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Diastereoselective In and Zn-mediated allylation of pyrazol-4-yl derived (*R*)-*tert*-butanesulfinyl imines: synthesis of enantiomerically pure 6-(pyrazol-4-yl)-piperidin-2,4-diones

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ABSTRACT

The In and Zn-mediated allylation of substituted pyrazol-4-yl derived (*R*)-*N*-*tert*-butanesulfinyl imines proceeds with high diastereoselectivity depending on the conditions and additives (up to 99.4% de). Thus, the synthesized diastereomeric homoallylsulfinamides were isolated and characterized as pure diastereomers, which were then converted into the corresponding pyrazol-4-yl-derived *N*-Boc-homoallylamines via consecutive treatment with HCl and Boc_2O. The latter were then subjected to a sequence of reactions: cyclobromocarbamation with NBS and enolate–isocyanate rearrangement with *t*BuOK to give novel enantiomerically pure (*S*)-6-(pyrazol-4-yl)-piperidine-2,4-diones in 88–96% yield. The absolute configurations of the allylation products were assigned by X-ray single crystal analysis of the intermediate bromomethylurethanes.

1. Introduction

Among heterocycles, that are found in a variety of natural products, piperidines occupy one of the privileged places.[1] The excellent biological activity of this particular class of nitrogen heterocycles has stimulated the search for novel syntheses of known molecules as well as the design of new piperidine derivatives. Over the course of our studies, we turned our attention to piperidine-2,4-diones, which are valuable building blocks, since they can be readily functionalized at different sites of the piperidine ring. Moreover, piperidine-2,4-diones have shown high biological activity (Fig. 1).[2] Amid the available 6-substituted piperidine-2,4-diones, there are only a few examples with heterocyclic units at the 6-position.[3] Moreover, until now there has been no convenient method described for the preparation of enantiomerically pure piperidine-2,4-dione derivatives with a heterocyclic substituent.

Recently, we have elaborated upon a concise and efficient approach to 6-substituted piperidine-2,4-diones based on the transformations of homoallylamines (Fig. 2).[4]

In order to expand upon the scope of our method, we have targeted the preparation of diones with a heteroaryl substituent.

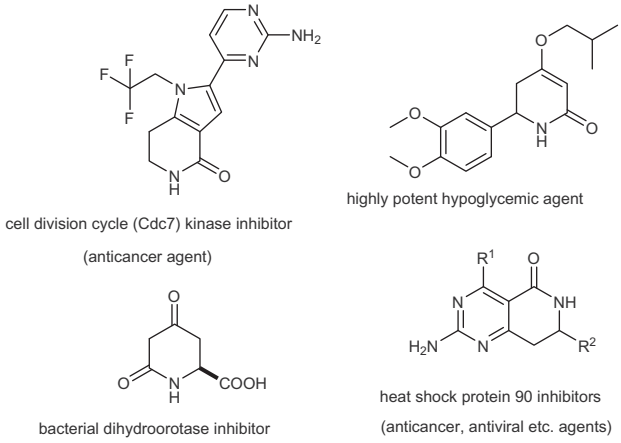

Figure 1. Biologically active piperidine-2,4-dione derivatives.

Among the variety of heteroaryls, we selected pyrazoles for the stereoselective synthesis of new 6-pyrazole substituted piperidine-2,4-diones. Over the past decades, interest in pyrazole chemistry has significantly increased mainly due to the discovery of interesting biological properties exhibited by a great number of pyrazole derivatives.[5] We believe that the combination of pyrazole and piperidine-2,4-dione fragments might be helpful in the design

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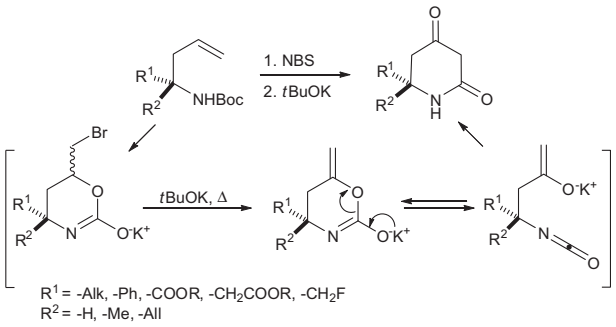


Figure 2. Transformation of *N*-Boc-homoallylamines into piperidine-2,4-diones.

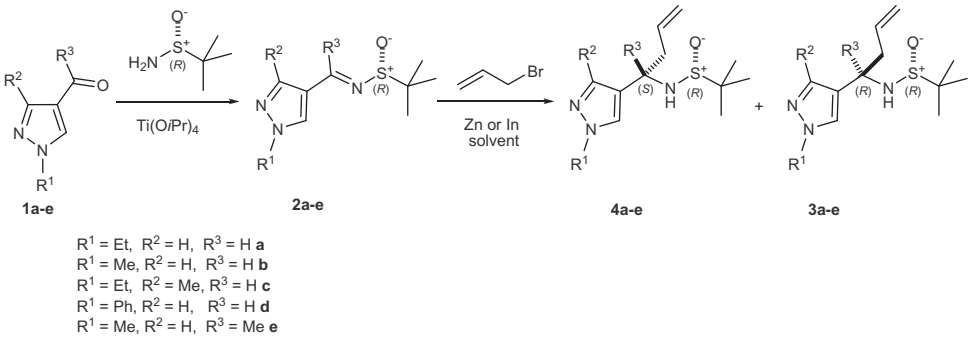
and synthesis of new pharmaceuticals, because both of these fragments are active pharmacophores.

There are many methods for the stereoselective synthesis of homoallyamines,[6] but for our particular synthetic task, we carried out the allylation of *N-tert*-butanesulfinyl imines with the corresponding Zn and In derivatives.[7] It has been shown that allylation of *N-tert*-butanesulfinyl imines with Zn/HMPA or In/THF proceeds with a high level of diastereoselectivity.[8a] Xu et al. reported that Zn-mediated allylation of imines in DMF gave only 24% de, but with HMPA, the de level reached 98% (for a simple Ph-imine derivative). However, HMPA is not a common solvent for most reactions, because it is carcinogenic, so in a later publication, an ecologically friendly aqueous system was designed for the In mediated reaction, which was appropriate for heteroaryl imines as well.[8b] Carrying out the allylation in a saturated NaBr solution generally gave a high de of the product,[8b–e] however, low chemical yields were observed in some cases. Conversely, the Zn-mediated allylation of highly electrophilic trifluoromethyl imines in DMF proceeded well with up to 90% de[8f] being achieved. With regards to the In or Zn-mediated allylation of *N-tert*-butanesulfinyl ketimines in THF, the diastereoselectivity is less predictable and varies considerably depending on the ketimine structure, although in some cases can achieve >98% de.[8g] With these precedent studies in mind, we started the allylation of pyrazol-derived *N-tert*-butanesulfinyl imines with the aim of obtaining enantiomerically pure pyrazolyl-derived homolallyamines. The enantiomeric purity of amines is an important point because further amplification of ee for the isomeric bromourethanes or final diones is less fruitful.

2. Results and discussion

The starting *N-tert*-butanesulfinyl imines **2a**–**d**, (Scheme 1) were prepared in reasonable quantitative yield in THF by the reaction of carbonyl compounds **1a**–**d**, with (*R*)-*tert*-butanesulfinamide in the presence of titanium tetraisopropoxide at 50 °C. However, the preparation of ketimine **2e** suffered from it being a slow reaction and only the use of neat reagents provided satisfactory reactivity. We took advantage of the condensation procedure under microwave irradiation[9] at 85 °C, but even in this case, to bring the reaction to completion, it required 24 h. Although the microwave irradiation was not essential and could be substituted by conventional heating, the reaction under irradiation proceeded more cleanly.

Although the allylation of imines in general is well elaborated, the presence of a heterocyclic substrate may have considerable influence on the reactivity and diastereoselectivity of the allylation, due to the formation of additional coordination bonds with heteroatoms. The N-substituted pyrazols are appropriate heteroaryl models for the determination of such effects because of the expected coordination between the metal and nitrogen's lone pair. However, the strength of this coordination, how other factors interplay and their influence on the diastereoselectivity would be interesting to know. The allylation of imines **2** began with *N*-ethyl substituted derivative **2a**, which was allylated with an allylBr/Zn/DMF (Barbier conditions, all reagents mixed together) system at 0 °C (Table 1, run 1). The reaction proceeded well with the formation of diastereomeric allylamides **4a** and **3a**. The de of the allylamides was quite low (76%); decreasing the temperature to −10 °C led to a slight enhancement of the de up to 80% (run 2). The influence of Zn-coordination on the de was also determined, thus the addition of extra Zn ions with $Zn(OTf)_2$ strongly decreased the de to 50% (run 3). It should be noted that all of the reactions were homogeneous during all of the process except for the presence of insoluble metals, hence the variation of diastereoselectivity depends only on the nature of the interacting compounds rather than experimental variables. These results are in agreement with conception[7] that allylation (in generally nucleophilic addition) to *N-tert*-butanesulfinyl imines passes through two competing ways; with chelation control and open chain steric control (Fig. 3). In order to clarify the preferred routes for the pyrazolyl imines, the reaction was carried out in the presence of a chelate-breaking agent TMEDA, since it was shown that addition of TMEDA may totally reverse the diastereoselectivity in THF.[8a] A high level of diastereoselectivity was observed (98%, run 4) even at the expense of the yield and conversion, clearly indicating that the pathway via TS2 was a highly diastereoselective process, although the reactivity of the imine was not high enough. Allylation of **2a** with Zn in THF gave the reverse selectivity (run 5, 26% de) with the major (*R*,*S*)-isomer (see Scheme 1) being obtained, thus indicating the slight preference of chelation control TS1 in this case. It was suggested that the In-mediated allylation (Barbier conditions) may improve the selectivity, because it has to proceed via TS1. Indeed application of the protocol developed by Xu and Lin[8b] with In/NaBr aqueous saturated solution gave the major (*R*,*S*)-isomer with >98% de, although the yield was only 15% leaving the rest of **2a**



Scheme 1. Synthesis of pyrazol-4-yl *N-tert*-butanesulfinyl imines and the allylation reaction.

Table 1
Diastereoselective allylation of pyrazol-4-yl *N*-*tert*-butanesulfinyl imines

Run	Subst.	Metal	Additive	Temp (°C)	Time (h)	Solvent	**4**:**3**, dr[a]	Yield (%)
1	**2a**	Zn	—	0	1	DMF	12:88	85
2	**2a**	Zn	—	−10	0.5	DMF	10:90	75
3	**2a**	Zn	$Zn(OTf)_2$[b]	0	1	DMF	25:75	90
4	**2a**	Zn	TMEDA[c]	−15	1.5	DMF	1:99	50
5	**2a**	Zn	—	20	0.5	THF	63:37	92
6	**2a**	In	NaBr[d]	20	24	H_2O	>99:1	15
7	**2a**	In	—	0	4	DMF	94:6	90
8	**2a**	In	—	0	4	DMA	97:3	85
9	**2a**	In	DMF/H_2O[e]	20	14	THF	96:4	89
10	**2b**	In	DMF/H_2O[e]	20	14	THF	97:3	95
11	**2b**	In	DMF/H_2O[e]	20	14	THF	93:7[f]	95
12	**2b**	Zn	—	−10	0.5	DMF	11:89	75
13	**2b**	Zn	TMEDAc[c]	−15	1.5	DMF	1:99	56
14	**2c**	Zn	TMEDA[c]	−15	1.5	DMF	15:85	30
15	**2c**	In	DMF/H_2O[e]	20	14	THF	90:10	95
16	**2c**	Zn	—	20	0.5	THF	83:17	98
17	**2c**	In	—	0	6	DMF	99:1	80
18	**2c**	In	—	0	6	DMF	98:2[g]	88
19	**2d**	Zn	—	20	0.5	THF	73:27	98
20	**2d**	In	DMF/H_2O[e]	20	14	THF	97:3	70
21	**2d**	In	—	0	6	DMF	94:6	90
22	**2e**	Zn	—	20	3	THF	93:7	97
23	**2e**	Zn	$Zn(OTf)_2$[b]	20	0.5	THF	98.5:1.5	95
24	**2e**	Zn	$Zn(OTf)_2$[b]	0	0.5	THF	99.7:0.3[h]	98

Typical run: imine **2** (1 mmol), In (3 mmol) or Zn (3 mmol), allylBr (3 mmol), solvent (2 mL).
[a] dr was determined by integration of the intensities of the protons of the NH groups in PMR spectra; absolute configurations were assigned on the basis of X-ray data.
[b] 1 equiv to **2**.
[c] 1 equiv to Zn.
[d] NaBr saturated aqueous solution (7 mL).
[e] DMF (1.2 equiv)/H_2O (0.5 equiv) to In.
[f] 15 mmol scale.
[g] 10 mmol scale.
[h] HPLC analysis, Daicel Chiralpak IB-3, eluent *n*-C_6H_{14}/*iso*-PrOH = 4:1, rate 1 mL/min, UV 254 nm.

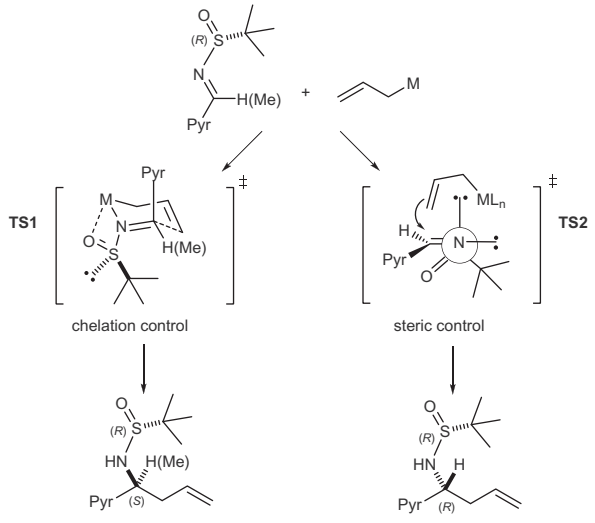


Figure 3. Proposed six-membered transition state with chelation **TS1** and open transition state with steric **TS2** control for the metal-mediated (*R*)-*N*-*tert*-butylsulfinyl imines allylation.

unchanged (run 6). Changing the solvent to DMF or DMA gave the product with high de and good yield (runs 7 and 8). Unexpectedly we found the use of the conventional protocol with In/THF system was not possible. The reaction does not proceed even at elevated temperature, since the In turnings were covered with a film of insoluble salt. It could be feasible that the pyrazol fragment responsible for this behavior of In, forms insoluble complexes which block the In surface. Nevertheless, the addition of some (Table 1, note d) DMF/H_2O (10:1) initiates the reaction and the product is formed in good yield and with similar selectivity to that in neat DMF (run 9).

Allylation of *N*-methyl derivative **2b** gave similar results (runs 10–13). The optimized conditions for the allylation of *N*-alkyl substituted substrates **2a**,**b** used either THF with a DMF/H_2O additive or neat DMF, with both systems showing close selectivity. However, when we attempted to scale up the reaction to 15 mmol the de decreased to 85%. The other substrate, imine **2c**, was less reactive for the allylation probably because of the unfavorable steric influence of the 3-methyl group in the pyrazole ring. TMEDA showed moderate de (70%) and low chemical yield (30%) of the allylation products **3c**/**4c** (run 14). This experiment could be a 'litmus test' for the reactivity toward organometallic compounds in the absence of activation of the imine's C=N bond via a chelation effect (TS1). The use of a more 'chelating' system In/THF with a DMF/H_2O additive improved the de (up to 80%) and chemical yield (run 15). It should be noted that a Zn/THF system gives the same major isomer as with In (run 16) which clearly demonstrates the poor reactivity of **2c** via an open transition state (compare runs 5 and 16). In-mediated allylation of **2c** in DMF perfectly matched the activation via a chelated transition state and the product was formed with 98% de. Scaling the reaction up to 10 mmol led to a slight deterioration in de (95%) (run 18). Allylation of phenyl-pyrazol derivative **2d** under the optimized conditions with In gave similar selectivities (compare runs 20, 21 with 7, 9, and 10) with Me- and Et-derivatives. However, the Zn-mediated allylations of **2d** (run 19, 46% de) and **2a** (run 5, 26% de) showed the slight influence of N-substituents on the de. Moreover, in case of **2c**, the presence of two Me-groups had a more profound effect (run 16, 66% de). This means that the 2-pyrazol nitrogen with a lone pair would participate in the transition state of allylation in THF via coordination with a metal ion. The more bulky substituents that are present around the 2-nitrogen of the pyrazole ring, the less accessible it be-

comes for coordination and weakens this undesirable effect. All of the products **3**/**4a**–**d** were separated by chromatography to diastereomerically pure compounds that allowed us to unambiguously detect isomers by proton NMR spectra and safely use isomers **4** for further synthetic transformations. It was assumed that ketimine **2e** would be inert toward non-activating open transition state TS2 and the best system could be In-based. Unfortunately, we were unable to initiate the In-mediated addition in our standard conditions. Therefore, we tested the Zn/THF system and found that the reaction proceeded smoothly to give a product with high de (86%) in nearly quantitative yield (run 19). The addition of $Zn(OTf)_2$ led to a further improvement of de of up to 97% (run 20). Decreasing the temperature to 0 °C and slightly changing the experimental conditions allowed us to obtain a pure diastereoisomer (it was impossible to detect the second isomer by NMR) thus avoiding tedious purification techniques, because we were unable to separate the mixture of **3e**/**4e** into individual isomers by using conventional chromatography. Having in hand enough of the pure material, we started the synthesis of the target piperidine-2,4-diones.

On the first stage sulfinylamides **4a**–**e** were converted to *N*-Boc derivatives **5a**–**e** in a one pot reaction (Scheme 2).

It is well documented that the acid catalyzed cleavage of sulfinylamides occurs without racemization[7] and gives the corresponding homoallylamines. Methanolic solutions of sulfinylamides **4a**–**e** were treated with 4 M HCl in dioxane. After the cleavage was completed, as was monitored by TLC, the excess HCl and MeOH were removed by evaporation. The resulting solid of the dihydrochloride of the pyrazolyl substituted homoallylamine was treated with Boc-anhydride in the presence of excess of Et_3N and after purification *N*-Boc amines **5a**–**e** were obtained in high yield. The cyclobromocarbamation reaction was carried out by the treatment of TFA salt **5a**–**e** with NBS to furnish mixtures of diastereoisomers **6a**–**e** in different ratios. It is worth noting that TFA addition was critical in this transformation. The action of NBS on unprotonated pyrazol derivatives only led to low yields of bromourethanes. The ratio of diastereomeric bromides **5a**–**c** was approximately 1.4:1, **5d**—2.5:1 and **5e** (1:3.4). The major isomers (*S*,*R*)-**6b** and (*S*,*S*)-**6e** were obtained in pure form via consecutive crystallizations of bromide mixtures from EtOAc. Their absolute configurations were established by X-ray single crystal analysis (Figs. 4 and 5), which allowed us to assign the configuration of all the products by analogy. The central six-membered heterocycle in (*S*,*R*)-**6b** adopts an unsymmetrical half-boat conformation with deviations of the C4 and C5 atoms from the mean plane of the other ring atoms. The bulky bromomethyl and 1-methyl-1*H*-pyrazole substituents occupy the more

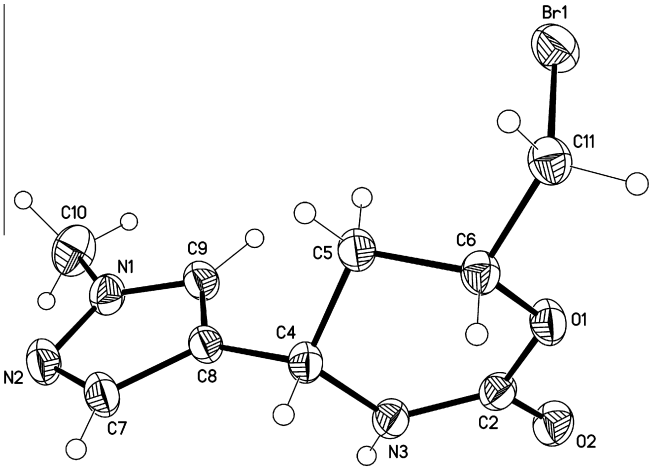


Figure 4. Major isomer (*S*,*R*)-**6b** with 50% probability ellipsoids.

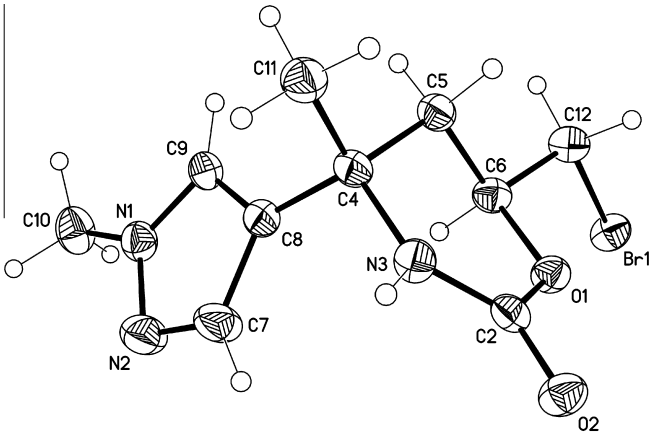
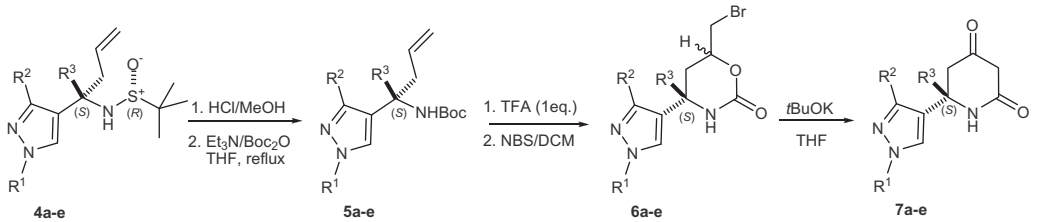


Figure 5. Major isomer (*S*,*S*)-**6e** with 50% probability ellipsoids.

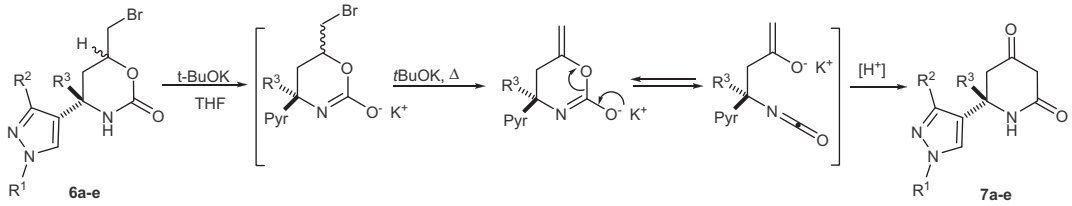
sterically favorable equatorial positions. The absolute configurations of the asymmetric centers were established as (4*S*,6*R*).

Compound **6e** crystallizes in the monoclinic space group $P2_1$ with two crystallographically independent molecules in the unit cell. The geometries of these independent molecules are very similar. The central six-membered heterocycle in **6e** adopts an unsymmetrical half-chair conformation with deviations of the C4 and C5 atoms from the mean plane of the other ring atoms. The bulky



R^1,	R^2,	R^3	**5**, Yield	**6**, Yield,	*cis*/*trans*	**7**, Yield
Et,	H,	H	**5a**, 91%	**6a**, 85%,	1.4:1	**7a**, 92%
Me,	H,	H	**5b**, 88%	**6b**, 83%,	1.4:1	**7b**, 96%
Et,	Me,	H	**5c**, 90%	**6c**, 78%,	1.5:1	**7c**, 90%
Ph,	H,	H	**5d**, 86%	**6d**, 78%,	2.5:1	**7d**, 88%
Me,	H,	Me	**5e**, 85%	**6e**, 92%,	1:3.4	**7e**, 95%

Scheme 2. Transformation of diastereomerically pure sulfinamides to (*S*)-6-pyrazolylpiperidine-2,4-diones.



Scheme 3. Base mediated enolate–isocyanate rearrangement to piperidine-2,4-diones.

bromomethyl substituent occupies the more sterically favorable equatorial position, whereas the bulky 1-methyl-1*H*-pyrazole substituent is in an axial position. The absolute configurations of the asymmetric centers were established as (4*S*,6*S*).

The relative configuration of the substituents in **6e** was also determined in a NOESY experiment where NOE was observed between the CH proton in the oxazinane cycle and one of the CH protons in the pyrazole ring. This means that all the major isomers **3** of allylated sulfinylamides have an (*S*,*R*)-configuration, if the allyl addition goes through the TS1 (Fig. 2).

The mixtures of isomeric bromourethanes **6a–e** were subjected to a base (*t*BuOK) mediated rearrangement in THF (Scheme 2).

All of the reactions proceeded smoothly when using 2.5 equiv of *t*BuOK at 20–25 °C and were completed within 30–40 min. The potassium salt of the diones precipitated during the reaction; quenching the reaction mixture with acetic acid gave the target 6-(pyrazol-4-yl)-piperidine-2,4-diones in high yields. It should be noted that upon acidification, the temperature of the reaction mixture must not be higher than −10 °C, otherwise side products are formed. The proposed mechanism of the transformation includes several stages (Scheme 3).[4]

At first, *t*BuOK abstracts the acidic N–H proton to form a potassium salt. In the next stage, the abstraction of HBr occurred via an anionic substrate giving an unstable anionic enolate, which undergoes enolate–isocyanate rearrangement in the third stage. The resulting enolato-isocyanate is irreversibly cyclized to the piperidine-2,4-dione potassium salt, while the latter after acidification with AcOH releases the final product. Compounds **7a–e** were isolated in pure form by flash chromatography.

3. Conclusion

The In and Zn-mediated allylation of substituted pyrazol-4-yl derived (*R*)-*N*-*tert*-butanesulfinyl imines was found to proceed with highly diastereoselectivity (up to >99%) depending on the conditions and additives. The diastereomeric homoallylsulfinamides synthesized were isolated and characterized as pure diastereomers, which were then converted via consecutive treatment with HCl and Boc_2O into the corresponding pyrazol-4-yl-derived *N*-Boc-homoallylamines. The *N*-Boc-protected amines was subjected to a sequence of reactions: cyclobromocarbamation with NBS and enolate–isocyanate rearrangement with *t*BuOK, to give new enantiomerically pure (*S*)-6-(pyrazol-4-yl)-piperidine-2,4-diones in high yields.

4. Experimental section

4.1. General

The manipulations were carried out under an inert atmosphere of dry Ar. NMR spectra were recorded on Bruker Avance-300, 400 and 600 MHz instruments. Mass spectra were recorded on Finnigan Polaris Q Ion Trap spectrometer. Column chromatography was carried out using silica gel 60–230 mesh (Merck). Elemental analyses were performed in the microanalysis department of the Nesmeyanov Institute of Organoelement Compounds RAS (Moscow).

4.2. Experimental procedures

4.2.1. (*R*)-*N*-[(1-Ethyl-1*H*-pyrazol-4-yl)methylidene]-2-methyl-2-propanesulfinamide 2a

A solution of 1-ethyl-1*H*-pyrazole-4-carbaldehyde (1.20 g, 9.67 mmol), (*R*)-2-methyl-2-propanesulfinamide (1.28 g, 10.63 mmol), and Ti(O*i*Pr)$_4$ (14.2 g, 15 mL, 50 mmol) in THF (30 mL) was stirred with heating on a water bath at 50 °C for 20 h. The resulting mixture was poured into water (70 mL) with stirred for 15 min, then filtered and the precipitate was washed twice with DCM. The filtrate was diluted with water (100 mL) and extracted with DCM (20 mL × 3). The combined extracts were dried over K_2CO_3, filtered through the pad of silica gel, and evaporated under reduced pressure and dried in vacuo to afford pure **2a** 2.09 g (95.8%). $[\alpha]_D^{25} = -121.5$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H, CH=N), 7.86 (s, 1H, CH_{pyr}), 7.82 (s, 1H, CH_{pyr}), 4.17 (q, *J* = 7.3 Hz, 2H, Et), 1.48 (t, *J* = 7.3 Hz, 3H, Et), 1.17 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.42, 139.82, 130.48, 119.56, 57.30, 47.47, 22.41 3C, 15.27. MS (70 eV, EI): *m*/*z* (%) = 228 (14) $[MH]^+$, 185 (12), 171 (100), 144 (11), 137 (14), 123 (49), 122 (20), 97 (14), 96 (12), 95 (40), 94 (29), 68 (11), 41 (7). $C_{10}H_{17}N_3OS$ (227.3): calcd C 52.83, H 7.54, N 18.48; found C 52.62, H 7.41, N 18.35.

4.2.2. (*R*)-2-Methyl-*N*-[(1-methyl-1*H*-pyrazol-4-yl)methylidene]-2-propanesulfinamide 2b

A solution of 1-methyl-1*H*-pyrazole-4-carbaldehyde (2.73 g, 24.80 mmol), (*R*)-2-methyl-2-propanesulfinamide (3.30 g, 27.30 mmol), and Ti(O*i*Pr)$_4$ (35.2 g, 37.1 mL, 0.124 mol) in THF (60 mL) was stirred with heating on a water bath at 50 °C for 20 h. The resulting mixture was poured into water (100 mL) with stirring for 15 min, then filtered and the precipitate was washed twice with DCM. The filtrate was diluted with water (100 mL) and extracted with DCM (20 mL × 3). The combined extracts were dried over K_2CO_3, filtered through the pad of silica gel, and evaporated under reduced pressure and dried in vacuo to afford pure **2b** 5.16 g (97%). $[\alpha]_D^{25} = -130.7$ (*c* 1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H, CH=N), 7.83 (s, 1H, CH_{pyr}), 7.78 (s, 1H, CH_{pyr}), 3.89 (s, 3H, Me), 1.15 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.28, 139.91, 132.14, 119.86, 57.30, 39.29, 22.39 3C. MS (70 eV, EI): *m*/*z* (%) = 214 (60) $[MH]^+$, 157 (100), 130 (10), 109 (56), 108 (48), 83 (18), 82 (20), 81 (8), 41 (7). $C_9H_{15}N_3OS$ (213.3): calcd C 50.68, H 7.09, N 19.70, S 15.03, found C 50.42, H 7.11, N 19.55, S 14.88.

4.2.3. (*R*)-*N*-[(1-Ethyl-3-methyl-1*H*-pyrazol-4-yl)methylidene]-2-methyl-2-propanesulfinamide 2c

A solution of 1-ethyl-3-methyl-1*H*-pyrazole-4-carbaldehyde (1.40 g, 10.1 mmol), (*R*)-2-methyl-2-propanesulfinamide (1.36 g, 11.2 mmol), and Ti(O*i*Pr)$_4$ (14.2 g, 15 mL, 50 mmol) in THF (30 mL) was stirred with heating on a water bath at 50 °C for 20 h. The resulting mixture was poured into water (70 mL) with

stirring for 15 min, then filtered and the precipitate was washed twice with DCM. The filtrate was diluted with water (100 mL) and extracted with DCM (20 mL × 3). The combined extracts were dried over K_2CO_3, filtered through the pad of silica gel, evaporated under reduced pressure, and dried in vacuo that afford pure **2c** 2.72 g (97%). $[\alpha]_D^{25} = -93.7$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H, CH=N), 7.72 (s, 1H, CH_{pyr}), 4.09 (q, *J* = 7.2 Hz, 2H, Et), 2.41 (s, 3H, Me), 1.45 (t, *J* = 7.2 Hz, 3H, Et), 1.17 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.57, 149.67, 131.99, 116.92, 56.95, 47.12, 22.34 3C, 15.27, 13.40. MS (70 eV, EI): *m*/*z* (%) = 242 (10) $[MH]^+$, 202 (7), 185 (45), 138 (10), 137 (68), 136 (10), 111 (19), 110 (25), 109 (26), 108 (17), 83 (11). $C_{11}H_{19}N_3OS$ (241.3): calcd C 54.74, H 7.93, N 17.41; found C 54.60, H 7.88, N 17.49.

4.2.4. (*R*)-2-Methyl-*N*-[(1-phenyl-1*H*-pyrazol-4-yl)methylidene]-2-propanesulfinamide 2d

A solution of 1-phenyl-1*H*-pyrazole-4-carbaldehyde (5.0 g, 29.0 mmol), (*R*)-2-methyl-2-propanesulfinamide (3.51 g, 29.0 mmol) and Ti(O*i*Pr)$_4$ (47.7 g, 50 mL, 0.168 mol) in THF (50 mL) was stirred with heating on a water bath at 50 °C for 20 h. The resulting mixture was poured into water (250 mL) with stirring for 15 min, then filtered, and the precipitate was washed twice with DCM. The filtrate was diluted with water (200 mL) and extracted with DCM (50 mL × 3). The combined extracts were dried over K_2CO_3, filtered through the pad of silica gel and evaporated under reduced pressure, and crystallized from *i*Pr$_2$O/*n*-hexane to afford pure **2d** 6.78 g (85%). R_f: 0.5 (EtOAc/*n*-hexane, 1:1) $[\alpha]_D^{25} = -98.7$ (*c* 1, $CHCl_3$). Mp 67.5–68.5 °C (*i*Pr$_2$O/*n*-hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H, CH=N), 8.34 (s, 1H, CH_{pyr}), 8.13 (s, 1H, CH_{pyr}), 7.72 (d, *J* = 7.9 Hz, 2H, Ph), 7.51–7.47 (m, 2H, Ph), 7.38–7.34 (m, 1H, Ph), 1.26 (s, 9H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.21, 141.15, 139.33, 129.63 2C, 128.62, 127.59, 121.38, 119.56 2C, 57.56, 22.51 3C ppm. MS (70 eV, EI): *m*/*z* (%) = 276 (27) $[MH]^+$, 220 (14), 219 (91), 218 (11), 172 (21), 171 (100), 170 (24), 145 (12), 144 (52), 77 (11). $C_{14}H_{17}N_3OS$ (275.4): calcd C 61.06, H 6.22, N 15.26, S 11.64; found C 60.93, H 6.19, N 15.25, S 11.64.

4.2.5. (*R*)-2-Methyl-*N*-[1-(1-methyl-1*H*-pyrazol-4-yl)ethylidene]-2-propanesulfinamide 2e

1-(1-Methyl-1*H*-pyrazol-4-yl)-1-ethanone (1.05 g, 8.46 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.96 g, 7.9 mmol) and Ti(O*i*Pr)$_4$ (9.1 g, 9.57 mL, 32 mmol) were mixed in a high pressure tube, sealed and irradiated in a microwave reactor at 85 °C (50 W) for 24 h. The progress of the reaction was monitored by ^1H NMR. After disappearance of the sulfinamide signals, the reaction mixture was diluted with THF (30 mL) and poured into water (70 mL). After 20 min of stirring, the suspension was filtered through a pad of Super Cel, and the precipitate was washed two times with DCM. The filtrate was diluted with water (100 mL) and extracted with DCM (20 mL × 3). The combined extracts were dried over K_2CO_3 and evaporated under reduced pressure. The residue was recrystallized from diethyl ether to afford **2e** (1.59 g, 88%) as a beige crystalline solid. R_f: 0.26 (EtOAc). $[\alpha]_D^{25} = -73.7$ (*c* 1, $CHCl_3$). Mp 88–89 °C (Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H, CH_{pyr}), 7.81 (s, 1H, CH_{pyr}), 3.93 (s, 3H, NMe), 2.60 (s, 3H, MeC=N), 1.27 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.19, 139.40, 130.98, 124.47, 56.74, 39.36, 22.26 3C, 20.87. MS (70 eV, EI): *m*/*z* (%) = 228 (12) $[MH]^+$, 211 (2), 172 (12), 171 (100), 170 (12), 130 (51), 123 (36), 108 (72), 107 (18), 89 (12), 82 (34), 81 (10). $C_{10}H_{17}N_3OS$ (227.3): calcd C 52.83, H 7.54, N 18.48, S 14.11; found C 52.80, H 7.55, N 18.35, S 13.97.

4.2.6. (*R*)-*N*-[(1*R*)-1-(1-Ethyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-methyl-2-propanesulfinamide 3a and (*R*)-*N*-[(1*S*)-1-(1-ethyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-methyl-2-propanesulfinamide 4a

To a solution of **2a** (1.44 g, 6.0 mmol) in THF (12 mL) were added In turnings (2.07 g, 18.0 mmol), allylBr (2.18 g, 1.57 mL, 18.0 mmol), an activating additive—DMF/H_2O (10:1, 0.6 mL) and the mixture was stirred for 14 h at 20 °C. The reaction mixture was quenched with satd NH_4Cl (40 mL), extracted with Et_2O (20 mL × 3), and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to dryness. The ratio of diastereomers **4a**/**3a** was 96:4 in the residue, and were separated by FC on silica gel with *n*-hexane/EtOAc = 1:2 to afford (1.38 g) **4a** and (0.052 g) **3a** as oils, total yield: 1.43 g (89%). Compound **4a**, R_f max: 0.12 (*n*-hexane/EtOAc, 1:2). $[\alpha]_D^{25} = -81.5$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H, CH_{pyr}), 7.32 (s, 1H, CH_{pyr}), 5.77–5.67 (m, 1H, CH=), 5.16–5.11 (m, 2H, CH_2=), 4.44 (td, *J* = 3.5, 7.0 Hz, 1H, CHN), 4.13 (q, *J* = 7.3 Hz, 2H, Et), 3.94 (d, *J* = 3.2 Hz, 1H, NH), 2.60–2.47 (m, 2H, CH_2), 1.44 (t, *J* = 7.3 Hz, 3H, Et), 1.17 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.52, 133.98, 127.33, 122.04, 119.14, 55.80, 49.71, 46.91, 42.59, 22.62 3C, 15.43. $C_{13}H_{23}N_3OS$ (269.4): calcd C 57.96, H 8.61, N 15.60; found C 57.82, H 8.65, N 15.44. Compound **3a** R_f min: 0.06 (*n*-hexane/EtOAc, 1:2). $[\alpha]_D^{25} = -33.8$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H, CH_{pyr}), 7.39 (s, 1H, CH_{pyr}), 5.72–5.63 (m, 1H, CH=), 5.06–5.01 (m, 2H, CH_2=), 4.39 (td, *J* = 6.3, 5.6 Hz, 1H, CHN), 4.07 (q, *J* = 7.3 Hz, 2H, Et), 3.40 (d, *J* = 5.6 Hz, 1H, NH), 2.60–2.48 (m, 2H, CH_2), 1.40 (t, *J* = 7.3 Hz, 3H, Et), 1.15 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.18, 134.17, 127.61, 123.07, 118.20, 56.04, 51.50, 47.00, 41.02, 22.66 3C, 15.45. MS (70 eV, EI): *m*/*z* (%) = 270 (2.5) $[MH]^+$, 213 (25), 172 (17), 170 (12), 150 (56), 149 (100), 147 (14), 135 (10), 122 (12), 121 (17), 109 (10), 108 (10), 97 (11), 94 (37), 41 (7). $C_{13}H_{23}N_3OS$ (269.4): calcd C 57.96, H 8.61, N 15.60; found C 57.79, H 8.70, N 15.66.

4.2.7. (*R*)-2-Methyl-*N*-[(1*R*)-1-(1-methyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-propanesulfinamide 3b and (*R*)-2-methyl-*N*-[(1*S*)-1-(1-methyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-propanesulfinamide 4b

The procedure was the same as that described for the synthesis of **4a**/**3a** mixture (2 mmol scale). After work-up and evaporation, a residue was obtained consisting of two diastereomers **4b**/**3b** = 96.7:3.3, which were separated by FC on silica gel with *n*-hexane/EtOAc, 1:2 to afford (0.47 g) **4b** and (0.015 g) **3b** as oils, total yield: 0.49 g (95%). Compound **4b**, R_f max: 0.34 (EtOAc). $[\alpha]_D^{25} = -110.2$ (*c* 1, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, CH_{pyr}), 7.25 (s, 1H, CH_{pyr}), 5.71 (dddd, *J* = 6.4, 7.9, 10.3, 6.6 Hz, 1H, CH=), 5.15–5.11 (m, 2H, CH_2=), 4.44–4.40 (m, 1H, CHN), 3.83 (s, 3H, Me), 3.57 (d, *J* = 2.8 Hz, 1H, NH), 2.58–2.43 (m, 2H, CH_2), 1.15 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.87, 134.01, 128.8, 122.58, 119.30, 55.58, 49.26, 42.78, 38.97, 22.61 3C. MS (70 eV, EI): *m*/*z* (%) = 256 (8) $[MH]^+$, 199 (32), 158 (18), 136 (71), 135 (100), 133 (22), 121 (12), 109 (21), 108 (47), 95 (17), 94 (25), 93 (12), 83 (17), 67 (9), 41 (7). $C_{12}H_{21}N_3OS$ (255.4): calcd C 56.44, H 8.29, N 16.45; found C 56.39, H 8.27, N 16.30. Compound **3b**, R_f min: 0.19 (EtOAc). $[\alpha]_D^{25} = -40.6$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H, CH_{pyr}), 7.36 (s, 1H, CH_{pyr}), 5.71 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, CH=), 5.07–5.12 (m, 2H, CH_2=), 4.38 (q, *J* = 6.3 Hz, 1H, CHN), 3.80 (s, 3H, Me), 3.34 (d, *J* = 5.7 Hz, 1H, NH), 2.59–2.47 (m, 2H, CH_2), 1.15 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.42, 134.10, 129.25, 123.47, 118.26, 55.99, 51.38, 41.02, 38.96, 22.66 3C. $C_{12}H_{21}N_3OS$ (255.4): calcd C 56.44, H 8.29, N 16.45; found C 56.40, H 8.19, N 16.25.

4.2.8. (*R*)-*N*-[(1*R*)-1-(1-Ethyl-3-methyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-methyl-2-propanesulfinamide 3c and (*R*)-*N*-[(1*S*)-1-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-methyl-2-propanesulfinamide 4c

To a solution of **2c** (2.30 g, 9.54 mmol) in DMF (30 mL) were added In turnings (3.28 g, 28.6 mmol) and allylBr (4.60 g, 3.30 mL, 38.0 mmol) and the mixture was stirred for 6 h at 0 °C. The reaction mixture was quenched with sat. NH_4Cl (20 mL), filtered through a pad of Super Cel and the filtrate was extracted with Et_2O (20 mL × 3). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to dryness. The residue consisted of two diastereomers **4c**/**3c** = 97.5:2.5, which were separated by FC on silica gel with *n*-hexane/EtOAc, 1:2 to afford **2c** (0.2 g), **4c** (2.32 g), and **3c** (0.059 g) as oils, total yield: 2.38 g (88%). Compound **4c** R_f max: 0.09 (*n*-hexane/EtOAc, 1:2). $[\alpha]_D^{25} = -107.7$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (s, 1H, CH_{pyr}), 5.79–5.65 (m, 1H, CH=), 5.17–5.11 (m, 2H, CH_2=), 4.39–4.34 (m, 1H, CHN), 4.04 (q, *J* = 7.3 Hz, 2H, Et), 3.54 (d, *J* = 1.9 Hz, 1H, NH), 2.60–2.44 (m, 2H, CH_2), 2.23 (s, 3H, Me), 1.42 (t, *J* = 7.3 Hz, 3H, Et), 1.16 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.31, 134.43, 127.86, 118.89, 118.75, 55.38, 49.12, 46.68, 41.99, 22.62 3C, 15.53, 12.44. MS (70 eV, EI): *m*/*z* (%) = 284 (33) $[MH]^+$, 227 (6), 226 (6), 186 (11), 164 (25), 163 (100), 161 (10), 149 (15), 135 (16), 133 (9), 111 (16), 108 (12), 94 (9). $C_{14}H_{25}N_3OS$ (283.4): calcd C 59.33, H 8.89, N 14.83; found C 59.42, H 8.90, N 14.76. Compound **3c** R_f min: 0.04 (*n*-hexane/EtOAc, 1:2). $[\alpha]_D^{25} = -63.5$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H, CH_{pyr}), 5.74–5.64 (m, 1H, CH=), 5.12–5.06 (m, 2H, CH_2=), 4.39 (ddd, *J* = 3.3, 6.4, 7.0 Hz, 1H, CHN), 4.07 (q, *J* = 7.2 Hz, 2H, Et), 3.37 (d, *J* = 2.6 Hz, 1H, NH), 2.66 (dt, *J* = 6.8, 13.8 Hz, 1H, CH_AH_B) 2.53 (dt, *J* = 7.0, 13.8 Hz, 1H, CH_AH_B), 2.25 (s, 3H, Me), 1.45 (t, *J* = 7.2 Hz, 3H, Et), 1.20 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.08, 134.23, 127.69, 119.34, 118.26, 55.69, 50.28, 46.76, 40.73, 22.62 3C, 15.55, 12.30. $C_{14}H_{25}N_3OS$ (283.4): calcd C 59.33, H 8.89, N 14.83; found C 59.26, H 8.84, N 14.79.

4.2.9. (*R*)-2-Methyl-*N*-[(1*R*)-1-(1-phenyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-propanesulfinamide 3d and (*R*)-2-methyl-*N*-[(1*S*)-1-(1-phenyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-propanesulfinamide 4d

The procedure was the same as that used for the preparation of **3c**/**4c**. Isomers **3d**/**4d** were separated by FC on silica gel with *n*-hexane/EtOAc/*i*PrOH, 10:10:0.15 to afford **3d** (0.12 g) as an oil and **4d** (1.81 g) as a solid, total yield: 1.93 g (90%). Compound **4d** R_f min: 0.33 (*n*-hexane/EtOAc/*i*PrOH, 10:10:0.15). Mp 84–85 °C (Et_2O/*n*-hexane), $[\alpha]_D^{25} = -100.9$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H, CH_{pyr}), 7.69 (s, 1H, CH_{pyr}), 7.67–7.66 (narr.m, 2H, Ph), 7.48–7.44 (m, 2H, Ph), 7.29–7.28 (m, 1H, Ph), 5.86–5.75 (m, 1H, CH=), 5.25–5.21 (m, 2H, CH_2=), 4.60–4.56 (m, 1H, CHN), 3.68 (d, *J* = 2.2 Hz, NH), 2.71–2.56 (m, 2H, CH_2), 1.23 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.97, 139.77, 133.79, 129.44 2C, 126.46, 125.43, 124.59, 119.62, 118.89 2C, 55.70, 49.28, 42.66, 22.63 3C. MS (70 eV, EI): *m*/*z* (%) = 318 (14) $[MH]^+$, 261 (27), 260 (8), 220 (8), 199 (8), 198 (53), 197 (100), 195 (8), 182 (9), 171 (11), 170 (14), 145 (15), 77 (12). $C_{17}H_{23}N_3OS$ (317.4): calcd C 64.32, H 7.30, N 13.24, S 10.10, found C 64.18, H 7.25, N 13.26, S 10.11. Compound **3d** R_f max: 0.43 (*n*-hexane/EtOAc/*i*PrOH, 10:10:0.15). $[\alpha]_D^{25} = -30.2$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H, CH_{pyr}), 7.67 (s, 2H, Ph), 7.65 (s, 1H, CH_{pyr}), 7.43–7.39 (m, 2H, Ph), 7.27–7.23 (m, 1H, Ph), 5.82–5.72 (m, 1H, CH=), 5.15–5.10 (m, 2H, CH_2=), 4.53 (dd, *J* = 6.4, 12.6 Hz, 1H, CHN), 3.49 (d, *J* = 5.9 Hz, 1H, NH), 2.71–2.59 (m, 2H, CH_2), 1.22 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.94, 139.40, 133.90, 129.38 2C, 126.48, 126.04, 125.38, 119.03 2C, 118.59, 56.15, 51.46, 40.95, 22.69 3C. $C_{17}H_{23}N_3OS$ (317.4): calcd C 64.32, H 7.30, N 13.24, S 10.10, found C 64.25, H 7.33, N 13.25, S 10.09.

4.2.10. (*R*)-2-Methyl-*N*-[(1*S*)-1-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-3-butenyl]-2-propanesulfinamide 4e

To Zn (0.53 g, 8.2 mmol) dust activated by stirring for 10 min with two drops of TMSCl in THF (20 mL) allylBr (0.99 g, 0.71 mL, 8.2 mmol) and $Zn(OTf)_2$ (0.98 g, 2.7 mmol) were added at 0 °C. The mixture was then stirred at this temperature for a minute followed by the dropwise addition of **2e** (0.62 g, 2.7 mmol) in THF (4 mL) for 5 min. The reaction mixture was stirred additionally for 30 min (TLC control) and quenched with a satd NH_4Cl solution. The reaction mixture was diluted with ether, and the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give pure **4e** (0.72 g, 98%). According to crude ^{1}H NMR, only a single diastereomer was detected. An analytical sample was obtained by passing crude **4e** through a short pad of silica gel in EtOAc/*n*-hexane = 2:1. The ratio of **4e**/**3e** isomers was determined by chiral HPLC to be 99.7:0.3; retention times: major peak—2.53 min; minor peak—2.06 min. Column Diacel Chiralpak IB-3, eluent *n*-C_6H_{14}/*i*PrOH = 4:1, rate 1 mL/min, UV 254 nm. Compound **4e**, R_f min: 0.09 (EtOAc/*n*-hexane, 2:1). $[\alpha]_D^{25} = -75.5$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H, CH_{pyr}), 7.32 (s, 1H, CH_{pyr}), 5.79–5.68 (m, 1H, CH=), 5.18–5.15 (m, 2H, CH_2=), 3.89 (s, 3H, NMe), 3.56 (s, 1H, NH), 2.63 (dd, *J* = 6.6, 13.5 Hz, 1H, CH_AH_B), 2.56 (dd, *J* = 8.0, 13.5 Hz, 1H, CH_AH_B), 1.67 (s, 3H, Me), 1.20 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.49, 133.24, 128.32, 127.49, 119.89, 55.93, 55.42, 49.15, 39.03, 28.32, 22.73 3C. MS (70 eV, EI): *m*/*z* (%) = 270 (10) $[MH]^+$, 228 (4), 172 (18), 150 (37), 149 (100), 147 (8), 135 (12), 108 (24), 95 (24), 83 (6). $C_{13}H_{23}N_3OS$ (269.4): calcd C 57.96, H 8.61, N 15.60, S 11.90, found C 57.78, H 8.65, N 15.55, S 11.79.

4.2.11. General procedure for the transformation of sulfinamides to *N*-Boc derivatives

Sulfinamide (6 mmol) was dissolved in MeOH (10 mL) after which HCl 4 M solution in dioxane (6 mL, 24 mmol) was added and the mixture was left for 2 h. The solution was then evaporated under reduced pressure to dryness. To the solid residue were added THF (15 mL) and Et_3N (3.0 g, 4.2 mL, 30 mmol), after which the suspension was stirred at reflux for 10 min; next Boc_2O (2.18 g, 10 mmol) was added and the heating was continued for 2 h. The suspension was concentrated on a rotary evaporator, then diluted with *n*-hexane (15 mL) and water (10 mL). The organic layer was separated, dried over K_2CO_3, evaporated, and the residual oil was subjected to FC in *n*-hexane/EtOAc, 4:1 to remove the excess Boc_2O, then in *n*-hexane/EtOAc, 2:1 to afford the *N*-Boc derivative.

4.2.12. (*S*)-*tert*-Butyl *N*-[1-(1-ethyl-1*H*-pyrazol-4-yl)-3-butenyl] carbamate 5a

Yield: 91%. R_f: 0.43 (EtOAc). $[\alpha]_D^{25} = -40.8$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1H, CH_{pyr}), 7.29 (s, 1H, CH_{pyr}), 5.75 (ddt, *J* = 7.0, 9.9, 14.0 Hz, 1H, CH=), 5.13–5.06 (m, 2H, CH_2=), 4.75 (br m, 2H, NH and CHN), 4.11 (q, *J* = 7.3 Hz, 2H, Et), 2.57–2.46 (br m, 2H, CH_2), 1.45 (t, *J* = 7.3 Hz, 3H, Et), 1.43 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.26, 136.93, 134.13, 126.33, 123.09, 118.08, 79.35, 46.95, 45.97, 40.35, 28.38 3C, 15.49. MS (70 eV, EI): *m*/*z* (%) = 266 (3) $[MH]^+$, 168 (100), 150 (12), 149 (12), 124 (57), 122 (13), 97 (25), 96 (33), 69 (14), 41 (7). $C_{14}H_{23}N_3O_2$ (265.4): calcd C 63.37, H 8.74, N 15.84, found C 63.41, H 8.69, N 15.75.

4.2.13. (*S*)-*tert*-Butyl *N*-[1-(1-methyl-1*H*-pyrazol-4-yl)-3-butenyl] carbamate 5b

Yield: 88%. R_f: 0.38 (EtOAc). $[\alpha]_D^{25} = -41.2$ (*c* 1, $CHCl_3$). Mp 62–63 °C (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H, CH_{pyr}), 7.22 (s, 1H, CH_{pyr}), 5.71 (ddt, *J* = 7.0, 10.2, 17.2 Hz, 1H, CH=), 5.12–5.06 (m, 2H, CH_2=), 4.77–4.07 (br m, 2H, NH and CHN), 3.80 (s, 3H, NMe), 2.54–2.41 (m, 2H, CH_2), 1.39 (s, 9H, *t*Bu). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 155.22, 137.15, 134.08, 128.01, 123.49, 118.11, 79.35, 45.91, 40.34, 38.89, 28.37 3C. MS (70 eV, EI): *m*/*z* (%) = 252 (2) $[MH]^+$, 210 (4), 155 (7), 154 (100), 136 (12), 135 (11), 110 (49), 108 (14), 83 (42), 41 (7). $C_{13}H_{21}N_3O_2$ (251.32): calcd C 62.13, H 8.42, N 16.72, found C 62.20, H 8.41, N 16.69.

4.2.14. (*S*)-*tert*-Butyl *N*-[1-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-3-butenyl]carbamate 5c

Yield: 90%. R_f: 0.49 (EtOAc). $[\alpha]_D^{25}$ = −39.1 (*c* 1, $CHCl_3$). Mp 68–69 °C (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H, CH_{pyr}), 5.78–5.68 (m, 1H, CH=), 5.11–5.04 (m, 2H, CH_2=), 4.64 (br m, 2H, NH and CHN), 4.03 (q, *J* = 7.3 Hz, 2H, Et), 2.49 (br m, 2H, CH_2), 2.22 (s, 3H, Me), 1.43–1.39 (m, 12H, Et and *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.08, 146.00, 134.39, 126.56, 120.03, 117.75, 79.27 br, 46.64, 45.77 br, 40.21, 28.36 3C, 15.61, 12.13. MS (70 eV, EI): *m*/*z* (%) = 280 (5) $[MH]^+$, 183 (10), 182 (100), 164 (9), 163 (13), 138 (40), 136 (9), 111 (47), $C_{15}H_{25}N_3O_2$ (279.4): calcd C 64.49, H 9.02, N 15.04, found C 64.45, H 9.06, N 14.96.

4.2.15. (*S*)-*tert*-Butyl *N*-[1-(1-phenyl-1*H*-pyrazol-4-yl)-3-butenyl]carbamate 5d

The product was precipitated from *n*-hexane extracts during isolation and after recrystallization from *n*-heptane, the yield was 86%. R_f: 0.62 (EtOAc/*n*-hexane, 1:2). $[\alpha]_D^{25}$ = −53.7 (*c* 1, $CHCl_3$). Mp 107–108 °C (*n*-heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H, CH_{pyr}), 7.67 (s, 1H, CH_{pyr}), 7.64 (s, 2H, Ph), 7.46–7.42 (m, 2H, Ph), 7.30–7.26 (m, 1H, Ph), 5.85–5.75 (m, 1H, CH=), 5.19–5.12 (m, 2H, CH_2=), 4.84 (br s, 2H, NH and CHN), 2.65–2.53 (br m, 2H, CH_2), 1.46 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.26, 140.05, 139.22, 133.83, 129.42 2C, 126.43, 125.42 br, 124.69 br, 118.97 2C, 118.49, 79.63 br, 45.95 br, 40.26 br, 28.41 3C. MS (70 eV, EI): *m*/*z* (%) = 314 (14) $[MH]^+$, 272 (8), 217 (12), 216 (97), 198 (15), 197 (16), 173 (12), 172 (100), 145 (35), 118 (8), 77 (10), 41 (9). $C_{18}H_{23}N_3O_2$ (313.4): calcd C 68.98, H 7.40, N 13.41, found C 69.04, H 7.50, N 13.41.

4.2.16. (*S*)-*tert*-Butyl *N*-[1-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-3-butenyl]carbamate 5e

Yield: 85%. R_f: 0.56 (EtOAc/*n*-hexane, 1:2). $[\alpha]_D^{25}$ = −21.3 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H, CH_{pyr}), 7.23 (s, 1H, CH_{pyr}), 5.72–5.61 (m, 1H, CH=), 5.11–5.07 (m, 2H, CH_2=), 4.81 (br s, 1H, NH), 3.82 (s, 3H, NMe), 2.75–2.70 (br m, 1H, CH_AH_B, allyl), 2.53 (dd, *J* = 7.4, 13.5 Hz, 1H, CH_AH_B, allyl), 1.56 (s, 3H, Me), 1.37 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.21 br, 136.61, 133.53, 128.43 br, 127.36, 118.93, 79.01 br, 52.24, 45.89 br, 38.91, 28.34 3C, 26.92 br. MS (70 eV, EI): *m*/*z* (%) = 266 (14) $[MH]^+$, 224 (8), 169 (9), 168 (100), 150 (16), 149 (25), 124 (67), 108 (9), 83 (39), 42 (12), 41 (9). $C_{14}H_{23}N_3O_2$ (265.4): calcd C 63.37, H 8.74, N 15.84, found C 63.30, H 8.81, N 15.82.

4.2.17. General procedure of the bromocyclocarbamation reaction

To a solution of *N*-Boc derivative (2 mmol) in DCM was added TFA (1 equiv) dropwise, followed by the addition of NBS (1.4 equiv). The mixture was stirred for 2 h, the progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure, after which the residue was treated with an Et_2O/EtOAc (2:1) mixture (15 mL) and NaOH 10% (5 mL) with rigorous stirring for 15 min. The organic layer was separated, dried over $MgSO_4$, evaporated, and the residue was subjected to FC in EtOAc to give a mixture of diastereomeric bromides. Where indicated, the bromides were obtained as single isomers by recrystallization from EtOAc.

4.2.18. (4*S*,6*R*)-6-(Bromomethyl)-4-(1-ethyl-1*H*-pyrazol-4-yl)-1,3-oxazinan-2-one 6a

Yield: 85% as a mixture *cis*/*trans* = 1.4:1, *cis*-**6a**. Mp 166–167 °C (EtOAc), $[\alpha]_D^{25}$ = +1.6 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H, CH_{pyr}), 7.42 (s, 1H, CH_{pyr}), 6.01 (s, 1H, NH), 4.63 (dd, *J* = 4.3, 11.6 Hz, 1H, C*H*NH), 4.52 (dddd, *J* = 2.2, 4.4, 6.8, 11.4 Hz, 1H, C*H*O), 4.13 (q, *J* = 7.3 Hz, 2H, Et), 3.56 (dd, *J* = 4.4, 10.7 Hz, 1H, CH_aH_bBr), 3.45 (dd, *J* = 6.7, 10.7 Hz, 1H, CH_aH_bBr), 2.42 (dddt, *J* = 1.7, 3.8, 13.7 Hz, 1H, CH_aH_bCHN), 1.86 (dt, *J* = 11.6, 13.7 Hz, 1H, CH_aH_bCHN), 1.45 (t, *J* = 7.3 Hz, 3H, Et) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.97, 136.73, 126.27, 121.08, 75.66, 47.29, 46.58, 34.47, 32.60, 15.47 ppm. MS (70 eV, EI): *m*/*z* (%) = 288/286 (2) $[M-H]^+$, 209 (10), 208 (100), 164 (65), 162 (15), 137 (28), 122 (15), 108 (17), 107 (40), 95 (20), 83 (12), 41 (10). $C_{10}H_{14}BrN_3O_2$ (288.14): calcd C 41.68, H 4.90, N 14.58, Br 27.73, found C 41.52, H 4.75, N 14.45, Br 27.93.

4.2.19. (4*S*,6*R*)-6-(Bromomethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1,3-oxazinan-2-one 6b

Yield: 83% as a mixture *cis*/*trans* = 1.4:1, *cis*-**6b**. Mp 185–186 °C (EtOAc), $[\alpha]_D^{25}$ = +0.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H, CH_{pyr}), 7.42 (s, 1H, CH_{pyr}), 6.26 (s, 1H, NH), 4.65 (dd, *J* = 4.4, 11.8 Hz, 1H, C*H*NH), 4.57–4.52 (m, 1H, C*H*O), 3.89 (s, 3H, Me), 3.59 (dd, *J* = 4.4, 10.5 Hz, 1H, CH_aH_bBr), 3.47 (dd, *J* = 6.7, 10.5 Hz, 1H, CH_aH_bBr), 2.42 (dm, *J* = 11.4 Hz, 1H, CH_aH_bCHN), 1.88 (dt, *J* = 11.4, 13.4 Hz, 1H, CH_aH_bCHN). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.08, 136.90, 127.98, 121.43, 75.65, 46.46, 39.20, 34.42, 32.61. MS (70 eV, EI): *m*/*z* (%) = 274/272 (4) $[M-H]^+$, 195 (12), 194 (100), 150 (61), 148 (11), 123 (25), 109 (21), 108 (50), 107 (12), 95 (19), 83 (13), 41 (10). $C_9H_{12}BrN_3O_2$ (274.1): calcd C 39.43, H 4.41, N 15.33, Br 29.15, found C 39.46, H 4.50, N 15.28, Br 28.97.

4.2.20. (4*S*,6*R*)-6-(Bromomethyl)-4-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-1,3-oxazinan-2-one 6c

Yield: 78% as a mixture *cis*/*trans* = 1.4:1. Major isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H, CH_{pyr}), 6.04 (s, 1H, NH), 4.59–4.51 (m, 2H, C*H*NH and C*H*O), 4.05 (q, *J* = 7.3 Hz, 2H, Et), 3.56 (dd, *J* = 4.4, 10.8 Hz, 1H, CH_aH_bBr), 3.46 (dd, *J* = 6.5, 10.8 Hz, 1H, CH_aH_bBr), 2.35 (d, *J* = 13.7 Hz, 1H, CH_aH_bCHN), 2.21 (s, 3H, Me), 1.83 (dt, *J* = 11.7, 13.7 Hz, 1H, CH_aH_bCHN), 1.43 (t, *J* = 7.3 Hz, 3H, Et). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.21, 145.32, 126.83, 118.11, 75.66, 46.91, 46.43, 33.87, 32.78, 15.50, 12.03. MS (70 eV, EI): *m*/*z* (%) = 303/301 (1) $[M]^+$, 302/300 (2) $[M-H]^+$, 223 (14), 222 (100), 179 (13), 178 (38), 161 (28), 151 (19), 137 (15), 136 (18), 135 (12), 123 (10), 111 (27), 109 (23), 108 (25). $C_{11}H_{16}BrN_3O_2$ (302.2): calcd C 43.72, H 5.34, N 13.91, Br 26.44, found C 43.86, H 5.40, N 13.83, Br 26.30.

4.2.21. (4*S*,6*R*)-6-(Bromomethyl)-4-(1-phenyl-1*H*-pyrazol-4-yl)-1,3-oxazinan-2-one 6d

Yield: 78% as a mixture *cis*/*trans* = 2.5:1; *cis*-**6d**. Mp 103–104 °C (CCl_4), $[\alpha]_D^{25}$ = +5.6 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H, CH_{pyr}), 7.64–7.62 (m, 3H, CH_{pyr}, Ph), 7.44–7.40 (m, 2H, Ph), 7.29–7.25 (m, 1H, Ph), 6.63 (s, 1H, NH), 4.69 (dd, *J* = 4.3, 11.6 Hz, 1H, C*H*NH), 4.55–4.50 (m, 1H, C*H*O), 3.54 (dd, *J* = 4.4, 10.7 Hz, 1H, CH_aH_bBr), 3.46 (dd, *J* = 6.6, 10.8 Hz, 1H, CH_aH_bBr), 2.44 (dm, *J* = 13.7 Hz, 1H, CH_aH_bCHN), 1.83 (dt, *J* = 11.6, 13.7 Hz, 1H, CH_aH_bCHN). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.29, 139.77, 138.66, 129.53 2C, 126.89, 124.90, 123.30, 119.16 2C, 75.60, 46.45, 34.26, 32.61. MS (70 eV, EI): *m*/*z* (%) = 335/337 (16) $[M]^+$, 257 (17), 256 (100), 212 (37), 198 (11), 197 (14), 185 (16), 171 (18), 170 (31), 169 (20), 145 (22), 144 (24), 143 (10), 117 (8), 104 (11), 77 (18), 41 (8). $C_{14}H_{14}BrN_3O_2$ (336.18): calcd C 50.02, H 4.20, N 12.50, Br 23.77, found C 50.10, H 4.23, N 12.42, Br 23.68.

4.2.22. (4*S*,6*S*)-6-(Bromomethyl)-4-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1,3-oxazinan-2-one 6e

Yield: 92% as a mixture *trans*/*cis* = 3.4:1, R_f: 0.18 (EtOAc), *trans*-**6e**. Mp 125–126 °C (EtOAc), $[\alpha]_D^{25}$ = +17.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 2H, $2CH_{pyr}$), 7.22 (s, 1H, NH), 4.33–4.30 (m, 1H, CHO), 3.88 (s, 3H, NMe), 3.50 (dd, *J* = 10.8, 4.5 Hz, 1H, CH_AH_BBr), 3.45 (dd, *J* = 10.8, 6.1 Hz, 1H, CH_AH_BBr), 2.28 (d, *J* = 13.4 Hz, 1H, CH_AH_B), 1.96 (dd, *J* = 12.0, 13.4 Hz, 1H, CH_AH_B), 1.61 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.62, 135.66 br, 128.52 br, 127.82 br, 73.44, 51.79, 40.07, 39.15, 32.86, 31.60. MS (70 eV, EI): *m*/*z* (%) = 290/288 (6) $[MH]^+$, 274/272 (100), 230/228 (27), 208 (6), 165 (5), 164 (7), 149 (14), 148 (92), 123 (15), 122 (14), 121 (12), 108 (39), 107 (58), 95 (12), 83 (11), 42 (10). $C_{10}H_{14}BrN_3O_2$ (288.14): calcd C 41.68, H 4.90, N 14.58, Br 27.73, found C 41.60, H 4.83, N 14.62, Br 27.62.

4.2.23. General procedure for the *t*BuOK-mediated rearrangement to 6-pyrazolyl-piperidine-2,4-diones

To a solution of a mixture of the isomeric bromides was added *t*BuOK (2.5 equiv). The mixture was then stirred for 1 h at ambient temperature. The progress of the reaction was monitored by TLC (EtOAc/MeOH, 9:1). After completion (30–40 min), the reaction mixture was cooled to −10 °C and quenched with AcOH (3.0 equiv) in THF. Water was then added to precipitate the salts and the suspension was filtered through a pad of Super Cel. The filtrate was evaporated under reduced pressure at 40 °C and the residue was subjected to FC on silica gel first in EtOAc in order to remove the excess AcOH then in EtOAc/MeOH, 9:1 for product elution to finally afford the target dione.

4.2.24. (*S*)-6-(1-Ethyl-1*H*-pyrazol-4-yl)-piperidine-2,4-dione 7a

Yield: 92% as an oil, R_f: 0.28 (EtOAc/MeOH, 9:1), $[\alpha]_D^{25}$ = −28.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H, CH_{pyr}), 7.40 (br s, 1H, NH), 7.37 (s, 1H, CH_{pyr}), 4.84–4.80 (m, 1H, C*H*NH), 4.11 (q, *J* = 7.4 Hz, 2H, Et), 3.29 (d, *J* = 19.9 Hz, 1H, CH_aH_bCON), 3.21 (d, *J* = 19.9 Hz, 1H, CH_aH_bCON), 2.85 (dd, *J* = 4.5, 16.3 Hz, 1H, CH_aH_bCH), 2.73 (dd, *J* = 8.0, 16.3 Hz, 1H, CH_aH_bCH), 1.43 (t, *J* = 7.2 Hz, 3H, Et). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.71, 169.21, 136.75, 126.28, 120.54, 47.29, 47.25, 45.93, 44.62, 15.43. MS (70 eV, EI): *m*/*z* (%) = 207 (50) $[M]^+$, 165 (80), 164 (30), 150 (100), 137 (30), 136 (36), 124 (21), 123 (20), 122 (80), 121 (26), 97 (17), 96 (32), 95 (57), 94 (97), 93 (20), 81 (17), 80 (10), 69 (23), 68 (17), 67 (12). $C_{10}H_{13}N_3O_2$ (207.2): calcd C 57.96, H 6.32, N 20.28, found C 57.90, H 6.44, N 20.17.

4.2.25. (*S*)-6-(1-Methyl-1*H*-pyrazol-4-yl)-piperidine-2,4-dione 7b

Yield: 96% as a solid, R_f: 0.24 (EtOAc/MeOH, 9:1). Mp 154–155 °C (EtOAc), $[\alpha]_D^{25}$ = −54.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H, NH), 7.41 (s, 1H, CH_{pyr}), 7.36 (s, 1H, CH_{pyr}), 4.85–4.82 (m, 1H, C*H*NH), 3.87 (s, 3H, Me), 3.29 (d, *J* = 20.0 Hz, 1H, CH_aH_bCON), 3.21 (d, *J* = 20.0 Hz, 1H, CH_aH_bCON), 2.86 (dd, *J* = 4.4, 16.5 Hz, 1H, CH_aH_bCH), 2.74 (dd, *J* = 7.6, 16.5 Hz, 1H, CH_aH_bCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.73, 169.28, 136.93, 127.69, 120.99, 47.25, 45.89, 44.52, 39.17. MS (70 eV, EI): *m*/*z* (%) = 193 (30) $[M]^+$, 151 (85), 150 (40), 136 (100), 123 (30), 122 (38), 108 (80), 107 (35), 82 (20), 81 (63), 80 (90), 64 (22), 57 (15). $C_9H_{11}N_3O_2$ (193.2): calcd C 55.95, H 5.74, N 21.75, found C 56.03, H 5.77, N 21.67.

4.2.26. (*S*)-6-(1-Ethyl-3-methyl-1*H*-pyrazol-4-yl)-piperidine-2,4-dione 7c

Yield: 90% as a solid, R_f: 0.14 (EtOAc/MeOH, 9:1). Mp 130–131 °C (EtOAc) $[\alpha]_D^{25}$ = −70.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H, CH_{pyr}), 6.97 (s, 1H, NH), 4.11 (ddd, *J* = 1.9, 4.1, 8.9 Hz, 1H, C*H*NH), 4.07 (q, *J* = 7.3 Hz, 2H, Et), 3.36 (d, *J* = 19.7 Hz, 1H, CH_aH_bCON), 3.28 (d, *J* = 20.0 Hz, 1H, CH_aH_bCON), 2.84 (dd, *J* = 4.1, 16.5 Hz, 1H, CH_aH_bCH), 2.71 (dd, *J* = 8.9, 16.5 Hz, 1H, CH_aH_bCH), 2.25 (s, 3H, Me), 1.44 (t, *J* = 7.3 Hz, 3H, Et). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.79, 168.91, 145.54, 126.62, 117.42, 47.28, 46.99, 45.65, 44.49, 15.49, 12.09. MS (70 eV, EI): *m*/*z* (%) = 221 (35) $[M]^+$, 179 (58), 178 (21), 177 (24), 164 (100), 163 (20), 137 (44), 136 (76), 109 (50), 108 (46), 81 (16), 32 (44), 28 (83). $C_{11}H_{15}N_3O_2$ (221.2): calcd C 59.71, H 6.83, N 18.99, found C 59.73, H 6.80, N 19.06.

4.2.27. (*S*)-6-(1-Phenyl-1*H*-pyrazol-4-yl)-piperidine-2,4-dione 7d

Yield: 88% as a solid, R_f: 0.27 (EtOAc/*iso*PrOH, 60:1). Mp 149–150 °C (EtOAc), $[\alpha]_D^{25}$ = −27.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H, CH_{pyr}), 7.69 (s, 1H, CH_{pyr}), 7.66 (d, *J* = 8.0 Hz, 2H, Ph), 7.48–7.44 (m, 2H, Ph), 7.40 (s, 1H, NH), 7.34–7.31 (m, 1H, Ph), 4.95–4.94 (m, 1H, CHN), 3.37 (d, *J* = 20.0 Hz, 1H, CH_AH_BCON), 3.32 (d, *J* = 20.0 Hz, 1H, CH_AH_BCON), 2.96 (dd, *J* = 4.5, 16.4 Hz, 1H, CH_AH_B), 2.84 (d, *J* = 7.9, 16.4 Hz, 1H, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.26, 169.09, 139.65, 138.66, 129.58 2C, 127.10, 124.74, 122.77, 119.21 2C, 47.37, 45.92, 44.67. MS (70 eV, EI): *m*/*z* (%) = 256 (20) $[MH]^+$, 255 (100) $[M]^+$, 213 (73), 212 (29), 199 (10), 198 (78), 185 (18), 184 (13), 172 (30), 171 (39), 170 (52), 169 (19), 145 (28), 144 (51), 143 (12), 118 (11), 117 (11), 116 (10), 115 (11), 77 (24), 51 (11). $C_{14}H_{13}N_3O_2$ (255.27): calcd C 65.87, H, 5.13, N, 16.46, found: C 65.75, H, 5.23, N, 16.29.

4.2.28. (*S*)-6-Methyl-6-(1-methyl-1*H*-pyrazol-4-yl)-piperidine-2,4-dione 7e

Yield: 95% as an oil, R_f: 0.32 (EtOAc/MeOH, 9:1). $[\alpha]_D^{25}$ = +49.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H, NH), 7.36 (s, 1H, CH_{pyr}), 7.25 (s, 1H, CH_{pyr}), 3.85 (s, 3H, NMe), 3.22 (d, *J* = 20.7 Hz, 1H, CH_AH_BCON), 3.13 (d, *J* = 20.8 Hz, 1H, CH_AH_BCON), 2.97 (d, *J* = 15.7 Hz, 1H, CH_AH_B), 2.75 (d, *J* = 15.7 Hz, 1H, CH_AH_B), 1.64 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.70, 169.46, 136.09, 127.04, 126.89, 52.72, 51.24, 45.74, 39.16, 31.22. MS (70 eV, EI): *m*/*z* (%) = 208 (1.5) $[MH]^+$, 193 (11), 192 (100), 179 (7), 164 (7), 150 (20), 124 (20), 108 (26), 107 (44), 83 (8), 42 (6). $C_{10}H_{13}N_3O_2$ (207.23): calcd C 57.96, H 6.32, N 20.28, found: C 57.74, H 6.40, N 20.17.

4.2.29. X-ray structure determination

The crystal of (*S*,*R*)-**6b** ($C_9H_{12}N_3O_2Br$, *M* = 274.13) was orthorhombic, space group $P2_12_12_1$, at *T* = 100 K: *a* = 7.0532(2) Å, *b* = 8.1579(3) Å, *c* = 18.7940(6) Å, *V* = 1081.39(6) Å^3, *Z* = 4, d_{calcd} = 1.684 g/cm^3, *F*(000) = 552, μ = 3.786 mm^{-1}. 14278 total reflections (3131 unique reflections, R_{int} = 0.032) were measured on a three-circle Bruker APEX-II CCD diffractometer (λ (MoKα)-radiation, graphite monochromator, φ and ω scan mode, $2\theta_{max}$ = 60°) and corrected for absorption (T_{min} = 0.451, T_{max} = 0.601).[10a] The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The absolute structure was objectively determined by the refinement of the Flack parameter, which has become equal to 0.015(8). The hydrogen atom of the NH-group was localized in the difference-Fourier map and included in the refinement with fixed positional and isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)]. The final divergence factors were R_1 = 0.026 for 2890 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.062 for all independent reflections, *S* = 1.004. All calculations were carried out using the SHELXTL program.[10b]

The crystal of (*S*,*S*)-**6e** ($C_{10}H_{14}N_3O_2Br$, *M* = 288.15) was monoclinic, space group $P2_1$, at *T* = 120 K: *a* = 8.2769(8) Å,

b = 7.5148(7) Å, c = 19.0336(18) Å, β = 97.266(2)°, V = 1174.37(19) Å^3, Z = 2, d_{calcd} = 1.630 g/cm^3, $F(000)$ = 584, μ = 3.490 mm^{-1}. 15086 total reflections (6803 unique reflections, R_{int} = 0.037) were measured on a three-circle Bruker APEX-II CCD diffractometer (λ(MoKα)-radiation, graphite monochromator, φ and ω scan mode, $2\theta_{max}$ = 60°) and corrected for absorption (T_{min} = 0.421, T_{max} = 0.542).[10a] The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The absolute structure was objectively determined by the refinement of the Flack parameter, which has become equal to 0.008(6). The hydrogen atom of the NH-group was localized in the difference-Fourier map and included in the refinement with fixed positional and isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)]. The final divergence factors were R_1 = 0.034 for 5807 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.068 for all independent reflections, S = 0.919. All calculations were carried out using the SHELXTL program.[10b]

Crystallographic data for the investigated compounds have been deposited with the Cambridge Crystallographic Data Center, CCDC 952411 for (*S*,*R*)-**6b** and CCDC 952410 for (*S*,*S*)-**6e**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

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