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Design and synthesis of long-acting inhibitors of dipeptidyl peptidase IV

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Abstract—A series of (4-substituted prolyl)prolinenitriles were synthesized and evaluated as inhibitors of dipeptidylpeptidase IV (DPP-IV). Among those tested, the 4β-[4-(hydroxyphenyl)prolyl]prolinenitriles showed a potent inhibitory activity with a long duration of action. Metabolic formation of the corresponding phenol glucuronates was found to contribute to their long duration of action. The activity profiles of the synthesized compounds are reported and structure–activity relationships are also presented.

1. Introduction

Recently, the prevalence of type 2 diabetes mellitus has increased dramatically, possibly as a consequence of a more sedentary lifestyle and the adoption of a Western diet.[1] Current treatment strategies include reducing insulin resistance by using glitazones,[2] supplementing the insulin deficiency with exogenous insulin,[3] increasing endogenous insulin secretion with sulfonylureas,[4] reducing hepatic glucose output with biguanides,[5] and limiting glucose absorption with glucosidase inhibitors.[6] To complement these currently available treatments for diabetes, new approaches are emerging. Of particular interest is the pharmacology surrounding glucagon-like peptide 1 (GLP-1).[7] LP-1 is a hormone that stimulates the secretion of insulin in a glucose-dependent manner, which is beneficial for the control of glucose homeostasis in patients with type 2 diabetes.[8]

GLP-1 is rapidly truncated after its secretion in the ileum by dipeptidyl peptidase IV (DPP-IV, EC3.4.14.5) located on the capillary endothelium proximal to the L-cells from which GLP-1 is secreted. Inhibition of DPP-IV prevents the degradation of incretin hormones such as GLP-1 and glucose-dependent insulinotropic peptide (GIP), and has been demonstrated to increase the levels of these peptides in various species.[9]

DPP-IV is a 240 kDa, 766 residue *N*-terminal dipeptidyl exopeptidase that is composed of two 110 kDa subunits and exists as both a membrane-bound protein and as a soluble protein in plasma.[10] It is a nonclassical serine protease that exhibits a high specificity for peptides with proline or alanine at the *P1* position.

Clinical evidence has shown that low molecular weight inhibitors of DPP-IV lower the blood glucose level, increase glucose tolerance, and improve the insulin response to an oral glucose load in patients with type 2 diabetes.[11] Low molecular weight reversible inhibitors of DPP-IV have been studied for the past several years, and structure–activity relationship (SAR) data have been accumulated.[12]

Many inhibitors with a cyanopyrrolidine structure have been reported, as illustrated in Figure 1, and some of them are currently undergoing clinical evaluation for the treatment of type 2 diabetes.[13–15] It is well known that DPP-IV inhibitors possessing prolylprolinenitrile scaffold suffer from chemical instability as illustrated in Scheme 1a. In an effort to solve this problem, several types of inhibitors of this class have been reported.[16] But no report on inhibitors possessing 4-β-phenylprolylprolinenitrile has been found. Here we report the discovery of [4-(hydroxyphenyl)prolyl]prolinenitrile dipeptides that are highly effective long-acting inhibitors

Keywords: DPP-IV inhibitor; Prolylprolinenitriles; Glucuronate.
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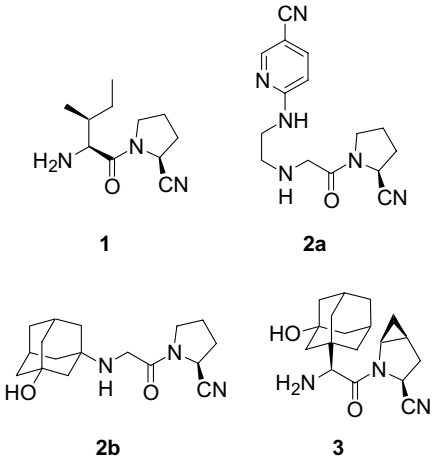


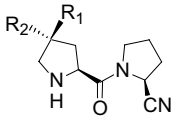
Figure 1. Prolinenitrile-derived dipeptidyl peptidase IV inhibitors.

of DPP-IV. We also present data demonstrating that these phenolic DPP-IV inhibitors, which form the corresponding glucuronate as an active metabolite after oral administration, effectively reduce plasma DPP-IV activity in rats and show a long duration of action (Fig. 2).

2. Chemistry

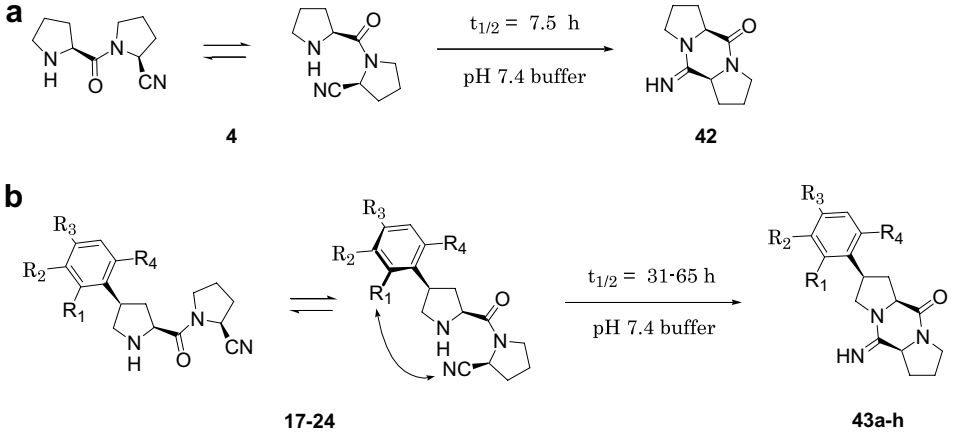
Synthesis of the test compounds listed in Tables 1 and 2 is outlined in Schemes 2–4. Synthesis of the initial lead 4-phenylprolylprolinenitriles **11**–**12** is described in Scheme 2. Condensation of **25a**, which was prepared from the corresponding amine,[17] with L-prolinenitrile in the presence of 1-methanesulfonyloxy-1*H*-benzotriazole afforded **26a**. Another diastereomer **26b** was prepared from commercially available **25b** by the same procedure. Acidic deprotection of **26a**–**b** resulted in the production of **11**–**12** as acid salts.

Table 1. In vitro inhibition for human DPP-IV and ex vivo plasma DPP-IV inhibition in normal rats



Compound	R_1	R_2	Human DPP-IV IC_{50} (nM)	Plasma DPP-IV inhibition (%) at 1 mg/kg po, normal rats 6 h
4	H	H	20	20
5	allyl	H	3.5	38
6	propyl	H	3.4	50
7	methallyl	H	5.7	27
8	isobutyl	H	2.9	40
9	c-hexyl	H	2.4	38
10	2-adamantyl	H	7.8	47
11	Ph	H	3.5	60
12	H	Ph	16	17
13	2,6-diMe-Ph	H	6.1	91

The synthesis of 4β-alkylprolylprolinenitriles **5**–**10** is described in Scheme 3. Key intermediates **32a**–**b** were prepared from dimethyl L-glutamate **27**. Stereoselective C4-alkylation of **27** with allyl bromide and methallyl bromide afforded **28a** and **28b**,[18] respectively. Acidic



Scheme 1. Presumed intramolecular cyclization.

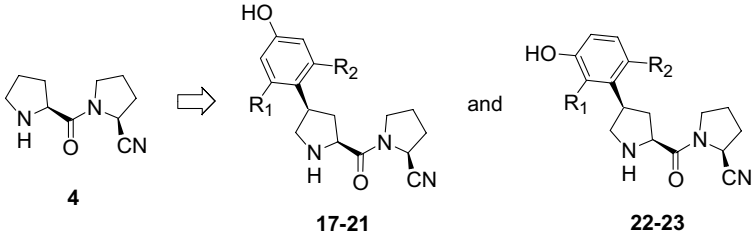
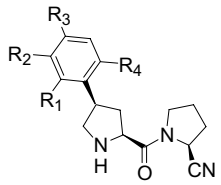


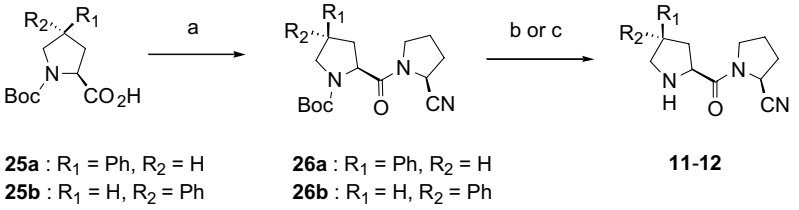
Figure 2. Molecular design of long-acting dipeptidyl peptidase IV inhibitors.

Table 2. In vitro inhibition for human DPP-IV, ex vivo plasma DPP-IV inhibition in normal rats, bio availability, and solution stability



Compound	R_1	R_2	R_3	R_4	Human DPPIV IC_{50} (nM)	Plasma DPP-IV inhibition (%) at 1 mg/kg po, normal rats		*F* (%)	Solution stability (pH 7.4) $t_{1/2}$ (h)
						6 h	10 h		
14	OH	H	H	H	9.1	43	NT[a]	NT[a]	3.2
15	H	OH	H	H	3.9	77	NT[a]	NT[a]	20
16	H	H	OH	H	2.5	85	NT[a]	NT[a]	21
17	Me	H	OH	Me	3.3	88	57	3	31
18	OMe	H	OH	Me	8.3	90	73	0.1	49
19	OMe	H	OH	OMe	23	81	66	NT[a]	59
20	Me	H	OH	Et	8.9	86	NT[a]	NT[a]	39
21	OEt	H	OH	OEt	22	79	50	NT[a]	NT[a]
22	Me	OH	H	Me	4.9	95	83	3	65
23	OMe	OH	H	Me	7.1	94	86	2	NT[a]
24	Me	OH	Me	Me	5.3	39	NT[a]	NT[a]	40

[a] Not tested.



25a : R_1 = Ph, R_2 = H
25b : R_1 = H, R_2 = Ph

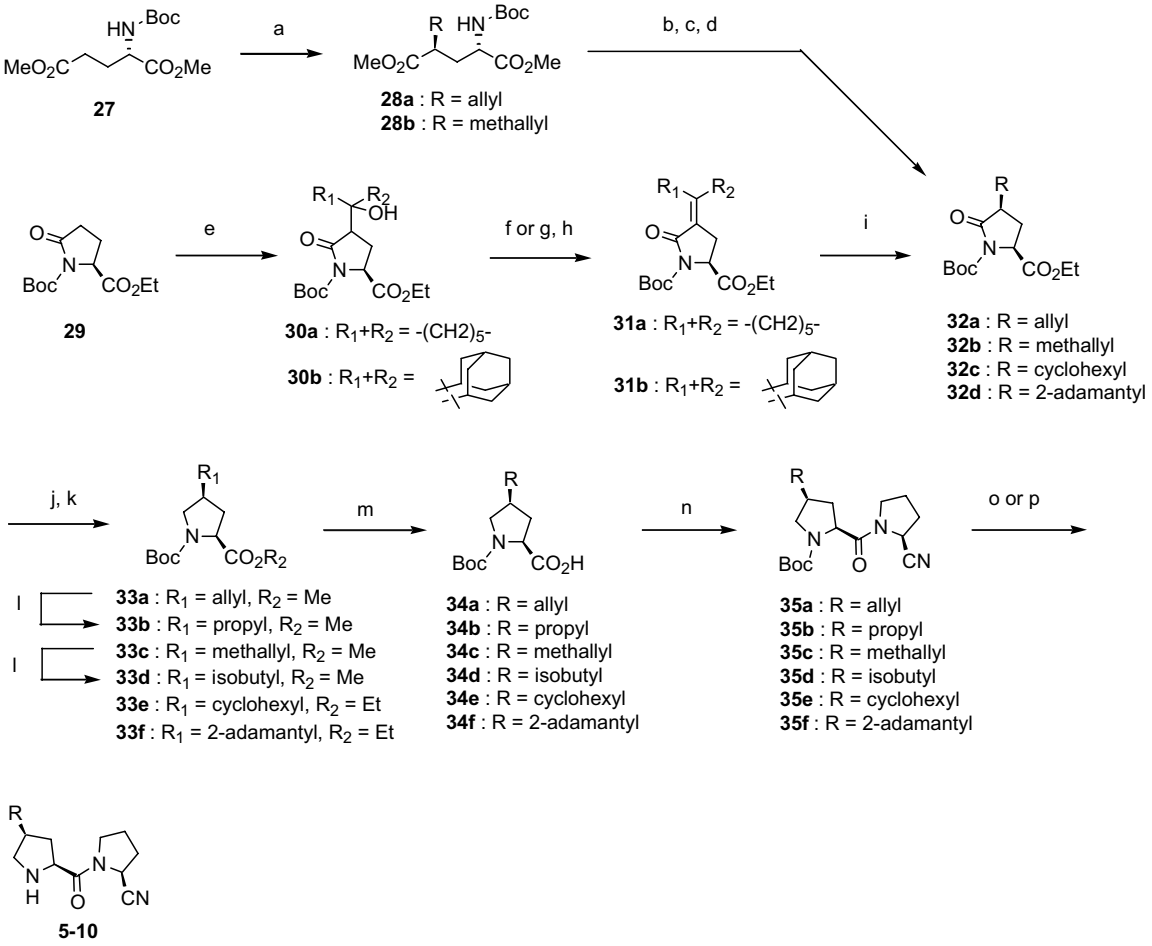
26a : R_1 = Ph, R_2 = H
26b : R_1 = H, R_2 = Ph

11-12

Scheme 2. Synthesis of **11**–**12**. Reagents: (a) L-ProCN, MsOBt, Et_3N, DMF; (b) $PhSO_3H$, EtOH; (c) 4 N HCl/EtOAc.

deprotection of **28a**–**b**, followed by intramolecular cyclization and then *N*-protection, resulted in **32a**–**b**, respectively. Other key intermediates **32c**–**d** were prepared from ethylpyroglutamate **29** as described below. C4-Alkylation of **29** with cyclohexanone and 2-adamantanone afforded **30a**–**b**,[19] respectively. Dehydration of **30a**–**b** gave **31a**–**b**, respectively. Stereoselective catalytic hydrogenation of **31a**–**b** was carried out in the presence of platinum oxide, resulting in **32c**–**d**,[19] respectively. Lithium triethyl borohydride reduction of **32a**–**d**, followed by treatment with triethylsilane in the presence of boron trifluoride–etherate, led to **33a**, **33c**, and **33e**–**f**,[20] respectively. Catalytic hydrogenation of **33a** and **33c** produced a propyl derivative and an isobutyl derivative **33b** and **33d**, respectively. Alkaline hydrolysis of **33a**–**f** afforded their corresponding carboxylic acids **34a**–**f**, respectively. Dehydrative condensation of **34a**–**f** with L-prolinenitrile resulted in **35a**–**f**, respectively. Acidic deprotection of **35a**–**f** with *p*-toluenesulfonic acid or 4 N hydrogen chloride in dioxane gave **5**–**10**, respectively, as the corresponding acid salts.

The synthesis of **13**–**24** is outlined in Scheme 4. Treatment of **36** with sodium hexamethyldisilazane, followed by the addition of *N*-phenyl-bis(trifluoromethanesulfonimide), provided **37**, after which the Suzuki coupling reaction with an appropriate phenylboronic acid or pinacol phenylborate afforded **38a**–**l**, respectively. Stereoselective catalytic hydrogenation of **38a**–**g**, **38i**, and **38l** gave **39a**–**g**, **39i**, and **39l**, respectively. Catalytic hydrogenation of **38h** and **38j**–**k** was carried out after removal of the *N*-Boc residue, because the reaction then proceeded more smoothly for steric reasons. For such a reason, acidic deprotection of **38h** and **38j**–**k** was carried out prior to catalytic hydrogenation. Stereoselective hydrogenation, followed by reprotection of the corresponding deprotected products, gave **39h** and **39j**–**k**, respectively. Protection of **39b**, **39e**, and **39k** as a benzyl ether led to **39m**, **39p**, and **39q**, respectively. Protection of **39c** and **39d** as a tetrahydropyranylether afforded **39n** and **39o**, respectively. Alkaline hydrolysis of **39a**, **39m**–**p**, **39f**–**j**, **39q**, and **39l** resulted in **40a**–**l**, respectively. Dehydrative condensation of **40a**–**l** with L-prolinenitrile in the presence of EDC afforded **41a**–**l**, respectively. Catalytic hydrogenation of **41b**, **41e**, and **41k** gave the corresponding phenol derivatives **41m**–**o**, respectively. Acidic deprotection of **41a**, **41m**, **41c**–**d**, **41n**, **41f**–**j**, **41o**, and **41l** with 4 N hydrogen chloride or



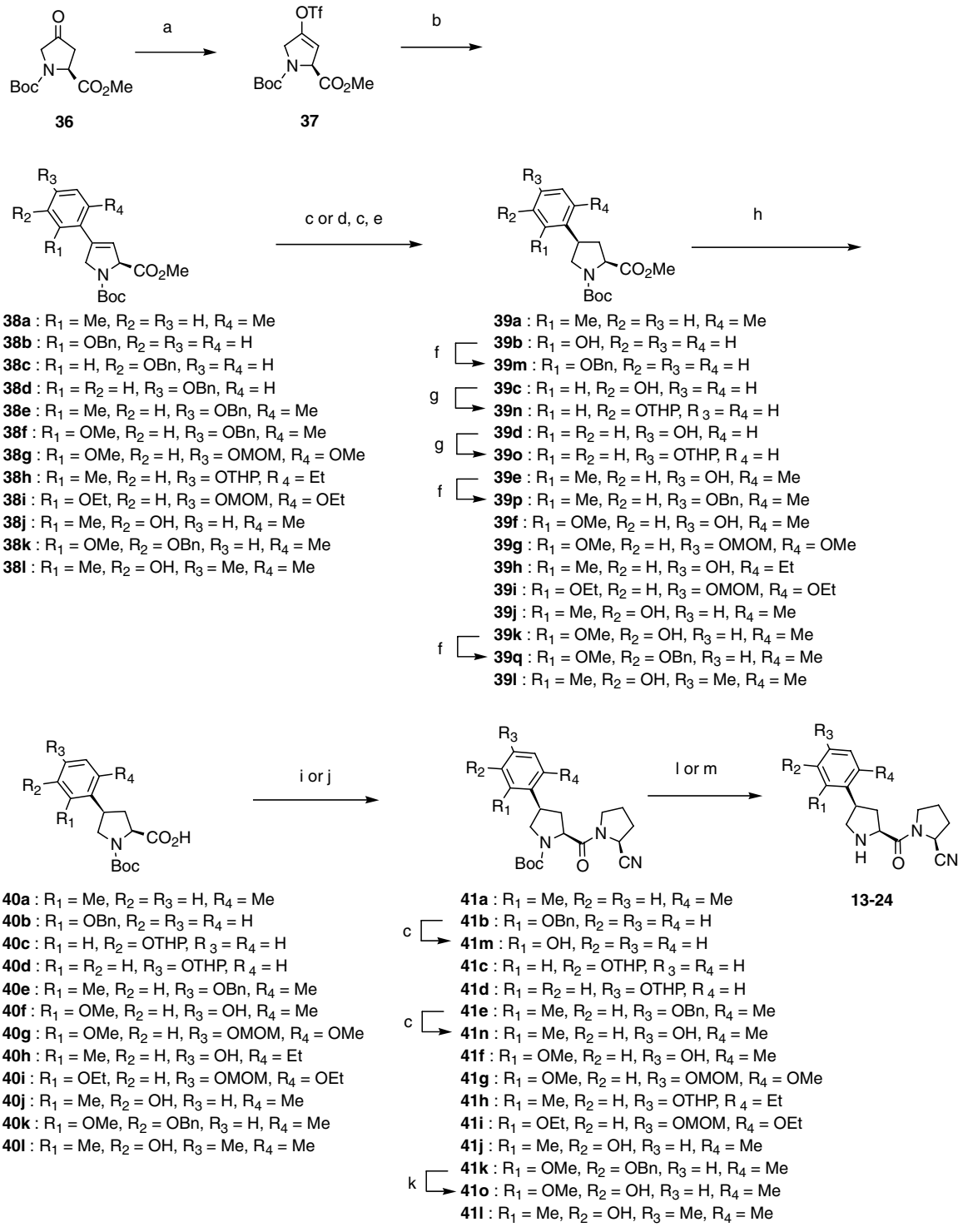
Scheme 3. Synthesis of **5**–**8**. Reagents: (a) LiHMDS, RBr, THF; (b) TFA, CH_2Cl_2; (c) toluene, reflux; (d) Boc_2O, DMAP, CH_3CN; (e) LiHMDS, $R_1R_2C=O$, $BF_3{\cdot}OEt_2$, THF; (f) MsCl, Et_3N, CH_2Cl_2; (g) *p*-TsOH·H_2O, toluene; (h) Boc_2O, DMAP, CH_2Cl_2; (i) H_2, PtO_2; (j) $LiEt_3BH$, THF; (k) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (l) H_2, 10% Pd–C, MeOH; (m) NaOH aq, MeOH; (n) L-ProCN, MsOBt, Et_3N, DMF; (o) TsOH·H_2O, EtOH; (p) 4N HCl/1,4-dioxane.

p-toluenesulfonic acid led to the production of **13**–**24**, respectively.

3. Results and discussion

All of the compounds listed in Tables 1 and 2 were tested in vitro against purified human DPP-IV.[21] Inhibition was determined by using the synthetic substrate H-Gly-Pro-AMC. Production of 7-amino-4-methyl coumarin (AMC) was measured over 15 min at 460 nm.[22] Plasma DPP-IV inhibition (%) after oral administration (1 mg/kg) was monitored over 6 h and/or 10 h periods in normal rats as an ex vivo experiment.

During the screening of long-acting DPP-IV inhibitors, we discovered that 4β-(4-alkylprolyl)prolinenitriles showed stronger inhibitory activity relative to the unsubstituted prolylprolinenitrile analog **4**, as seen in Table 1. Because of the relative ease of synthesis,[23] a 4β-allyl analog **5** and a 4β-metallyl analog **7** were synthesized and evaluated. Both **5** and **7** showed more potent in vitro activity than **4**. Other 4β-alkyl analogs **6** and **8**–**10** also showed more potent in vitro activity and a longer duration of ex vivo activity than **4**. Based on the above data, the *S*2 pocket of DPP-IV was shown to accept fairly large substituents, such as 2-adamantyl and isobutyl. Introduction of a phenyl residue at the 4-position of the prolyl residue of **4** afforded two 4-phenylprolyl analogs **11** and **12**. The 4β-phenyl analog **11** exhibited stronger inhibitory activity and a longer duration of action than **4**, while the corresponding 4α-isomer **12** exhibited nearly the same inhibitory activity and duration of action as **4**. In order to prevent intramolecular cyclization (as shown in Scheme 1b) that might deactivate the inhibitors, a 2,6-dimethylphenyl residue was introduced at the 4β-position of the prolyl moiety, producing **13** with retained inhibitory activity and a longer duration of action. Ex vivo monitoring of plasma DPP-IV inhibition after oral administration revealed an interesting difference between aliphatic and aromatic analogs. As illustrated in Figure 3, the 4β-phenyl analog **11** once showed a reduction of DPP-IV inhibitory activity at 1 h after oral dosing, followed by the recovery of potent inhibitory activity, while alkyl analog **6** showed the predicted inhibition curve followed by regular recovery of plasma DPP-IV activity. These unexpected ex vivo data for **11** after oral dosing prompted us to search for an active metabolite. As a result, a glucuronated metabolite, which was thought to be produced by metabolic



Scheme 4. Synthesis of **13**–**24**. Reagents: (a) NaHMDS, $PhNTf_2$, THF; (b) $ArB(OH)_2$ or ArBPin, Na_2CO_3 aq, $Pd(Ph_3P)_4$, 1,4-dioxane; (c) H_2, 10% Pd–C, MeOH; (d) 4N HCl/1,4-dioxane; (e) Boc_2O, $NaHCO_3$ aq, THF; (f) BnBr, K_2CO_3, DMF; (g) DHP, PPTS, CH_2Cl_2; (h) NaOH aq, MeOH; (i) L-ProCN, EDC, HOBt, NMM, DMF; (j) L-ProCN, MsOBt, Et_3N, DMF; (k) H_2, 20% $Pd(OH)_2$–C, EtOAc; (l) 4N HCl/1,4-dioxane; (m) *p*-TsOH·H_2O, EtOH.

hydroxylation of the phenyl residue followed by glucuronidation of the hydroxy residue thus formed, was detected by LC/MS/MS of plasma.[24]

Based on our speculation about the metabolic pathway of **11** (hydroxylation of the phenyl residue, followed by glucuronidation of the phenol residue thus formed), molecular design focused on chemical modification of phenol analogs, as illustrated in Table 2. Three phenol isomers (*ortho*-, *meta*, and *para* isomers) **14**–**16** were prepared and evaluated. Among them, the *meta*- and *para* isomers of **15** and **16** showed almost the same in vitro activity and duration of ex vivo activity, while the *ortho* isomer **14** was less potent in vitro and had a shorter

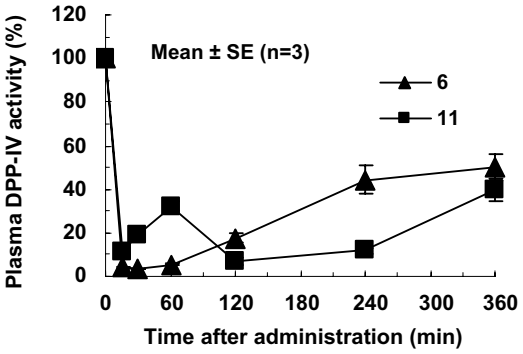


Figure 3. Plasma DPP-IV activities after oral administration of compounds **6** and **11** in normal rats.

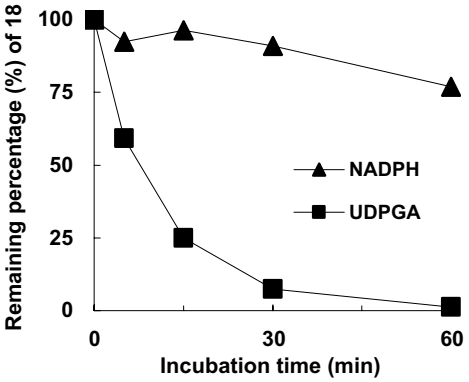


Figure 4. Metabolism of **18** in rat liver microsome.

duration of ex vivo activity. The stability of these three isomers **14**–**16** in solution at pH 7.4 was also evaluated. The *meta* and *para* isomers **15** and **16** exhibited more stability than the *ortho* isomer **14**. Based on the information shown in Table 1, a series of 4-(2,6-disubstituted hydroxyphenyl) analogs **17**–**21** were prepared and evaluated. All of these compounds (**17**–**21**) showed a relatively long duration of ex vivo activity regardless of their in vitro inhibitory potency. These compounds tended to inhibit plasma DPP-IV activity by >50% at 10 h after oral dosing. A series of 4-(2,6-disubstituted 3-hydroxyphenyl) analogs **22**–**24** was also synthesized and evaluated. Among them, the trisubstituted analogs **22**–**23** showed the longest duration of action, while the tetra-substituted analog **24** showed an unexpectedly short duration of ex vivo activity despite its considerably increased stability in solution. With **24**, plasma DPP-IV inhibition at 6 h after oral dosing showed a shorter duration than for **14**–**17**. Analogs **17**–**24** tended to show increased stability in solution relative to **14**–**16**.

Despite their long duration of ex vivo activity, analogs **17**–**18** and **22**–**23** showed very low bioavailability, which strongly suggested the production of an active metabolite after oral dosing. Difficulty in achieving glucuronate formation by **14** and **24** because of their sterically hindered phenol residues was thought to cause the shorter duration of actions, while the other compounds listed in Table 2 were estimated to show a long duration of action like their corresponding active metabolites (glucuronates).

Compound **18** is one of the compounds which showed long duration of action for its extremely low bioavailability. For such a reason, we investigated metabolism of **18** as a representative example among them. To evaluate glucuronate formation in rat liver microsomes and the inhibitory activity of the glucuronate, compound **18** was incubated with rat liver microsomes in the presence of NADPH or UDPGA. As shown in Figure 4, incubation of the phenol analog **18** by rat liver microsomes in the presence of NADPH produced no metabolites, while incubation of **18** with rat liver microsomes in the presence of UDPGA resulted in rapid disappearance of the parent compound due to the presumed production of the corresponding glucuronate, the structure of which was determined by LC/MS/MS. This glucuronate had almost the same inhibitory activity as the parent compound **18**, as shown in Figure 5. Incubation of **18** with rat liver microsomes in the presence of NADPH did not abolish its inhibitory activity, while incubation of **18** with rat liver microsomes in the presence of UDPGA maintained nearly the same inhibitory activity as the parent compound.

To evaluate the contribution of glucuronate formation to the long duration of action, the blood concentration profile of **18** (longer duration) and **24** (shorter duration) was monitored after oral dosing, as shown in Table 3. Without glucuronidase treatment of the plasma, the

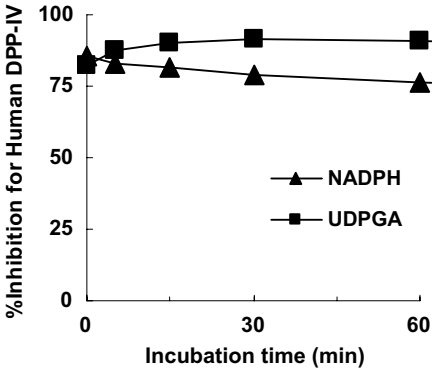


Figure 5. Inhibitory activity of the metabolite of **18** in rat liver microsome.

Table 3. Blood concentration of test compounds **18** and **24** after their oral dosing (1 mg/kg)

Compound	Time (h) after administration	Blood concentration (ng/mL)	
		Without glucuronidase treatment	With glucuronidase treatment
18	0.25	0.49	88
	2	ND[a]	61
	6	ND[a]	39
24	0.25	9.7	100
	2	0.65	9.5
	6	0.95	ND[a]

[a] Not detected.

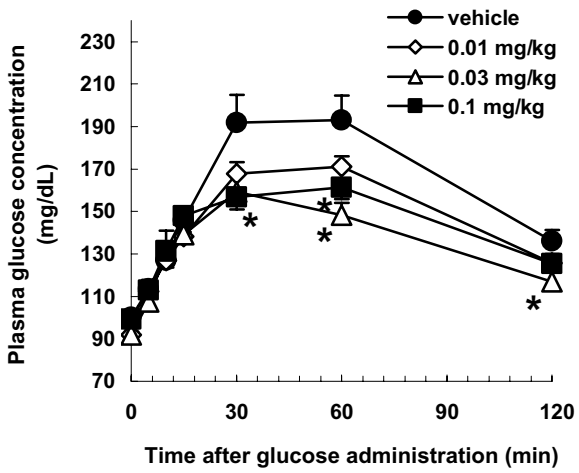


Figure 6. Effects of inhibitor **22** dosed at 0.01, 0.03, and 0.1 mg/kg po versus vehicle control on plasma glucose after an oGTT in normal rats. *$p < 0.05$ versus vehicle by Student's t-test. Mean ± SE ($n = 8$).

blood concentrations of both compounds at 0.25 h after oral dosing were very low, while their blood levels after glucuronidase treatment of plasma were extremely different. The blood concentration of **18** was much higher than that of **24**. On the basis of the data described above, compound **18** was considered to be much more effectively glucuronated than **24**. More effective glucuronidation was speculated to protect this compound from further inactivation by intramolecular cyclization and other mechanisms.

Compound **22**, which is one of the representative inhibitors from this series, was evaluated to determine its effect on the plasma glucose level after the oGTT in normal rats. The vehicle or the inhibitor **22** (0.01, 0.03, and 0.1 mg/kg) was given orally and the plasma glucose concentration was monitored after an oral glucose load (1 g/kg). As shown in Figure 6, dose-dependent suppression of plasma glucose was observed.

In summary, we discovered a series of 4β-[4-(hydroxyphenyl)prolyl]prolinenitriles that are long-acting inhibitors of DPP-IV. Their corresponding glucuronates, which were metabolically produced after oral administration, were found to show a long duration of ex vivo activity. Stability in solution was increased by 2,6-disubstitution (Scheme 1b) of the 4β-(hydroxyphenyl) residues, although glucuronate formation made a greater contribution to a longer duration of ex vivo activity than to an increase of stability. A representative compound exhibited a suppressive effect on the plasma glucose concentration. More details will be reported in due course.

4. Experimental

4.1. Chemistry

Analytical samples were homogeneous as confirmed by TLC and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra (^{1}H NMR) were taken on a Varian Mercury 300 spectrometer using deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) as the solvent. The chemical shift values are reported in parts per million (δ) and coupling constants (J) in hertz (Hz). Fast atom bombardment mass spectra (FAB-MS, HRMS) and electron ionization (EI) were obtained on a JEOL JMS-700 spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a HITACHI M-1200H spectrometer. Matrix-assisted laser desorption ionization (MALDI) mass spectra were obtained on a PerSeptive Biosystems VoyagerTM Elite spectrometer. Infrared spectra (IR) were measured in a JASCO FT/IR-430 spectrometer. Column chromatography was carried out on silica gel [Merck silica gel 60 (0.063–0.200 mm), Wako gel C200 or Fuji Silysia FL60D]. Thin-layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, silica gel 60 F254). The following abbreviations for solvents and reagents are used; tetrahydrofuran (THF), diethyl ether (Et_2O), dimethylsulfoxide (DMSO), ethyl acetate (EtOAc), dimethylformamide (DMF), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), methanol (MeOH), ethanol (EtOH), acetic acid (AcOH), and hydrochloric acid (HCl).

4.1.1. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-phenyl-2-pyrrolidinecarboxylic acid (25a). To a stirred solution of methyl (2*S*,4*R*)-4-phenyl-2-pyrrolidinecarboxylate (524 mg, 2.56 mmol) in EtOH (3 mL) was added di-*tert*-butyl-dicarbonate (655 mg, 3.00 mmol) at room temperature. After being stirred for 15 h, the reaction mixture was diluted with EtOAc. The organic layer was successively washed with 10% aqueous citric acid, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. To a stirred solution of the resulting residue in MeOH (5 mL) was added 1 M NaOH (3 mL) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with 1 M HCl (3 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield **25a** (635 mg, 85%) as a white powder. TLC $R_f = 0.36$ ($CHCl_3$/MeOH, 9/1); MS (APCI, Neg. 20 V) m/z 290 $(M-H)^-$; H NMR (300 MHz, $CDCl_3$) δ 1.45 and 1.49 (s, 9H), 2.01–2.47 (m, 1H), 2.54–2.87 (m, 1H), 3.16–3.56 (m, 2H), 3.91–4.21 (m, 1H), 4.24–4.64 (m, 1H), 7.02–7.48 (m, 5H).

4.1.2. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-phenyl-1-pyrrolidinecarboxylate (26a). To a stirred solution of **25a** (590 mg, 2.03 mmol) in DMF (10 mL) were added (2*S*)-2-pyrrolidinecarbonitrile hydrochloride (268 mg, 2.01 mmol), 1-methanesulfonyloxy-1*H*-benzotriazole (433 mg, 2.10 mmol), and triethylamine (0.57 mL, 4.1 mmol) at 0 °C. After being stirred at room temperature for 15 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was successively washed with 10% aqueous citric acid, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/2) as an eluant to yield **26a** (562 mg, 75%) as a white powder. TLC $R_f = 0.61$ ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 370 $(M+H)^+$; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.41 and 1.44 (s, 9H), 2.06–2.43 (m, 5H), 2.51–2.71 (m, 1H), 3.27–3.44 (m, 1H), 3.44–3.56 (m, 1H), 3.56–3.72 (m, 1H), 3.74–4.24 (m, 2H), 4.39–4.65 (m, 1H), 4.79–4.99 (m, 1H), 7.10–7.50 (m, 5H).

According to the same procedure as described above, **26b** was prepared from **25b**.

4.1.3. *tert*-Butyl (2*S*,4*S*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-phenyl-1- pyrrolidinecarboxylate (26b). Yield 66%. A white powder. TLC $R_f = 0.64$ (CH_2Cl_2/MeOH, 9/1); MS (APCI, pos. 20 V) *m*/*z* 370 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 and 1.45 (s, 9H), 2.09–2.43 (m, 6H), 3.32–3.54 (m, 1H), 3.56–3.91 (m, 3H), 3.98–4.16 (m, 1H), 4.51 and 4.62 (dd, $J = 8.1$, 2.3 Hz, 1H), 4.83–4.91 (m, 1H), 7.16–7.44 (m, 5H).

4.1.4. (2*S*)-1-{[(2*S*,4*R*)-4-Phenyl-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile benzenesulfonate (11). A solution of **26a** (1.61 g, 4.37 mmol) and benzenesulfonic acid (1.04 g, 6.56 mmol) in EtOH (8 mL) was refluxed for 3 h. The reaction mixture was concentrated in vacuo. The resulting crystalline solid was collected by filtration and washed with hexane–EtOAc to yield **11** (1.28 g, 69%) as a white powder. TLC $R_f = 0.45$ ($CHCl_3$/MeOH/H_2O, 10/2/0.1); MS (APCI, pos. 20 V) *m*/*z* 270 $(M+H)^+$; IR (KBr) 3448, 3085, 2244, 1660, 1226, 1161, 1148, 1123, 1015, 608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.74–1.89 (m, 1H), 1.95–2.09 (m, 2H), 2.09–2.34 (m, 2H), 2.89–3.03 (m, 1H), 3.18–3.29 (m, 1H), 3.49–3.66 (m, 3H), 3.66–3.77 (m, 1H), 4.61 (dd, $J = 10.6$, 7.6 Hz, 1H), 4.86 (dd, $J = 8.0$, 4.8 Hz, 1H), 7.23–7.40 (m, 8H), 7.55–7.62 (m, 2H), 9.21 (s, 2H); HRMS (FAB) calcd for $C_{16}H_{20}N_3O$: 270.1606. Found: 270.1606.

4.1.5. (2*S*)-1-{[(2*S*,4*S*)-4-Phenyl-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride (12). To a solution of **26b** (421 mg, 1.14 mmol) in EtOAc (4 mL) was added 4M HCl in EtOAc (2 mL). After 3 h, the reaction mixture was concentrated in vacuo. The resulting crystalline solid was washed with EtOAc to yield **12** (205 mg, 59%) as a white powder. TLC $R_f = 0.43$ (CH_2Cl_2/MeOH, 9/1); MS (APCI, pos. 20 V) *m*/*z* 270 $(M+H)^+$; IR (KBr) 3440, 2242, 1654, 1495, 1455, 1446, 1348, 763, 704, 523 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.96–2.34 (m, 4H), 2.41–2.48 (m, 1H), 3.07–3.29 (m, 1H), 3.34–3.51 (m, 1H), 3.52–3.85 (m, 4H), 4.75 (s, 1H), 4.84 (dd, $J = 7.9$, 4.6 Hz, 1H), 7.13–7.54 (m, 5H), 8.93 (s, 1H), 10.76 (s, 1H); HRMS (FAB) calcd for $C_{16}H_{20}N_3O$: 270.1606. Found: 270.1604.

4.1.6. Dimethyl (2*S*,4*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-(2-methyl-2-propen-1-yl)pentanedioate (28b). Compound **28b** was prepared from **27** according to the method reported by Hanessian et al.[18] To a stirred solution of lithium bis(trimethylsilyl)amide in THF (32 mL, 1.0 M) was added dropwise a solution of **27** (4.13 g, 15.0 mmol) in THF (45 mL) at −78 °C. After being stirred for 30 min, a solution of methallyl bromide (4.05 g, 30 mmol) in THF (45 mL) was added and the reaction mixture was stirred at −78 °C for additional 3 h. The reaction mixture was quenched with 1 M HCl and extracted with EtOAc. The organic layer was successively washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/5) as an eluant to yield **28b** (4.41 g, 89%) as a colorless oil. TLC $R_f = 0.55$ (EtOAc/hexane, 1/2); MS (APCI, pos. 20 V) *m*/*z* 330 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.71 (s, 3H), 1.93–2.03 (m, 2H), 2.20 (dd, $J = 14.0$, 7.1 Hz, 1H), 2.29–2.41 (m, 1H), 2.64–2.76 (m, 1H), 3.65 (s, 3H), 3.73 (s, 3H), 4.31–4.42 (m, 1H), 4.68–4.72 (m, 1H), 4.76–4.82 (m, 1H), 4.91–5.02 (m, 1H).

4.1.7. 1-*tert*-Butyl 2-methyl (2*S*,4*S*)-4-(2-methyl-2-propen-1-yl)-5-oxo-1,2-pyrrolidinedicarboxylate (32b). Compound **32b** was prepared from **28b** according to the method reported by Hanessian and Margarita[18] To a stirred solution of **28b** (4.41 g, 13.4 mmol) in CH_2Cl_2 (13 mL) was added trifluoroacetic acid (13 mL) at room temperature. After being stirred for 50 min, the reaction mixture was concentrated in vacuo and diluted with EtOAc. The organic layer was successively washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was diluted with toluene (40 mL), refluxed for 2 h, and evaporated. To a stirred solution of the resulting residue in CH_2Cl_2 (55 mL) were added 4-(dimethylamino)pyridine (1.71 g, 14.0 mmol) and di-*tert*-butyl-dicarbonate (2.55 g, 11.7 mmol) at room temperature. After 18 h, the reaction mixture was diluted with EtOAc. The organic layer was successively washed with 1 M HCl, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/5) as an eluant to yield **32b** (1.98 g, 49%) as a colorless oil. TLC $R_f = 0.42$ (EtOAc/hexane, 1/3); MS (APCI, pos. 20 V) *m*/*z* 298 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.64–1.77 (m, 1H), 1.71 (s, 3H), 2.12 (dd, $J = 14.1$, 10.8 Hz, 1H), 2.38–2.52 (m, 1H), 2.61–2.70 (m, 1H), 2.70–2.80 (m, 1H), 3.78 (s, 3H), 4.52 (dd, $J = 9.0$, 6.6 Hz, 1H), 4.66 (s, 1H), 4.80 (s, 1H).

4.1.8. 1-*tert*-Butyl 2-ethyl (2*S*)-4-(1-hydroxycyclohexyl)-5-oxo-1,2-pyrrolidinedicarboxylate (30a). Compound **30a** was prepared from **29** according to the method reported by Ezquerra et al.[19] To a stirred solution of **29** (4.77 g, 18.5 mmol) in THF (50 mL) was added dropwise a solution of lithium bis(trimethylsilyl)amide in THF (20 mL, 1.0 M) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C prior to the addition of a solution of cyclohexanone (1.99 g, 20.2 mmol) and boron trifluoride etherate (2.6 mL, 21 mmol) in THF (50 mL). After being stirred for 2.5 h, the reaction mixture was quenched with aqueous NH_4Cl and concentrated in vacuo. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/3) as an eluant to yield **30a** (5.32 g, 80%) as a yellow oil. TLC $R_f = 0.52$ (acetone/hexane, 1/2); MS (APCI, pos. 20 V) *m*/*z* 356 $(M+H)^+$; ^1H

NMR (300 MHz, $CDCl_3$) δ 1.08–1.90 (m, 10H), 1.29 (t, J = 6.9 Hz, 3H), 2.05–2.25 (m, 2H), 2.77 (dd, J = 12.0, 9.0 Hz, 1H), 3.21 (s, 1H), 4.24 (q, J = 6.9 Hz, 2H), 4.54 (dd, J = 9.6, 1.8 Hz, 1H).

According to the same procedure as described above, **30b** was prepared from **29**.

4.1.9. 1-*tert*-Butyl 2-ethyl (2*S*)-4-(2-hydroxy-2-adamantyl)-5-oxo-1,2-pyrrolidinedicarboxylate (30b). Yield 66%. A colorless oil. R_f = 0.54 (acetone/hexane, 1/3); MS (APCI, pos. 20 V) m/z 408 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.34 (m, 3H), 1.34–2.03 (m, 13H), 1.50 (s, 9H), 2.07–2.27 (m, 2H), 2.36–2.50 (m, 1H), 2.84 (s, 1H), 3.34 (dd, J = 12.1, 8.5 Hz, 1H), 4.25 (q, J = 6.9 Hz, 2H), 4.56 (dd, J = 9.8, 1.2 Hz, 1H).

4.1.10. 1-*tert*-Butyl 2-ethyl (2*S*)-4-cyclohexylidene-5-oxo-1,2-pyrrolidinedicarboxylate (31a). Compound **31a** was prepared from **30a** according to the method reported by Ezquerra et al.[19] To a stirred solution of **30a** (5.32 g, 14.9 mmol) in CH_2Cl_2 (30 mL) were added methanesulfonyl chloride (1.88 g, 16.4 mmol) and triethylamine (23 mL, 165 mmol) at room temperature. After being stirred for 2 days, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/9) as an eluant to yield a mixture of **31a** and *endo*-olefin isomer (1.43 g). This compound was used for the next reaction without further purification.

4.1.11. 1-*tert*-Butyl 2-ethyl (2*S*)-5-oxo-4-tricyclo[3.3.1.1-3,7∼]dec-2-ylidene-1,2-pyrrolidinedicarboxylate (31b). To a stirred solution of **30b** (1.23 g, 3.02 mmol) in toluene (10 mL) was added *p*-toluenesulfonic acid (780 mg, 4.10 mmol). The reaction mixture was refluxed for 15 h, cooled to room temperature, and diluted with EtOAc. The organic layer was successively washed with 1 M HCl, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. To a stirred solution of the residue in CH_2Cl_2 (5 mL) were added 4-(dimethylamino)pyridine (54 mg, 0.44 mmol) and di-*tert*-butyl-dicarbonate (4.82 g, 22 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with EtOAc. The organic layer was successively washed with 1 M HCl, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/3) as an eluant to yield **31b** (825 mg, 69%) as a colorless oil. TLC R_f = 0.92 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 390 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.45–1.55 (m, 9H), 1.70–2.02 (m, 12H), 2.48–2.57 (m, 1H), 2.57 (dd, J = 16.3, 4.0 Hz, 1H), 2.95 (dd, J = 16.3, 10.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.49–4.55 (m, 1H), 4.51–4.59 (m, 1H).

4.1.12. 1-*tert*-Butyl 2-ethyl (2*S*,4*R*)-4-cyclohexyl-5-oxo-1,2-pyrrolidinedicarboxylate (32c). Compound **32c** was prepared from **31a** according to the method reported by Ezquerra et al.[19] To a mixture of **31a** and *endo*-olefin isomer (1.43 g, 4.24 mmol) in EtOAc (20 mL) was added platinum(IV) oxide (96 mg, 0.42 mmol). The mixture was vigorously stirred at room temperature under an atmospheric pressure of hydrogen for 18 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/8) as an eluant to yield **32c** (527 mg, 36%) as a colorless oil. TLC R_f = 0.56 (EtOAc/hexane, 1/2); MS (APCI, pos. 20 V) m/z 340 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96–1.20 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H), 1.49 (s, 9H), 1.60–1.95 (m, 8H), 2.30–2.40 (m, 1H), 2.45–2.53 (m, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.51 (dd, J = 8.4, 7.5 Hz, 1H).

According to the same procedure as described above, **32d** was prepared from **31b**.

4.1.13. 1-*tert*-Butyl 2-ethyl (2*S*,4*R*)-4-(2-adamantyl)-5-oxo-1,2-pyrrolidinedicarboxylate (32d). Yield 79%. A colorless oil. TLC R_f = 0.63 (EtOAc/toluene, 1/5); MS (APCI, pos. 20 V) m/z 392 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.34 (m, 3H), 1.45–1.55 (m, 9H), 1.56–2.00 (m, 15H), 2.37–2.50 (m, 1H), 2.57 (s, 1H), 2.76–2.97 (m, 1H), 4.16–4.30 (m, 2H), 4.46 (dd, J = 8.2, 7.1 Hz, 1H).

4.1.14. 1-*tert*-Butyl 2-methyl (2*S*,4*S*)-4-allyl-1,2-pyrrolidinedicarboxylate (33a). Compound **33a** was prepared from **32a** according to the method reported by Pedregal et al.[20] To a stirred solution of **32a** (2.88 g, 10.2 mmol) in THF (55 mL) was added a solution of lithium triethylborohydride in THF (12.2 mL, 1.0 M) at −78 °C. After being stirred for 40 min, the reaction mixture was quenched with aqueous $NaHCO_3$ and warmed to 0 °C. After the addition of 35% H_2O_2 (2 mL), the reaction mixture was stirred at 0 °C. After being stirred for 20 min, the reaction mixture was evaporated to remove organic solvent, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was used for the next reaction without further purification. To a stirred solution of the residue in CH_2Cl_2 (55 mL) were added triethylsilane (3.4 mL, 21 mmol) and boron trifluoride etherate (3.0 mL, 24 mmol) at −78 °C. After being stirred for 3 h, the reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/9) as an eluant to yield **33a** (2.45 g, 89%) as a colorless oil. TLC R_f = 0.42 (EtOAc/hexane, 1/4); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 and 1.40 (s, 9H), 1.60 (m, 1H) , 2.43–2.08 (m, 4H), 3.05 (m, 1H), 3.73 and 3.72 (s, 3H), 3.79–3.63 (m, 1H), 4.28–4.16 (m, 1H), 5.07–4.99 (m, 2H), 5.74 (m, 1H).

According to the same procedure as described above, **33c**, **33e**–**f** were prepared from **32b**–**d**, respectively.

4.1.15. 1-*tert*-Butyl 2-methyl (2*S*,4*S*)-4-(2-methyl-2-propen-1-yl)-1,2-pyrrolidinedicarboxylate (33c). Yield 77%. A colorless oil. TLC R_f = 0.35 (acetone/hexane, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.49 (m, 9H),

1.53–1.66 (m, 1H), 1.71 (s, 3H), 2.11 (d, J = 6.6 Hz, 2H), 2.27–2.47 (m, 2H), 2.97–3.09 (m, 1H), 3.69–3.77 (m, 3H), 4.15–4.32 (m, 1H), 4.69 (s, 1H), 4.74 (s, 1H).

4.1.16. 1-*tert*-Butyl 2-ethyl (2*S*,4*R*)-4-cyclohexyl-1,2-pyrrolidinedicarboxylate (33e). Yield 98%. A colorless oil. TLC R_f = 0.68 (acetone/hexane, 1/3); MS (APCI, pos. 20 V) m/z 326 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90–1.30 (m, 6H), 1.22 (m, 3H), 1.40 and 1.45 (s, 9H), 1.50–1.95 (m, 7H), 2.40 (m, 1H), 3.01 (t, J = 10.5 Hz, 1H), 3.63–3.83 (m, 1H), 4.10–4.30 (m, 3H).

4.1.17. 1-*tert*-Butyl 2-ethyl (2*S*,4*R*)-4-(2-adamantyl)-1,2-pyrrolidinedicarboxylate (33f). Yield 98%. A colorless oil. TLC R_f = 0.56 (EtOAc/hexane, 1/3); MS (APCI, pos. 20 V) m/z 378 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (m, 1H), 0.97 (m, 2H), 1.15–1.34 (m, 3H), 1.35–1.48 (m, 9H), 1.48–2.00 (m, 13H), 2.28–2.66 (m, 2H), 2.89–3.05 (m, 1H), 3.57–3.89 (m, 1H), 4.06–4.32 (m, 3H).

4.1.18. 1-*tert*-Butyl 2-methyl (2*S*,4*S*)-4-propyl-1,2-pyrrolidinedicarboxylate (33b). To a solution of **33a** (538 mg, 2.0 mmol) in MeOH (4 mL) was added 10 % palladium on carbon (200 mg). The reaction mixture was vigorously stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/9) as an eluant to yield **33b** (505 mg, 93%) as a colorless oil. TLC R_f = 0.47 (EtOAc/hexane, 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3H), 1.40 and 1.46 (s, 9H), 1.24–1.62 (m, 5H), 2.06–2.22 (m, 1H), 2.33–2.49 (m, 1H), 2.99 (t, J = 10.3 Hz, 1H), 3.72 and 3.73 (s, 3H), 3.61–3.82 (m, 1H), 4.07–4.30 (m, 1H).

According to the same procedure as described above, **33d** was prepared from **33c**.

4.1.19. 1-*tert*-Butyl 2-methyl (2*S*,4*S*)-4-isobutyl-1,2-pyrrolidinedicarboxylate (33d). Yield 91%. A colorless oil. TLC R_f = 0.38 (EtOAc/hexane, 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 6H), 1.20–1.33 (m, 2H), 1.36–1.49 (m, 9H), 1.49–1.66 (m, 2H), 2.11–2.31 (m, 1H), 2.33–2.46 (m, 1H), 2.97 (t, J = 10.3 Hz, 1H), 3.61–3.84 (m, 1H), 3.70–3.75 (m, 3H), 4.10–4.31 (m, 1H).

4.1.20. (2*S*,4*S*)-4-Allyl-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxylic acid (34a). To a stirred solution of **33a** (538 mg, 2.0 mmol) in MeOH (7 mL) was added 1 M NaOH (3 mL) at 0 °C. After being stirred at room temperature for 6 h, the reaction mixture was quenched with 1 M HCl (3 mL). The organic solvent was removed by evaporation, and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$ concentrated in vacuo. The resulting residue was solidified by hexane yielding **34a** (440 mg, 86%) as a white powder. TLC R_f = 0.24 ($CHCl_3$/MeOH, 19/1); MS (APCI, Neg. 20 V) m/z 255 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.45–1.59 (m, 1H), 2.05–2.46 (m, 4H), 2.91 (dd, J = 10.4, 8.5 Hz, 1H), 3.59 (dd, J = 10.4, 7.1 Hz, 1H), 4.08 (t, J = 8.0 Hz, 1H), 4.94–5.10 (m, 2H), 5.63–5.90 (m, 1H).

According to the same procedure as described above, **34b–f** were prepared from **33b–f**, respectively.

4.1.21. (2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-propyl-2-pyrrolidinecarboxylic acid (34b). Yield 67%. A white powder. TLC R_f = 0.27 (CH_2Cl_2/MeOH, 19/1); MS (APCI, Neg. 20 V) m/z 257 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.28–1.39 (m, 4H), 1.42 and 1.48 (s, 9H), 1.55–2.58 (m, 3H), 2.82–3.13 (m, 1H), 3.56–3.88 (m, 1H), 4.13–4.43 (m, 1H).

4.1.22. (2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(2-methyl-2-propen-1-yl)-2-pyrrolidinecarboxylic acid (34c). Yield 96%. A white powder. TLC R_f = 0.43 (CH_2Cl_2/MeOH, 9/1); MS (APCI, neg. 20 V) m/z 268 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.52 (m, 9H), 1.72 (s, 3H), 1.60–2.01 (m, 1H), 2.28–2.52 (m, 2H), 3.60–3.83 (m, 1H), 4.17–4.40 (m, 1H), 4.70 (s, 1H), 4.77 (s, 1H).

4.1.23. (2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-isobutyl-2-pyrrolidinecarboxylic acid (34d). Yield 100%. A white powder. TLC R_f = 0.52 (CH_2Cl_2/MeOH, 9/1); MS (APCI, neg. 20 V) m/z 270 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.93 (m, 6H), 1.22–1.33 (m, 2H), 1.38–1.50 (m, 9H), 1.51–1.84 (m, 2H), 2.13–2.53 (m, 2H), 2.95 (q, J = 10.6 Hz, 1H), 3.63–3.86 (m, 1H), 4.15–4.35 (m, 1H).

4.1.24. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-cyclohexyl-2-pyrrolidinecarboxylic acid (34e). Yield 89%. A white powder. TLC R_f = 0.15 (EtOAc/hexane, 1/3); MS (APCI, neg. 20 V) m/z 296 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–1.30 (m, 6H), 1.42 and 1.48 (s, 9H), 1.60–1.97 (m, 7H), 2.30–2.50 (m, 1H), 2.90–3.10 (m, 1H), 3.70–3.83 (m, 1H), 4.15–4.35 (m, 1H).

4.1.25. (2*S*,4*R*)-4-(2-Adamantyl)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxylic acid (34f). Yield 82%. A white powder. TLC R_f = 0.69 ($CHCl_3$/MeOH, 9/1); MS (APCI, neg. 20 V) m/z 348 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.53 (m, 9H), 1.17–1.96 (m, 16H), 2.24–2.61 (m, 2H), 2.81–3.05 (m, 1H), 3.64–3.90 (m, 1H), 4.17–4.45 (m, 1H).

According to the same procedure as described for the preparation of **26a** from **25a**, **35a–f** were prepared from **34a–f**, respectively.

4.1.26. *tert*-Butyl (2*S*,4*S*)-4-allyl-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-1- pyrrolidinecarboxylate (35a). Yield 76%. A white powder. TLC R_f = 0.24 (EtOAc/hexane, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 and 1.44 (s, 9H), 1.54–1.74 (m, 1H), 1.98–2.44 (m, 8H), 3.11 (t, J = 9.8 Hz, 1H), 3.47–3.88 (m, 3H), 4.26–4.44 (m, 1H), 4.84 (t, J = 9.6 Hz, 1H), 4.92–5.19 (m, 2H), 5.65–5.87 (m, 1H).

4.1.27. *tert*-Butyl (2*S*,4*S*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-propyl-1- pyrrolidinecarboxylate (35b). Yield 61%. A white powder. TLC R_f = 0.29 (EtOAc/hex-

ane, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3H), 1.18–1.49 (m, 4H), 1.38 and 1.37 (s, 9H), 1.50–1.72 (m, 1H), 2.03–2.43 (m, 6H), 2.92–3.16 (m, 1H), 3.51–3.89 (m, 3H), 4.23–4.45 (m, 1H), 4.71–4.95 (m, 1H).

4.1.28. *tert*-Butyl (2*S*,4*S*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(2-methyl-2- propen-1-yl)-1-pyrrolidinecarboxylate (35c). Yield 64%. A white powder. TLC R_f = 0.74 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 348 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.35 (s, 9H), 1.36–1.47 (m, 1H), 1.71 (s, 3H), 1.99–2.24 (m, 6H), 2.29–2.48 (m, 2H), 2.89–2.99 (m, 1H), 3.50–3.68 (m, 3H), 4.39 (t, J = 7.9 Hz, 1H), 4.68–4.76 (m, 2H), 4.74–4.82 (m, 1H).

4.1.29. *tert*-Butyl (2*S*,4*S*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-isobutyl-1- pyrrolidinecarboxylate (35d). Yield 59%. A white powder. TLC R_f = 0.78 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 350 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 0.89 (dd, J = 6.6, 1.5 Hz, 6H), 1.28 (t, J = 6.8 Hz, 3H), 1.35 (s, 9H), 1.49–1.65 (m, 1H), 1.99–2.11 (m, 2H), 2.11–2.28 (m, 3H), 2.40–2.47 (m, 1H), 2.87 (t, J = 10.2 Hz, 1H), 3.51–3.62 (m, 2H), 3.65 (dd, J = 10.2, 7.4 Hz, 1H), 4.37 (t, J = 8.1 Hz, 1H), 4.71–4.83 (m, 1H).

4.1.30. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-cyclohexyl-1-pyrrolidinecarboxylate (35e). Yield 60%. A colorless oil. TLC R_f = 0.76 (EtOAc/hexane, 1/2); MS (APCI, pos. 20 V) m/z 376 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 0.90–1.20 (m, 2H), 1.10–1.42 (m, 4H), 1.35 (s, 9H), 1.52–1.75 (m, 5H), 1.85–2.40 (m, 7H), 2.89–2.99 (m, 1H), 3.30–3.63 (m, 3H), 4.37 (t, J = 8.1 Hz, 1H), 4.71–4.83 (m, 1H).

4.1.31. *tert*-Butyl (2*S*,4*R*)-4-(2-adamantyl)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-1-pyrrolidinecarboxylate (35f). Yield 49%. A white powder. TLC R_f = 0.41 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 428 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.24–1.32 (m, 9H), 1.20–2.28 (m, 20H), 2.38–2.54 (m, 1H), 2.70–2.90 (m, 1H), 3.35–3.69 (m, 4H), 4.31–4.41 (m, 1H), 4.73–4.86 (m, 1H).

4.1.32. (2*S*)-1-{[(2*S*,4*S*)-4-Allyl-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (5). A solution of **35a** (866 mg, 2.60 mmol) and *p*-toluenesulfonic acid (740 mg, 3.9 mmol) in EtOH (5 mL) was refluxed for 3 h. After cooling to room temperature, the resulting precipitates were collected by filtration and dried under reduced pressure to yield **5** (891 mg, 84%) as a white powder. TLC R_f = 0.35 (CH_2 Cl_2/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 234 $(M+H)^+$; IR (KBr) 3852, 3152, 3083, 3002, 2603, 2464, 2241, 1916, 1809, 1667, 1492, 1460, 1383, 1268, 1236, 1162, 1118, 1032, 1010, 996, 920, 880 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32–1.50 (m, 1H) 1.95–2.07 (m, 2H) 2.09–2.25 (m, 4H) 2.28 (s, 3H) 2.32–2.45 (m, 1H) 2.54–2.69 (m, 1H) 2.82–2.99 (m, 1H) 3.28–3.35 (m, 1H) 3.46–3.66 (m, 2H) 4.34–4.57 (m, 1H) 4.82 (dd, J = 7.8, 4.7 Hz, 1H) 4.95–5.16 (m, 2H) 5.65–5.87 (m, 1H) 7.11 (d, J = 8.0 Hz, 2H) 7.47 (d, J = 8.0 Hz, 2H) 8.72 (s, 1H) 9.35 (s, 1H); Anal. Calcd for $C_{20}H_{27}N_3O_4S$: C, 59.24; H, 6.71; N, 10.36. Found: C, 59.34; H, 6.70; N, 10.07.

4.1.33. (2*S*)-1-{[(2*S*,4*S*)-4-Propyl-2- pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride (6). Compound **6** was obtained as a white powder in 91% yield from **35b** according to the same procedure as described for the preparation of **12** from **26b**. TLC R_f = 0.34 (CH_2Cl_2/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 236 $(M+H)^+$; IR (KBr) 3434, 2959, 2874, 2739, 2243, 1658, 1454, 1348, 1265, 1189, 739 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 7.0 Hz, 3H), 1.18–1.49 (m, 5H), 1.87–2.38 (m, 5H), 2.56–2.68 (m, 1H), 2.80 (s, 1H), 3.24–3.40 (m, 1H), 3.50–3.72 (m, 2H), 4.43 (s, 1H), 4.82 (dd, J = 7.8, 4.8 Hz, 1H), 8.66 (s, 1H), 10.38 (s, 1H); HRMS (FAB) calcd for $C_{13}H_{22}N_3O$: 236.1763. Found: 236.1767.

4.1.34. (2*S*)-1-{[(2*S*,4*S*)-4-(2-Methyl-2-propen-1-yl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (7). Compound **7** was obtained as a white powder in 45% yield from **35c** according to the same procedure as described for the preparation of **5** from **35a**. TLC R_f = 0.16 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 248 $(M+H)^+$; IR (KBr) 3438, 2984, 2594, 2242, 1664, 1235, 1164, 1121, 1034, 1011, 683, 569 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30–1.48 (m, 1H) 1.67 (s, 3H), 1.90–2.27 (m, 6H), 2.28 (s, 3H), 2.49–2.67 (m, 2H), 2.89 (dd, J = 11.0, 8.3 Hz, 1H), 3.24–3.40 (m, 1H), 3.48–3.63 (m, 2H), 4.42–4.55 (m, 1H), 4.71 (s, 1H), 4.75 (s, 1H), 4.82 (dd, J = 7.8, 4.7 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 8.85–9.24 (m, 2H); HRMS (FAB) calcd for $C_{14}H_{22}N_3O$: 248.1763. Found: 248.1762.

4.1.35. (2*S*)-1-{[(2*S*,4*S*)-4-Isobutyl-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (8). Compound **8** was obtained as a white powder in 60% yield from **35d** according to the same procedure as described for the preparation of **5** from **35a**. TLC R_f = 0.16 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 250 $(M+H)^+$; IR (KBr) 3442, 2956, 2870, 2239, 1661, 1161, 1010, 683 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (d, J = 6.5 Hz, 6H), 1.20–1.41 (m, 3H), 1.45–1.61 (m, 1H), 1.93–2.07 (m, 2H), 2.08–2.42 (m, 3H), 2.28 (s, 3H), 2.58–2.73 (m, 1H), 2.81 (t, J = 10.5 Hz, 1H), 3.31–3.41 (m, 1H), 3.56 (t, J = 6.6 Hz, 2H), 4.45 (dd, J = 9.7, 7.6 Hz, 1H), 4.82 (dd, J = 7.8, 4.7 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 8.49–9.47 (m, 2H); HRMS (FAB) calcd for $C_{14}H_{24}N_3O$: 250.1919. Found: 250.1921.

4.1.36. (2*S*)-1-{[(2*S*,4*R*)-4-Cyclohexyl-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride (9). Compound **9** was obtained as a white powder in 28% yield from **35e** according to the same procedure as described for the preparation of **12** from **26b**. TLC R_f = 0.37 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 276 $(M+H)^+$; IR (KBr) 3380, 2926, 2852, 2239, 1655, 1565, 1541, 1451, 1185 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83–1.01 (m, 2H), 1.09–1.29 (m, 4H), 1.32–1.47

(m, 1H), 1.53–1.76 (m, 5H), 1.93–2.08 (m, 3H), 2.08–2.32 (m, 2H), 2.53–2.67 (m, 1H), 2.78–2.94 (m, 1H), 3.29–3.40 (m, 1H), 3.59 (t, J = 6.5 Hz, 2H), 4.41 (dd, J = 10.0, 7.8 Hz, 1H), 4.82 (dd, J = 7.6, 4.6 Hz, 1H); HRMS (FAB) calcd for $C_{16}H_{26}N_3O$: 276.2076. Found: 276.2077.

4.1.37. (2*S*)-1-{[(2*S*,4*R*)-4-(2-Adamantyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (10). Compound **10** was obtained as a white powder in 57% yield from **35f** according to the same procedure as described for the preparation of **5** from **35a**. TLC R_f = 0.60 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) m/z 328 $(M+H)^+$; IR (KBr) 3448, 2906, 2239, 1662, 1455, 1216, 1190, 1181, 1171, 1123, 1033, 1010, 684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.21–1.39 (m, 1H), 1.44–1.91 (m, 15H), 1.94–2.08 (m, 2H), 2.08–2.26 (m, 2H), 2.28 (s, 3H), 2.55–2.74 (m, 2H), 2.82 (t, J = 10.5 Hz, 1H), 3.34–3.42 (m, 1H), 3.48–3.67 (m, 2H), 4.42–4.53 (m, 1H), 4.82 (dd, J = 7.9, 4.8 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 8.96 (s, 2H); HRMS (FAB) calcd for $C_{20}H_{30}N_3O$: 328.2389. Found: 328.2395.

4.1.38. 1-*tert*-Butyl 2-methyl (2*S*)-4-{[(trifluoromethyl)sulfonyl]oxy}-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (37). To a stirred solution of sodium bis(trimethylsilyl)amide (2.02 g, 11 mmol) in THF (20 mL) was added dropwise a solution of **36** (2.43 g, 10 mmol) in THF (7 mL) at −78 °C. After being stirred for 15 min, *N*-phenyl-bis(trifluoromethanesulfonimide) (3.57 g, 10 mmol) in THF (12 mL) was added and the reaction mixture was stirred at −78 °C for additional 3 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/15) as an eluant to yield **37** (2.89 g, 77%) as a colorless oil. TLC R_f = 0.37 (EtOAc/hexane, 1/4); MS (APCI, pos. 20 V) m/z 398 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 and 1.49 (s, 9H), 3.77 (s, 3H), 4.16–4.53 (m, 2H), 4.89–5.20 (m, 1H), 5.67–5.79 (m, 1H).

4.1.39. 1-*tert*-Butyl 2-methyl (2*S*)-4-(2,6-dimethylphenyl)-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38a). To a heterogeneous mixture of **37** (1.12 g, 3.0 mmol), 2,6-dimethylphenylboronic acid (540 mg, 3.6 mmol), and 2M Na_2CO_3 (3.5 mL), in 1,4-dioxane (28 mL) was added tetrakis(triphenylphosphine)palladium(0) (86 mg, 0.074 mmol). The reaction mixture was refluxed for 1.5 h under argon atmosphere. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/7) as an eluent to yield **38a** (933 mg, 100%) as a colorless oil. TLC R_f = 0.60 (EtOAc/hexane, 1/3); MS (APCI, pos. 20 V) m/z 332 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 1.35–1.44 (m, 9H), 2.16 (s, 6H), 3.65–3.73 (m, 3H), 4.18–4.24 (m, 2H), 5.04–5.11 (m, 1H), 5.59–5.67 (m, 1H), 7.04 (d, J = 6.6 Hz, 2H), 7.07–7.15 (m, 1H).

According to the same procedure as described above, **38b–l** were prepared from **37**.

4.1.40. 1-*tert*-Butyl 2-methyl (2*S*)-4-[2-(benzyloxy)phenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38b). Yield 72%. A colorless oil. TLC R_f = 0.63 (EtOAc/hexane, 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.41–1.52 (m, 9H), 3.67–3.77 (m, 3H), 4.52–4.77 (m, 2H), 5.05–5.18 (m, 3H), 6.35–6.41 (m, 1H), 6.92–7.02 (m, 2H), 7.19–7.30 (m, 2H), 7.30–7.46 (m, 5H).

4.1.41. 1-*tert*-Butyl 2-methyl (2*S*)-4-[3-(benzyloxy)phenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38c). Yield 89%. A colorless oil. TLC R_f = 0.28 (EtOAc/hexane, 1/4); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 and 1.52 (s, 9H), 3.75 and 3.76 (s, 3H), 4.44–4.73 (m, 2H), 5.03–5.09 (m, 2H), 5.09–5.22 (m, 1H), 5.99–6.11 (m, 1H), 6.89–7.04 (m, 3H), 7.23–7.48 (m, 6H).

4.1.42. 1-*tert*-Butyl 2-methyl (2*S*)-4-[4-(benzyloxy)phenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38d). Yield 75%. A colorless oil. TLC R_f = 0.39 (EtOAc/hexane, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42–1.54 (m, 9H), 3.71–3.79 (m, 3H), 4.44–4.70 (m, 2H), 5.05–5.21 (m, 3H), 5.87–5.98 (m, 1H), 6.95 (d, J = 8.8 Hz, 2H), 7.27–7.52 (m, 7H).

4.1.43. 1-*tert*-Butyl 2-methyl (2*S*)-4-[4-(benzyloxy)-2,6-dimethylphenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38e). Yield 90%. A colorless oil. TLC R_f = 0.52 (EtOAc/hexane, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 and 1.49 (s, 9H), 2.20 and 2.21 (s, 6H), 3.77 and 3.78 (s, 3H), 4.15–4.44 (m, 2H), 5.03 (s, 2H), 5.08–5.22 (m, 1H), 5.43–5.55 (m, 1H), 6.68 (s, 2H), 7.28–7.47 (m, 5H).

4.1.44. 1-*tert*-Butyl 2-methyl (2*S*)-4-[4-(benzyloxy)-2-methoxy-6-methylphenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38f). Yield 83%. A pale yellow powder. TLC R_f = 0.54 (EtOAc/hexane, 1/2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 and 1.49 (s, 9H), 2.21 (s, 3H), 3.73 and 3.75 (s, 3H), 3.77 (s, 3H), 4.31–4.48 (m, 2H), 5.04 (s, 2H), 5.11–5.18 (m, 1H), 5.50–5.53 (m, 1H), 6.45 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 7.30–7.46 (m, 5H).

4.1.45. 1-*tert*-Butyl 2-methyl (2*S*)-4-[2,6-dimethoxy-4-(methoxymethoxy)phenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38g). Yield 23%. A pale yellow oil. TLC R_f = 0.31 (EtOAc/hexane, 1/2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 and 1.52 (s, 9H), 3.49 (s, 3H), 3.70–3.80 (m, 9H), 4.28–4.76 (m, 2H), 5.05–5.13 (m, 1H), 5.18 (s, 2H), 5.84–5.98 (m, 1H), 6.27 (s, 2H).

4.1.46. 1-*tert*-Butyl 2-methyl (2*S*)-4-[2-ethyl-6-methyl-4-(tetrahydro-2H-pyran-2-yloxy)phenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38h). Yield 88%. A colorless oil. TLC R_f = 0.50 (EtOAc/hexane, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 and 1.15 (t, J = 7.5 Hz, 3H), 1.46 and 1.48 (s, 9H), 1.55–1.74 (m, 3H), 1.81–1.88 (m, 2H), 2.00 (m, 1H), 2.20 and 2.21 (s, 3H), 2.50 (q, J = 7.5 Hz, 2H), 3.61 (m, 1H), 3.77 (s, 3H), 3.92 (m, 1H), 4.15–4.42 (m, 2H), 5.11–5.18

(m, 1H), 5.42 (t, J = 3.0 Hz, 1H), 5.48–5.42 (m, 1H), 6.77 (m, 2H).

4.1.47. 1-*tert*-Butyl 2-methyl (2*S*)-4-[2,6-diethoxy-4-(methoxymethoxy)phenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38i). Yield 36%. An orange oil. TLC R_f = 0.29 (EtOAc/hexane, 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.43 (m, 6H), 1.43–1.53 (m, 9H), 3.48 (s, 3H), 3.72–3.76 (m, 3H), 3.94–4.04 (m, 4H), 4.54–4.63 (m, 2H), 5.05–5.12 (m, 1H), 5.15 (s, 2H), 5.93–6.11 (m, 1H), 6.25 (s, 2H).

4.1.48. 1-*tert*-Butyl 2-methyl (2*S*)-4-(3-hydroxy-2,6-dimethylphenyl)-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38j). Yield 35%. A colorlesss oil. TLC R_f = 0.44 (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 and 1.49 (s, 9H), 2.11–2.16 (m, 6H), 3.78 (s, 3H), 4.20–4.41 (m, 2H), 4.96 and 5.06 (s, 1H), 5.15–5.25 (m, 1H), 5.47–5.53 (m, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H).

4.1.49. 1-*tert*-Butyl 2-methyl (2*S*)-4-[3-(benzyloxy)-2-methoxy-6-methylphenyl]-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38k). Yield 61%. A pale yellow oil. TLC R_f = 0.45 (EtOAc/hexane, 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.50 (m, 9H), 2.14–2.20 (m, 3H), 3.75–3.83 (m, 6H), 4.29–4.55 (m, 2H), 5.09 (s, 2H), 5.11–5.26 (m, 1H), 5.52–5.64 (m, 1H), 6.80–6.90 (m, 2H), 7.28–7.47 (m, 5H).

Pale yellow viscous in 61% yield.

4.1.50. 1-*tert*-Butyl 2-methyl (2*S*)-4-(3-hydroxy-2,4,6-trimethylphenyl)-2,5-dihydro-1H-pyrrole-1,2-dicarboxylate (38l). Yield 35%. A colorless oil. TLC R_f = 0.44 (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 and 1.48 (s, 9H), 2.12 (s, 3H), 2.14 (s, 3H), 2.22 (s, 3H), 3.78 (s, 3H), 4.20–4.41 (m, 2H), 4.56 and 4.58 (s, 1H), 5.10–5.20 (m, 1H), 5.45–5.55 (m, 1H), 6.84 (s, 1H).

4.1.51. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(2,6-dimethylphenyl)-1,2-pyrrolidinedicarboxylate (39a). To a solution of **38a** (933 mg, 2.81 mmol) in MeOH (8 mL) was added 10% palladium on carbon (200 mg). The reaction mixture was vigorously stirred at room temperature under an atmospheric pressure of hydrogen for 13 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/7) as an eluant to yield **39a** (528 mg, 56%) as a colorless oil. TLC R_f = 0.59 (EtOAc/hexane, 1/3); MS (APCI, pos. 20 V) m/z 334 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31–1.42 (m, 9H), 2.12–2.31 (m, 2H), 2.34 (s, 6H), 3.50–3.63 (m, 2H), 3.63–3.73 (m, 3H), 3.76–3.97 (m, 1H), 4.30 (t, J = 8.5 Hz, 1H), 6.93–7.05 (m, 3H).

4.1.52. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(2-hydroxyphenyl)-1,2-pyrrolidinedicarboxylate (39b). Compound **39b** was obtained as a colorless oil in 98% yield from **38b** according to the same procedure as described for the preparation of **39a** from **38a**. TLC R_f = 0.63 (EtOAc/hexane, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.52 (m, 9H), 3.67–3.77 (m, 3H), 4.52–4.77 (m, 2H), 5.05–5.18 (m, 3H), 6.35–6.41 (m, 1H), 6.92–7.02 (m, 2H), 7.19–7.30 (m, 2H), 7.30–7.46 (m, 5H).

4.1.53. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(3-hydroxyphenyl)-1,2-pyrrolidinedicarboxylate (39c). Compound **39c** was obtained as a colorless oil in 91% yield from **38c** according to the same procedure as described for the preparation of **39a** from **38a**. TLC R_f = 0.37 (EtOAc/hexane, 2/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 and 1.46 (s, 9H), 1.96–2.17 (m, 1H), 2.54–2.72 (m, 1H), 3.19–3.52 (m, 2H), 3.76 (s, 3H), 3.89–4.07 (m, 1H), 4.27–4.45 (m, 1H), 5.61 and 5.88 (s, 1H), 6.65–6.85 (m, 3H), 7.08–7.22 (m, 1H).

4.1.54. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(4-hydroxyphenyl)-1,2-pyrrolidinedicarboxylate (39d). Compound **39d** was obtained as a colorless oil in 100% yield from **38d** according to the same procedure as described for the preparation of **39a** from **38a**. TLC R_f = 0.43 (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39–1.51 (m, 9H), 1.92–2.12 (m, 1H), 2.55–2.68 (m, 1H), 3.18–3.43 (m, 2H), 3.76 (s, 3H), 3.85–4.04 (m, 1H), 4.26–4.44 (m, 1H), 6.80 (d, J = 8.6 Hz, 2H), 5.73–8.14 (m, 1H), 7.03–7.12 (m, 2H).

4.1.55. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(4-hydroxy-2,6-dimethylphenyl)-1,2-pyrrolidinedicarboxylate (39e). Compound **39e** was obtained as a colorless oil in 92% yield from **38e** according to the same procedure as described for the preparation of **39a** from **38a**. TLC R_f = 0.42 (EtOAc/hexane, 2/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.52 (m, 9H), 2.25–2.54 (m, 8H), 3.77 (s, 6H), 4.26–4.45 (m, 1H), 4.80–5.03 (m, 1H), 6.51 (s, 2H).

4.1.56. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(4-hydroxy-2-methoxy-6-methylphenyl)-1,2-pyrrolidinedicarboxylate (39f). Compound **39f** was obtained as a colorless oil in 100% yield from **38f** according to the same procedure as described for the preparation of **39a** from **38a**. TLC R_f = 0.49 (EtOAc/hexane, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 and 1.46 (s, 9H), 2.27 and 2.29 (s, 3H), 2.50–2.71 (m, 1H), 3.48–3.68 (m, 2H), 3.73 (s, 3H), 3.77 (s, 3H), 3.84 (m, 1H), 4.31 and 4.40 (t, J = 8.4 Hz, 1H), 4.79 and 4.87 (br s, 1H), 6.25 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 2.4 Hz, 1H).

4.1.57. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[2,6-dimethoxy-4-(methoxymethoxy)phenyl]-1,2-pyrrolidinedicarboxylate (39g). Compound **39g** was obtained as a beige powder in 100% yield from **38g** according to the same procedure as described for the preparation of **39a** from **38a**. TLC R_f = 0.38 (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.51 (m, 9H), 2.17–2.42 (m, 1H), 2.46–2.68 (m, 1H), 3.45–3.53 (m, 3H), 3.72–3.80 (m, 9H), 3.80–3.97 (m, 3H), 4.20–4.45 (m, 1H), 5.16 (s, 2H), 6.27 (s, 2H).

4.1.58. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(2-ethyl-4-hydroxy-6-methylphenyl)-1,2-pyrrolidinedicarboxylate (39h). To a stirred solution of **38h** (933 mg, 2.81 mmol) in MeOH (3 mL) was added 4M HCl in 1,4-dioxane (2 mL). After being stirred for 3.5 h, the reaction

mixture was concentrated in vacuo. To a solution of the residue in MeOH (5 mL) was added 10% palladium on carbon (30 mg). The reaction mixture was vigorously stirred under an atmospheric pressure of hydrogen for 17 h at room temperature and additional 24 h at 50 °C. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. To a stirred solution of the residue in THF (2.5 mL) and water (2 mL) were added triethylamine (0.11 mL, 0.79 mmol) and di-*tert*-butyldicarbonate (171 mg, 0.79 mmol) at room temperature. After 30 min, the reaction mixture was diluted with EtOAc. The organic layer was successively washed with water, 1M HCl, brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/6) as an eluant to yield **39h** (204 mg, 75%) as a colorless oil. TLC $R_f = 0.64$ (EtOAc/hexane, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, $J = 7.3$ Hz, 3H), 1.44 and 1.46 (s, 9H), 2.35 and 2.38 (s, 3H), 2.25–2.50 (m, 2H), 2.64 (q, $J = 7.3$ Hz, 2H), 3.70 (m, 3H), 3.77 (s, 3H), 4.34 and 4.40 (t, $J = 8.4$ Hz, 1H), 4.80 and 4.90 (s, 1H), 6.51 (d, $J = 3.0$ Hz, 1H), 6.54 (d, $J = 3.0$ Hz, 1H).

4.1.59. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[2,6-diethoxy-4-(methoxymethoxy)phenyl]-1,2-pyrrolidinedicarboxylate (39i). Compound **39i** was obtained as a pale yellow oil in 69% yield from **38i** according to the same procedure as described for the preparation of **39a** from **38a**. TLC $R_f = 0.24$ (EtOAc/hexane, 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.51 (m, 15H), 2.17–2.32 (m, 1H), 2.61–2.81 (m, 1H), 3.46–3.51 (m, 3H), 3.72–3.78 (m, 3H), 3.80–3.91 (m, 2H), 3.91–4.05 (m, 5H), 4.24–4.41 (m, 1H), 5.13 (s, 2H), 6.24 (s, 2H).

4.1.60. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(3-hydroxy-2,6-dimethylphenyl)-1,2-pyrrolidinedicarboxylate (39j). Compound **39j** was obtained as a colorless oil in 70% yield from **38j** according to the same procedure as described for the preparation of **39h** from **38h**. TLC $R_f = 0.42$ (EtOAc/hexane, 1/2); MS (APCI, pos. 20 V) *m*/*z* 350 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 and 1.46 (s, 9H), 2.28–2.32 (m, 6H), 2.40–2.54 (m, 2H), 3.72–3.88 (m, 6H), 4.44–4.45 (m, 1H), 4.70–4.79 (m, 1H), 6.61 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H).

4.1.61. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(3-hydroxy-2-methoxy-6-methylphenyl)-1,2-pyrrolidinedicarboxylate (39k). Compound **39k** was obtained as a colorless oil in 87% yield from **38k** according to the same procedure as described for the preparation of **39h** from **38h**. TLC $R_f = 0.37$ (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–1.49 (m, 9H), 2.28–2.35 (m, 3H), 2.39–2.61 (m, 2H), 3.69–3.89 (m, 9H), 4.29–4.46 (m, 1H), 5.30 (s, 1H), 6.77 (d, $J = 8.2$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 1H).

4.1.62. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(3-hydroxy-2,4,6-trimethylphenyl)-1,2-pyrrolidinedicarboxylate (39l). Compound **39l** was obtained as a colorless oil in 77% yield from **38l** according to the same procedure as described for the preparation of **39a** from **38a**. TLC $R_f = 0.52$ (EtOAc/hexane, 1/2); MS (APCI, pos. 20 V) *m*/*z* 364 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 and 1.46 (s, 9H), 2.10–2.30 (m, 9H), 2.36–2.53 (m, 2H), 3.60–3.90 (m, 6H), 4.32–4.43 (m, 1H), 4.55–4.62 (m, 1H), 6.80 (s, 1H).

4.1.63. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[2-(benzyloxy)phenyl]-1,2-pyrrolidinedicarboxylate (39m). To a stirred solution of **39b** (466 mg, 1.45 mmol) in DMF (15 mL) were added K_2CO_3 (201 mg, 1.45 mmol) and benzyl bromide (0.18 mL, 1.5 mmol) at room temperature. After being stirred for 15 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/8) as an eluant to yield **39m** (586 mg, 98%) as a colorless oil. TLC $R_f = 0.24$ (EtOAc/hexane, 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.47 (m, 9H), 2.03–2.15 (m, 1H), 2.48–2.76 (m, 1H), 3.33–3.57 (m, 1H), 3.64–3.85 (m, 4H), 3.89–4.08 (m, 1H), 4.24–4.44 (m, 1H), 5.09 (s, 2H), 6.84–7.01 (m, 2H), 7.15–7.28 (m, 2H), 7.29–7.47 (m, 5H).

4.1.64. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[3-(tetrahydro-2H-pyran-2-yloxy)phenyl]-1,2-pyrrolidinedicarboxylate (39n). To a stirred solution of **39c** (466 mg, 1.45 mmol) in CH_2Cl_2 (3 mL) were added 3,4-dihydro-2*H*-pyran (0.41 mL, 4.5 mmol) and pyridinium *p*-toluenesulfonate (80 mg, 0.31 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/7) as an eluant to yield **39n** (1.28 g, 98%) as a colorless oil. TLC $R_f = 0.58$ (EtOAc/hexane, 2/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 and 1.47 (s, 9H), 1.55–1.74 (m, 3H), 1.85 (dd, $J = 8.4$, 3.3 Hz, 2H), 1.94–2.15 (m, 2H), 2.57–2.72 (m, 1H), 3.22–3.50 (m, 2H), 3.54–3.67 (m, 1H), 3.72 and 3.77 (s, 3H), 3.84–4.11 (m, 2H), 4.26–4.44 (m, 1H), 5.35–5.49 (m, 1H), 6.77–7.02 (m, 3H), 7.17–7.31 (m, 1H).

According to the same procedure as described above, **39o** was prepared from **39d**.

4.1.65. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]-1,2-pyrrolidinedicarboxylate (39o). Yield 95%. A colorless oil. TLC $R_f = 0.58$ (EtOAc/hexane, 2/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 and 1.46 (s, 9H), 1.52–1.78 (m, 3H), 1.80–2.10 (m, 4H), 2.58–2.68 (m, 1H), 3.22–3.44 (m, 2H), 3.56–3.63 (m, 1H), 3.74 and 3.76 (s, 3H), 3.84–4.05 (m, 2H), 4.28–4.40 (m, 1H), 5.39 (t, $J = 3.0$ Hz, 1H), 6.99–7.01 (m, 2H), 7.12–7.20 (m, 2H).

According to the same procedure as described for the preparation of **39m** from **39b**, **39p–q** were prepared from **39e** and **39k**, respectively.

4.1.66. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[4-(benzyloxy)-2,6-dimethylphenyl]-1,2-pyrrolidinedicarboxylate (39p). Yield 79%. A colorless oil. TLC $R_f = 0.40$ (EtOAc/hexane, 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 and 1.46 (s, 9H), 2.31–2.49 (m, 8H), 3.63–3.83 (m, 6H), 4.27–

4.45 (m, 1H), 5.01 (s, 2H), 6.66 (s, 2H), 7.28–7.47 (m, 5H).

4.1.67. 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[3-(benzyloxy)-2-methoxy-6-methylphenyl]-1,2-pyrrolidinedicarboxylate (39q). Yield 90%. A colorless oil. TLC $R_f = 0.34$ (EtOAc/hexane, 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–1.49 (m, 9H), 2.27–2.32 (m, 3H), 2.33–2.73 (m, 2H), 3.58–3.93 (m, 9H), 4.25–4.48 (m, 1H), 5.06 (s, 2H), 6.75–6.84 (m, 2H), 7.27–7.49 (m, 5H).

4.1.68. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(2,6-dimethylphenyl)-2-pyrrolidinecarboxylic acid (40a). Compound **40a** was obtained as a white powder in 56% yield from **39a** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.59$ (EtOAc/hexane, 1/3); MS (APCI, Neg. 20 V) *m*/*z* 318 $(M-H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31–1.42 (m, 9H), 2.12–2.31 (m, 2H), 2.34 (s, 6H), 3.50–3.63 (m, 2H), 3.63–3.73 (m, 3H), 3.76–3.97 (m, 1H), 4.30 (t, $J = 8.5$ Hz, 1H), 6.93–7.05 (m, 3H).

4.1.69. (2*S*,4*R*)-4-[2-(Benzyloxy)phenyl]-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxylic acid (40b). Compound **40b** was obtained as a white powder in 91% yield from **39m** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.36$ ($CHCl_3$/MeOH, 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 and 1.53 (s, 9H), 2.41–2.79 (m, 2H), 3.14–3.86 (m, 2H), 3.94–4.16 (m, 1H), 4.22–4.54 (m, 1H), 5.09 (s, 2H), 6.87–7.03 (m, 2H), 7.12–7.30 (m, 2H), 7.30–7.48 (m, 5H).

4.1.70. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-[3-(tetrahydro-2H-pyran-2-yloxy)phenyl]-2-pyrrolidinecarboxylic acid (40c). Compound **40c** was obtained as a white powder in 100% yield from **39n** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.41$ (CH_2Cl_2/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 and 1.49 (s, 9H), 1.55–1.77 (m, 3H), 1.80–1.90 (m, 2H), 1.93–2.04 (m, 1H), 2.09–2.49 (m, 1H), 2.57–2.81 (m, 1H), 3.26–3.52 (m, 2H), 3.56–3.66 (m, 1H), 3.84–3.96 (m, 1H), 3.99–4.09 (m, 1H), 4.29–4.52 (m, 1H), 5.42 (s, 1H), 6.82–7.01 (m, 3H), 7.19–7.28 (m, 1H)

4.1.71. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]-2-pyrrolidinecarboxylic acid (40d). Compound **40d** was obtained as a white powder in 86% yield from **39o** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.35$ ($CHCl_3$/MeOH, 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29–1.44 (m, 9H), 1.44–1.95 (m, 8H), 2.52–2.67 (m, 1H), 3.14 (m, 1H), 3.46–3.58 (m, 1H), 3.65–3.90 (m, 2H), 4.15 (t, $J = 8.4$ Hz, 1H), 5.41 (s, 1H), 6.95 (d, $J = 8.6$ Hz, 2H), 7.18 (d, $J = 8.6$ Hz, 2H), 12.57 (s, 1H).

4.1.72. (2*S*,4*R*)-4-[4-(Benzyloxy)-2,6-dimethylphenyl]-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxylic acid (40e). Compound **40e** was obtained as a colorless oil in 100% yield from **39p** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.75$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 and 1.48 (s, 9H), 2.38 (s, 6H), 2.41–2.75 (m, 2H), 3.63–3.90 (m, 3H), 4.29–4.50 (m, 1H), 5.01 (s, 2H), 6.66 (s, 2H), 7.27–7.46 (m, 5H).

4.1.73. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(4-hydroxy-2-methoxy-6-methylphenyl)-2-pyrrolidinecarboxylic acid (40f). Compound **40f** was obtained as a white powder in 100% yield from **39f** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.35$ ($CHCl_3$/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.26 and 2.27 (s, 3H), 2.34 (m, 1H), 2.68 (m, 1H), 2.70 (br s, 1H), 3.45–3.65 (m, 2H), 3.72 and 3.73 (s, 3H), 3.79 (m, 1H), 4.27 and 4.34 (t, $J = 8.6$ Hz, 1H), 6.28 (s, 2H), 8.66 (br s, 1H).

4.1.74. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-[2,6-dimethoxy-4-(methoxymethoxy)phenyl]-2-pyrrolidinecarboxylic acid (40g). Compound **40g** was obtained as a beige powder in 77% yield from **39g** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.22$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.56 (m, 9H), 2.20–2.44 (m, 1H), 2.81–3.01 (m, 1H), 3.49 (s, 3H), 3.57–4.02 (m, 9H), 4.28–4.54 (m, 1H), 5.16 (s, 2H), 6.27 (s, 2H).

4.1.75. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(2-ethyl-4-hydroxy-6-methylphenyl)-2-pyrrolidinecarboxylic acid (40h). Compound **40h** was obtained as a white powder in 91% yield from **39h** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.38$ ($CHCl_3$/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, $J = 7.5$ Hz, 3H), 1.46 and 1.49 (s, 9H), 2.37 (s, 3H), 2.48 (m, 2H), 2.65 (q, $J = 7.5$ Hz, 2H), 2.72 (m, 1H), 3.62–3.83 (m, 2H), 4.38 and 4.48 (m, 1H), 6.51 (d, $J = 3.0$ Hz, 1H), 6.55 (d, $J = 3.0$ Hz, 1H).

4.1.76. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-[2,6-diethoxy-4-(methoxymethoxy)phenyl]-2-pyrrolidinecarboxylic acid (40i). Compound **40i** was obtained as a brown powder in 72% yield from **39i** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.04$ (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.56 (m, 15H), 2.17–2.41 (m, 1H), 2.94–3.15 (m, 1H), 3.47 (s, 3H), 3.55–3.74 (m, 2H), 3.91–4.06 (m, 5H), 4.27–4.52 (m, 1H), 5.14 (s, 2H), 6.25 (s, 2H).

4.1.77. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(3-hydroxy-2,6-dimethylphenyl)-2-pyrrolidinecarboxylic acid (40j). Compound **40j** was obtained as a colorless oil in 92% yield from **39j** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.23$ ($CHCl_3$/MeOH, 9/1); MS (APCI, neg. 20 V) *m*/*z* 334 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 and 1.49 (s, 9H), 2.29 (s, 3H), 2.33 (s, 3H), 2.50–2.57 (m, 2H), 3.70–3.90 (m, 3H), 4.38–4.52 (m, 1H), 6.62 (d, $J = 8.2$ Hz, 1H), 6.88 (d, $J = 8.2$ Hz, 1H).

4.1.78. (2*S*,4*R*)-4-[3-(Benzyloxy)-2-methoxy-6-methylphenyl]-1-(*tert*-butoxycarbonyl)-2-pyrrolidinecarboxylic acid (40k). Compound **40k** was obtained as a white powder in 89% yield from **39q** according to the same

procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.75$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.31 (s, 3H), 2.39–2.97 (m, 2H), 3.55–3.87 (m, 3H), 3.91 (s, 3H), 4.33–4.52 (m, 1H), 5.06 (s, 2H), 6.75–6.86 (m, 2H), 7.28–7.51 (m, 5H).

4.1.79. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(3-hydroxy-2,4,6-trimethylphenyl)-2-pyrrolidinecarboxylic acid (40l). Compound **40l** was obtained as a white powder in 100% yield from **39l** according to the same procedure as described for the preparation of **34a** from **33a**. TLC $R_f = 0.52$ ($CHCl_3$/MeOH, 9/1); MS (APCI, neg. 20 V) *m*/*z* 348 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.52 (m, 9H), 2.19 (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 2.40–2.60 (m, 2H), 3.65–3.90 (m, 3H), 4.35–4.52 (m, 1H), 6.81 (s, 1H).

4.1.80. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(2,6-dimethylphenyl)-1-pyrrolidinecarboxylate (41a). Compound **41a** was obtained as a white powder in 99% yield from **40a** according to the same procedure as described for the preparation of **26a** from **25a**. TLC $R_f = 0.33$ ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) *m*/*z* 398 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36–1.59 (m, 9H), 2.42 (s, 6H), 2.46–2.82 (m, 2H), 3.62–3.96 (m, 3H), 4.30–4.53 (m, 1H), 6.95–7.11 (m, 3H).

4.1.81. *tert*-Butyl (2*S*,4*R*)-4-[2-(benzyloxy)phenyl]-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-1-pyrrolidinecarboxylate (41b). Compound **41b** was obtained as a white powder in 59% yield from **40b** according to the same procedure as described for the preparation of **26a** from **25a**. TLC $R_f = 0.61$ ($CHCl_3$/MeOH, 10/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26–1.40 (m, 9H), 1.75–2.30 (m, 5H), 2.54–2.74 (m, 1H), 3.05–3.44 (m, 2H), 3.51–3.71 (m, 2H), 3.81–3.98 (m, 1H), 4.43–4.57 (m, 1H), 4.75–4.89 (m, 1H), 5.05–5.20 (m, 2H), 6.93 (t, $J = 7.3$ Hz, 1H), 7.08 (t, $J = 8.8$ Hz, 1H), 7.16–7.27 (m, 2H), 7.28–7.54 (m, 5H).

4.1.82. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-[3-(tetrahydro-2H-pyran-2-yloxy)phenyl]-1-pyrrolidinecarboxylate (41c). Compound **41c** was obtained as a white powder in 60% yield from **40c** according to the same procedure as described for the preparation of **26a** from **25a**. TLC $R_f = 0.58$ (CH_2Cl_2/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 and 1.44 (s, 9H), 1.54–1.76 (m, 3H), 1.80–1.91 (m, 2H), 1.95–2.39 (m, 6H), 2.52–2.68 (m, 1H), 3.26–3.41 (m, 1H), 3.43–3.55 (m, 1H), 3.57–3.68 (m, 2H), 3.76–4.15 (m, 3H), 4.41–4.57 (m, 1H), 4.80–4.94 (m, 1H), 5.37–5.47 (m, 1H), 6.85–7.01 (m, 3H), 7.19–7.28 (m, 1H).

4.1.83. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]-1-pyrrolidinecarboxylate (41d). Compound **41d** was obtained as a white powder in 61% yield from **40d** according to the same procedure as described for the preparation of **26a** from **25a**. TLC $R_f = 0.62$ ($CHCl_3$/MeOH,10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36–1.49 (m, 9H), 1.51–1.77 (m, 3H), 1.79–1.89 (m, 2H), 1.92–2.39 (m, 6H), 2.50–2.65 (m, 1H), 3.21–3.39 (m, 1H), 3.38–3.51 (m, 1H), 3.53–4.10 (m, 5H), 4.39–4.56 (m, 1H), 4.81–4.93 (m, 1H), 5.40 (t, $J = 3.2$ Hz, 1H), 6.94–7.06 (m, 2H), 7.18 (t, $J = 8.0$ Hz, 2H).

4.1.84. *tert*-Butyl (2*S*,4*R*)-4-[4-(benzyloxy)-2,6-dimethylphenyl]-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-1-pyrrolidinecarboxylate (41e). Compound **41e** was obtained as a white powder in 93% yield from **40e** according to the same procedure as described for the preparation of **26a** from **25a**. TLC $R_f = 0.38$ (EtOAc/hexane, 2/1); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.38 (s, 9H), 1.94–2.33 (m, 5H), 2.34 (s, 6H), 2.52–2.66 (m, 1H), 3.28–3.47 (m, 1H), 3.51–3.72 (m, 3H), 3.72–3.90 (m, 1H), 4.56 (t, $J = 8.2$ Hz, 1H), 4.73–4.86 (m, 1H), 5.04 (s, 2H), 6.66 (s, 2H), 7.26–7.46 (m, 5H).

4.1.85. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(4-hydroxy-2-methoxy-6-methylphenyl)-1-pyrrolidinecarboxylate (41f). To a stirred solution of **40f** (9.10 g, 23.8 mmol) in DMF (60 mL) were added (2*S*)-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (7.65 g, 28.6 mmol), 4-methylmorpholine (5.8 mL, 52 mmol), 1-hydroxybenzotriazole (3.21 g, 23.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.47 g, 28.5 mmol) at room temperature. After being stirred for 15 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was successively washed with 10% aqueous citric acid, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/1) as an eluant to yield **41f** (5.20 g, 51%) as a white powder. TLC $R_f = 0.48$ ($CHCl_3$/MeOH, 19/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31 and 1.38 (s, 9H), 2.20 and 2.22 (s, 3H), 1.97–2.44 (m, 6H), 3.39–3.68 (m, 5H), 3.64 and 3.65 (s, 3H), 4.43 (m, 1H), 4.80 and 4.95 (m, 1H), 6.17 (m, 1H), 6.23 (m, 1H), 9.22 (s, 1H).

4.1.86. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-[2,6-dimethoxy-4-(methoxymethoxy)phenyl]-1-pyrrolidinecarboxylate (41g). Compound **41g** was obtained as a white powder in 53% yield from **40g** according to the same procedure as described for the preparation of **26a** from **25a**. TLC $R_f = 0.23$ (EtOAc/hexane, 2/1); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.37 (s, 9H), 1.98–2.11 (m, 2H), 2.11–2.25 (m, 2H), 2.29–2.39 (m, 2H), 3.41 (s, 3H), 3.43–3.67 (m, 4H), 3.74 (s, 6H), 3.77–3.87 (m, 1H), 4.47 (t, $J = 8.3$ Hz, 1H), 4.75–4.86 (m, 1H), 5.16 (s, 2H), 6.32 (s, 2H).

4.1.87. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(2-ethyl-4-hydroxy-6-methylphenyl)-1-pyrrolidinecarboxylate (41h). Compound **41h** was obtained as a brown oil in 63% yield from **40h** according to the same procedure as described for the preparation of **41f** from **40f**. TLC $R_f = 0.47$ ($CHCl_3$/MeOH, 9/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, $J = 7.2$ Hz, 3H), 1.30 and 1.37 (s, 9H), 1.97–2.30 (m, 4H), 2.25 and 2.26 (s, 3H), 2.26–2.45 (m, 4H), 3.40–3.80 (m, 4H), 4.51 and 4.54 (m, 1H), 4.81 and 4.98 (m, 1H), 6.39 (m, 2H), 9.05 and 9.06 (s, 1H).

4.1.88. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-[2,6-diethoxy-4-(methoxymethoxy)phenyl]--1-pyrrolidinecarboxylate (41i). Compound **41i** was obtained as a brown powder in 51% yield from **40i** according to the same procedure as described for the preparation of **41f** from **40f**. TLC R_f = 0.32 (EtOAc/hexane, 2/1); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.28–1.44 (m, 15H), 1.99–2.34 (m, 5H), 2.41–2.52 (m, 1H), 3.40 (s, 3H), 3.41–3.88 (m, 5H), 3.94–4.09 (m, 4H), 4.43–4.52 (m, 1H), 4.74–4.85 (m, 1H), 5.13 (s, 2H), 6.29 (s, 2H).

4.1.89. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(3-hydroxy-2,6-dimethylphenyl)-1-pyrrolidinecarboxylate (41j). Compound **41j** was obtained as a colorless oil in 72% yield from **40j** according to the same procedure as described for the preparation of **26a** from **25a**. TLC R_f = 0.49 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) *m*/*z* 414 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.38 (s, 9H), 2.00–2.20 (m, 5H), 2.18 (s, 3H), 2.26 (s, 3H), 2.50–2.60 (m, 1H), 3.60–3.67 (m, 4H), 3.82–3.90 (m, 1H), 4.57 (t, J = 8.2 Hz, 1H), 4.75–4.85 (m, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 8.55 (s, 1H).

4.1.90. *tert*-Butyl (2*S*,4*R*)-4-[3-(benzyloxy)-2-methoxy-6-methylphenyl]-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-1-pyrrolidinecarboxylate (41k). Compound **41k** was obtained as a white powder in 63% yield from **40k** according to the same procedure as described for the preparation of **41f** from **40f**. TLC R_f = 0.39 (EtOAc/hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.50 (m, 9H), 2.09–2.72 (m, 9H), 3.55–3.99 (m, 8H), 4.44–4.63 (m, 1H), 4.81–4.97 (m, 1H), 5.06 (s, 2H), 6.74–6.85 (m, 2H), 7.28–7.51 (m, 5H).

4.1.91. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(3-hydroxy-2,4,6-trimethylphenyl)-1-pyrrolidinecarboxylate (41l). Compound **41l** was obtained as a white powder in 36% yield from **40l** according to the same procedure as described for the preparation of **26a** from **25a**. TLC R_f = 0.69 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) *m*/*z* 428 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.38 (s, 9H), 2.00–2.23 (m, 5H), 2.11 (s, 3H), 2.21 (s, 3H), 2.24 (s, 3H), 2.50–2.60 (m, 1H), 3.55–3.65 (m, 4H), 3.70–3.90 (m, 1H), 4.56 (t, J = 8.3 Hz, 1H), 4.75–4.85 (m, 1H), 6.70 (s, 1H), 7.49 (s, 1H).

4.1.92. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(2-hydroxyphenyl)-1-pyrrolidinecarboxylate (41m). To a solution of **41b** (294 mg, 0.62 mmol) in MeOH (6 mL) was added 10 % palladium on carbon (29 mg). The reaction mixture was vigorously stirred at room temperature under an atmospheric pressure of hydrogen for 5 h. The catalyst was removed by filtration and the filtrate was evaporated. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (1/2) as an eluant to yield **41m** (76 mg, 42%) as a white powder. TLC R_f = 0.39 (EtOAc/hexane, 2/1); MS (APCI, pos. 20 V) *m*/*z* 386 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28–1.41 (m, 9H), 1.75–2.31 (m, 5H), 2.53–2.78 (m, 1H), 3.10–3.23 (m, 1H), 3.42–3.71 (m, 3H), 3.86 (dd, J = 9.9, 7.3 Hz, 1H), 4.40–4.54 (m, 1H), 4.76–4.88 (m, 1H), 6.67–6.86 (m, 2H), 6.97–7.18 (m, 2H), 9.53 (s, 1H).

According to the same procedure as described above, **41n** was prepared from **41e**.

4.1.93. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(4-hydroxy-2,6-dimethylphenyl)-1-pyrrolidinecarboxylate (41n). Yield 56%. A white powder. TLC R_f = 0.60 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 and 1.45 (s, 9H), 2.07–2.51 (m, 12H), 3.51–3.87 (m, 5H), 4.41–4.60 (m, 1H), 4.80–4.92 (m, 1H), 6.50 (s, 2H).

4.1.94. *tert*-Butyl (2*S*,4*R*)-2-{[(2*S*)-2-cyano-1-pyrrolidinyl]carbonyl}-4-(3-hydroxy-2-methoxy-6-methylphenyl)-1-pyrrolidinecarboxylate (41o). To a solution of **41k** (142 mg, 0.273 mmol) in EtOAc (3 mL) was added 20 % palladium hydroxide on carbon (28 mg). The reaction mixture was vigorously stirred at room temperature under an atmospheric pressure of hydrogen for 2.5 h. The catalyst was removed by filtration and the filtrate was evaporated. The resulting residue was purified by silica gel chromatography using EtOAc/hexane (2/1) as an eluant to yield **41o** (100 mg, 85%) as a white powder. TLC R_f = 0.28 (EtOAc/hexane, 2/1); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 1.38 (s, 9H), 1.99–2.38 (m, 5H), 2.24 (s, 3H), 2.40–2.58 (m, 1H), 3.46–3.70 (m, 5H), 3.75 (s, 3H), 4.53 (t, J = 8.3 Hz, 1H), 4.75–4.86 (m, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 8.64 (s, 1H).

4.1.95. (2*S*)-1-{[(2*S*,4*R*)-4-(2,6-Dimethylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride (13). Compound **13** was obtained as a white powder in 76% yield from **41a** according to the same procedure as described for the preparation of **12** from **26b**. TLC R_f = 0.43 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) *m*/*z* 298 $(M+H)^+$; IR (KBr) 3434, 2974, 2885, 2242, 1656, 1544, 1363, 1340, 1154, 556 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.94–2.08 (m, 2H), 2.08–2.27 (m, 4H), 2.33 (s, 6H), 2.68–2.85 (m, 1H), 3.43–3.71 (m, 4H), 3.88–4.20 (m, 1H), 4.68 (t, J = 8.6 Hz, 1H), 4.81–4.90 (m, 1H), 6.93–7.09 (m, 3H); HRMS (FAB) calcd for $C_{18}H_{24}N_3O$: 298.1919. Found: 298.1916.

4.1.96. (2*S*)-1-{[(2*S*,4*R*)-4-(2-Hydroxyphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (14). Compound **14** was obtained as an ivory powder in 42% yield from **41m** according to the same procedure as described for the preparation of **5** from **35a**. TLC R_f = 0.24 ($CHCl_3$/MeOH, 5/1); MS (APCI, pos. 20 V) *m*/*z* 286 $(M+H)^+$; IR (KBr) 3588, 2243, 1656, 1455, 1170, 1124, 1034, 1009, 683, 567 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88–2.08 (m, 3H), 2.09–2.26 (m, 2H), 2.28 (s, 3H), 2.74–2.89 (m, 1H), 3.20–3.37 (m, 1H), 3.48–3.81 (m, 4H), 4.54–4.69 (m, 1H), 4.85 (dd, J = 7.7, 4.6 Hz, 1H), 6.73–6.86 (m, 2H), 7.05–7.14 (m, 3H), 7.14–7.20 (m, 1H), 7.46 (d, J = 8.0 Hz, 2H), 8.82 (s, 1H), 9.47 (s, 1H), 9.76 (s, 1H); HRMS (FAB) calcd for $C_{16}H_{20}N_3O_2$: 286.1556. Found: 286.1555.

4.1.97. (2*S*)-1-{[(2*S*,4*R*)-4-(3-Hydroxyphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (15). Compound **15** was obtained as a white powder in 87% yield from **41c** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.20$ (CH_2Cl_2/MeOH, 9/1); MS (MALDI, pos.) *m*/*z* 286 $(M+H)^+$; IR (KBr) 3165, 2243, 1661, 1601, 1589, 1454, 1161, 1122, 1033, 1009, 682, 568 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.65–1.87 (m, 1H), 1.95–2.09 (m, 2H), 2.09–2.26 (m, 2H), 2.28 (s, 3H), 2.82–3.04 (m, 1H) 3.08–3.31 (m, 1H), 3.45–3.55 (m, 1H), 3.56–3.74 (m, 3H), 4.51–4.69 (m, 1H), 4.85 (dd, $J = 7.7$, 4.8 Hz, 1H), 6.61–6.81 (m, 3H), 7.06–7.19 (m, 3H), 7.46 (d, $J = 8.0$ Hz, 2H), 8.78–9.05 (m, 1H), 9.31–9.63 (m, 2H); HRMS (FAB) calcd for $C_{16}H_{20}N_3O_2$: 286.1556. Found: 286.1554.

4.1.98. (2*S*)-1-{[(2*S*,4*R*)-4-(4-Hydroxyphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (16). Compound **16** was obtained as an ivory powder in 92% yield from **41d** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.25$ ($CHCl_3$/MeOH, 2/1); MS (APCI, pos. 20 V) *m*/*z* 286 $(M+H)^+$; IR (KBr) 3290, 2242, 1660, 1615, 1519, 1449, 1213, 1164, 1122, 1009, 684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.62–1.84 (m, 1H), 1.92–2.08 (m, 2H), 2.09–2.27 (m, 2H), 2.28 (s, 3H), 2.80–2.97 (m, 1H), 3.06–3.22 (m, 1H), 3.35–3.53 (m, 2H), 3.55–3.70 (m, 2H), 4.47–4.68 (m, 1H), 4.85 (dd, $J = 7.8$, 4.7 Hz, 1H), 6.72 (d, $J = 8.0$ Hz, 2H), 7.11 (dd, $J = 8.2$, 2.9 Hz, 4H), 7.47 (d, $J = 8.0$ Hz, 2H), 8.69–9.12 (m, 1H), 9.27–9.60 (m, 2H); HRMS (FAB) calcd for $C_{16}H_{20}N_3O_2$: 286.1556. Found: 286.1558.

4.1.99. (2*S*)-1-{[(2*S*,4*R*)-4-(4-Hydroxy-2,6-dimethylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (17). Compound **17** was obtained as an ivory powder in 100% yield from **41n** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.25$ ($CHCl_3$/MeOH, 5/1); MS (APCI, pos. 20 V) *m*/*z* 314 $(M+H)^+$; IR (KBr) 3169, 2243, 1662, 1611, 1593, 1453, 1150, 1122, 1033, 1009, 682, 568 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.95–2.22 (m, 5H), 2.23 (s, 6H), 2.28 (s, 3H), 2.61–2.80 (m, 1H), 3.34–3.66 (m, 4H), 3.75–3.97 (m, 1H), 4.54–4.74 (m, 1H), 4.86 (dd, $J = 7.8$, 4.7 Hz, 1H), 6.42 (s, 2H), 7.07–7.13 (m, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 9.00 (s, 1H), 9.18 (s, 1H), 9.41 (s, 1H); HRMS (FAB) calcd for $C_{18}H_{24}N_3O_2$: 314.1869. Found: 314.187.

4.1.100. (2*S*)-1-{[(2*S*,4*R*)-4-(4-Hydroxy-2-methoxy-6-methylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride (18). Compound **18** was obtained as a white powder in 69% yield from **41f** according to the same procedure as described for the preparation of **12** from **26b**. TLC $R_f = 0.19$ ($CHCl_3$/MeOH, 9/1); MS (EI, pos.) *m*/*z* 329 $(M+H)^+$; IR (KBr) 3129, 2939, 2237, 1644, 1618, 1609, 1586, 1455, 1381, 1371, 1155 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.93–2.07 (m, 2H), 2.20 (s, 3H), 2.07–2.34 (m, 3H), 2.53–2.67 (m, 1H), 3.25–3.40 (m, 1H), 3.44–3.64 (m, 3H), 3.68 (s, 3H), 3.64–3.81 (m, 1H), 4.49–4.64 (m, 1H), 4.86 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.21 (d, $J = 2.2$ Hz, 1H), 6.27 (d, $J = 2.2$ Hz, 1H), 8.64 (s, 1H), 9.39 (s, 1H), 10.15 (s, 1H); Anal. Calcd for $C_{18}H_{24}N_3O_3$: C, 59.09; H, 6.61; N, 11.49. Found: C, 58.79; H, 6.68; N, 11.03.

4.1.101. (2*S*)-1-{[(2*S*,4*R*)-4-(4-Hydroxy-2,6-dimethoxyphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (19). Compound **19** was obtained as a beige powder in 100% yield from **41g** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.43$ (CH_2Cl_2/MeOH, 5/1); MS (APCI, pos. 20 V) *m*/*z* 346 $(M+H)^+$; IR (KBr) 3194, 2245, 1662, 1615, 1600, 1196, 1153, 1121, 1033, 1009, 682 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.91–2.06 (m, 2H), 2.07–2.33 (m, 3H), 2.28 (s, 3H), 2.45–2.62 (m, 1H), 3.19–3.81 (m, 4H), 3.69 (s, 6H), 3.86–4.08 (m, 1H), 4.49–4.72 (m, 1H), 4.85 (dd, $J = 8.0$, 4.7 Hz, 1H), 6.07 (s, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 8.67 (s, 1H), 9.33 (s, 1H), 9.56 (s, 1H); HRMS (FAB) calcd for $C_{18}H_{24}N_3O_4$: 346.1767. Found: 346.1768.

4.1.102. (2*S*)-1-{[(2*S*,4*R*)-4-(2-Ethyl-4-hydroxy-6-methylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (20). Compound **20** was obtained as a pale pink powder in 85% yield from **41h** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.25$ ($CHCl_3$/MeOH, 5/1); MS (APCI, neg. 20 V) *m*/*z* 326 $(M-H)^-$; IR (KBr) 3377, 2967, 2245, 1661, 1611, 1454, 1146, 1123, 1033, 1009, 682 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.07–1.15 (m, 3H), 1.94–2.09 (m, 2H), 2.10–2.32 (m, 3H), 2.23 (s, 3H), 2.28 (s, 3H), 2.44–2.58 (m, 2H), 2.63–2.80 (m, 1H), 3.30–3.50 (m, 2H), 3.51–3.72 (m, 2H), 3.64 (s, 1H), 3.78–3.95 (m, 1H), 4.61–4.75 (m, 1H), 4.86 (dd, $J = 7.6$, 4.7 Hz, 1H), 6.40–6.47 (m, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 9.05 (s, 1H), 9.42 (s, 1H); HRMS (FAB) calcd for $C_{19}H_{26}N_3O_2$: 328.2025. Found: 328.2023.

4.1.103. (2*S*)-1-{[(2*S*,4*R*)-4-(2,6-Diethoxy-4-hydroxyphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (21). Compound **21** was obtained as a white powder in 93% yield from **41i** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.36$ ($CHCl_3$/MeOH, 5/1); MS (APCI, pos. 20 V) *m*/*z* 374 $(M+H)^+$; IR (KBr) 3186, 2978, 2243, 1662, 1599, 1461, 1159, 1121, 1033, 1009, 682 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.22–1.37 (m, 6H), 1.91–2.32 (m, 4H), 2.28 (s, 3H), 2.36–2.66 (m, 2H), 3.15–3.82 (m, 5H), 3.82–4.04 (m, 4H), 4.53–4.69 (m, 1H), 4.73–4.90 (m, 1H), 6.00–6.08 (m, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 8.67 (s, 1H), 9.35 (s, 1H), 9.48 (s, 1H); HRMS (FAB) calcd for $C_{20}H_{28}N_3O_4$: 374.208. Found: 374.2082.

4.1.104. (2*S*)-1-{[(2*S*,4*R*)-4-(3-Hydroxy-2,6-dimethylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (22). Compound **22** was obtained as a white powder in 92% yield from **41j** according to the same procedure as described for the preparation of **5** from **35a**. TLC $R_f = 0.28$ ($CHCl_3$/

MeOH, 9/1); MS (APCI, pos. 20 V) *m/z* 314 $(M+H)^+$; IR (KBr) 3148, 2244, 1662, 1452, 1281, 1156, 1122, 1033, 1009, 682, 567 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.95–2.26 (m, 5H), 2.10 (s, 3H), 2.22 (s, 3H), 2.28 (s, 3H), 2.67–2.83 (m, 1H), 3.44–3.69 (m, 4H), 3.90–4.12 (m, 1H), 4.63–4.79 (m, 1H), 4.86 (dd, J = 7.8, 4.9 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 9.07 (s, 2H), 9.20–9.70 (m, 1H); HRMS (FAB) calcd for $C_{18}H_{24}N_3O_2$: 314.1869. Found: 314.1868.

4.1.105. (2*S*)-1-{[(2*S*,4*R*)-4-(3-Hydroxy-2-methoxy-6-methylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (23). Compound **23** was obtained as a white powder in 97% yield from **41o** according to the same procedure as described for the preparation of **5** from **35a**. TLC R_f = 0.26 (CH_2Cl_2/MeOH/AcOH, 100/10/1); MS (APCI, pos. 20 V) *m/z* 330 $(M+H)^+$; IR (KBr) 3396, 2961, 2776, 2244, 1661, 1452, 1174, 1123, 1034, 1009, 683 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.92–2.35 (m, 4H), 2.20 (s, 3H), 2.28 (s, 3H), 2.43–2.59 (m, 1H), 2.64–2.84 (m, 1H), 3.38–3.75 (m, 5H), 3.77 (s, 3H), 4.56–4.73 (m, 1H), 4.80–5.14 (m, 1H), 6.64–6.75 (m, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 8.75–8.92 (m, 1H), 9.18–9.55 (m, 2H); HRMS (FAB) calcd for $C_{18}H_{24}N_3O_3$: 330.1818. Found: 330.1817.

4.1.106. (2*S*)-1-{[(2*S*,4*R*)-4-(3-Hydroxy-2,4,6-trimethylphenyl)-2-pyrrolidinyl]carbonyl}-2-pyrrolidinecarbonitrile 4-methylbenzenesulfonate (24). Compound **24** was obtained as a beige powder in 90% yield from **41l** according to the same procedure as described for the preparation of **5** from **35a**. TLC R_f = 0.24 ($CHCl_3$/MeOH, 9/1); MS (APCI, pos. 20 V) *m/z* 328 $(M+H)^+$; IR (KBr) 3408, 2976, 2244, 1662, 1574, 1452, 1122, 1033, 1009, 683, 568 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.94–2.26 (m, 5H), 2.09 (s, 3H), 2.14 (s, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 2.64–2.83 (m, 1H), 3.41–4.02 (m, 5H), 4.58–4.78 (m, 1H), 4.86 (dd, J = 7.6, 4.7 Hz, 1H), 6.73 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 8.94–9.15 (m, 1H), 9.33–9.65 (m, 1H); HRMS (FAB) calcd for $C_{19}H_{26}N_3O_2$: 328.2025. Found: 328.2021.

4.1.107. Chemical stability assay. Test compounds were dissolved in pH 7.4 Tris buffer (100 mM) to produce a solution of 1 mg/mL. Samples were incubated at room temperature and analyzed by LC/MS, with the first sample injected being designated as the time zero sample. Then the peak area of the remaining samples was measured at the intervals of 0 h, 2 h, 6 h, and 24 h. Reactions were analyzed using a first-order kinetics model, in which a plot of log(peak area/peak area at time zero) versus time was linear. The half-life was obtained by linear fitting to the plot using Microsoft Excel 2000.

4.2. Biological methods

4.2.1. Purification of human DPP-IV. Human DPP-IV was purified according to the published procedure with some modifications.[21] Briefly, the enzyme was prepared from pooled plasmaobtained from healthy volunteers by ammonium sulfate precipitation (50–70%). After extensive dialysis against 25 mM Tris–HCl (pH 7.4), the material was mixed with DEAE cellulose, DE52 (Whatman Chemical Separation, Inc., USA) for 60 min, and eluted with buffer containing100 mM NaCl. Fractions of 10 mL were collected, and the fraction with maximal DPP-IV activity was dialyzed against 25 mM MES–NaOH (pH 6.0). DPP-IV-containing fractions were detected by the ability to hydrolyze Gly-Pro-7-amido-4-methyl-coumarin (Gly-Pro-AMC) (Sigma–Aldrich, USA) using the standard method described below. The DE52 elute was loaded onto a SP Sepharose Fast Flow column (GE Healthcare, Sweden), and the flow-through fraction containing DPP-IV was then applied to a DEAE cellulose column (Whatman DE52). Bounded proteins were eluted with 25 mM Tris–HCl (pH 7.8) containing150 mM NaCl. Fractions of 10 ml were collected, and the fraction with maximum DPP-IVactivity was concentrated using polyethylene glycol 20000 (PEG20000). The concentrated material was applied to a Sephacryl S-300 High Resolution 26/60 column (GE Healthcare, Sweden), and was eluted at a flow rate of 0.1 ml/min. Fractions of 1 ml were collected, and the fractions containing DPP-IV activity were pooled.

4.2.2. Enzyme assays. Enzymatic activity was determined at 37 °C by the cleavage rate of a substrate, Gly-Pro-AMC (30 μM) (Sigma–Aldrich, USA).[22] Briefly, 10 μL of DPP-IV solution was added to each well of a 96-well flat-bottomed microtiter plate, followed by the addition of 50 μL of 60 μM Gly-Pro-AMC, 10 μL of 500 mM Tris–HCl (pH 7.4), 20 μL of distilled water, and 10 μL of a test compound. The change of fluorescence was monitored at 37 °C using a spectrofluorometer (excitation at 355 nm/emission at 460 nm) (f_{max}, Molecular Devices, USA). The initial rate of DPP-IV enzyme activity was calculated over the first 15 min of the reaction, with units/mL being defined as the rate of increase in the fluorescence intensity (arbitrary units) under these conditions. The percent inhibition relative to addition of the solvent alone was calculated and IC_{50} values were determined by logistic analysis.

4.2.3. DPP-IV inhibition in rats. Male Sprague–Dawley (SD) rats were purchased from Charles River Laboratories Japan. The rats were housed in an air-conditioned animal room with a controlled temperature (24 ± 2 °C), humidity (55 ± 5%), and lighting (12:12 h light/dark cycle), and were provided with standard pellet food for rodents CRF-1 (Oriental Yeast, Japan) and water ad libitum. All procedures were conducted according to the ONO Pharmaceutical Animal Care Committee guidelines. After at least 8 h fast, male SD rats (6–7 weeks of age) were orally administered test compounds dissolved in 0.5% methylcellulose at a single dose of 1 mg/kg. Blood samples were collected from the jugular vein before, and 0.25, 0.5, 1, 2, 4, 6, and 10 h after administration. Blood was centrifuged immediately to obtain plasma and its DPP-IV activity was determined. Then 50 μL of plasma was added to each well of a 96-well flat-bottomed microtiter plate, followed by the addition of 50 μL of 60 μM substrate. The initial rate

of DPP-IV enzyme activity was calculated using the standard method described above. The percent inhibition relative to basal DPP-IV activity was calculated.

4.2.4. Oral glucose tolerance test in rats. The effect of inhibitor **22** on glucose levels was assessed in male SD rats (400–460 g). Rats were fasted for at least 20 h before the start of the study. On the day of the experiment, animals were dosed orally with the vehicle (0.5% methylcellulose) or compound **22** (0.01, 0.03, or 0.1 mg/kg) at −30 min. Blood samples (75 μL) were collected at −5 min from the tail into heparinized tubes. Glucose (1 g/kg) was administered orally at 0 min and additional blood samples (75 μL) were collected at 5, 10, 15, 30, 60, and 120 min. Plasma was extracted after centrifugation and stored at −80 °C until the determination of plasma glucose levels. Measurement of plasma glucose was done with a glucose oxidase peroxidase dye system (Diacolor GC, Toyobo, Japan).

4.2.5. Pharmacokinetic (PK) and bioavailability (*F*) studies in rats. Male Sprague–Dawley rats (5–7 weeks old) were purchased from Charles River Laboratories and fasted for 24 h prior to dosing. Test compounds were prepared as solutions in saline (0.15 mg/mL) for intravenous (iv) administration and as solutions in 0.5% methylcellulose (0.2 mg/mL) for oral administration (po). An intravenous dose of 0.3 mg/2 mL/kg was administered as a slow bolus via the jugular vein, while an oral dose of 1 mg/5 mL/kg was administered to other rats ($n = 3$ each). The bioavailability of **17**, **22**, and **23** was calculated based on the data obtained after dosing.

The bioavailability of **18** was calculated from data obtained after an oral dose of 10 mg/5 ml/kg and an intravenous dose of 0.3 mg/2 mL/kg.

Blood samples (250 μL) were collected from the jugular vein using a heparinized syringe at multiple times from 0 to 24 h. The blood was chilled on ice and then centrifuged at 12,000 rpm for 3 min at 4 °C to obtain plasma. Plasma protein was precipitated by acetonitrile and the supernatant was evaporated. Then the sample was reconstituted in the mobile phase and analyzed by LC/MS/MS. The AUC was obtained by measuring the changes of the plasma concentration of each test compound over time.

F was calculated according to the following equation:

$$F(\%) = (\mathrm{AUC_{po}}/\mathrm{D_{po}})/(\mathrm{AUC_{iv}}/\ \mathrm{D_{iv}}) \times 100$$

where $\mathrm{AUC_{po}}$, AUC after oral dosing; $\mathrm{AUC_{iv}}$, AUC after intravenous dosing; $\mathrm{D_{po}}$, oral dose; $\mathrm{D_{iv}}$, intravenous dose.

4.2.6. Plasma analysis after glucuronidase treatment. β-Glucuronidase/arylsulfatase was purchased from Roche Diagnostics Corporation. Then 0.5 mol/L acetate buffer (pH 5.0) : β-glucuronidase/arylsulfatase = 40 : 1 was added to the evaporated supernatant prepared from a blood sample according to the procedure as described above and incubated for 2 h at 37 °C. Incubation was terminated by the addition of acetonitrile and the supernatant was evaporated. The sample was reconstituted in the mobile phase and analyzed by LC/MS/MS.

4.2.7. Assessment of hepatic microsomal metabolism. Rat liver microsomes were purchased from Xenotech Corporation. Reaction mixtures contained 50 mmol/L sodium phosphate, 8 mmol/L magnesium chloride, 25 μg/mL alamethicin, 1 mg/mL microsomal protein, and 100 ng/mL test compound. Reactions were initiated by the addition of 2 mM NADPH or UDPGA and were carried out for up to 60 min in a water bath at 37 °C. Incubation was terminated by addition of acetonitrile and the supernatant was evaporated. Then the sample was reconstituted in the mobile phase and analyzed by LC/MS/MS.

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23. Compounds **5** and **7** were stereoselectively synthesized according to the method reported in Ref. 18.
24. Blood plasma sampled at 2 h after oral dosing was fractionated by HPLC (column: YMC-Pack ODS-A, 4.6×150 mm, 5 μm; eluent A: H_2O with 0.1 % formic acid; eluant B: CH_3CN, linear gradient 5% to 80% of eluent B in eluent A in 25 min; flow rate: 1 mL/min). The fractions (retention time, 5–6 min), which showed inhibitory activity, were collected and analyzed by LC/MS/MS. The only metabolite detected was the one possessing $m/z = 462$, which corresponds to glucuronated phenolic metabolite of **11**. The metabolite was treated with glucuronidase and then analyzed by HPLC under the same condition as described above. The resulting material (retention time, 11 min) was found to be identical with that of *para*-phenolic analog **16**, which was not detected in the above-described experimental condition.