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An Approach to 2,4-Substituted Pyrazolo[1,5-*a*]pyridines and Pyrazolo[1,5-*a*]azepines by Ring-Closing Metathesis

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The ring-closing metathesis (RCM) reactions of dienylpyrazoles have been employed in the synthesis of pyrazolo[1,5-*a*]pyridine and pyrazolo[1,5-*a*]azepine derivatives. Based on this approach, the diastereoselective synthesis of potential peptidomimetics containing four amino acid residues with the second (*i*+1) and third (*i*+2) fragments having been substituted by bicyclic frameworks is described.

Introduction

The chemistry of pyrazoles is attracting increasing interest due to the broad range of applications shown by a large number of pyrazole derivatives. The pyrazole ring is present in a number of small molecules that possess a wide range of biological activities that can be exploited in the fields of agriculture and pharmaceuticals. Moreover, some pyrazoles constitute scaffolds in supramolecular and polymer chemistry as well as in the food industry.[1]

Among pyrazole-fused bicyclic substructures, the pyrazolo[1,5-*a*]pyridine framework is especially relevant because it is present in many pharmacologically active compounds, for example, in inhibitors of p38 kinase,[2] dopaminergics,[3] inhibitors of herpes simplex viruses,[4] non-xanthine adenosine A_1 receptor antagonists,[5] and melatonine receptor ligands[6] (Figure 1). This substructure has also been proposed as a stable bioisoster of the indole nucleus to circumvent problems arising from the metabolic instability of indoles.[7]

The most generally useful approach to achieving this system involves the [3+2] cycloaddition reactions of *N*-aminopyridinium salts with substituted alkynes.[2–7,8] Other methods have also been reported.[2a,9] Charrette and co-workers recently reported a new methodology for the synthesis of 2-substituted pyrazolo[1,5-*a*]pyridines through direct cascade alkenylation/cyclization reactions.[10] In contrast, methods for the preparation of pyrazolo[1,5-*a*]azepine derivatives are very scarce. In fact, to the best of our knowledge, only two procedures dealing with the synthesis of this class of bicyclic heterocycles have been reported to date.[11] The first one allowed the formation of two substituted pyrazolo[1,5-*a*]-azepines through the cycloaddition reaction of a diazoketone and an activated acetylene,[11a] and the second one involved an intramolecular acylation of the C-5 pyrazole carbon by a Parham-type cyclization of a pyrazole-1-carboxylic acid.[11b]

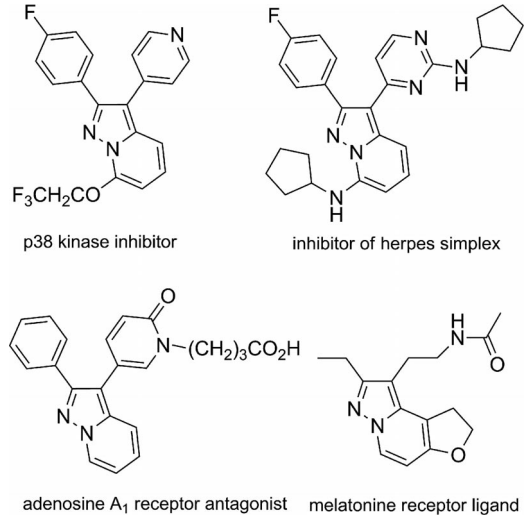

Figure 1. Pharmacologically active pyrazolo[1,5-*a*]pyridine derivatives.

As a continuation of our investigation of new strategies for the preparation of biologically active simple pyrazoles,[12] we focused our attention on the synthesis of pyr-

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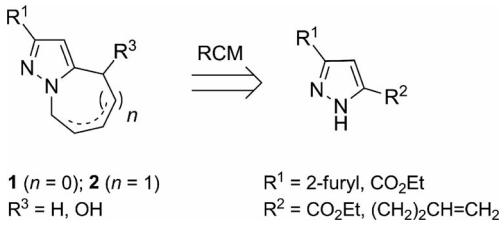
azolo[1,5-*a*]pyridine (**1**) and pyrazolo[1,5-*a*]azepine (**2**) derivatives (Scheme 1). Based on the ring-closing metathesis (RCM) reaction, we have investigated new synthetic pathways to accessing these fused heterobicyclic compounds. Despite the utility of RCM for the preparation of medium- and large-sized carbo- and heterocyclic compounds,[13] only a few reports on the application of this methodology to the synthesis of fused bicyclic heteroaromatic compounds have been published,[14] and none on the synthesis of pyrazolo[1,5-*a*]pyridine or pyrazolo[1,5-*a*]azepine derivatives.



Scheme 1. Synthetic strategy to pyrazolo[1,5-*a*]pyridine and pyrazolo[1,5-*a*]azepine derivatives.

Results and Discussion

Synthesis of Pyrazolo[1,5-*a*]pyridines 1 and Pyrazolo[1,5-*a*]azepines 2

Synthetic strategies for accessing the target fused bicyclic compounds **1** and **2** are depicted in Schemes 2 and 3. Thus, 3,5-disubstituted pyrazoles **4a** and **4b** were obtained in good yields by condensation of the previously prepared 1,3-dicarbonyl compounds **3a** and **3b**,[15] respectively, with anhydrous hydrazine following standard procedures (Scheme 2, *Pathway A*).[16] The best result for the *N*-allylation of **4b** was obtained by using NaH as a base followed by the addition of allyl bromide. The diolefinic pyrazole **5b** was obtained as the only product in 66% yield.[17] However, under these reaction conditions, **4a** led to a mixture of regioisomers **5aa** and **5ab** in 80% yield, the major component (93%) being the undesired **5ab**. To improve the yield of **5aa**, the *N*-allylation of **4a** was carried out under the reaction conditions described by Moreno-Mañas et al.[18] for the allylation of uracils. The catalytic complex $[Pd_2(dba)_3]$/dppb was added to a solution of **4a** in THF, followed by the addition of allyl acetate. After warming at 60 °C for 18 h, a mixture of **5aa** and **5ab** (ratio 4:1) was formed in almost quantitative yield. Both regioisomers were easily separated and purified by flash chromatography, and characterized by spectral analysis. NOESY experiments allowed the unambiguous assignment of their structures.

The ethoxycarbonyl group of **5aa** was then converted into aldehyde **6a** in a two-step sequence involving reduction to a primary alcohol (90% yield) followed by oxidation of the hydroxylic function with activated MnO_2 in acetonitrile (75% yield; Scheme 2, *Pathway B*). Dienylpyrazoles **7a** and **8a**, precursors of the 5,6- and 5,7-pyrazoles, were obtained in high yields by the addition of vinyl- and allylmagnesium bromide, respectively, to a solution of **6a** in THF at 0 °C. Subsequent RCM of **7a** and **8a** by using 5 mol-% of the Hoveyda–Grubbs' catalyst [Ru-**III**] in dichloromethane (DCM; for **7a**) or in dichloroethane (DCE; for **8a**) at reflux afforded the bicyclic alcohols **1a** and **2a** in excellent yields,[19] which on dehydration with a solution of 1 M HCl in THF at reflux gave 2-(2-furyl)pyrazolo[1,5-*a*]pyridine (**1c**) and 2-(2-furyl)pyrazolo[1,5-*a*]azepine (**2c**) in excellent yields. Cyclization of the dienylpyrazole **5b** was also found to be feasible when the reaction mixture was heated at reflux in DCM for 4 h in the presence of the [Ru-**III**] catalyst leading to ethyl 5,8-dihydro-4*H*-pyrazolo[1,5-*a*]azepine-2-carboxylate (**2b**) in good yield. The yield increased substantially (up to 80%) when the process was carried out under microwave irradiation at 80 °C with a significant drop in reaction time (1 h).

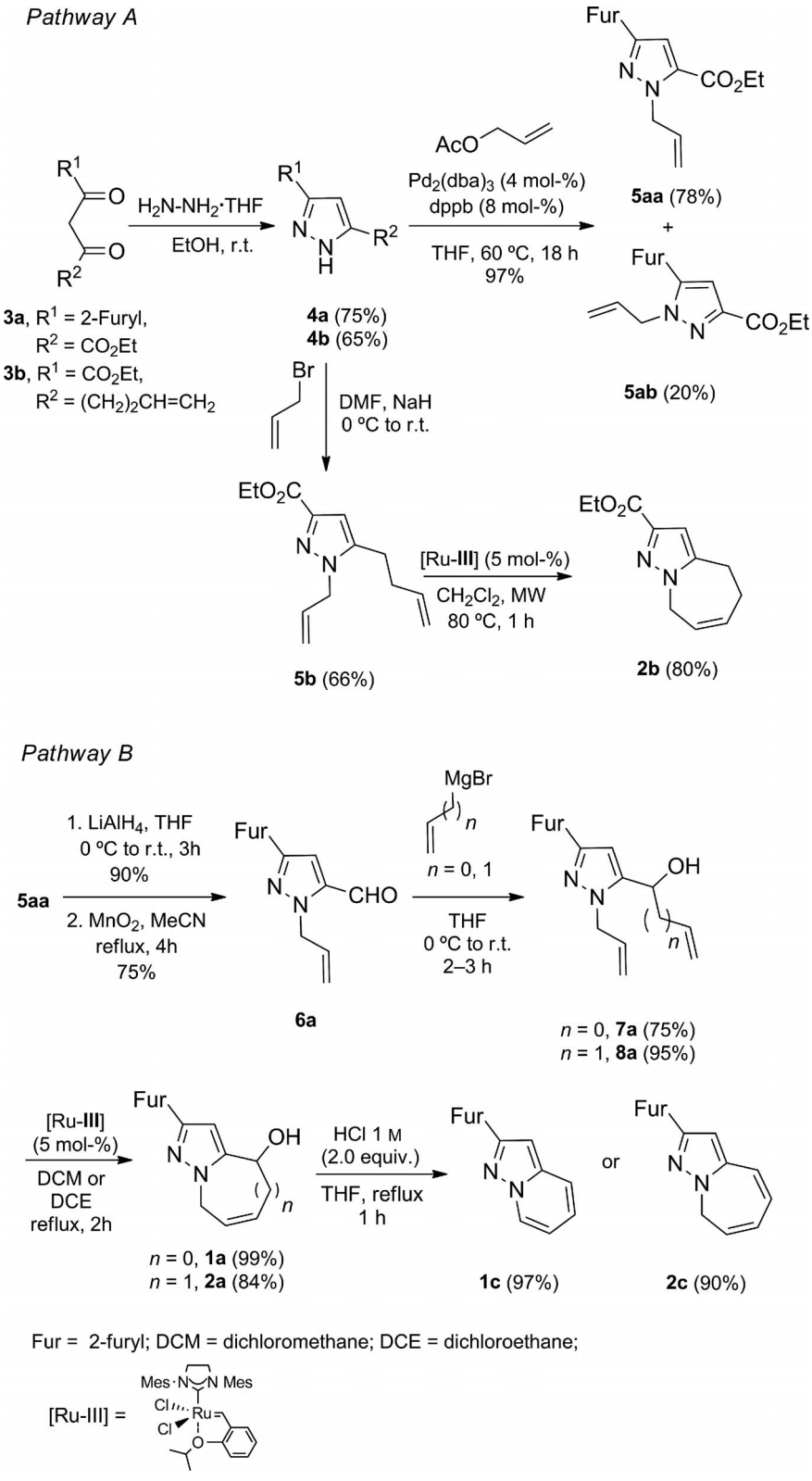
Synthesis of Potential Peptidomimetics 9 and 10

In the last two decades, research in the field of peptidomimetics has gained considerable momentum due to their potential use as precursors of small molecules that display more favorable therapeutic properties than natural peptides. The design and synthesis of conformationally restricted peptidomimetics is an important approach towards improving the potency, selectivity, and metabolic stability of peptide-based drugs.[20] In this sense, some bicyclic ring systems, such as azabicycloalkane amino acids, have proven to be versatile and effective scaffolds that mimic secondary peptide structures.[21] Incidentally, bicyclic templates restrict conformations by a combination of structural constraints and steric interactions, which are influenced by the stereochemistry of the scaffold, the presence of substituents, and the frame size in particular.

On the basis of the success of our strategy for the synthesis of 5,6- and 5,7-fused pyrazole derivatives by RCM, we extended this protocol to the diastereoselective synthesis of bicyclic ring amino acids **9**,**10aa** and **9**,**10ab** (Scheme 3). These structures mimic peptides containing four amino acid residues, the second (*i*+1) and third (*i*+2) fragments having been substituted by bicyclic frameworks.

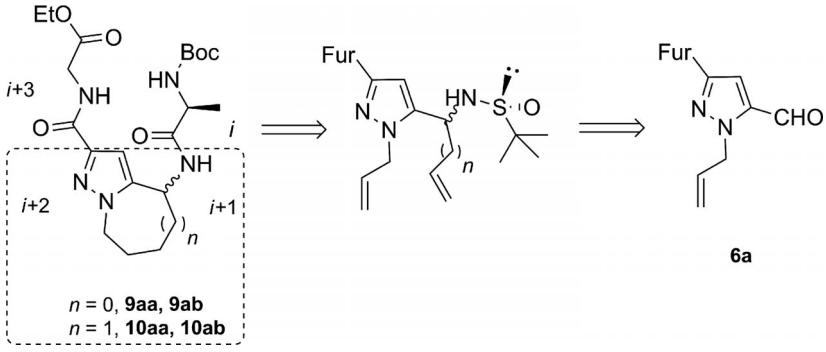
The retrosynthetic analysis of **9** and **10** from the formylpyrazole **6a** is depicted in Scheme 3. The key step is the stereoselective creation of a stereocenter at C-4. In principle, one of the most versatile methods for the asymmetric synthesis of amines is the 1,2-addition of nucleophiles such as organometallic reagents to chiral imines.[22] However, when imines react with basic nucleophiles, electron-withdrawing substituents on nitrogen are necessary to activate the C=N double bond. The *tert*-butanesulfinyl group has proved to be an ideal N-substituent for the nucleophilic addition to imines, providing a highly efficient approach to the asymmetric synthesis of many different types of amines. This group can be easily introduced by condensation of a carbonyl compound with enantiomerically pure *tert*-butanesulfinamide in the presence of a Lewis acid.[23]

The condensation of **6a** with (*R*)-*tert*-butanesulfinamide in the presence of 4 equiv. of $Ti(OEt)_4$ led to imine **11a** in

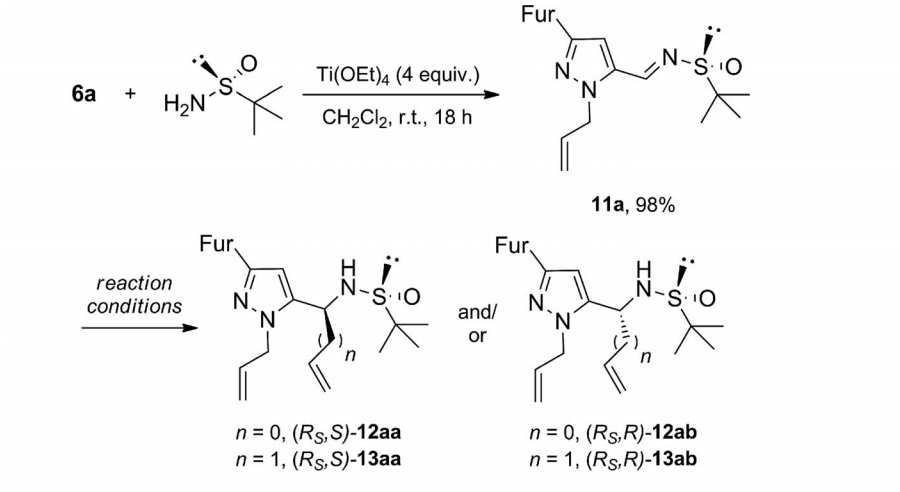


Scheme 2. Synthesis of pyrazolo[1,5-*a*]pyridine and pyrazolo[1,5-*a*]azepine derivatives.

almost quantitative yield (Scheme 4). Following Ellman and co-workers' procedure,[24] when allylmagnesium bromide was added to a CH_2Cl_2 (DCM) solution of **11a** at –60 °C, a mixture of two diastereoisomeric dienylpyrazoles (R_S,*S*)-**13aa** and (R_S,*R*)-**13ab** was obtained in 84% yield (**13aa**/**13ab** = 4:1; Method A), which were separated by flash chromatography.[25] On the other hand, the diastereoselective allylation of **11a** with allyl bromide and indium in a



Scheme 3. Strategy for the synthesis of peptidomimetics **9** and **10**.



Reaction conditions:
1) Method A: CH_2=$CHCH_2MgBr$, DCM, –60 °C, overnight: rd **13aa:13ab** 4:1 (84 %).
CH_2=$CHMgBr$, CH_2Cl_2, –60 °C, overnight: rd **12aa:12ab** 1.5:1 (98 %).
2) Method B: CH_2=$CHCH_2Br$, In, satd. NaBr aq, r.t., 4 d: rd **13aa:13ab** >99:1 (50 % at 75 % conversion).
3) Method C: CH_2=$CHCH_2Br$, Zn, HMPA, H_2O, r.t., 15 h: rd **13aa:13ab** 1:>99 (58 %).
4) Method D: CH_2=$CHMgBr$, Me_2Zn, THF, –78 °C, overnight: rd **12aa:12ab** 4:96 (98 %)

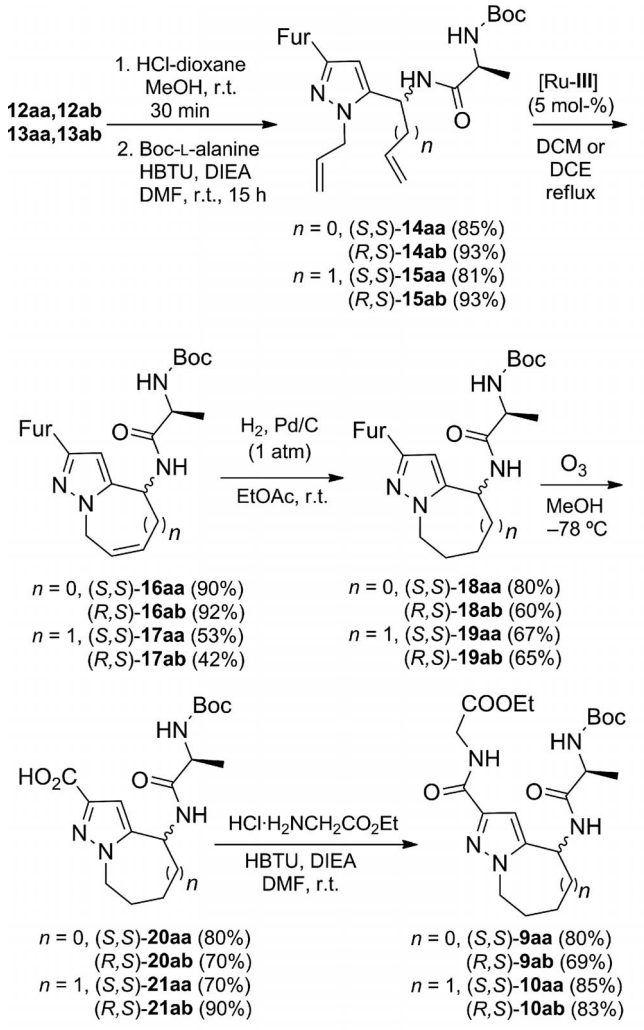
Scheme 4. Synthesis of dienylpyrazoles **12** and **13**.

NaBr saturated aqueous solution at room temperature led to the diastereoisomer (R_S,*S*)-**13aa** as the sole product (50% yield at 75% conversion; Method B).[26] Furthermore, addition of allylzinc bromide to **11a** using hexamethylphosphoramide (HMPA) as solvent at room temperature gave the diastereoisomer (R_S,*R*)-**13ab** as the only product in 58% yield (Method C).[27]

For the addition of the vinylic chain, the best diastereomeric results were obtained (**12aa/12ab** = 4:96) when a previously prepared solution of dimethylzinc and vinylmagnesium bromide in THF was added to a THF solution of **11a** at –78 °C (Method D).[28] When applying Ellman and co-workers' reaction conditions, the chemical yield was good (98%), but the selectivity was very low, **12aa/12ab** = 1.5:1 (Method A; Scheme 4).

With the dienylpyrazoles **12** and **13** in hand, the RCM reaction was conducted. Despite many attempts under different reaction conditions, the outcome was not satisfactory, probably due to the presence of the *tert*-butanesulfinyl group. As the L-alanine residue is present in the side-chain at C-4 in the final products **9** and **10**, another strategy involving the substitution of the *tert*-butanesulfinyl group in **12** and **13** with *N*-Boc-L-alanine was adopted. The *tert*-butanesulfinyl group was removed by adding a solution of HCl in dioxane to a solution of the respective dienylpyrazole **12** or **13** in MeOH at room temperature, followed by stirring for 30 min. A solution of *N*-Boc-L-alanine in DMF was then added followed by the coupling agent 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diisopropylethylamine (DIEA) as base. As expected, the respective dienylpyrazoles **14** and **15** were obtained in high yields (Scheme 5). The relative configuration of the newly created stereocenter (C-α of the side-chain attached to the C-5 of the pyrazole ring) in **15aa** was assigned *S* by means of X-ray crystallography.[29]

Compounds **14** and **15** underwent the RCM reaction in the presence of 5 mol-% Hoveyda–Grubbs' catalyst [Ru-**III**] leading to the bicyclic fused pyrazole derivatives **16** and **17**



Scheme 5. Synthesis of peptidomimetics **9** and **10**.

(Scheme 5). The cyclization reactions of dienyl pyrazoles **14** in DCM at reflux were found to be very efficient resulting in **16** in excellent yields. However, the dienylpyrazoles **15** did not produce satisfactory results under similar conditions. The best results were obtained when **15** was heated at reflux in DCE for 18 h, although the starting materials were not totally transformed. The C=C double bond in the unsaturated bicyclic compounds **16** and **17** was then hydrogenated by treatment with hydrogen in the presence of Pd/C to afford **18** and **19** in good yields. To introduce the second amino acid unit at C-2 of the pyrazole ring, the furyl group must be oxidized. Thus, ozone was bubbled into colorless solutions of **18** and **19** in MeOH at –78 °C until the blue color became permanent. Bicyclic carboxylic acids **20** and **21** were formed in high yields. Finally, these compounds were subjected to condensation with the ethyl glycinate salt under the same reaction conditions as employed for the introduction of L-alanine to give the final products **9** and **10** in good yields. The *S* configuration at C-4 in the tetrahydropyridine ring in **9aa** was determined by X-ray crystallographic analysis (Figure 2).[30]

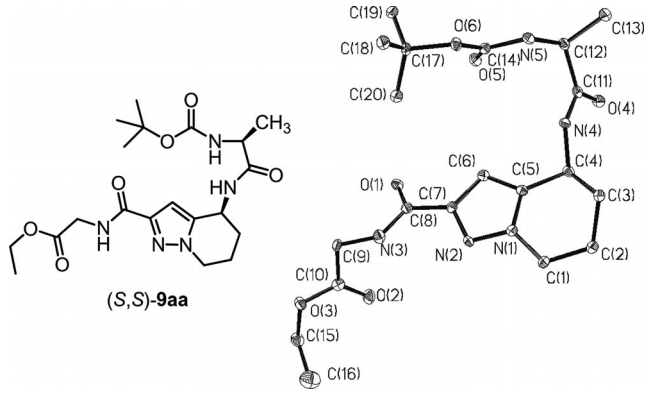


Figure 2. ORTEP diagram of (*S*,*S*)-**9aa**.

The propensity of **9aa**, **9ab**, **10aa**, and **10ab** to mimic peptide structures is currently under investigation. Preliminary results seem to indicate the presence of an intramolecular hydrogen bond between the amide proton on the substituent on the pyrazole ring and the carbonyl oxygen of the amido group in the substituent of the tetrahydropyridine ring in **9aa**, which could mimic a β-turn secondary structure. Further applications of the new substrates are currently being investigated in our laboratory.

Conclusions

We have developed a new approach to the synthesis of 2,4-substituted pyrazolo[1,5-*a*]pyridines and pyrazolo[1,5-*a*]azepines from readily available 3,5-disubstituted 1*H*-pyrazoles. These pyrazoles were *N*-allylated to afford 1,5-diolefinic intermediates, which underwent ring-closing metathesis (RCM) in the presence of 5 mol-% of the Hoveyda–Grubbs' catalyst to afford the target products in excellent yields. This approach has been applied to the diastereoselective synthesis of four potential peptidomimetics containing four amino acid residues with the second (*i*+1) and third (*i*+2) fragments having been substituted by bicyclic frameworks.

Experimental Section

General Methods: All reactions were carried out under nitrogen. The solvents were purified prior to use: THF was distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25-mm precoated silica gel plates. Visualization was carried out with UV light. Flash column chromatography was performed on silica gel 60 (particle size 0.040–0.063 mm) with the solvents indicated in each case. Melting points were measured with a Büchi B-540 apparatus. ^{1}H and ^{13}C NMR spectra were recorded with 300 MHz Bruker AC300 and 400 MHz Bruker Avance spectrometers. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q represent

multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br. indicate that the signal is broad.

Microwave reactions were carried out in a 0.5–2 mL vial with a Biotage Initiator™ 2.0 microwave synthesizer. The solutions were stirred before the irradiation was started and the absorbance of the solvent was set as "normal". The reaction time was initiated as soon the system reached the input temperature, although it took approximately 2 min to reach it.

High-resolution mass spectra were recorded with a VGmAutospec (VG Analytical, Micromass Instruments) by the Universitat de València Mass Spectrometry Service.

Ethyl 5-(3-Butenyl)-1*H*-pyrazole-3-carboxylate (4b):[15] Yellow oil (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.0 Hz, 3 H, CH_3), 2.35 (dt, ^1J = 8.1, ^2J = 6.6 Hz, 2 H, CH_2), 2.75 (t, J = 7.2 Hz, 2 H, CH_2), 4.31 (q, J = 7.0 Hz, 2 H, CH_2), 4.93–5.03 (m, 2 H, CH_2), 5.71–5.84 (m, 1 H, C*H*), 5.65 (s, 1 H, C*H*), 8.71 (br., 1 H, N*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 25.9, 33.4, 61.3, 106.8, 116.2, 137.4, 162.3 ppm. HRMS (EI): calcd. for $C_{10}H_{14}N_2O_2$ $[M]^+$ 194.1059; found 194.1055.

Ethyl 1-Allyl-3-(2-furyl)-1*H*-pyrazole-5-carboxylate (5a): A mixture of allyl acetate (1.75 mL, 16.2 mmol) in THF (10 mL), bis(dibenzylideneacetone)palladium (201.4 mg, 0.22 mmol), and 1,4-bis(diphenylphosphanyl)butane (184.3 mg, 0.432 mmol) was added to a solution of **4a** (1′103 g, 5.4 mmol) in THF (15 mL). After heating at 60 °C for 18 h, the mixture was extracted with EtOAc and washed with H_2O. The organic layer was dried and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc, 4:1) to afford **5aa** as a pale-yellow oil (1.03 g, 78%) and **5ab** as a yellow oil (259.0 mg, 20%). For **5aa**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 4.28 (q, J = 7.2 Hz, 2 H, CH_2), 5.02 (d, J = 17.3 Hz, 1 H, C*H*H), 5.08–5.15 (m, 3 H, CH*H*, CH_2), 5.91–6.04 (m, 1 H, C*H*), 6.39 (dd, ^1J = 3.4, ^2J = 1.7 Hz, 1 H, C*H*), 6.62 (d, J = 3.4 Hz, 1 H, C*H*), 6.99 (s, 1 H, C*H*), 7.38 (d, J = 1.7 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 54.6, 61.6, 106.6, 108.3, 111.7, 117.9, 133.5, 142.5, 143.2, 148.3, 159.7 ppm. HRMS (EI): calcd. for $C_{13}H_{14}N_2O_3$ $[M]^+$ 246.0960; found 246.0964. For **5ab**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 4.35 (q, J = 7.2 Hz, 2 H, CH_2), 4.95–4.99 (m, 3 H, CH*H*, CH_2), 5.13 (d, J = 10.6 Hz, 1 H, C*H*H), 5.87–5.99 (m, 1 H, C*H*), 6.44 (dd, ^1J = 3.4, ^2J = 1.9 Hz, 1 H, C*H*), 6.53 (d, J = 3.4 Hz, 1 H, C*H*), 6.95 (s, 1 H, C*H*), 7.45 (dd, ^1J = 1.9, ^2J = 1.1 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8, 54.6, 61.5, 108.4, 110.0, 111.9, 118.3, 132.6, 135.6, 143.5, 162.5 ppm. HRMS (EI): calcd. for $C_{13}H_{14}N_2O_3$ $[M]^+$ 246.0960; found 246.0962.

Ethyl 1-Allyl-5-(3-butenyl)-1*H*-pyrazole-3-carboxylate (5b): NaH (18.4 mg, 0.77 mmol) was added portionwise to a solution of **4b** (124′1 mg, 0.64 mmol) in DMF (5 mL) at 0 °C, and the mixture was stirred for 20 min. Then allyl bromide (68 μL, 0.77 mmol) was added and the mixture was stirred for 3 h. The solvent was concentrated under vacuum and the crude mixture extracted with EtOAc. After washing with H_2O, the organic layer was dried and concentrated. Flash chromatography (*n*-hexane/EtOAc, 4:1) afforded **5b** as a pale-yellow oil (98.8 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H, CH_3), 2.36 (dt, ^1J = 7.5, ^2J = 6.6 Hz, 2 H, CH_2), 2.62 (t, J = 7.5 Hz, 2 H, CH_2), 4.33 (q, J = 7.1 Hz, 2 H, CH_2), 4.73 (dt, ^1J = 5.3, ^2J = 1.7 Hz, 2 H, CH_2), 4.94 (dd, ^1J = 16.1, ^2J = 0.8 Hz, 1 H, C*H*H), 4.98 (d, J = 9.7 Hz, 1 H, CH*H*), 5.02 (dd, ^1J = 16.1, ^2J = 1.5 Hz, 1 H, C*H*H), 5.15 (dd, ^1J = 9.7, ^2J = 0.9 Hz, 1 H, CH*H*), 5.70–5.82 (m, 1 H, C*H*), 5.84–5.95 (m, 1 H, C*H*), 6.57 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8, 25.2, 32.4, 53.0, 61.2, 107.9, 116.1, 118.1, 132.7, 136.9, 143.0, 144.4, 162.9 ppm. HRMS (EI): calcd. for $C_{13}H_{18}N_2O_2$ $[M]^+$ 234.1368; found 234.1361.

1-Allyl-3-(2-furyl)-1*H*-pyrazole-5-carbaldehyde (6a):[12b] Yellow oil (880 mg, 67.5% from **5aa**, two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.01–5.13 (m, 4 H, CH_2, CH_2), 5.85–5.98 (m, 1 H, C*H*), 6.38 (dd, ^1J = 3.4, ^2J = 1.9 Hz, 1 H, C*H*), 6.63 (dd, ^1J = 3.4, ^2J = 0.8 Hz, 1 H, C*H*), 6.99 (s, 1 H, C*H*), 7.37 (dd, ^1J = 1.9, ^2J = 0.8 Hz, 1 H, C*H*), 9.76 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 54.6, 106.9, 111.5, 111.8, 118.5, 132.9, 139.9, 142.7, 144.0, 147.8, 179.8 ppm. HRMS (EI): calcd. for $C_{11}H_{10}N_2O_2$ $[M]^+$ 202.0742; found 202.0750.

Addition of Grignard Reagents: The Grignard reagent (1 M in THF, 1.5 mmol) was slowly added to a solution of **6a** (203.5 mg, 1.0 mmol) in dry THF (6 mL) cooled to 0 °C. After stirring for 3 h (TLC), a saturated NH_4Cl solution was added and the crude mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, concentrated under vacuum, and purified by flash chromatography.

1-Allyl-3-(2-furyl)-5-(1-hydroxy-2-propenyl)-1*H*-pyrazole (7a): Flash chromatography (*n*-hexane/EtOAc, 2:1). Pale-yellow oil (172.5 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.70 (ddt, ^1J = 16.2, ^2J = 5.3, ^3J = 1.5 Hz, 1 H, C*H*H), 4.78 (ddt, ^1J = 16.2, ^2J = 5.6, ^3J = 1.5 Hz, 1 H, CH*H*), 4.97 (dd, ^1J = 17.1, ^2J = 1.1 Hz, 1 H, C*H*H), 5.10 (dd, ^1J = 10.6, ^2J = 1.5 Hz, 1 H, C*H*H), 5.16 (br., 1 H, C*H*), 5.22 (dd, ^1J = 10.2, ^2J = 1.1 Hz, 1 H, CH*H*), 5.31 (dd, ^1J = 17.1, ^2J = 1.1 Hz, 1 H, CH*H*), 5.84–5.96 (m, 1 H, C*H*), 5.98–6.07 (m, 1 H, C*H*), 6.31 (s, 1 H, C*H*), 6.34 (dd, ^1J = 3.4, ^2J = 1.9 Hz, 1 H, C*H*), 6.53 (dd, ^1J = 3.4, ^2J = 0.8 Hz, 1 H, C*H*), 7.33 (dd, ^1J = 1.9, ^2J = 0.8 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 52.4, 66.4, 101.9, 105.6, 111.2, 116.6, 117.8, 133.3, 136.9, 141.6, 142.8, 144.2, 148.5 ppm. HRMS (EI): calcd. for $C_{13}H_{14}N_2O_2$ $[M]^+$ 230.1015; found 230.1011.

1-Allyl-3-(2-furyl)-5-(1-hydroxy-3-butenyl)-1*H*-pyrazole (8a): Flash chromatography (*n*-hexane/EtOAc, 1:1). Pale-yellow oil (231 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 1 H, O*H*), 2.57–2.62 (m, 2 H, CH_2), 4.72 (dd, ^1J = 7.4, ^2J = 7.3 Hz, 1 H, C*H*), 4.80–4.84 (m, 2 H, CH_2), 5.01 (dd, ^1J = 17.2, ^2J = 1.1 Hz, 1 H, C*H*H), 5.13–5.18 (m, 2 H, CH_2), 5.19 (dd, ^1J = 17.2, ^2J = 1.3 Hz, 1 H, CH*H*), 5.73–5.87 (m, 1 H, C*H*), 5.91–6.04 (m, 1 H, C*H*), 6.39 (dd, ^1J = 3.4, ^2J = 1.9 Hz, 1 H, C*H*), 6.58 (dd, ^1J = 3.4, ^2J = 0.7 Hz, 1 H, C*H*), 7.38 (dd, ^1J = 1.9, ^2J = 0.7 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 41.2, 52.8, 65.1, 101.6, 106.0, 111.6, 117.7, 119.5, 133.8, 133.9, 142.1, 143.3, 145.8, 149.1 ppm. HRMS (EI): calcd. for $C_{14}H_{16}N_2O_2$ $[M]^+$ 244.1212; found 244.1193.

Ring-Closing Metathesis of 7a, 8a and 5b: The second-generation Hoveyda–Grubbs' catalyst (5 mol-%) was added to a solution of **7a** (202 mg, 0.88 mmol) [or **8a** (0.60 mg, 0.61 mmol) or **5b** (100 mg, 0.43 mmol)] in DCE (0.05 M) (or DCM), and the mixture was heated at reflux for 2 h for **7a** and **8a** (**5b** was heated under microwaves at 80 °C for 1 h). The solvent was evaporated and the crude mixture was purified by flash chromatography (*n*-hexane/EtOAc, 1:1, for **1a** and **2a**; *n*-hexane/EtOAc, 2:1, for **2b**).

2-(2-Furyl)-4,7-dihydropyrazolo[1,5-*a*]pyridin-4-ol (1a): White solid (176 mg, 99%); m.p. 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.63–4.81 (m, 2 H, CH_2), 5.28 (d, J = 3.6 Hz, 1 H, C*H*), 6.07–6.19 (m, 2 H, CH, C*H*), 6.53 (dd, ^1J = 3.4, ^2J = 1.8 Hz, 1 H, C*H*), 6.62 (s, 1 H, C*H*), 6.72 (dd, ^1J = 3.4, ^2J = 0.8 Hz, 1 H, C*H*), 7.56 (dd, ^1J = 1.8, ^2J = 0.8 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 48.3, 61.8, 101.7, 107.3, 112.7, 124.1, 127.7, 143.7 145.4, 150.3 ppm. HRMS (EI): calcd. for $C_{11}H_{10}N_2O_2$ $[M]^+$ 202.0742; found 202.0739.

2-(2-Furyl)-5,8-dihydro-4*H*-pyrazolo[1,5-*a*]azepin-4-ol (2a): Yellow oil (118.6 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57–2.60 (m, 3 H, CH_2, O*H*), 4.77 (ddd, ^1J = 17.3, ^2J = 4.7, ^3J = 1.2 Hz, 1 H, C*H*H), 4.93 (ddd, ^1J = 17.3, ^2J = 4.1, ^3J = 1.7 Hz, 1 H, CH*H*), 5.07 (dd, ^1J = 5.5, ^2J = 5.1 Hz, 1 H, C*H*), 5.65–5.82 (m, 2 H, C*H*, C*H*), 6.35 (s, 1 H, C*H*), 6.39 (dd, ^1J = 3.3, ^2J = 1.7 Hz, 1 H, C*H*), 6.55 (dd, ^1J = 3.3, ^2J = 0.6 Hz, 1 H, C*H*), 7.37 (dd, ^1J = 1.7, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 36.0, 50.7, 64.8, 101.6, 105.8, 111.6, 123.3, 127.5, 142.3, 142.4, 146.3, 149.1 ppm. HRMS (EI): calcd. for $C_{12}H_{12}N_2O_2$ $[M]^+$ 216.0899; found 216.0907.

Ethyl 5,8-Dihydro-4*H*-pyrazolo[1,5-*a*]azepin-2-carboxylate (2b): Pale-yellow oil (70.8 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.0 Hz, 3 H, CH_3), 2.34 (dt, ^1J = 3.4, ^2J = 2.1 Hz, 2 H, CH_2), 2.92 (t, J = 5.8 Hz, 2 H, CH_2), 4.33 (q, J = 7.0 Hz, 2 H, CH_2), 4.87 (d, J = 2.5 Hz, 2 H, CH_2), 5.66–5.77 (m, 2 H, CH, C*H*), 6.55 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8, 23.2, 28.1, 50.5, 61.2, 107.7, 121.7, 131.8, 141.9, 144.9, 162.9 ppm. HRMS (EI): calcd. for $C_{11}H_{14}N_2O_2$ $[M]^+$ 206.1055; found 206.1059.

Dehydration of 1a and 2a: A solution of 1 M HCl (0.50 mmol) was added to a solution of **1a** (50 mg, 0.247 mmol) [or **2a** (55 mg, 0.255 mmol)] in THF (3 mL) at room temperature and the mixture was heated at reflux for 1 h. The crude mixture was extracted with EtOAc. The combined organic extracts were washed with H_2O, then with brine, and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude mixture was purified by flash chromatography (*n*-hexane/EtOAc, 3:1).

2-(2-Furyl)pyrazolo[1,5-*a*]pyridine (1c): White solid (44.6 mg, 97%); m.p. 75–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.47 (dd, ^1J = 3.4, ^2J = 1.9 Hz, 1 H, C*H*), 6.68 (s, 1 H, C*H*), 6.70 (dd, ^1J = 6.8, ^2J = 1.3 Hz, 1 H, C*H*), 6.81 (dd, ^1J = 3.4, ^2J = 0.8 Hz, 1 H, C*H*), 7.06 (ddd, ^1J = 8.8, ^2J = 6.8, ^3J = 1.1 Hz, 1 H, C*H*), 7.45 (dd, ^1J = 8.8, ^2J = 1.0 Hz, 1 H, C*H*), 7.48 (dd, ^1J = 1.8, ^2J = 0.8 Hz, 1 H, C*H*), 8.41 (dd, ^1J = 6.8, ^2J = 1.0 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 92.3, 106.3, 110.5, 110.9, 116.9, 122.7, 127.5, 140.2, 141.6, 144.7, 147.7 ppm. HRMS (EI): calcd. for $C_{11}H_8N_2O$ $[M]^+$ 184.0637; found 184.0633.

2-(2-Furyl)pyrazolo[1,5-*a*]azepine (2c): Yellow oil (44.5 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.73 (d, J = 6.4 Hz, 2 H, CH_2), 5.90 (dt, ^1J = 10.2, ^2J = 6.4 Hz, 1 H, C*H*), 6.24 (dd, ^1J = 20.0, ^2J = 5.5 Hz, 1 H, C*H*), 6.28 (dd, ^1J = 20.0, ^2J = 5.9 Hz, 1 H, C*H*) 6.40 (dd, ^1J = 3.4, ^2J = 1.1 Hz, 1 H, C*H*), 6.44 (s, 1 H, C*H*), 6.56 (dd, ^1J = 3.4, ^2J = 0.8 Hz, 1 H, C*H*), 6.67 (d, J = 11.1 Hz, 1 H, C*H*), 7.39 (dd, ^1J = 1.9, ^2J = 0.8 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 49.4, 102.4, 105.5, 111.3, 121.5, 125.4, 127.9, 130.7, 141.2, 141.8, 143.4, 148.8 ppm. HRMS (EI): calcd. for $C_{12}H_{10}N_2O$ $[M]^+$ 198.0793; found 198.0783.

***N*-[(*R*$_S$)-*tert*-Butylsulfinyl][1-allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-methanimine (11a):** (*R*)-(+)-2-Methyl-2-propanesulfinamide (307 mg, 2.5 mmol) and $Ti(OEt)_4$ (0.8 mL, 3.84 mmol) were added to a solution of **6a** (418 mg, 2.07 mmol) in dry CH_2Cl_2 (20 mL) in a round-bottomed flask, and the mixture was stirred at room temperature for 20 h. Then H_2O/ice (10 mL) was added until white titanium salts precipitated. The suspension was filtered through a short pad of Celite® and washed with CH_2Cl_2. The clear solution was concentrated under vacuum to afford **11a**. Yellow oil (620 mg, 98%). $[\alpha]_D^{25}$ = –95.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 9 H, 3 CH_3), 4.91 (d, J = 17.1 Hz, 1 H, C*H*H), 5.02–5.23 (m, 3 H, CH*H*, CH_2), 5.86–5.99 (m, 1 H, C*H*), 6.38 (dd, ^1J = 3.4, ^2J = 1.9 Hz, 1 H, C*H*), 6.63 (d, J = 3.4 Hz, 1 H, C*H*), 6.89 (s, 1 H, C*H*), 7.38 (dd, ^1J = 1.9, ^2J = 0.8 Hz, 1 H, C*H*), 8.45 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.4, 52.9, 56.9, 105.4, 107.7, 110.4, 116.4, 131.9, 136.6, 141.2, 142.8, 146.7, 149.4 ppm. HRMS (EI): calcd. for $C_{15}H_{19}N_3O_2S$ $[M]^+$ 305.1197; found 305.1192.

Addition of Organometallic Reagents: Method A: Grignard reagent;[24] method B: allyl bromide/In;[26] method C: allyl bromide/Zn;[26] method D: Grignard reagent/Me_2Zn.[28]

(*R*$_S$)-*N*-{(1*S*)-1-[1-Allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-2-propenyl}-*tert*-butylsulfinamide (12aa): Pale-yellow oil (177 mg, 59%, method A; 11.7 mg, 3.9%, method D). $[\alpha]_D^{25}$ = –55.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 9 H, 3 CH_3), 3.48 (d, J = 5.1 Hz, 1 H, N*H*), 4.84 (m, 2 H, CH_2), 5.02–5.09 (m, 2 H, CH_2), 5.21–5.25 (m, 1 H, C*H*), 5.29–5.35 (m, 2 H, CH_2), 5.93–6.12 (m, 2 H, 2 C*H*), 6.43 (dd, ^1J = 3.4, ^2J = 1.8 Hz, 1 H, C*H*), 6.44 (s, 1 H, C*H*), 6.63 (dd, ^1J = 3.4, ^2J = 0.7 Hz, 1 H, C*H*), 7.42 (dd, ^1J = 1.8, ^2J = 0.7 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.5, 52.4, 53.5, 56.2, 102.7, 105.6, 111.2, 117.6, 118.4, 132.9, 136.3, 141.7, 142.5, 143.3, 148.6 ppm. HRMS (FAB): calcd. for $C_{17}H_{24}N_3O_2S$ [M + H]$^+$ 334.1584; found 334.1596.

(*R*$_S$)-*N*-{(1*R*)-1-[1-Allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-2-propenyl}-*tert*-butylsulfinamide (12ab): Pale-yellow oil (117 mg, 39%, method A; 282 mg, 94%, method D). $[\alpha]_D^{25}$ = –51.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H, 3 CH_3), 3.56 (d, J = 2.7 Hz, 1 H, N*H*), 4.76–4.93 (m, 2 H, CH_2), 5.18–5.39 (m, 3 H, C*H*, CH_2), 5.87–6.03 (m, 2 H, CH_2), 6.40 (dd, ^1J = 3.3, ^2J = 1.8 Hz, 1 H, C*H*), 6.43 (s, 1 H, C*H*), 6.60 (dd, ^1J = 3.3, ^2J = 0.6 Hz, 1 H, C*H*), 7.39 (dd, ^1J = 1.8, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.4, 51.9, 52.3, 55.7, 102.3, 105.5, 111.0, 117.4, 118.5, 133.0, 135.4, 141.5, 142.5, 143.0, 148.3 ppm. HRMS (FAB): calcd. for $C_{17}H_{24}N_3O_2S$ [M + H]$^+$ 334.1584; found 334.1597.

(*R*$_S$)-*N*-{(1*S*)-1-[1-Allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-3-butenyl}-*tert*-butylsulfinamide (13aa): Pale-yellow oil (200.9 mg, 67%, method A; 57 mg, 50% at 75% conversion, method B). $[\alpha]_D^{25}$ = –93.6 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 9 H, 3 CH_3), 2.57–2.62 (m, 2 H, CH_2), 3.58 (d, J = 3.9 Hz, 1 H, N*H*), 4.47–4.53 (m, 1 H, C*H*), 4.80 (d, J = 5.3 Hz, 2 H, CH_2), 5.01 (d, J = 17.1 Hz, 1 H, C*H*H), 5.13 (d, J = 10.4 Hz, 1 H, CH*H*), 5.17 (d, J = 10.6 Hz, 2 H, CH_2), 5.60–5.74 (m, 1 H, C*H*), 5.88–6.01 (m, 1 H, C*H*), 6.38 (s, 1 H, C*H*), 6.39 (dd, ^1J = 3.4, ^2J = 1.8 Hz, 1 H, C*H*), 6.58 (d, J = 3.4 Hz, 1 H, C*H*), 7.37 (dd, ^1J = 1.8, ^2J = 0.8 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.9, 41.6, 49.9, 52.8, 56.4, 102.4, 105.9, 111.6, 118.0, 120.4, 133.4, 133.5, 142.1, 143.7, 144.2, 149.1 ppm. HRMS (EI): calcd. for $C_{18}H_{25}N_3O_2S$ $[M]^+$ 347.1667; found 347.1670.

(*R*$_S$)-*N*-{(1*R*)-1-[1-Allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-3-butenyl}-*tert*-butylsulfinamide (13ab): Pale-yellow oil (50.9 mg, 17%, method A; 66 mg, 58%, method C). $[\alpha]_D^{25}$ = –1.4 (c = 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9 H, 3 CH_3), 2.58–2.67 (m, 2 H, CH_2), 3.52 (d, J = 3.6 Hz, 1 H, N*H*), 4.43 (td, ^1J = 7.1, ^2J = 3.8 Hz, 1 H, C*H*), 4.74–4.89 (m, 2 H, CH_2), 4.96 (dd, ^1J = 17.2, ^2J = 17.1 Hz, 1 H, CH*H*), 5.02–5.15 (m, 3 H, CH*H*, CH_2), 5.56–5.68 (m, 1 H, C*H*), 5.87–5.99 (m, 1 H, C*H*), 6.37 (dd, ^1J = 3.4, ^2J = 1.5 Hz, 1 H, C*H*), 6.43 (s, 1 H, C*H*), 6.56 (d, J = 3.4 Hz, 1 H, C*H*), 7.35 (d, J = 1.5 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.9, 40.8, 50.3, 52.5, 56.5, 102.7, 106.1, 111.6, 117.8, 119.6, 133.4, 133.8, 142.1, 143.5, 143.6, 149.0 ppm. HRMS (EI): calcd. for $C_{18}H_{25}N_3O_2S$ $[M]^+$ 347.1667; found 347.1661.

Addition of L-Alanine: At room temperature, hydrogen chloride (5.0 equiv., 4 M in dioxane) was added to a solution of sulfinamine **12** (143.6 mg, 0.43 mmol) [or **13** (150 mg, 0.43 mmol)] in MeOH

(0.1 M), and the solution was stirred for 30 min (TLC). After removing the solvents, the crude mixture was dissolved in DMF (0.1 M) and *N*-Boc-L-alanine (90 mg, 0.47 mmol), HBTU (328 mg, 0.86 mmol), and DIEA (1.30 mmol, 0.23 mL) were sequentially added. The solution was stirred for 15 h at room temperature, and then concentrated under vacuum. The crude mixture was extracted with EtOAc. The organic extract was washed with citric acid (3 mL), satd. $NaHCO_3$ (3 mL), and brine, dried with anhydrous Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (*n*-hexane/EtOAc, 1:1, for **14**; *n*-hexane/EtOAc, 4:1, for **15**).

(2*S*)-2-(*N*-Boc-amino)-*N*-{(1*S*)-1-[1-allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-2-propenyl}propanamide (14aa): White solid (146.5 mg, 85%). $[\alpha]_D^{25}$ = –132.4 (*c* = 1.0, $CHCl_3$); m.p. 85–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$), 1.42 (s, 9 H, 3 C*H*$_3$), 4.13 (dq, ^1J = 6.9, ^2J = 6.8 Hz, 1 H, CH), 4.80–4.88 (m, 3 H, C*H*$_2$, N*H*), 5.04–5.32 (m, 4 H, 2 C*H*$_2$), 5.74–5.78 (m, 1 H, C*H*), 5.93–6.06 (m, 2 H, 2 C*H*), 6.38 (s, 1 H, C*H*), 6.44 (dd, ^1J = 3.4, ^2J = 1.8 Hz, 1 H, C*H*), 6.61 (dd, ^1J = 3.4, ^2J = 0.9 Hz, 1 H, C*H*), 6.65 (br., 1 H, N*H*), 7.42 (dd, ^1J = 1.8, ^2J = 0.9 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.3, 28.2, 46.1, 50.1, 52.2, 80.5, 102.4, 105.6, 111.2, 116.5, 117.5, 133.0, 134.4, 141.7, 142.5, 143.1, 148.6, 155.7, 171.7 ppm. HRMS (FAB): calcd. for $C_{21}H_{29}N_4O_4$ [M + H]$^+$ 401.2183; found 401.2183.

(2*S*)-2-(*N*-Boc-amino)-*N*-{(1*R*)-1-[1-allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-2-propenyl}propanamide (14ab): White solid (160 mg, 93%). $[\alpha]_D^{25}$ = +142.6 (*c* = 1.5, $CHCl_3$); m.p. 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$), 1.39 (s, 9 H, 3 C*H*$_3$), 4.18 (m, 1 H, C*H*), 4.70–4.85 (m, 2 H, C*H*$_2$), 4.95 (d, *J* = 7.2 Hz, 1 H, N*H*), 5.20–5.30 (m, 4 H, 2 C*H*$_2$), 5.72–5.76 (m, 1 H, C*H*), 5.90–6.04 (m, 2 H, 2 C*H*), 6.34 (s, 1 H, C*H*), 6.42 (dd, ^1J = 3.3, ^2J = 1.8 Hz, 1 H, C*H*), 6.58 (dd, ^1J = 3.3, ^2J = 0.6 Hz, 1 H, C*H*), 6.81 (br., 1 H, N*H*), 7.39 (dd, ^1J = 1.8, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.6, 28.2, 46.0, 50.0, 52.2, 80.5, 102.3, 105.5, 111.2, 116.7, 117.5, 133.0, 134.4, 141.6, 142.5, 143.1, 148.6, 155.6, 171.7 ppm. HRMS (FAB): calcd. for $C_{21}H_{29}N_4O_4$ [M + H]$^+$ 401.2183; found 401.2197.

(2*S*)-2-(*N*-Boc-amino)-*N*-{(1*S*)-1-[1-allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-3-butenyl}propanamide (15aa): White solid (144.2 mg, 81%). $[\alpha]_D^{25}$ = –121.22 (*c* = 1.1, $CHCl_3$); m.p. 44–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$), 1.36 (s, 9 H, 3 C*H*$_3$), 2.46–2.63 (m, 2 H, C*H*$_2$), 3.99–4.08 (m, 1 H, C*H*), 4.76 (d, *J* = 4.7 Hz, 2 H, C*H*$_2$), 4.87 (d, *J* = 5.5 Hz, 1 H, N*H*), 4.99–5.15 (m, 5 H, C*H*$_2$, C*H*$_2$, C*H*), 5.63–5.73 (m, 1 H, C*H*), 5.87–5.98 (m, 1 H, C*H*), 6.38 (s, 1 H, C*H*), 6.39 (dd, ^1J = 3.2, ^2J = 1.7 Hz, 1 H, C*H*), 6.52 (br., 1 H, N*H*), 6.57 (d, *J* = 3.2 Hz, 1 H, C*H*), 7.37 (dd, ^1J = 1.7, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.4, 27.2, 37.9, 42.7, 49.0, 51.2, 79.5, 100.1, 104.5, 110.2, 116.4, 117.8, 131.9, 132.2, 140.7, 142.1, 142.6, 147.7, 154.6, 170.8 ppm. HRMS (EI): calcd. for $C_{22}H_{30}N_4O_4$ [M]$^+$ 414.2267; found 414.2269.

(2*S*)-2-(*N*-Boc-amino)-*N*-{(1*R*)-1-[1-allyl-3-(2-furyl)-1*H*-5-pyrazolyl]-3-butenyl}propanamide (15ab): Pale-yellow solid (165.5 mg, 93%). $[\alpha]_D^{25}$ = +80.6 (*c* = 0.9, $CHCl_3$); m.p. 44–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.35 (s, 9 H, 3 C*H*$_3$), 2.45–2.63 (m, 2 H, C*H*$_2$), 4.05 (q, *J* = 7.0 Hz, 1 H, C*H*), 4.70–4.82 (m, 2 H, C*H*$_2$), 4.85 (d, *J* = 7.0 Hz, 1 H, N*H*), 5.00 (dd, ^1J = 17.1, ^2J = 1.1 Hz, 1 H, C*H*), 5.05–5.15 (m, 4 H, C*H*$_2$, C*H*$_2$), 5.64–5.73 (m, 1 H, C*H*), 5.86–5.98 (m, 1 H, C*H*), 6.34 (s, 1 H, C*H*), 6.39 (dd, ^1J = 3.2, ^2J = 1.7 Hz, 1 H, C*H*), 6.56 (d, *J* = 3.2 Hz, 1 H, CH), 6.63 (br., 1 H, N*H*), 7.36 (dd, ^1J = 1.7, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.1, 28.6, 39.4, 44.1, 50.3, 52.5, 80.8, 101.5, 105.9, 111.6, 117.8, 119.4, 133.3, 133.7, 142.1, 143.5, 144.1, 149.1, 156.0, 172.2 ppm. HRMS (EI): calcd. for $C_{22}H_{30}N_4O_4$ [M]$^+$ 414.2267; found 414.2252.

Ring-Closing Metathesis of 14 and 15: The second-generation Hoveyda–Grubbs' catalyst (15.4 mg; 0.02 mmol) was added to a solution of **14** (196.5 mg, 0.49 mmol) [or **15** (202.8 mg, 0.49 mmol)] in DCM (0.05 M) (or DCE). The mixture was heated at reflux for 18 h for **14**, and for 6 h followed by stirring for 10 h at room temperature for **15**. The solvent was evaporated and the crude mixture was purified by flash chromatography (*n*-hexane/EtOAc, 1:2, for **16**; *n*-hexane/EtOAc, 2:1, for **17**).

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*S*)-2-(2-furyl)-4,7-dihydropyrazolo-[1,5-*a*]pyridin-4-yl]propanamide (16aa): White solid (164.5 mg, 90%). $[\alpha]_D^{25}$ = +22.8 (*c* = 0.9, $CHCl_3$); m.p. 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, 3 C*H*$_3$), 1.36 (d, *J* = 8.1 Hz, 3 H, C*H*$_3$), 4.17–4.22 (m, 1 H, C*H*), 4.63–4.78 (m, 2 H, C*H*$_2$), 5.13 (br., 1 H, N*H*), 5.77–5.91 (m, 2 H, C*H*H, C*H*), 6.04–6.08 (m, 1 H, CH*H*), 6.41 (s, 1 H, C*H*), 6.42 (dd, ^1J = 3.3, ^2J = 1.8 Hz, 1 H, C*H*), 6.58 (dd, ^1J = 3.3, ^2J = 0.6 Hz, 1 H, C*H*), 6.88 (br., 1 H, N*H*), 7.39 (dd, ^1J = 1.8, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.4, 28.1, 42.1, 46.8, 50.1, 80.2, 100.1, 105.8, 111.2, 123.1, 123.7, 138.7, 141.8, 143.8, 148.6, 155.3, 172.3 ppm. HRMS (FAB): calcd. for $C_{19}H_{25}N_4O_4$ [M + H]$^+$ 373.1870; found 373.1852.

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*R*)-2-(2-furyl)-4,7-dihydropyrazolo-[1,5-*a*]pyridin-4-yl]propanamide (16ab): White solid (168.1 mg, 92%). $[\alpha]_D^{25}$ = –57.5 (*c* = 1.0, $CHCl_3$); m.p. 178–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, 3 C*H*$_3$), 1.35 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$), 4.13–4.18 (m, 1 H, C*H*), 4.61–4.77 (m, 2 H, C*H*$_2$), 5.13 (d, *J* = 7.2 Hz, 1 H, N*H*), 5.75–5.79 (m, 1 H, C*H*), 5.85–5.90 (m, 1 H, C*H*H), 6.02–6.08 (m, 1 H, CH*H*), 6.38 (s, 1 H, C*H*), 6.41 (dd, ^1J = 3.3, ^2J = 1.8 Hz, 1 H, C*H*), 6.57 (dd, ^1J = 3.3, ^2J = 0.6 Hz, 1 H, C*H*), 6.96 (br., 1 H, N*H*), 7.39 (dd, ^1J = 1.8, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.9, 28.1, 42.0, 46.8, 49.9, 80.3, 100.1, 105.7, 111.1, 123.1, 123.7, 138.6, 141.7, 143.8, 148.6, 155.5, 172.2 ppm. HRMS (FAB): calcd. for $C_{19}H_{25}N_4O_4$ [M + H]$^+$ 373.1870; found 373.1873.

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*S*)-2-(2-furyl)-5,8-dihydro-4*H*-pyrazolo[1,5-*a*]azepin-4-yl]propanamide (17aa): White solid (87.9 mg, 53% at 96% conversion). $[\alpha]_D^{25}$ = –68.7 (*c* = 0.9, $CHCl_3$); m.p. 68–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.39 (s, 9 H, 3 C*H*$_3$), 2.35–2.55 (m, 2 H, C*H*$_2$), 4.15 (dq, ^1J = 7.2, ^2J = 7.0 Hz, 1 H, C*H*), 4.78–4.93 (m, 2 H, C*H*$_2$), 5.09 (d, *J* = 7.2 Hz, 1 H, N*H*), 5.35 (td, ^1J = 8.6, ^2J = 5.3 Hz, 1 H, C*H*), 5.67–5.79 (m, 2 H, C*H*, C*H*), 6.32 (s, 1 H, C*H*), 6.36 (dd, ^1J = 3.3, ^2J = 1.7 Hz, 1 H, C*H*), 6.51 (d, *J* = 3.3 Hz, 1 H, C*H*), 7.17 (br., 1 H, N*H*), 7.34 (d, *J* = 1.7 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 18.1, 28.7, 34.3, 44.4, 50.6, 80.9, 101.5, 111.6, 123.8, 128.0, 142.0, 142.5, 145.0, 149.0, 156.2, 172.5 ppm. HRMS (EI): calcd. for $C_{20}H_{26}N_4O_4$ [M]$^+$ 386.1954; found 386.1957.

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*R*)-2-(2-furyl)-5,8-dihydro-4*H*-pyrazolo[1,5-*a*]azepin-4-il]propanamide (17ab): White solid (69.7 mg, 42% at 75% conversion). $[\alpha]_D^{25}$ = +7.2 (*c* = 0.9, $CHCl_3$); m.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.41 (s, 9 H, 3 C*H*$_3$), 2.39–2.61 (m, 2 H, CH$_2$), 4.14 (dq, ^1J = 7.2, ^2J = 7.1 Hz, 1 H, C*H*), 4.79–4.92 (m, 2 H, C*H*$_2$), 4.93 (d, *J* = 7.3 Hz, 1 H, N*H*), 5.37 (td, ^1J = 9.0, ^2J = 3.6 Hz, 1 H, C*H*), 5.70–5.81 (m, 2 H, C*H*, C*H*), 6.33 (s, 1 H, C*H*), 6.37 (dd, ^1J = 3.1, ^2J = 1.7 Hz, 1 H, C*H*), 6.52 (d, *J* = 3.1 Hz, 1 H, CH), 7.10 (br., 1 H, C*H*), 7.34 (dd, ^1J = 1.7, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 17.2, 28.7, 34.4, 44.4, 50.6, 81.1, 101.5, 105.8, 111.6, 123.6, 128.1, 141.9, 142.4, 144.9, 149.1, 156.5,

172.2 ppm. HRMS (EI): calcd. for $C_{20}H_{26}N_4O_4$ $[M]^+$ 386.1954; found 386.1959.

Hydrogenation Reaction: A solution of **16** (205 mg, 0.55 mmol) [or **17** (212 mg, 0.55 mmol)] in dry EtOAc (11 mL) and 10% palladium on carbon (58.4 mg, 0.055 mmol) was stirred under 1 atm of H_2 for 18 h at room temp. At this time, the catalyst was filtered off through a plug of Celite and the filtrate concentrated under reduced pressure. The crude mixture was purified by flash chromatography (*n*-hexane/EtOAc, 1:2, for **18**; *n*-hexane/EtOAc, 2:1, for **19**).

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*S*)-2-(2-furyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-4-yl]propanamide (18aa): White solid (165 mg, 80%). $[\alpha]_D^{25}$ = –10.8 (*c* = 1.0, $CHCl_3$); m.p. 61–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 5.4 Hz, 3 H, CH_3), 1.37 (s, 9 H, 3 CH_3), 1.94–2.23 (m, 4 H, 2 CH_2), 4.01–4.10 (m, 1 H, C*H*), 4.14–4.21 (m, 2 H, CH_2), 5.12–5.21 (m, 2 H, C*H*, N*H*), 6.32 (s, 1 H, C*H*), 6.40 (dd, ^1J = 3.3, ^2J = 1.8 Hz, 1 H, C*H*), 6.56 (dd, ^1J = 3.3, ^2J = 0.7 Hz, 1 H, C*H*), 6.87 (br., 1 H, N*H*), 7.37 (dd, ^1J = 1.8, ^2J = 0.7 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.2, 20.8, 27.8, 28.2, 43.5, 47.6, 50.2, 80.2, 100.2, 105.5, 111.3, 140.9 ppm. HRMS (EI): calcd. for $C_{19}H_{27}N_4O_4$ $[M + H]^+$ 375.2027; found 375.2021.

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*R*)-2-(2-furyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-4-yl]propanamide (18ab): White solid (123.7 mg, 60%). $[\alpha]_D^{25}$ = –28.8 (*c* = 0.9, $CHCl_3$); m.p. 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.39 (s, 9 H, 3 CH_3), 1.96–2.24 (m, 4 H, 2 CH_2), 4.03–4.21 (m, 3 H, CH_2, C*H*), 5.06 (d, *J* = 7.2 Hz, 1 H, N*H*), 5.12–5.22 (m, 1 H, C*H*), 6.32 (s, 1 H, C*H*), 6.41 (dd, ^1J = 3.3, ^2J = 1.6 Hz, 1 H, C*H*), 6.56 (dd, ^1J = 3.3, ^2J = 0.6 Hz, 1 H, C*H*), 6.87 (br., 1 H, N*H*), 7.38 (dd, ^1J = 1.6, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.2, 20.4, 27.4, 27.8, 43.0, 47.2, 49.6, 79.9, 99.9, 105.8, 110.7, 140.5, 141.2, 143.0, 148.3, 155.3, 171.7 ppm. HRMS (FAB): calcd. for $C_{19}H_{27}N_4O_4$ $[M + H]^+$ 375.2027; found 375.2032.

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*S*)-2-(2-furyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepin-4-yl]propanamide (19aa): White solid (142′9 mg, 67%). $[\alpha]_D^{25}$ = –67.0 (*c* = 0.8, $CHCl_3$); m.p. 75–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.42 (s, 9 H, 3 CH_3), 1.67–1.91 (m, 6 H, 3 CH_2), 4.08–4.18 (m, 2 H, CH_2), 4.43 (dq, ^1J = 14.2, ^2J = 6.5 Hz, 1 H, C*H*), 4.97 (d, *J* = 6.5 Hz, 1 H, N*H*), 5.10 (t, *J* = 8.8 Hz, 1 H, C*H*), 6.28 (s, 1 H, C*H*), 6.37 (dd, ^1J = 3.2, ^2J = 1.8 Hz, 1 H, C*H*), 6.51 (d, *J* = 3.2 Hz, 1 H, C*H*), 6.99 (br., 1 H, C*H*), 7.35 (d, *J* = 1.8 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.3, 20.4, 29.9, 30.6, 31.3, 37.1, 49.8, 56.4, 83.6, 104.4, 108.3, 114.1, 144.5, 144.8, 148.3, 151.7, 158.9, 174.6 ppm. HRMS (EI): calcd. for $C_{20}H_{28}N_4O_4$ $[M]^+$ 388.2110; found 388.2107.

(2*S*)-2-(*N*-Boc-amino)-*N*-[(4*R*)-2-(2-furyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepin-4-yl]propanamide (19ab): White solid (138.7 mg, 65%). $[\alpha]_D^{25}$ = +14.5 (*c* = 1.0, $CHCl_3$); m.p. 195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.41 (s, 9 H, 3 CH_3), 1.62–1.93 (m, 6 H, 3 CH_2), 4.07–4.17 (m, 2 H, CH_2), 4.41 (dq, ^1J = 14.5, ^2J = 6.0 Hz, 1 H, C*H*), 4.98 (d, *J* = 7.4 Hz, 1 H, N*H*), 5.08 (t, *J* = 9.4 Hz, 1 H, C*H*), 6.28 (s, 1 H, C*H*), 6.36 (dd, ^1J = 3.2, ^2J = 1.4 Hz, 1 H, C*H*), 6.50 (d, *J* = 3.2 Hz, 1 H, C*H*), 7.03 (br., 1 H, N*H*), 7.33 (dd, ^1J = 1.4, ^2J = 0.6 Hz, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.4, 27.4, 27.9, 28.7, 31.3, 34.5, 47.3, 53.8, 81.1, 101.8, 105.6, 111.5, 141.9, 142.1, 145.7, 149.2, 156.5, 171.9 ppm. HRMS (EI): calcd. for $C_{20}H_{28}N_4O_4$ $[M]^+$ 388.2110; found 388.2114.

Oxidation of the Furyl Ring: A solution of **18** (127.5 mg, 0.34 mmol) [or **19** (132 mg, 0.34 mmol)] in MeOH (33 mL) was cooled to –78 °C. Ozone was passed through the solution until the blue color persisted. Then the reaction was stopped and O_2 gas bubbled through the solution to remove excess ozone. Evaporation of the solvent gave the crude product, which was purified by flash chromatography (*n*-hexane/EtOAc, 1:2; 2% HOAc, for **20**; *n*-hexane/EtOAc, 1:1; 2% HOAc, for **21**).

(4*S*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2-carboxylic Acid (20aa): White solid (96.1 mg, 80%). $[\alpha]_D^{25}$ = –9.6 (*c* = 0.9, MeOH); m.p. 148–150 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.33 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.44 (s, 9 H, 3 CH_3), 1.76–2.27 (m, 4 H, 2 CH_2), 4.01–4.24 (m, 3 H, CH_2, C*H*), 5.12–5.17 (m, 1 H, C*H*), 6.59 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 18.4, 21.9, 28.3, 28.8, 44.7, 49.2, 51.9, 80.7, 107.2, 143.5, 145.3, 157.6, 166.1, 175.7 ppm. HRMS: calcd. for $C_{16}H_{25}N_4O_5$ $[M + H]^+$ 3531819; found 353.1824.

(4*R*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2-carboxylic acid (20ab): White solid (84.0 mg, 70%). $[\alpha]_D^{25}$ = –30.0 (*c* = 0.9, MeOH); m.p. 136–138 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.32 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.44 (s, 9 H, 3 CH_3), 1.77–2.23 (m, 4 H, 2 CH_2), 4.03–4.23 (m, 3 H, CH_2, C*H*), 5.12–5.16 (m, 1 H, C*H*), 6.66 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 18.2, 21.9, 28.2, 28.7, 44.7, 49.2, 51.8, 80.7, 107.4, 143.3, 145.3, 157.7, 166.1, 175.6 ppm. HRMS (FAB): calcd. for $C_{16}H_{25}N_4O_5$ $[M + H]^+$ 353.1819; found 353.1809.

(4*S*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine-2-carboxylic Acid (21aa): White solid (87.3 mg, 70%). $[\alpha]_D^{25}$ = –85.7 (*c* = 0.8, MeOH); m.p. 128–130 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.37 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.48 (s, 9 H, 3 CH_3), 1.58–2.09 (m, 6 H, 3 CH_2), 4.13 (q, *J* = 7.1 Hz, 1 H, C*H*), 4.22 (dd, ^1J = 14.2, ^2J = 11.1 Hz, 1 H, C*H*H), 4.51 (dd, ^1J = 14.2, ^2J = 5.5 Hz, 1 H, CH*H*), 5.06 (d, *J* = 10.2 Hz, 1 H, C*H*), 6.61 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 18.4, 28.5, 28.6, 28.8, 34.9, 48.5, 51.8, 54.7, 80.7, 107.8, 142.8, 148.3, 157.7, 165.4, 175.3 ppm. HRMS (EI): calcd. for $C_{17}H_{26}N_4O_5$ $[M]^+$ 366.1903; found 366.1898.

(4*R*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine-2-carboxylic Acid (21ab): White solid (112.3 mg, 90%). $[\alpha]_D^{25}$ = +46.5 (*c* = 0.8, MeOH); m.p. 126–128 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.34 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.46 (s, 9 H, 3 CH_3), 1.60.2.16 (m, 6 H, 3 CH_2), 4.13 (q, *J* = 7.1 Hz, 1 H, C*H*), 4.23 (dd, ^1J = 14.3, ^2J = 11.2 Hz, 1 H, C*H*H), 4.51 (dd, ^1J = 14.3, ^2J = 5.6 Hz, 1 H, CH*H*), 5.02 (d, *J* = 9.9 Hz, 1 H, C*H*), 6.74 (s, 1 H, C*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 19.3, 29.7, 29.8, 29.9, 36.1, 49.4, 52.9, 55.9, 81.9, 109.6, 143.9, 149.4, 159.0, 166.6, 176.6 ppm. HRMS (FAB): calcd. for $C_{17}H_{27}N_4O_5$ $[M + H]^+$ 367.1981; found 367.1966.

Addition of Glycine: The same procedure as used for the Addition of L-Alanine (see above) was used but by using glycine instead of L-alanine. Flash chromatography was performed by using *n*-hexane/EtOAc (1:3) as eluent.

(4*S*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-2-(ethoxycarbonylmethylcarbamoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (9aa): White solid (70 mg, 80%). $[\alpha]_D^{25}$ = –19.9 (*c* = 1.0, CH_3OH); m.p. 73–75 °C. ^{1}H NMR (300 MHz, CD_3CN): δ = 1.22 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.27 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.38 (s, 9 H, 3 CH_3), 1.68–2.20 (m, 4 H, 2 CH_2), 3.97–4.12 (m, 3 H, CH_2, C*H*), 4.01 (dd, ^1J = 6.1, ^2J = 1.2 Hz, 2 H, CH_2), 4.14 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.04–5.12 (m, 1 H, C*H*), 5.66 (br., 1 H, N*H*), 6.46 (d, *J* = 0.9 Hz, 1 H, C*H*), 7.12 (d, *J* = 8.4 Hz, 1 H, N*H*), 7.48 (t, *J* = 6.1 Hz, 1 H, N*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 14.4, 18.4, 21.5, 27.8, 28.5, 41.5, 44.1, 48.8, 51.4, 61.9, 80.0, 104.3, 143.6, 145.8,

156.4, 163.2, 170.9, 173.8 ppm. HRMS (FAB): calcd. for $C_{20}H_{31}N_5O_6$ [M + H]$^+$ 438.2347; found 438.2346.

(4*R*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-2-(ethoxycarbonylmethylcarbamoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (9ab): White solid (60.4 mg, 69%). $[\alpha]_D^{25}$ = +7.3 (*c* = 1.0, CH_3OH); m.p. 79–81 °C. ^{1}H NMR (300 MHz, CD_3CN): δ = 1.23 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.27 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.39 (s, 9 H, 3 C*H*$_3$), 1.60–2.17 (m, 4 H, 2 C*H*$_2$), 3.96–4.12 (m, 3 H, C*H*$_2$, C*H*), 4.02 (dd, ^1J = 6.0, ^2J = 2.7 Hz, 2 H, C*H*$_2$), 4.15 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$), 5.05–5.12 (m, 1 H, C*H*), 5.65 (br., 1 H, N*H*), 6.49 (d, *J* = 0.9 Hz, 1 H, C*H*), 7.05 (d, *J* = 8.4 Hz, 1 H, N*H*), 7.42 (t, *J* = 6.0 Hz, 1 H, N*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 14.4, 18.2, 21.4, 27.9, 28.5, 41.4, 44.1, 48.8, 51.3, 61.8, 79.8, 104.5, 143.5, 145.9, 156.4, 162.9, 171.0, 173.4 ppm. HRMS (FAB): calcd. for $C_{20}H_{31}N_5O_6$ [M + H]$^+$ 438.2347; found 438.2347.

(4*S*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-2-(ethoxycarbonylmethylcarbamoyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine (10aa): White solid (76.6 mg, 85%). $[\alpha]_D^{25}$ = –53.8 (*c* = 1.1, $CHCl_3$); m.p. 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28, (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.37 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$), 1.45 (s, 9 H, 3 C*H*$_3$), 1.61–2.03 (m, 6 H, 3 C*H*$_2$), 4.15–4.20 (m, 4 H, C*H*$_2$, C*H*, C*H*H), 4.22 (q, *J* = 6.9 Hz, 2 H, C*H*$_2$), 4.44 (dd, ^1J = 14.3, ^2J = 5.2 Hz, 1 H, CH*H*), 5.04 (d, *J* = 7.0 Hz, 1 H, N*H*), 5.12 (dd, ^1J = 9.5, ^2J = 9.3 Hz, 1 H, C*H*), 6.62 (s, 1 H, C*H*), 7.15 (br., 1 H, N*H*), 7.26 (t, *J* = 5.6 Hz, 1 H, N*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1, 14.2, 17.8, 27.1, 27.4, 28.3, 34.1, 41.0, 46.9, 50.1, 53.8, 61.4, 80.3, 104.8, 143.6, 146.3, 162.1, 169.9, 171.3 ppm. HRMS (EI): calcd. for $C_{21}H_{33}N_5O_6$ [M]$^+$ 451.2431; found 451.2434.

(4*R*)-4-[(2*S*)-2-(*N*-Boc-amino)propanoylamino]-2-(ethoxycarbonylmethylcarbamoyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine (10ab): White solid (74.8 mg, 83%). $[\alpha]_D^{25}$ = +36.5 (*c* = 1.0, MeOH); m.p. 105–107 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.41 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.54 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.57 (s, 9 H, 3 C*H*$_3$), 1.76–2.27 (m, 6 H, 3 C*H*$_2$), 4.25 (d, *J* = 5.8 Hz, 2 H, C*H*$_2$), 4.31–4.38 (m, 2 H, C*H*H, C*H*), 4.34 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$), 4.57 (dd, ^1J = 14.5, ^2J = 5.8 Hz, 1 H, CH*H*), 5.16–5.25 (m, 2 H, C*H*, N*H*), 6.61 (s, 1 H, C*H*), 7.09 (br., 1 H, N*H*), 7.39 (t, *J* = 4.8 Hz, 1 H, N*H*) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 14.5, 18.4, 28.4, 28.7, 28.8, 34.9, 41.9, 51.8, 54.8, 62.3, 80.8, 106.0, 144.6, 148.0, 157.5, 164.9, 171.4, 175.2 ppm. HRMS (EI): calcd. for $C_{21}H_{33}N_5O_6$ [M]$^+$ 451.2431; found 451.2430.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all new compounds, crystallographic data for compounds **9aa** and **15aa**.

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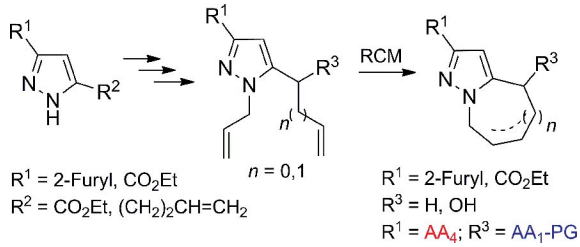

The *N*-allylation of readily available 3,5-substituted pyrazoles followed by ring-closing metathesis of the resulting 1,5-diolefinic derivatives leads to the formation of 2,4-substituted pyrazolo[1,5-*a*]pyridines and pyrazolo[1,5-*a*]azepines in high yields. The application of this protocol to the diastereoselective synthesis of potential peptidomimetics is described.

Keywords: Synthetic methods / Asymmetric synthesis / Metathesis / Peptidomimetics / Nitrogen heterocycles

