Tetrahedron 70 (2014) 2054–2058

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric synthesis of *syn* and *anti* methyl 2,3-diamino-3-phenylpropanoate derivatives from *N*-substituted imines and *Schöllkopf*'s bislactim ether

Giuseppe Cremonesi [†], Piero Dalla Croce, Maddalena Gallanti [‡], Concetta La Rosa [*]

Università degli Studi di Milano, DISFARM, Sezione di Chimica Generale e Organica "A. Marchesini", V. Venezian 21, I-20133 Milano, Italy

ARTICLE INFO

Article history:
Received 6 November 2013
Received in revised form 7 January 2014
Accepted 20 January 2014
Available online 5 February 2014

Keywords:
2,3-Diamino propanoates
α,β-Diamino acids
Imines
Schöllkopf bislactim ether

ABSTRACT

The reaction between differently *N*-substituted benzaldimines and (2*R*)-*Schöllkopf*'s bislactim ether was studied: the azaenolate addition to imines followed by hydrolysis of the resulting adducts gave *syn*-(2*S*,3*R*) and *anti*-(2*S*,3*S*)-methyl 2,3-diamino-3-phenylpropanoate derivatives in good yields. The configurations of the newly formed stereocenters of α,β-diamino acids were assigned on the basis of the ^{1}H NMR analysis and by comparison with known products. The diastereoisomeric ratios were explained taking into account the effect of the substituent present on the imine nitrogen on the transition state stability. This method represents a new approach for stereoselective synthesis of α,β-diamino acids.

1. Introduction

Non-proteinogenic, optically active 2,3-diamino acids are key structural units of numerous natural products, and they present important biological properties and can be versatile building blocks in organic synthesis. For example, (*S*)-2,3-diaminopropanoic acid is present in several natural antibiotic cyclopeptides,[1] and (2*S*,3*R*)-2,3-diamino-3-phenylpropanoic acid has been utilized as an analogue of the Taxol side chain improving the water solubility of this antitumour compound.[2] 2,3-Diamino acids have also been incorporated into peptides, which are used to modulate secondary and tertiary structural conformations.[3] For these reasons they have received a growing interest through the years.[4] Accordingly, the development of efficient and general methods in their preparation has received considerable attention, especially as regards the synthesis of enantiopure compounds.[5] Among the various methods of synthesis one of the most useful was the nucleophilic addition of chiral glycinate derivatives to imines.[6] *Schöllkopf*'s bislactim ether, (i.e., (2*R*)- or (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine),[7] is a particularly attractive chiral glycine equivalent because it has proved to be highly diastereoselective in aldol-type reactions and is commercially available in both (*R*) and (*S*)-forms. For many years our research group has studied the stereoselective synthesis of new α-amino acids by means of the reaction between the *Schöllkopf*'s bislactim ether and various electrophiles, such as alkyl halides,[8] heterocyclic-carbaldehydes,[9] or ketones.[10] In these two latter cases, β-hydroxy-α-amino acids were obtained, with an asymmetric, enantiomerically pure quaternary carbon in the β position when ketones were used.[10]

So we were interested in the possibility of obtaining enantiopure α,β-diamino acids derivatives by reacting *Schöllkopf*'s bislactim ether with the electrophilic carbon of imines. An analysis of the literature revealed that this reagent has been used with different types of electrophiles, especially aldehydes, but it had never been added to imines. Only in a publication of 1986, *Schöllkopf* reported that the anion of the (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine initially reacted with the azomethine double bond of 2-(benzylideneamino)ethylbromide affording, after an intramolecular cyclization, an aziridine compound.[11] The synthesis of 2,3-diamino acids by 'the bislactim ether method' was also accomplished in 1991 by Mittendorf reacting the lithium azaenolate of (2*S*)-5-alkyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine with dibromomethane followed by nucleophilic substitution of bromide with sodium azide and final hydrolysis.[12]

Our interest in the stereoselective synthesis of enantiopure α-amino acids, led us to report a novel and efficient method to obtain enantiopure α,β-diamino acids by means of the reaction between

* Corresponding author. Tel.: +39 02 503 14473; fax: +39 02 503 14476; e-mail address: concetta.larosa@unimi.it (C. La Rosa).
† Present address: Sifavitor S.r.l., Via Livelli 1, I-26852 Mairano di Casaletto Lodigiano (LO), Italy.
‡ Present address: Abcam Biochemicals, Unit 3 Victoria Rd, Bristol BS11 9DB, United Kingdom.

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.01.040

the lithium enolate of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **1** and *N*-substituted imines. In order to obtain differently *N*-protected diamino acids and also to evaluate the steric and electronic effects of the nitrogen substituent on the diastereoselectivity of the addition, we decided to conduct our investigation using variously *N*-substituted benzaldimines (*E*)-**2a**–**f**, bearing both electron withdrawing and electron donating groups. This should enable us to obtain, after acid hydrolysis, differently N_β-protected α,β-diamino acids (Fig. 1).

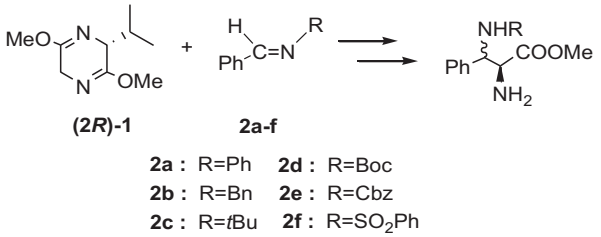


Fig. 1. Synthetic pathway for N_β-protected α,β-diamino acids.

2. Results and discussion

Various experimental conditions and counter-ions were examined to optimize yields and evaluate the diastereoselectivity of the reaction. In these experiments imine **2a** was taken as reference. A THF solution of imine was added to the anion of the bislactim ether (2*R*)-**1** generated by the addition of *n*BuLi in THF at *T*=−78 °C. The reaction mixture was then maintained at variable temperatures and times (representative conditions are listed in Table 1, entries 1–4). In all cases the reaction gave mixtures of two diastereoisomeric adducts **3a**/**4a** whose ratio was determined from integration of the H-2 (4.35/4.56 δ) or H-5 (3.59/3.10 δ) signals in the ^{1}H NMR spectra of the crude reaction mixtures (Scheme 1).

The observed diastereoselectivity was generally poor, similarly to that found in the case of ketones.[10] Under experimental conditions providing the best yield, the two adducts were formed in almost the same amount (Table 1, entry 1). It was observed that when conducted at higher temperatures (*T*=−20 °C or +4 °C rather than −78 °C) the ratio between the two diastereoisomers was inverted and the yield decreased (Table 1, entries 2–4). This was not due to the reversibility of the addition as the two adducts were found to be stable under the reaction conditions. In fact, after having separated them, they were treated with *n*BuLi at temperatures between −78 and +4 °C for 24 h but they were recovered unaffected. Generally, the observed diastereoselectivity could also be influenced by the nature of the counter-ion. To assess this, the lithium azaenolate was treated with $ZnCl_2$, $TiCl(O^iPr)_3$[13] or $SnCl_4$ to give the corresponding transmetalated azaenolates before the addition of the imine (Table 1, entries 5–7): only in the last case did the reaction afforded a mixture of **3a**/**4a** at almost the same ratio but in a lower yield.

The best experimental conditions reported in Table 1 entry 1, were then applied to the reaction of (2*R*)-**1** with imines **2b**–**f**. In the case of imines **2b**, **c** the reaction led to unreacted reagents and traces of products (Table 1, entries 8, 9). In particular, the treatment of imine **2b** with the anion of (2*R*)-**1**, produced an intense pink colour due to the deprotonation of the benzylic carbon[14] and extensive delocalization of the corresponding anion prevented the addition.[15] In the case of imine **1c**, failure to obtain the products has been attributed to the steric hindrance generated by the bulky *tert*-butyl group, as already observed.[16] On the contrary, the reaction of the imines **2d**, **e** afforded mixtures of the two diastereoisomeric adducts **3d**/**4d** and **3e**/**4e** in good yields and, with imine **2e**, also with a better diastereoselectivity (Table 1, entries 10, 11). Only with imine **2f** the formation of all the four possible diastereoisomers was observed but with a preference for adduct **4f** (Table 1, entry 12).

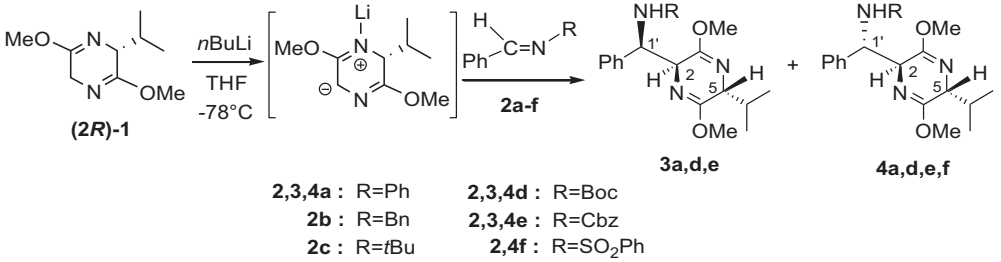
Diastereoisomers **3a**, **d**, **e** and **4a**, **d**–**f** were easily isolated by means of flash chromatography on silica gel, and their structures were confirmed on the basis of analytical and spectroscopic data (HSQC, COSY and NOESY experiments). The (2*S*)-configuration was established using the $^5J_{H2/H5}$ coupling constant value of approximately 3.5 Hz, which corresponds to a *trans* relationship between the H-2 and H-5 protons of the pyrazine ring.[17] The (*R*)- and (*S*)-configuration were assigned to the C-1′ of the adducts **3** and 4, respectively, by means of comparison with each other and using the data reported in the literature for the corresponding α,β-diamino acids obtained after hydrolysis (see below).

The reactions of (2*R*)-**1** with aldehydes[9,7b] or ketones[10,18] always afforded mixtures of the two (2*S*)-epimers arising from the attack of the azaenolate–pyrazine from the less hindered side opposite the isopropyl group, according to the *Zimmerman–Traxler* six-membered ring model,[19] and our present results confirm the 2,5-*trans*-relationship in the adducts **3**/**4**.

Table 1
Total yields and ratios of compounds **3**/**4**

Entry	Imine	R	Counter-ion	*T* (°C)	*t* (h)	Total yield (%)	**3** (%)	**4** (%)
1	**2a**	Ph	Li^+	−78	8	72	53	47
2	**2a**	Ph	Li^+	−20	6	56	45	55
3	**2a**	Ph	Li^+	+4	4	51	33	67
4	**2a**	Ph	Li^+	+4	16	55	42	58
5	**2a**	Ph	Zn^{2+}	−20	6	—	—	—
6	**2a**	Ph	Ti^{4+}	−20	6	—	—	—
7	**2a**	Ph	Sn^{4+}	−20	6	34	40	60
8	**2b**	Bn	Li^+	−78	8	Trace	—	—
9	**2c**	^{t}Bu	Li^+	−78	8	Trace	—	—
10	**2d**	Boc	Li^+	−78	8	65	41	59
11	**2e**	Cbz	Li^+[a]	−78	8	75	13	87
12	**2f**	SO_2Ph	Li^+	−78	8	70	38[b]	62

[a] The reported results were obtained using 2 equiv of LDA as base.
[b] Total ratio of three inseparable diastereoisomers.



Scheme 1.

Transition state models **TS1** and **TS2** can be proposed to rationalize the observed diastereoisomeric ratio for the reaction of (2*R*)-**1** with imine (*E*)-**2a** (Fig. 2). As in the case of aldehydes,[3] in **TS1** the anion of (2*R*)-**1** approaches the *Si* face of *E*-imine leading to (*R*) configuration of the benzylic carbon, and this approach should be the preferred one because the *C*-phenyl group is far from the methoxy group. Owing to the *E* geometry of the imine, the coordination of the metal with the nitrogen-imine lone pair is prevented, but a stabilization of the **TS1** could arise from an interaction with the π system of the *N*-phenyl group. Actually, when R=Ph, both transition states seem to have approximately the same stability leading to a mixture about 50:50 of the two diastereoisomers. On the contrary, when R=Boc, Cbz or SO_2Ph approach like **TS2** becomes the predominant one leading to adducts **4**. In this case the coordination of the imine nitrogen lone pair with the metal allows a more stable six-membered ring transition state.[12]

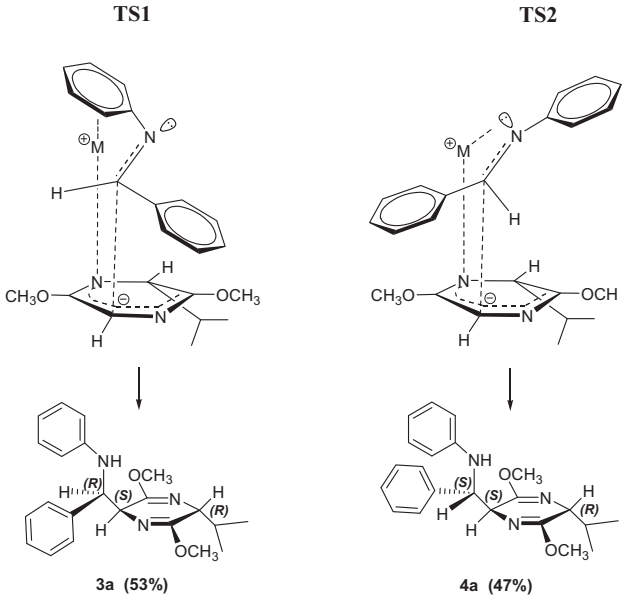
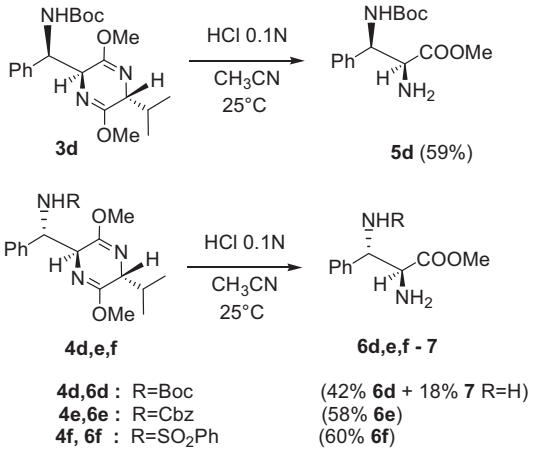


Fig. 2. Proposed transition states.

Finally, the adducts **3a**, **4a**, **3d**, **4d**, **4e** and **4f** were hydrolysed under controlled acidic conditions: they were treated with 3 equiv of 0.1 N HCl in acetonitrile at room temperature for 54–72 h. In the case of the *N*-phenyl derivatives **3a**/**4a** the removal of the valine chiral auxiliary lead to a complete degradation of the corresponding α,β-diamino acids,[20a] as already noted by other authors.[20b] The hydrolysis of the adduct **3d** led to the α,β-diamino acid **5d** in good yield while with **4d** the reaction afforded a mixture, separable by chromatography, of the N_β-Boc-α,β-diamino acid **6d** together with the deprotected methyl 2,3-diamino-3-phenylpropanoate **7** with a total yield of 60%. With similar yields the α,β-diamino acids **6e**, **f** were obtained from the corresponding compounds **4e**, **f** (Scheme 2).

By comparison with the data reported in the literature for methyl (2*R*,3*S*)-2-amino-3-[(*tert*-butoxycarbonyl)amino]-3-phenyl propanoate[21] and for methyl (2*S*,3*S*)-2-amino-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate[21] it was possible to assign the (3*R*) configuration to **5d** and the (3*S*) configuration to the C-3 of compounds **6d** and **7**. Moreover, the latter shows a great analogy with its ethyl ester.[22] Similarly, the same (3*S*) configuration has been attributed to the N_β-phenylsulfonyl-α,β-diamino acid **6f** showing a ^{1}H NMR spectrum in accordance with that of the enantiomer of the N_β-tosyl derivative.[23] Finally, the same (3*S*) configuration was assigned to compound **6e** according to the analogy between the NMR spectra of adducts **3e**/**4e** and **3d**/**4d**. In fact all NMR spectra of products **3a**–**f** are similar to each other likewise for the all NMR spectra of compounds **4a**–**f** (see Experimental).



Scheme 2.

3. Conclusions

A new methodology has been introduced for the asymmetric synthesis of N_β-protected α,β-diamino acids, key structural units of natural products. Our procedure involves addition of the anion of the *Schöllkopf*'s reagent to imines followed by mild acidic hydrolysis. With electron-withdrawing imine-substituted the reaction proceeds with good diastereoselectivity mainly providing the *anti* isomers of enantiomerically pure N_β-protected 2,3-diamino esters. The observed ratios seem to be influenced by the stereoelectronic effects of the substituents of the imine nitrogen atom.

4. Experimental section

4.1. General

Melting points were determined on a *Büchi* B-540 apparatus. Elemental analyses were performed by the Microanalytical Laboratory of the Department. ^{1}H and ^{13}C NMR spectra were recorded using a *Varian-Gemini 200 MHz* spectrometer. Chemical shifts (δ) are given in parts per million in relation to TMS; the solvent was $CDCl_3$ unless otherwise specified. All of the coupling constants (*J*) are in Hertz. The MS spectra were recorded with a *Thermo-Finnigan LCQ* advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions. The optical rotation values were measured at 25 °C. The bislactim ether (2*R*)-**1** and imines **2a**, **b**, **f** were commercially available, imines **2c**,[24] **2d**,[25] and **2e**[26] were prepared following the reported methods.

4.2. General procedure for the addition of bislactim ether (2*R*)-1 azaenolate to imines

Butyl lithium (1.6 N solution in hexane, 1.05 equiv) was added to a solution of (2*R*)-**1** (1 equiv) in anhydrous THF (5 mL) cooled to −78 °C, and the mixture was stirred for 45 min. Imine **2a**–**f** (1 equiv) in THF (4 mL) was added, and the mixture was stirred at −78 °C for 8 h. The reaction mixture was allowed to warm to −10 °C, after which a pH=7 phosphate buffer solution (10 mL) was

added, and the mixture was extracted with ethyl acetate (3×10 mL). The organic phase was separated and dried with Na_2SO_4, and the solvent was evaporated in vacuo. Compounds **3**, **4** were purified by means of flash chromatography (SiO_2, CH_2Cl_2/hexane=40/60 for **3a** (R_f 0.2) and **4a** (R_f 0.4); CH_2Cl_2/ethyl acetate=95/5 for **3d** (R_f 0.4) and **4d** (R_f 0.5), **3e** (R_f 0.5) and **4e** (R_f 0.6); CH_2Cl_2/ethyl acetate=98/2 for **4f** (R_f 0.6)).

*4.2.1. N-{(R)-[(2S,5R)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methyl}-N-phenylamine (**3a**).* Colourless solid (138.7 mg, 38%); mp 89–91 °C (hexane). $[\alpha]_D^{20}$ +92.3 (*c* 1.9, $CHCl_3$). ^{1}H NMR: δ 0.66, 0.98 (2d, *J*=6.8, 6H, CH(C*H*$_3$)$_2$); 2.18 (m, 1H, C*H*(CH$_3$)$_2$); 3.59 (t, *J*=3.5, 1H, H-5); 3.71 (s, 3H, OCH$_3$); 3.73 (s, 3H, OCH$_3$); 4.35 (t, *J*=3.5, 1H, H-2); 4.55 (broad s, 1H, NH); 5.01 (d, *J*=2.2, 1H, H-1′); 6.54–6.66 (m, 3H, Ph); 7.05–7.35 (m, 7H, Ph). ^{13}C NMR: δ 16.7, 19.0 (CH(*C*H$_3$)$_2$); 31.7 (*C*H(CH$_3$)$_2$); 52.6 (3- and 6-OCH$_3$); 59.1 (C-1′); 60.6, 60.7 (C-2 and C-5); 113.8–129.0 (Ph); 140.4, 146.9 (Ph); 161.3, 165.9 (C-3 and C-6). IR (Nujol): 3453 (ν_{NH}, NH), 1693 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.25; H 7.36; N, 11.33. MS-ESI$^+$ (*m*/*z*): 366 [M+H]$^+$.

*4.2.2. N-{(S)-[(2S,5R)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methyl}-N-phenylamine (**4a**).* Amorphous solid (124.1 mg, 34%). $[\alpha]_D^{20}$ +61.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 0.60, 0.91 (2d, *J*=6.9, 6H, CH(C*H*$_3$)$_2$); 2.11 (m, 1H, C*H*(CH$_3$)$_2$); 3.10 (t, *J*=3.5, 1H, H-5); 3.73 (s, 3H, OCH$_3$); 3.78 (s, 3H, OCH$_3$); 4.56 (t, *J*=3.5, 1H, H-2); 5.04 (d, *J*=3.7, 1H, H-1′); 6.58–6.64 (m, 3H, Ph); 7.06–7.25 (m, 7H, Ph); 7.55 (broad s, 1H, NH). ^{13}C NMR: δ 16.7, 19.4 (CH(*C*H$_3$)$_2$); 31.2 (*C*H(CH$_3$)$_2$); 52.1, 52.5 (3- and 6-OCH$_3$); 58.4 (C-1′); 59.8, 60.0 (C-2 and C-5); 113.5–131.3 (Ph); 138.2, 146.7 (Ph); 160.3, 164.9 (C-3 and C-6). IR (Nujol): 3428 (ν_{NH}, NH), 1696 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.20; H 7.33; N, 11.42. MS-ESI$^+$ (*m*/*z*): 366 [M+H]$^+$.

*4.2.3. tert-Butyl (R)-[(2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methylcarbamate (**3d**).* Amorphous solid (105.0 mg, 27%). $[\alpha]_D^{20}$ +20.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR: δ 0.63, 0.96 (2d, *J*=6.8, 6H, CH(C*H*$_3$)$_2$); 1.41 (s, 9H, C(CH$_3$)$_3$); 2.17 (m, 1H, C*H*(CH$_3$)$_2$); 3.64 (t, *J*=3.3, 1H, H-5); 3.69 (s, 3H, OCH$_3$); 3.75 (s, 3H, OCH$_3$); 4.29 (broad s, 1H, H-2); 5.22–5.35 (broad m, 2H, H-1′, NH); 7.24–7.53 (m, 5H, Ph). ^{13}C NMR: δ 16.9, 19.2 (CH(*C*H$_3$)$_2$); 28.5 (C(*C*H$_3$)$_3$); 31.9 (*C*H(CH$_3$)$_2$); 52.9 (3- and 6-OCH$_3$); 56.4 (C-1′); 60.5, 60.9 (C-2 and C-5); 79.7 (*C*(CH$_3$)$_3$); 127.3–130.0 (Ph); 140.3 (Ph); 155.1 (CO); 161.5, 163.2 (C-3 and C-6). Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.76; H, 8.02; N, 10.79. Found: C, 64.55; H 7.87; N, 10.65. MS-ESI$^+$ (*m*/*z*): 390 [M+H]$^+$.

*4.2.4. tert-Butyl (S)-[(2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methylcarbamate (**4d**).* Amorphous solid (147.8 mg, 38%). $[\alpha]_D^{20}$ +20.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ 0.58, 0.89 (2d, *J*=7.0, 6H, CH(C*H*$_3$)$_2$); 1.45 (s, 9H, C(CH$_3$)$_3$); 2.11 (m, 1H, C*H*(CH$_3$)$_2$); 3.19 (t, *J*=3.3, 1H, H-5); 3.67 (s, 3H, OCH$_3$); 3.76 (s, 3H, OCH$_3$); 4.39 (t, *J*=3.6, 1H, H-2); 5.32 (dd, *J*=3.6, 8.8, 1H, H-1′); 6.00 (broad d, *J*=8.8, 1H, NH); 7.05–7.37 (m, 5H, Ph). ^{13}C NMR: δ 16.6, 19.1 (CH(*C*H$_3$)$_2$); 28.5 (C(*C*H$_3$)$_3$); 31.6 (*C*H(CH$_3$)$_2$); 52.3, 52.8 (3- and 6-OCH$_3$); 55.8 (C-1′); 60.0, 60.4 (C-2 and C-5); 79.7 (*C*(CH$_3$)$_3$); 127.5–127.9 (Ph); 138.4 (Ph); 155.3 (CO); 160.4, 165.3 (C-3 and C-6). Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.76; H, 8.02; N, 10.79. Found: C, 64.61; H 7.92; N, 10.70. MS-ESI$^+$ (*m*/*z*): 390 [M+H]$^+$.

*4.2.5. Benzyl (R)-[(2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methylcarbamate (**3e**).* Amorphous solid (42.3 mg, 10%). ^{1}H NMR: δ 0.63, 0.96 (2d, *J*=6.9, 6H, CH(C*H*$_3$)$_2$); 2.13 (m, 1H, C*H*(CH$_3$)$_2$); 3.61 (t, *J*=3.7, 1H, H-5); 3.68 (s, 3H, OCH$_3$); 3.74 (s, 3H, OCH$_3$); 4.29 (t, *J*=3.3, 1H, H-2); 5.1 (AB system, *J*=12.1, 25.3, 2H, C*H*$_2$); 5.55 (dd, *J*=3.3, 9.5, 1H, H-1′); 5.38 (d, *J*=9.5, 1H, NH); 7.25–7.41 (m, 10H, Ph). MS-ESI$^+$ (*m*/*z*): 424 [M+H]$^+$.

*4.2.6. Benzyl (S)-[(2S,5R)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methylcarbamate (**4e**).* Amorphous solid (275.0 mg, 65%). $[\alpha]_D^{20}$ +19.8 (*c* 0.3, $CHCl_3$). ^{1}H NMR: δ 0.59, 0.91 (2d, *J*=6.7, 6H, CH(C*H*$_3$)$_2$); 2.11 (m, 1H, C*H*(CH$_3$)$_2$); 3.24 (t, *J*=3.3, 1H, H-5); 3.68 (s, 3H, OCH$_3$); 3.74 (s, 3H, OCH$_3$); 4.42 (t, *J*=3.6, 1H, H-2); 5.1 (AB system, *J*=12.1, 25.3, 2H, C*H*$_2$); 5.38 (dd, *J*=3.6, 9.2, 1H, H-1′); 6.31 (broad d, *J*=9.2, 1H, NH); 7.05–7.45 (m, 10H, Ph). ^{13}C NMR: δ 16.7, 19.1 (CH(*C*H$_3$)$_2$); 31.6 (*C*H(CH$_3$)$_2$); 52.3, 52.8 (3- and 6-OCH$_3$); 56.2 (C-1′); 59.8, 60.5 (C-2 and C-5); 67.1 (*C*H$_2$); 127.6–129.9 (Ph); 136.7 (Ph); 138.1 (Ph); 155.8 (CO); 160.2, 165.5 (C-3 and C-6). Anal. Calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 67.89; H 6.85; N, 9.78. MS-ESI$^+$ (*m*/*z*): 424 [M+H]$^+$.

*4.2.7. N-[(R)-[(2S,5R)-5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl](phenyl)methyl]benzenesulfonamide (**4f**).* Colourless solid (184.5 mg, 43%); mp 180–181 °C (ethanol). $[\alpha]_D^{20}$ +79.9 (*c* 0.4, $CHCl_3$). ^{1}H NMR: δ 0.60, 0.90 (2d, *J*=6.9, 6H, CH(C*H*$_3$)$_2$); 2.10 (m, 1H, C*H*(CH$_3$)$_2$); 3.28 (t, *J*=3.5, 1H, H-5); 3.65 (s, 3H, OCH$_3$); 3.77 (s, 3H, OCH$_3$); 4.36 (t, *J*=3.9, 1H, H-2); 5.12 (dd, *J*=3.9, 9.5, 1H, H-1′); 6.21 (broad d, *J*=9.5, 1H, NH); 6.91–7.44 (m, 8H, Ph); 7.72 (d, *J*=7.6, 2H, Ph). ^{13}C NMR: δ 16.4, 18.8 (CH(*C*H$_3$)$_2$); 31.5 (*C*H(CH$_3$)$_2$); 52.0, 52.8 (3- and 6-OCH$_3$); 58.0 (C-1′); 59.8, 60.4 (C-2 and C-5); 126.8–132.0 (Ph); 135.9 (Ph); 140.9 (Ph); 159.5, 165.5 (C-3 and C-6). Anal. Calcd for $C_{22}H_{27}N_3O_4S$: C, 61.52; H, 6.34; N, 9.78. Found: C, 61.47; H 6.27; N, 9.64. MS-ESI$^+$ (*m*/*z*): 430 [M+H]$^+$.

4.3. General procedure for the hydrolysis of adducts 3, 4

Aqueous HCl 0.1 N (4.5 mL, 3 equiv) was added to a solution of adduct **3**, **4** (0.15 mmol, 1 equiv) in CH_3CN (1.5 mL). The mixture was stirred for 54–72 h at room temperature and then extracted with diethyl ether in order to remove non-basic organic compounds. It was then treated with 25% ammonia solution under stirring until pH=8–10, and extracted with AcOEt (4×5 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed in vacuo. Compounds **6d** and **7** were separated by means of flash chromatography (SiO_2, toluene/ethanol=2/1, developer: ninhydrin). Compounds **5d**, **6e** and **f** were purified by means of column chromatography (SiO_2, toluene/ethanol=2/1 for **5d**, AcOEt/methanol=95/5 for **6e** and AcOEt/methanol=98/2 for **6f**, developer: ninhydrin).

*4.3.1. Methyl (2S,3R)-2-amino-3-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate (**5d**).* Amorphous solid (26.0 mg, 59%). $[\alpha]_D^{20}$ +22.5 (*c* 0.2, $CHCl_3$). Lit.[21] for (2*R*,3*S*) derivate: $[\alpha]_D^{20}$ −23.7 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 1.40 (s, 9H, C(CH$_3$)$_3$); 2.55 (broad s, 2H, NH$_2$); 3.76 (s, 3H, OCH$_3$); 3.92 (d, *J*=2.9, 1H, H-3); 5.23 (m, 1H, H-2); 5.81 (broad d, *J*=8.8, 1H, NH); 7.22–7.35 (m, 5H, Ph). ^{13}C NMR: δ 28.5 (C(*C*H$_3$)$_3$); 52.7 (OCH$_3$); 56.6 (C-3); 58.7 (C-2); 79.9 (*C*(CH$_3$)$_3$); 126.6–139.9 (Ph); 155.3 (CO); 173.0 (CO). IR (Nujol): 3415 (ν_{NH}, NH$_2$), 1734 ($\nu_{C=O}$, C=O), 1692 ($\nu_{C=O}$, C=O). Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.05; H 7.48; N, 9.38. MS-ESI$^+$ (*m*/*z*): 295 [M+H]$^+$.

*4.3.2. Methyl (2S,3S)-2-amino-3-[(tert-butoxycarbonyl)amino]-3-phenylpropanoate (**6d**).* Amorphous solid (18.5 mg, 42%). $[\alpha]_D^{20}$ +24.9 (*c* 0.4, $CHCl_3$). Lit.[21] $[\alpha]_D^{20}$ +26.7 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 1.40 (s, 9H, C(CH$_3$)$_3$); 1.55 (broad s, 2H, NH$_2$); 3.68 (s, 3H, OCH$_3$); 3.85 (d, *J*=4.3, 1H, H-3); 5.11 (broad s, 1H, H-2); 5.86 (broad d, *J*=7.2, 1H, NH); 7.20–7.40 (m, 5H, Ph). ^{13}C NMR: δ 28.6 (C(*C*H$_3$)$_3$); 52.3 (OCH$_3$); 56.4 (C-3); 58.8 (C-2); 80.0 (*C*(CH$_3$)$_3$); 126.9–138.0 (Ph); 155.4 (CO); 173.8 (CO). IR (Nujol): 3376 (ν_{NH}, NH$_2$), 1726 ($\nu_{C=O}$, C=O), 1698

($\nu_{C=O}$, C=O). Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.11; H 7.46; N, 9.44. MS-ESI$^+$ (m/z): 295 $[M+H]^+$.

*4.3.3. Methyl (2S,3S)-2,3-diamino-3-phenylpropanoate (**7**).* Amorphous solid (5.5 mg, 18%). $[\alpha]_D^{20}$ +20.6 (c 0.1, $CHCl_3$). ^{1}H NMR: δ 1.95 (broad s, 4H, NH_2); 3.68 (s, 3H, OCH_3); 3.70 (d, J=5.9, 1H, H-3); 4.24 (d, J=5.9, 1H, H-2); 7.20–7.40 (m, 5H, Ph). ^{13}C NMR: δ 52.1 (OCH_3); 58.9 (C-3); 60.8 (C-2); 126.9–128.7 (Ph); 141.6 (Ph); 174.5 (CO). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.79; H 7.18; N, 14.35. MS-ESI$^+$ (m/z): 195 $[M+H]^+$.

*4.3.4. Methyl (2S,3S)-2-amino-3-{[(benzyloxy)carbonyl]amino}3-phenylpropanoate (**6e**).* Amorphous solid (28.5 mg, 58%). $[\alpha]_D^{20}$ +10.1 (c 1.4, $CHCl_3$). ^{1}H NMR: δ 1.58 (broad s, 2H, NH_2); 3.69 (s, 3H, OCH_3); 3.83 (d, J=4.4, 1H, H-3); 5.08 (AB system, J=12.1, 18.8, 2H, CH_2); 5.21 (broad dd, J=4.4, 8.6 1H, H-2); 6.18 (broad d, J=8.6, 1H, NH); 7.18–7.40 (m, 10H, Ph). ^{13}C NMR: δ 52.6 (OCH_3); 56.8 (C-3); 58.6 (C-2); 67.1 (CH_2); 126.6–128.9 (Ph); 136.7 (Ph); 137.9 (Ph); 155.8 (CO); 173.6 (CO). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.76; H 6.04; N, 8.45. MS-ESI$^+$ (m/z): 329 $[M+H]^+$.

*4.3.5. Methyl (2S,3S)-2-amino-3-phenyl-3-[(phenylsulfonyl)amino] propanoate (**6f**).* Amorphous solid (30.1 mg, 60%). $[\alpha]_D^{20}$ +28.6 (c 0.8, $CHCl_3$). ^{1}H NMR: δ 1.61 (broad s, 2H, NH_2); 3.61 (s, 3H, OCH_3); 3.76 (d, J=4.4, 1H, H-3); 4.90 (broad s, 1H, H-2); 6.20 (broad s, 1H, NH); 6.93–7.41 (m, 8H, Ph); 7.63 (d, J=7.3, 2H, Ph). ^{13}C NMR: δ 52.3 (OCH_3); 58.7 (C-3); 59.0 (C-2); 125.5–132.4 (Ph); 135.8 (Ph); 140.9 (Ph); 173.0 (CO). Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.39; H 5.38; N, 8.30. MS-ESI$^+$ (m/z): 335 $[M+H]^+$.

Acknowledgements

The authors thank Dr. Marta Brambilla for helpful assistance.

References and notes

1. Kleinkauf, H.; von Döhren, H. *Eur. J. Biochem.* **1990**, *192*, 1–15.
2. Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279–10286.
3. (a) Groebke, K.; Renold, P.; Tsang, K. Y.; Allen, T. J.; McClure, K. F.; Kemp, D. S. *Proc. Natl. Acad. Sci.* **1996**, *93*, 4025–4029; (b) Battiste, J. L.; Mao, H.; Rao, N. S.; Tan, R.; Mahandiram, D. R.; Kay, L. E.; Frankel, A. D.; Williamson, J. R. *Science* **1996**, *273*, 1547–1551; (c) Kretsinger, J. K.; Schneider, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 7907–7913.
4. For reviews on α,β-diamino acids, see: (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196; (b) Viso, A.; Fernández de la Pradilla, R.; Tortosa, M.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1–PR42.
5. For a review on synthesis of α,β-diamino acids, see: Wang, J.; Zhang, L.; Jiang, H.; Liu, H. *Curr. Pharm. Des.* **2010**, *16*, 1252–1259.
6. For a recent example see: Zhang, H.; Hu, X.; Wang, X.; Luo, Y.; Xu, P. *J. Org. Chem.* **2008**, *73*, 3634–3637 and references therein.
7. (a) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65–84; (b) Grauert, M.; Schöllkopf, U. *Liebigs Ann. Chem.* **1985**, 1817–1824; (c) Undheim, K. *Amino Acids* **2008**, *34*, 357–402.
8. (a) Dalla Croce, P.; La Rosa, C.; Pizzatti, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2635–2642; (b) Cremonesi, G.; Dalla Croce, P.; La Rosa, C.; Pizzatti, E. *Heterocycles* **2003**, *61*, 563–567.
9. (a) Dalla Croce, P.; Ferraccioli, R.; La Rosa, C.; Pizzatti, E. *Heterocycles* **2000**, *52*, 1337–1344; (b) Cremonesi, G.; Dalla Croce, P.; Fontana, F.; La Rosa, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2637–2641; (c) Cremonesi, G.; Dalla Croce, P.; Fontana, F.; Forni, A.; La Rosa, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1667–1675; (d) Cremonesi, G.; Dalla Croce, P.; Fontana, F.; Fiorelli, C.; La Rosa, C. *Tetrahedron: Asymmetry* **2008**, *19*, 2850–2855; (e) Cremonesi, G.; Dalla Croce, P.; Forni, A.; Gallanti, M.; Gandolfi, R.; La Rosa, C. *Tetrahedron: Asymmetry* **2009**, *20*, 1940–1947.
10. Cremonesi, G.; Dalla Croce, P.; Forni, A.; Gallanti, M.; La Rosa, C. *Tetrahedron* **2011**, *67*, 2925–2933.
11. Schöllkopf, U.; Busse, U.; Lonsky, R.; Hinrichs, R. *Liebigs Ann. Chem.* **1986**, 2150–2163.
12. Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939–941.
13. Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421–1440.
14. (a) O'Donnell, M. J.; Bennet, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520–8525; (b) Malkhasyan, A. T. S.; Asatryan, E. M.; Mirakyan, S. M.; MartiroSyan, G. T.; Beletskava, I. P. *Zh. Org. Khim.* **1981**, *17*, 467–470.
15. The addition was unsuccessful even using 2 equiv of the anion of (2*R*)-1 or using LDA as the base.
16. (a) Cliffe, I. A.; Crossley, R.; Shephed, R. G. *Synthesis* **1985**, 1138–1140; (b) Emling, B. L.; Horvath, R. J.; Saraceno, A. J.; Ellermeyer, E. F.; Haile, L.; Hudac, L. D. *J. Org. Chem.* **1959**, *24*, 657–660.
17. (a) Busch, K.; Groth, U. M.; Kühnle, W.; Schöllkopf, U. *Tetrahedron* **1992**, *48*, 5607–5618; (b) Efskind, J.; Hope, H.; Undheim, K. *Eur. J. Org. Chem.* **2002**, 464–467.
18. (a) Schöllkopf, U.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 977–978; (b) Schöllkopf, U.; Nozulak, J.; Groth, U. *Synthesis* **1982**, 864–866; (c) Schöllkopf, U.; Groth, U.; Gull, M.; Nozulak, J. *Liebigs Ann. Chem.* **1983**, 1133–1151; (d) Neubauer, H.; Baeza, J.; Freer, J.; Schöllkopf, U. *Liebigs Ann. Chem.* **1985**, 1508–1511; (e) Kim, S.; Kim, E.; Ko, H.; Jung, Y. H. *Synthesis* **2003**, 2194–2198.
19. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
20. (a) Despite the mild conditions used, the NMR analysis of the crude reaction mixture showed the absence of the signals due to the phenyl group. (b) Tasheva, D.; Angelova, O.; Dryanska, V. *J. Chem. Res., Synop.* **1998**, 428–429.
21. Lee, S.; Yoon, J.; Chung, S.; Lee, Y. *Tetrahedron* **2001**, *57*, 2139–2145.
22. Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789–2792.
23. Zhou, X.; Lin, Y.; Dai, L. *Tetrahedron: Asymmetry* **1999**, *10*, 855–862.
24. Boudou, C.; Bergès, M.; Sagnes, C.; Sopková-de Oliveira Santos, J.; Perrio, S.; Metznert, P. J. *Org. Chem.* **2007**, *72*, 5403–5406.
25. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
26. Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191–1193.