



Synthesis of cucurbitine derivatives: facile straightforward approach to methyl 3-amino-4-aryl-1-methylpyrrolidine-3-carboxylates

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ABSTRACT

A general three- or four-step synthesis of cis- and trans-substituted cucurbitine (3-aminopyrrolidine-3-carboxylic acid) derivatives from methyl 2-nitroacetate is reported. The first step utilizes a Knoevenagel condensation with five different aromatic imines or their corresponding aldehydes to form (*Z/E*)-mixtures of α -nitro acrylates. The second step gives rise to the pyrrolidine-core structures of the title compounds by a 1,3-dipolar cycloaddition reaction using an azomethine ylide. The last step consists of reduction of the nitro group to yield both diastereoisomers of the corresponding 4-aryl cucurbitine methyl esters.

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1. Introduction

Cucurbitine **1** (Fig. 1), (–)-(*S*)-3-aminopyrrolidine-3-carboxylic acid, is a natural product found in the pumpkin seed and other Cucurbitaceae possessing antiparasitic, and more specifically anthelmintic, activity against *Schistosoma japonicum*.¹ Cucurbitine is also known as a hypohistaminaemic agent as it inhibits the formation of histamine, a well-known mediator of allergies. The hypohistaminaemic activity arises from the ability to block the usual function of histidine decarboxylase, the enzyme responsible for the conversion of histidine to histamine. The administration of cucurbitine contributes to a decreased histamine concentration in the blood serum and tissues. Cucurbitine is also used in cosmetic (notably dermatologic) products in order to soothe greatly irritated, stressed, or allergy affected skin.²

Although much is known about cucurbitine itself, information on 4-aryl derivatives is rather scarce. The latter compounds possess

the 2-arylethyl amine moiety **2** (Fig. 1), which is encountered in numerous compounds that are active in the central nervous system. This moiety is present in neurotransmitters such as dopamine, epinephrine, norepinephrine and serotonin.³ Salmeterol⁴ and venlafaxine,⁵ 2 of the 10 best-selling prescription drugs in 2006,⁶ also contain this moiety. Moreover, this feature is present in many hallucinogenic drugs, such as LSD, MDMA (ecstasy), mescaline and psilocybin (magic mushrooms).⁷

There is only one example in the literature of methyl 4-phenylcucurbitinate⁸ and a few random and isolated examples of the synthesis of 4-aryl derivatives,⁹ but there are no examples of 4-heteroaryl containing compounds. The idea of combining two known privileged structures (cucurbitine and 2-arylethyl amine) to generate a product with the possibility of new biological activity is interesting from a pharmaceutical point of view (Scheme 1). In this case, the 2-arylethyl amine moiety is contained twice within the structure.

Herein we present a general procedure for the synthesis of both diastereoisomers (trans and cis) of 4-aryl substituted cucurbitine

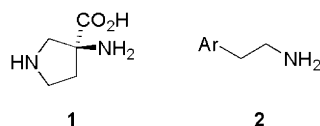
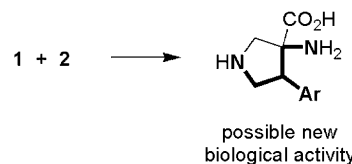


Figure 1. Cucurbitine **1** and the 2-arylethyl amine moiety **2**.



Scheme 1. Combination of two privileged structures.

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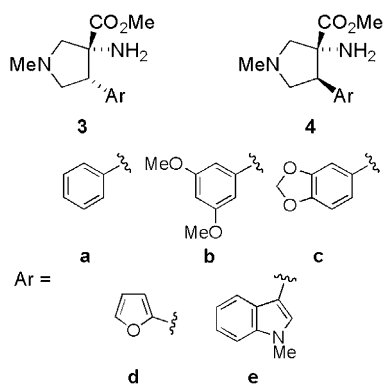


Figure 2. Target compounds.

derivatives (**3** and **4**), possessing different aryl groups such as phenyl **a**, alkoxyphenyl **b** and **c**, furyl **d** and indolyl **e** (Fig. 2).

2. Results and discussion

We envisioned that a suitable strategy to these compounds may proceed as shown retrosynthetically in Scheme 2. The amino group of compounds **3** and **4** could be derived from a masked amino function, such as a nitro group, by reduction. Compounds **5** and **6** possess two electron-withdrawing groups on carbon three of the pyrrolidine, rendering it a perfect pattern for a 1,3-cycloaddition reaction between azomethine ylides and electron-deficient alkenes. This would leave the 3-aryl-2-nitroacrylates **7** as starting materials, which could be obtained by a Knoevenagel condensation reaction between methyl 2-nitroacetate **8** and any aromatic aldehyde.

The synthesis of compound classes **3** and **4** commenced with the condensation of methyl 2-nitroacetate **8** with aromatic *N*-phenyl imines **9a–e** to obtain the α -nitro acrylates **7a–e**. Since the conditions for the Knoevenagel condensation of these strongly activated methylene compounds with aldehydes are critical and, therefore, often low yielding,¹¹ the corresponding imines, which had previously given good results for similar reactions,¹² were used. To this end, we developed a highly practical procedure for the synthesis of *N*-phenyl imines **9b,c** and **9e** starting from the solid aromatic aldehydes **10b,c** and **10e**. Addition of aniline to the neat aromatic aldehyde, with MgSO_4 as dehydrating agent and reaction at the melting point temperature of the aldehydes for 4–6 h, gave conversions of >90%. Addition of dichloromethane, removal of the solid by filtration and subsequent distillation of dichloromethane and water provided the corresponding *N*-phenyl imines in quantitative yields. For liquid aldehydes **10a** and **10d** the reaction was run in THF at room temperature (Table 1).¹³

With *N*-phenyl imines **9a–e** in hand, we proceeded with the Knoevenagel condensations, which were run overnight with

Table 1
Formation of *N*-phenyl imines **9a–e**

Entry	Substrate	Solvent	<i>T</i> (°C)	Product	Yield ^a (%)
1	10a	THF	21	9a	99
2	10b	—	46	9b	99
3	10c	—	37	9c	99
4	10d	THF	21	9d	90 ^b
5	10e	—	70	9e	99

^a Isolated yield.

^b Conversion, not isolated yield.

Table 2
Knoevenagel condensation to form the α -nitro acrylates **7a–e**

Entry	Imine	Product	Ratio ^a (Z/E)	Yield (%)
1	9a	7a	3:1	81
2	9b	7b	3:2	88
3	9c	7c	3:1	69
4	9d	7d	2:1	69
5	9e	7e	40:1 ^b	74

^a Calculated by integration of the ¹H NMR signals of the crude reaction mixture.

^b The product obtained by precipitation of the reaction mixture.

methyl 2-nitroacetate **8** in acetic anhydride to yield the α -nitro acrylates **7a–e** in generally good yields^{12,14} and varying (Z/E)-ratios (Table 2).¹⁵

In spite of our best endeavours, it was proven that the yield for the condensation of **9d** dropped dramatically when an attempt was made to scale up the reaction to 10 g. To solve this inconvenience, the reaction was repeated using aldehyde **10d** instead. Under the conditions depicted in Scheme 3,¹⁶ product **7d** was then synthesized in a higher yield, independent of the scale. All other reactions could be readily scaled up under the stated conditions.

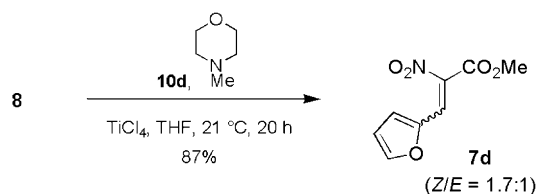
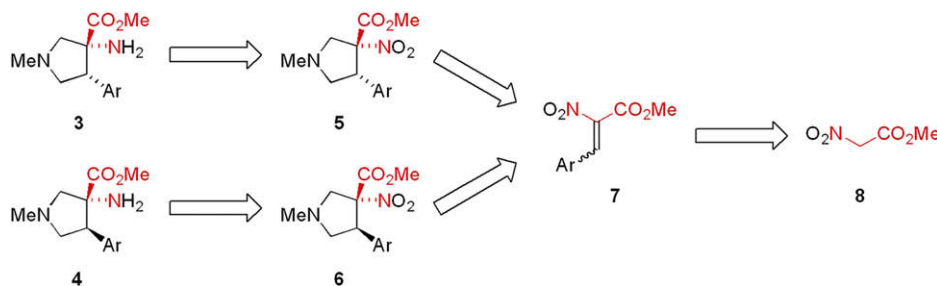
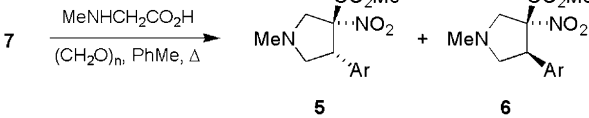
Scheme 3. Knoevenagel condensation of aldehyde **10d**.Scheme 2. Retrosynthetic analysis for the synthesis of compound classes **3** and **4**.

Table 3
1,3-Dipolar cycloaddition reaction to form the pyrrolidine-core structures **5** and **6**



Entry	Acrylate	Time (min)	Products	Yield ^a (%)
1	7a	45	5a+6a	90
2	7b	60	5b+6b	84
3	7c	110	5c+6c	85
4	7d	60	5d+6d	82
5	7e	105	5e+6e	82

^a Combined yield.

Although in some cases the separation of the (*Z/E*)-mixtures could be achieved by recrystallization,¹⁵ this was not investigated any further as it was apparent from the next step that (*Z/E*)-isomerization proceeds considerably faster than the cycloaddition, probably due to the *push-pull effect*.¹⁷

The next step in the synthesis was the formation of the pyrrolidine-core structures by a 1,3-dipolar cycloaddition reaction using an azomethine ylide. The decarboxylative condensation of α -amino acids with aldehydes, typically heated in toluene or dimethylformamide, was chosen to generate the ylide. This reaction has been previously used in the synthesis of natural products.¹⁸ Thus, the use of sarcosine (*N*-methylglycine) with paraformaldehyde in refluxing toluene in the presence of the α -nitro acrylates **7** cleanly provided a ca. 1:1 mixture of the diastereoisomeric cycloadducts **5** and **6**,¹⁹ independent of the (*Z/E*)-ratio of the substrate (Table 3). The separation of these products using column chromatography was straightforward as a result of the large *R_f* difference between the diastereoisomers in all cases. The *cis*-isomers **6** present a chemical shift for the methyl group of the ester 0.38–0.88 ppm lower than the *trans*-isomers **5**, due to the shielding effect of the aryl group.

The cycloaddition reaction also gave trace amounts of the trans-(methoxycarbonyl)ated products **11a–e** via a Krapcho reaction (Fig. 3).²⁰

The reduction of nitro compounds is perhaps the most versatile reduction of a functional group in organic chemistry, potentially giving rise to a variety of products. Reduction of the nitro group may lead to nitroso compounds, oximes, hydroxylamines, amines, hydrocarbons, azoxy compounds, azo compounds and hydrazo compounds.²¹ In principle, there are optimal conditions for obtaining any of these products, but it is fairly common to form mixtures, especially for aliphatic nitro compounds. In our case, the reduction of the nitro group to the amine was more problematic than anticipated. Initially, we tried the conditions previously optimized in our group ($\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, THF/ H_2O) for nitro groups on molecules with a similar structure,¹² but the reaction provided the desired amines in a low yield (<30%) accompanied by a mixture of unidentified side products. Among the different products obtained, we identified rearranged amine **12**

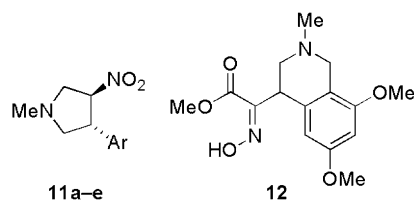
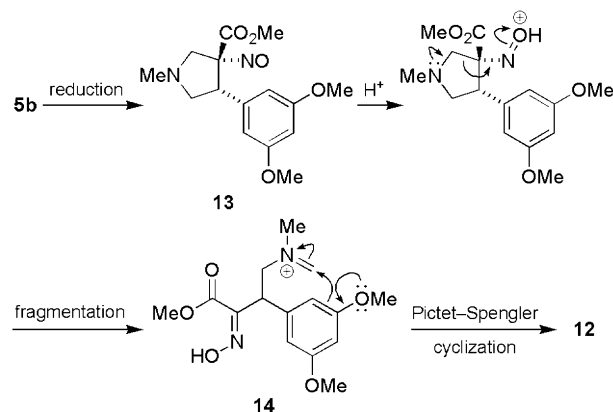


Figure 3. Side products **11a–e** and **12**.

(Fig. 3) resulting from acid catalyzed fragmentation of nitroso compound **13**, the first product from the reduction of the nitro group, followed by Pictet–Spengler cyclization of the intermediate iminium ion **14** (Scheme 4).



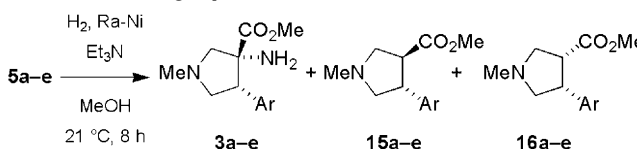
Scheme 4. Possible reaction sequence for the formation of **12**.

As a result of the above observations, it was decided not to use dissolving metal conditions for this type of reaction. Instead, the reduction was performed using catalytic hydrogenation with Raney nickel in methanol at room temperature. It appeared that addition of Et_3N activated the metal,²² leading to the exclusive formation of the amine, rather than the anticipated mixture of the amine and the corresponding hydroxylamine.²³ Thus, compounds **5a–e** were reacted under these conditions to complete the synthesis of 4-aryl cucurbitinates. After elimination of Raney nickel by filtration through Celite and evaporation of methanol and Et_3N , the reaction gave the compounds **3a–e** as the major products (ratio $\geq 90\%$ by NMR spectroscopy). Compounds **3a–e** were isolated in pure form after column chromatography, completing the synthesis of cucurbitinates. The minor side products **15a–e** and **16a–e** were also formed along with the cucurbitinates, resulting from reduction of carbon three of the heterocycle (Table 4) and will be discussed in detail below.^{24,25}

When compounds **6a–e** were reacted under the reduction conditions used above, the products **4a–e** were obtained with yields similar to those for **3a–e** and similar ratios of the side products (Table 5). To the best of our knowledge, this is the only general procedure for the synthesis of either diastereomer of 4-aryl cucurbitinate.

A speculative explanation of how products **15** and **16** are formed (reaction sequence shown only for **5**) is outlined in Scheme 5. The regular nitro reduction to give the amine is in competition with

Table 4
Reduction of the nitro groups from the trans-diastereoisomers

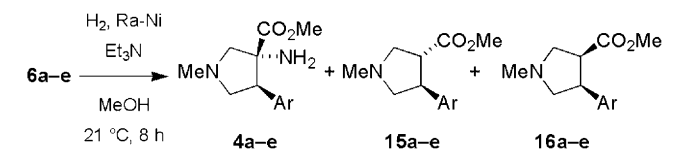


Entry	Substrate	Products	Ratio ^a (3/15/16)	Yield (%) ^b
1	5a	3a+15a+16a	94:5:1	80
2	5b	3b+15b+16b	93:5:2	79
3	5c	3c+15c+16c	92:6:2	80
4	5d	3d+15d+16d	92:7:1	65
5	5e	3e+15e+16e	93:6:1	62

^a Calculated by integration of the ^1H NMR signals of the crude reaction mixture.

^b Isolated yield of the major products **3a–e**.

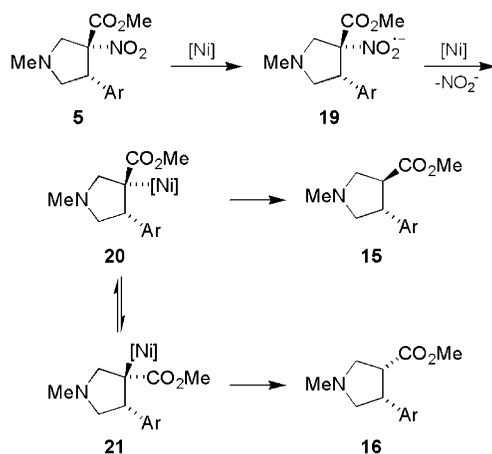
Table 5
Reduction of the nitro groups from the cis-diastereoisomers



Entry	Substrate	Products	Ratio ^a (4/15/16)	Yield ^b (%)
1	6a	4a+15a+16a	93:4:3	77
2	6b	4b+15b+16b	90:6:4	71
3	6c	4c+15c+16c	90:7:3	76
4	6d	4d+15d+16d	90:7:3	61
5	6e	4e+15e+16e	88:8:4	60

^a Calculated by integration of the ¹H NMR signals of the crude reaction mixture.

^b Isolated yield of the major products **4a–e**.



Scheme 5. Reaction sequence for the denitration of compounds **5**.

a radical reduction of this group.²⁶ Thus, the nitro group is adsorbed onto the surface of Raney nickel and reduced to the radical anion **19**. This intermediate cleaves to form a carbon-centred radical,²⁷ which is reduced to the nickel C-enolate **20**. The C-enolate is partially hydrogenated to **15** and partially equilibrated, through the O-enolate, to the C-enolate **21**.²⁸ Finally, both C-enolates **20** and **21** are hydrogenated to **15** and **16**, respectively.

3. Conclusion

In summary, we have developed a general method for the synthesis of 4-aryl substituted cucurbitine derivatives. We have shown that these aryl groups could be phenyl, electron-rich aryls (3,5-dimethoxyphenyl, 1,3-benzodioxol-5-yl) and electron-rich heteroaryls (2-furyl, 1-methylindol-3-yl). As a result, we anticipate that this methodology can be successfully applied for a wide range of aromatic groups. These compounds combine the structure of cucurbitine (an allergy mediator and an anthelmintic agent) with the 2-arylethyl amine moiety (core structure with central nervous system activity), rendering it a potentially interesting motive from the pharmaceutical point of view. In addition, we have developed a high yielding method for the synthesis of *N*-phenyl imines from solid aromatic aldehydes.

4. Experimental section

4.1. General

Reagents were obtained from commercial suppliers and used without purification. Solvents were distilled from appropriate

drying agents prior to use and stored under nitrogen. Reactions were followed, and *R_f* values obtained, using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F₂₅₄) with the indicated solvent mixture. Detection was performed with UV light and/or by charring at ca. 150 °C after dipping into a solution of KMnO₄. Column or flash chromatography was carried out using ACROS silica gel (0.035–0.070 mm, pore diameter ca. 6 nm). IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. NMR spectra were recorded at 298 K on a Bruker DMX 300 (300 MHz) and a Varian 400 (400 MHz) spectrometer in CDCl₃ solutions. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm) as internal standard. Coupling constants are reported as *J* values in hertz (Hz). Multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and app (apparent). Peak assignment in ¹³C spectra is based on 2D gHSQC and gHMBC spectra, and DEPT 135 when needed. Chain numbering corresponds to IUPAC nomenclature, so unprimed atoms belong to the principal chain and primed atoms belong to the substituents.

4.2. General procedure for imine formation

A mixture of the aromatic aldehyde **10**, aniline (1.02 equiv for **9b,c** and 1.20 equiv for **9e**) and MgSO₄ (0.28 equiv) was stirred without solvent and heated at the melting point temperature of the aldehyde for 4 h for **9b,c** and for 6 h for **9e**. The reaction was cooled down to room temperature and the solid residue was dissolved in dichloromethane (40 mL for **9b,c** and 300 mL for **9e**). The solid hydrated MgSO₄ was filtered off and the filtrate was concentrated under reduced pressure. When the solvent was evaporated, the sample was kept under reduced pressure for 1 h (water bath 40 °C) for **9b,c** and 2 h (water bath 75 °C) for **9e**. The sample was left overnight under high vacuum. The product was recrystallized from heptane.

4.2.1. (*E*)-*N*-(3,5-Dimethoxybenzylidene)aniline **9b**

According to the general procedure, the reaction of aldehyde **10b** (10.0 g, 60.2 mmol) with aniline (5.7 g, 61.4 mmol) afforded **9b** (14.5 g, 99%) as a light yellow solid. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.37 (s, 1 ¹H, CHN), 7.43–7.36 (m, 2 ¹H, 3-CH+5-CH), 7.27–7.18 (m, 3 ¹H, 2-CH+4-CH+6-CH), 7.07 (d, *J*=2.4 Hz, 2 ¹H, 2'-CH+6'-CH), 6.59 (t, *J*=2.4 Hz, 1 ¹H, 4'-CH), 3.86 (s, 6 ¹H, 2×OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 161.2 (3'-C+5'-C), 160.4 (CHN), 152.1 (1-C), 138.4 (1'-C), 129.3 (3-C+5-C), 126.1 (4-C), 121.0 (2-C+6-C), 106.6 (2'-C+6'-C), 104.4 (4'-C), 55.7 (2×OCH₃). FTIR [*ν* (cm⁻¹), neat]: 2836, 1633, 1594, 1151, 833, 764, 691. HRMS [EI (*m/z*)] calcd for C₁₅H₁₅NO₂=241.1103, found for [M⁺]=241.1095 (Δ=3.2 ppm), peaks at (relative intensity): 241 (100), 240 (89), 211 (26), 104 (16), 77 (55), 51 (15). *R_f*: 0.53 (AcOEt/heptane, 1:2). Mp=45–46 °C.

4.2.2. (*E*)-*N*-Piperonylideneaniline **9c**

According to the general procedure, the reaction of aldehyde **10c** (10.0 g, 66.6 mmol) with aniline (6.3 g, 67.9 mmol) afforded **9c** (15.0 g, 99%) as a light yellow solid. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.33 (s, 1 ¹H, CHN), 7.53 (d, *J*=1.6 Hz, 1 ¹H, 4'-CH), 7.41–7.35 (m, 2 ¹H, 3-CH+5-CH), 7.27 (dd, *J*=8.1, 1.6 Hz, 1 ¹H, 6'-CH), 7.24–7.16 (m, 3 ¹H, 2-CH+4-CH+6-CH), 6.88 (d, *J*=8.1 Hz, 1 ¹H, 7'-CH), 6.04 (s, 2 ¹H, OCH₂O). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 159.5 (CHN), 152.2 (1-C), 150.7 (7'a-C), 148.6 (3'a-C), 131.4 (5'-C), 129.3 (3-C+5-C), 125.8 (4-C+6'-C), 121.0 (2-C+6-C), 108.4 (7'-C), 107.0 (4'-C), 101.8 (OCH₂O). FTIR [*ν* (cm⁻¹), neat]: 3059, 2892, 2783, 1624, 1600, 1581, 1453, 1262, 935, 812, 766, 698. HRMS [EI (*m/z*)] calcd for C₁₄H₁₁NO₂=225.0790, found for [M⁺]=225.0790 (Δ=0.0 ppm), peaks at (relative intensity): 225 (100), 224 (78), 77 (34), 51 (10). Elem. Anal. Calcd for C₁₄H₁₁NO₂: C 74.65%, H 4.92%, N 6.22%; found:

C 74.87%, H 4.79%, N 6.06%. *R_f*: 0.51 (AcOEt/heptane, 1:3). Mp=67–68 °C (from heptane, white cotton-like solid).

4.2.3. (E)-N-[(1-Methyl-1H-indol-3-yl)methylidene]aniline **9e**

According to the general procedure, the reaction of aldehyde **10e** (10.0 g, 62.8 mmol) with aniline (7.0 g, 75.4 mmol) afforded **9e** (14.6 g, 99%) as a light yellow solid. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.63 (s, 1 ¹H, CHN), 8.50–8.45 (m, 1 ¹H, 4'-CH), 7.54 (s, 1 ¹H, 2'-CH), 7.42–7.27 (m, 5 ¹H, 3-CH+5-CH+5'-CH+6'-CH+7'-CH), 7.25–7.21 (m, 2 ¹H, 2-CH+6-CH), 7.20–7.14 (m, 1 ¹H, 4-CH), 3.86 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 154.3 (CHN), 153.7 (1-C), 138.0 (7'a-C), 134.3 (2'-C), 129.2 (3-C+5-C), 126.2 (3'a-C), 124.9 (4-C), 123.4 (6'-C), 122.4 (4'-C), 121.8 (5'-C), 121.1 (2-C+6-C), 115.2 (3'-C), 109.6 (7'-C), 33.5 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3055, 2848, 1612, 1583, 1573, 1463, 1372, 771, 750, 696. HRMS [EI (*m/z*)] calcd for C₁₆H₁₄N₂=234.1157, found for [M⁺]=234.1157, (|Δ|=0.0 ppm), peaks at (relative intensity): 234 (100), 233 (89), 218 (10), 77 (19). Elem. Anal. Calcd for C₁₆H₁₄N₂: C 82.02%, H 6.02%, N 11.96%; found: C 81.90%, H 6.05%, N 11.75%. *R_f*: 0.36 (AcOEt/heptane, 1:2). Mp: 132–134 °C (from heptane).

4.3. General procedure for Knoevenagel condensation

A solution of methyl 2-nitroacetate **8** in Ac₂O (1.0 M) was heated to 50 °C. Compound **9** (1.1 equiv) was added to this solution and stirred at 50 °C for 17 h. After this time, H₂O (100 mL) was added. The reaction mixture was stirred for 10 min and then extracted with dichloromethane (3×100 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo.

4.3.1. Methyl 2-nitro-3-phenylacrylate (Z)-**7a**/(E)-**7a** (3:1)

According to the general procedure, the reaction of methyl 2-nitroacetate **8** (3.57 g, 30.0 mmol) with imine **9a** (5.98 g, 33.0 mmol) afforded **7a** (5.04 g, 81% yield), as a yellow sticky solid, after column chromatography (AcOEt/heptane, 1:4). FTIR [ν (cm⁻¹), neat]: 3059, 2956, 1735, 1731, 1643, 1536, 1533, 1269, 765, 687. *R_f*: 0.28 (AcOEt/heptane, 1:4). Compound (Z)-**7a**: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.55 (s, 1 ¹H, 3-CH), 7.54–7.40 (m, 5 ¹H, Ph), 3.92 (s, 3 ¹H, OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 159.8 (CO₂), 140.0 (2-C), 133.4 (3-C), 132.4 (4'-C), 129.9 (2'-C+6'-C), 129.54 (3'-C+5'-C), 129.00 (1'-C), 53.69 (OCH₃). Compound (E)-**7a**: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.10 (s, 1 ¹H, 3-CH), 7.54–7.40 (m, 5 ¹H, Ph), 3.96 (s, 3 ¹H, OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 161.8 (CO₂), 141.9 (2-C), 137.1 (3-C), 132.6 (4'-C), 130.5 (2'-C+6'-C), 129.51 (3'-C+5'-C), 129.02 (1'-C), 53.8 (OCH₃).

4.3.2. Methyl 3-(3,5-dimethoxyphenyl)-2-nitroacrylate (Z)-**7b**/(E)-**7b** (3:2)

According to the general procedure, the reaction of methyl 2-nitroacetate **8** (3.57 g, 30.0 mmol) with imine **9b** (8.0 g, 33.0 mmol) afforded **7b** (7.0 g, 88% yield), as a yellow solid, after column chromatography (AcOEt/heptane, 1:4→1:3). FTIR [ν (cm⁻¹), neat]: 3003, 2958, 2841, 1736, 1731, 1643, 1536, 1205, 844. HRMS [EI (*m/z*)] calcd for C₁₂H₁₃NO₆=267.0743, found for [M⁺]=267.0742 (|Δ|=0.3 ppm), peaks at (relative intensity): 267 (100), 166 (82), 135 (26), 59 (43). Elem. Anal. Calcd for C₁₂H₁₃NO₆: C 53.93%, H 4.90%, N 5.24%; found: C 54.15%, H 4.83%, N 5.23%. *R_f*: 0.41 (AcOEt/heptane, 1:2). Mp=46–49 °C. Compound (Z)-**7b**: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.48 (s, 1 ¹H, 3-CH), 6.58–6.54 (m, 3 ¹H, 2'-CH+4'-CH+6'-CH), 3.92 (s, 3 ¹H, CO₂CH₃), 3.78 (s, 6 ¹H, 2×OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 161.4 (3'-C+5'-C), 159.8 (CO₂), 140.3 (2-C), 133.5 (3-C), 130.58 (1'-C), 107.5 (2'-C+6'-C), 104.7 (4'-C), 55.63 (2×OCH₃), 53.7 (CO₂CH₃). Compound (E)-**7b**: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.02 (s, 1 ¹H, 3-CH), 6.63 (d, *J*=2.2 Hz, 2 ¹H, 2'-CH+6'-CH), 6.59 (t, *J*=2.2 Hz, 1 ¹H, 4'-CH), 3.96 (s, 3 ¹H, CO₂CH₃),

3.80 (s, 6 ¹H, 2×OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 161.8 (CO₂), 161.4 (3'-C+5'-C), 142.2 (2-C), 137.1 (3-C), 130.61 (1'-C), 108.2 (2'-C+6'-C), 104.8 (4'-C), 55.64 (2×OCH₃), 53.8 (CO₂CH₃).

4.3.3. Methyl 3-(1,3-benzodioxol-5-yl)-2-nitroacrylate (Z)-**7c**/(E)-**7c** (3:1)

According to the general procedure, the reaction of methyl 2-nitroacetate **8** (3.57 g, 30.0 mmol) with imine **9c** (7.4 g, 33.0 mmol) afforded **7c** (5.2 g, 69% yield), as a yellow solid, after column chromatography (AcOEt/heptane, 1:4→1:3). FTIR [ν (cm⁻¹), neat]: 3003, 2950, 2846, 2784, 1721, 1630, 1528, 1502, 1244, 827. HRMS [EI (*m/z*)] calcd for C₁₁H₉NO₆=251.0430, found for [M⁺]=251.0420 (|Δ|=3.9 ppm), peaks at (relative intensity): 251 (100), 204 (43), 173 (31), 146 (48), 59 (31). Elem. Anal. Calcd for C₁₁H₉NO₆: C 52.60%, H 3.61%, N 5.58%; found: C 52.49%, H 3.66%, N 5.59%. *R_f*: 0.26 (AcOEt/heptane, 1:3). Mp=114–116 °C (from heptane, yellow crystals). Compound (Z)-**7c**: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.42 (s, 1 ¹H, 3-CH), 7.00 (dd, *J*=8.0, 2.0 Hz, 1 ¹H, 6'-CH), 6.87 (d, *J*=2.0 Hz, 1 ¹H, 4'-CH), 6.84 (d, *J*=8.0 Hz, 1 ¹H, 7'-CH), 6.04 (s, 2 ¹H, OCH₂O), 3.90 (s, 3 ¹H, OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 160.9 (CO₂), 151.5 (7'a-C), 149.0 (3'a-C), 138.2 (2-C), 133.1 (3-C), 127.7 (6'-C), 122.92 (5'-C), 109.2 (7'-C), 108.3 (4'-C), 102.3 (OCH₂O), 53.5 (OCH₃). Compound (E)-**7c**: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.00 (s, 1 ¹H, 3-CH), 7.09 (dd, *J*=8.0, 2.0 Hz, 1 ¹H, 6'-CH), 6.94 (d, *J*=2.0 Hz, 1 ¹H, 4'-CH), 6.88 (d, *J*=8.0 Hz, 1 ¹H, 7'-CH), 6.07 (s, 2 ¹H, OCH₂O), 3.98 (s, 3 ¹H, OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 162.2 (CO₂), 151.9 (7'a-C), 148.9 (3'a-C), 140.0 (2-C), 137.1 (3-C), 128.7 (6'-C), 122.91 (5'-C), 109.3 (7'-C), 108.8 (4'-C), 102.4 (OCH₂O), 53.8 (OCH₃).

4.3.4. Methyl (Z)-3-(1-methyl-1H-indol-3-yl)-2-nitroacrylate (Z)-**7e**

According to the general procedure, the reaction of methyl 2-nitroacetate **8** (3.57 g, 30.0 mmol) with imine **9e** (7.7 g, 33.0 mmol) afforded **7e** (5.8 g, 74% yield), as a bright yellow solid, after washing the precipitate from the reaction mixture with cold (–70 °C) AcOEt. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.98 (s, 1 ¹H, 3-CH), 7.79–7.76 (m, 1 ¹H, 4'-CH), 7.69 (s, 1 ¹H, 2'-CH), 7.41–7.30 (m, 3 ¹H, 5'-CH+6'-CH+7'-CH), 3.92 (s, 3 ¹H, OCH₃), 3.86 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 161.0 (CO₂), 137.0 (7'a-C), 134.7 (2-C), 133.7 (2'-C), 128.4 (3'a-C), 127.0 (3-C), 123.9 (6'-C), 122.5 (5'-C), 118.4 (4'-C), 110.4 (7'-C), 105.8 (3'-C), 53.1 (OCH₃), 34.0 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3119, 3035, 2955, 1710, 1621, 1523, 1261, 747. HRMS [EI (*m/z*)] calcd for C₁₃H₁₂N₂O₄=260.0797, found for [M⁺]=260.0806 (|Δ|=3.4 ppm), peaks at (relative intensity): 260 (100), 213 (27), 158 (20), 155 (40), 149 (62), 121 (41). Elem. Anal. Calcd for C₁₃H₁₂N₂O₄: C 60.00%, H 4.65%, N 10.76%; found: C 60.02%, H 4.84%, N 10.56%. *R_f*: 0.33 (AcOEt/heptane, 1:2). Mp=170–171 °C (from AcOEt, bright yellow needles).

4.3.4.1. Methyl (E)-3-(1-methyl-1H-indol-3-yl)-2-nitroacrylate (E)-**7e** (taken from a 2:1 mixture of (Z)-**7e**/(E)-**7e**). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 8.51 (s, 1 ¹H, 3-CH), 7.99 (s, 1 ¹H, 2'-CH), 7.79–7.75 (m, 1 ¹H, 4'-CH), 7.41–7.30 (m, 3 ¹H, 5'-CH+6'-CH+7'-CH), 3.98 (s, 3 ¹H, OCH₃), 3.89 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 163.5 (CO₂), 137.4 (7'a-C), 135.8 (2'-C), 135.5 (2-C), 131.8 (3-C), 128.9 (3'a-C), 124.1 (6'-C), 122.8 (5'-C), 118.6 (4'-C), 110.6 (7'-C), 106.1 (3'-C), 53.3 (OCH₃), 34.1 (NCH₃).

4.3.5. Procedure for methyl 3-(2-furyl)-2-nitroacrylate **7d**

A 0.1 M solution of TiCl₄ (133.6 mmol) in THF (1.2 L) was prepared by the addition of a 1.0 M solution of TiCl₄ in CH₂Cl₂ at 0 °C, followed by the addition of a mixture of methyl 2-nitroacetate **8** (8.00 g, 66.8 mmol) and furfural **10d** (9.62 g, 100.2 mmol) in THF (130 mL) at 0 °C. A 1.0 M solution of 4-methylmorpholine (27.10 g, 267.5 mmol) in THF (235 mL) was then added by syringe over 2 h at 0 °C. The reaction mixture was stirred at room temperature for

24 h. Water (800 mL) was then added and the solution was extracted with Et₂O (3 × 800 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The brown solid residue was purified by recrystallization from methanol to afford pure (Z)-**7d** (5.23 g, 40% yield) as light brown crystals. The filtrate was concentrated under reduce pressure and purified by column chromatography (AcOEt/heptane, 1:3) to afford a 1.7:1 mixture of (Z)-**7d**/(E)-**7d** (6.21 g, 47% yield) as a dark brown solid. Total yield 87%.

4.3.5.1. Methyl (Z)-3-(2-furyl)-2-nitroacrylate (Z)-7d. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.62 (d, *J*=1.8 Hz, 1 ¹H, 5'-CH), 7.37 (s, 1 ¹H, 3-CH), 6.94 (d, *J*=3.5 Hz, 1 ¹H, 3'-CH), 6.57 (dd, *J*=3.5, 1.8 Hz, 1 ¹H, 4'-CH), 3.90 (s, 3 ¹H, OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 160.0 (CO₂), 148.2 (5'-C), 145.5 (2'-C), 136.2 (2-C), 121.0 (3'-C), 120.0 (3-C), 113.4 (4'-C), 53.6 (OCH₃). FTIR [*ν* (cm⁻¹), neat]: 3131, 3059, 2957, 1721, 1642, 1535, 1263, 1210. HRMS [EI (*m/z*)] calcd for C₈H₇NO₅=197.0324, found for [M⁺]=197.0324 (|Δ|=0.0 ppm), peaks at (relative intensity): 197 (14), 122 (15), 96 (28), 92 (25), 83 (100), 63 (34). Elem. Anal. Calcd for C₈H₇NO₅: C 48.74%, H 3.58%, N 7.10%; found C 48.84%, H 3.58%, N 7.11%. *R*_f: 0.40 (AcOEt/heptane, 1:2). Mp=84–85 °C (from methanol).

4.3.5.2. Methyl (E)-3-(2-furyl)-2-nitroacrylate (E)-7d (from the mixture). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.87 (s, 1 ¹H, 3-CH), 7.66 (d, *J*=1.8 Hz, 1 ¹H, 5'-CH), 7.07 (d, *J*=3.5 Hz, 1 ¹H, 3'-CH), 6.62 (dd, *J*=3.5, 1.8 Hz, 1 ¹H, 4'-CH), 4.00 (s, 3 ¹H, OCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 161.4 (CO₂), 148.7 (5'-C), 145.4 (2'-C), 138.6 (2-C), 122.9 (3-C+3'-C), 113.9 (4'-C), 53.6 (OCH₃).

4.4. General procedure for 1,3-dipolar cycloaddition

A round-bottomed flask fitted with a Dean–Stark apparatus, a reflux condenser, and a drying tube containing calcium chloride was charged with α-nitro acrylate **7**, MgSO₄ (0.5 equiv) and toluene (0.20–0.25 M). When the mixture was under reflux, sarcosine (*N*-methylglycine; 1.2 equiv) and paraformaldehyde (3.6 equiv) were added. This addition was repeated every 45 min until the substrate had completely reacted. Water (20 mL) was then added and the layers were separated. The aqueous layer was extracted with Et₂O (3 × 30 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo.

4.4.1. (±)-Methyl (3*R*,4*R*)-1-methyl-3-nitro-4-phenylpyrrolidine-3-carboxylate **5a** and (±)-methyl (3*R*,4*S*)-1-methyl-3-nitro-4-phenylpyrrolidine-3-carboxylate **6a**

According to the general procedure, α-nitro acrylate **7a** (2.51 g, 12.1 mmol) afforded **5a** (1.38 g, 43%), as a colourless oil, and **6a** (1.50 g, 47%), as a yellow oil, after column chromatography (AcOEt/heptane, 1:3 → 1:2).

4.4.1.1. Compound 5a. ¹H NMR [300 MHz, δ (ppm), CDCl₃]: 7.34–7.21 (m, 5 ¹H, Ph), 4.49 (app t, *J*=7.5 Hz, 1 ¹H, 4-CH), 3.83 (s, 3 ¹H, OCH₃), 3.78 (d, *J*=11.7 Hz, 1 ¹H, 2-CHH), 3.26 (d, *J*=11.7 Hz, 1 ¹H, 2-CHH), 3.10 (dd, *J*=9.4, 7.2 Hz, 1 ¹H, 5-CHH), 3.06 (dd, *J*=9.4, 7.8 Hz, 1 ¹H, 5-CHH), 2.48 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 164.5 (CO₂), 136.0 (1'-C), 128.62, 128.35, 128.2 (4'-C), 101.1 (3-C), 63.5 (2-C), 61.1 (5-C), 54.0 (OCH₃), 51.5 (4-C), 41.8 (NCH₃). FTIR [*ν* (cm⁻¹), neat]: 2954, 2845, 2792, 1755, 1552, 1342, 1247, 780, 754, 698. *R*_f: 0.23 (AcOEt/heptane, 1:1).

4.4.1.2. Compound 6a. ¹H NMR [300 MHz, δ (ppm), CDCl₃]: 7.34–7.19 (m, 5 ¹H, Ph), 4.72 (app t, *J*=8.1 Hz, 1 ¹H, 4-CH), 3.65 (d, *J*=11.4 Hz, 1 ¹H, 2-CHH), 3.52 (d, *J*=11.4 Hz, 1 ¹H, 2-CHH), 3.31 (app t, *J*=8.4 Hz, 1 ¹H, 5-CHH), 3.16 (s, 3 ¹H, OCH₃), 2.80 (app t, *J*=9.0 Hz, 1 ¹H, 5-CHH), 2.43 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]:

164.8 (CO₂), 136.2 (1'-C), 129.0, 128.2, 127.8 (4'-C), 102.9 (3-C), 64.9 (2-C), 61.7 (5-C), 53.0 (CO₂CH₃), 51.4 (4-C), 41.5 (NCH₃). FTIR [*ν* (cm⁻¹), neat]: 2950, 2837, 2788, 1750, 1554, 1338, 1243, 789, 754, 699. *R*_f: 0.54 (AcOEt/heptane, 1:1).

4.4.2. (±)-Methyl (3*R*,4*R*)-4-(3,5-dimethoxyphenyl)-1-methyl-3-nitropyrrolidine-3-carboxylate **5b** and (±)-methyl (3*R*,4*S*)-4-(3,5-dimethoxyphenyl)-1-methyl-3-nitropyrrolidine-3-carboxylate **6b**

According to the general procedure, α-nitro acrylate **7b** (9.99 g, 37.4 mmol) afforded **5b** (4.85 g, 40%), as a yellow oil, and **6b** (5.33 g, 44%), as a yellow solid, after column chromatography (AcOEt/heptane, 1:3 → 1:2).

4.4.2.1. Compound 5b. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.51 (d, *J*=2.3 Hz, 2 ¹H, 2'-CH+6'-CH), 6.36 (t, *J*=2.3 Hz, 1 ¹H, 4'-CH), 4.42 (app t, *J*=7.4 Hz, 1 ¹H, 4-CH), 3.85 (s, 3 ¹H, CO₂CH₃), 3.77 (d, *J*=11.6 Hz, 1 ¹H, 2-CHH), 3.75 (s, 6 ¹H, 2 × OCH₃), 3.26 (d, *J*=11.6 Hz, 1 ¹H, 2-CHH), 3.08 (dd, *J*=9.4, 6.9 Hz, 1 ¹H, 5-CHH), 3.02 (dd, *J*=9.4, 7.9 Hz, 1 ¹H, 5-CHH), 2.47 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 166.7 (CO₂), 160.5 (3'-C+5'-C), 138.4 (1'-C), 107.0 (2'-C+6'-C), 100.9 (3-C), 99.9 (4'-C), 63.3 (2-C), 61.0 (5-C), 55.2 (2 × OCH₃), 53.8 (CO₂CH₃), 51.4 (4-C), 41.4 (NCH₃). FTIR [*ν* (cm⁻¹), neat]: 2951, 2838, 2792, 1752, 1594, 1552, 1202, 1154, 845, 693. HRMS [EI (*m/z*)] calcd for C₁₅H₂₀N₂O₆=324.1321, found for [M⁺]=324.1314 (|Δ|=2.3 ppm), peaks at (relative intensity): 324 (13), 278 (100), 246 (73), 235 (57), 218 (49), 175 (91). *R*_f: 0.17 (AcOEt/heptane, 1:1).

4.4.2.2. Compound 6b. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.49 (d, *J*=2.4 Hz, 2 ¹H, 2'-CH+6'-CH), 6.36 (t, *J*=2.4 Hz, 1 ¹H, 4'-CH), 4.65 (dd, *J*=8.6, 7.6 Hz, 1 ¹H, 4-CH), 3.77 (s, 6 ¹H, 2 × OCH₃), 3.66 (d, *J*=11.6 Hz, 1 ¹H, 2-CHH), 3.51 (d, *J*=11.6 Hz, 1 ¹H, 2-CHH), 3.31 (dd, *J*=9.2, 7.6 Hz, 1 ¹H, 5-CHH), 3.30 (s, 3 ¹H, CO₂CH₃), 2.75 (app t, *J*=9.1 Hz, 1 ¹H, 5-CHH), 2.42 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 165.2 (CO₂), 160.7 (3'-C+5'-C), 138.7 (1'-C), 107.2 (2'-C+6'-C), 102.9 (3-C), 99.8 (4'-C), 64.8 (2-C), 61.6 (5-C), 55.4 (2 × OCH₃), 53.1 (CO₂CH₃), 51.4 (4-C), 41.3 (NCH₃). FTIR [*ν* (cm⁻¹), neat]: 2950, 2839, 2793, 1749, 1594, 1554, 1343, 1203, 1155, 841, 696. HRMS [EI (*m/z*)] calcd for C₁₅H₂₀N₂O₆=324.1321, found for [M⁺]=324.1309 (|Δ|=3.8 ppm), peaks at (relative intensity): 324 (5), 278 (99), 246 (100), 235 (72), 218 (34), 175 (99). *R*_f: 0.42 (AcOEt/heptane, 1:1). Mp=82–85 °C (from hexane, small white crystals).

4.4.3. (±)-Methyl (3*R*,4*R*)-4-(1,3-benzodioxol-5-yl)-1-methyl-3-nitropyrrolidine-3-carboxylate **5c** and (±)-methyl (3*R*,4*S*)-4-(1,3-benzodioxol-5-yl)-1-methyl-3-nitropyrrolidine-3-carboxylate **6c**

According to the general procedure, α-nitro acrylate **7c** (10.05 g, 40.0 mmol) afforded **5c** (4.92 g, 40%), as a colourless oil, and **6c** (5.52 g, 45%), as a yellow oil, after column chromatography (AcOEt/heptane, 1:3 → 1:2).

4.4.3.1. Compound 5c. ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.88 (d, *J*=1.8 Hz, 1 ¹H, 4'-CH), 6.80 (ddd, *J*=8.0, 1.9, 0.4 Hz, 1 ¹H, 6'-CH), 6.69 (d, *J*=8.0 Hz, 1 ¹H, 7'-CH), 5.90 (s, 2 ¹H, OCH₂O), 4.42 (app t, *J*=7.3 Hz, 1 ¹H, 4-CH), 3.83 (s, 3 ¹H, OCH₃), 3.77 (d, *J*=11.8 Hz, 1 ¹H, 2-CHH), 3.21 (d, *J*=11.8 Hz, 1 ¹H, 2-CHH), 3.04 (dd, *J*=9.4, 6.9 Hz, 1 ¹H, 5-CHH), 2.99 (dd, *J*=9.4, 7.6 Hz, 1 ¹H, 5-CHH), 2.45 (s, 3 ¹H, NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 166.7 (CO₂), 147.6 (3'-a-C), 147.5 (7'-a-C), 129.7 (5'-C), 122.4 (6'-C), 109.1 (4'-C), 108.1 (7'-C), 101.2 (OCH₂O), 101.0 (3-C), 63.2 (2-C), 61.1 (5-C), 53.8 (OCH₃), 51.1 (4-C), 41.5 (NCH₃). FTIR [*ν* (cm⁻¹), neat]: 2966, 2878, 2782, 1753, 1552, 1237, 730. HRMS [EI (*m/z*)] calcd for C₁₄H₁₆N₂O₆=308.1008, found for [M⁺]=308.1002 (|Δ|=2.1 ppm), peaks at (relative intensity): 308 (16), 262 (71), 219 (83), 202 (29), 189 (74), 159 (43). *R*_f: 0.22 (AcOEt/heptane, 1:1).

4.4.3.2. Compound 6c. ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 6.88 (d, $J=1.7$ Hz, 1 ^1H , 4'-CH), 6.82 (dd, $J=8.0$, 1.7 Hz, 1 ^1H , 6'-CH), 6.73 (d, $J=8.0$ Hz, 1 ^1H , 7'-CH), 5.94 (s, 2 ^1H , OCH_2O), 4.64 (app t, $J=8.1$ Hz, 1 ^1H , 4-CH), 3.62 (d, $J=11.4$ Hz, 1 ^1H , 2-CHH), 3.53 (d, $J=11.4$ Hz, 1 ^1H , 2-CHH), 3.33 (s, 3 ^1H , OCH_3), 3.28 (dd, $J=9.3$, 7.6 Hz, 1 ^1H , 5-CHH), 2.74 (app t, $J=9.0$ Hz, 1 ^1H , 5-CHH), 2.42 (s, 3 ^1H , NCH_3). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 165.3 (CO_2), 147.7 (3'-a-C), 147.3 (7'-a-C), 130.0 (5'-C), 122.7 (6'-C), 109.6 (4'-C), 108.1 (7'-C), 102.8 (3-C), 101.3 (OCH_2O), 64.8 (2-C), 61.8 (5-C), 53.2 (OCH_3), 51.2 (4-C), 41.4 (NCH_3). FTIR [ν (cm^{-1}), neat]: 2951, 2844, 2789, 1748, 1555, 1251, 1237, 1038. HRMS [EI (m/z)] calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_6=308.1008$, found for $[\text{M}^+]=308.1001$ ($|\Delta|=2.4$ ppm), peaks at (relative intensity): 308 (10), 262 (86), 219 (100), 202 (33), 189 (83), 159 (51). R_f : 0.48 (AcOEt/heptane, 1:1).

4.4.4. ($\pm$)-Methyl (3R,4R)-4-(2-furyl)-1-methyl-3-nitropyrrolidine-3-carboxylate 5d and ($\pm$)-methyl (3R,4S)-4-(2-furyl)-1-methyl-3-nitropyrrolidine-3-carboxylate 6d

According to the general procedure, α -nitro acrylate **7d** (8.00 g, 40.6 mmol) afforded **5d** (4.02 g, 39%), as a yellow oil, and **6d** (4.44 g, 43%), as a yellow oil, after column chromatography (AcOEt/heptane, 1:3 $\rightarrow$ 1:2).

4.4.4.1. Compound 5d. ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 7.33 (dd, $J=1.9$, 0.9 Hz, 1 ^1H , 5'-CH), 6.29 (dd, $J=3.4$, 1.9 Hz, 1 ^1H , 4'-CH), 6.26 (br d, $J=3.2$ Hz, 1 ^1H , 3'-CH), 4.61 (dd, $J=8.9$, 7.3 Hz, 1 ^1H , 4-CH), 3.86 (s, 3 ^1H , OCH_3), 3.66 (d, $J=11.4$ Hz, 1 ^1H , 2-CHH), 3.42 (d, $J=11.4$ Hz, 1 ^1H , 2-CHH), 3.21 (dd, $J=9.2$, 7.3 Hz, 1 ^1H , 5-CHH), 2.98 (app t, $J=9.1$ Hz, 1 ^1H , 5-CHH), 2.47 (s, 3 ^1H , NCH_3). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 166.3 (CO_2), 149.2 (2'-C), 143.0 (5'-C), 110.6 (4'-C), 109.2 (3'-C), 98.9 (3-C), 62.7 (2-C), 59.1 (5-C), 54.0 (OCH_3), 45.5 (4-C), 41.6 (NCH_3). FTIR [ν (cm^{-1}), neat]: 2953, 2845, 2796, 1754, 1554, 1254, 743. HRMS [EI (m/z)] not found for $[\text{M}^+]$, calcd for $(\text{C}_{11}\text{H}_{14}\text{NO}_3)^+=208.0974$, found=208.0977 ($|\Delta|=1.9$ ppm); [CI (m/z)] calcd for $(\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5+\text{H})^+=255.0981$, found 255.0981 ($|\Delta|=0.0$ ppm). R_f : 0.19 (AcOEt/heptane, 1:1).

4.4.4.2. Compound 6d. ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 7.36 (dd, $J=1.8$, 0.8 Hz, 1 ^1H , 5'-CH), 6.32 (dd, $J=3.2$, 1.9 Hz, 1 ^1H , 4'-CH), 6.26 (d, $J=3.2$ Hz, 1 ^1H , 3'-CH), 4.84 (app t, $J=8.4$ Hz, 1 ^1H , 4-CH), 3.74 (d, $J=11.2$ Hz, 1 ^1H , 2-CHH), 3.48 (s, 3 ^1H , OCH_3), 3.39 (d, $J=11.2$ Hz, 1 ^1H , 2-CHH), 3.41–3.35 (m, 1 ^1H , 5-CHH), 2.73 (app t, $J=9.2$ Hz, 1 ^1H , 5-CHH), 2.41 (s, 3 ^1H , NCH_3). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 164.9 (CO_2), 149.9 (2'-C), 142.7 (5'-C), 110.7 (4'-C), 109.0 (3'-C), 101.1 (3-C), 64.1 (2-C), 59.4 (5-C), 53.6 (OCH_3), 45.3 (4-C), 41.2 (NCH_3). FTIR [ν (cm^{-1}), neat]: 2953, 2845, 2794, 1750, 1558, 1258, 741. HRMS [EI (m/z)] not found for $[\text{M}^+]$, calcd for $(\text{C}_{11}\text{H}_{14}\text{NO}_3)^+=208.0974$, found=208.0978 ($|\Delta|=2.1$ ppm); [CI (m/z)] calcd for $(\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5+\text{H})^+=255.0981$, found 255.0981 ($|\Delta|=0.0$ ppm). R_f : 0.49 (AcOEt/heptane, 1:1).

4.4.5. ($\pm$)-Methyl (3R,4R)-1-methyl-4-(1-methyl-1H-indol-3-yl)-3-nitropyrrolidine-3-carboxylate 5e and ($\pm$)-methyl (3R,4S)-1-methyl-4-(1-methyl-1H-indol-3-yl)-3-nitropyrrolidine-3-carboxylate 6e

According to the general procedure, α -nitro acrylate **7e** (9.01 g, 34.6 mmol) afforded **5e** (4.17 g, 38%), as a yellow solid, and **6e** (4.83 g, 44%), as a light yellow solid, after column chromatography (AcOEt/heptane, 1:3 $\rightarrow$ 1:2).

4.4.5.1. Compound 5e. ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 7.82 (app dt, $J=7.9$, 1.0 Hz, 1 ^1H , 4'-CH), 7.23 (ddd, $J=8.2$, 1.5, 0.8 Hz, 1 ^1H , 7'-CH), 7.20 (ddd, $J=8.2$, 6.5, 1.2 Hz, 1 ^1H , 6'-CH), 7.13 (ddd, $J=7.9$, 6.5, 1.5 Hz, 1 ^1H , 5'-CH), 6.95 (s, 1 ^1H , 2'-CH), 4.88 (dd, $J=9.2$, 6.9 Hz, 1 ^1H , 4-CH), 3.82 (s, 3 ^1H , OCH_3), 3.77 (d, $J=11.7$ Hz, 1 ^1H , 2-CHH), 3.68 (s, 3 ^1H , 1'- NCH_3), 3.44 (d, $J=11.7$ Hz, 1 ^1H , 2-CHH), 3.18 (dd, $J=9.2$, 6.9 Hz,

1 ^1H , 5-CHH), 2.98 (t, $J=9.2$ Hz, 1 ^1H , 5-CHH), 2.49 (s, 3 ^1H , 1- NCH_3). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 167.0 (CO_2), 136.6 (7'-a-C), 128.1 (3'-a-C), 127.5 (2'-C), 122.0 (6'-C), 119.6 (5'-C), 119.5 (4'-C), 109.3 (7'-C), 109.0 (3'-C), 101.2 (3-C), 63.6 (2-C), 61.9 (5-C), 53.8 (OCH_3), 43.9 (4-C), 41.7 (1- NCH_3), 32.9 (1'- NCH_3). FTIR [ν (cm^{-1}), neat]: 3049, 2948, 2844, 2790, 1752, 1548, 1473, 1251, 740. HRMS [EI (m/z)] calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_4=317.1376$, found for $[\text{M}^+]=317.1386$ ($|\Delta|=3.2$ ppm), peaks at (relative intensity): 317 (16), 271 (18), 228 (100), 168 (22). Elem. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_4$: C 60.56%, H 6.03%, N 13.24%; found C 60.74%, H 6.06%, N 13.30%. R_f : 0.16 (AcOEt/heptane, 1:1). Mp=117–119 $^\circ\text{C}$ (from methanol, light yellow crystals).

4.4.5.2. Compound 6e. ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 7.76 (br d, $J=7.9$ Hz, 1 ^1H , 4'-CH), 7.25 (br d, $J=8.4$ Hz, 1 ^1H , 7'-CH), 7.20 (br t, $J=7.5$ Hz, 1 ^1H , 6'-CH), 7.13–7.09 (m, 1 ^1H , 5'-CH), 7.00 (s, 1 ^1H , 2'-CH), 5.12 (app t, $J=8.0$ Hz, 1 ^1H , 4-CH), 3.73 (s, 3 ^1H , 1'- NCH_3), 3.67 (d, $J=11.6$ Hz, 1 ^1H , 2-CHH), 3.55 (d, $J=11.6$ Hz, 1 ^1H , 2-CHH), 3.38 (app t, $J=8.3$ Hz, 1 ^1H , 5-CHH), 2.94 (s, 3 ^1H , OCH_3), 2.77 (app t, $J=8.9$ Hz, 1 ^1H , 5-CHH), 2.44 (s, 3 ^1H , 1- NCH_3). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 165.5 (CO_2), 136.7 (7'-a-C), 128.1 (2'-C), 127.6 (3'-a-C), 122.1 (6'-C), 119.9 (5'-C), 119.5 (4'-C), 109.7 (3'-C), 109.2 (7'-C), 102.9 (3-C), 64.6 (2-C), 62.2 (5-C), 52.5 (OCH_3), 43.0 (4-C), 41.4 (1- NCH_3), 32.9 (1'- NCH_3). FTIR [ν (cm^{-1}), neat]: 3049, 2947, 2841, 2791, 1749, 1552, 1473, 1254, 742. HRMS [EI (m/z)] calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_4=317.1376$, found for $[\text{M}^+]=317.1384$ ($|\Delta|=2.8$ ppm), peaks at (relative intensity): 317 (11), 271 (7), 228 (100), 168 (20). R_f : 0.34 (AcOEt/heptane, 1:1). Mp=109–112 $^\circ\text{C}$.

4.5. General procedure for reduction

An excess (7–8 heaped teaspoons) of freshly washed (with MeOH) Raney nickel was added to separate solutions of the α -nitro esters **5** and **6** with Et_3N (ca. 1 equiv) in methanol (0.25–0.30 M). The mixtures were stirred for 8 h at room temperature under a hydrogen atmosphere (1 atm). The catalyst was separated by filtration with suction through a glass filter with a 0.5 cm layer of Celite. The catalyst was washed thoroughly with methanol. The methanolic solutions were concentrated on a rotary evaporator.

4.5.1. ($\pm$)-Methyl (3R,4R)-3-amino-1-methyl-4-phenylpyrrolidine-3-carboxylate 3a

According to the general procedure, α -nitro ester **5a** (1.03 g, 3.9 mmol) afforded **3a** (731 mg, 80%), as a light yellow oil, after column chromatography (MeOH/ CHCl_3 , 1:20 $\rightarrow$ 1:10). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 7.34–7.18 (m, 5 ^1H , Ph), 3.89 (t, $J=8.3$ Hz, 1 ^1H , 4-CH), 3.79 (s, 3 ^1H , OCH_3), 3.42 (d, $J=9.8$ Hz, 1 ^1H , 2-CHH), 3.09 (d, $J=8.3$ Hz, 2 ^1H , 5-CH $_2$), 2.57 (d, $J=9.8$ Hz, 1 ^1H , 2-CHH), 2.47 (s, 3 ^1H , NCH_3), 1.75 (br s, 2 ^1H , NH_2). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 176.3 (CO_2), 136.8 (1'-C), 129.1, 128.6, 127.5 (4'-C), 68.2 (2-C), 66.5 (3-C), 59.8 (5-C), 53.3 (4-C), 52.8 (OCH_3), 42.5 (NCH_3). FTIR [ν (cm^{-1}), neat]: 3372, 3298, 2949, 2842, 2790, 1730, 1453, 1342, 1223, 770, 702.

4.5.2. ($\pm$)-Methyl (3R,4S)-3-amino-1-methyl-4-phenylpyrrolidine-3-carboxylate 4a

According to the general procedure, α -nitro ester **6a** (0.95 g, 3.6 mmol) afforded **4a** (649 mg, 77%), as a yellow oil, after column chromatography (MeOH/ CHCl_3 , 1:20 $\rightarrow$ 1:10). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 7.32–7.15 (m, 5 ^1H , Ph), 3.36 (dd, $J=9.3$, 6.9 Hz, 1 ^1H , 4-CH), 3.27 (dd, $J=9.3$, 6.9 Hz, 1 ^1H , 5-CHH), 3.23 (d, $J=9.9$ Hz, 1 ^1H , 2-CHH), 3.19 (s, 3 ^1H , OCH_3), 2.89 (app t, $J=9.2$ Hz, 1 ^1H , 5-CHH), 2.87 (d, $J=9.9$ Hz, 1 ^1H , 2-CHH), 2.47 (s, 3 ^1H , NCH_3), 2.07 (br s, 2 ^1H , NH_2). ^{13}C NMR [75 MHz, δ (ppm), CDCl_3]: 173.6 (CO_2), 138.3 (1'-C), 127.89, 127.87, 126.9 (4'-C), 70.2 (3-C), 67.2 (2-C), 61.1 (5-C), 60.5 (4-C), 51.7 (OCH_3), 42.3 (NCH_3). FTIR [ν (cm^{-1}), neat]: 3369, 3300, 2952, 2842, 2792, 1731, 1450, 1342, 1221, 768, 699.

4.5.3. (±)-Methyl (3*R*,4*R*)-3-amino-4-(3,5-dimethoxyphenyl)-1-methylpyrrolidine-3-carboxylate **3b**

According to the general procedure, α -nitro ester **5b** (2.01 g, 6.2 mmol) afforded **3b** (1.44 g, 79%), as a colourless-whitish oil, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.36 (s, 3 ¹H, 2'-CH+4'-CH+6'-CH), 3.84 (t, *J*=8.3 Hz, 1 ¹H, 4-CH), 3.79 (s, 3 ¹H, CO₂CH₃), 3.77 (s, 6 ¹H, 2 $\times$ OCH₃), 3.37 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 3.04 (d, *J*=8.3 Hz, 2 ¹H, 5-CH₂), 2.54 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 2.45 (s, 3 ¹H, NCH₃), 1.52 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 176.3 (CO₂), 160.9 (3'-C+5'-C), 139.5 (1'-C), 107.2 (2'-C+6'-C), 99.1 (4'-C), 68.4 (2-C), 66.6 (3-C), 59.7 (5-C), 55.4 (2 $\times$ OCH₃), 53.5 (4-C), 52.7 (CO₂CH₃), 42.4 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3375, 2943, 2836, 2787, 1728, 1594, 1203, 1153, 838. HRMS [EI (*m/z*)] calcd for C₁₅H₂₂N₂O₄=294.1580, found for [M⁺]=294.1569 ($|\Delta|$ =3.6 ppm), peaks at (relative intensity): 294 (53), 206 (24), 164 (62), 57 (100), 42 (65). *R*_f: 0.29 (MeOH/CH₂Cl₂, 1:8). Mp=56–59 °C.

4.5.4. (±)-Methyl (3*R*,4*S*)-3-amino-4-(3,5-dimethoxyphenyl)-1-methylpyrrolidine-3-carboxylate **4b**

According to the general procedure, α -nitro ester **6b** (2.01 g, 6.2 mmol) afforded **4b** (1.30 g, 71%), as a whitish oil, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.37 (d, *J*=2.2 Hz, 2 ¹H, 2'-CH+6'-CH), 6.33 (t, *J*=2.2 Hz, 1 ¹H, 4'-CH), 3.77 (s, 6 ¹H, 2 $\times$ OCH₃), 3.33 (s, 3 ¹H, CO₂CH₃), 3.32 (dd, *J*=9.3, 6.8 Hz, 1 ¹H, 4-CH), 3.27 (dd, *J*=8.8, 6.8 Hz, 1 ¹H, 5-CHH), 3.21 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 2.92 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 2.87 (app t, *J*=9.0 Hz, 1 ¹H, 5-CHH), 2.48 (s, 3 ¹H, NCH₃), 2.26 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 174.1 (CO₂), 160.6 (3'-C+5'-C), 140.5 (1'-C), 106.3 (2'-C+6'-C), 99.1 (4'-C), 70.0 (3-C), 67.1 (2-C), 61.0 (5-C), 60.4 (4-C), 55.4 (2 $\times$ OCH₃), 51.9 (CO₂CH₃), 42.2 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3373, 3305, 2944, 2837, 2784, 1728, 1594, 1203, 1152, 842. HRMS [EI (*m/z*)] calcd for C₁₅H₂₂N₂O₄=294.1580, found for [M⁺]=294.1586 ($|\Delta|$ =2.1 ppm), peaks at (relative intensity): 294 (25), 206 (29), 164 (66), 57 (100), 42 (20). *R*_f: 0.22 (MeOH/CH₂Cl₂, 1:8).

4.5.5. (±)-Methyl (3*R*,4*R*)-3-amino-4-(1,3-benzodioxol-5-yl)-1-methylpyrrolidine-3-carboxylate **3c**

According to the general procedure, α -nitro ester **5c** (3.00 g, 9.7 mmol) afforded **3c** (2.17 g, 80%), as a light yellow oil, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.75 (d, *J*=8.0 Hz, 1 ¹H, 7'-CH), 6.74 (d, *J*=1.5 Hz, 1 ¹H, 4'-CH), 6.66 (dd, *J*=8.0, 1.5 Hz, 1 ¹H, 6'-CH), 5.94 (d, *J*=1.5 Hz, 1 ¹H, OCHHO), 5.93 (d, *J*=1.5 Hz, 1 ¹H, OCHHO), 3.81 (app t, *J*=8.3 Hz, 1 ¹H, 4-CH), 3.78 (s, 3 ¹H, OCH₃), 3.44 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 3.09 (app t, *J*=8.4 Hz, 1 ¹H, 5-CHH), 3.03 (app t, *J*=9.2 Hz, 1 ¹H, 5-CHH), 2.59 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 2.49 (s, 3 ¹H, NCH₃), 1.88 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 176.0 (CO₂), 147.9 (3'-a-C), 147.0 (7'-a-C), 130.2 (5'-C), 122.3 (6'-C), 109.4 (4'-C), 108.3 (7'-C), 101.2 (OCH₂O), 68.0 (2-C), 66.5 (3-C), 60.0 (5-C), 53.0 (4-C), 52.8 (OCH₃), 42.6 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3376, 3317, 2946, 2841, 2785, 1727, 1252, 1236, 1036, 929. *R*_f: 0.21 (MeOH/CH₂Cl₂, 1:8).

4.5.6. (±)-Methyl (3*R*,4*S*)-3-amino-4-(1,3-benzodioxol-5-yl)-1-methylpyrrolidine-3-carboxylate **4c**

According to the general procedure, α -nitro ester **6c** (3.50 g, 11.4 mmol) afforded **4c** (2.40 g, 76%), as a off-white solid, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 6.76 (d, *J*=1.7 Hz, 1 ¹H, 4'-CH), 6.71 (d, *J*=8.1 Hz, 1 ¹H, 7'-CH), 6.68 (dd, *J*=8.1, 1.7 Hz, 1 ¹H, 6'-CH), 5.91 (s, 2 ¹H, OCH₂O), 3.34 (s, 3 ¹H, OCH₃), 3.29 (dd, *J*=8.6, 6.8 Hz, 1 ¹H, 4-CH), 3.23 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 3.23 (dd, *J*=8.8, 6.8 Hz, 1 ¹H, 5-CHH), 2.87 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 2.84 (app t, *J*=8.8 Hz, 1 ¹H, 5-CHH), 2.47 (s, 3 ¹H, NCH₃), 2.15 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 174.1 (CO₂), 147.5 (3'-a-C), 146.7 (7'-a-C), 132.0 (5'-C), 121.4 (6'-C), 108.5

(4'-C), 108.0 (7'-C), 101.0 (OCH₂O), 70.0 (3-C), 67.0 (2-C), 61.2 (5-C), 60.1 (4-C), 51.9 (OCH₃), 42.2 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3363, 3293, 2946, 2844, 2786, 1728, 1488, 1249, 1037, 807. HRMS [EI (*m/z*)] calcd for C₁₄H₁₈N₂O₄=278.1267, found for [M⁺]=278.1260 ($|\Delta|$ =2.4 ppm), peaks at (relative intensity): 278 (30), 148 (87), 57 (100), 42 (27). *R*_f: 0.20 (MeOH/CH₂Cl₂, 1:8). Mp=56–59 °C.

4.5.7. (±)-Methyl (3*R*,4*R*)-3-amino-4-(2-furyl)-1-methylpyrrolidine-3-carboxylate **3d**

According to the general procedure, α -nitro ester **5d** (3.10 g, 12.2 mmol) afforded **3d** (1.78 g, 65%), as a yellow oil, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.36 (dd, *J*=2.0, 0.7 Hz, 1 ¹H, 5'-CH), 6.32 (dd, *J*=3.2, 2.0 Hz, 1 ¹H, 4'-CH), 6.18 (dt, *J*=3.2, 0.7 Hz, 1 ¹H, 3'-CH), 3.95 (dd, *J*=9.3, 7.8 Hz, 1 ¹H, 4-CH), 3.80 (s, 3 ¹H, OCH₃), 3.39 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 3.10 (dd, *J*=9.3, 7.8 Hz, 1 ¹H, 5-CHH), 2.95 (t, *J*=9.3 Hz, 1 ¹H, 5-CHH), 2.48 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 2.43 (s, 3 ¹H, NCH₃), 1.59 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 175.8 (CO₂), 151.9 (2'-C), 142.3 (5'-C), 110.3 (4'-C), 108.1 (3'-C), 68.2 (2-C), 66.4 (3-C), 58.4 (5-C), 52.8 (OCH₃), 47.8 (4-C), 42.3 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3379, 3314, 2946, 2838, 2786, 1728, 1224, 736. HRMS [EI (*m/z*)] calcd for C₁₁H₁₆N₂O₃=224.1161, found for [M⁺]=224.1150 ($|\Delta|$ =4.9 ppm), peaks at (relative intensity): 224 (16), 101 (26), 94 (42), 57 (100), 42 (39). *R*_f: 0.24 (MeOH/CH₂Cl₂, 1:8).

4.5.8. (±)-Methyl (3*R*,4*S*)-3-amino-4-(2-furyl)-1-methylpyrrolidine-3-carboxylate **4d**

According to the general procedure, α -nitro ester **6d** (3.16 g, 12.4 mmol) afforded **4d** (1.70 g, 61%), as a yellow oil, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.30 (dd, *J*=1.9, 0.6 Hz, 1 ¹H, 5'-CH), 6.28 (dd, *J*=3.2, 1.9 Hz, 1 ¹H, 4'-CH), 6.07 (d, *J*=3.2 Hz, 1 ¹H, 3'-CH), 3.49 (dd, *J*=9.8, 7.0 Hz, 1 ¹H, 4-CH), 3.44 (s, 3 ¹H, OCH₃), 3.29 (dd, *J*=9.2, 7.0 Hz, 1 ¹H, 5-CHH), 3.11 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 2.89 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 2.78 (app t, *J*=9.5 Hz, 1 ¹H, 5-CHH), 2.45 (s, 3 ¹H, NCH₃), 2.12 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 173.9 (CO₂), 152.2 (2'-C), 141.6 (5'-C), 110.1 (4'-C), 106.3 (3'-C), 68.7 (3-C), 66.3 (2-C), 59.1 (5-C), 53.4 (4-C), 52.1 (OCH₃), 41.9 (NCH₃). FTIR [ν (cm⁻¹), neat]: 3374, 3297, 2946, 2840, 2785, 1726, 1207, 735. HRMS [EI (*m/z*)] calcd for C₁₁H₁₆N₂O₃=224.1161, found for [M⁺]=224.1150 ($|\Delta|$ =4.9 ppm), peaks at (relative intensity): 224 (16), 101 (26), 94 (42), 57 (100), 42 (39). *R*_f: 0.21 (MeOH/CH₂Cl₂, 1:8).

4.5.9. (±)-Methyl (3*R*,4*R*)-3-amino-1-methyl-4-(1-methyl-1*H*-indol-3-yl)pyrrolidine-3-carboxylate **3e**

According to the general procedure, α -nitro ester **5e** (2.90 g, 9.1 mmol) afforded **3e** (1.63 g, 62%), as a light brown sticky solid, after column chromatography (MeOH/CHCl₃, 1:20 $\rightarrow$ 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.49 (d, *J*=8.1 Hz, 1 ¹H, 4'-CH), 7.29 (d, *J*=8.1 Hz, 1 ¹H, 7'-CH), 7.21 (ddd, *J*=8.1, 6.5, 1.2 Hz, 1 ¹H, 6'-CH), 7.09 (ddd, *J*=8.1, 6.5, 1.0 Hz, 1 ¹H, 5'-CH), 7.01 (s, 1 ¹H, 2'-CH), 4.27 (dd, *J*=9.8, 7.6 Hz, 1 ¹H, 4-CH), 3.77 (s, 3 ¹H, OCH₃), 3.76 (s, 3 ¹H, 1'-NCH₃), 3.53 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 3.17 (dd, *J*=8.9, 7.6 Hz, 1 ¹H, 5-CHH), 3.06 (app t, *J*=9.5 Hz, 1 ¹H, 5-CHH), 2.59 (d, *J*=9.8 Hz, 1 ¹H, 2-CHH), 2.50 (s, 3 ¹H, 1-NCH₃), 1.65 (br s, 2 ¹H, NH₂). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 176.3 (CO₂), 136.9 (7'-a-C), 127.89 (3'-a-C), 127.86 (2'-C), 121.9 (6'-C), 119.3 (5'-C), 119.1 (4'-C), 109.3 (7'-C), 108.9 (3'-C), 68.0 (2-C), 65.4 (3-C), 60.1 (5-C), 52.6 (OCH₃), 45.6 (4-C), 42.6 (1-NCH₃), 32.8 (1'-NCH₃). FTIR [ν (cm⁻¹), neat]: 3369, 3299, 3047, 2945, 2836, 2783, 1725, 1474, 1216, 741. HRMS [ESI (*m/z*)] calcd for (C₁₆H₂₁N₃O₂+H)⁺=288.17120, found 288.17104 ($|\Delta|$ =0.57 ppm). *R*_f: 0.16 (MeOH/CH₂Cl₂, 1:8).

4.5.10. (±)-Methyl (3*R*,4*S*)-3-amino-1-methyl-4-(1-methyl-1*H*-indol-3-yl)pyrrolidine-3-carboxylate **4e**

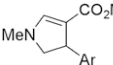
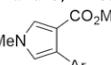
According to the general procedure, α -nitro ester **6e** (3.20 g, 10.1 mmol) afforded **4e** (1.74 g, 60%), as a light yellow oil, after

column chromatography (MeOH/CHCl₃, 1:20 → 1:10). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.66 (app dt, *J*=8.1, 1.0 Hz, 1 ¹H, 4'-CH), 7.23 (app dt, *J*=8.3, 1.0 Hz, 1 ¹H, 7'-CH), 7.18 (ddd, *J*=8.0, 6.8, 1.2 Hz, 1 ¹H, 6'-CH), 7.09 (ddd, *J*=8.0, 6.8, 1.2 Hz, 1 ¹H, 5'-CH), 6.89 (s, 1 ¹H, 2'-CH), 3.77 (dd, *J*=10.0, 6.8 Hz, 1 ¹H, 4-CH), 3.69 (s, 3 ¹H, 1'-NCH₃), 3.31 (dd, *J*=9.3, 6.8 Hz, 1 ¹H, 5-CHH), 3.29 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 3.12 (s, 3 ¹H, OCH₃), 2.96 (d, *J*=10.0 Hz, 1 ¹H, 2-CHH), 2.94 (app t, *J*=9.5 Hz, 1 ¹H, 5-CHH), 2.55 (br s, 2 ¹H, NH₂), 2.51 (s, 3 ¹H, 1-NCH₃). ¹³C NMR [75 MHz, δ (ppm), CDCl₃]: 174.4 (CO₂), 136.7 (7'-a-C), 128.0 (3'-a-C), 126.5 (2'-C), 121.7 (6'-C), 119.2, 119.1, 110.9 (3'-C), 109.1 (7'-C), 70.1 (3-C), 66.5 (2-C), 61.5 (5-C), 51.6 (OCH₃), 51.5 (4-C), 42.3 (1-NCH₃), 32.7 (1'-NCH₃). FTIR [*ν* (cm⁻¹), neat]: 3361, 3295, 3049, 2944, 2840, 2787, 1727, 1473, 1210, 740. HRMS [EI (*m/z*)] calcd for C₁₆H₂₁N₃O₂=287.1634, found for [M⁺]=287.1636 (Δ=0.8 ppm), peaks at (relative intensity): 287 (29), 157 (100), 144 (32), 57 (45). *R*_f: 0.14 (MeOH/CH₂Cl₂, 1:8).

Supplementary data

Experimental details and full characterization data, copies of ¹H and ¹³C NMR spectra for all new compounds, are available free of charge via the Internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.059.

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