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Scientific paper

A Four-step Synthesis of Novel (*S*)-1-(heteroaryl)-1-aminoethanes from (*S*)-Boc-alanine

Luka Šenica,[1] Nejc Petek,[1] Uroš Grošelj[1] and Jurij Svete[1,2,*]

[1] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI – 1000 Ljubljana, Slovenia.*

[2] *Centre of Excellence EN-FIST, Trg osvobodilne fronte 13, SI – 1000 Ljubljana, Slovenia*

** Corresponding author: E-mail: jurij.svete@fkkt.uni-lj.si*
Tel.: +386 1 2419 254. Fax.: +386 1 2419 220

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Dedicated to Professor Branko Stanovnik, University of Ljubljana, on the occasion of his 75th anniversary.

Abstract

A series of (*S*)-1-(pyrimidin-4-yl)-, and regioisomeric (*S*)-1-(pyrazolo[1,5-*a*]pyrimidin-7-yl)-, and (*S*)-1-(pyrazolo[1,5-*a*]pyrimidin-5-yl)-1-aminoethanes were prepared by cyclisation of (*S*)-*N*-Boc-alanine-derived ynone with *N,N*-1,3-dinucleophiles, such as amidines and α-aminoazoles, followed by acidolytic removal of the Boc group. Stereoselective catalytic hydrogenation of (*S*)-1-(pyrazolo[1,5-*a*]pyrimidin-7-yl)-1-aminoethanes lead to saturation of the pyrimidine ring to afford ~4:1 mixture of diastereomeric 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines. The structures of novel compounds were elucidated with NMR spectroscopy.

Keywords: Amines, amino acids, chirality, heterocycles, synthesis

1. Introduction

Nonracemic amines represent an important group of organic compounds, which found a widespread use in various applications. They are used as reagents and bases in organic synthesis, resolving agents, and chiral auxiliaries, ligands, and organocatalysts in asymmetric synthesis.[1] Typical examples of synthetically useful enantiomerically pure alkylamines are (*R*)-1-phenylethylamine (**1**), amphetamine (**2**), (2*S*,5*S*)-5-benzyl-2-(*tert*-butyl) -3-methylimidazolidin-4-one (**3**), quinidine (**4**), and (1*R*,2*R*)-1,2-diaminocyclohexane (**5**) (Figure 1).

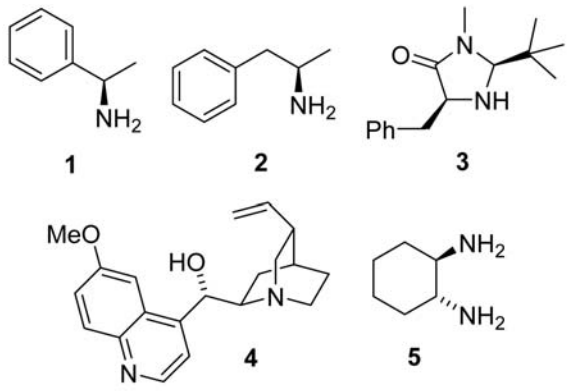


Figure 1. Examples of important chiral alkylamines **1**–**5**.

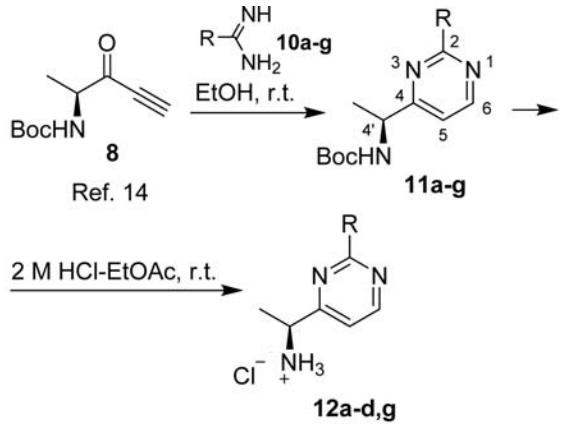
In the last three decades, the studies on alkyl 2-substituted 3-(dimethylamino)prop-2-enoates and related enaminones have shown, that they are useful and versatile reagents for the preparation of various dehydroalanine derivatives, heterocyclic systems, and natural product analogues.[2,3] In extension, chiral cyclic enaminones derived from (*S*)-α-amino acids and (+)-camphor have been employed in the synthesis of functionalized heterocycles and heterocyclic analogues of peptides.[2,4–7] Furthermore, enaminones have also been successfully employed in a combinatorial synthesis of dehydroalanine derivatives[8] and functionalized heterocycles.[9]

The usual way to prepare 3-(dimethylamino)prop-2-enoates and related enaminones comprise treatment of a suitably functionalized methylene compound with formamide acetal, *e.g.*, with *N,N*-dimethylformamide dimethyl acetal or with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent).[2,10] Alternative way of preparation proposed by Giacomelli and co-workers comprises treatment of Weinreb amides of a suitably protected α-amino acid with (trimethylsilyl)magnesium bromide followed by

reaction of the so formed silylynone with diethylamine. These enamino ketones were then used as the key-intermediates in the synthesis of chiral pyrazole-containing peptidomimetics[11] and α-pyrazolylglycines.[12] Later on, we also reported similar preparation of chiral enamino ketones from α-amino acids and their utilization in a two-step synthesis of 1-(heteroaryl)-2-phenyl-1-aminoethanes and 1-(heteroaryl)-1-aminopropan-2-ols.[5] Another important example is ynone-based synthesis of chiral α-aminoalkylpyrimidines using an enantioselective three-component reaction.[13]

In continuation of our work in this field, we became interested in the Boc-α-amino acid derived ynones and enaminones again, as they turned out to be suitable precursors for the synthesis of vinylogous peptides[14] and as chiral non-racemic dipolarophiles in regio- and stereo-selective 1,3-dipolar cycloadditions.[15] As these reagents were available in sufficient amounts, we decided to further investigate their cyclisation reactions with *N*,*N*-1,3-dinucleophiles leading to chiral non-racemic 1-(heteroaryl)-1-ethylamines. These novel primary amines are interesting as chiral bases, ligands, or organocatalysts in asymmetric applications. Furthermore, alkylamines bearing fluorescent azolo[*a*]pyrimidin-6-one residues could also be used in fluorescence-related applications, e.g. as fluorescent markers.

Herein, we report the results of this study, i.e. the synthesis and some transformations of novel pyrimidin-2-yl, pyrazolo[1,5-*a*]pyrimidin-5-yl, and pyrazolo[1,5-*a*] pyrimidin-7-yl substituted (*S*)-1-(heteroaryl)-1-aminoethanes.



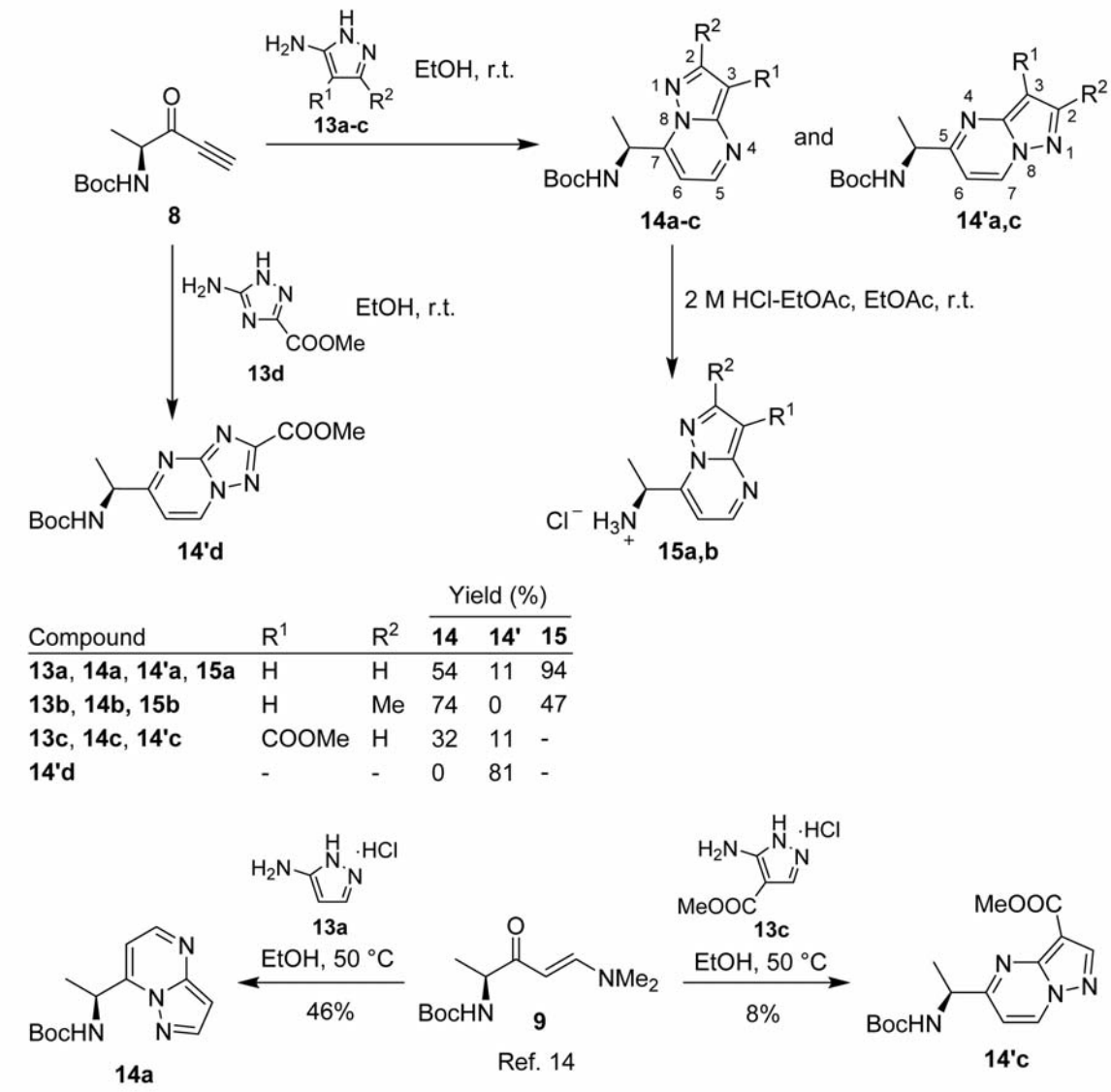
Compd.	R	Yield (%) 11	12
10a, **11a**	H	23	79
10b, **11b**	Me	30	84
10c, **11c**	Ph	31	82
10d, **11d**	3-Nitrophenyl	59	89
10e, **11e**	4-Aminophenyl	51	-
10f, **11f**	1*H*-Benzo[*d*]imidazol-2-yl	44	-
10g, **11g**	1*H*-Pyrazol-1-yl	25	84

Scheme 1. Synthesis of (*S*)-(1-(pyrimidin-2-yl)ethyl)carbamates **11a**–**g**, and (*S*)-1-(pyrimidin-2-yl)-1-ethylamines **12a**–**d**,**g**.

2. Results and Discussion

The first reagent, (*S*)-*tert*-butyl (3-oxopent-4-yn-2-yl)carbamate (**8**) was prepared in two steps from commercially available (*S*)-Boc-alanine (**6**) via transformation into the corresponding Weinreb amide **7**[16,17] and treatment with ethynylmagnesium bromide following the literature procedure.[14] Quite expectedly,[5,13] treatment of ynone **8** with simple amidines **10a**–**g** furnished the corresponding *tert*-butyl (*S*)-(1-(5-substituted-pyrimidin-2-yl)ethyl)carbamates **11a**–**g** in 23–59% yields. The free 1-(pyrimidin-2-yl)-1-ethylamines **12a**–**d**,**g** were then obtained by acidolytic removal of the Boc N-protecting group of **11a**–**d**,**g** with 2 M HCl in EtOAc. In this manner, the free amines **12a**–**d**,**g** were obtained in 79–89% yields upon simple evaporative workup (Scheme 1).

Reactions of **8** with unsymmetrical cyclic amidines, 3-aminopyrazoles **13a**–**c** and methyl 5-amino-1*H*-1,2,4-triazole-3-carboxylate (**13d**), afforded two regioisomeric products, *tert*-butyl (*S*)-(1-(pyrazolo[1,5-*a*]pyrimidin-7-yl)ethyl)carbamates **14a**–**c** and *tert*-butyl (*S*)-(1-(pyrazolo-[1,5-*a*]pyrimidin-5-yl)ethyl)carbamates **14'a**–**c** and methyl (*S*)-7-(1-((*tert*-butoxycarbonyl)-amino)ethyl)[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carboxylate (**14'd**). Thus, treatment of **8** with 3-amino-1*H*-pyrazole (**13a**) and methyl 5-amino-1*H*-pyrazole-4-carboxylate (**13c**) gave mixtures of the major 7-regioisomers **14a**,**c** and the minor 5-regioisomers **14'a**,**c**, which were separated by medium performance liquid chromatography (MPLC) to give isomerically pure compounds **14a**,**c** and **14'a**,**c** in 11–54% yields. On the other hand, cyclisations of **8** with 3-amino-5-methyl-1*H*-pyrazole (**13b**) and methyl 5-amino-1*H*-1,2,4-triazole-3-carboxylate (**13d**) furnished the corresponding products **14b** and **14'd** as the only regioisomers in 74% and 81% yield, respectively. Since known cyclisations of enaminones with ambident nucleophiles generally proceed regioselectively,[5] we reasoned that cyclisations of the corresponding enaminone reagent **9** with 3-aminopyrazoles **13** should be regioselective to produce the regioisomers **14**, exclusively. (*S*,*E*)-*tert*-Butyl (5-(dimethylamino)-3-oxopent-4-en-2-yl)carbamate (**9**) was prepared from **8** and dimethylamine following the literature procedure.[14] Indeed, treatment of enaminone **9** with **13a** in the presence of one equivalent of HCl afforded **14a** as the only isomer, though in somewhat lower yield (46% *vs.* 54% *via* the ynone **8**). On the other hand, reaction of **9** with **13c** produced the other regioisomer **14'c** in poor yield. Treatment of **14a** and **14b** with 2 M HCl in EtOAc at room temperature furnished the corresponding free ami-



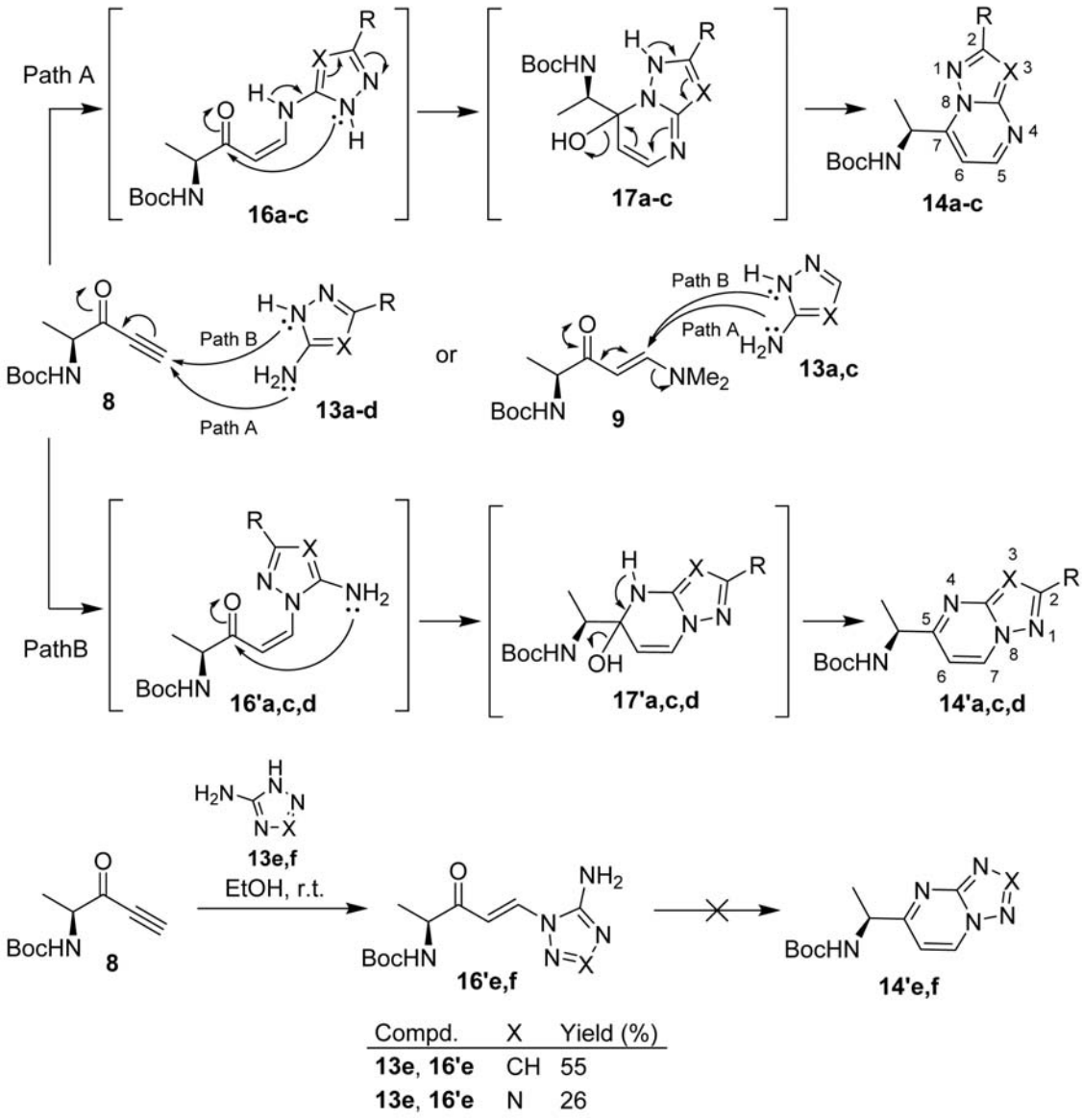
Compound	R^1	R^2	Yield (%) 14	14'	15
13a, **14a**, **14'a**, **15a**	H	H	54	11	94
13b, **14b**, **15b**	H	Me	74	0	47
13c, **14c**, **14'c**	COOMe	H	32	11	-
14'd	-	-	0	81	-

Scheme 2. Synthesis of *tert*-butyl (*S*)-(1-(pyrazolo[1,5-*a*]pyrimidin-7-yl)ethyl)carbamates **14a**–**c**, their pyrazolo[1,5-*a*]pyrimidin-5-yl regioisomers **14'a**,**c**,**d**, and the free amines **15a**,**b**.

nes **15a** and **15b** in 94% and 47% yield, respectively (Scheme 2).

The formation of regioisomeric products **14** and **14'** is explainable in the following way. 1,4-Addition of a heterocyclic amidine **13** to the ynone **8** (and similarly to the enaminone **9**) can take place, either via the primary amino group (Path A), or via the ring NH group (Path B) to give the regioisomeric adducts **16** and **16'**. Further cyclisation *via* addition of the other amino group leads to the bicyclic intermediates **17** and **17'**, which undergo elimination of water to furnish regioisomeric products **14** and **14'**. Analogously, also formation of regioisomeric products **14a** and **14'c** from the enaminone reagent **9** can be explained by initial substitution of the dimethylamino group followed by cyclisation. Selective reaction of enaminones with the primary amino group of various non-symmetrical cyclic amidines is well documented in the literature.[2] The formation of the regioisomeric intermediate **16'a**,**c**,**d**, on the other hand, is supported by the reactions of **8** with 5-amino-1*H*-1,2,4-triazole (**13e**) and 5-amino-1*H*-tetrazole (**13f**), which did not give the desired cyclisation products **14'e** and **14'f**, but rather the addition intermediates **16'e** and **16'f** in 55% and 26% yield, respectively (Scheme 3).

Finally, saturation of the pyrimidine ring of pyrazolo[1,5-*a*]pyrimidines **14a** and **14c** was carried out by catalytic hydrogenation. Reduction of **14a**,**c** afforded ~4:1 mixtures of diastereomeric 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines **18a/18'a** and **18c/18'c** in 90% and 99% yield, respectively. Subsequent separation by MPLC furnished isomerically pure compounds, the major isomers **18a** and **18c** and the minor isomers **18'a** and **18'c** in 11–78% yields (Scheme 4).

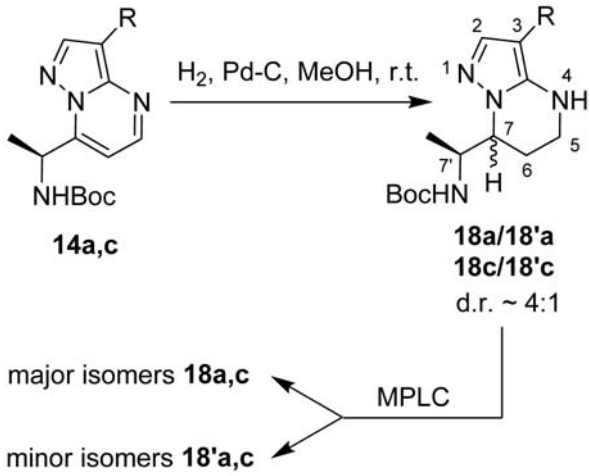


Compd.	X	Yield (%)
13e, **16'e**	CH	55
13e, **16'e**	N	26

Scheme 3. Regioselectivity of cyclisations of the reagents **8** and **9** with non-symmetrical cyclic amidines **13.**

The structures of all novel compounds **11a**–**g**, **12a**–**d**,**g**, **14a**–**c**, **14'a**,**c**,**d**, **16e**,**f**, **18a**,**c**, and **18'a**,**c** were determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS) and by elemental analyses for C, H, and N. Compounds **11d**, **14b**, **14'd**, and **16'e**,**f** were obtained in analytically pure form. On the other hand, compounds **11a**–**c**,**e**–**g**, **12a**–**d**,**g**, **14a**,**c**, **14'a**,**c**, **15a**,**b**, **18a**,**c**, and **18'a**,**c** were not obtained in analytically pure form. Their identities were established by ^{1}H NMR, ^{13}C NMR, and HRMS.

The regiochemistry of compounds **14a**–**c** and **14'a**,**c**,**d** was established by ^{1}H NMR on the basis of vicinal coupling constants, $^3J_{5H–6H}$ (compounds **14**) and $^3J_{6H–7H}$ (compounds **14'**). Thus, a small vicinal coupling constant, $^3J_{5H–6H}$ = 4.2 Hz, in compounds **14** was in agreement with the literature data for 7-substituted pyrazolo[1,5-*a*]pyrimidines, whereas a larger vicinal coupling constant, $^3J_{6H–7H}$ = 7.2 Hz, in compounds **14'** supported the pronounced CH=CH character and was in agreement with the literature data for 5-substituted pyrazolo[1,5-*a*]pyrimidines.[18–20] The ^{1}H NMR data for compounds **14** were also in agreement with the literature data for closely related *tert*-butyl (*S*)-(2-phenyl-1-(pyrazolo[1,5-*a*]pyrimidin-7-yl)ethyl)carbamate with its structure confirmed by X-ray analysis.[5] Cyclization of 5-amino-1,2,4-triazole **13d** (*cf.* Scheme 2) can take place, either at N(1), or at N(4) to give the isomeric 1,2,4-triazolo[1,5-*a*]pyrimidine **14'd** or 1,2,4-triazolo[4,3-*a*]pyrimidine **14''d**, respectively. The structure of **14'd** was determined by HMBC spectroscopy. Correlation of H(7) with three carbon nuc-



		Yield (%)		
Compound	R	18/18'	18	18'
18a, **18'a**	H	90	41	13
18c, **18'c**	COOMe	99	78	11

Scheme 4. Stereoselective hydrogenation of compounds **14a** and **14c**.

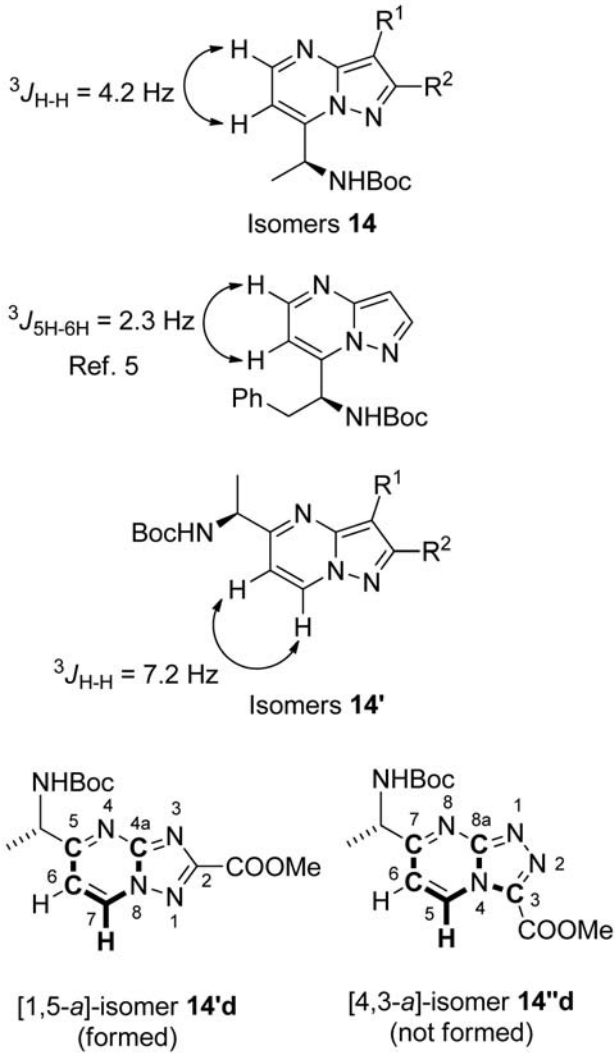


Figure 2. Structure determination by ^{1}H NMR and HMBC spectroscopy.

lei, C(4a), C(5), and C(6), was in agreement with the proposed [1,5-*a*]-isomer **14'd**. On the other hand, the corresponding H(5) in the [4,3-*a*]-isomer **14"d** should correlate with four carbon nuclei, C(3), C(6), C(7), and C(8a) (Figure 2).

Unfortunately, we were not able to determine the absolute configuration of compounds **14b**, **14'a**,**c**,**d**, **18a**,**c**, and **18'a**,**c**, since numerous attempts to obtain suitable single crystals of compounds **14b**, **14'a**,**c**,**d**, **18a**,**c**, and **18'a**,**c** for X-Ray diffraction analysis were not successful.

3. Experimental

3. 1. General Methods

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$ and DMSO-d_6 (with TMS as the internal standard) as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on a Bruker FTIR Alpha Platinum ATR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN analyser 2400 II. Dry-vacuum flash chromatography (DVFC)[21,22] was performed on silica gel (Fluka, Silica gel 60, particle size 35–70 μm). Medium performance liquid chromatography (MPLC) was performed on a Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChroprep® Si 60, 15–25 μm), column dimensions: 23 × 460 mm, backpressure: 10 Bar, detection: UV (254 nm).

(*S*)-*N*-Boc-Alanine (**6**), *N*,*O*-dimethylhydroxylamine, CDI, ethynylmagnesium bromide, amidines **10a**–**g**, aminopyrazoles **13a**,**b**, methyl 5-amino-1*H*-1,2,4-triazole-3-carboxylate (**13d**), 5-amino-1*H*-1,2,4-triazole (**13e**), and 5-amino-1*H*-tetrazole (**13f**) (Sigma Aldrich) are commercially available. *tert*-Butyl (*S*)-1-[methoxy(methyl) amino]-1-oxopropan-2-yl)carbamate (**7**),[16] *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**8**),[14,23] *tert*-butyl (*S,E*)-(5-(dimethylamino)-3-oxopent-4-en-2-yl)carbamate (**9**),[14] and methyl 5-amino-1*H*-pyrazole-4-carboxylate (**13c**)[24] were prepared following the literature procedures.

3. 2. General procedure for the synthesis of *tert*-butyl (*S*)-(1-(5-substituted pyrimidin-2-yl) ethyl)carbamates 11a–f.

A mixture of amidine hydrochloride **10** (1.1 mmol), *t*-BuOK (112 mg, 1 mmol), and MeOH (5 mL) was stirred at r.t. for 15 min. The so formed suspension was added to a solution of ynone **8** (197 mg, 1 mmol) in EtOH (10 mL) and the mixture was stirred at r.t. for 72 h. In the case of free amidines **10**, neutralisation with *t*-BuOK in MeOH was omitted. Volatile components were evaporated in vacuo and the residue was purified by DVFC (EtOAc/hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give **11**.

The following compounds were prepared in this manner:

3. 2. 1. *tert*-Butyl (*S*)-(1-(pyrimidin-4-yl)ethyl) carbamate (11a).

Prepared from **8** (197 mg, 1 mmol) and formimidamide acetate **10a** (115 mg, 1.1 mmol). Yield: 52 mg (23%) of brownish oil; $[\alpha]_D^{22}$ –0.8 (*c* 0.55, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (9H, s, *t*-Bu); 1.46 (3H, d, *J* = 7.2 Hz, 4'-CH_3); 4.82 (1H, p, *J* = 7.2 Hz, 4'-H); 5.48 (1H, br d, *J* = 8.6 Hz, NHBoc); 7.29 (1H, d, *J* = 5.2 Hz, 5-H); 8.68 (1H, d, *J* = 5.2 Hz, 6-H); 9.16 (1H, br d, *J* = 0.8 Hz, 2-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.8, 28.4, 50.8, 79.8, 118.3, 155.1, 157.2, 158.7, 170.3. *m/z* (ESI) = 224 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{11}H_{18}N_3O_2$, 224.1394; found, 224.1386. IR (ATR) υ 3227, 2976, 2929, 2859, 1703, 1581, 1553, 1468, 1356, 1366, 1299, 1267, 1247, 1171, 1105, 1073, 1056, 1019, 998, 870, 859, 782, 756, 731, 676, 611 cm^{-1}.

3. 2. 2. *tert*-Butyl (*S*)-(1-(2-methylpyrimidin-4-yl) ethyl)carbamate (11b).

Prepared from **8** (99 mg, 0.5 mmol) and acetimidamide hydrochloride **10b** (52 mg, 0.55 mmol). Yield: 36 mg (30%) of brownish oil; $[\alpha]_D^{22}$ +0.6 (*c* 1.8, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (3H, d, *J* = 7.2 Hz, 4'-Me); 1.45 (9H, s, *t*-Bu); 2.72 (3H, s, 2-Me); 4.76 (1H, p, *J* = 7.0 Hz, 4'-H); 5.61 (1H, br d, *J* = 7.3 Hz, NHBoc); 7.06 (1H, d, *J* = 5.1 Hz, 5-H); 8.57 (1H, d, *J* = 5.2 Hz, 6-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 26.0, 28.4, 50.8, 79.7, 114.9, 155.1, 157.2, 168.0, 170.2. *m/z* (ESI) = 238 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{12}H_{20}N_3O_2$, 238.1550; found, 238.1549. IR (ATR) υ 3226, 2977, 2933, 1698, 1576, 1557, 1530, 1441, 1406, 1363, 1303, 1250, 1160, 1116, 1071, 1042, 1022, 999, 864, 842, 785, 733, 642, 629 cm^{-1}.

3. 2. 3. *tert*-Butyl (*S*)-(1-(2-phenylpyrimidin-4-yl) ethyl)carbamate (11c).

Prepared from **8** (99 mg, 0.5 mmol) and benzimidamide hydrochloride **10c** (86 mg, 0.55 mmol). Yield: 47 mg (31%) of yellow oil; $[\alpha]_D^{22}$ –4.2 (*c* 1.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (9H, s, *t*-Bu); 1.52 (3H, d, *J* = 6.9 Hz, 4'-Me); 4.88 (1H, p, *J* = 7.2 Hz, 4'-H); 5.61 (1H, br d, *J* = 5.6 Hz, NHBoc); 7.14 (1H, d, *J* = 5.1 Hz, 5-H); 7.47–7.52 (3H, m, *o,p*-Ph); 8.44–8.49 (2H, m, *m*-Ph); 8.74 (1H, d, *J* = 5.1 Hz, 6-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.0, 28.4, 50.9, 79.7, 115.9, 128.2, 128.5, 130.8, 137.5, 155.2, 157.6, 164.3, 170.2. *m/z* (ESI) = 300 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{17}H_{22}N_3O_2$, 300.1707; found, 300.1709. IR (ATR) υ 3344, 2977, 2932, 1694, 1588, 1554, 1517, 1454, 1428, 1386, 1365, 1245, 1161, 1053, 1026, 845, 813, 760, 724, 696, 646 cm^{-1}.

3. 2. 4. (*S*)-*tert*-butyl (1-(2-(3-nitrophenyl) pyrimidin-4-yl)ethyl)carbamate (11d).

Prepared from **8** (197 mg, 1 mmol) and 3-nitrobenzimidamide hydrochloride **10d** (222 mg, 1.1 mmol). Yield: 202 mg (59%) of yellowish crystals; m.p. 89–92 °C; $[\alpha]_D^{22}$ –16.7 (*c* 0.55, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (9H, s, *t*-Bu); 1.55 (3H, d, *J* = 7.0 Hz, 4'-Me); 4.91 (1H, p, *J* = 7.4 Hz, 4'-H); 5.41 (1H, br d, *J* = 8.0 Hz, NHBoc); 7.26 (1H, d, *J* = 5.5 Hz, 5-H); 7.68 (1H, t, *J* = 8.0 Hz, 6''-H); 8.32–8.37 (1H, m, 5''-H); 8.80 (1H, d, *J* = 5.0 Hz, 6-H); 8.83 (1H, d, *J* = 7.8 Hz, 4''-H); 9.32 (1H, t, *J* = 1.9 Hz, 2''-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.7, 28.4, 51.1, 80.0, 116.9, 123.3, 125.2, 129.5, 134.0, 139.3, 148.7, 155.2, 157.9, 162.2, 171.2. *m/z* (ESI) = 345 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{17}H_{21}N_4O_4$, 345.1557; found, 345.1553. Anal. Calcd for $C_{17}H_{20}N_4O_4 \cdot ¼H_2O$: C 58.53, H 5.92, N 16.06. Found: C 58.87, H 5.84, N 15.83. IR (ATR) υ 3363, 2977, 1682, 1587, 1568, 1553, 1510, 1460, 1398, 1366, 1346, 1295, 1248, 1158, 1098, 1056, 1000, 923, 899, 855, 832, 816, 801, 786, 760, 738, 698, 689, 639, 606 cm^{-1}.

3. 2. 5. (*S*)-*tert*-butyl (1-(2-(3-aminophenyl) pyrimidin-4-yl)ethyl)carbamate (11e).

Prepared from **8** (197 mg, 1 mmol) and 4-aminobenzimidamide hydrochloride **10e** (189 mg, 1.1 mmol). Yield: 160 mg (51%) of brown oil; $[\alpha]_D^{22}$ –6.0 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (9H, s, *t*-Bu); 1.49 (3H, d, *J* = 7.4 Hz, CH_3CH); 4.00 (2H, br s, NH_2); 4.82 (1H, p, *J* = 7.2 Hz, 4'-H); 5.67 (1H, br d, *J* = 6.8 Hz, NHBoc); 6.75 (2H, d, *J* = 8.4 Hz, 2H of Ar); 7.00 (1H, d, *J* = 5.1 Hz, 5-H); 8.29 (2H, d, *J* = 8.5 Hz, 2H of Ar); 8.63 (1H, d, *J* = 5.0 Hz, 6-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 28.4, 50.8, 79.6, 114.5, 114.6, 127.7, 129.8, 149.1, 155.3, 157.3, 164.4, 169.7. *m/z* (ESI) = 315 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{17}H_{23}N_4O_2$, 315.1816; found, 315.1812. IR (ATR) υ 3458, 3368, 3215, 2974, 1682, 1627, 1605, 1579, 1553, 1520, 1450, 1422, 1388, 1365, 1333, 1300, 1244, 1167, 1060, 1008, 868, 836, 801, 755, 736, 675 cm^{-1}.

3. 2. 6. *tert*-Butyl (*S*)-(1-(2-((1*H*-benzo[*d*] imidazol- 2-yl)amino)pyrimidin-4-yl)ethyl) car-bamate (11f).

Prepared from **8** (99 mg, 0.5 mmol) and 1*H*-benzo[*d*]imidazole-2-carboximidamide hydrochloride **10f** (98 mg, 0.55 mmol). Yield: 78 mg (44%) of brown oil; $[\alpha]_D^{22}$ –18.9 (*c* 0.95, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (9H, s, *t*-Bu); 1.53 (3H, d, *J* = 7.1 Hz, C$\underline{H}_3$CH); 4.82 (1H, br s, 4'-H); 5.38 (1H, br s, N$\underline{H}$Boc); 6.88 (1H, d, *J* = 5.1 Hz, 5-H); 7.18, 7.23, 7.45, and 7.89 (4H, 4 br s, 1:1:1:1, 4H of Ar); 8.56 (1H, br s, 6-H); 11.83 (1H, br s, NH); 1'(3')-H exchanged. ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.4, 29.7, 50.9, 80.0, 110.2, 117.3, 120.8, 121.9, 131.6, 140.9, 149.4, 155.4, 158.8. *m/z* (ESI) = 355 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{18}H_{23}N_6O_2$, 355.1877; found, 355.1874. IR (ATR) υ 3343, 2976, 1684, 1643, 1606, 1555, 1511, 1457, 1435, 1393, 1365, 1319, 1271, 1245, 1163, 1061, 1006, 898, 861, 821, 795, 737, 693, 669, 608 cm^{-1}.

3. 2. 7. *tert*-Butyl (*S*)-(1-(2-(1*H*-pyrazol-1-yl) pyrimidin-4-yl)ethyl)carbamate (11g).

Prepared from **8** (197 mg, 1 mmol) and 1*H*-pyrazole-1-carboximidamide hydrochloride **10g** (161 mg, 1.1 mmol). Yield: 72 mg (25%) of yellow oil; $[\alpha]_D^{22}$ –12.3 (*c* 1.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (9H, s, *t*-Bu); 1.52 (3H, d, *J* = 7.0 Hz, C$\underline{H}_3$CH); 4.88 (1H, p, *J* = 6.8 Hz, 4'-H); 5.47 (1H, br d, *J* = 6.1 Hz, N$\underline{H}$Boc); 6.50 (1H, dd, *J* = 2.5, 1.7 Hz, 4''-H); 7.19 (1H, d, *J* = 5.0 Hz, 5-H); 7.84 (1H, d, *J* = 0.8 Hz, 3''-H); 8.62 (1H, d, *J* = 2.7 Hz, 5''-H); 8.70 (1H, d, *J* = 5.0 Hz, 6-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.5, 28.4, 51.0, 79.9, 108.6, 115.4, 129.3, 143.7, 155.1, 155.8, 159.3, 173.1. *m/z* (ESI) = 290 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{14}H_{20}N_5O_2$, 290.1612; found, 290.1609. IR (ATR) υ 3318, 2977, 1697, 1585, 1558, 1524, 1435, 1395, 1365, 1294, 1246, 1162, 1113, 1039, 946, 914, 842, 760, 733, 648 cm^{-1}.

3. 3. General procedures for the synthesis of *tert*-butyl (*S*)-(1-(pyrazolo[1,5-*a*] pyrimidin-7-yl)ethyl)carbamates 14a–c, tert-butyl (*S*)-(1-(pyrazolo[1,5-*a*] pyrimidin-5-yl)ethyl)carbamates 14'a,c,d, *tert*-butyl (*S,E*)-(5-(5-amino-1*H* -1,2,4-triazol-1-yl)-3-oxopent-4-en-2-yl) carbamate (16'e) and *tert*-butyl (*S,E*) -(5-(5-amino-1*H*-tetrazol-1-yl)-3 -oxopent -4-en-2-yl)carbamate (16'f).

General procedure A. Aminoazole **13** (1.1 mmol) was added to a solution of ynone **8** (197 mg, 1 mmol) in EtOH (10 mL) and the mixture was stirred at r.t. for 72 h. Volatile components were evaporated in vacuo and the residue was purified by DVFC (EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give **14/14'**. Mixtures of regioisomers **14a/14'a** and **14c/14'c** were separated by MPLC (EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give isomerically pure compounds **14a**, **14c**, **14'a**, and **14'c**.

General procedure B. Enaminone **9** (242 mg, 1 mmol) was dissolved in EtOH (10 mL), aminoazole hydrochloride **13** (1.1 mmol) was added, and the mixture was stirred at 50 °C for 72 h. Volatile components were evaporated in vacuo and the residue was purified by DVFC (EtOAc/hexanes, 1:2) to give **14**, **14'**, and **16'**.

The following compounds were prepared in this manner:

3. 3. 1. (*S*)-*tert*-butyl (1-(pyrazolo[1,5-*a*] pyrimidin-7-yl)ethyl)carbamate (14a) and (*S*)-*tert*-butyl (1-(pyrazolo[1,5-*a*] pyrimidin-5-yl)ethyl)carbamate (14'a).

Prepared from 3-amino-1*H*-pyrazole **13a** (91 mg, 1.1 mmol), and ynone **8** (197 mg, 1 mmol, G.P.A) or enaminone **9** (242 mg, 1 mmol, G.P.B), DVFC (EtOAc), MPLC (EtOAc/hexanes, 1:1).

*Major isomer **14a***. Yield: 141 mg (54%, G.P.A) and 120 mg (46%, G.P.B) of yellowish oil; $[\alpha]_D^{22}$ –63.7 (*c* 0.30, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (9H, s, *t*-Bu); 1.67 (3H, d, *J* = 7.2 Hz, 7'-Me); 5.43 (1H, p, *J* = 7.6 Hz, 7'-H); 6.16 (1H, br d, *J* = 8.5 Hz, N$\underline{H}$Boc); 6.73 (1H, br d, *J* = 2.4 Hz, 3-H); 6.80 (1H, d, *J* = 4.1 Hz, 6-H); 8.15 (1H, br d, *J* = 2.4 Hz, 2-H); 8.47 (1H, d, *J* = 4.3 Hz, 5-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.5, 28.3, 47.6, 80.0, 96.7, 104.1, 144.4, 149.2, 149.2, 149.5, 154.9. *m/z* (ESI) = 263 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{13}H_{19}N_4O_2$, 263.1503; found, 263.1502. IR (ATR) υ 3326, 2977, 1691, 1614, 1514, 1454, 1391, 1366, 1330, 1294, 1244, 1160, 114, 1061, 1014, 992, 900, 862, 826, 775, 739, 636 cm^{-1}.

*Minor isomer **14'a***. Yield: 28 mg (11%, G.P.A) of yellowish crystals; m.p. 89–93 °C; $[\alpha]_D^{22}$ –100.8 (*c* 0.35, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (9H, s, *t*-Bu); 1.51 (3H, d, *J* = 6.9 Hz, 5'-Me); 4.89 (1H, p, *J* = 7.2 Hz, 5'-H); 5.71 (1H, br d, *J* = 7.5 Hz, N$\underline{H}$Boc); 6.62 (1H, br d, *J* = 2.3 Hz, 3-H); 6.79 (1H, d, *J* = 7.2 Hz, 6-H); 8.10 (1H, d, *J* = 2.0 Hz, 2-H); 8.62 (1H, d, *J* = 7.2 Hz, 7-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.6, 28.4, 51.0, 79.7, 96.3, 106.2, 135.3, 145.3, 147.9, 155.2, 162.0. *m/z* (ESI) = 263 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{13}H_{19}N_4O_2$, 263.1503; found, 263.1501. IR (ATR) υ 3365, 2962, 2930, 2860, 1717, 1681, 1617, 1511, 1455, 1411, 1364, 1326, 1311, 1296, 1266, 1247, 1161, 1116, 1060, 1019, 1001, 907, 858, 809, 783, 766, 731, 636 cm^{-1}.

3. 3. 2. *tert*-Butyl (*S*)-(1-(2-methylpyrazolo [1,5-*a*]pyrimidin-7-yl)ethyl)carbamate (14b).

Prepared from ynone **8** (197 mg, 1 mmol) and 3-amino-5-methyl-1*H*-pyrazole **13b** (107 mg, 1.1 mmol), G.P.A, DVFC (EtOAc/hexanes, 1:2). Yield: 205 mg (74%) of white crystals; m.p. 100–105 °C; $[\alpha]_D^{22}$ –64.5 (*c* 0.45, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (9H, s, *t*-Bu); 1.66 (3H, d, *J* = 7.1 Hz, 7'-Me); 2.53 (3H, s, 2-Me); 5.35 (1H, p, *J* = 7.3 Hz, 7'-H); 6.09 (1H, br d, *J* = 9.2 Hz, NHBoc); 6.49 (1H, s, 3-H); 6.68 (1H, d, *J* = 4.2 Hz, 6-H); 8.37 (1H, br d, *J* = 4.2 Hz, 5-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.8, 18.7, 28.3, 47.8, 80.0, 95.9, 103.4, 148.6, 149.0, 150.0, 154.8, 154.9. *m*/*z* (ESI) = 277 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{14}H_{21}N_4O_2$, 277.1659; found, 277.1656. Anal. Calcd for $C_{14}H_{20}N_4O_2$: C 60.85, H 7.30, N 20.28. Found: C 61.11, H 7.58, N 20.14. IR (ATR) υ 3352, 2984, 2933, 1682, 1616, 1549, 1519, 1478, 1417, 1393, 1367, 1352, 1331, 1300, 1266, 1248, 1211, 1160, 1112, 1076, 1059, 1020, 862, 847, 822, 780, 736, 666, 628 cm^{-1}.

3. 3. 3. Methyl (S)-7-(1-((*tert*-butoxycarbonyl) amino)ethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (14c) and methyl (*S*)-5 -(1-((*tert*-butoxycarbonyl)amino)ethyl) pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (14'c).

Prepared from methyl 5-amino-1*H*-pyrazole-4-carboxylate **13c** (423 mg, 3.3 mmol), and ynone **8** (591 mg, 3 mmol, G.P.A) or enaminone **9** (727 mg, 3 mmol, G.P.B), DVFC (EtOAc), MPLC (EtOAc/hexanes, 1:1).

Major isomer ***14c***. Yield: 312 mg (32%, G.P.A) of brownish oil; $[\alpha]_D^{22}$ –30.9 (*c* 0.55, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (9H, s, *t*-Bu); 1.68 (3H, d, *J* = 7.1 Hz, 7'-Me); 3.98 (3H, s, OMe); 5.43 (1H, p, *J* = 7.8 Hz, 7'-H); 5.73 (1H, br s, NHBoc); 6.99 (1H, d, *J* = 4.2 Hz, 6-H); 8.62 (1H, s, 2-H); 8.76 (1H, d, *J* = 4.4 Hz, 5-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.6, 28.3, 47.7, 51.8, 80.5, 102.8, 106.2, 147.5, 148.2, 151.0, 152.8, 154.7, 163.0. *m*/*z* (ESI) = 321 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{15}H_{21}N_4O_4$, 321.1557; found, 321.1558. IR (ATR) υ 3341, 2979, 2248, 1692, 1618, 1549, 1514, 1486, 1453, 1367, 1323, 1281, 1249, 1226, 1161, 1112, 1088, 1062, 1009, 969, 909, 861, 835, 802, 784, 758, 728, 645 cm^{-1}.

Minor isomer ***14'c***. Yield: 110 mg (11%, G.P.A) and 72 mg (8%, G.P.B) of yellowish crystals; m.p. 102–106 °C; $[\alpha]_D^{22}$ –122.0 (*c* 0.40, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (9H, s, *t*-Bu); 1.57 (3H, d, *J* = 7.0 Hz, 5'-Me); 3.94 (3H, s, OMe); 4.99 (1H, p, *J* = 6.9 Hz, 5'-H); 5.82 (1H, d, *J* = 5.6 Hz, NHBoc); 7.04 (1H, d, *J* = 7.2 Hz, 6-H); 8.55 (1H, s, 2-H); 8.70 (1H, d, *J* = 7.1 Hz, 7-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.4, 28.4, 51.3, 51.5, 79.8, 102.4, 108.1, 136.2, 147.2, 148.0, 155.3, 162.9, 166.0. *m*/*z* (ESI) = 321 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{15}H_{21}N_4O_4$, 321.1557; found, 321.1556. IR (ATR) υ 3339, 2983, 1685, 1624, 1542, 1521, 1476, 1447, 1411, 1365, 1318, 1293, 1248, 1226, 1198, 1164, 1104, 1067, 1052, 1004, 938, 905, 866, 824, 782, 690, 633 cm^{-1}.

3. 3. 4. Methyl (*S*)-5-(1-((*tert*-butoxycarbonyl) amino)ethyl)[1,2,4]triazolo[1,5-*a*]pyrimidi -ne-2-carboxylate (14'd).

Prepared from **8** (197 mg, 1 mmol) and methyl 5-amino-1*H*-1,2,4-triazole-3-carboxylate (**13d**) (156 mg, 1.1 mmol), G.P.A, DVFC (EtOAc/hexanes, 1:2). Yield: 260 mg (81%) of white crystals; m.p. 191–195 °C; $[\alpha]_D^{22}$ –2.6 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (9H, s, *t*-Bu); 1.57 (3H, d, *J* = 7.0 Hz, 5'-Me); 4.09 (3H, s, OMe); 5.04 (1H, p, *J* = 7.3 Hz, 5'-H); 5.61(1H, br d, *J* = 7.9 Hz, NHBoc); 7.30 (1H, d, *J* = 7.1 Hz, 6-H); 8.86 (1H, d, *J* = 7.0 Hz, 7-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 28.3, 51.4, 53.3, 80.1, 110.7, 136.3, 155.0, 155.3, 157.5, 160.3, 170.7. *m*/*z* (ESI) = 322 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{14}H_{20}N_5O_4$, 322.1510; found, 322.1508. Anal. Calcd for $C_{14}H_{19}N_5O_4$: C 52.33, H 5.96, N 21.79. Found: C, 51.90; H, 5.63; N, 21.27. IR (ATR) υ 3379, 3083, 2982, 1732, 1682, 1627, 1510, 1474, 1387, 1367, 1333, 1303, 1245, 1217, 1163, 1059, 1022, 998, 970, 948, 861, 844, 782, 761, 743, 717, 656 cm^{-1}.

3. 3. 5. *tert*-butyl (*S,E*)-(5-(3-amino-4*H*-1,2,4-triazol-4-yl)-3-oxopent-4-en-2-yl)carbamate (16'e).

Prepared from **8** (99 mg, 0.5 mmol) and **13e** (98 mg, 0.5 mmol) and , General Procedure A. Yield: 72 mg (55%) of white crystals; m.p. 188–191 °C; $[\alpha]_D^{22}$ –27.1 (*c* 0.20, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.18 (3H, d, *J* = 7.2 Hz, CH_3CH); 1.38 (9H, s, *t*-Bu); 4.18 (1H, p, *J* = 7.3 Hz, CHCH$_3$); 6.66 (1H, d, *J* = 13.2 Hz, CH=CHN); 7.33 (1H, d, *J* = 7.4 Hz, NHBoc); 7.35 (2H, b s, NH_2); 7.62 (1H, s, 5-H); 8.15 (1H, d, *J* = 13.3 Hz, CH=CHN). ^{13}C NMR (126 MHz, DMSO-d_6): δ 16.2, 28.2, 54.4, 78.1, 108.5, 133.9, 152.3, 155.2, 156.9, 199.0. *m*/*z* (ESI) = 282 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{12}H_{20}N_5O_3$, 282.1561; found, 282.1567. Anal. Calcd for $C_{12}H_{19}N_5O_3$: C 51.23, H 6.81, N 24.90. Found: C 50.80, H 6.65, N 24.54. IR (ATR) υ 3357, 3119, 2980, 1683, 1610, 1516, 1456, 1428, 1389, 1366, 1310, 1290, 1251, 1201, 1168, 1081, 1055, 1027, 957, 888, 856, 817, 780, 742, 695, 640, 625 cm^{-1}.

3. 3. 6. *tert*-butyl (*S,E*)-(5-(5-amino-1*H*-tetrazol-1 -yl)-3-oxopent-4-en-2-yl)carbamate (16'f).

Prepared from **8** (99 mg, 0.5 mmol) and **13f** (98 mg, 0.5 mmol), General Procedure A. Yield: 36 mg (26%) of yellowish crystals; m.p. 144–147 °C; $[\alpha]_D^{22}$ –37.7 (*c* 0.47,

MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (3H, d, *J* = 7.2 Hz, C$\underline{H}_3$CH); 1.38 (9H, s, *t*-Bu); 4.22 (1H, p, *J* = 7.2 Hz, C$\underline{H}$CH$_3$); 7.03 (1H, d, *J* = 13.8 Hz, C$\underline{H}$=CHN); 7.43 (1H, d, *J* = 7.1 Hz, N$\underline{H}$Boc); 7.65 (2H, br s, N$\underline{H}_2$); 8.13 (1H, d, *J* = 13.8 Hz, CH=C$\underline{H}$N). ^{13}C NMR (126 MHz, DMSO-d_6): δ 15.8, 28.1, 54.6, 78.3, 112.8, 130.6, 155.3, 155.4, 198.6. *m*/*z* (ESI) = 283 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{11}H_{19}N_6O_2$, 283.1513; found, 283.1504. Anal. Calcd for $C_{11}H_{18}N_6O_3$: C 46.80, H 6.43, N 29.77. Found: C 46.35, H 6.15, N 30.04. IR (ATR) υ 3353, 3152, 2980, 2143, 1682, 1618, 1592, 1516, 1455, 1390, 1366, 1311, 1252, 1161, 1112, 1048, 991, 959, 856, 780, 701, 626 cm^{-1}.

3. 4. General procedure for the synthesis of (*S*)-1-(pyrimidin-2-yl)-1-ethylaminium chlorides 12a–d,g and (*S*)-1-(pyrazolo [1,5-*a*]pyrimidin-7-yl)-1-ethylaminium chlorides 15a,b.

2 M HCl in ethyl acetate (1 mL, 2 mmol) was added to a stirred solution of **11** or **14** (0.2 mmol) in ethyl acetate (5 mL) and the mixture was stirred at r.t. for 3 h. Volatile components were evaporated to give the crude products **12** and **15**.

The following compounds were prepared in this manner:

3. 4. 1. (*S*)-1-(Pyrimidin-4-yl)-1-ethylaminium chloride (12a).

Prepared from **11a** (8 mg, 0.04 mmol). Yield: 5 mg (79%) of brownish oil; $[\alpha]_D^{22}$ +15.6 (*c* 0.20, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.55 (3H, d, *J* = 6.9 Hz, 4'-Me); 4.58 (1H, p, *J* = 6.4 Hz, 4'-H); 7.77 (1H, dd, *J* = 5.3, 1.3 Hz, 5-H); 8.77 (3H, br s, N$\underline{H}_3^+$); 8.92 (1H, d, *J* = 5.2 Hz, 6-H); 9.29 (1H, br d, *J* = 1.3 Hz, 2-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.2, 50.5, 120.1, 158.9, 159.1, 167.1. *m*/*z* (ESI) = 124 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_6H_{10}N_3$, 124.0869; found, 124.0866. IR (ATR) υ 2927, 2858, 1720, 1627, 1580, 1505, 1463, 1386, 1266, 1246, 1155, 1116, 1101, 1019, 842, 790, 730 cm^{-1}.

3. 4. 2. (*S*)-1-(2-Methylpyrimidin-4-yl)-1 -ethylaminium chloride (12b).

Prepared from **11b** (36 mg, 0.1 mmol). Yield: 16 mg (84%) of yellowish oil; $[\alpha]_D^{22}$ +8.9 (*c* 0.70, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.54 (3H, d, *J* = 6.9 Hz, 4'-Me); 2.71 (3H, s, 2-Me); 4.51 (1H, p, *J* = 6.1 Hz, 4'-H); 7.64 (1H, d, *J* = 5.3 Hz, 5-H); 8.84 (1H, d, *J* = 5.3 Hz, 6-H); 8.85 (3H, br s, N$\underline{H}_3^+$). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.2, 26.3, 50.7, 117.1, 158.1, 167.6, 168.0. *m*/*z* (ESI) = 138 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_7H_{12}N_3$, 138.1026; found, 138.1028. IR (ATR) υ 2916, 2251, 2076, 1622, 1577, 1508, 1439, 1397, 1297, 1202, 1098, 1043, 996, 930, 833, 728 cm^{-1}.

3. 4. 3. (*S*)-1-(2-Phenylpyrimidin-4-yl) -1-ethylaminium chloride (12c).

Prepared from **11c** (37 mg, 0.12 mmol). Yield: 23 mg (82%) of yellowish oil; $[\alpha]_D^{22}$ +7.9 (*c* 1.1, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.63 (3H, d, *J* = 6.8 Hz, 4'-Me); 4.63 (1H, p, *J* = 6.4 Hz, 4'-H); 7.54–7.60 (3H, m, 3H of Ar); 7.66 (1H, d, *J* = 5.1 Hz, 5-H); 8.59 (2H, dd, *J* = 7.5, 2.3 Hz, 2H of Ar); 8.94 (3H, br s, N$\underline{H}_3^+$); 8.99 (1H, d, *J* = 5.1 Hz, 6-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.2, 50.7, 117.9, 129.2, 129.6, 132.2, 137.7, 159.4, 164.0, 167.5. *m*/*z* (ESI) = 200 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_{12}H_{14}N_3$, 200.1182; found, 200.1184. IR (ATR) υ 2875, 1973, 1588, 1559, 1499, 1460, 1427, 1389, 1373, 1198, 1175, 1129, 1098, 1081, 1069, 1025, 991, 940, 909, 844, 816, 762, 723, 694, 646 cm^{-1}.

3. 4. 4. (*S*)-1-(2-(3-Nitrophenyl)pyrimidin-4-yl) -1-ethylaminium chloride (12d).

Prepared from **11d** (13 mg, 0.04 mmol). Yield: 10 mg (89%) of yellowish crystals; m.p. 214–220 °C; $[\alpha]_D^{22}$ –22.4 (*c* 0.40, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.64 (3H, d, *J* = 6.9 Hz, C$\underline{H}_3$CH); 4.72 (1H, p, *J* = 6.1 Hz, C$\underline{H}$CH$_3$); 7.76 (1H, d, *J* = 5.2 Hz, 5-H); 7.92 (1H, t, *J* = 8.0 Hz, 5''-H); 8.46 (1H, ddd, *J* = 8.2, 2.3, 0.8 Hz 4''-H); 8.89 (3H, br s, N$\underline{H}_3^+$); 9.04 (1H, dt, *J* = 7.8, 1.3 Hz, 6''-H); 9.09 (1H, d, *J* = 5.1 Hz, 6-H); 9.32 (1H, t, *J* = 2.0 Hz, 2''-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.1, 50.5, 119.0, 123.4, 126.7, 131.5, 135.3, 139.3, 149.4, 159.8, 162.0, 167.9. *m*/*z* (ESI) = 245 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_{12}H_{13}N_4O_2$, 245.1033; found, 245.1035. IR (ATR) υ 2977, 2847, 2016, 1967, 1684, 1587, 1557, 1528, 1481, 1426, 1393, 1348, 1247, 1194, 1168, 1141, 1099, 1062, 993, 926, 907, 887, 844, 826, 801, 738, 699, 682, 645, 616 cm^{-1}.

3. 4. 5. (*S*)-1-(2-(1*H*-Pyrazol-1-yl)pyrimidin-4-yl)-1-ethylaminium chloride (12g).

Prepared from **11g** (72 mg, 0.25 mmol). Yield: 47 mg (84%) of brownish oil; $[\alpha]_D^{22}$ +7.1 (*c* 1.8, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.62 (3H, d, *J* = 6.8 Hz, 4'-Me); 4.65 (1H, p, *J* = 5.9 Hz, 4'-H); 6.67 (1H, dd, *J* = 2.7, 1.6 Hz, 4''-H); 7.67 (1H, d, *J* = 5.1 Hz, 5-H); 7.92 (1H, d, *J* = 1.5 Hz, 3''-H); 8.95 (1H, d, *J* = 5.1 Hz, 6-H); 8.99 (3H, br s, N$\underline{H}_3^+$); 9.06 (1H, d, *J* = 2.7 Hz, 5''-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.1, 50.5, 109.9, 117.4, 131.5, 144.6, 155.8, 161.3, 169.4. *m*/*z* (ESI) = 190 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_9H_{12}N_5$, 190.1087; found, 190.1084. IR (ATR) υ 2823, 1589, 1561, 1523, 1467, 1439, 1393, 1344, 1220, 1166, 1100, 1069, 1043, 992, 947, 902, 835, 809, 703, 648, 606 cm^{-1}.

3. 4. 6. (*S*)-1-(Pyrazolo[1,5-*a*]pyrimidin-7-yl) -1-ethylaminium chloride (15a).

Prepared from **14a** (40 mg, 0.15 mmol). Yield: 28 mg (94%) of yellowish oil; $[\alpha]_D^{22}$ +8.0 (*c* 1.4, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.73 (3H, d, *J* = 6.8 Hz, 7'-Me); 5.19 (1H, p, *J* = 6.2 Hz, 7'-H); 6.89 (1H, d, *J* = 2.4 Hz, 3-H); 7.43 (1H, d, *J* = 4.3 Hz, 6-H); 8.36 (1H, d, *J* = 2.4 Hz, 2-H); 8.70 (1H, d, *J* = 4.3 Hz, 5-H); 9.30 (3H, br d, *J* = 4.4 Hz, N$\underline{H}_3^+$). ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.6, 45.8, 98.0, 106.4, 145.7, 146.6, 149.3, 150.6. *m*/*z* (ESI) = 163 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_8H_{11}N_4$, 163.0978; found, 163.0979. IR (ATR) υ 2858, 2084, 1721, 1617, 1543, 1456, 1373, 1310, 1269, 1245, 1176, 1117, 1021, 995, 903, 821, 776, 742, 634 cm^{-1}.

3. 4. 7. (*S*)-1-(2-Methylpyrazolo[1,5-*a*]pyrimidin -7-yl)-1-ethylaminium chloride (15b).

Prepared from **14b** (52 mg, 0.2 mmol). Yield: 20 mg (47%) of yellowish oil; $[\alpha]_D^{22}$ +16.5 (*c* 0.40, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.72 (3H, d, *J* = 6.8 Hz, 7'-Me); 2.51 (3H, s, 2-Me); 5.16 (1H, p, *J* = 6.5 Hz, 7'-H); 6.68 (1H, s, 3-H); 7.30 (1H, d, *J* = 4.4 Hz, 6-H); 8.62 (1H, d, *J* = 4.4 Hz, 5-H); 9.21 (3H, br d, *J* = 4.4 Hz, N$\underline{H}_3^+$). ^{13}C NMR (126 MHz, DMSO-d_6): δ 15.4, 17.5, 45.6, 97.2, 105.5, 146.0, 149.9, 150.2, 155.2. *m*/*z* (ESI) = 321 (M^+). HRMS–ESI (*m*/*z*): [M^+] calcd for $C_9H_{13}N_4$, 177.1135; found, 177.1134. IR (ATR) υ 2848, 1611, 1572, 1534, 1483, 1405, 1343, 1249, 1208, 1152, 998, 777, 738 cm^{-1}.

3. 5. Catalytic hydrogenation of pyrazolo [1,5-*a*]pyrimidines 14a and 14'c. Synthesis of 4,5,6,7-tetrahydropyrazolo [1,5-*a*]pyrimidines 18 and 18'.

A mixture of pyrazolo[1,5-*a*]pyrimidine **14** (0.5 mmol), MeOH (30 mL), and 10% Pd-C (15 mg) was hydrogenated under 3 Bar of H_2 at r.t. for 16 h. The catalyst was removed by filtration through a glass-sintered funnel, washed with MeOH (10 mL), and the combined filtrate was evaporated in vacuo to give **18/18'**. The mixture of isomers **18** and **18'** was first purified by DVFC (EtOAc). The combined eluate was evaporated in vacuo to give the purified mixture of diastereomers **18** and **18'**, which were separated by MPLC (EtOAc/hexanes, 1:1). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure compounds **18** and **18'**.

The following compounds were prepared in this manner:

3. 6. 1. t*ert*-Butyl (7*S*,7'*S*)-1-((4,5,6,7-tetrahydropyra- zolo[1,5-*a*]pyrimidin-7-yl)ethyl)-carbamate (18a) and its (7*R*,7'*S*)-isomer 18'a.

Prepared from **14a** (131 mg, 0.5 mmol). Yield: 120 mg (90%) of reddish oil, **18a**:**18'a** = 80:20.

*Data for the major isomer **18a**.* Yield: 55 mg (41%) of reddish oil; $[\alpha]_D^{22}$ –1.4 (*c* 0.70, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (3H, d, *J* = 6.8 Hz, 7'-Me); 1.46 (9H, s, *t*-Bu); 1.98 (1H, br dtd, *J* = 3.9, 10.3, 13.6 Hz, 1H of 6-Ha); 2.14 (1H, br dddd, *J* = 3.1, 5.1, 8.3, 13.6 Hz, 6-Hb); 3.24 (1H, br td, *J* = 11.0, 2.8 Hz, 5-Ha); 3.34 (1H, br dt, *J* = 11.5, 4.5 Hz, 5-Hb); 4.01 (1H, br p, *J* = 6.8 Hz, 7'-H); 4.11 (1H, br s, 4-H); 4.27 (1H, br tdd, *J* = 1.7, 5.7, 8.2 Hz, 7-H); 5.34 (1H, br d, *J* = 2.0 Hz, 3-H); 6.59 (1H, d, *J* = 9.8 Hz, N$\underline{H}$Boc); 7.25 (1H, br d, *J* = 2.0 Hz, 2-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.0, 26.7, 28.5, 39.3, 49.9, 59.1, 79.0, 86.4, 138.7, 146.5, 155.5. *m*/*z* (ESI) = 267 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{13}H_{23}N_4O_2$, 267.1816; found, 267.1816. IR (ATR) υ 3339, 2976, 2934, 1687, 1578, 1499, 1450, 1391, 1363, 1340, 1293, 1242, 1162, 1083, 1061, 1045, 1026, 990, 923, 886, 846, 729, 631 cm^{-1}.

*Data for the minor isomer **18'a**.* Yield: 17 mg (13%) of reddish oil; $[\alpha]_D^{22}$ –24.2 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, d, *J* = 7.0 Hz, 7'-Me); 1.39 (9H, s, *t*-Bu); 2.11 and 2.15 (2H, 2 br dddd, *J* = 4.1, 4.6, 8.9, 13.6 Hz, 6-Ha and 6-Hb); 3.28 (1H, ddd, *J* = 3.9, 6.9, 11.2 Hz, 5-Ha); 3.40 (1H, ddd, *J* = 3.6, 8.7, 11.9 Hz, 5-Hb); 4.06 and 4.13 (3H, 2 br s, 2:1, 7'-H, 4-H, and 7-H); 5.12 (1H, br s, N$\underline{H}$Boc); 5.33 (1H, br d, *J* = 2.0 Hz, 3-H); 7.26 (1H, br d, *J* = 2.0 Hz, 2-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.4, 25.3, 28.4, 37.8, 49.8, 58.1, 79.2, 86.2, 139.0, 145.5, 155.7. *m*/*z* (ESI) = 267 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{13}H_{23}N_4O_2$, 267.1816; found, 267.1818. IR (ATR) υ 3320, 2975, 2932, 1689, 1579, 1518, 1452, 1391, 1364, 1293, 1245, 1162, 1062, 988, 923, 872, 729 cm^{-1}.

3. 6. 2. Methyl (5*S*,5'*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (18c) and its (5*R*,5'*S*)-isomer 18'c.

Prepared from **14c** (320 mg, 1 mmol). Yield: 322 mg (99%) of yellowish oil; **18c**:**18'c** = 84:16.

*Data for the major isomer **18c**.* Yield: 254 mg (78%) of colourless resin; $[\alpha]_D^{22}$ –0.3 (*c* 0.70, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* = 6.7 Hz, 7'-Me); 1.46 (9H, s, *t*-Bu); 1.98–2.08 (1H, m, 6-Ha); 2.09–2.18 (1H, m, 6-Hb); 3.32–3.41 (1H, m, 5-Ha); 3.45–3.52 (1H, m, 5-Hb); 3.78 (3H, s, OMe); 3.99–4.08 (1H, br m, 7'-H); 4.17–4.24 (1H, br m, 7-H); 5.81 (1H, br s, 4-H); 6.12 (1H, br d, *J* = 9.8 Hz; N$\underline{H}$Boc); 7.187.58 (1H, s, 2-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.6, 25.4, 28.4, 37.7, 49.4, 50.7, 58.9, 79.4, 93.5, 139.1, 149.3, 155.4, 164.6. *m*/*z* (ESI) = 325 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{15}H_{25}N_4O_4$, 325.1870; found, 325.1863. IR (ATR) υ 3369, 2977, 2249, 1680, 1599, 1541, 1501, 1443, 1391, 1365, 1339, 1287, 1235, 1212, 1163, 1125, 1086, 1061, 1027, 990, 939, 919, 846, 807, 779, 729, 646 cm^{-1}.

*Data for the minor isomer **18'c**.* Yield: 36 mg (11%) of colourless resin; $[\alpha]_D^{22}$ +2.0 (*c* 0.35, CH_2Cl_2). ^{1}H NMR

(500 MHz, $CDCl_3$): δ 1.34 (3H, d, *J* = 5.4 Hz, 7'-Me); 1.31 (9H, s, *t*-Bu); 2.05–2.15 (2H, m, 6-CH_2); 3.40 (1H, dtd, *J* = 12.2, 5.1, 2.6 Hz, 5-Ha); 3.48 (1H, br dddd, *J* = 13.3, 8.4, 4.8, 1.6 Hz, 5-Hb); 3.70 (3H, s, OMe); 3.95–4.06 (1H, br p, *J* = 6.0 Hz, 7-H); 4.09 (1H, br p, *J* = 5.4 Hz, 7'-H); 4.88 (1H, br d, *J* = 5.4 Hz, NHBoc); 5.85 (1H, br s, 4-H); 7.57 (1H, s, 2-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.3, 24.3, 28.3, 36.4, 49.6, 50.7, 57.9, 79.5, 93.3, 139.4, 148.6, 155.5, 164.7. *m/z* (ESI) = 325 (MH^+). HRMS–ESI (*m/z*): [MH^+] calcd for $C_{15}H_{25}N_4O_4$, 325.1870; found, 325.1868. IR (ATR) υ 3350, 2975, 1678, 1599, 1540, 1442, 1391, 1364, 1289, 1232, 1212, 1163, 1082, 1061, 981, 938, 925, 870, 807, 778, 734, 697 cm^{-1}.

4. Conclusions

Novel (*S*)-*N*-Boc-1-(heteroaryl)-1-ethylamines **11**, **14**, and **14'** were prepared by cyclocondensation of (*S*)-*N*-Boc-alanine (**6**)-derived ynone **8** with amidines **10** and α-aminoazoles **13**. Acidolytic removal of the Boc *N*-protecting group then furnished the free amines **12** and **15** in moderate yields over two steps. Reactions of **8** with non-symmetrical cyclic amidines **13** were generally not regioselective and gave mixtures of isomeric products **14** and **14'**. Since **14** and **14'** were separable by chromatography, this lack of regioselectivity can also be advantageous, due to increase of diversity of the products. Catalytic hydrogenation of (*S*)-*tert*-butyl (1-(pyrazolo[1,5-*a*]pyrimidin-7-yl)ethyl)carbamates **14** was quite stereoselective to furnish the corresponding 4,5,6,7-tetrahydro derivatives as separable mixtures of diastereomers **18** and **18'** in a ratio of 4:1. In summary, the present method allows a short and simple synthesis of various (*S*)-1-(heteroaryl)-1-ethylamines from commercially available α-amino acids. The title compounds could be useful generally as chiral non-racemic amines and ligands in asymmetric applications, whereas (*S*)-1-(pyrazolo[1,5-*a*]pyrimidinyl)-1-ethylamines are additionally applicable in fluorescence-related applications.

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6. References

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Povzetek

(*S*)-*terc*-butil (3-oksopent-4-in-2-il)karbamat, pripravljen v dveh stopnjah iz (*S*)-*N*-Boc-alanina, smo ciklizirali z različnimi *N,N*-1,3-dinukleofili, kot so amidini in α-aminoazoli ter tako po acidolitski odstranitvi Boc skupine sintetizirali seriji (*S*)-1-(pirimidin-4-il)- in regioizomernih (*S*)-1-(pirazolo[1,5-*a*]pirimidin-7-il)- in (*S*)-1-(pirazolo[1,5-*a*]pirimidin-5-il)-1-aminoetanov. Stereoselektivno katalitsko hidrogeniranje (*S*)-1-(pirazolo[1,5-*a*]pirimidin-7-il)-1-aminoetanov je vodilo do nasičenja pirimidinskega obroča in nastanka zmesi diastereomernih 4,5,6,7-tetrahidropirazolo[1,5-*a*]pirimidinov v razmerju 4:1. Strukture vseh novih spojin so bile pojasnjene z NMR spektroskopijo.