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Stereoselective synthesis of δ-heteroaryl substituted β-hydroxy-γ,δ-unsaturated α-amino acids

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Abstract—Enantiomerically pure δ-heteroaryl substituted β-hydroxy-γ,δ-unsaturated α-amino acids were stereoselectively synthesized starting from (2*R*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (*Schöllkopf*'s reagent) and suitable β-heteroaryl-α,β-unsaturated aldehydes. The stereocontrolled addition gave a mixture of two diastereoisomers whose configurations were assigned on the basis of spectroscopic data and the accepted model for aldol condensation of the *Schöllkopf*'s reagent. Upon controlled hydrolysis the adducts were transformed into the corresponding methyl esters of δ-heteroaryl substituted β-hydroxy-γ,δ-unsaturated α-amino acids.

1. Introduction

β-Hydroxy-α-amino acids are an important class of amino acids as they occur naturally as amino acids (serine, threonine, 3-hydroxyproline) and also as components of complex natural products with wide-ranging biological properties.[1] For example, β-hydroxy-α-amino acids (β-hydroxy-tyrosine or β-hydroxy-phenylalanine) are found in clinically important glycopeptide antibiotics or immunosuppressants. They are also useful chiral building blocks for the asymmetric synthesis of numerous compounds such as β-lactams or sugars.[2]

As a consequence, the stereoselective synthesis of β-hydroxy-α-amino acids is of considerable relevance and has been extensively studied.[3] Among the numerous methods are those involving aldol condensation using chiral enolates,[4] which were enabled by '*Schöllkopf*'s reagent', namely (2*R*)- or (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine; this is particularly attractive due to its commercial availability in both the enantiopure (*R*)- and (*S*)-forms and the number of reported examples in asymmetric synthesis.[5]

We have already utilized this chiral auxiliary to synthesise β-heterocyclic substituted serines,[6a] alanines[6b] and, more recently, the antibiotic azatyrosine.[6c] As part of our interest in the stereoselective synthesis of heteroaromatic α-amino acid derivatives, we have extended our studies to the reaction of β-heteroaryl-α,β-unsaturated aldehydes with the *Schöllkopf*'s reagent with the aim of obtaining new non-proteinogenic γ-substituted β-hydroxy-α-amino acids with a vinylheterocyclic residue group, eventually susceptible of further functionalization. To the best of our knowledge, no examples of this type of β-hydroxy-α-amino acid have been reported up to date.

2. Results and discussion

To investigate the condensation reaction between (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **1** and β-heteroaryl-α,β-unsaturated aldehydes, we have chosen the aldehydes **2a**–**e** vinyl homologous of those previously used.[6a]

According to the general procedure, the anion of bislactim ether (*R*)-**1** was generated by *n*-BuLi in THF, at $T = -78$ °C and treated with diisopropoxytitanium(IV) dichloride[7] to give the corresponding titanium compound α to which a solution of aldehyde **2** was successively added (Scheme 1).

Except in the case of **2c**, TLC analysis and the ^{1}H NMR spectrum of the crude reaction mixtures showed only two of the four possible diastereoisomers. Their ratios were

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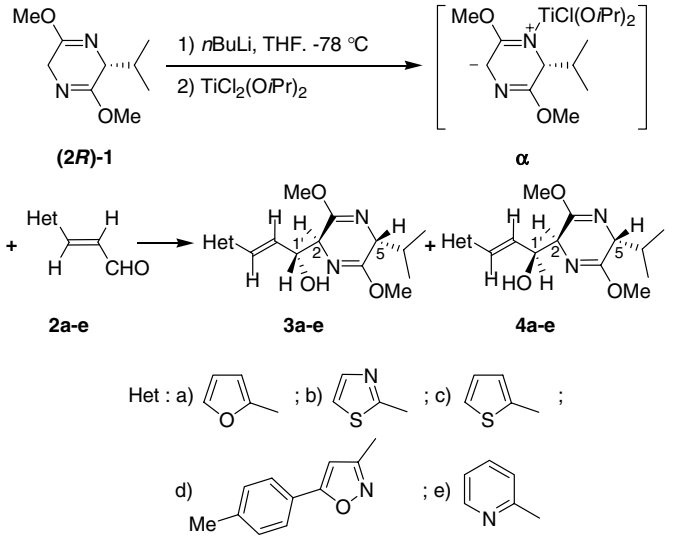


Scheme 1.

determined by the integration of the pairs of doublets corresponding to the isopropyl groups present in the ^{1}H NMR spectrum (Table 1).

Table 1.

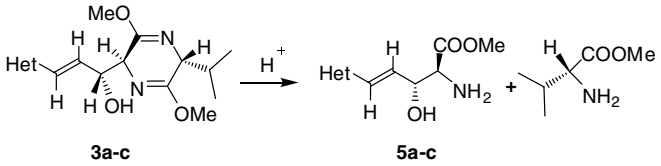
Entry	2	Solvent	Counter ion	Total yield (%)	Ratio **3**:**4** (1′*R*,2*S*,5*R*):(1′*S*,2*S*,5*R*)
1	**a**	Et_2O	Li	42	50:50
2	**a**	THF	Li	68	48:52
3	**a**	THF	Ti	71	91:9
4	**b**	THF	Ti	55	78:22
5	**c**	THF	Ti	25	100:0
6	**d**	THF	Ti	15	65:35
7	**e**	THF	Ti	10	68:32

As indicated in Table 1, for aldehyde **2a**, the use of diethyl ether as a solvent lowers the yield with respect to the use of THF (entries 1 and 2). Moreover, the presence of the titanium instead of lithium as a counter ion changes drastically the diastereoisomeric ratio from 48:52 to 91:9 (entries 2 and 3). Similar results were observed with the other aldehydes and were in agreement with the previous authors view on the reaction of **1** with heteroaromatic aldehydes[6a] and with cinnamaldehydes.[8]

Except in the case of **3e**/**4e**, the pairs of diastereoisomers were separated by flash chromatography on silica gel and their structures and configurations assigned on the basis of analytical and spectroscopic data. In particular a complete correspondence was observed between the chemical shifts in the ^{1}H and ^{13}C NMR spectra of our major diastereoisomer and the reported values for the known corresponding phenyl derivative.[8] In this way, the (1′*R*,2*S*,5*R*)- and (1′*S*,2*S*,5*R*)-configurations could be assigned to the more and the less abundant aldol adducts **3a**–**e** and **4a**–**e**, respectively. These configurations are also in agreement with the well accepted model for aldol type addition of **1** to achiral aldehydes.[9] According to this model the exclusive formation of the two (2*S*)-epimers can be explained with a transition state in which the aldehyde attacks the pyrazine α (Scheme 1) from the less hindered side, opposite to the isopropyl group. Moreover, the predominance of the (1′*R*)-epimer comes from a more favourable transition state in which the aldehyde residue is removed from the methoxy group and from the metal atom. For comparison, we carried out a reaction between the enantiomer (2*S*)-**1** and the aldehyde **2a**: in this way the adducts with the opposite configurations (1′*S*,2*R*,5*S*)-**3a** and (1′*R*,2*R*,5*S*)-**4a** were obtained with a 65% yield and 85:15 ratio, respectively.

The adducts were not very stable under mild aqueous acid conditions giving rise to elimination products probably assisted by extra conjugation. Furthermore the protection of the hydroxyl group of adduct **3a** by acetylation afforded an *O*-acetyl derivative that did not show an increased stability towards the acid medium.

Therefore the hydrolysis of adducts **3a**–**c** and **4b** were conducted in acetonitrile with 2 equiv of 0.2 N HCl at $T = 0$–5 °C for 24 h: in this way the β-hydroxy-α-amino esters **5a**–**c** and **6b** were obtained in moderate to good yields (Scheme 2).



Scheme 2.

Alternative conditions (3 equiv of 0.1 M aqueous TFA at room temperature for 24 h) reported to be a smooth method of hydrolysis,[10] surprisingly led to complex mixtures of the expected amino esters plus the trifluoroacetylated dipeptide esters derived from a partial cleavage of the pyrazine ring. We have observed quite different behaviour between furan or thiophene substituted adducts **5a**,**c** and those thiazole substituted compounds **5b**, **6b**. In fact the furan or thiophene derivatives are very unstable also at low temperature and did not allow us a complete spectroscopic characterization.

3. Experimental

3.1. General methods

Melting points were measured using a *Büchi* apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise specified) on a *Bruker AC 300* spectrometer; chemical shifts (δ) are given in ppm relative to TMS and all of the coupling constants are in hertz. Optical rotation values were measured at 25 °C on a *Perkin–Elmer 241* spectropolarimeter. The MS spectra were determined using a *VG Analytical 7070 EQ* mass spectrometer with an attached *VG analytical 11/250* data system.

The IR spectra were determined using a *Perkin–Elmer 1725X FT-IR* spectrometer, in cm^{-1}.

(2*R*)- or (2*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine **1** and aldehydes **2a** and **2d** were obtained from commercial sources; aldehydes **2b**,[11] **2c**[12] and **2e**[13] were prepared according to the reported method.

3.2. General procedure for the reactions of (*RS*)-1 with 2a–e

To a solution of **1** (0.7 mL, 3.88 mmol) in anhydrous THF (10 mL), cooled at −78 °C, butyl lithium (4.08 mmol, 2.55 mL of a 1.6 M solution in hexane) was added and the mixture was stirred for 45 min. A solution of diisopropoxytitanium(IV) dichloride (4.18 mmol) prepared mixing titanium tetraisopropoxide (2.09 mmol, 0.62 mL) in anhydrous THF (2 mL) and titanium tetrachloride (2.09 mmol, 2.09 mL of a 1 M solution in toluene), was added and stirring continued for 45 min. The appropriate aldehyde **2** (3.88 mmol) in THF (10 mL) was added and then the mixture stirred at −78 °C for 6 h. The reaction mixture was allowed to warm to 0 °C and phosphate buffer solution (25 mL) was added. The solvent was evaporated and the residue taken up with ether. The organic phase was separated and dried with Na_2SO_4, the solvent evaporated in vacuo and the residue was flash chromatographed on silica gel (diethyl ether for **2a**; diethyl ether/ethyl acetate = 90/10 for **2b**; toluene/ethyl acetate = 90/10 for **2c–e**). In this way the following compounds were isolated.

3.3. (1′*R*,2*S*,5*R*)-(*E*)-3-Furan-2-yl-1-(5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-prop-2-en-1-ol 3a

Colourless solid (65%); mp 65–67 °C (*n*-hexane); $[\alpha]_D^{20} = -73.65$ (*c* 0.72, Et_2O). ^1H NMR: δ 0.74, 1.06 (6H, 2d, $J = 6.9$, $CH(CH_3)_2$); 2.28 (1H, dsp, $J = 3.5$, 6.9, $CH(CH_3)_2$); 2.70 (1H, br, OH); 3.75, 3.78 (6H, 2s, 3- and 6-OCH_3); 4.02 (1H, t, $J = 3.5$, 5-H); 4.15 (1H, t, $J = 3.5$, 2-H); 4.64 (1H, br, C*H*–OH); 6.25 (1H, d, $J = 3.3$, 3-H furan); 6.32 (1H, dd, $J = 3.5$, 15.9, furan–CH=C*H*); 6.38 (1H, dd, $J = 1.9$, 3.3, 4-H furan); 6.53 (1H, dd, $J = 1.0$, 15.9, furan–C*H*=CH); 7.36 (1H, d, $J = 1.9$, 5-H furan). ^{13}C NMR: δ 16.81, 18.96 ($CH(CH_3)_2$); 32.03 ($CH(CH_3)_2$); 52.71 (3- and 6-OCH_3); 60.13, 61.09 (2-C and 5-C); 73.03 (CHOH); 107.98, 111.20, 119.64, 127.91, 141.88, 152.25 (C–furan and CH=CH); 161.51, 165.99 (3-C and 6-C). MS-EI (*m*/*z*): 306 (M^+), 245, 184, 141, 123, 67. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.75; H, 7.19; N, 9.15. Found: C, 62.97; H 7.37; N, 9.00. IR (Nujol): 1697 ($\nu_{C=N}$, C=N), 3407 (ν_{OH}).

3.4. (1′*S*,2*S*,5*R*)-(*E*)-3-Furan-2-yl-1-(5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-prop-2-en-1-ol 4a

Oil (6%); $[\alpha]_D^{20} = +58.2$ (*c* 0.74, Et_2O). ^1H NMR: δ 0.74, 1.05 (6H, 2d, $J = 6.8$, $CH(CH_3)_2$); 2.27 (1H, dsp, $J = 3.4$, 6.8, $CH(CH_3)_2$); 3.30 (1H, br, OH); 3.74, 3.75 (6H, 2s, 3- and 6-OCH_3); 3.99 (1H, t, $J = 3.4$, 5-H); 4.32 (1H, t, $J = 4.11$, 2-H); 4.73 (1H, br, C*H*–OH); 5.93 (1H, dd, $J = 5.8$, 15.8, furan–CH=C*H*); 6.21 (1H, d, $J = 3.3$, 3-H furan); 6.36 (1H, dd, $J = 1.9$, 3.3, 4-H furan); 6.45 (1H, dd, $J = 1.1$, 15.8, furan–C*H*=CH); 7.33 (1H, d, $J = 1.9$, 5-H furan). ^{13}C NMR: δ 16.68, 18.91 ($CH(CH_3)_2$); 32.00 ($CH(CH_3)_2$); 52.44 and 52.70 (3- and 6-OCH_3); 59.58, 61.14 (2-C and 5-C); 71.82 (CHOH); 107.88, 111.14, 120.10, 126.41, 147.77, 152.52 (C–furan and CH=CH); 161.95, 165.30 (3-C and 6-C). MS-EI (*m*/*z*): 306 (M^+), 288, 245, 184, 141, 123, 67. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.75; H, 7.19; N, 9.15. Found: C, 62.57; H 7.08; N, 9.02. IR (Nujol): 1696 ($\nu_{C=N}$, C=N), 3445 (ν_{OH}).

3.5. (1′*S*,2*R*,5*S*)-(*E*)-3-Furan-2-yl-1-(5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-prop-2-en-1-ol 5a

This compound has the same analytical and spectroscopic data as **3a**. $[\alpha]_D^{20} = +68.9$ (*c* 0.83, Et_2O).

3.6. (1′*R*,2*R*,5*S*)-(*E*)-3-Furan-2-yl-1-(5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-prop-2-en-1-ol 6a

This compound has the same analytical and spectroscopic data as **4a**. $[\alpha]_D^{20} = -49.9$ (*c* 0.57, Et_2O).

3.7. (1′*R*,2*S*,5*R*)-(*E*)-1-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-3-thiazol-2-yl-prop-2-en-1-ol 3b

Colourless solid (43%); mp 119–120 °C (*i*-PrO_2); $[\alpha]_D^{20} = -99.1$ (*c* 0.89, Et_2O). ^1H NMR: δ 0.76, 1.07 (6H, 2d, $J = 6.9$, $CH(CH_3)_2$); 2.26 (1H, dsp, $J = 3.6$, 6.9, $CH(CH_3)_2$); 2.70 (1H, br, OH); 3.75, 3.79 (6H, 2s, 3- and 6-OCH_3); 4.05 (1H, t, $J = 3.6$, 5-H); 4.18 (1H, t, $J = 3.5$, 2-H); 4.71 (1H, br, C*H*–OH); 6.77 (1H, dd, $J = 5.3$, 15.9, thiazole–CH=C*H*); 6.97 (1H, d, $J = 15.9$, thiazole–C*H*=CH); 7.25 (1H, d, $J = 3.3$, 4-H thiazole); 7.78 (1H, d, $J = 3.3$, 5-H thiazole). ^{13}C NMR: δ 16.8, 18.95 ($CH(CH_3)_2$); 32.05 ($CH(CH_3)_2$); 52.72 (3- and 6-OCH_3); 59.82, 61.10 (2-C and 5-C); 72.43 (CHOH); 118.15, 124.16, 136.24, 143.22, 161.17 (C–thiazole and CH=CH); 166.18, 166.52 (3-C and 6-C). MS-EI (*m*/*z*): 323 (M^+), 184, 141. Anal. Calcd for $C_{15}H_{21}N_3O_3S$: C, 55.73; H, 6.50; N, 13.00. Found: C, 55.67; H 6.27; N, 12.87. IR (Nujol): 1697 ($\nu_{C=N}$, C=N), 3321 (ν_{OH}).

3.8. (1′*S*,2*S*,5*R*)-(*E*)-1-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-3-thiazol-2-yl-prop-2-en-1-ol 4b

Colourless solid (12%); mp 100–102 °C (*n*-hexane); $[\alpha]_D^{20} = +82.9$ (*c* 0.57, Et_2O). ^1H NMR: δ 0.75, 1.06 (6H, 2d, $J = 6.8$, $CH(CH_3)_2$); 2.27 (1H, dsp, $J = 3.5$, 6.8, $CH(CH_3)_2$); 3.40 (1H, br, OH); 3.74, 3.77 (6H, 2s, 3- and 6-OCH_3); 3.99 (1H, t, $J = 3.5$, 5-H); 4.33 (1H, t, $J = 4.06$, 2-H); 4.79 (1H, br, C*H*–OH); 6.39 (1H, dd, $J = 5.3$, 15.8, thiazole–CH=C*H*); 6.89 (1H, dd, $J = 1.29$, 15.8, thiazole–C*H*=CH); 7.24 (1H, d, $J = 3.2$, 4-H thiazole); 7.76 (1H, d, $J = 3.2$, 5-H thiazole). ^{13}C NMR: δ 16.78, 18.89 ($CH(CH_3)_2$); 32.08 ($CH(CH_3)_2$); 52.70 and 52.76 (3- and 6-OCH_3); 59.33, 61.22 (2-C and 5-C); 71.50 (CHOH); 118.15, 124.87, 134.60, 143.25, 160.66 (C–thiazole and CH=CH); 165.54, 166.33 (3-C and 6-C). MS-EI (*m*/*z*): 323 (M^+), 184, 141. Anal. Calcd for $C_{15}H_{21}N_3O_3S$: C, 55.73; H, 6.50; N, 13.00. Found: C, 55.60; H 6.21; N, 12.83. IR (Nujol): 1695 ($\nu_{C=N}$, C=N), 3427 (ν_{OH}).

3.9. (1′*R*,2*S*,5*R*)-(*E*)-1-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-3-thiophen-2-yl-prop-2-en-1-ol 3c

Oil (25%); $[\alpha]_D^{20} = -28.4$ (*c* 1.2, Et_2O). ^1H NMR: δ 0.72, 1.04 (6H, 2d, $J = 6.8$, $CH(CH_3)_2$); 2.28 (1H, dsp, $J = 3.5$, 6.8, $CH(CH_3)_2$); 2.60 (1H, br, OH); 3.74, 3.76 (6H, 2s, 3- and 6-OCH_3); 4.02 (1H, t, $J = 3.5$, 5-H); 4.14 (1H, t, $J = 3.5$, 2-H); 4.62 (1H, br, C*H*–OH); 6.22 (1H, dd, $J = 6.2$, 15.8, thiophene–CH=C*H*); 6.79 (1H, d, $J = 15.8$, thiophene–C*H*=CH); 6.95 (2H, m, 3-H and 4-H thiophene); 7.15 (1H, m, 5-H thiophene). ^{13}C NMR: δ 16.79, 18.98 ($CH(CH_3)_2$); 31.98 ($CH(CH_3)_2$); 52.66 (3- and 6-OCH_3); 60.18, 61.05 (2-C and 5-C); 73.14 (CHOH); 124.20, 124.49, 125.68, 127.29, 128.97, 142.03 (C–thiophene and CH=CH); 161.41, 166.02 (3-C and 6-C). MS-EI (*m*/*z*): 322 (M^+), 305, 263. Anal. Calcd for $C_{16}H_{22}N_2O_3S$: C, 59.63; H, 6.83; N, 8.70. Found: C, 59.57; H 6.75; N, 8.58. IR (Nujol): 1696 ($\nu_{C=N}$, C=N), 3334 (ν_{OH}).

3.10. (1′*R*,2*S*,5*R*)-(*E*)-1-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-3-(5-*p*-tolyl-isoxazol-3-yl)-prop-2-en-1-ol 3d

Colourless solid (9.8%); mp 148–9 °C (*n*-hexane); $[\alpha]_D^{20} = -82.4$ (*c* 0.66, Et_2O). ^1H NMR: δ 0.73, 1.05 (6H, 2d, $J = 6.8$, $CH(CH_3)_2$); 2.28 (1H, dsp, $J = 3.6$, 6.8, $CH(CH_3)_2$); 2.40 (3H, s, CH_3 tolyl); 2.65 (1H, br, OH); 3.74, 3.76 (6H, 2s, 3- and 6-OCH_3); 4.02 (1H, t, $J = 3.6$, 5-H); 4.15 (1H, t, $J = 3.5$, 2-H); 4.70 (1H, br, C*H*–OH); 6.55 (1H, dd, $J = 5.4$, 16.1, isoxazole–CH=C*H*); 6.60 (1H, s, 4-H isoxazole); 6.78 (1H, d, $J = 16.1$, isoxazole–C*H*=CH); 7.26 (2H, d, $J = 8.2$, tolyl); 7.68 (2H, d, $J = 8.2$, tolyl). ^{13}C NMR: δ 16.78, 18.93 ($CH(CH_3)_2$); 21.36 (CH_3 tolyl); 32.03 ($CH(CH_3)_2$); 52.68 (3- and 6-OCH_3); 59.82, 61.11 (2-C and 5-C); 72.59 (CHOH); 96.10, 119.13, 124.69, 125.68, 129.56, 137.44, 140.34, 161.18, 161.53 (C–tolyl, C–isoxazole and CH=CH); 166.24, 169.82 (3-C and 6-C). MS-EI (*m*/*z*): 397 (M^+), 320. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.50; H, 6.80; N, 10.58. Found: C, 66.43; H 6.67; N, 10.41. IR (Nujol): 1692 ($\nu_{C=N}$, C=N), 3418 (ν_{OH}).

3.11. (1′*S*,2*S*,5*R*)-(*E*)-1-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-3-(5-*p*-tolyl-isoxazol-3-yl)-prop-2-en-1-ol 4d

Oil (5.2%); $[\alpha]_D^{20} = +63.5$ (*c* 0.20, Et_2O). ^1H NMR: δ 0.72, 1.05 (6H, 2d, $J = 6.9$, $CH(CH_3)_2$); 2.24 (1H, dsp, $J = 3.5$, 6.9, $CH(CH_3)_2$); 2.40 (3H, s, CH_3 tolyl); 2.45 (1H, br, OH); 3.72, 3.74 (6H, 2s, 3- and 6-OCH_3); 3.95 (1H, t, $J = 3.5$, 5-H); 4.30 (1H, t, $J = 4.6$, 2-H); 4.80 (1H, br, C*H*–OH); 6.18 (1H, dd, $J = 5.2$, 16.1, isoxazole–CH=C*H*); 6.48 (1H, s, 4-H isoxazole); 6.73 (1H, d, $J = 16.1$, isoxazole–C*H*=CH); 7.26 (2H, d, $J = 8.1$, tolyl); 7.68 (2H, d, $J = 8.1$, tolyl). ^{13}C NMR: δ 16.73, 18.92 ($CH(CH_3)_2$); 21.42 (CH_3 tolyl); 32.22 ($CH(CH_3)_2$); 52.63 and 52.83 (3- and 6-OCH_3); 59.25, 61.31 (2-C and 5-C); 71.48 (CHOH); 96.06, 119.95, 124.70, 125.72, 129.60, 135.81, 140.41, 160.83, 161.44 (C–tolyl, C–isoxazole and CH=CH); 165.52, 169.89 (3-C and 6-C). MS-EI (*m*/*z*): 397 (M^+), 320. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.50; H, 6.80; N, 10.58. Found: C, 66.38; H 6.62; N, 10.39. IR (Nujol): 1695 ($\nu_{C=N}$, C=N), 3408 (ν_{OH}).

3.12. (*E*)-1-(5-Isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazin-2-yl)-3-pyridin-2-yl-prop-2-en-1-ol 3e and 4e

Oil (10%). It was not possible to separate the mixture of adducts by means of column chromatography. Only the ^1H NMR of the mixture was recorded. ^1H NMR (major diastereoisomer **3e**): δ 0.72, 1.04 (6H, 2d, $J = 6.9$, $CH(CH_3)_2$); 1.80 (1H, br, OH); 2.28 (1H, dsp, $J = 3.5$, 6.9, $CH(CH_3)_2$); 3.72, 3.78 (6H, 2s, 3- and 6-OCH_3); 4.02 (1H, t, $J = 3.5$, 5-H); 4.15 (1H, t, $J = 3.5$, 2-H); 4.70 (1H, br, C*H*–OH); 6.8–8.5 (6H, m, H–pyridine and pyridine–CH=CH). ^1H NMR (minor diastereoisomer **4e**): δ 0.70, 1.02 (6H, 2d, $J = 6.9$, $CH(CH_3)_2$); 2.28 (1H, dsp, $J = 3.5$, 6.9, $CH(CH_3)_2$); 2.70 (1H, br, OH); 3.68, 3.76 (6H, 2s, 3- and 6-OCH_3); 3.93 (1H, t, $J = 3.5$, 5-H); 4.32 (1H, t, $J = 4.6$, 2-H); 4.79 (1H, br, C*H*–OH); 6.45 (1H, dd, $J = 5.5$, 15.7 pyridine–CH=C*H*); 6.70 (1H, dd, $J = 1.31$, 15.7 pyridine–C*H*=CH); 7.1–8.6 (4H, m, H–pyridine).

3.13. General procedure for the hydrolysis of adducts 3a–c and 4b

Adducts **3a**–**c** and **4b** (2.0 mmol) were dissolved in acetonitrile (20 mL) and the solution was cooled to $T = 0$–5 °C. A 0.2 M solution of HCl (20 mL, 4.0 mmol) was added and the mixture was stirred for 24 h at the same temperature. The mixture was treated with 10% ammonia until pH = 8–10 and the acetonitrile was evaporated off at reduced pressure. The product was extracted with dichloromethane (2 × 20 mL). The organic phase was dried with Na_2SO_4 and the solvent removed in vacuo. The residue was purified by flash chromatography (SiO_2, ethyl acetate–methanol=98:2).

3.14. (2*S*,3*R*)-(*E*)-2-Amino-5-furan-2-yl-3-hydroxy-pent-4-enoic acid methyl ester 5a

Oil (83%); $[\alpha]_D^{20} = +27.0$ (*c* 0.45, CH_3COCH_3). ^1H NMR (CD_3COCD_3): δ 3.60 (1H, d, $J = 4.2$, 2-H); 3.75 (3H, s, $COOCH_3$); 4.55 (1H, t, $J = 4.7$, 3-H); 6.20 (1H, dd, $J = 5.7$, 15.8, 4-H); 6.30 (1H, d, $J = 3.2$, 3-H furan); 6.42 (1H, dd, $J = 1.8$, 3.2, 4-H furan); 6.55 (1H, dd, $J = 1.1$, 15.8, 5-H); 7.37 (1H, d, $J = 1.8$, 5-H furan).

3.15. (2*S*,3*R*)-(*E*)-2-Amino-3-hydroxy-5-thiazol-2-yl-pent-4-enoic acid methyl ester 5b

Oil (45%); $[\alpha]_D^{20} = +14.5$ (*c* 0.54, CH_3COCH_3). ^1H NMR (CD_3COCD_3): δ 3.76 (3H, s, $COOCH_3$); 3.90 (1H, d, $J = 7.7$, 2-H); 4.50 (1H, t, $J = 4.7$, 3-H); 6.74 (1H, dd, $J = 5.9$, 15.8, 4-H); 6.90 (1H, d, $J = 15.8$, 5-H); 7.55 (1H, d, $J = 3.3$, 4-H thiazole); 7.80 (1H, d, $J = 3.3$, 5-H thiazole). ^{13}C NMR (CD_3COCD_3): δ 52.26 (2-C); 65.94 (OCH_3); 80.30 (3-C); 119.45, 124.57 (CH=CH); 135.51, 143.93 (4-C and 5-C thiazole); 161.54, 162.08 (2-C thiazole

and C=O). MS-EI (*m*/*z*): 228 (M^+), 211, 140. IR (Nujol): 1680 ($\nu_{C=O}$, C=O), 3375 (ν_{OH}).

3.16. (2*S*,3*S*)-(*E*)-2-Amino-3-hydroxy-5-thiazol-2-yl-pent-4-enoic acid methyl ester 6b

Oil (44%); $[\alpha]_D^{20} = +14.0$ (*c* 0.5, CH_3COCH_3). ^1H NMR (CD_3COCD_3): δ 3.70 (3H, s, $COOCH_3$); 4.38 (1H, d, $J = 8.2$, 2-H); 4.90 (1H, dt, $J = 1.2$, 8.2, 3-H); 6.40 (1H, dd, $J = 6.5$, 15.8, 4-H); 6.85 (1H, d, $J = 15.8$, 5-H); 7.52 (1H, d, $J = 3.2$, 4-H thiazole); 7.80 (1H, d, $J = 3.2$, 5-H thiazole). ^{13}C NMR (CD_3COCD_3): δ 52.41 (2-C); 64.92 (OCH_3); 77.76 (3-C); 119.46, 125.61 (CH=CH); 133.76, 144.36 (4-C and 5-C thiazole); 161.87, 162.34 (2-C thiazole and C=O). MS-EI (*m*/*z*): 228 (M^+), 211, 140. IR (Nujol): 1679 ($\nu_{C=O}$, C=O), 3375 (ν_{OH}).

3.17. (2*S*,3*R*)-(*E*)-2-Amino-3-hydroxy-5-thiophen-2-yl-pent-4-enoic acid methyl ester 5c

Oil (35%); ^1H NMR (CD_3COCD_3): δ 3.65 (1H, d, $J = 4.5$, 2-H); 3.78 (3H, s, $COOCH_3$); 4.50 (1H, t, $J = 4.8$, 3-H); 6.10 (1H, dd, $J = 6.0$, 15.7, 4-H); 6.83 (1H, d, $J = 15.7$, 5-H); 7.0 (2H, m, 3-H and 4-H thiophene); 7.20 (1H, d, $J = 4.7$, 5-H thiophene).

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