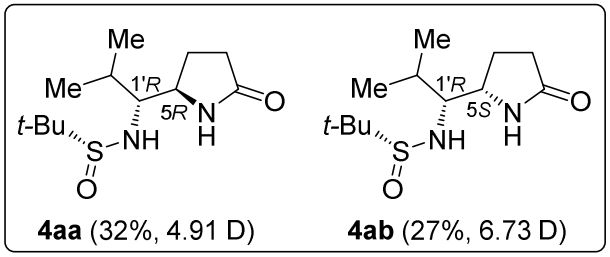
Scheme 3. Synthesis of β-nitro amine derivatives **3**

The construction of the 2-pyrrolidone system was envisioned as arising from a cyclization involving the amino group, which is formed upon reduction of the nitro group in compounds **3**, and the ester functionality.[16] Reduction of the nitro group was achieved with hydrogen (1 atm) and Raney-nickel in ethanol at room temperature for 40 hours. Other known methodologies to perform the reduction of nitro groups (e.g. Fe/AcOH, Zn/NH_4HCO_2, $NaBH_4/NiCl_2.6H_2O$)[17] did not work on these substrates. The initially formed amine derivatives underwent cyclization leading to 2-pyrrolidones **4** as a mixture of diastereoisomers. It was possible to isolate substituted 2-pyrrolidones **4** in an almost diastereomerically pure form from the diastereomeric mixtures, except in the case of compound **4c** derived from the imine of nonanal (Table 1). The yields were slightly higher for less polar isomers (silica gel, ethyl acetate/ethanol). The absolute configuration of these compounds was primarily assigned on the basis of the correlation observed between the dipole moments and R_f values (the larger dipole moment, the smaller R_f value).[18] Dipole moments were calculated by semi-empirical methods at the AM1 level, and were always smaller for compounds with (5*R*,1'*R*) configuration [Table 1, compare, for instance, compounds **4aa** (4.91 D) and **4ab** (6.73 D)].

Table 1. Synthesis of 5-(1-aminoalkyl)-2-pyrrolidones **4**.[a,b]

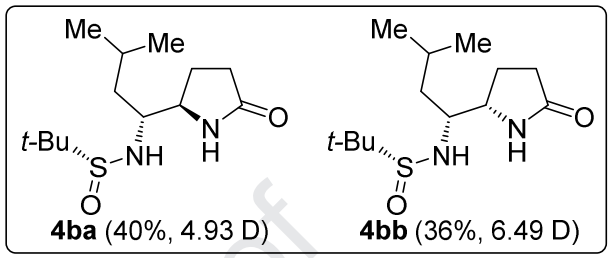


3 **4**



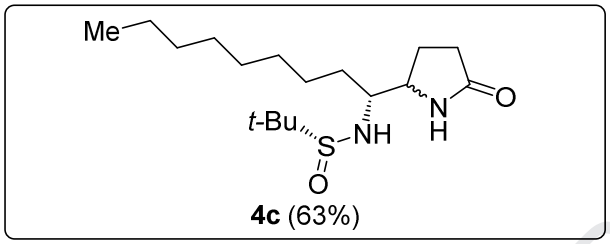
4aa (32%, 4.91 D)

4ab (27%, 6.73 D)

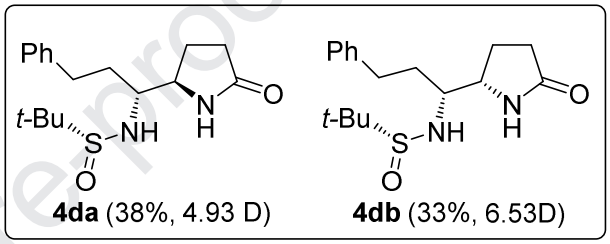


4ba (40%, 4.93 D)

4bb (36%, 6.49 D)



4c (63%)



4da (38%, 4.93 D)

4db (33%, 6.53D)

[a] Reactions were carried out starting from 0.5 mmol of the corresponding compound **3**. [b] Isolated yields after column chromatography purification, and calculated dipole moments are shown in parenthesis.

The proposed absolute configuration was also assigned on the basis of VCD analysis and was in agreement with that proposed for compound **4ba** based on the correlation between the calculated dipole moment and R_f value. Both diastereoisomers **4ba** and **4bb** exhibited opposite theoretical VCD patterns for the carbonyl group of the amide functionality. The theoretical VCD (blue dots plot) and the measured spectra (dashed black plot - red line) for diastereoisomer **4ba** matched quite well (Fig. 1).

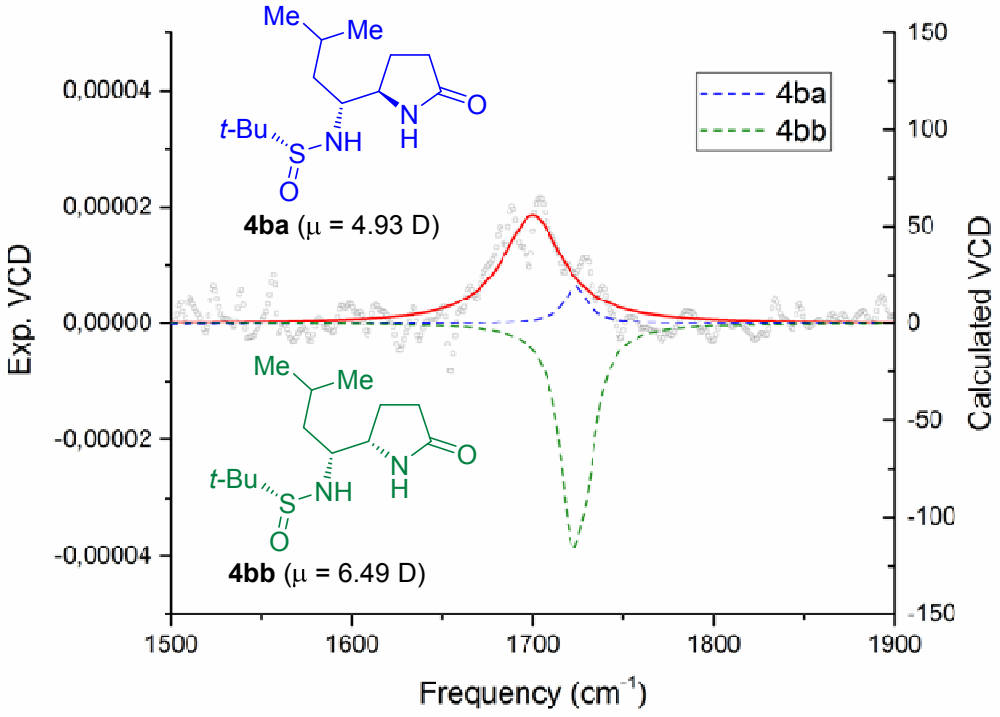
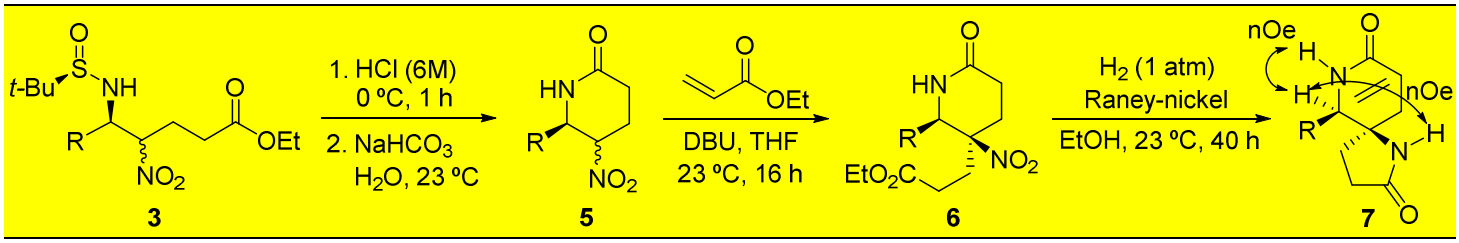
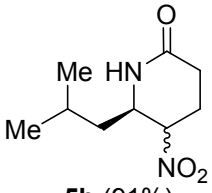
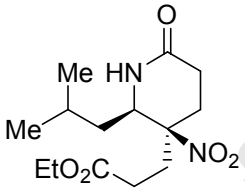
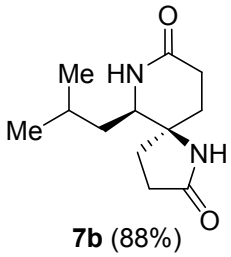
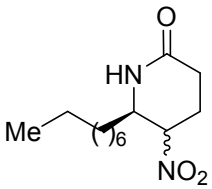
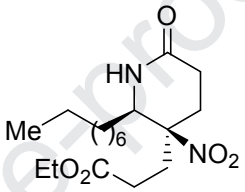
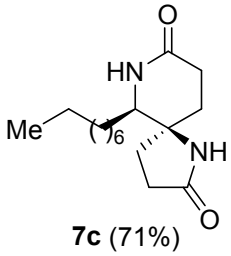
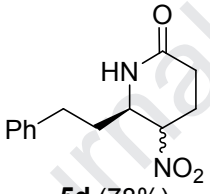
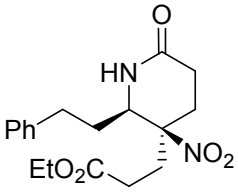
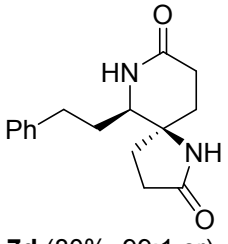
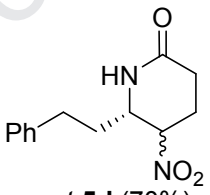
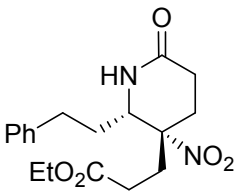
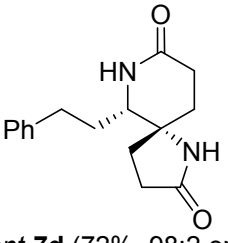


Figure 1. VCD analysis of product **4ba** and its diastereoisomer **4bb**. Dashed black plot (red line) corresponds to the experimentally measured VCD, whilst the dashed blue plot is VCD calculated with a B3LYP/6-311G+(2d,2p) level for configuration **4ba** (green in the case of diastereoisomer **4bb**).

The synthesis of 1,7-diazaspiro[4.5]decane-2,8-diones from nitro amine derivatives **3** required a longer reaction sequence. The first reaction intermediates in this sequence are piperidin-2-ones **5**. These compounds were prepared in a two-step process by first performing the removal of the *tert*-butanesulfinyl group under acidic conditions, followed by treatment of the initially formed ammonium chloride salt with an aqueous saturated solution of sodium bicarbonate. The resulting free amine underwent rapid cyclization to give in moderate to high yields, 6-substituted 5-nitropiperidin-2-ones **5**, as a mixture of diastereoisomers in different ratios, the *trans*-isomer being the major component of the mixture (Table 2). Pure diastereoisomers could be obtained after column chromatography purification.[19] However, the configuration of the stereogenic center bearing the nitro group does not affect the stereochemical outcome of the next transformation in the sequence to the target spiro compounds **7**. For this reason, the reaction of 5-nitropiperidin-2-ones **5** as an epimeric mixture with ethyl acrylate, in the presence of DBU, in THF at room temperature, led to the expected compounds **6** as an almost single diastereoisomer (>95:5 dr). The conjugate addition to the acrylate took place from the less hindered face of the planar nitronate formed under basic conditions, resulting in a relative *trans* disposition with respect to the alkyl substituent at C6 of the ring of piperidin-2-one **5**. This conjugative addition is extremely sensitive to steric interactions. In the case of compound **5a** (R = *i*-Pr), the expected reaction product was obtained in less than 5% yield and is not shown in Table 2. In the final step of the sequence, a second cyclization involving the nitro group and the ester groups was carried out under the same reaction conditions depicted in Table 1. In this case, starting from a single diastereoisomer gave rise to an almost enantiopure diazaspiro compound **7**, in moderate to high yields in all cases (Table 2). In addition, the relative configuration was unambiguously determined by NOESY experiments for compounds **7**. Through this methodology it is also possible to access to the corresponding enantiomer starting from the (S_S)-*N*-*tert*-butanesulfinyl imine (Table 2, entry 4). The stereochemical integrity of compounds **7d** and *ent*-**7d** was determined by chiral HPLC, exhibiting high enantiomeric ratios (>95:5 er). Compounds **7b** and **7c** should be of similar enantiomeric purity, since all of them were prepared following the same synthetic strategy. It is worth noting that diazaspiro moieties[20] are interesting structural motifs present in molecules which display promising biological activities.[21]

Table 2. Synthesis of 1,7-diazaspiro[4.5]decane-2,8-diones **7** from compounds **3**.[a,b]



Entry	R	Compounds **5**	Compounds **6**	Compounds **7**
1	*i*-Bu	 **5b** (91%)	 **6b** (83%)	 **7b** (88%)
2	$Me(CH_2)_7$	 **5c** (88%)	 **6c** (20%)	 **7c** (71%)
3	$Ph(CH_2)_2$	 **5d** (78%)	 **6d** (54%)	 **7d** (80%, 99:1 er)
4[c]	$Ph(CH_2)_2$	 *ent*-**5d** (70%)	 *ent*-**6d** (56%)	 *ent*-**7d** (72%, 98:2 er)

[a] Isolated yields after column chromatography purification are shown in parenthesis. [b] Enantiomeric ratios were determined by chiral HPLC. [c] Starting from (S_S)-*N*-*tert*-butanesulfinyl imine *ent*-**1d**.

3. Conclusion

In summary, 2-pyrrolidones bearing 1-aminoalkyl substituents at the 5-position were prepared from chiral *N*-*tert*-butanesulfinyl imines and ethyl 4-nitrobutanoate. (a) Diastereoselective aza-Henry reaction, (b) selective reduction of the nitro group to amines, and (c) intramolecular cyclization leading to the formation of the lactam ring, are the three steps in these transformations. The aza-Henry adducts could also be precursors of 6-alkyl substituted 1,7-diazaspiro[4.5]decane-2,8-diones. In this protocol, (a) successive removal of the sulfinyl group, (b) cyclization of the resulting free amine leading to 5-nitropiperidin-2-ones, (c) conjugate addition to ethyl acrylate of a nitronate intermediate generated under basic conditions, (d) reduction of the remaining nitro group, and (e) final lactam formation involving the amine and ester functionalities allowed access to the diazaspiro system.

4. Experimental

4.1. General

tert-Butanesulfinamides (*R* and *S*) were a gift from Medalchemy (> 99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230- 400 mesh). Melting points are uncorrected. Optical rotations were measured using a Jasco P-1030 polarimeter with a thermally jacketed 5 cm cell at approximately 23 ºC and concentrations (*c*) are given in g/100 mL. VCD analysis was recorded in a Jasco FVS-6000. Infrared analyses were performed with an ATR Jasco FT/IR-4100 spectrophotometer; wave numbers are given in cm^{-1}. Low-resolution mass spectra (EI) were obtained with an Agilent GC/MS5973N spectrometer at 70 eV; and fragment ions in *m/z* with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were also carried out in the electron impact mode (EI) at 70 eV and on a Finnigan MAT95S spectrometer equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR with a Bruker AV300 Oxford or a Bruker AV400 spectrometers, respectively, using $CDCl_3$ as the solvent and TMS as internal standard (0.00 ppm). The data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. Compounds **1a** (R = *i*-Pr),[22] **1b** (R = *i*-Bu),[23] **1c** [(R = $Me(CH_2)_7$],[24] and**1d** and *ent*-**1d** [R = $Ph(CH_2)_2$],[25] were prepared from the corresponding aldehyde and (*R*)- or (*S*)-*tert*-butanesulfinamide in THF, in the presence of two equivalents of titanium tetraethoxide.

*4.2. Preparation of β-nitroamine derivatives **3** from ethyl 4-nitrobutanoate (**2**) and chiral imines **1**. General procedure.*

To a mixture of ethyl 4-nitrobutanoate (**2**) (0.485 g, 3.0 mmol), and the corresponding chiral imine **1** (1.0 mmol) was added a 2M solution of NaOEt in EtOH (0.05 mL, 0.1 mmol) at room temperature, which was stirred for 3 h. Then, a 2M solution of NaOEt in EtOH (0.05 mL, 0.1 mmol) was also added and the resulting reaction mixture was stirred at the same temperature for an additional 13 h. The resulting mixture was hydrolyzed with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **3**. Yields are given in Scheme 3. Compounds **3b**, **3c** and **3d** were characterized by comparison of their physical and spectroscopic data with those reported in the literature.[19] The corresponding physical, spectroscopic, and analytical data for new compound **3a** follow.

*4.2.1. (4*R*,*5*R,R_S*)-Ethyl* N-*(*tert-*butanesulfinyl)-5-amino-6-methyl-4-nitroheptanoate (**3a**).*- Mixture of diastereoisomers (1:1); yellow oil; R_f 0.48 (hexane/EtOAc: 1/1); IR *v* (film) 3250, 2964, 1733, 1549, 1466, 1366, 1302, 1251, 1181, 1059, 856, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (ddd, *J* = 10.4, 8.6, 2.1 Hz, 2H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.22–4.08 (m, 4H), 3.92 (d, *J* = 8.5 Hz, 1H), 3.59 (td, *J* = 8.5, 2.7 Hz, 1H), 2.76–2.10 (m, 6H), 1.84–1.65 (m, 1H), 1.63–1.47 (m, 4H), 1.36–1.10 (m, 24H), 1.06–0.80 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.1 (C), 89.3, 87.5 (CH), 63.9, 63.5 (CH), 61.0, 60.9 (CH_2), 57.3, 57.1 (C), 32.7 (CH), 30.2, 29.8 (CH_2), 29.7 (CH), 27.4, 26.1 (CH_2), 23.2, 20.9, 20.3 (CH_3), 19.1, 15.4, 14.3, 14.2 (CH_3); LRMS (EI) *m/z* 280 (M^+–C_4H_8, 3.3%), 138 (13), 119 (30), 116 (23), 95 (18), 82 (16), 72 (11), 57 (100), 56 (32), 55 (20), 43 (16), 41 (35); HRMS (ESI-TOF) Calcd for $C_{12}H_{23}N_2O_4S$ [M^+–C_2H_5O] 291.1379, found 291.1378.

*4.3. Preparation of 2-pyrrolidones **4** from β-nitroamine derivatives **3**. General procedure.*

To a solution of the corresponding β-nitroamine derivative **3** (0.50 mmol) in EtOH (4.0 mL) was added commercially available Raney nickel (1.0 g, 0.4 mL, 50% slurry in water) and the mixture was vigorously stirred at room temperature under a hydrogen atmosphere (1 atm) for 40 h. The resulting suspension was filtered through a short pad of Celite with EtOH (40 mL) and concentrated in vacuo (15 Torr). The residue was purified by column chromatography (silica gel, EtOAc/MeOH) to yield pure compounds **4**. Yields are given in Table 1. Physical, spectroscopic, and analytical data follow.

*4.3.1. (5*R,*1'*R,R$_S$*)-5-[1-(*tert-*Butanesulfinylamino)-2-methylpropyl]pyrrolidin-2-one (**4aa**)*.- White solid; mp 150–152 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +1.5 (*c* = 0.46, CH_2Cl_2); R_f 0.31 (EtOAc/EtOH: 9/1); IR *ν* (film) 3394, 3224, 3062, 2977, 1697, 1538, 1423, 1164, 1029, 917, 779, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (br s, 1H), 3.68–3.62 (m, 1H), 3,33 (d, *J* = 10.0 Hz, 1H), 2.88 (ddd, *J* = 9.9, 8.5, 2.8 Hz, 1H), 2.37 (dd, *J* = 10.1, 5.8 Hz, 2H), 2.18–2.14 (m, 1H), 1.95–1.88 (m, 1H), 1.80–1.75 (m, 1H), 1.27 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C), 68.3, 57.8 (CH), 56.8 (C), 31.2 (CH_2), 29.1 (CH), 25.7 (CH_2), 23.0, 20.8, 15.6 (CH_3); LRMS (EI) *m/z* 203 (M^+–C_4H_9, 6%), 192 (12), 167 (13), 113 (20), 111 (21), 99 (18), 85 (28), 84 (99), 83 (21), 72 (89), 57.2 (100), 56 (20), 55 (28), 43 (31), 41 (50); HRMS (ESI-TOF) Calcd for $C_8H_{15}N_2O_2S$ [M^+–C_4H_9] 203.0854, found 203.853.

*4.3.2. (5*S,*1'*R,R$_S$*)-5-[1-(*tert-*Butanesulfinylamino)-2-methylpropyl]pyrrolidin-2-one (**4ab**)*.- White solid; mp 142–144 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ –3.4 (*c* = 0.49, CH_2Cl_2); R_f 0.26 (EtOAc/EtOH: 9/1); IR *ν* (film) 3166, 2969, 2923, 1677, 1535, 1465, 1149, 1025, 790, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (br s, 1H), 3.85–3.80 (m, 1H), 3,57 (d, *J* = 7.6 Hz, 1H), 3.16–3.12 (m, 1H), 2.40–2.23 (m, 3H), 2.14–2.10 (m, 1H), 1.93–1.88 (m, 1H), 1.27 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5 (C), 64.5 (CH), 56.8 (C), 57.8 (CH), 56.6 (CH), 30.1 (CH_2), 29.7 (CH), 24.0 (CH_2), 23.0, 20.5, 16.9 (CH_3); LRMS (EI) *m/z* 203 (M^+–C_4H_9, 8%), 167 (13), 149 (30), 135 (31), 111 (18), 99 (16), 85 (35), 84 (88), 72 (80), 57 (100), 56 (23), 55 (47), 43 (60), 41 (51); HRMS (ESI-TOF) Calcd for $C_8H_{14}NO$ [M^+–C_4H_9NOS-CH_3] 140.1075, found 140.1068.

*4.3.3. (5*R,*1'*R,R$_S$*)-5-[1-(*tert-*Butanesulfinylamino)-3-methylbutyl]pyrrolidin-2-one (**4ba**)*.- White solid; mp 115–117 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ –24.8 (*c* = 0.46, CH_2Cl_2); R_f 0.63 (EtOAc/EtOH: 9/1); IR *ν* (film) 3297, 3220, 2954, 2877, 1697, 1666, 1415, 1168, 1041, 983, 914, 887, 829 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 3.50 (q, *J* = 7.7 Hz, 1H), 3,31 (d, *J* = 10.3 Hz, 1H), 3.13–2.95 (m, 2H), 2.40–2.32 (m, 2H), 2.23–2.10 (m, 2H), 1.87–1.65 (m, 2H), 1.24 (s, 9H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C), 62.3, 60.2 (CH), 56.8 (C), 41.6, 31.1, 25.6 (CH_2), 24.1 (CH), 23.8, 22.9, 20.9 (CH_3); LRMS (EI) *m/z* 218 (M^+–C_4H_8, 26%), 218 (27), 134 (28), 112 (13), 86 (16), 84 (100), 57 (23), 43 (15), 41 (17); HRMS (ESI-TOF) Calcd for $C_5H_9N_2O$ [M^+–C_4H_9NOS–C_4H_8] 113.0715, found 113.0710.

*4.3.4. (5*S,*1'*R,R$_S$*)-5-[1-(*tert-*Butanesulfinylamino)-3-methylbutyl]pyrrolidin-2-one (**4bb**)*.- White solid; mp 35–37 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +6.3 (*c* = 0.55, CH_2Cl_2); R_f 0.57 (EtOAc/EtOH: 9/1); IR *ν* (film) 3409, 3208, 2954, 2869, 1681, 1458, 1365, 1268, 1168, 1041, 914, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br s, 1H), 4.29 (d, *J* = 9.1 Hz, 1H), 4.20–4.05 (m, 1H), 3.39–3.18 (m, 1H), 2.42–2.27 (m, 2H), 2.26–2.08 (m, 1H), 1.88–1.67 (m, 2H), 1.47–1.31 (m, 2H), 1.23 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9 (C), 59.4, 59.0 (CH), 56.8 (C), 38.5, 30.4, 24.4 (CH_2), 23.8 (CH), 23.0, 22.9, 21.4 (CH_3); LRMS (EI) *m/z* 218 (M^+–C_4H_8, 33%), 218 (33), 134 (36), 112 (18), 86 (17), 85 (10), 84 (100), 57 (26), 43 (13), 41 (20); HRMS (ESI-TOF) Calcd for $C_5H_9N_2O$ [M^+–C_4H_9NOS–C_4H_8] 113.0715, found 113.0716.

*4.3.5. (5*R*,*1'*R,R$_S$*)-5-[1-(*tert-*Butanesulfinylamino)nonyl]pyrrolidin-2-one (**4c**)*.- Mixture of diastereoisomers (1:1); yellow oil; R_f 0.31 (hexane/EtOAc: 1/1); IR *ν* (film) 3220, 2923, 2858, 1681, 1454, 1261, 1033, 929 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.49 (2 br s, 1H), 4.37 (d, *J* = 8.5, Hz, 1H), 4.06–4.01 (m, 1H), 3.87 (d, *J* = 9.6 Hz, 1H), 3.56 (q, *J* = 7.4 Hz, 1H), 3.19–3.13 (m, 1H), 2.99–2.92 (m, 1H), 2.34–2.24 (m, 4H), 2.18–2.09 (m, 2H), 1.82–1.72 (m, 2H), 1.49–1.21 (m, 26H), 1.20 (s, 9H), 1.18 (s, 9H), 0.83 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 177.8 (C), 63.4, 60.6, 59.3, 59.1 (CH), 56.6, 56.5 (C), 32.4, 31.8, 31.0, 30.3, 29.6, 29.4, 29.3, 29.1, 26.0, 25.6, 25.0 (CH_2), 22.8 (CH_3), 22.7, 22.6 (CH_2), 14.0 (CH_3); LRMS (EI) *m/z*

273.2 (M^+–C_4H_9, 25%), 274 (25), 190 (24), 142 (21), 85 (11), 84 (100), 57 (22), 43 (10), 41 (15); HRMS (ESI-TOF) Calcd for C_5H_6NO [M^+–$C_4H_{11}NOS$–C_8H_{17}] 96.0449, found 96.0452.

*4.3.6. (5*R,*1'*R,R*S*)*-5-[1-(*tert-*Butanesulfinylamino)-3-phenylpropyl]pyrrolidin-2-one (**4da**).-* White solid; mp 48–50 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ –4.1 (*c* = 0.56, CH_2Cl_2); R_f 0.69 (EtOAc/EtOH: 9/1); IR *v* (film) 3220, 2931, 2865, 1681, 1454, 1423, 1265, 1168, 1037, 952, 860, 737, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.34–7.12 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 1H), 3.65–3.54 (m, 1H), 3.08–2.94 (m, 1H), 2.93–2.79 (m, 1H), 2.70–2.53 (m, 1H), 2.37–2.25 (m, 2H), 2.15 (dq, *J* = 13.1, 6.5 Hz, 1H), 1.96–1.80 (m, 1H), 1.79–1.59 (m, 2H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 141.2 (C), 128.7, 128.4, 126.3 (CH), 63.2, 59.4 (CH), 56.8 (C), 34.6, 32.0, 31.0, 25.4 (CH_2), 23.1 (CH_3); LRMS (EI) *m/z* 266 (M^+–C_4H_{10}, 40%), 266 (40), 164 (13), 134 (21), 117 (26), 112 (20), 91 (37), 84 (100), 57 (19), 41 (13); HRMS (ESI-TOF) Calcd for $C_{13}H_{18}N_2O_2S$ [M^+–C_4H_8] 266.1089, found 266.1091.

*4.3.7. (5*S,*1'*R,R*S*)*-5-[1-(*tert-*Butanesulfinylamino)-3-phenylpropyl]pyrrolidin-2-one (**4db**).-* White solid; mp 48–50 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ –4.4 (*c* = 1.05, CH_2Cl_2); R_f 0.63 (EtOAc/EtOH: 9/1); IR *v* (film) 3228, 2931, 1681, 1454, 1265, 1176, 1041, 944, 848, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.34–7.24 (m, 2H), 7.24–7.12 (m, 3H), 4.43 (d, *J* = 8.6 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.30–3.17 (m, 1H), 2.93–2.77 (m, 1H), 2.59 (dt, *J* = 13.7, 8.2 Hz, 1H), 2.33–2.21 (m, 2H), 2.21–2.06 (m, 1H), 1.80–1.65 (m, 2H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 141.4 (C), 128.7, 128.6, 126.2 (CH), 60.2, 59.0 (CH), 56.9 (C), 32.3, 32.1, 30.3, 23.1 (CH_2), 22.9 (CH_3); LRMS (EI) *m/z* 266 (M^+–C_4H_{10}, 50%), 266 (50), 164 (16), 134 (22), 117 (32), 112 (26), 91 (42), 84 (100), 57 (24), 41 (16); HRMS (ESI-TOF) Calcd for $C_{13}H_{18}N_2O_2S$ [M^+–C_4H_8] 266.1089, found 266.1088.

*4.4. Preparation of 6-substituted 5-nitropiperidin-2-ones **5** from β-nitroamine derivatives **3**. General procedure.*

To a solution of the corresponding β-nitroamino derivative **9** (0.5 mmol) in EtOH (5.0 mL) was added dropwise a 2M solution of HCl in Et_2O (2.5 mL, 5.0 mmol) at 0 ºC. The reaction mixture was stirred at this temperature for 30 min. After that all volatiles were removed under vacuum (15 Torr) and the resulting residue was dissolved in EtOH (20 mL). A 2M solution of NaOEt in EtOH (0.5 mL, 1.0 mmol) was added to this ethanolic solution, and the reaction mixture was stirred at 23 ºC for 12 h. Then, EtOH was removed under vacuum (15 Torr), and the resulting residue was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (30 mL), and brine (15 mL), and extracted with EtOAc (3 × 25 mL). The organic layer was dried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield compounds **5** as a mixture of diastereoisomers. Yields are given in Table 2. Compounds **5b-d** were characterized by comparison of their physical and spectroscopic data with those reported in the literature.[19]

*4.5. Preparation of compounds **6** from 6-substituted 5-nitropiperidin-2-ones **5**. General procedure.*

Ethyl acrylate (0.100 g, 1.0 mmol, 0.11 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.152 g, 0.1 mmol, 0.15 mL) were successively added to a solution of the corresponding nitropiperidinone **5** (0.5 mmol) in dry THF (2.0 mL) at 23 ºC, and the mixture was stirred for 12 h at the same temperature. The resulting mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The aqueous layer was acidified with a 2M aqueous solution of HCl (2.0 mmol, 0.1 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield compounds **6** as a single stereoisomer. Yields are given in Table 2. Physical, spectroscopic, and analytical data follow.

*4.5.1. (5*S,*6*R*)-5-(2-Ethoxycarbonylethyl)-6-isobutyl-5-nitropiperidin-2-one (**6b**).-* White solid; mp 56–58 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +59.6 (*c* = 1.01, CH_2Cl_2); R_f 0.28 (hexane/EtOAc: 1/3); IR *v* (film) 3182, 2962, 2924, 2871, 1724, 1671, 1538, 1451, 1409, 1352, 1301, 1243, 1198, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.72−3.69 (m, 1H), 2.85–2.06 (m, 8H), 1.76 (ddt, *J* = 13.6, 6.6, 3.7 Hz, 1H), 1.46 (ddd, *J* = 14.1, 10.9, 3.6 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.13 (ddd, *J* = 13.1, 10.5, 2.0 Hz, 1H), 0.95 (d, J

= 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.9 (C), 89.2 (C), 61.2 (CH_2), 56.6 (CH), 41.0, 30.7, 28.4, 27.6 (CH_2), 24.4 (CH), 23.9 (CH_3), 23.4 (CH_2), 20.8, 14.2 (CH_3); LRMS (EI) *m/z* 254 (M^+–NO_2, 73%), 255 (15), 254 (73), 210 (14), 197 (100), 170 (20), 166 (59), 110 (42), 108 (16), 55 (15); HRMS (ESI-TOF) Calcd for $C_{14}H_{24}N_2O_5$ [M^+] 300.1685, found 300.1679.

*4.5.2. (5*S,*6*R*)-5-(2-Ethoxycarbonylethyl)-5-nitro-6-octylpiperidin-2-one (**6c**).*- White solid; mp 47–50 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +61.9 (*c* = 0.98, CH_2Cl_2); R_f 0.40 (hexane/EtOAc: 1/3); IR *v* (film) 3209, 2926, 2855, 1720, 1666, 1536, 1447, 1352, 1304, 1020, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (br s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.67–3.45 (m, 1H), 2.71–2.07 (m, 8H), 1.58–1.35 (m, 2H), 1.36–1.19 (m, 15H), 0.96–0.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.4 (C), 89.2 (C), 61.1 (CH_2), 58.7 (CH), 32.2, 31.8, 30.6, 29.3, 29.1, 29.1, 28.3, 27.6, 26.0, 23.3, 22.6 (CH_2), 14.1, 14.0 (CH_3); LRMS (EI) *m/z* 310 (M^+–NO_2, 58%), 240 (45), 222 (20), 197 (64), 184 (11), 127 (16), 125 (12), 110 (27), 99 (23), 97 (36), 85 (56), 83 (34), 71 (73), 69 (35), 57 (100), 55 (50), 43 (68); HRMS (ESI-TOF) Calcd for $C_{18}H_{32}NO_3$ [M^+–NO_2] 310.2382, found 310.2390.

*4.5.3. (5*S,*6*R*)-5-(2-Ethoxycarbonylethyl)-5-nitro-6-phenethylpiperidin-2-one (**6d**).*- White solid; mp 119–120 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +59.9 (*c* = 1.08, CH_2Cl_2); R_f 0.25 (hexane/EtOAc: 1/3); IR *v* (film) 3225, 2980, 2913, 1722, 1664, 1532, 1450, 1351, 1288, 1200, 1027, 747, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.11 (m, 5H), 6.98 (br s, 1H), 4.14 (q, *J* = 7.1, 2.6 Hz, 2H), 3.60 (m, 1H), 3.02–2.84 (m, 1H), 2.80–2.10 (m, 9H), 1.89–1.67 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 171.2, 139.6 (C), 128.9, 128.5, 126.8 (CH), 89.1 (C), 61.3 (CH_2), 58.0 (CH), 33.7, 32.0, 30.7, 28.4, 27.5, 23.1 (CH_2), 14.3 (CH_3); LRMS (EI) *m/z* 302 (M^+–NO_2, 100%), 214 (38), 197 (21), 170 (13), 110 (27), 91 (94), 55 (13); HRMS (ESI-TOF) Calcd for $C_{10}H_{24}NO_3$ [M^+–NO_2] 302.1756, found 302.1761.

*4.5.4. (5*R,*6*S*)-5-(2-Ethoxycarbonylethyl)-6-isobutyl-5-nitropiperidin-2-one (*ent-**6d**).*- Physical and spectroscopical data were found to be the same as for **6d**. $[\alpha]_D^{20}$ –63.2 (*c* = 0.99, CH_2Cl_2).

*4.6. Preparation of diazaspiro compounds **7** from substituted piperidinones **6**. General procedure.*

Commercially available Raney nickel (0.25 g, 0.1 mL, 50% slurry in water) was added to a solution of the corresponding piperidinone **6** (0.1 mmol) in EtOH (2.0 mL). The mixture was vigorously stirred at room temperature under a hydrogen atmosphere (1 atm) for 40 h. The resulting suspension was filtered through a short pad of Celite with EtOH (50 mL) and concentrated in vacuo (15 Torr). The residue was dissolved in a mixture of THF (1 mL) and MeOH (1 mL), and a 2M solution of NaOEt in EtOH (0.15 mL, 0.3 mmol) was added to this solution, stirring at room temperature for 12 h. The resulting mixture was hydrolyzed with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was dried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **7**. Yields are given in Table 3. Physical, spectroscopic, and analytical data follow.

*4.6.1. (5*R,*6*R*)-6-Isobutyl-1,7-diazaspiro[4.5]decane-2,8-dione (**7b**).*- White solid; mp 193–195 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ –9.1 (*c* = 0.07, CH_2Cl_2); R_f 0.26 (hexane/EtOAc: 1/3); IR *v* (film) 2959, 2922, 2850, 1730, 1648, 1046, 970, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 6.61 (br s, 1H), 3.33 (d, *J* = 10.4 Hz, 1H), 2.57–2.40 (m, 4H), 2.11–1.90 (m, 4H), 1.74–1.70 (m, 1H), 1.49–1.39 (m, 1H), 1.30–1.25 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7 (C), 171.4 (C), 59.1 (CH), 57.8 (C), 39.7, 33.0, 30.3, 29.6, 28.0 (CH_2), 24.3 (CH), 24.1, 21.1 (CH_3); LRMS (EI) *m/z* 224 (M^+, 41%), 224 (41), 181 (24), 138 (57), 127 (26), 111 (39), 110 (83), 97 (20), 86 (100), 84 (58), 82 (26), 55 (30); HRMS (ESI-TOF) Calcd for $C_{12}H_{20}N_2O_2$ [M^+] 224.1525, found 224.1524.

*4.6.2. (5*R,*6*R*)-6-Octyl-1,7-diazaspiro[4.5]decane-2,8-dione (**7c**).*- White solid; mp 104–107 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +49.8 (*c* = 0.81, CH_2Cl_2); R_f 0.48 (hexane/EtOAc: 1/3); IR *v* (film) 3187, 2922, 2853, 1697, 1654, 1464, 1411, 1375, 1349, 1320, 1288, 819, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (br s, 1H), 6.30 (br s, 1H), 3.21 (d, *J* = 10.3 Hz, 1H), 2.60–2.36 (m, 4H), 2.21–1.76 (m, 4H), 1.65–1.44 (m, 2H), 1.45–1.14 (m, 12H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 171.0 (C), 60.0 (CH), 58.9 (C), 32.5,

31.8, 30.8, 30.4, 29.5, 29.4, 29.2, 27.9, 25.9, 22.6 (CH_2), 14.1 (CH_3); LRMS (EI) *m/z* 280 (M^+, 48%), 142 (100), 138 (30), 112 (39), 110 (98), 98 (16), 82 (30), 70 (25), 56 (19), 55 (27); HRMS (ESI-TOF) Calcd for $C_{16}H_{28}N_2O_2$ [M^+] 280.2151, found 280.2146.

*4.6.3. (5*R,*6*R*)-6-Phenethyl-1,7-diazaspiro[4.5]decane-2,8-dione (**7d**).*- White solid; 99:1 er [HPLC (Chiralpak AD column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm): t_{major} = 25.08 min, t_{minor} = 28.08 min]; mp 169–170 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +15.1 (*c* = 1.19, CH_2Cl_2); R_f 0.35 (hexane/EtOAc: 1/3); IR *v* (film) 3185, 2923, 2853, 1655, 1455, 1410, 1374, 1347, 1319, 1285, 1253, 1030, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (br s, 1H), 7.32–7.17 (m, 5H), 6.97 (br s, 1H), 3.21–3.18 (m, 1H), 2.93–2.86 (m, 1H), 2.70–2.36 (m, 5H), 2.06–1.67 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 171.7, 140.4 (C), 128.9, 128.5, 126.6 (CH), 59.2, 59.0 (CH), 32.9, 32.5, 32.1, 30.5, 29.8, 29.6 (CH_2); LRMS (EI) *m/z* 272 (M^+, 26%), 207 (16), 181 (89), 138 (100), 134 (46), 132 (20), 117 (24), 111 (23), 110 (69), 91 (84), 82 (34), 65 (20), 56 (31), 55 (28), 44 (73); HRMS (ESI-TOF) Calcd for $C_{16}H_{20}N_2O_2$ [M^+] 272.1525, found 272.1542.

*4.6.4. (5*S,*6*S*)-6-Phenethyl-1,7-diazaspiro[4.5]decane-2,8-dione (*ent-***7d**).*- Physical and spectroscopical data were found to be the same as for **7d**. 2:98 er [HPLC (Chiralpak AD column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm): t_{minor} = 25.69 min, t_{major} = 28.08 min]; $[\alpha]_D^{20}$ –19.1 (*c* = 0.84, CH_2Cl_2).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://.....

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This article is of interest for the following reasons:

1) The here described procedures allows an efficient synthesis of enantioenriched 5-substituted pyrrolidines and 1,7-diazaspiro[4.5]decane-2,8-diones starting from aldehydes, *tert*-butanesulfinamide, nitromethane and ethyl acrylate. All starting materials are commercially available at reasonable prices.

2) The aza-Henry reaction of *N*-*tert*-butanesulfinyl imines and ethyl 4-nitrobutanoate proceeds under mild basic reaction conditions and is highly diastereoselective, considering the addition to the imine group, the configuration of the newly created stereogenic center at the imine carbon being determined by the configuration of the sulfur atom of the *tert*-butanesulfinyl unit.

3) The resulting polyfunctionalized pyrrolidones are of potential interest as ligands in organometallic compounds and also as organocatalysts. On the other hand, different diazaspiro compounds have been found to display a broad range of promising biological activities.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: