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Tosylhydrazide-Promoted Diastereoselective Intramolecular 1,3-Dipolar Cycloadditions: Synthesis of Tetrahydropyrrolo[3,4-*c*]pyrazoles

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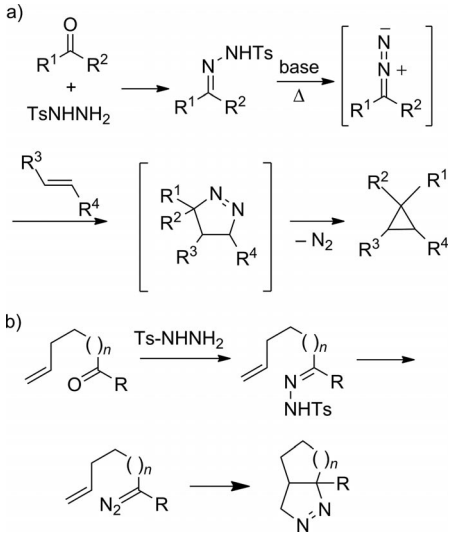
A very straightforward diastereoselective synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles by intramolecular 1,3-dipolar cycloaddition is described. The starting materials for the synthetic route are *N*-Boc-protected α-amino acids, which are first transformed into *N*-allyl-α-amino ketones through conventional methodologies. Then, a one-pot sequence that involves formation of a tosylhydrazone from the ketone, base-induced decomposition of the hydrazone, and intramolecular 1,3-dipolar cycloaddition of the diazo compound generated, gives rise to the bicyclic systems with total diastereoselectivity and high preservation of the enantiomeric purity. However, the analogous process employing α-amino aldehydes lacks stereoselectivity. DFT computational modeling has been carried out to account for the different behavior of the two types of systems.

Introduction

The desire for practical and synthetically efficient organic transformations has led to the discovery of many innovative strategies, concepts and methodologies. In this context, tosylhydrazones are versatile synthetic intermediates that have been used for the unconventional transformation of carbonyl compounds through different types of transition metal-catalyzed as well as metal-free processes.[1] Over the last few years, we and others have demonstrated that, in the presence of a metal catalyst, mainly Pd and Cu, tosylhydrazones can be used as a general source of diazo compounds without any limitation in the structure of the carbonyl precursor. Indeed, several important transformations such as cross-couplings,[2] oxidative cross-coupling[3] and cascade reactions[4] have been devised. The same strategy has been applied in the absence of a metal catalyst to provide for new metal-free carbon–carbon and carbon–heteroatom bond forming reactions.[5] Thus, tosylhydrazones can be seen as a vehicle to accomplish a variety of unconventional modifications of carbonyl compounds. Importantly, we have also demonstrated that this strategy is very useful for the elaboration of α-chiral carbonyl compounds, even if they are configurationally unstable, without erosion of the enantiomeric purity.[6]

On the other hand, and in continuing with our interest in metal-free processes employing tosylhydrazones, we have recently reported a new and general procedure for the synthesis of cyclopropanes by in situ base-promoted decomposition of tosylhydrazones in the presence of alkenes (Scheme 1, a).[7] This intermolecular process is postulated to proceed through diastereoselective construction of a pyrazoline ring by 1,3-dipolar cycloaddition followed by a spontaneous extrusion of nitrogen with retention of configuration of the pyrazoline stereocenters.[8]



Scheme 1. (a) Synthesis of cyclopropanes from tosylhydrazones by 1,3-dipolar cycloaddition/nitrogen extrusion sequence. (b) Synthesis of bicyclic diazenes by intramolecular 1,3-dipolar cycloaddition.

The intramolecular version of this type of 1,3-dipolar cycloaddition was reported for the first time by Padwa in 1980 by heating ω-alkenyltosylhydrazones in the presence of NaH to give 1-pyrazolines.[9] Over the last few years, this

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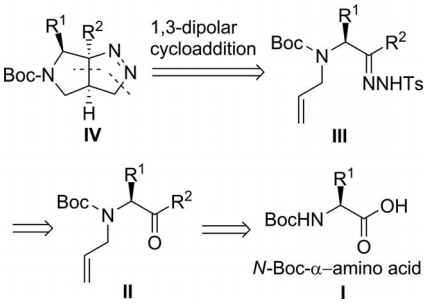
methodology has been very useful for the construction of bicyclic and/or tricyclic diazenes (Scheme 1, b).[10] Recently, Taber modified this procedure to generate the tosylhydrazone species in situ to deliver carbobicyclopropanes after irradiation of the corresponding bicyclic diazene derivatives.[11,12]

The construction of heterobicyclic systems is of great importance in the preparation of structurally complex and biologically important natural products.[13] With this in mind, and continuing with our interest in metal-free processes employing tosylhydrazones, we envisioned the possibility of an asymmetric one-pot synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles **IV** by an intramolecular 1,3-dipolar cycloaddition reaction, starting with α-amino acids derivatives **I** and following the retrosynthetic pathway shown in Scheme 2.

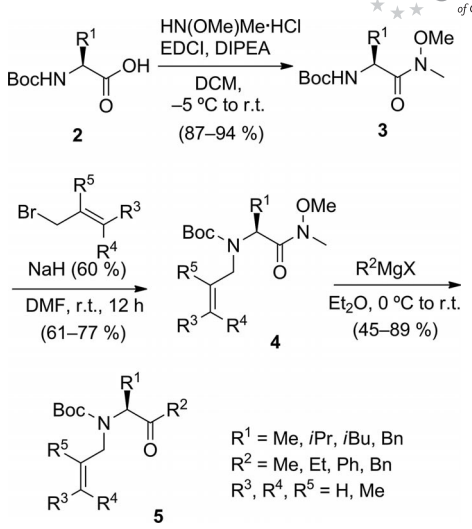


Scheme 2. Retrosynthetic analysis for the synthesis of heterobicyclic compounds.

As usual for intramolecular 1,3-dipolar cycloadditions, the present protocol would allow for the formation of a fused-ring bicyclic core. Furthermore, two novel stereocenters were envisioned to arise from enantiopure and readily accessible starting materials. Carbonyl compounds **II** would be obtained by conventional transformations from corresponding Boc-protected α-amino acids **I**. Pyrrolo[3,4-*c*]pyrazoles are important core structures found in a variety of molecules with a wide range of biological activities, such as antiinflamatory and antitumor drugs as well as protein kinase inhibitors.[14] Herein we present our results, which have led to the development of a new methodology for diastereoselective synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles from enantiomerically pure α-amino acids.

Results and Discussion

α-Allylamino ketones **5** were prepared following the protocol shown in Scheme 3. Thus, commercially available *N*-Boc-L-amino acids **2** were converted to corresponding Weinreb amide[15] **3** under standard conditions. Allylation using NaH as a base afforded derivatives of type **4** in moderate yields.[16] Subsequent reaction with several Grignard reagents yielded α-allylamino ketones **5**, as precursors of bicyclic compounds **6**.

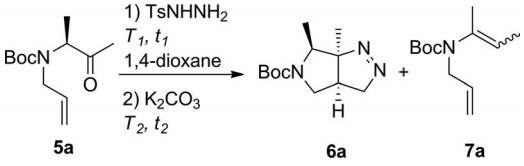


Scheme 3. Synthetic protocol for the preparation of the α-allylamino ketones **5**.

We started with the α-allylamino ketone **5a** to study the intramolecular 1,3-dipolar cycloaddition leading to triazabicyclo adduct **6a**. In this case, the putative tosylhydrazone intermediate was not isolated under the reaction conditions. Therefore we decided to develop a one-pot cycloaddition procedure following the reaction conditions previously reported by us for the intermolecular cycloaddition of diazoalkanes generated from the corresponding tosylhydrazones.[7]

Thus, **5a** was heated in 1,4-dioxane at 70 °C with tosylhydrazide for 2 h to generate tosylhydrazone, and subsequently, the base (K_2CO_3, 6 equiv.) was added, and the mixture was heated for an additional 12 h. Desired bicyclic compound **6a** was formed as the minor product whereas major adduct **7a** resulted from elimination of the starting tosylhydrazone (Bamford–Stevens reaction)[17] (Table 1, En-

Table 1. Influence of the reaction conditions in the formation of **6a** by intramolecular 1,3-dipolar cycloaddition.[a]



Entry	T_1/T_2 [°C]	t_1/t_2 [h]	K_2CO_3 [equiv.]	**6a/7a**[b]
1	70/70	2/12	6	1: 4.6
2	70/70	5/12	6	1: 4.6
3	85/110	12/12	6	1.7:1
4[c]	**85/110**	**2/12**	**6**	**1.9:1**
5	85/110	2/12	10	1.8:1
6	85	12	6	–
7	110	12	6	–
8	150 (MW)[d]	1	6	–

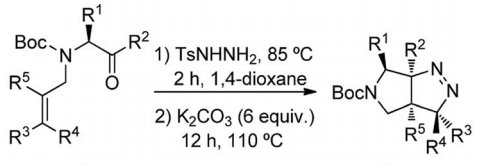
[a] Reaction conditions: α-allylamino ketone **5a** (0.3 mmol), *N*-tosylhydrazide (0.33 mmol), 1,4-dioxane (3.5 mL). [b] Calculated by ^{1}H NMR on the reaction crude mixture. [c] Optimized reaction conditions. [d] Reaction carried out in the presence of water (10 μL).

try 1). Longer reaction time (t_1) for the formation of the *N*-tosylhydrazone did not furnish better results (Entry 2).

On the other hand, increasing temperature in both steps (T_1 and T_2) gave encouraging results, changing the ratio to 2:1 in favor of the desired bicycle **6a** (Table 1, Entries 3–5). No product was obtained under multicomponent conditions (simultaneous addition of the ketone, tosylhydrazide and base), either under heating (Table 1, Entries 6, 7), or at higher temperature under microwave irradiation (Table 1, Entry 8). Therefore, we deemed it necessary to form the tosylhydrazone in situ prior to generation of the 1,3-dipole, with the optimal conditions being 85 °C and 2 h for the tosylhydrazone formation followed by 110 °C, 12 h in the presence of 6 equiv. of K_2CO_3 for the intramolecular 1,3-dipolar cycloaddition (Table 1, Entry 4).

These results prompted us to investigate the scope of this reaction under the optimized conditions, using α-amino ketone derivatives from L-Boc-alanine **5a**–**d** and **5i**–**k** (Table 2, Entries 1–4 and 9–11), L-Boc-valine **5e** (Table 2, Entry 5), L-Boc-leucine **5f** and **5l** (Table 2, Entries 6 and 12) and L-Boc-phenylalanine **5g**, **5h** and **5m** (Table 2, Entries 7, 8 and 13); and a set of different Grignard reagents bearing Me (Table 2, Entries 1, 5–7, 9, 11 and 13), Et (Table 2, Entries 2 and 8), Ph (Table 2, Entry 3), and Bn (Table 2, Entries 4 and 10). We observed that the transformation proceeds efficiently when using the methylketone of L-Boc-alanine (Table 2, Entry 1), whereas bulkier substituents (Table 2, Entries 2–4) provided moderate yields, due probably to increased steric hindrance in the transition state of the dipolar cycloaddition. Similarly, when the reaction was

Table 2. General synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles **6a**–**m** by intramolecular 1,3-dipolar cycloaddition.[a]



5a–m **6a–m**

Entry	Ketone **5**	Product **6**	Yield (%)[b]	Entry	Ketone **5**	Product **6**	Yield (%)[b]
1	**5a**	**6a**	64	8	**5h**	**6h**	63
2	**5b**	**6b**	32	9	**5i**	**6i**	61
3	**5c**	**6c**	36	10	**5j**	**6j**	46
4	**5d**	**6d**	65	11	**5k**	**6k**	65
5	**5e**	**6e**	50	12	**5l**	**6l**	31
6	**5f**	**6f**	52	13	**5m**	**6m**	78
7	**5g**	**6g**	35				

[a] Reaction conditions: α-allyl amino ketone **5** (0.3 mmol), *N*-tosylhydrazide (0.33 mmol), 1,4-dioxane (3.5 mL). [b] Isolated yield of **6** as a pure diastereoisomer after flash chromatography.

carried out using the methylketone of L-Boc-valine (Table 2, Entry 5), the reaction proceeded in moderate yields (50% vs. 81%) (Table 2, Entry 5 vs. 1) probably as a consequence of the larger steric requirements of the *i*Pr versus the Me group. From these results we suggest that the TS (transition state) of the reaction is highly dependent on steric hindrance, since variations in R^1 and/or R^2 can significantly affect the yield of the cycloaddition product.

Moreover, the reaction tolerates substitution on the olefinic double bond with only a slight reduction in yield. Thus, when $R^3 = R^4 = Me$, (Table 2, Entries 9 and 10), adducts **6i–j** were obtained, albeit with lower yields than adducts obtained with the monosubstituted olefin. Surprisingly, the cycloaddition was found to takes place also with sterically encumbered *N*-2-methylallyl derivatives **5k–m** (R^5 = Me) affording the trisubstituted tetrahydropyrrolopyrazoles **6k–m**, featuring two vicinal quaternary centers, with moderate yields.

It is important to point out that desired tetrahydropyrrolo[3,4-*c*]pyrazoles **6a–m** were obtained as single diastereoisomers, whose structures were confirmed by NOESY experiments on compounds **6b** and **6l** (see Supporting Information for details) (Figure 1). A strong nuclear Overhauser enhancement (NOE) was observed between the two protons H_a and H_b, with the two diastereotopic protons H_c and $H_{c'}$ on the ethyl group, suggesting that the R^1 and R^2 groups (from the α-amino acid and the Grignard reagent, respectively) are in a *trans* arrangement and that R^2 is *cis* with protons H_a and H_b.

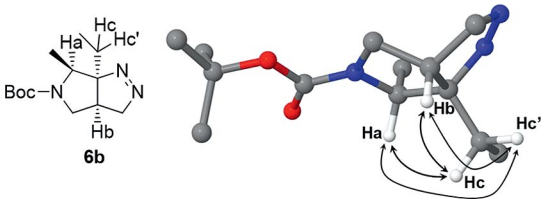
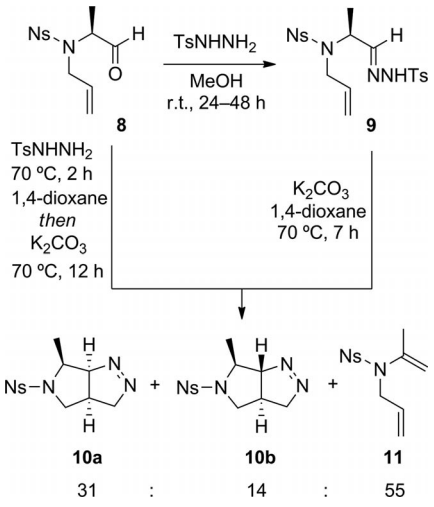


Figure 1. Relevant NOEs observed in compound **6b**. Some hydrogens have been omitted for clarity.

Moreover, it has been previously demonstrated that tosylhydrazones can be employed to carry out transformations on α-chiral ketones without erosion of enantiomeric purity, and in particular, in tosylhydrazones derived from *N*-Boc-α-amino acids.[18,6] To investigate whether this feature is retained in the present transformation, racemic derivatives were prepared for derivatives **6f** and **6g** and the enantiomeric excesses determined by HPLC. The values obtained, (*ee* > 99% for **6f**, and *ee* > 95% for **6g**) indicate that, again, enantiomeric purity is preserved during these transformations. Therefore, this method allows for the preparation of enantiomerically enriched tetrahydropyrrolo[3,4-*c*]pyrazoles featuring three stereocenters, inclusive of one or two quaternary stereogenic centers.

Consequently, the reaction was extended to α-allylamino aldehyde **8**[19] affording bicycloadduct **10** (Scheme 4). In this case, tosylhydrazone **9** was successfully isolated from the reaction, and then subjected to the intramolecular 1,3-dipolar cycloaddition in the presence of K_2CO_3 as a base, to afford the tetrahydropyrrolo[3,4-*c*]pyrazole as a mixture of two diastereoisomers **10a** and **10b**, together with the Bamford–Stevens side product **11** in a 31:14:55 ratio. As seen in previous cycloaddition trials, the reaction could be performed applying the one-pot protocol from compound **8** with the same result. Unfortunately, for this system, tetrahydropyrrolopyrazole **10** was obtained as a mixture of diastereoisomers **10a** and **10b** in about a 2:1 ratio, and the major isomer could be isolated in only 25% yield. In this case, neither the yield or diastereoselectivity could be improved upon by altering reaction conditions. Beyond this point, we deemed that the reaction warranted no further evaluation.

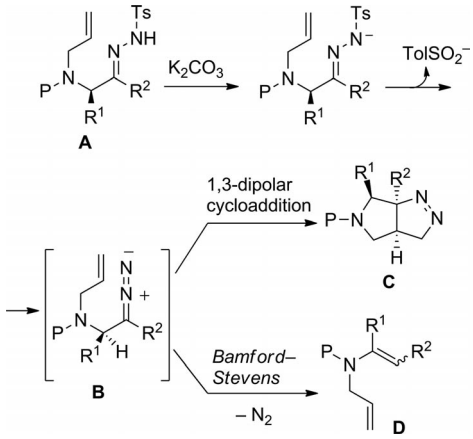


Scheme 4. Synthesis of tetrahydropyrrolo[3,4-*c*]pyrazole **10** as a mixture of diastereoisomers.

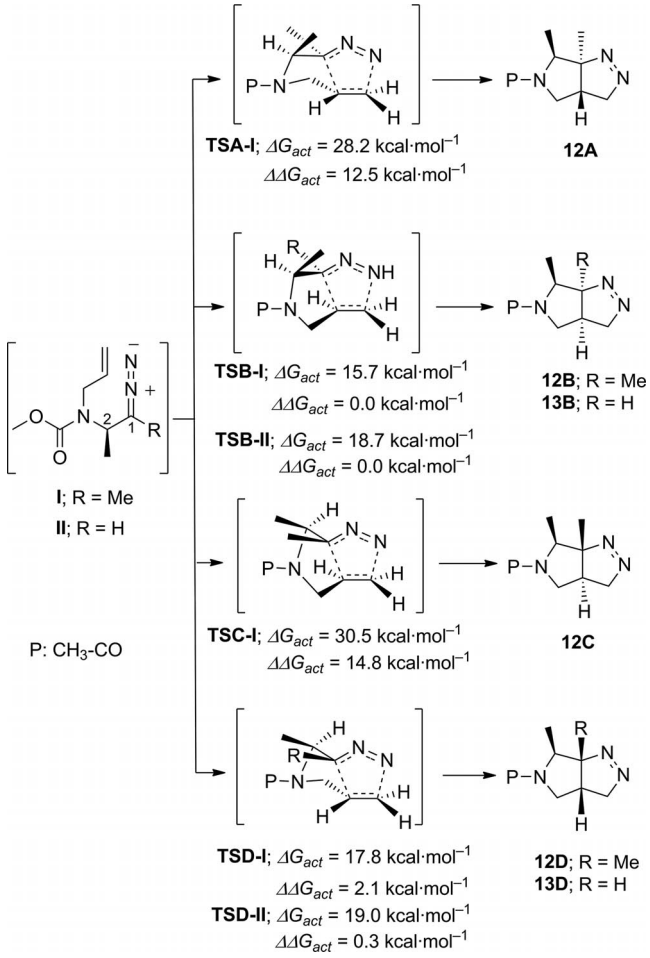
To explain the formation of heterobicyclics **6** and **10** we propose the following mechanism as is supported by the literature (Scheme 5). First, condensation of the carbonyl compound with the *N*-tosylhydrazide generates *N*-tosylhydrazone **A** in situ, which undergoes base-promoted decomposition to furnish diazo compound **B**. Intermediate **B** is envisioned to have two possible reaction paths available to it. These include: (a) intramolecular 1,3-dipolar cycloaddition with the terminal olefin to afford desired bicyclic product **C**; and (b) Bamford–Stevens degradation to give undesired diene **D** concomitant with generation of N_2.

The intramolecular 1,3-dipolar cycloaddition to form tetrahydropyrrolo[3,4-*c*]pyrazoles **6** proceeds with complete diasteroselectivity, whereas the formation of compounds **10** takes place with very poor diastereoselectivity. To understand the different behaviors of diazo compounds generated from ketones **5** and aldehyde **8** respectively, DFT based computations of the possible transition states (TS) for the dipolar cycloadditions were performed on model structures **I** and **II** at the B3LYP/6-311++G** level (Scheme 6).[20]

We started our studies with diazo compound **I** (R = Me) (Scheme 6) which derives from methyl ketone **5a**. Four competing transition states (**TSA-I** – **TSD-I**) lead to corresponding diastereomeric tetrahydropyrrolopyrazoles (**12A–D**, Scheme 6). The transition states corresponding to the



Scheme 5. Possible mechanistic pathways for the 1,3-dipolar cycloaddition from tosylhydrazone derivatives of α-amino ketones and/or α-amino aldehydes.



Scheme 6. Energy calculations of the transition states from the model diazo compounds **I** and **II** at the B3LYP/6-311++G** level of theory.

bicyclic systems with a *cis*-fusion (**TSB-I** and **TSD-I**) are clearly favored, whereas those that would furnish *trans*-fused bicyclic **12A** and **12C**, feature very distorted transition states and are energetically very disfavoured (**TSA-I** and **TSC-I**). The results of the computations indicated that **TSB-I**, leading to bicyclic **12B**, is more stable by 2.10 kcal/mol than **TSD-I**, which leads to diastereoisomer **12D**. In **TSD-I**, the methyl substituents at C1 and C2 are in a *syn*-periplanar disposition, and therefore, significant steric interactions are present. Conversely, in **TSB-I**, the methyl substituents are in a nearly *anti*-periplanar arrangement (Figure 2). Consequently, we envision that the minimized steric interactions in **TSB-I** are largely responsible for cycloaddition diastereoselectivity.

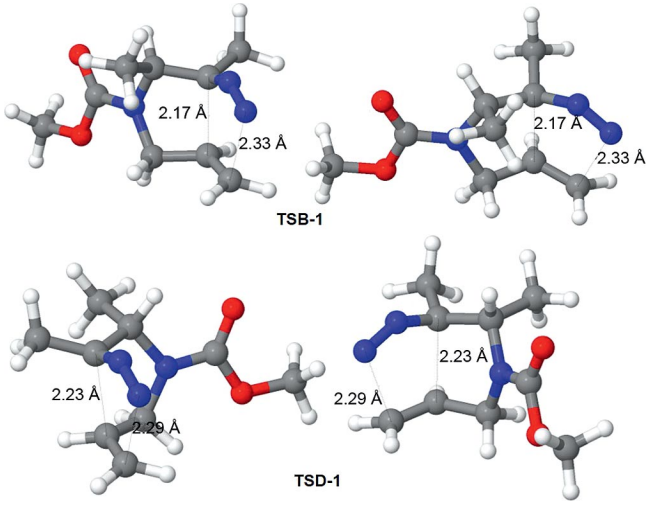


Figure 2. Molecular models obtained for **TSB-I** and **TSD-I** (b3lyp/6-311++G**).

Lastly, we studied the cycloaddition with diazo compound **II** derived from aldehyde **8** (R = H) (Scheme 6). Taking into consideration the results presented above, we considered only the transition states **TSB-II** and **TSD-II**, leading to *cis*-fused bicyclics **13B** and **13D** respectively (Scheme 6). In this case, both TSs featured very similar energy values, ΔG_{act} = 18.7 and 19.0 kcal/mol for **TSB-II** and **TSD-II** respectively, which is in agreement with the lack of stereoselectivity observed in the reaction. This small energy difference between **TSB-II** and **TSD-II** (0.3 kcal/mol) could be explained considering that now, since R = H, there is no significant steric interaction between substituents at C1 and C2 in **TSD-II**, and therefore, the energy of both transition states is very close.

Conclusions

In summary, we have developed a new metal-free procedure for the diastereoselective synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles by base-promoted intramolecular 1,3-dipolar cycloaddition of tosylhydrazones of α-allylamino ketones. Notably, the starting materials are readily available from α-amino acids. Interestingly, the stereogenic center in the α-amino acid is not affected during the synthetic sequence. The stereochemistry of the final products was assigned by two-dimensional NMR studies and also by computational analysis of the competing transition states. From these results we conclude that the TS of the reaction, and thus the yield of product, is highly sensitive to the steric

hindrance. The major advantage of this procedure is the operational simplicity, in that it is not essential to use an inert atmosphere or ultra-dry solvents. Moreover, the reaction can be conducted in a one-pot manner directly from the carbonyl-containing starting material; the tosylhydrazone intermediate does not have to be isolated. Finally, this approach allows the construction of more than one heterocyclic ring at a time with control of new stereogenic centers. For these reasons, we believe that this short, metal-free protocol may become a useful tool for the construction of biologically important scaffolds in both organic synthesis and medicinal chemistry.

Experimental Section

General Methods: Dioxane, dichloromethane, diethyl ether and dimethylformamide were dried accoding to literature procedures.[25] All amino acids, allyl halides and Grignard reagents are commercially available. NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 600, 400 or 300 MHz for ^1H and 150 or 75 MHz for ^{13}C, with tetramethylsilane as internal standard for ^1H and the residual solvent signals as standard for ^{13}C. The data is being reported as s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quaduplet and m = multiplet or unresolved, chemical shifts in ppm and coupling constant(s) in Hz. The 2D experimental NOESY using the pulse program NOESYGPPH from Bruker instruments with a mixing time of 0.5 s. was used. MS and HRMS were measured in EI, ESI or FAB mode, and the mass analyzer of the HRMS was TOF. Melting points are uncorrected. The microwave-assisted reactions were conducted using a focused microwave unit (Biotage Initiator TM 2.0). The temperature was monitored with an infrared temperature sensor. In all experiments the microwave temperature was held constant. Reactions were performed in 0.5–2 mL glass vessels, which were sealed with a cap with septum. Enantiomeric ratios were determined by chiral HPLC analyses (with a V-UV 2996 or 996 photodiode Array detector) in comparison with the authentic racemic products, which were synthesized employing the same route from the racemic starting materials. Specific rotations were generated using an automatic polarimeter with a sodium lamp and MeOH or CH_2Cl_2 as solvent (*c*, g/100 mL).

General Procedure for the Synthesis of Amides 3 Derived from Boc-Amino Acids:[6a,16,21] To a solution of a commercially available Boc-amino acid (5 mmol, 1 equiv.) in dry DCM was added HN(OMe)-Me·HCl (1 equiv.) and DIPEA (99%, 1 equiv.) at –5 °C. After stirring several minutes, a solution of EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1 equiv.), in dry DCM was added dropwise under nitrogen atmosphere and the resulting mixture was stirred at –5 °C for 2 h. When the reaction was completed, the crude was washed two times with 1 N HCl. Then the organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The amide was obtained pure enough to be used in the next reaction step.

***tert*-Butyl {(*S*)-1-[Methoxy(methyl)amino]-1-oxopropan-2-yl}carbamate (3a):** White solid, 87% yield; m.p. 145–146 °C. R_f = 0.64 (hexane/EtOAc, 1:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.44 (s, 9 H, Boc), 3.22 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3O), 4.69 (m, 1 H, CH), 5.30 (m, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.6 (CH_3), 28.3 (Boc), 32.1 (CH), 46.5 (CH_3), 61.6 (CH_3O), 79.5 (C-Boc), 155.2 (C), 173.6 (C) ppm. $[a]_D^{22}$ = +1.31 (*c* = 1.15, CH_2Cl_2). CAS: 87694–49–3.

***tert*-Butyl {(*S*)-1-[Methoxy(methyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate (3b):** Colorless oil, 94% yield; R_f = 0.20 (hexane/EtOAc, 1:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (m, 6 H, *i*Pr), 1.36 (s, 9 H, Boc), 1.92 (m, 1 H, CH *i*Pr), 3.15 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3O), 4.50 (m, 1 H, CH), 5.14 (m, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4 (CH_3-*i*Pr), 19.2 (CH_3-*i*Pr), 28.1 (Boc), 31.1 (CH), 31.6 (CH), 54.8 (CH_3), 61.3 (OCH_3), 79.0 (C-Boc), 155.6 (C), 172.7 (C) ppm. EI HRMS: calcd. for $C_{12}H_{24}N_2O_4$: 260.1809, found 260.1804. $[a]_D^{25}$ = +6.47 (*c* = 1.70, CH_2Cl_2). CAS: 87694–52–8.

***tert*-Butyl {(*S*)-1-[Methoxy(methyl)amino]-4-methyl-1-oxopentan-2-yl}carbamate (3c):** White solid, 96% yield; m.p. 105–107 °C; R_f = 0.43 (hexane/EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m, 6 H, *iso*-Bu), 1.35 (s, 11 H, Boc and CH_2), 1.63 (m, 1 H, CH), 3.12 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3O), 4.65 (m, 1 H, CH), 5.08 (m, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.5 (CH_3), 23.3 (CH), 24.6 (CH_3), 28.3 (Boc), 32.0 (CH), 41.9 (CH_2), 48.9 (CH_3), 61.5 (OCH_3), 79.2 (C-Boc), 155.5 (C), 173.8 (C) ppm. $[a]_D^{21}$ = –5.00 (*c* = 0.46, CH_2Cl_2). CAS: 87694–50–6.

***tert*-Butyl {(*S*)-1-[Methoxy(methyl)amino]-1-oxo-3-phenylpropan-2-yl}carbamate (3d):** White solid, 90% yield; m.p. 135–136 °C; R_f = 0.18 (hexane/EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, Boc), 2.85 (dd, *J* = 6.0, 13.1 Hz, 1 H, CH_2), 3.03 (dd, *J* = 6.1, 13.5 Hz, 1 H, CH_2), 3.14 (s, 3 H, CH_3), 3.63 (s, 3 H, CH_3O), 4.92 (m, 1 H, CH), 5.20 (m, 1 H, NH), 7.21 (5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (Boc), 32.1 (CH), 38.8 (CH_2), 51.5 (CH_3), 61.5 (OCH_3), 79.5 (C-Boc), 126.7 (CH), 128.3 (2 × CH), 129.4 (2 × CH), 136.6 (C-Ph), 155.2 (C), 172.3 (C) ppm. FAB HRMS: calcd. for $C_{16}H_{25}N_2O_4$: 309.1814 $[M + H]^+$, found 309. 1811. $[a]_D^{17}$ = +20.37 (*c* = 0.27, CH_2Cl_2). CAS: 87694–53–9.

General Procedure for the Synthesis of α-Allylamides 4 Derived from Boc-Amino Acid Amides: To a solution of amide **3** (3 mmol, 1 equiv.) in dry DMF was added NaH (60%, 2 equiv.) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Then, allyl bromide (1 equiv.) was added and the mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with KOH 3M (3 mL) and H_2O (10 mL). The residual mixture was extracted three times with EtOAc and DCM. The organic layers were washed three times with sat $Na_2S_2O_3$, dried with anhydrous Na_2SO_4, filtered and concentrated. The pure product was isolated by flash chromatography on silica gel using a mixture of hexane/ethyl acetate as eluent.

***tert*-Butyl *N*-Allyl-*N*-{(*S*)-1-[methoxy(methyl)amino]-1-oxopropan-2-yl}carbamate (4a):** Colorless oil, 61% yield; R_f = 0.42 (hexane/EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.46 (s, 9 H, Boc), 3.18 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3O), 4.65 (m, 1 H, CH), 5.26 (dd, *J* = 1.2, 10.4 Hz, 1 H, CH_2), 5.35 (dd, *J* = 1.5, 17.2 Hz, 1 H, CH_2), 5.93 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (CH_3), 28.12 (Boc), 31.7 (CH_3), 46.0 (CH_2), 49.8 (CH), 61.2 (CH_3O), 79.5 (C-Boc), 114.9 (CH_2), 115.4 (CH_2), 135.8 (CH), 135.3 (CH), 155.2 (C), 172.9 (C) [some signals are duplicated due to presence of rotamers] ppm. EI HRMS: calcd. for $C_{10}H_{15}N_2O_4$: 216.1110 [-*t*Bu + H]$^+$, found 216.1116. $[a]_D^{18}$ = –30.97 (*c* = 1.40, CH_2Cl_2).

***tert*-Butyl *N*-Allyl-*N*-{(*S*)-1-[methoxy(methyl)amino]-3-methyl-1-oxobutan-2-yl}carbamate (4b):** Colorless oil, 94% yield. R_f = 0.20 (hexane/EtOAc, 1:1). Following the previous procedure, in this example 3 equiv. of NaH (99%) were used; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.5 Hz, 6 H, CH_3-*i*Pr), 1.40 (br. s, 9 H, Boc), 2.20 (m, 1 H, CH-*i*Pr), 3.09 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3O), 3.85 (m, 2 H, CH_2), 4.87 (m, 1 H, CH), 4.95 (m, 2 H, CH_2), 5.72 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (CH_3-*i*Pr), 19.3 (CH_3-*i*Pr), 27.1 (CH-*i*Pr), 28.0 (Boc), 31.8 (CH), 44.9 (CH_3), 45.4 (CH_3), 58.0 (CH_2), 59.5 (CH_3O), 61.6

(CH_3O), 79.4 (C-Boc), 115.3 (CH_2), 134.2 (CH), 135.0 (CH), 154.8 (C), 155.5 (C), 171.6 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{15}H_{28}N_2O_4$: 300.2049, found 300.2051. $[\alpha]_D^{25}$ = +6.47 (*c* = 1.70, CH_2Cl_2).

***tert*-Butyl *N*-Allyl-*N*-{(*S*)-1-[methoxy(methyl)amino]-4-methyl-1-oxopentan-2-yl}carbamate (4c):** Colorless oil, 72% yield; R_f = 0.46 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (m, 6 H, *iso*-Bu), 1.37 (s, 9 H, Boc), 1.47 (m, 1 H, CH *iso*-Bu), 1.51 (CH_2 *iso*-Bu), 3.07 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3O), 3.75 (CH_2), 4.94 (m, 1 H, CH), 5.04 (CH_2), 5.23 (m, 1 H, CH), 5.74 (m, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_3), 21.5 (CH_3), 24.0 (CH), 27.7 (Boc), 30.4 (DMF), 35.5 (DMF), 37.8 (CH_2), 45.5 (CH_2), 51.1 (CH_3), 52.3 (CH), 60.9 (CH_3O), 79.0 (C-Boc), 114.8 (CH_2), 134.8 (CH), 135.4 (CH), 154.1 (C), 154.8 (C), 161.6 (DMF), 171.1 (C), 172.0 (C) ppm [some signals are duplicated due to the existence of rotamers]. EI HRMS: calcd. for $C_{16}H_{30}N_2O_4$: 314.2206, found 314.2198. $[\alpha]_D^{21}$ = –67.93 (*c* = 0.27, CH_2Cl_2).

***tert*-Butyl *N*-Allyl-*N*-{(*S*)-1-[methoxy(methyl)amino]-1-oxo-3-phenylpropan-2-yl}carbamate (4d):** Pale yellow oil, 67% yield; R_f = 0.32 (hexane/EtOAc, 2:1); Following the previous procedure, in this example 1.5 equiv. of NaH (99%) were used; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, Boc), 2.92 (m, 1 H, CH_2), 3.08 (br. s, 4 H, CH_3 and 1 H, CH_2), 3.57 (s, 3 H, CH_3O), 3.82 (m, 2 H, CH_2), 5.14 (m, 2 H, CH_2), 5.51 (m, 1 H, CH), 5.76 (m, 1 H, CH), 7.20 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (Boc), 35.8 (CH_2), 45.8 (CH_2), 54.5 (CH), 56.5 (CH_3), 61.4 (CH_3O), 79.8 (C-Boc), 115.6 (CH_2), 116.0 (CH_2), 126.3 (CH), 128.2 (2 × CH), 129.5 (2 × CH), 134.5 (CH), 135.3 (CH), 137.4 (C-Ph), 138.0 (C-Ph), 154.4 (C), 155.2 (C), 171.4 (C) ppm [some signals are duplicated due to the existence of rotamers]. EI HRMS: calcd. for $C_{19}H_{28}N_2O_4$: 348.2049, found 348.2042. $[\alpha]_D^{22}$ = –17.54 (*c* = 3.61, CH_2Cl_2).

***tert*-Butyl *N*-{(*S*)-1-[Methoxy(methyl)amino]-1-oxopropan-2-yl}-*N*-(3-methylbut-2-en-1-yl)carbamate (4e):** Colorless oil, 61% yield; R_f = 0.35 (hexane/EtOAc, 2:1); Following the previous procedure, in this example 1-bromo-3-methyl-but-2-ene was used instead of allyl bromide; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.46 (s, 9 H, Boc), 1.64 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 3.17 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3O), 3.85 (m, 2 H, CH_2), 5.14 (m, 2 H, 2 × CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 17.9 (CH_3), 25.7 (CH_3), 28.4 (Boc), 42.0 (CH_2), 46.7 (CH), 50.1 (CH_3), 61.4 (CH_3O), 79.6 (C-Boc), 123.1 (CH), 132.1 (C), 155.6 (C), 173.4 (C) ppm. EI HRMS: calcd. for $C_{15}H_{28}N_2O_4$: 300.2049, found 300.2054. $[\alpha]_D^{22}$ = –7.83 (*c* = 1.09, CH_2Cl_2).

***tert*-Butyl *N*-{(*S*)-1-[Methoxy(methyl)amino]-1-oxopropan-2-yl}-*N*-(2-methylprop-2-en-1-yl)carbamate (4f):** Colorless oil, 79% yield. R_f = 0.32 (hexane/EtOAc, 3:1). Following the previous procedure, in this example 3-bromo-2-methylpropene was used instead of allyl bromide; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.38 (s, 9 H, Boc), 1.65 (s, 3 H, CH_3), 3.11 (s, 3 H, CH_3), 3.72 (m, 4 H, CH_2 and CH_3O), 3.83 (m, 1 H, CH_2), 4.69 (s, 1 H, CH_2), 4.73 (s, 1 H, CH_2), 5.17 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (CH_3), 15.2 (CH_3), 20.2 (CH_3), 28.2 (Boc), 32.1 (CH), 49.2 (CH_2), 49.8 (CH_2), 50.2 (CH_3), 52.0 (CH_3), 61.4 (CH_3O), 79.6 (C-Boc), 80.0 (C-Boc), 109.1 (CH_2), 109.8 (CH_2), 142.7 (C), 143.1 (C), 155.7 (C), 173.3 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{14}H_{26}N_2O_4$: 286.1893, found 286.1885. $[\alpha]_D^{22}$ = +18.49 (*c* = 1.65, CH_2Cl_2).

***tert*-Butyl *N*-{(*S*)-1-[Methoxy(methyl)amino]-4-methyl-1-oxopentan-2-yl}-*N*-(2-methylprop-2-en-1-yl)carbamate (4 g):** Following the previous procedure, in this example 1.5 equiv. of NaH (99%) were used and 3-bromo-2-methylpropene was used instead of allyl bromide. Colorless oil, 79% yield; R_f = 0.46 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (m, 6 H, *iso*-Bu), 1.34 (s, 9 H, Boc), 1.41 (m, 1 H, CH *iso*-Bu), 1.59 (s, 3 H, CH_3), 1.64 (m, 2 H, CH_2 *iso*-Bu), 3.12 (s, 3 H, CH_3), 3.66 (m, 2 H, CH_2), 3.71 (m, 3 H, CH_3O), 4.63 (m, 2 H, CH_2), 5.07 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_3), 21.4 (CH_3), 22.5 (CH), 22.6 (CH), 23.2 (CH_3), 24.6 (CH_3), 28.2 (Boc), 32.0 (CH_3), 38.3 (CH_2), 41.9 (CH_2), 48.9 (CH_3), 51.8 (CH), 61.4 (CH_3O), 79.3 (C-Boc), 109.0 (CH_2), 141.8 (CH), 142.5 (CH), 155.6 (C), 173.8 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{17}H_{32}N_2O_4$: 328.2362, found 328.2369. $[\alpha]_D^{21}$ = - 64.22 (*c* = 0.55, CH_2Cl_2).

***tert*-Butyl *N*-{(*S*)-1-[Methoxy(methyl)amino]-1-oxo-3-phenylpropan-2-yl}-*N*-(2-methylprop-2-en-1-yl)carbamate (4h):** Following the previous procedure, in this example 1.5 equiv. of NaH (99%) were used and 3-bromo-2-methylpropene was used instead of allyl bromide. Colorless oil, 65% yield; R_f = 0.47 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, Boc), 1.68 (s, 3 H, CH_3), 2.91 (m, 1 H, CH_2), 3.05 (s and m, 4 H, CH_3 and 1 H, CH_2), 3.56 (s, 3 H, CH_3O), 3.76 (m, 2 H, CH_2), 4.70 (s, 1 H, CH_2), 4.74 (s, 1 H, CH_2) 5.19 (m, 1 H, CH), 7.21 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (CH_3), 28.3 (Boc), 32.0 (CH_2), 38.8 (CH), 43.2 (CH_2), 51.5 (CH_3), 61.5 (CH_3O), 79.5 (C-Boc), 109.8 (CH_2), 126.7 (CH), 128.3 (2 × CH), 129.4 (2 × CH), 136.6 (C-Ph), 143.9 (C), 155.2 (C), 172.3 (C) ppm. EI HRMS: calcd. for $C_{20}H_{30}N_2O_4$: 362.2206, found 362.2213. $[\alpha]_D^{18}$ = +13.76 (*c* = 2.58, CH_2Cl_2).

General Procedure for the Synthesis of α-Allylamino Ketones (5): To a solution of the α-allylamide **4** (1 mmol, 1 equiv.) in dry Et_2O (30 mL) was added the magnesium halide (1.4 equiv.) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous solution NH_4Cl (25 mL) and then extracted three times with Et_2O. The organic layers were washed three times with H_2O, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel (mixtures of hexane/EtOAc).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(3-oxobutan-2-yl)carbamate (5a):** Colorless oil, 89% yield; R_f = 0.71 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.44 (br. s, 9 H, Boc), 2.13 (s, 3 H, CH_3), 3.65 (dd, *J* = 6.5, 14.7 Hz, 1 H, CH_2), 3.75 (dd, *J* = 6.5, 14.7 Hz, 1 H, CH_2), 4.64 (m, 1 H, CH), 5.24 (dd, *J* = 1.2, 10.4 Hz 1 H, CH_2), 5.30 (dd, *J* = 1.4, 17.2 Hz, 1 H, CH_2), 5.90 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4 (CH_3), 13.7 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 28.1 (Boc), 48.7 (CH_2), 50.2 (CH_2), 60.8 (CH), 61.7 (CH), 80.4 (C-Boc), 81.0 (C-Boc), 116.8 (CH_2), 118.2 (CH_2), 134.1 (CH), 134.6 (CH), 154.3 (C), 155.1 (C), 206.1 (C), 206.8 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{10}H_{18}NO_2$: 184.1338 [-C(O)-CH_3]$^+$, 184.1333. $[\alpha]_D^{26}$ = –10.90 (*c* = 1.96, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(3-oxopentan-2-yl)carbamate (5b):** Colorless oil, 77% yield; R_f = 0.33 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (m, 3 H, CH_3-Et), 1.27 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.42 (m, 9 H, Boc), 2.48 (m, 2 H, CH_2-Et), 3.72 (m, 2 H, CH_2), 4.32 (m, 1 H, CH), 5.13 (m, 2 H, CH_2), 5.84 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3-Et), 22.6 (CH_3), 28.2 (Boc), 31.3 (CH_2-Et), 31.9 (CH_2-Et), 48.4 (CH_2), 50.2 (CH_2), 59.8 (CH), 60.9 (CH), 80.3 (C-Boc), 80.9 (C-Boc), 116.6 (CH_2), 118.1 (CH_2), 134.3 (CH), 134.9 (CH), 154.4 (C), 155.2 (C), 208.7 (C), 209.6 (C) ppm [some signals are duplicated due to the

presence of rotamers]. FAB MS: calcd. for $C_8H_{15}NO$: 141.11 [-Boc + H]$^+$, found 141.15. $[\alpha]_D^{19}$ = –54.32 (c = 1.85, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(1-oxo-1-phenylpropan-2-yl)carbamate (5c):** Colorless oil, 48% yield; R_f = 0.35 (hexane/EtOAc, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, J = 7.4 Hz, 3 H, CH_3), 1.39 (s, 9 H, Boc), 3.55 (d, J = 16.0 Hz, 1 H, CH_2), 3.68 (d, J = 16.0 Hz, 1 H, CH_2), 4.95 (m, 2 H, CH_2), 5.10 (m, 1 H, CH), 5.63 (m, 1 H, CH), 7.44 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_3), 15.0 (CH_3), 28.2 (Boc), 46.7 (CH_2), 48.6 (CH_2), 54.8 (CH), 57.3 (CH), 80.3 (C-Boc), 116.0 (CH_2), 116.9 (CH_2), 128.4 (CH), 133.0 (CH), 135.2 (CH), 135.7 (C-Ph), 155.2 (C), 199.6 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{17}H_{23}NO_3$: 289.1678, found 289.1679. $[\alpha]_D^{18}$ = –73.87 (c = 0.38, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-allyl-*N*-(3-oxo-4-phenylbutan-2-yl)carbamate (5d):** Colorless oil, 56% yield; R_f = 0.32 (hexane/EtOAc, 6:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (br. s, 3 H, CH_3), 1.44 (br. s, 9 H, Boc), 3.61 (m, 1 H, CH_2-Bn), 3.71 (m, 1 H, CH_2-Bn), 3.85 (m, 2 H, CH_2), 4.40 (m, 1 H, CH), 5.15 (m, 2 H, CH_2), 5.85 (m, 1 H, CH), 7.29 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 14.1 (CH_3), 28.3 (Boc), 45.4 (CH_2-Bn), 46.0 (CH_2-Bn), 48.7 (CH_2), 50.5 (CH_2), 59.6 (CH_3O), 60.7 (CH_3O), 80.6 (C-Boc), 81.4 (C-Boc), 117.0 (CH_2), 118.4 (CH_2), 127.0 (CH), 128.6 (2×CH), 129.5 (2×CH), 134.2 (CH), 134.8 (C-Ph), 154.5 (C), 206.4 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{18}H_{25}NO_3$: 303.1810, found 303.1821. $[\alpha]_D^{25}$ = –46.65 (c = 1.51, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(2-methyl-4-oxopentan-3-yl)carbamate (5e):** Colorless oil, 80% yield; R_f = 0.66 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (m, 6 H, CH_3-*i*Pr), 1.34 (m, 1 H, CH-*i*Pr), 1.39 (s, 9 H, Boc), 2.06 (br. s, 3 H, CH_3), 3.58 (m, 2 H, CH_2), 4.23 (m, 1 H, CH), 5.05 (m, 2 H, CH_2), 5.67 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_3-*i*Pr), 19.0 (CH_3-*i*Pr), 20.0 (CH_3-*i*Pr), 21.1 (CH_3-*i*Pr), 25.6 (CH-*i*Pr), 26.7 (CH-*i*Pr), 28.3 (Boc), 29.2 (CH_3), 47.3 (CH_2), 49.7 (CH_2), 68.1 (CH), 70.4 (CH), 80.3 (C-Boc), 80.8 (C-Boc), 117.0 (CH_2), 118.0 (CH_2), 133.7 (CH), 134.0 (CH), 154.7 (C), 155.9 (C), 204.8 (C), 205.8 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI MS: calcd. for $C_{12}H_{22}NO_2$: 212.17 [-C(O)CH_3]$^+$, found 212.17. $[\alpha]_D^{25}$ = +161.91 (c = 0.47, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(5-methyl-2-oxohexan-3-yl)carbamate (5f):** Colorless oil, 92% yield; R_f = 0.59 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (m, 6 H, *iso*-Bu), 1.37 (m, 9 H, Boc), 1.44 (m, 1 H, CH *iso*-Bu), 1.68 (m, 2 H, CH_2 *iso*-Bu), 2.05 (s, 3 H, CH_3), 3.43 (m, 1 H, CH), 3.85 (m, 2 H, CH_2), 5.07 (m, 2 H, CH_2), 5.80 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (CH), 21.9 (CH_3), 23.0 (CH_3), 27.0 (CH_3), 27.3 (CH_3), 28.2 (Boc), 36.3 (CH_2), 37.3 (CH_2), 48.0 (CH_2), 49.5 (CH_2), 62.6 (CH), 63.9 (CH), 80.3 (C-Boc), 80.8 (C-Boc), 116.8 (CH_2), 117.9 (CH_2), 134.2 (CH), 134.7 (CH), 154.7 (C), 155.6 (C), 206.4 (C), 207.1 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{15}H_{27}NO_3$: 269.1991, found 269.2002. $[\alpha]_D^{21}$ = –137.38 (c = 0.65, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(3-oxo-1-phenylbutan-2-yl)carbamate (5 g):** Colorless oil, 78% yield; R_f = 0.76 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, Boc), 2.15 (br. s, 3 H, CH_3), 2.94 (m, 2 H, CH_2), 3.32 (m, 2 H, CH_2), 4.07 (m, 1 H, CH), 5.05 (m, 2 H, CH_2), 5.65 (m, 1 H, CH), 7.18 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7 (CH_3), 27.2 (CH_3), 28.3 (Boc), 34.8 (CH_2), 35.8 (CH_2), 50.8 (CH_2), 51.3 (CH_2), 67.1 (CH), 67.7 (CH), 79.9 (C-Boc), 80.6 (C-Boc), 117.8 (CH_2), 119.1 (CH_2), 126.3 (CH), 128.2 (2×CH), 128.5 (2×CH), 129.5 (CH), 133.5 (CH), 138.6 (C-Ph), 154.3 (C), 155.0 (C), 205.3 (C), 205.8 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{15}H_{20}NO_3$: 262.1443 [-CH_2=CH-CH_2)]$^+$, found 262.1440. $[\alpha]_D^{21}$ = –160.23 (c = 3.90, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-Allyl-*N*-(3-oxo-1-phenylpentan-2-yl)carbamate (5h):** Colorless oil, 57% yield; R_f = 0.73 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, J = 7.3 Hz, 3 H, CH_3), 1.45 (s, 9 H, Boc), 1.59 (m, 2 H, CH_2), 2.61 (m, 2 H, CH_2), 3.91 (m, 2 H, CH_2), 4.70 (m, 1 H, CH), 5.20 (m, 2 H, CH_2), 5.86 (m, 1 H, CH), 7.29 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.7 (CH_3), 28.3 (Boc), 31.9 (CH_2), 32.8 (CH_2), 34.9 (CH_2), 35.8 (CH_2), 50.0 (CH_2), 51.1 (CH_2), 65.8 (CH), 68.9 (CH), 79.9 (C-Boc), 81.2 (C-Boc), 117.5 (CH_2), 118.9 (CH_2), 126.3 (CH), 126.4 (2×CH), 129.5 (2×CH), 133.7 (CH), 134.2 (CH), 138.7 (C-Ph), 154.3 (C), 155.1 (C), 207.9 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{10}H_{18}NO_2$: 184.1338 [-C(O)CH_3]$^+$, found 184.1333. $[\alpha]_D^{17}$ = +32.40 (c = 0.25, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-(3-Methylbut-2-en-1-yl)-*N*-(2-oxobutan-2-yl)carbamate (5i):** Colorless oil, 76% yield; R_f = 0.87 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.5 Hz, 3 H, CH_3), 1.44 (br. s, 9 H, Boc), 1.69 (s, 3 H, CH_3), 1.75 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 3.58 (m, 2 H, CH_2), 4.13 (m, 1 H, CH), 5.27 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2 (CH_3), 13.6 (CH_3), 17.7 (CH_3), 25.7 (CH_3), 26.1 (CH_3), 28.3 (Boc), 29.6 (CH_3), 43.9 (CH_2), 44.7 (CH_2), 60.8 (CH), 61.6 (CH), 80.2 (C-Boc), 80.9 (C-Boc), 120.2 (CH), 121.2 (CH), 134.6 (C), 136.6 (C), 155.2 (C), 206.6 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{14}H_{25}NO_3$: 255.1834, 255.1834. $[\alpha]_D^{17}$ = +12.86 (c = 0.07, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-(3-Methylbut-2-en-1-yl)-*N*-(3-oxo-4-phenylbutan-2-yl)carbamate (5j):** Colorless oil, 76% yield. R_f = 0.61 (hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.7 Hz, 3 H, CH_3), 1.47 (br. s, 9 H, Boc), 1.62 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 2.95 (dd, J = 4.4, 12.1 Hz, 1 H, CH_2-Bn), 3.28 (m, 1 H, CH_2-Bn), 3.48 (m, 2 H, CH_2), 4.12 (q, J = 6.8 Hz, 1 H, CH), 5.18 (m, 1 H, CH), 7.25 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 17.7 (CH_3), 25.6 (CH_3), 28.3 (Boc), 32.3 (CH_2-Bn), 41.8 (CH_2), 63.5 (CH), 79.4 (C-Boc), 123.0 (CH), 127.0 (CH), 128.7 (2×CH), 129.5 (2×CH), 131.9 (C), 134.5 (C), 155.4 (C), 207.8 (C) ppm. EI HRMS: calcd. for $C_{20}H_{29}NO_3$: 331.2147, found 331.2151. $[\alpha]_D^{22}$ = –8.74 (c = 2.50, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-(2-Methylallyl)(3-oxobutan-2-yl)carbamate (5k):** Colorless oil, 69% yield; R_f = 0.61 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.4 Hz, 3 H, CH_3), 1.42 (br. s, 9 H, Boc), 1.77 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 3.57 (m, 2 H, CH_2), 4.03 (m, 1 H, CH), 4.57 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2 (CH_3), 13.7 (CH_3), 20.1 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 28.2 (Boc), 52.4 (CH_2), 53.7 (CH_2), 61.3 (CH), 62.0 (CH), 80.4 (C-Boc), 81.2 (C-Boc), 112.2 (CH_2), 113.9 (CH_2), 141.8 (C), 154.8 (C), 155.3 (C), 206.2 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{13}H_{23}NO_3$: 241.1678, found 241.1679. $[\alpha]_D^{22}$ = +65.41 (c = 0.91, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-(2-Methylallyl)-*N*-(5-methyl-2-oxohexan-3-yl)carbamate (5l):** Colorless oil, 68% yield. R_f = 0.69 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (m, 6 H, *iso*-Bu), 1.45 (s, 9 H, Boc), 1.60 (m, 1 H, CH_2 *iso*-Bu), 1.76 (m, 4 H, CH *iso*-Bu and CH_3), 1.87 (m, 1 H, CH_2 *iso*-Bu), 2.13 (s, 3 H, CH_3), 3.49 (m, 1 H, CH_2), 3.84 (m, 1 H, CH_2), 4.12 (m, 1 H, CH), 4.85 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH), 22.8 (CH_3), 22.9 (CH_3), 27.0 (CH_3), 27.5 (CH_3), 28.2 (Boc), 36.7 (CH_2), 37.9 (CH_2), 51.6 (CH_2), 53.0 (CH_2), 63.1 (CH), 64.3 (CH), 80.4 (C-

Boc), 81.0 (C-Boc), 112.3 (CH_2), 113.8 (CH_2), 141.8 (C), 155.8 (C), 206.2 (C) ppm. EI HRMS: calcd. for $C_{12}H_{20}NO_3$: 226.1443 [-*i*Pr-CH_2]$^+$, found 226.1440. $[\alpha]_D^{21}$ = –103.55 (*c* = 2.91, CH_2Cl_2).

***tert*-Butyl (*S*)-*N*-(2-Methylallyl)-*N*-(3-oxo-1-phenylbutan-2-yl)carbamate (5m):** Colorless oil, 72% yield; R_f = 0.80 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, Boc), 1.67 (br. s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.92 (m, 1 H, CH_2), 3.07 (m, 1 H, CH_2), 3.40 (m, 1 H, CH_2), 3.76 (m, 1 H, CH_2), 4.02 (m, 1 H, CH), 4.81 (s, 1 H, CH_2), 4.85 (s, 1 H, CH_2), 7.24 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_3), 26.8 (CH_3), 27.3 (CH_3), 28.3 (Boc), 34.1 (CH_2), 35.1 (CH_2), 54.1 (CH_2), 54.5 (CH_2), 67.1 (CH), 67.8 (CH), 80.6 (C-Boc), 81.4 (C-Boc), 114.0 (CH_2), 115.1 (CH_2), 126.5 (CH), 128.4 (2×CH), 129.4 (2×CH), 138.7 (C), 141.4 (C), 154.7 (C), 205.1 (C), 205.6 (C) ppm [some signals are duplicated due to the presence of rotamers]. EI HRMS: calcd. for $C_{19}H_{27}NO_3$: 317.1991, found 317.2002. $[\alpha]_D^{21}$ = –183.14 (*c* = 0.26, CH_2Cl_2).

General Procedure for the Synthesis of *N*-Boc-tetrahydropyrrolo[3,4-*c*]pyrazoles (6): A carousel reaction tube was charged with the corresponding α-allylamino ketone **5** (0.3 mmol, 1 equiv.), *N*-tosylhydrazide (1.1 equiv.) and dioxane (3 mL). The system was heated at 85 °C with stirring for 2 h. Then, K_2CO_3 (6 equiv.) was added and the reaction mixture was allowed to refluxed for 24 h. After cooling to room temperature, the 1,4-dioxane was removed under reduced pressure. The reaction crude was treated with a 1:1 mixture of EtOAc and H_2O and extracted three times with EtOAc. The organic layers were washed three times with H_2O, dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was isolated by flash chromatography on silica gel (mixtures of hexane/EtOAc).

***tert*-Butyl (6*S*,6a*S*)-6,6a-Dimethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6a):** Colorless oil, 64% yield; R_f = = 0.62 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.47 (s, 9 H, Boc), 2.24 (dd, *J* = 2.0, 9.0 Hz, 1 H, CH), 2.66 (dd, *J* = 9.0, 11.8 Hz, 1 H, CH_2), 3.84 (dd, *J* = 9.3, 11.7 Hz, 1 H, CH_2), 4.08 (q, *J* = 6.7 Hz, 1 H, CH), 4.33 (dd, *J* = 7.2, 17.8 Hz, 1 H, CH_2), 4.60 (dd, *J* = 1.9, 17.8 Hz, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8 (CH_3), 21.3 (CH_3), 28.4 (Boc), 31.0 (acetone), 39.8 (CH), 50.7 (CH_2), 62.1 (CH), 79.7 (C-Boc), 80.4 (CH_2), 101.4 (C), 153.6 (C) ppm. EI HRMS: calcd. for $C_{12}H_{22}N_3O_2$: 240.1712 [M + H]$^+$, found 240.1721. $[\alpha]_D^{19}$ = –20.00 (*c* = 0.03, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6a-Ethyl-6-methyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6b):** Colorless oil, 32% yield; R_f = 0.25 (hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 3 H, CH_3-Et), 1.33 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.47 (s, 9 H, Boc), 1.77 (q, *J* = 7.4 Hz, 1 H, CH_2-Et), 1.97 (q, *J* = 7.4 Hz, 1 H, CH_2-Et), 2.31 (ddd, *J* = 2.7, 7.8, 12.2 Hz, 1 H, CH), 2.70 (dd, *J* = 7.8, 11.8 Hz, 1 H, CH_2), 3.88 (dd, *J* = 9.4, 11.7 Hz, 1 H, CH_2), 4.19 (q, *J* = 6.7 Hz, 1 H, CH), 4.33 (dd, *J* = 7.9, 18.0 Hz, 1 H, CH_2), 4.50 (dd, *J* = 2.7, 18.0 Hz, 1 H, CH_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 8.4 (CH_3-Et), 16.0 (CH_3), 28.4 (CH_3-Boc), 29.4 (CH_2), 30.9 (acetone), 37.4 (CH), 50.9 (CH_2), 60.4 (CH), 79.8 (C-Boc), 81.8 (CH_2), 105.7 (C), 153.5 (C) ppm. EI HRMS: calcd. for $C_{13}H_{23}N_3O_2$: 253.1790, found 253.1798. $[\alpha]_D^{18}$ = 10.77 (*c* = 0.07, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*R*)-6-Methyl-6a-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6c):** Colorless oil, 36% yield; R_f = 0.76 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, Boc), 1.51 (d, *J* = 6.7 Hz, 3 H, CH_3), 2.79 (ddd, *J* = 2.1, 7.6, 14.8 Hz, 1 H, CH), 2.83 (dd, *J* = 7.6, 17.1 Hz; 1 H, CH_2), 4.05 (dd, *J* = 7.9, 10.5 Hz; 1 H, CH_2), 4.27 (dd, *J* = 7.0, 17.7 Hz, 1 H, CH_2), 4.47 (q, *J* = 6.7 Hz, 1 H, CH), 4.70 (dd, *J* = 1.9, 17.9 Hz; 1 H, CH_2), 7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.9 (CH_3-Ala), 28.5 (CH_3-Boc), 41.3 (CH), 50.9 (CH_2), 64.5 (CH), 80.0 (C-Boc), 81.2 (CH_2), 105.8 (C), 125.1 (2×CH), 127.8 (CH), 128.4 (C-Ph), 128.8 (2×CH), 140.6 (C), 153.5 (C) ppm. EI HRMS: calcd. for $C_{17}H_{23}N_3O_2$: 301.1790, found 301.1790. $[\alpha]_D^{27}$ = –250.00 (*c* = 0.01, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6a-Benzyl-6-methyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6d):** Colorless oil, 65% yield; R_f = 0.38 (hexane/EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.48 (s, 9 H, Boc), 2.39 (ddd, *J* = 2.0, 7.4, 17.1 Hz, 1 H, CH), 2.62 (dd, *J* = 8.0, 11.6 Hz, 1 H, CH_2), 2.93 (d, *J* = 13.8 Hz, 1 H, CH_2-Bn), 3.32 (dd, *J* = 7.5, 17.8 Hz; 1 H, CH_2), 3.45 (d, *J* = 13.8 Hz, 1 H, CH_2-Bn), 3.84 (dd, *J* = 9.4, 11.6 Hz; 1 H, CH_2), 4.30 (m, 2 H, CH and CH_2), 7.24 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (CH_3), 28.5 (Boc), 37.2 (CH), 41.9 (CH_2-Bn), 50.6 (CH_2), 61.2 (CH), 79.8 (C-Boc), 81.5 (CH_2), 106.6 (C), 127.0 (CH), 128.3 (2×CH), 130.0 (2×CH), 135.4 (C), 153.4 (C) ppm. EI MS: calcd. for $C_{18}H_{26}N_3O_2$: 316.20 [M + 1]$^+$, found 316.21. $[\alpha]_D^{20}$ = –10.00 (*c* = 0.03, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6-Isopropyl-6a-methyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6e):** Colorless oil, 50% yield; R_f = 0.29 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.20 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.47 (s, 9 H, Boc), 2.04 (m, 1 H, CH), 2.19 (m, 1 H, CH), 2.38 (m, 1 H, CH_2), 4.01 (m, 1 H, CH_2), 4.06 (m, 1 H, CH), 4.17 (dd, *J* = 7.2, 18.0 Hz, 1 H, CH_2), 4.49 (dd, *J* = 1.5, 18.0 Hz; 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (CH), 20.5 (CH_3), 24.1 (CH_3), 28.4 (Boc), 30.0 (CH_3), 41.9 (CH), 50.5 (CH_2), 71.2 (CH), 77.9 (CH_2), 79.8 (C-Boc), 103.1 (C), 154.2 (C) ppm. EI HRMS: calcd. for $C_{14}H_{26}N_3O_2$: 268.2025 [M + H]$^+$, found 268.2017. $[\alpha]_D^{10}$ = –27.50 (*c* = 1.80, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6-isobutyl-6a-methyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6f):** Colorless oil, 52% yield; R_f = 0.32 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.43 (m, 1 H, CH), 1.47 (s, 9 H, Boc), 2.13 (m, 2 H, CH_2), 2.23 (dd, *J* = 2.3, 7.6 Hz, 1 H, CH), 2.49 (dd, *J* = 9.2, 11.9 Hz, 1 H, CH_2), 3.99 (dd, *J* = 9.1, 11.8 Hz, 1 H, CH_2), 4.21 (t, *J* = 8.5 Hz, 1 H, CH), 4.25 (dd, *J* = 7.5, 17.9 Hz, 1 H, CH_2), 4.50 (dd, *J* = 2.3, 18.0 Hz, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_3), 23.5 (CH), 24.8 (CH_3), 28.3 (CH_3), 28.5 (Boc), 40.0 (CH_2), 41.5 (CH), 49.9 (CH_2), 63.7 (CH), 79.1 (CH_2), 79.8 (C-Boc), 102.3 (C), 153.5 (C) ppm. EI HRMS: calcd. for $C_{11}H_{18}N_3O_2$: 224.1399 [-*i*Pr-CH_2]$^+$, found 224.1392. $[\alpha]_D^{14}$ = –4.14 (*c* = 0.58, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6-Benzyl-6a-methyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6 g):** Colorless oil, 35% yield; R_f = 0.32 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 1.44 (s, 9 H, Boc), 2.24 (ddd, *J* = 1.5, 9.2, 17.6 Hz, 1 H, CH), 2.53 (dd, *J* = 2.5, 8.9 Hz, 1 H, CH_2), 3.07 (m, 2 H, CH_2-Bn), 4.00 (m, 1 H, CH_2), 4.20 (dd, *J* = 6.9, 17.8 Hz, 1 H, CH_2), 4.36 (t, *J* = 7.6 Hz, 1 H, CH), 4.60 (dd, *J* = 1.5, 17.8 Hz, 1 H, CH_2), 7.32 (m, 5 H, CH-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5 (CH_3), 28.4 (Boc), 36.4 (CH_2-Bn), 41.2 (CH), 50.2 (CH_2), 67.8 (CH), 78.9 (CH_2), 80.0 (C-Boc), 101.7 (C), 126.2 (CH), 128.2 (2×CH), 130.0 (2×CH), 138.7 (C), 153.5 (C) ppm. EI HRMS: calcd. for $C_{18}H_{26}N_3O_2$: 316.2027 [M + H]$^+$, found 316.2030. $[\alpha]_D^{14}$ = –14.74 (*c* = 0.19, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6-Benzyl-6a-ethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6h):** Colorless oil, 63% yield. R_f = 0.24 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ =

0.67 (t, J = 7.4 Hz, 3 H, CH_3), 1.33 (s, 9 H, Boc), 1.66 (q, J = 7.1 Hz, 2 H, CH_2), 2.33 (dd, J = 8.9, 17.0 Hz, 1 H, CH), 2.60 (dd, J = 2.1, 11.9 Hz, 2 H, CH_2), 2.96 (dd, J = 7.5, 13.3 Hz, 1 H, CH_2), 4.09 (m, 1 H, CH_2), 4.25 (dd, J = 7.9, 18.1 Hz, 1 H, CH_2), 4.44 (t, J = 7.1 Hz, 1 H, CH), 4.50 (dd, J = 2.4, 18.0 Hz, 1 H, CH_2), 7.34 (m, 5 H, CH-Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.2 (CH_3), 28.2 (Boc), 30.0 (CH_2), 36.3 (CH_2), 38.2 (CH), 50.4 (CH_2), 65.7 (CH), 79.9 (CH_2), 79.9 (C-Boc), 101.8 (C), 126.1 (CH), 128.1 (2 × CH), 129.9 (2 × CH), 138.7 (C), 153.3 (C) ppm. EI MS: calcd. for $C_{19}H_{28}N_3O_2$: 330.22 [M + 1]$^+$, found 330.96. $[\alpha]_D^{14}$ = –37.71 (c = 0.18, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-3,3,6,6a-Tetramethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6i):** Colorless oil, 61% yield. R_f = 0.30 (hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.7 Hz, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.46 (s, 9 H, Boc), 1.52 (s, 3 H, CH_3), 1.90 (dd, J = 6.3, 10.1 Hz, 1 H, CH), 3.17 (dd, J = 6.3, 12.1 Hz, 1 H, CH_2), 3.56 (dd, J = 10.1, 12.1 Hz, 1 H, CH_2), 3.92 (q, J = 6.7 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (CH_3), 21.7 (CH_3), 25.1 (CH_3), 28.4 (CH_3), 28.4 (Boc), 46.5 (CH_2), 49.4 (CH), 62.9 (CH), 79.8 (C-Boc), 90.2 (C), 102.4 (C), 154.1 (C) ppm. EI HRMS: calcd. for $C_{14}H_{26}N_3O_2$: 268.2027 [M + H]$^+$, found 268.2014. $[\alpha]_D^{20}$ = +11.39 (c = 0.36, CH_2Cl_2).

***tert*-Butyl (6*S*,6a*S*)-6a-Benzyl-3,3,6-trimethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6j):** Colorless oil, 36% yield; R_f = 0.49 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, J = 6.7 Hz, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.47 (s, 9 H, Boc), 1.61 (s, 3 H, CH_3), 1.93 (dd, J = 4.5, 9.2 Hz, 1 H, CH), 2.95 (d, J = 13.8 Hz, 1 H, CH_2-Bn), 3.28 (dd, J = 4.5, 12.2 Hz, 1 H, CH_2), 3.50 (dd, J = 9.4, 12.2 Hz, 1 H, CH_2), 3.67 (d, J = 13.4 Hz, 1 H, CH_2-Bn), 4.11 (q, J = 6.7 Hz, 1 H, CH), 7.23 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8 (CH_3), 21.7 (CH_3), 27.0 (CH_3), 28.4 (Boc), 43.7 (CH_2), 45.0 (CH), 46.6 (CH_2), 61.5 (CH), 79.9 (C-Boc), 91.0 (C), 106.9 (C), 127.0 (CH), 128.3 (2 × CH), 130.6 (2 × CH), 135.9 (C), 154.3 (C) ppm. EI HRMS: calcd. for $C_{20}H_{30}N_3O_2$: 344.2340 [M + H]$^+$, found 344.2338. $[\alpha]_D^{11}$ = –21.43 (c = 0.14, CH_2Cl_2).

***tert*-Butyl (3a*R*,6*S*,6a*S*)-3a,6,6a-Trimethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6k):** Colorless oil, 65% yield. R_f = 0.27 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.47 (s, 9 H, Boc), 1.59 (d, J = 6.7 Hz, 3 H, CH_3), 2.80 (d, J = 11.5 Hz, 1 H, CH_2), 3.45 (d, J = 11.5 Hz, 1 H, CH_2), 3.92 (d, J = 17.4 Hz, 1 H, CH_2), 4.00 (q, J = 6.6 Hz, 1 H, CH), 4.70 (d, J = 17.4 Hz, 1 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.6 (CH_3), 17.4 (CH_3), 28.2 (CH_3), 28.4 (Boc), 43.5 (C), 56.9 (CH_2), 62.0 (CH), 79.8 (C-Boc), 85.2 (CH_2), 99.5 (C), 154.0 (C) ppm. EI MS: calcd. for $C_{13}H_{22}N_3O_2$: 252.17, found 252.19. $[\alpha]_D^{21}$ = +2.69 (c = 0.78, CH_2Cl_2).

***tert*-Butyl (3a*R*,6*S*,6a*S*)-6-Isobutyl-3a,6a-dimethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6l):** Colorless oil, 31% yield. R_f = 0.47 (hexane/EtOAc, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.64 (s, 3 H, CH_3), 0.75 (br. s, 1 H, CH), 0.89 (s, 3 H, CH_3), 1.21 (m, 6 H, 2 × CH_3), 1.56 (s, 9 H, Boc), 1.84 (m, 1 H, CH_2), 2.06 (m, 1 H, CH_2), 2.49 (s, 1 H, CH_2), 2.51 (s, 1 H, CH_2), 3.35 (d, J = 17.4 Hz, 1 H, CH_2), 4.18 (d, J = 17.4 Hz, 1 H, CH_2), 4.34 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1 (CH) 18.6 (CH_3), 22.0 (CH_3), 23.6 (CH_3), 24.8 (CH_3), 28.5 (Boc), 40.6 (CH_2), 44.9 (C), 55.8 (CH_2), 63.8 (CH), 79.8 (C-Boc), 83.9 (CH_2), 100.0 (C), 154.1 (C) ppm. EI HRMS: calcd. for $C_{16}H_{30}N_3O_2$: 296.2340 [M + H]$^+$, found 296.2339. $[\alpha]_D^{21}$ = –3.98 (c = 1.16, CH_2Cl_2).

***tert*-Butyl (3a*R*,6*S*,6a*S*)-6-Benzyl-3a,6a-dimethyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazole-5(3*H*)-carboxylate (6m):** Colorless oil, 78% yield; R_f = 0.58 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, C_6D_6): δ = 0.55 (s, 3 H, CH_3), 0.58 (s, 3 H, CH_3), 1.57 (s, 9 H, Boc), 2.49 (d, J = 10.9 Hz, 1 H, CH_2), 3.18 (d, J = 17.2 Hz, 1 H, CH_2), 3.46 (m,1 H, CH_2-Bn), 3.53 (d, J = 10.2 Hz, 1 H, CH_2), 3.65 (m, 1 H, CH), 4.20 (d, J = 16.9 Hz, 1 H, CH_2), 4.39 (m, 1 H, CH_2), 7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 (CH_3), 17.4 (CH_3), 28.2 (Boc), 37.0 (CH_2-Bn), 44.4 (C) 56.3 (CH_2), 68.1 (CH), 79.1 (C-Boc), 84.0 (CH_2), 107.4 (C), 126.3 (CH), 127.5 (2 × CH), 128.1 (2 × CH), 139.6 (C), 153.7 (C) ppm. EI HRMS: calcd. for $C_{19}H_{27}N_3O_2$: 329.2102, found 329.2396. $[\alpha]_D^{24}$ = –12.03 (c = 0.62, CH_2Cl_2).

(*S*)-*N*-Allyl-*N*-[1-(2-tosylhydrazono)propan-2-yl]-4-nitrobenzenesulfonamide (9): Aldehyde **8** (0.2 mmol, 1 equiv.) was added to a stirred slurry of *N*-tosylhydrazide (1.1 equiv.) in methanol (3 mL). After 2–3 d, the tosylhydrazone precipitated from solution. It was isolated by suction filtration, washed with cold methanol and dried in vacuo. Orange oil, 79% yield; R_f = = 0.26 (hexane/EtOAc, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, J = 7.0 Hz, 3 H, CH_3), 1.64 (s, 1 H, NH), 2.45 (s, 3 H, CH_3), 3.69 (m, 2 H, CH_2), 4.64 (m, 1 H, CH), 5.02 (m, 2 H, CH_2), 5.56 (m, 1 H, CH), 7.03 (d, J = 3.5 Hz, 1 H, HCN), 7.35–7.79 (m, 4 H, Ts), 7.97–8.31 (m, 4 H, Ns) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (CH_3), 21.6 (CH_3), 47.1 (CH_2), 56.6 (CH), 119.0 (CH_2), 124.4 (2 × CH), 127.9 (2 × CH), 128.3 (2 × CH), 129.7 (2 × CH), 134.0 (CH), 135.0 (C), 136.1 (C), 142.6 (C), 144.9 (C), 148.1 (C) ppm. FAB MS: calcd. for $C_{13}H_{17}N_3O_2S$: 279.10 [M – Ns], found 279.01. $[\alpha]_D^{21}$ = –20.00 (c = 0.04, MeOH).

(3a*S*,6*S*,6a*S*)-6-Methyl-5-[(4-nitrophenyl)sulfonyl]-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazole (10a). Method A: One-Pot Procedure Starting from Aldehyde 8:[19] A carousel reaction tube was charged with the corresponding aldehyde (0.3 mmol, 1 equiv.), *N*-tosylhydrazide (1.1 equiv.) and dioxane (3 mL). The system was heated at 70 °C for 2 h. Then, K_2CO_3 (6 equiv.) was added and the reaction mixture was allowed to stirring at 70 °C for 24 h. After cooling to room temperature, the 1,4-dioxane was removed under reduced pressure. The reaction crude was dissolved in a mixture of EtOAc and H_2O 1:1 and extracted three times with EtOAc and with H_2O. The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was isolated by flash chromatography on silica gel (a mixture of hexane/EtOAc, 1:2).

Method B: Starting from Tosylhydrazone 9: A carousel reaction tube was charged with the corresponding *N*-tosylhydrazone (0.3 mmol), K_2CO_3 (6 equiv.) and dioxane (3.5 mL). The system was heated at 70 °C for 7 h. After cooling to room temperature, the 1,4-dioxane was removed under reduced pressure. The reaction crude was dissolved in a mixture of EtOAc and H_2O 1:1 and extracted three times with EtOAc and with H_2O. The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was isolated by flash chromatography on silica gel (a mixture of hexane/EtOAc, 1:2); yellow oil, 25% yield. R_f = = 0.67 (hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (d, J = 6.7 Hz, 3 H, CH_3), 2.45 (m, 1 H, CH), 3.14 (dd, J = 4.4, 10.8 Hz, 1 H, CH_2), 3.30 (dd, J = 8.1, 10.9 Hz, 1 H, CH_2), 3.80 (q, J = 6.8 Hz, 1 H, CH), 4.58 (m, 2 H, CH_2), 4.96 (m, 1 H, CH), 8.01–8.42 (m, 4 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9 (CH_3), 31.9 (CH), 54.4 (CH_2), 59.5 (CH), 83.5 (CH_2), 95.3 (CH), 124.5 (2 × CH), 128.4 (2 × CH), 142.6 (C), 150.3 (C) ppm. EI HRMS: calcd. for $C_{12}H_{14}N_4O_4S$: 310.0736, found 310.0731. $[\alpha]_D^{28}$ = +12.61 (c = 0.03, CH_2Cl_2).

DFT Molecular Modelling Studies: All calculations were performed with the Gaussian09, Revision B.01 package of programs.[22] Full geometry optimizations were carried out with the b3lyp density functional method.[23] Geometry optimizations were performed employing the standard 6-311++G** basis set for H, C and N. Harmonic force constants were computed at the optimized geometries employing the same basis set to characterize the stationary points as minima or saddle points. Zero-point vibrational corrections were determined from the harmonic vibrational frequencies to convert the total energies E_{el} to ground-state energies E_0 and Gibbs free energies G. The relative energy values indicated refer to Gibbs free energies and are denoted in hartee. Computational data, three-dimensional models and cartesian coordinates for all the stationary points found are included below. The three-dimensional models have been obtained with Jmol 13.0.12.[24] Energy values, three dimensional models and Cartesian coordinates are available in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all the compounds described. Two-dimensional NOESY experiments for compounds **6b** and **6l**. HPLC chromatograms for **6f** and **6g**. Experimental procedure for the synthesis of aldehyde **8**. Computational details, energy values, three dimensional models and cartesian coordinates.

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