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Original article

Synthesis and biological evaluation of new GABA-uptake inhibitors derived from proline and from pyrrolidine-2-acetic acid

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Abstract

Several synthetic approaches to *N*-alkylated derivatives of 4-hydroxypyrrolidine-2-carboxylic acid and 4-hydroxypyrrolidine-2-acetic acid are described. The final compounds have been evaluated as potential inhibitors of the GABA transport proteins GAT-1 and GAT-3. The biological assays used were based on bovine material or porcine brain. As compared to the corresponding 4-unsubstituted compounds, the 4-hydroxypyrrolidine-2-carboxylic acid and 4-hydroxypyrrolidine-2-acetic acid derivatives showed a significant decrease in the inhibitory potency at both GAT-1 and GAT-3 with only four compounds having reasonable affinity to GAT-1 (IC_{50}: 5.1, 6.6 and 9.4 μM) or GAT-3 (IC_{50}: 19.9 μM), respectively. The biological data of the 4-hydroxypyrrolidine-2-acetic acid derivatives indicates that (2*S*)-configuration at the C-2 position for potent inhibition of GAT-1 and (4*R*)-configuration at the C-4 position for potent inhibition of GAT-3 may be crucial.

Keywords: GABA-uptake inhibitors; Antiepileptic; GAT-1; GAT-3; Pyrrolidines

1. Introduction

Dysfunctioning of GABAergic synapses resulting in a decrease of GABAergic transmission has been invoked for diseases such as epilepsy [1], Huntington's chorea [2], and Parkinson's disease [3]. Sodium-dependent GABA-uptake systems have been found to be the principal means by which GABA in the synaptic cleft is inactivated. In contrast to the direct enhancement of GABA neurotransmission by $GABA_A$ agonists and benzodiazepines, inhibition of the GABA transport system palliates GABA deficiency in vivo without giving rise to the development of tolerance [4]. Four different GABA transporters have been identified thus far (GAT-1 [5], GAT-2 [5b], GAT-3 [6] and BGT-1 [7]) differing in their regional distribution in the brain and the body and in their sensitivity to pharmacological agents [8]. GAT-1 and GAT-3 are high affinity transporters for GABA expressed specifically in the CNS thereby being valid targets to modulate GABA-uptake. Potent inhibitors of GAT-1 such as SK&F 89976-A (**1**), (±)-*cis*-SK&F 100591-A (**2**) [9] and tiagabine (**3**) [10] (Fig. 1) have been synthesized and their pharmacology was intensively investigated. Dhar succeeded in the synthesis of the first GAT-3 selective, highly active inhibitor (*S*)-SNAP-5114 (**4**) (Fig. 1) exhibiting an IC_{50} value of 5 μM and a selectivity of 78:1 (GAT-3:GAT-1) [11]. However, for drug design and further pharmacological studies of GABA neurotransmission, it is still highly desirable to find GABA-uptake inhibitors having high potency and selectivity.

Previously, we reported the synthesis of the pyrrolidine derivatives **5** and **6** exhibiting potent inhibition of GAT-1 and GAT-3 and high selectivity (Fig. 2) [12].

Herein, we present the synthesis and biological evaluation of new pyrrolidine analogues having further structural modifications. The affinity of (±)-*cis*-SK&F 100591-A [9] (**2**) (Fig. 1) to GAT-1 implies that a hydroxy group in the *N*-heterocycle is likely to be acceptable for GABA-uptake transporters. Thus, we introduced a hydroxy group into the C-4 position of pyrrolidine-2-carboxylic acid and pyrrolidine-

Abbreviations: Bn, benzyl; Cbz, benzyl carboxylate; CC, column chromatography; DEAD, diethyl azodicarboxylate; DMAP, (4-dimethylamino)-pyridine; GAT, GABA transport protein; LDA, lithium diisopropylamide; prep., preparative; r.t., room temperature; TBAF, tetrabutylammonium fluoride; TBDMSCl, (*tert*-butyl)dimethlylsilyl chloride; TEA, triethylamine; TMSCl, trimethylsilyl chloride.

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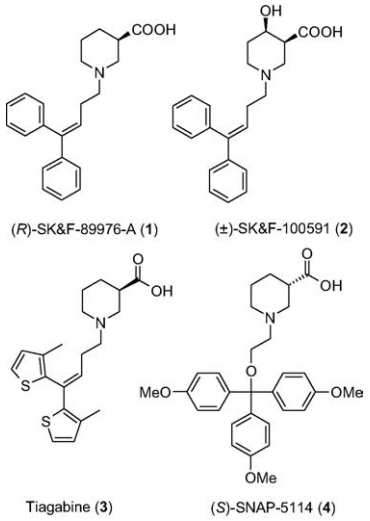


Fig. 1. Structures of representative known GABA-uptake inhibitors.

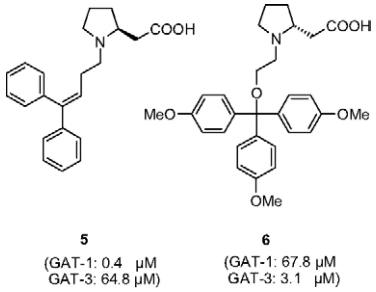


Fig. 2. Structures of GABA-uptake inhibitors having a pyrrolidine core structure.

2-acetic acid. The nitrogen atom of potent GABA-uptake inhibitors is generally substituted by appropriate bulky lipophilic groups. Therefore, four typical *N*-substituents **a**–**d** were chosen and two different series of pyrrolidine derivatives **7** and **8** were prepared in enantiomerically pure form as potential GABA-uptake inhibitors. In addition, the four stereoisomers of 4-hydroxypyrrolidine-2-acetic acid **9** were synthesized (Fig. 3). Compounds **7**–**9** were evaluated for their selectivity and inhibitory potency at GAT-1 and GAT-3. The results are expected to contribute to the optimization of structure–activity relationships.

2. Chemistry

L-*trans*-4-Hydroxypyrrolidine [(2*S*,4*R*)-**10**] was chosen as a precursor for the synthesis of the four key intermediates (2*S*,4*R*)-**11**, (2*R*,4*R*)-**11**, (2*S*,4*R*)-**12** and (2*R*,4*R*)-**13** (Fig. 4)

Compounds (2*S*,4*R*)-**11** [13] and (2*R*,4*R*)-**11** [13,14] were prepared from (2*S*,4*R*)-**10** according to literature procedures.

The synthesis of the intermediate (2*S*,4*R*)-**12** is illustrated in Fig. 5. The amino and the hydroxy functionality of (2*S*,4*R*)-**10** were protected with a Cbz and a Bn group, respectively, according to literature procedures [15]. Following transformation into the diazoketone (2*S*,4*R*)-**16** employing $(COCl)_2$ and diazomethane at 0 °C (yield: 80%), Wolff rearrangement initiated by AcOAg-TEA in MeOH afforded (2*S*,4*R*)-**17** in 81% yield. A simultaneous N,O-deprotection of (2*S*,4*R*)-**17** led to (2*S*,4*R*)-**12** in 90% yield (47% overall yield).

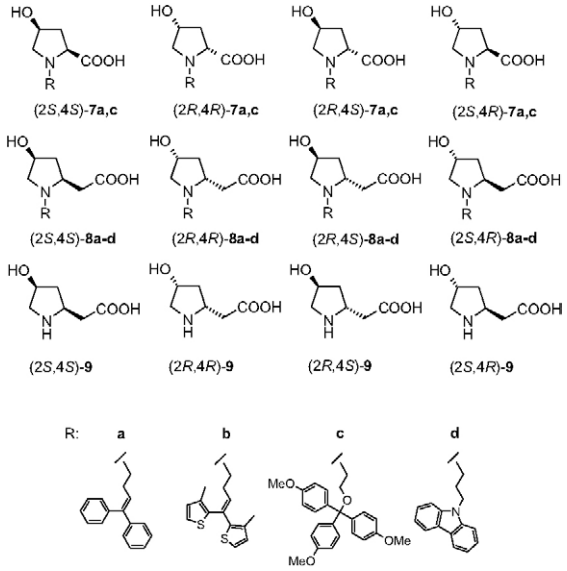


Fig. 3. The structures of the target compounds.

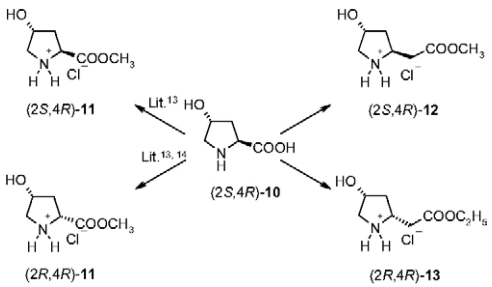


Fig. 4. The structures of the four key intermediates prepared from (2*S*,4*R*)-**10**.

Compound (2*R*,4*R*)-**13** was prepared as depicted in Fig. 6. The nitrogen atom of (2*S*,4*R*)-**10** was protected according to Ref. [15a]. Subsequent anodic oxidation in methanol gave the α-methoxy pyrrolidine derivative **18** as a mixture of diastereomers in 97% yield (*ds* = 41/59) [16]. Protection of the hydroxy group using TBDMSCl in the presence of imidazole (yield: 85%) followed by the nucleophilic addition of 1-ethoxy-1-(trimethylsilyloxy)ethene afforded (2*R*,4*R*)-**20** as the major product (yield: (2*R*,4*R*)-**20**: 79%, (2*S*,4*R*)-**20**: 9%) [17]. O-deprotection of (2*R*,4*R*)-**20** was accomplished in 88% yield by means of TBAF in THF [18]. Finally, the resulting product (2*R*,4*R*)-**21** was subjected to hydrogenation over 10% Pd-C in conc. HCl/EtOH to give (2*R*,4*R*)-**13** in 89% yield (46% overall yield).

To synthesize the lipophilic target structures shown in Fig. 7, the key intermediates (2*S*,4*R*)-**11** and (2*R*,4*R*)-**11** were *N*-alkylated with the respective halides of **a** and **c** (see Fig. 7). Subsequent saponification led to the target compounds (2*S*,4*R*)-**7a**, **c** and (2*R*,4*R*)-**7a**, **c** in moderate yields. Inversion of the stereocenter at C-4 of the pyrrolidine cycle was achieved via an intramolecular Mitsunobu reaction of (2*S*,4*R*)-

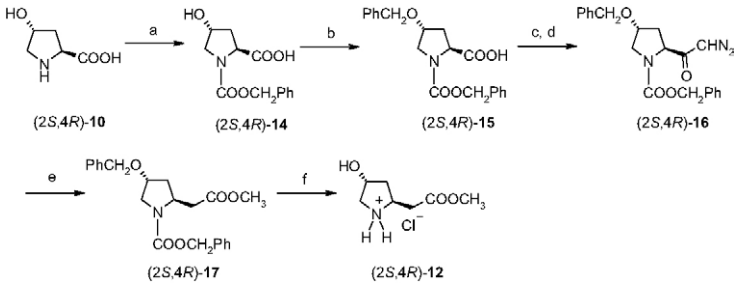


Fig. 5. Synthetic route leading to (2*S*,4*R*)-**12**. (a) Ref. [15a]; (b) Ref. [15b]; (c) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (d) CH_2N_2, Et_2O, 0 °C, 80%; (e) AcOAg/TEA, MeOH, 25–60 °C, 81%; (f) H_2/10% Pd-C, MeOH, 25 °C, 5 d, 90%.

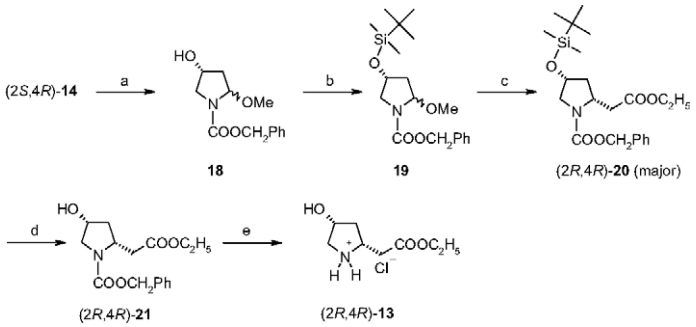


Fig. 6. Synthetic route leading to (2*R*,4*R*)-**13**. (a) Electrolysis, TEA, MeOH, 10 °C, 97%; (b) TBDMSCl, imidazole, CH_2Cl_2, 25 °C, 85%; (c) $BF_3{\cdot}Et_2O$, 1-ethoxy-1-(trimethylsilyloxy)ethene, CH_2Cl_2, –78 °C, 79%; (d) TBAF, THF, 25 °C, 88%; (e) H_2/10% Pd-C, 37% HCl/EtOH, 25 °C, 89%.

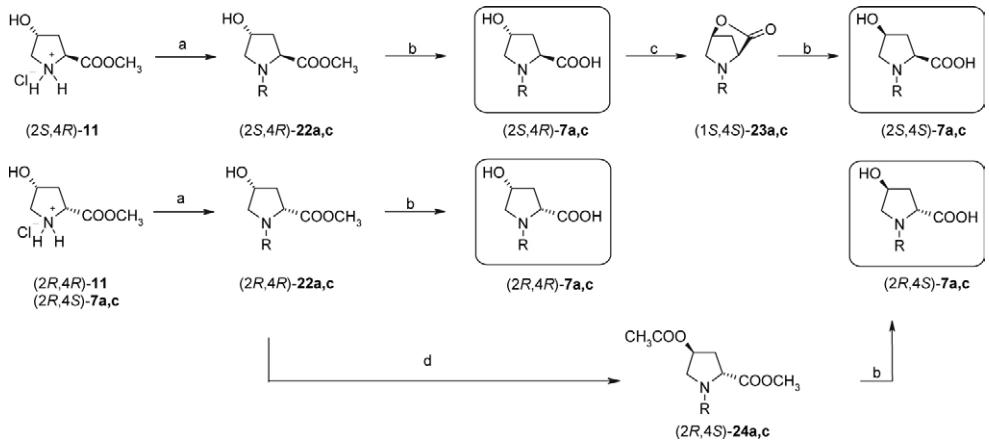


Fig. 7. The synthetic routes leading to the proline derivatives **7a**, **c**. (a) K_2CO_3/KI, bromides of **a** and **c**, acetone, r.t.; (b) 0.85 M KOH (or 1.0 M NaOH) in EtOH (or MeOH), r.t.; (c) Ph_3P/DEAD, THF, 0 °C; (d) Ph_3P/DEAD, AcOH, THF, 0 °C.

7a, **c** providing lactones (1*S*,4*S*)-**23a**, **c** [19]. From the latter upon basic hydrolysis the *N*-substituted target compounds (2*S*,4*S*)-**7a**, **c** were obtained. The *N*-substituted target compounds (2*R*,4*S*)-**7a**, **c** were made available by subjecting (2*R*,4*R*)-**22a**, **c** to an intermolecular Mitsunobu reaction with acetic acid as nucleophile to transform the configuration of the stereocenter in 4-position into (4*S*). Basic hydrolysis of the resulting compounds (2*R*,4*S*)-**24a**, **c** eventually led to (2*R*,4*S*)-**7a**, **c**. Similarly to the aforementioned syntheses, starting from (2*S*,4*R*)-**12** and (2*R*,4*R*)-**13**, the four sets of stereoisomeric pyrrolidine-2-acetic acid derived target compounds (2*S*,4*R*)-**8a–d**, (2*R*,4*R*)-**8a–d**, (2*S*,4*S*)-**8a–d** and (2*R*,4*S*)-**8a–d** were obtained as shown in Fig. 8.

To access each of the four stereoisomers of 4-hydroxypyrrolidine-2-acetic acid **9** in enantiomerically pure form, first, the *N*-Cbz-protected derivatives (2*S*,4*R*)-**28**, (2*R*,4*R*)-**28**, (2*S*,4*S*)-**28** and (2*R*,4*S*)-**28** were synthesized in close analogy to the preparation of the corresponding *N*-alkyl derivatives as outlined in Fig. 8. The enantiopure compounds **28** were eventually subjected to hydrogenation providing each of the four stereoisomers of **9** in excellent yields (89–100%; see Fig. 9).

3. Biological evaluation

The final compounds **7a**, **c**, **8a–d** and **9** were evaluated for their inhibitory potency regarding GAT-1- and GAT-3-mediated GABA-uptake. Measurements of inhibitory potency at GABA-uptake were performed according to a literature procedure based on subcellular membrane fractions from fron-

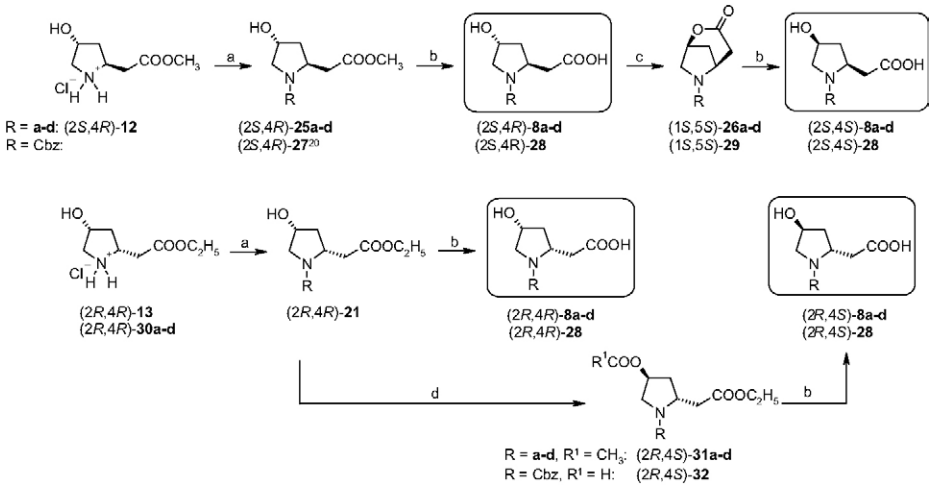


Fig. 8. The synthetic routes leading to the homoproline derivatives **8** and **28**. (a) K_2CO_3/KI, bromides of **a**–**d**, acetone, r.t.; (b) 0.85 M KOH (or 1.0 M NaOH) in EtOH (or MeOH), r.t.; (c) Ph_3P/DEAD, THF, 0 °C; (d) Ph_3P/DEAD, AcOH or HCOOH, THF, 0 °C.

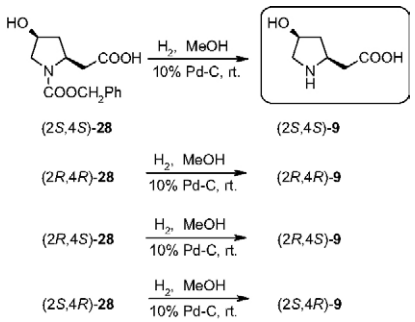


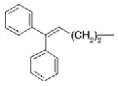
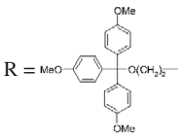
Fig. 9. The synthetic route leading to **9**.

tal cortex (bfcP2B) and brain stem (bbsP2C), which had been modified to allow a higher throughput [20]. Due to the emergence of bovine spongiform encephalitis in Germany, calf brain (cfcP2B, cbsP2C) was temporarily used instead of the bovine brain material for the biological tests and finally porcine brain material (pfcP2B, pbsP2C) was applied. But species differences seemed to be negligible, as no significant differences could be detected for a set of standard GABA-uptake inhibitors with respect to their potency evaluated when membrane fractions from different species were used.

4. Results and discussion

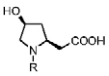
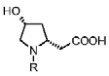
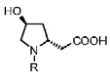
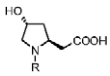
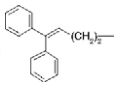
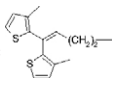
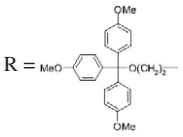
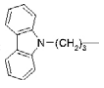
The stereoisomers of pyrrolidine-2-carboxylic acid derivatives **7a** and **7c** showed a significant decrease of inhibitory potency at both GAT-1 and GAT-3 (Tables 1 and 2) as compared with the corresponding compounds lacking a hydroxy group at the 4-position of the pyrrolidine moiety. The latter displayed IC_{50} values up to 2.56 μM for GAT-1 when R = **a** and 18.5 μM for GAT-3 when R = **c** was present [12b]. In case of compounds **7**, only (2*R*,4*R*)-**7a** showed a reasonable potency at GAT-1. However, it was still approximately three times less potent at GAT-1 (IC_{50} = 9.4 μM) than the corresponding 4-unsubstituted compounds [R = **a**, (*S*)-configuration: IC_{50} = 56 μM, (*R*)-configuration: IC_{50} = 2.97 μM [12b]]. The loss of potency due to the presence of a 4-hydroxy substituent was even more prevalent for GAT-3 with all compounds actually being devoid of any reasonable activity (IC_{50} values > 100 μM). As compared to the corresponding 4-hydroxy-pyrrolidine-2-carboxylic acid derivatives **7a**, the 4-hydroxy-pyrrolidine-2-acetic acid derivatives (2*S*,4*R*)-**8a** and (2*S*,4*S*)-**8a** showed higher affinity for GAT-1 having IC_{50} values of 3.29 and 4.92 μM, respectively. The observed IC_{50} values of the two (2*S*)-configurated stereoisomers of series **8b** were in the same range as the IC_{50} value of (2*S*,4*R*)-**8a** [IC_{50} of (2*S*,4*R*)-**8b** = 5.14 μM, IC_{50} of (2*S*,4*S*)-**8b** = 6.56 μM]. Interestingly, according to these data, the stereochemistry at the 2-position plays a key role for the potency with (2*S*)-configurated derivatives being of high potency at GAT-1 (see (2*S*,4*S*)-**8a**, (2*S*,4*R*)-**8a**, (2*S*,4*S*)-**8b**, (2*S*,4*R*)-**8b** and also (2*S*,4*R*)-**7a**) as compared to the (2*R*)-configurated counterparts. This observation is in line with the results found for the corresponding compounds lacking a 4-hydroxy group [12]. Only (2*R*,4*R*)-**7a** represents an exemption not following this general trend. The inhibitory potency of the stereoisomers of **8c** at GAT-1 with IC_{50} values greater than 100 μM was very low if not negligible at all. Actually, it is a common finding, that *N*-residues like R = **a** or R = **b** are more beneficial for a high activity at GAT-1 but not at GAT-3, whereas for R = **c** the opposite is observed. This is especially well illustrated by the parent compound **9**, which are devoid of any significant activity at GAT-1 or GAT-3. For some stereoisomers of series **8** provided with the residues R = **a** or R = **b** reasonable potency at GAT-1 are seen. Analogously, the presence of R = **c** in series **8c** leads to a distinct increase in potency at GAT-3 as compared to the parent compound **9**. It is interesting to note, that the lower homologues **10** do not gain potency at GAT-3 upon *N*-substitution with R = **c** with all compounds **7c** being devoid of a reasonable activity (IC_{50} > 100 μM). Within the series of compounds **8c**, stereoisomer (2*R*,4*S*)-**8c** appears to be the most potent substance (IC_{50} 19.9 μM). However, as referred to the corresponding 4-unsubstituted compound

Table 1
The uptake inhibition [IC_{50} (μM)] at GAT-1 or GAT-3 exhibited by 4-hydroxyproline-2-carboxylic acid derivatives[I, II, III]

								
	IC_{50} ± S.E.M. (μM)		IC_{50} ± S.E.M. (μM)		IC_{50} ± S.E.M. (μM)		IC_{50} ± S.E.M. (μM)	
	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3
R = H	–	–	>10 mM[a]	>10 mM[b]	–	–	4328 ± 708[a]	1340 ± 290[b]
			(2*R*,4*R*)-**10**[14]				(2*S*,4*R*)-**10**[13]	
R = 	>100[a]	>100[b]	9.4 ± 0.4[a]	313 ± 39[b]	>100[a]	>100[b]	79.6[a]	>100[b]
	(2*S*,4*S*)-**7a**		(2*R*,4*R*)-**7a**		(2*R*,4*S*)-**7a**		(2*S*,4*R*)-**7a**	
R = 	>100[a]	>100[b]	>100[a]	>100[b]	>100[a]	>100[b]	>100[a]	>100[b]
	(2*S*,4*S*)-**7c**		(2*R*,4*R*)-**7c**		(2*R*,4*S*)-**7c**		(2*S*,4*R*)-**7c**	

[I] The abbreviations a–b specify the used biological material: [a] bfcP2B, [b] bbsP2C.
[II] All results were processed and evaluated in triplicate.
[III] Each IC_{50} was given as mean ± S.E.M. Whenever preliminary experiments indicated that the IC_{50} value is larger than 100 μM, no exact value was established.

Table 2
The uptake inhibition [IC_{50} (μM)] at GAT-1 or GAT-3 exhibited by 4-hydroxypyrrolidine-2-acetic acid derivatives[I, II, III]

								
	IC_{50} ± S.E.M. (μM)		IC_{50} ± S.E.M. (μM)		IC_{50} ± S.E.M. (μM)		IC_{50} ± S.E.M. (μM)	
	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3
R = H	>100[c]	>100[d]	>100[c]	>100[d]	>1.0 mM[a]	>1.0 mM[d]	>1.0 mM[c]	>1.0 mM[d]
	(2*S*,4*S*)-**9**		(2*R*,4*R*)-**9**		(2*R*,4*S*)-**9**		(2*S*,4*R*)-**9**	
R = 	4.92 ± 0.42[a]	>100[b]	40.7 ± 8[a]	>100[b]	28.9 ± 11.6[a]	>100[f]	3.29 ± 0.54[a]	>100[b]
	(2*S*,4*S*)-**8a**		(2*R*,4*R*)-**8a**		(2*R*,4*S*)-**8a**		(2*S*,4*R*)-**8a**	
R = 	5.14 ± 2.8[c]	>100[b]	96.6[a] *n* = 1	>100[b]	6.56 ± 0.7[a]	>100[b]	3.15 ± 0.30[a]	>100[b]
	(2*S*,4*S*)-**8b**		(2*R*,4*R*)-**8b**		(2*R*,4*S*)-**8b**		(2*S*,4*R*)-**8b**	
R = 	>100[c]	58.6 ± 17.1[d]	>100[a]	126 ± 7.0[b]	>100[c]	19.9 ± 1.1[d]	>100[a]	>100[b]
	(2*S*,4*S*)-**8c**		(2*R*,4*R*)-**8c**		(2*R*,4*S*)-**8c**		(2*S*,4*R*)-**8c**	
R = 	>100[a]	>100[f]	>100[a]	>100[b]	>100[a]	>100[b]	>100[e]	>100[b]
	(2*S*,4*S*)-**8d**		(2*R*,4*R*)-**8d**		(2*R*,4*S*)-**8d**		(2*S*,4*R*)-**8d**	

[I] The abbreviations a–f specify the used biological material: [a] bfcP2B, [b] bbsP2C, [c] pfcP2B, [d] pbsP2C, [e] cfcP2B, [f] cbsP2C.
[II] All results were processed and evaluated in triplicate.
[III] Each IC_{50} was given as mean ± S.E.M. Whenever preliminary experiments indicated that the IC_{50} value is larger than 100 μM, no exact value was established.

(GAT-1: IC_{50} = 67.8 μM; GAT-3: IC_{50} = 3.0 μM [12]), the introduction of the 4-hydroxy substituent leading to (2*R*,4*S*)-**8c** caused a severe decrease in inhibitory potency at both GAT-1 (IC_{50} = 100 μM) and GAT-3 (IC_{50} = 19.9 μM).

The amino acids series **8d** bearing a carbazole moiety on the pyrrolidine nitrogen atom showed no inhibition at GAT-1 as well as GAT-3 when tested at a concentration of 100 μM. Thus far, residue **d** has been reported only for GAT inhibi-

tions based on a 4-hydroxypiperidine skeleton. According to our results, the carbazole moiety **d** seems not to be beneficial in compounds having skeletons derived from amino acids.

5. Conclusion

The biological results presented herein indicate that, in general, a 4-hydroxy group at C-4 position of the pyrrolidine ring of proline and pyrrolidine-2-acetic acid derivatives decreases the potency of GABA-uptake inhibitors at both GAT-1 and GAT-3. Furthermore, it was found that, as referred to the pyrrolidine-2-acetic acids derivatives, the (2*S*)-configuration for potent inhibition at GAT-1 or (2*R*)-configuration for potent inhibition at GAT-3 may be crucial.

6. Experimental section

6.1. Chemistry

6.1.1. General

Tetrahydrofuran and diisopropylamine were distilled from sodium under nitrogen. Triethylamine was refluxed with benzoyl chloride and then distilled under nitrogen. Other common solvents for recrystallization, column chromatography, analytical HPLC and preparative HPLC were distilled before use. Purchased chemical reagents were used without further purification. Aqueous buffer (pH 5.5, 0.42 M and pH 6.6, 0.42 M) was prepared from KH_2PO_4 and KOH. TLC plates were made from silica gel 60 F_{254} on aluminum sheets (Merck). Compounds were stained with 5% $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 0.2% $Ce(SO_4)_2{\cdot}4H_2O$ and 5% conc. H_2SO_4. If nothing else is stated, Merck silica gel (mesh 230–400) was used as stationary phase for flash chromatography (CC). Analytical HPLC: Column LiChrospher Si 60 (5 μm, 250 × 4 mm with precolumn 4 × 4 mm). Preparative HPLC: Column LiChrospher Si 60 (7 μm, 250 × 25 mm). Optical rotations: Polarimeter 241 MC at λ 589 cm^{-1}. Melting points: m.p. (uncorrected) were determined with a Büchi 510 Melting Point apparatus. Elementary analysis: Elementaranalysator Rapid (Heraeus). IR spectroscopy: FT-IR Spectrometer 1600 and Paragon 1000 (Perkin Elmer), oils were measured as film, solid samples as KBr-pellets for measurements. Mass spectrometry: Mass Spectrometer 5989 A with 59,980 B particle beam LC/MS interface (Hewlett Packard), method: chemical ionization (CH_5^+) unless otherwise stated. NMR spectroscopy: NMR spectra were recorded on JNMR-GX (JEOL, 400 and 500 MHz) with TMS as internal standard and integrated with the program of NMR-software Nuts (2D Version 5.097, Acorn NMR, 1995). If nothing else is stated, measurements were performed at 400 MHz at room temperature.

6.1.2. General procedure 1 (GP1)

The respective alkyl halide RX (1.0 equiv.) and KI (0.2 equiv.) were added to a mixture of the pyrrolidine derivative (1.0 equiv. hydrochloride) and K_2CO_3 (5.0 equiv.) in acetone (4–8 ml $mmol^{-1}$). The reaction mixture was stirred at r.t. for 72–144 h. Inorganic salts were removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by CC.

6.1.3. General procedure 2 (GP2)

The respective ester (1 equiv.) was hydrolyzed in EtOH or MeOH (10–50 ml $mmol^{-1}$) at r.t. with aq. 0.85 M KOH or 1.0 M NaOH (3, 6 equiv. for derivatives having two ester groups) and for the time given. Following neutralization with aq. 1.0 M HCl to pH 7, a buffer (pH 5.5–6.6) was added and the mixture was evaporated. The residue was purified by CC and subsequent recrystallization.

6.1.4. General procedure 3 (GP3)

The respective ester (1.00 equiv.) was hydrolyzed with 1.0 M NaOH (2.05–4.10 equiv.) in MeOH (10–50 ml $mmol^{-1}$) at r.t. for the time given. After MeOH had been removed in vacuo, the residue was dissolved in a small amount of water and acidified to pH 1–2 with aq. 1.0 M HCl. The mixture was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and evaporated to yield the respective carboxylic acid.

6.1.5. General procedure 4 (GP4)

DEAD (1.2–1.5 equiv.) was added at 0 °C to a solution of the *N*-substituted or *N*-protected 4-hydroxypyrrolidine derivative (1.0 equiv.) and Ph_3P (1.0–1.5 equiv.) in THF (10–50 ml $mmol^{-1}$). The resulting yellow solution was stirred for 10 min followed by the addition of AcOH or HCOOH (1.05–1.50 equiv.) at 0 °C (for intramolecular Mitsunobu reaction no additional acid was used). Stirring was continued at 0 °C for the time given. The solvent was evaporated in vacuo and the residual oil was purified by CC. The purification of some compounds required prep. HPLC.

6.1.6. General procedure 5 (GP5)

To a solution of the respective *N*-protected pyrrolidine (1 equiv.) in MeOH or EtOAc (40–50 ml $mmol^{-1}$) 10% Pd-C (0.5–1.0 w/w) was added. This mixture was hydrogenated at r.t. and 1 bar for the time given. The reaction mixture was filtrated and evaporated to give the *N*-deprotected amine.

*6.1.7. (2S,4R)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2S,4R)-**7a**]*

According to GP2 from 185 mg (0.527 mmol) of (2*S*,4*R*)-**22a**, 1.85 ml (1.58 mmol) of aq. 0.85 M KOH in 7 ml of EtOH; reaction time: 1.5 h. Yield: 170 mg (96%); colorless crystals, m.p. 162–165 °C (acetone). $[\alpha]_D^{22} = -49.2$ ($c = 0.85$, EtOH). ^{1}H NMR (CD_3OD): δ = 2.09 (ddd, J = 13.7, 10.6, 4.4 Hz, 1H, NCHCH_2), 2.39 (ddt, J = 13.7, 7.6, 1.9 Hz, 1H, NCHCH_2), 2.55 (q, J = 7.6 Hz, 2H, NCH$_2$CH_2), 3.00 (dt, J = 12.3, 1.9 Hz, 1H, NCH_2CHOH), 3.35 (dt, J = 12.4, 7.6 Hz, 1H, NCH_2CH$_2$), 3.46 (dt, J = 12.4, 7.6 Hz, 1H, NCH_2CH$_2$), 3.64 (dd, J = 12.3, 4.4 Hz, 1H, NCH_2CHOH), 4.05 (dd,

J = 10.6, 7.6 Hz, 1H, NC*H*), 4.43–4.45 (m, 1H, C*H*OH), 6.09 (t, *J* = 7.6 Hz, 1H, = C*H*CH_2,) 7.17–7.43 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 3424 cm^{-1}, 1628. MS; *m/z* (%): 338 (100) $[M + 1]^+$. $C_{21}H_{23}NO_3$ (337.42).

*6.1.8. (2*R*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*R*,4*S*)-**7a**]*

According to GP2 from 85 mg (0.21 mmol) of (2*R*,4*S*)-**24a**, 1.26 ml (1.26 mmol) of aq. 1.0 M NaOH in 6 ml of EtOH; reaction time: 3 d. Yield: 65 mg (92%); colorless crystals, m.p. 181–184 °C (EtOH/*i*Pr_2O). $[\alpha]_D^{20}$ = +50.6 (*c* = 0.93, EtOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**7a**. $C_{21}H_{23}NO_3 \cdot H_2O$ (355.44).

*6.1.9. (2R,4R)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*R*,4*R*)-**7a**]*

According to GP2 from 68 mg (0.19 mmol) of (2*R*,4*R*)-**22a**, 0.58 ml (0.58 mmol) of aq. 1.0 M NaOH in 3 ml of EtOH; reaction time: 3 h. Yield: 58 mg (92%); colorless crystals, m.p. 112–116 °C (C_6H_6/*i*Pr_2O). $[\alpha]_D^{20}$ = +43.1 (*c* = 0.90, EtOH). ^{1}H NMR (CD_3OD, 500 MHz): δ = 2.15–2.21 (m, 1H, NCHCH_2), 2.48–2.63 (m, 3H, NCHCH_2 and NCH_2CH_2), 3.03 (dd, *J* = 11.5, 3.8 Hz, 1H, NCH_2CHOH), 3.18–3.24 (m, 1H, NCH_2CH_2), 3.32–3.41 (m, 2H, NCH_2CH_2 and NCH_2CHOH), 3.79 (dd, *J* = 10.6, 4.4 Hz, 1H, NC*H*), 4.36–4.39 (m, 1H, C*H*OH), 6.07 (dd, *J* = 7.9, 6.9 Hz, 1H, =C*H*CH_2), 7.17–7.44 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 3274 cm^{-1}, 1633. MS; *m/z* (%): 338 (36) $[M + 1]^+$. $C_{21}H_{23}NO_3 \cdot 1.2\ H_2O$ (362.88).

*6.1.10. (2*S*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*S*,4*S*)-**7a**]*

According to GP2 from 157 mg (0.491 mmol) of (1*S*,4*S*)-**23a**, 2.1 ml (1.800 mmol) of aq. 0.85 M KOH in 12 ml of EtOH; reaction time: 40 min. Yield: 158 mg (95%); colorless crystals, m.p. 138–140 °C (acetone). $[\alpha]_D^{24}$ = –42.8 (*c* = 1.00, EtOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**7a**. $C_{21}H_{23}NO_3$ (337.42).

*6.1.11. (2*S*,4*R*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*S*,4*R*)-**7c**]*

According to GP2 from 299 mg (0.574 mmol) of (2*S*,4*R*)-**22c**, 1.7 ml (1.500 mmol) of aq. 0.85 M KOH in 23 ml of EtOH; reaction time: 4 h. Yield: 243 mg (85%); colorless crystals, m.p. 142–144 °C (acetone). $[\alpha]_D^{20}$ = –24.8 (*c* = 1.12, EtOH). ^{1}H NMR (CD_3OD): δ = 2.15 (ddd, *J* = 13.8, 10.1, 4.7 Hz, 1H, NCHCH_2), 2.41 (ddt, *J* = 13.8, 7.8, 1.9 Hz, 1H, NCHCH_2), 3.08 (br. d, *J* = 12.4 Hz, 1H, NCH_2CHOH), 3.29–3.35 (m, 1H, NCH_2CH_2), 3.40–3.61 (m, 4H, NCH_2CH_2, NCH_2CHOH and NCH_2CH_2), 3.76 (s, 9H, ArOCH_3), 4.19 (dd, *J* = 10.1, 7.8 Hz, 1H, NCH), 4.43–4.46 (m, 1H, C*H*OH), 6.85–6.88 (m, 6H, H_{aromat}), 7.32–7.36 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 3464 cm^{-1}, 1607. $C_{29}H_{33}NO_7$ (507.58).

*6.1.12. (2*R*,4*S*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*R*,4*S*)-**7c**]*

According to GP2 from 80 mg (0.14 mmol) of (2*R*,4*S*)-**24c**, 0.85 ml (0.85 mmol) of aq. 1.0 M NaOH in 3.5 ml of MeOH; reaction time: 3 d. Yield: 68 mg (94%); colorless crystals, m.p. 135–137 °C (C_6H_6/*i*Pr_2O). $[\alpha]_D^{20}$ = +20.6 (*c* = 0.90, EtOH). The spectra (^{1}H NMR, MS and IR) were identical with those of (2*S*,4*R*)-**7c**. $C_{29}H_{33}NO_7 \cdot 1.5\ H_2O$ (534.61).

*6.1.13. (2*R*,4*R*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*R*,4*R*)-**7c**]*

According to GP2 from 66 mg (0.13 mmol) of (2*R*,4*R*)-**22c**, 0.38 ml (0.38 mmol) of aq. 1.0 M NaOH in 2.5 ml of EtOH; reaction time: 2 h; purification by CC (Al_2O_3, pH 7 ± 0.5; EtOH/H_2O, 4:1). Yield: 43 mg (67%); colorless crystals, m.p. 126–130 °C (petrol ether). $[\alpha]_D^{20}$ = +12.1 (*c* = 0.7, EtOH). ^{1}H NMR (CD_3OD): δ = 2.23–2.29 (m, 1H, NCHCH_2), 2.54 (ddd, *J* = 13.9, 11.0, 4.4 Hz, 1H, NCHCH_2), 3.06 (dd, *J* = 11.6, 3.6 Hz, 1H, NCH_2CHOH), 3.23–3.37 (m, 3H, NCH_2CHOH and NCH_2CH_2), 3.51–3.61 (m, 2H, NCH_2CH_2), 3.77 (s, 9H, OCH_3), 3.98 (dd, *J* = 11.0, 4.0 Hz, 1H, NCH), 4.38–4.41 (m, 1H, C*H*OH), 6.86–6.90 (m, 6H, H_{aromat}), 7.34–7.38 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 3414 cm^{-1}, 1638. $C_{29}H_{33}NO_7 \cdot H_2O$ (525.60).

*6.1.14. (2*S*,4*S*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*S*,4*S*)-**7c**]*

According to GP4 from 151 mg (0.298 mmol) of (2*S*,4*R*)-**7c** and 161 mg (0.596 mmol) of PPh_3 (67 mg, 0.39 mmol) of DEAD in 6.5 ml of THF; reaction time: 20 h. Purification by CC (Al_2O_3, pH 7.5 ± 0.5, gradient elution, *n*-heptane/acetone = 2:1 → EtOH/H_2O = 4:1) directly yielded (2*S*,4*S*)-**7c**. Yield: 115 mg (76%); colorless crystals, m.p. 147–149 °C (EtOH/H_2O). $[\alpha]_D^{24}$ = –11.9 (*c* = 0.75, EtOH). The spectra (^{1}H NMR, and IR) were identical with those of (2*R*,4*R*)-**7c**. $C_{29}H_{33}NO_7$ (507.58).

*6.1.15. (2*R*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*R*)-**8a**]*

According to GP2 from 53 mg (0.14 mmol) of (2*R*,4*R*)-**30a**, 0.42 ml (0.42 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; reaction time: 41 h. Yield: 41 mg (84%); colorless crystals, m.p. 70–76 °C (MeOH/*i*Pr_2O). $[\alpha]_D^{20}$ = +52.2 (*c* = 0.50, MeOH). ^{1}H NMR (CD_3OD): δ = 1.71–1.77 (m, 1H, CH_2CHCH_2COO), 2.46–2.57 (m, 4H, CH_2COO, CH_2CHCH_2COO and 2H of NCH_2CH_2), 2.63 (dd, *J* = 16.7, 6.3 Hz, 1H, CH_2COO), 2.92–3.01 (m, 2H, NCH_2CH_2 and NCH_2CHO), 3.17–3.29 (m, 1H, NCH_2CHO), 3.46–3.57 (m, 2H, NCH_2CH_2 and NC*H*), 4.35–4.40 (m, 1H, C*H*OH), 6.02 (t, *J* = 7.3 Hz, 1H, =C*H*CH_2), 7.14–7.40 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 3388 cm^{-1}, 1608. MS; *m/z* (%): 352 (23) $[M + 1]^+$. $C_{22}H_{25}NO_3$ (351.45)·1.0 H_2O.

*6.1.16. (2S,4S)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2S,4S)-**8a**]*

According to GP2 from 60 mg (0.18 mmol) of (1*S*,5*S*)-**26a**, 0.54 ml (0.54 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 20 h. Yield: 49 mg (78%); colorless crystals, m.p. 95–97 °C (C_6H_6). $[\alpha]_D^{20}$ = –51.5 (*c* = 0.47, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**8a**. HRMS (CI) Calc. for $C_{22}H_{25}NO_3$: 352.1913. Found: 352.1895.

*6.1.17. (2R,4S)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2R,4S)-**8a**]*

According to GP2 from 36 mg (0.085 mmol) of (2*R*,4*S*)-**31a**, 0.51 ml (0.510 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 3 d. Yield: 28 mg (93%); colorless crystals, m.p. 57–60 °C (C_6H_6/*i*Pr_2O). $[\alpha]_D^{20}$ = +65.6 (*c* = 0.5, MeOH). ^{1}H NMR (CD_3OD): δ = 1.93 (ddd, *J* = 13.6, 11.4, 5.1 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.13 (ddt, *J* = 13.6, 6.5, 1.7 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.46 (dd, *J* = 16.5, 3.0 Hz, 1H, CH$_2$COO), 2.56 (q, *J* = 7.4 Hz, 2H, NCH$_2$C*H*$_2$), 2.70 (dd, *J* = 16.5, 5.9 Hz, 1H, CH$_2$COO), 2.82 (d, *J* = 12.5 Hz, 1H, NC*H*$_2$CHO), 3.03–3.10 (m, 1H, NC*H*$_2$CH$_2$), 3.46–3.53 (m, 2H, NC*H*$_2$CH$_2$ and NC*H*$_2$CHO), 3.74–3.80 (m, 1H, NCH), 4.38–4.41 (m, 1H, C*H*OH), 6.09 (t, *J* = 7.4 Hz, 1H, =C*H*CH$_2$), 7.21–7.46 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 3295 cm^{-1}, 1624. MS; *m*/*z* (%): 352 (19) [M + 1]$^+$. $C_{22}H_{25}NO_3$ (351.45)·1.3 H_2O.

*6.1.18. (2S,4R)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2S,4R)-**8a**]*

According to GP2 from 50 mg (0.14 mmol) of (2*S*,4*R*)-**25a**, 0.42 ml (0.42 mmol) of aq. 1.0 M NaOH in 3 ml of EtOH; reaction time: 3 h. Yield: 40 mg (83%); colorless oil. $[\alpha]_D^{20}$ = –69.4 (*c* = 0.95, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**8a**. $C_{22}H_{25}NO_3$ (351.45).

*6.1.19. (2R,4R)-1-[4,4-Di(3-methylthien-2-yl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2R,4R)-**8b**]*

According to GP2 from 47 mg (0.12 mmol) of (2*R*,4*R*)-**30b**, 0.56 ml (0.56 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; reaction time: 2 d. Yield: 43 mg (95%); slightly yellow powder, m.p. 69–74 °C (C_6H_6/petrol ether). $[\alpha]_D^{20}$ = +34.8 (*c* = 0.46, MeOH). ^{1}H NMR (CD_3OD): δ = 1.72–1.78 (m, 1H, C*H*$_2$CHCH$_2$COO), 1.97 (s, 3 H, thienyl-C*H*$_3$), 2.03 (s, 3 H, thienyl-C*H*$_3$), 2.46–2.60 (m, 5 H, C*H*$_2$CHCH$_2$COO, C*H*$_2$COO and NCH$_2$C*H*$_2$), 2.95–3.04 (m, 1H, NC*H*$_2$CH$_2$), 3.08 (dd, *J* = 11.9, 5.5 Hz, 1H, NC*H*$_2$CHO), 3.30–3.60 (m, 3H, NC*H*$_2$CHO, NC*H*$_2$CH$_2$ and NC*H*), 4.38–4.44 (m, 1H, NCH$_2$C*H*O), 6.05 (t, *J* = 7.3 Hz, 1H, =C*H*CH$_2$), 6.78 (d, *J* = 5.2 Hz, 1 H, SC=CH), 6.91 (d, *J* = 5.2 Hz, 1H, SC=CH), 7.16 (d, *J* = 5.2 Hz, 1H, SCH=), 7.35 (d, *J* = 5.2 Hz, 1H, SCH=). IR: $\tilde{\nu}$ = 3396 cm^{-1}, 1591, 1399, 1097, 713. MS; *m*/*z* (%): 392 (12) [M + 1]$^+$, 374 140 (100). $C_{20}H_{25}NO_3S_2$ (391.54)·0.8 H_2O.

*6.1.20. (2S,4S)-1-[4,4-Di(3-methylthien-2-yl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2S,4S)-**8b**]*

According to GP2 from 67 mg (0.18 mmol) of (1*S*,5*S*)-**26b**, 0.54 ml (0.54 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 25 h. Yield: 59 mg (84%); colorless powder, m.p. 72–78 °C (C_6H_5/*i*Pr_2O). $[\alpha]_D^{20}$ = –34.4 (*c* = 0.52, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**8b**. $C_{20}H_{25}NO_3S_2$·1.1 H_2O.

*6.1.21. (2R,4S)-1-[4,4-Di(3-methylthien-2-yl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2R,4S)-**8b**]*

According to GP2 from 70 mg (0.15 mmol) of (2*R*,4*S*)-**31b**, 0.91 ml (0.91 mmol) of aq. 1.0 M NaOH in 4 ml of MeOH; reaction time: 3 d. Yield: 56 mg (94%); pale yellow crystals, m.p. 58–62 °C (C_6H_6/*i*Pr_2O). $[\alpha]_D^{20}$ = +57.5 (*c* = 0.52, MeOH). ^{1}H NMR (CD_3OD): δ = 1.87–1.94 (m, 1H, CH$_2$CHCH$_2$COO), 1.99 (s, 3H, thienyl-CH$_3$), 2.04 (s, 3H, thienyl-CH$_3$), 2.13 (dd, *J* = 13.6, 6.5 Hz, 1H, CH$_2$CHCH$_2$COO), 2.49 (dd, *J* = 16.6, 3.2 Hz, 1H, CH$_2$COO), 2.50–2.61 (m, 2H, NCH$_2$CH$_2$), 2.63 (dd, *J* = 16.6, 6.0 Hz, 1H, CH$_2$COO), 2.85 (br. d, *J* = 12.1 Hz, 1H, NCH$_2$CHO), 2.99–3.05 (m, 1H, NCH$_2$CH$_2$), 3.42 (dt, *J* = 12.4, 8.2 Hz, 1H, NCH$_2$CH$_2$), 3.60 (dd, *J* = 12.1, 4.9 Hz, 1H, NCH$_2$CHO), 3.68–3.76 (m, 1H, NCH), 4.40–4.43 (m, 1H, CHOH), 6.05 (t, *J* = 7.4 Hz, 1H, =CHCH$_2$), 6.77 (d, *J* = 5.2 Hz, 1H, SC=CH), 6.91 (d, *J* = 5.2 Hz, 1H, SC=CH), 7.15 (d, *J* = 5.2 Hz, 1H, SCH=), 7.36 (d, *J* = 5.2 Hz, 1H, SCH=). IR: $\tilde{\nu}$ = 3380 cm^{-1}, 1588. MS; *m*/*z* (%): 392 (45) [M + 1]$^+$. $C_{22}H_{25}NO_3S_2$ (391.54)·1.0 H_2O.

*6.1.22. (2S,4R)-1-[4,4-Di(3-methylthien-2-yl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2S,4R)-**8b**]*

According to GP2 from 90 mg (0.22 mmol) of (2*S*,4*R*)-**25b**, 0.67 ml (0.67 mmol) of aq. 1.0 M NaOH in 3.5 ml of MeOH; reaction time: 3 h. Yield: 80 mg (92%); yellow foam (MeOH), m.p. 74–80 °C (C_6H_6/*i*Pr_2O). $[\alpha]_D^{20}$ = –58.3 (*c* = 1.00, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**8b**. $C_{20}H_{25}NO_3S_2$·1.0 H_2O (391.54).

*6.1.23. (2R,4R)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2R,4R)-**8c**]*

According to GP2 from 54 mg (0.098 mmol) of (2*R*,4*R*)-**30c**, 0.30 ml (0.300 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; reaction time: 2 d; purification by CC (Al_2O_3). Yield: 40 mg (78%); colorless crystals, m.p. 85–88 °C (C_6H_6/*i*Pr_2O). $[\alpha]_D^{20}$ = +17.9 (*c* = 0.90, MeOH). ^{1}H NMR (CD_3OD): δ = 1.83 (ddd, *J* = 13.4, 9.0, 4.3 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.50–2.62 (m, 2H, C*H*$_2$COO and C*H*$_2$CHCH$_2$COO), 2.74 (dd, *J* = 16.7, 6.2 Hz, 1H, CH$_2$COO), 2.98–3.04 (m, 1H, NC*H*$_2$CH$_2$), 3.14 (dd, *J* = 11.9, 5.7 Hz, 1H, NC*H*$_2$CHO), 3.28–3.34 (m, 1H, NC*H*$_2$CHO), 3.39–3.60 (m, 4H, NC*H*$_2$CH$_2$, NC*H* and NCH$_2$C*H*$_2$), 3.77 (s, 9H, ArOC*H*$_3$), 4.41–4.46 (m, 1H, C*H*OH), 6.85–6.89 (m, 6H, H_{aromat}), 7.32–7.36 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 3420 cm^{-1}, 1607. MS (ESI$^+$); *m*/*z* (%): 522 [M + 1]$^+$ (6). $C_{30}H_{35}NO_7$ (521.61)·1.0 H_2O.

*6.1.24. (2S,4S)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2S,4S)-**8c**]*

According to GP2 from 112 mg (0.227 mmol) of (1*S*,5*S*)-**26c**, 0.67 ml (0.670 mmol) of aq. 1.0 M NaOH in 7.3 ml of MeOH; reaction time: 2 d. Yield: 102 mg (96%); colorless crystals, m.p. 95–103 °C (C_6H_6/iPr_2O). $[\alpha]_D^{20}$ = –16.8 (*c* = 0.75, MeOH). The spectra (^{1}H NMR and IR) were identical with those of (2*R*,4*R*)-**8c**. HRMS (CI) Calc. for [$C_{30}H_{35}NO_7$ + Na^+]: 544.2311. Found: 544.2342.

*6.1.25. (2R,4S)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2R,4S)-**8c**]*

According to GP2 from 70 mg (0.12 mmol) of (2*R*,4*S*)-**31c**, 0.71 ml (0.71 mmol) of aq. 1.0 m NaOH in 6.3 ml of MeOH; reaction time: 48 h. Yield: 52 mg (85%); colorless crystals, m.p. 98–105 °C (C_6H_6/iPr_2O). $[\alpha]_D^{20}$ = +31.5 (*c* = 0.60, MeOH). ^{1}H NMR (CD_3OD): δ = 1.93 (ddd, *J* = 13.5, 11.5, 4.6 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.12 (ddt, *J* = 13.5, 6.5, 1.6 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.39 (dd, *J* = 16.9, 2.4 Hz, 1H, CH$_2$COO), 2.72 (dd, *J* = 16.9, 5.3 Hz, 1H, CH$_2$COO), 3.00 (dt, *J* = 12.6, 1.6 Hz, 1H, NC*H*$_2$CHO), 3.10–3.16 (m, 1H, NC*H*$_2$CH$_2$), 3.38–3.53 (m, 4H, NC*H*$_2$CHO, NC*H*$_2$CH$_2$ and NCH$_2$C*H*$_2$), 3.75 (s, 9H, ArOC*H*$_3$), 3.79–3.86 (m, 1H, NCH), 4.39–4.43 (m, 1H, C*H*OH), 6.83–6.87 (m, 6H, H_{aromat}), 7.29–7.33 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 3398 cm^{-1}, 1607. $C_{30}H_{35}NO_7$ (521.61)·0.8 H_2O.

*6.1.26. (2S,4R)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2S,4R)-**8c**]*

According to GP2 from 149 mg (0.279 mmol) of (2*S*,4*R*)-**25c**, 0.85 ml (0.850 mmol) of aq. 1.0 M NaOH in 5 ml of MeOH; reaction time: 4 h; purification by CC (Al_2O_3). Yield: 120 mg (83%); colorless crystals, m.p. 95–103 °C (C_6H_6/petrol ether). $[\alpha]_D^{20}$ = –33.2 (*c* = 1.00, MeOH). The spectra (^{1}H NMR and IR) were identical with those of (2*R*,4*S*)-**8c**. $C_{30}H_{35}NO_7$ (521.61)·0.5 H_2O.

*6.1.27. (2R,4R)-1-[3-(Carbazol-9-yl)-1-propyl]-4-hydroxy-pyrrolidine-2-acetic acid [(2R,4R)-**8d**]*

According to GP2 from 88 mg (0.23 mmol) of (2*R*,4*R*)-**30d**, 0.70 ml (0.70 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 14 h. Yield: 73 mg (90%); colorless crystals, m.p. 93–97 °C (MeOH/EtOAc). $[\alpha]_D^{20}$ = +31.2 (*c* = 0.26, MeOH). ^{1}H NMR (CD_3OD): δ = 1.71–1.78 (m, 1H, C*H*$_2$CHCH$_2$COO), 2.18–2.32 (m, 2H, CHNCH$_2$C*H*$_2$), 2.43–2.51 (m, 1H, C*H*$_2$CHCH$_2$COO), 2.58–2.62 (m, 2H, CH$_2$COO), 2.90–3.02 (m, 2H, C*H*$_2$NCH and NC*H*$_2$CHO), 3.41–3.55 (m, 3H, NC*H*, C*H*$_2$NCH and NC*H*$_2$CHO), 4.34–4.51 (m, 3H, C*H*OH and 2H of C*H*$_2$-carbazole), 7.17–7.21 (m, 2H, H_{aromat}), 7.46–7.53 (m, 4H, H_{aromat}), 8.05–8.08 (m, 2H, H_{aromat}). IR: $\tilde{\nu}$ = 3385 cm^{-1}, 1595. MS; *m*/*z* (%): 353 (2) [M + 1]$^+$. HRMS (CI) Calc. for $C_{21}H_{24}N_2O_3$: 353.1865. Found: 353.1875.

*6.1.28. (2S,4S)-1-[3-(Carbazol-9-yl)-1-propyl]-4-hydroxy-pyrrolidine-2-acetic acid [(2S,4S)-**8d**]*

According to GP2 from 54 mg (0.16 mmol) of (1*S*,5*S*)-**26d**, 0.49 ml (0.49 mmol) of aq. 1 M NaOH in 4.5 ml of MeOH; reaction time: 12 h. Yield: 54 mg (95%); colorless crystals, m.p. 102–108 °C (MeOH/EtOAc). $[\alpha]_D^{20}$ = –31.0 (*c* = 0.51, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**8d**. HRMS (70 eV) Calc. for $C_{21}H_{24}N_2O_3$: 352.1787. Found: 352.1764.

*6.1.29. (2R,4S)-1-[3-(Carbazol-9-yl)-1-propyl]-4-hydroxy-pyrrolidine-2-acetic acid [(2R,4S)-**8d**]*

According to GP2 from 94 mg (0.22 mmol) of (2*R*,4*S*)-**31d**, 1.3 ml (1.30 mmol) of aq. 1.0 M NaOH in 6.5 ml of MeOH; reaction time: 3 d. Yield: 73 mg (93%); colorless crystals, m.p. 193–197 °C (MeOH/iPr_2O). $[\alpha]_D^{20}$ = +44.4 (*c* = 0.80, MeOH). ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.93 (ddd, *J* = 13.7, 11.3, 4.7 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.13 (ddt, *J* = 13.7, 6.4, 1.7 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.21–2.37 (m, 2H, CHNCH$_2$C*H*$_2$), 2.45 (dd, *J* = 16.5, 3.0 Hz, 1H, CH$_2$COO), 2.65 (dd, *J* = 16.5, 6.0 Hz, 1H, CH$_2$COO), 2.93 (br. d, *J* = 12.4 Hz, 1H, NC*H*$_2$CHO), 2.96–3.03 (m, 1H, C*H*$_2$NCH), 3.36–3.42 (m, 1H, C*H*$_2$NCH), 3.64–3.74 (m, 2H, NC*H*$_2$CHO and NC*H*), 4.39–4.43 (m, 1H, C*H*OH), 4.45–4.55 (m, 2H, C*H*$_2$-carbazole), 7.21–7.26 (m, 2H, H_{aromat}), 7.49–7.55 (m, 2H, H_{aromat}), 7.62–7.67 (m, 2H, H_{aromat}), 8.08–8.10 (m, 2H, H_{aromat}). IR: $\tilde{\nu}$ = 3405 cm^{-1}, 1594. MS; *m*/*z* (%): 353 (3) [M + 1]$^+$. $C_{21}H_{24}N_2O_3$·1.0 H_2O (370.46).

*6.1.30. (2S,4R)-1-[3-(Carbazol-9-yl)-1-propyl]-4-hydroxy-pyrrolidine-2-acetic acid [(2S,4R)-**8d**]*

According to GP2 from 105 mg (0.286 mmol) of (2*S*,4*R*)-**25d**, 0.86 ml (0.860 mmol) of aq. 1.0 M NaOH in 4 ml of MeOH; reaction time: 6 h. Yield: 89 mg (88%); colorless crystals, m.p. 207–209 °C (MeOH/iPr_2O). $[\alpha]_D^{20}$ = –43.5 (*c* = 0.93, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**8d**. $C_{21}H_{24}N_2O_3$ (352.44).

*6.1.31. (2S,4R)-4-Hydroxypyrrolidine-2-acetic acid [(2S,4R)-**9**]*

According to GP5 from 76 mg (0.270 mmol) of (2*S*,4*R*)-**28** and 38 mg (0.036 mmol) of 10% Pd-C in 10 ml of MeOH; reaction time: 1 h. Yield: 35 mg (89%); colorless crystals, m.p. 238–240 °C (decomp.). $[\alpha]_D^{20}$ = +1.3 (*c* = 0.31, H_2O). ^{1}H NMR (D_2O): δ = 1.83 (ddd, *J* = 14.1, 11.4, 4.4 Hz, 1H, C*H*$_2$CHCH$_2$COO), 2.14–2.20 (m, 1H, C*H*$_2$CHCH$_2$COO), 2.55 (dd, *J* = 16.6, 7.7 Hz, 1H, CH$_2$COO), 2.64 (dd, *J* = 16.6, 5.5 Hz, 1H, CH$_2$COO), 3.22 (dt, *J* = 12.8, 1.5 Hz, 1H, NCH$_2$), 3.43 (dd, *J* = 12.8, 4.2 Hz, 1H, NCH$_2$), 4.02–4.08 (m, 1H, NCH), 4.56–4.59 (m, 1H, C*H*OH). IR: $\tilde{\nu}$ = 3231 cm^{-1}, 1643. MS; *m*/*z* (%): 146 (100) [M + 1]$^+$. $C_6H_{11}NO_3$ (145.16).

*6.1.32. (2R,4S)-4-Hydroxypyrrolidine-2-acetic acid [(2R,4S)-**9**]*

According to GP5 from 50 mg (0.180 mmol) of (2*R*,4*S*)-**28** and 25 mg (0.024 mmol) of 10% Pd-C in 8 ml of MeOH;

reaction time 1 h. Yield: 24 mg (92%); colorless crystals, m.p. 235–237 °C (MeOH, decomp.). $[\alpha]_D^{20} = -2.6$ ($c = 0.23$, H_2O). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**9**. $C_6H_{11}NO_3$ (145.16). HRMS (70 eV) Calc. for $C_6H_{11}NO_3$: 145.0738. Found: 145.0771.

*6.1.33. (2*R*,4*R*)-4-Hydroxypyrrolidine-2-acetic acid [(2*R*,4*R*)-**9**]*

According to GP5 from 59 mg (0.210 mmol) of (2*R*,4*R*)-**28** and 30 mg of 10% Pd-C (0.028 mmol) in 10 ml of MeOH, reaction time: 1 h. Yield: 31 mg (100%); colorless crystals, m.p. 210–212 °C (MeOH, decomp.). $[\alpha]_D^{20} = -4.8$ ($c = 0.33$, H_2O). ^{1}H NMR (D_2O): δ = 1.77 (dddd, J = 14.2, 7.3, 3.6, 1.4 Hz, 1H, CH_2CHCH$_2$COO), 2.55 (ddd, J = 14.2, 8.8, 6.0 Hz, 1H, CH_2CHCH$_2$COO), 2.72–2.74 (m, 2H, CH$_2$COO), 3.32 (ddd, J = 12.5, 2.4, 1.4 Hz, 1H, NCH$_2$), 3.38 (dd, J =12.5, 4.9 Hz, 1H, NCH$_2$), 3.93–3.99 (m, 1H, NCH), 4.62–4.65 (m, 1H, C*H*OH). IR: $\tilde{\nu}$ = 3175 cm^{-1}, 1662. MS; *m*/*z* (%): 146 (100) [M + 1]$^+$. $C_6H_{11}NO_3$ (145.16).

*6.1.34. (2*S*,4*S*)-4-Hydroxypyrrolidine-2-acetic acid [(2*S*,4*S*)-**9**]*

According to GP5 from 80 mg (0.290 mmol) of (2*S*,4*S*)-**28** and 40 mg of 10% Pd-C (0.038 mmol) in 8 ml of MeOH; reaction time 1 h. Yield: 41 mg (99%); colorless crystals, m.p. 238–240 °C (MeOH, decomp.). $[\alpha]_D^{20} = +5.3$ ($c = 0.32$, H_2O). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**9**. $C_6H_{11}NO_3$ (145.16).

*6.1.35. Methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-acetate hydrochloride [(2*S*,4*R*)-**12**]*

To a solution of 325 mg (0.848 mmol) of (2*S*,4*R*)-**17** and 80 μl (0.960 mmol) of aq. 37% HCl in 10 ml of MeOH, 162 mg (0.153 mmol) of 10% Pd-C was added. The mixture was subjected to hydrogen under ambient pressure at r.t. for 5 d and then filtrated. The filtrate was evaporated and its residue was crystallized from *i*Pr$_2$O. Yield: 149 mg (90%); colorless crystals, m.p. 116–117 °C (*i*Pr$_2$O). $[\alpha]_D^{20}$ = +42.8 ($c = 0.43$, MeOH). ^{1}H NMR (CD_3OD): δ = 1.71 (ddd, J = 13.7, 11.4, 4.0 Hz, 1H, CH_2CHCH$_2$COO), 2.09 (ddt, J = 13.7, 6.4, 1.5 Hz, 1H, CH_2CHCH$_2$COO), 2.69 (dd, J = 18.0, 9.9 Hz, 1H, CH$_2$COO), 2.82 (dd, J = 18.0, 4.0 Hz, 1H, CH$_2$COO), 3.09 (dd, J = 12.2, 1.5 Hz, 1H, NCH$_2$), 3.25 (dd, J = 12.2, 3.7 Hz, 1H, NCH$_2$), 3.62 (s, 3H, CH$_3$), 3.99–4.07 (m, 1H, NCH), 4.38–4.41 (m, 1H, C*H*OH). IR: $\tilde{\nu}$ = 1735 cm^{-1}. MS; *m*/*z* (%): 160 (100) [M – HCl]$^+$. $C_7H_{14}ClNO_3$ (195.46).

*6.1.36. Ethyl (2*R*,4*R*)-4-hydroxypyrrolidine-2-acetate hydrochloride [(2*R*,4*R*)-**13**]*

To a solution of 187 mg (0.608 mmol) of (2*R*,4*R*)-**21** in 10 ml of EtOH, 93 mg (0.087 mmol) of 10% Pd-C and 55 μl (0.66 mmol) of aq. 37% HCl were added. The mixture was subjected to hydrogen at r.t. under ambient pressure for 2 h, and then filtrated and finally concentrated. The residue was recrystallized from EtOH/*i*Pr$_2$O. Yield: 114 mg (89%); colorless crystals, m.p. 150–151 °C (EtOH/*i*Pr$_2$O). $[\alpha]_D^{20} = -34.0$ ($c = 1.00$, EtOH). ^{1}H NMR (CD_3OD): δ = 1.29 (t, J = 7.4 Hz, 3H, CH$_2$CH_3), 1.79 (ddt, J = 14.1, 4.7, 1.9 Hz, 1H, CH_2CHCH$_2$COO), 2.43 (ddd, J = 14.1, 9.8, 5.0 Hz, 1H, CH_2CHCH$_2$COO), 2.92 (dd, J = 18.0, 5.2 Hz, 1H, CH$_2$COO), 2.98 (dd, J = 18.0, 9.4 Hz, 1H, CH$_2$COO), 3.22 (dd, J = 11.9, 3.6 Hz, 1H, NCH$_2$), 3.27 (dt, J = 11.9, 1.9 Hz, 1H, NCH$_2$), 4.00–4.08 (m, 1H, NCH), 4.21 (q, J = 7.4 Hz, 2H, CH_2CH$_3$), 4.50–4.53 (m, 1H, C*H*OH). IR: $\tilde{\nu}$ = 3303 cm^{-1}, 1721. MS; *m*/*z* (%): 174 (100) [M – HCl]$^+$. $C_8H_{16}ClNO_3$ (209.67).

*6.1.37. Benzyl (2*S*,4*R*)-4-benzyloxy-2-diazoacetyl-pyrrolidine-1-carboxylate [(2*S*,4*R*)-**16**]*

2.10 g (16.5 mmol) of $(COCl)_2$ was added to a solution of 3.90 g (11.0 mmol) of (2*S*,4*R*)-**15** [15] and 50 μl of DMF in 26 ml of CH_2Cl_2 at 0 °C. The mixture was stirred for 1 h at 0 °C. Following evaporation under vacuo, the obtained yellow oil was dissolved in 4.5 ml of Et$_2$O. The mixture was slowly added at 0 °C to a solution of 2.22 g (52.8 mmol) of CH_2N_2 in 150 ml of Et$_2$O. Following 1 h stirring, excess of CH_2N_2 was decomposed by addition of AcOH and the solvent was evaporated. Purification by CC (*iso*-hexane/acetone = 7:3). Yield: 3.33 g (80%); yellow oil. $[\alpha]_D^{20}$ = –55.5 ($c = 1.00$, EtOAc). ^{1}H NMR ($CDCl_3$, –30 °C): Two rotamers δ = 2.01–2.07, 2.10–2.16 (m, 1H, NCHCH_2), 2.30–2.37, 2.41–2.48 (m, 1H, NCHCH_2), 3.55–3.59, 3.61–3.65 (m, 1H, NCH$_2$), 3.69–3.73, 3.88–3.92 (m, 1H, NCH$_2$), 4.14–4.23 (m, 1H, NCH$_2$C*H*O), 4.37–4.53 (m, 3H, NCH and PhCH_2OCH), 5.00–5.23 (m, 2H, PhCH_2OCO), 5.26, 5.54 (s, 1H, CHN$_2$), 7.28–7.38 (m, 10H, H$_{aromat}$). IR: $\tilde{\nu}$ = 2107 cm^{-1}, 1704, 1650. MS; (*m*/*z*): 380 [M + 1]$^+$. $C_{21}H_{21}N_3O_4$ (379.42).

*6.1.38. Methyl (2*S*,4*R*)-4-benzyloxy-1-benzyloxy-carbonylpyrrolidine-2-acetate [(2*S*,4*R*)-**17**]*

To a solution of 390 mg (1.03 mmol) of (2*S*,4*R*)-**16** in 3 ml of MeOH, a solution of 1.5 ml of MeOH containing 17 mg (0.10 mmol) of AgOAc and 61 mg (0.61 mmol) of TEA was added at r.t. The resulting mixture was warmed to 60 °C for 30 min. Following decolorization using charcoal, the solvent was evaporated under vacuo. Purification by CC (*n*-heptane/acetone, 3:1). Yield: 317 mg (81%); colorless oil. $[\alpha]_D^{20}$ = –33.8 (c = 0.95, EtOAc). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.07–2.13 (m, 1H, CH_2CHCH$_2$COO), 2.41–2.47 (m, 1H, CH_2CHCH$_2$COO), 2.62 (dd, J = 15.4, 8.4 Hz, 1H, CH$_2$COO), 3.07 (dd, J = 15.4, 3.7 Hz, 1H, CH$_2$COO), 3.62 (dd, J = 11.8, 4.8 Hz, 1H, NCH$_2$), 3.66 (s, 3H, CH$_3$), 3.91 (br. d, J = 11.8 Hz, 1H, NCH$_2$), 4.24–4.29 (m, 1H, NCH$_2$C*H*O), 4.50–4.54 (m, 1H, NCH), 4.56 (s, 2H, PhCH_2OCH), 5.26 (s, 2H, COOCH_2Ph), 7.25–7.45 (m, 10H, H$_{aromat}$). IR: $\tilde{\nu}$ = 1746 cm^{-1}, 1712. MS; *m*/*z* (%): 384 (22) [M + 1]$^+$. $C_{22}H_{25}NO_5$ (383.44).

*6.1.39. Benzyl (2*R*,4*R*)-4-hydroxy-2-methoxypyrrolidine-1-carboxylate [(2*R*,4*R*)-**18**] and benzyl (2*S*,4*R*)-4-hydroxy-2-methoxypyrrolidine-1-carboxylate [(2*S*,4*R*)-**18**]*

A solution of 145 mg (1.44 mmol) of TEA and 1.90 g (7.17 mmol) of (2*S*,4*R*)-**14** in 60 ml of MeOH was subjected

to anodic oxidation at 10–15 °C (U = 13 V, platinum as cathode, a platinum wire as anode, for 7 h) followed by evaporation of MeOH (T < 25 °C). Purification and separation of the diastereomers by CC (iPr$_2$O/EtOH, 92:8). Total yield: 1.74 g (97%). Analytical (n-heptane/EtOAc, 40:60; 1.5 ml min^{-1}, t_R = 10.5 min [Diastereomer I], 9.4 min [Diastereomer II]): ds = 41:59 (Diastereomer II: Diastereomer I).

Diastereomer I: Colorless oil. $[\alpha]_D^{20}$ = +1.2 (c = 1.76, EtOH). ^{1}H NMR ($CDCl_3$): Two rotamers δ = 1.91–2.01 (m, 1H, NCHCH_2), 2.15–2.19 (m, 1H, NCHCH_2), 3.23, 3.37 (2s, 3H, OCH_3), 3.45–3.49, 3.67–3.71 (m, 2H, NCH_2), 4.60–4.64 (m, 1H, CHOH), 5.11–5.31 (m, 3H, NCH and OCH_2Ph), 7.29–7.36 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 3429 cm^{-1}, 1704. MS; m/z (%): 220 (100) [M-OCH_3]. $C_{13}H_{17}NO_4$ (251.28) Calc. C 62.14, H 6.82, N 5.57. Found: C 62.00, H 7.00, N 5.53.

Diastereomer II: Colorless oil. $[\alpha]_D^{20}$ = –31.7 (c = 1.20, EtOH). ^{1}H NMR ($CDCl_3$): two rotamers δ = 1.91–1.97 (m, 1H, NCHCH_2), 2.12–2.18 (m, 1H, NCHCH_2), 3.10–3.24, 3.58–3.71 (m, 2H, NCH_2), 3.31–3.44 (m, 3H, OCH_3), 4.34–4.37 (m, 1H, CHOH), 5.13–5.38 (m, 3H, NCH and OCH_2Ph), 7.30–7.38 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 3466 cm^{-1}, 1708. MS; m/z (%): 252 (92) [M-OCH_3]. $C_{13}H_{17}NO_4$ (251.28).

*6.1.40. Benzyl (2*R*,4*R*)-4-(tert-butyl)dimethylsilyloxy-2-methoxypyrrolidine-1-carboxylate [(2*R*,4*R*)-**19**] and benzyl (2*S*,4*R*)-4-(tert-butyl)dimethylsilyloxy-2-methoxypyrrolidine-1-carboxylate [(2*S*,4*R*)-**19**]*

A solution of 0.770 g (5.11 mmol) of TBDMSCl in 6 ml of CH_2Cl_2 was added to a solution of 0.986 g (3.93 mmol) of a mixture of (2*R*,4*R*)-**18** and (2*S*,4*R*)-**18** and 0.401 g (5.89 mmol) of imidazole in 14 ml of CH_2Cl_2 at r.t. The mixture was stirred for 16 h, washed with H_2O, dried (Na_2SO_4), and evaporated to afford a colorless oil. Purification by CC (n-heptane/EtOAc, 7:1). Yield: 1.22 g (85%). Separation of the diastereomers by prep. HPLC (n-heptane/EtOAc, 7:1; 12 ml min^{-1}; t_R = 21.6 min [Diastereomer I], 24.6 min [Diastereomer II]).

Diastereomer I: Colorless oil. $[\alpha]_D^{20}$ = –10.9 (c = 0.82, EtOAc). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.11 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.93 [s, 9H, $SiC(CH_3)_3$], 2.00 (dt, J = 13.9, 1.5 Hz, 1H, NCHCH_2), 2.35 (dt, J = 13.9, 6.4 Hz, 1H, NCHCH_2), 3.41–3.45 (m, 4H, NCH_2 and OCH_3), 3.99 (dd, J = 11.2, 6.6 Hz, 1H, NCH_2), 4.44–4.49 (m, 1H, CHOSi), 5.24 (d, J = 12.6 Hz, 1H, CH_2Ph), 5.28 (d, J = 12.6 Hz, 1H, CH_2Ph), 5.36 (dd, J = 6.4, 1.5 Hz, 1H, NCH), 7.25–7.44 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 3034 cm^{-1}, 1714. MS; m/z (%): 334 (1) [M-OCH_3]$^+$. $C_{19}H_{31}NO_4Si$ (365.55).

Diastereomer II: Colorless oil. $[\alpha]_D^{20}$: +14.4 (c = 1.07, EtOAc). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.10 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 2.00 (dd, J = 12.9, 7.2 Hz, 1H, NCHCH_2), 2.20 (ddd, J = 12.9, 5.8, 1.5 Hz, 1H, NCHCH_2), 3.38 (s, 3H, OCH_3), 3.50 (dd, J = 11.1, 5.2 Hz, 1H, NCH_2), 3.72 (dd, J = 11.1, 6.3 Hz, 1H, NCH_2), 4.66–4.73 (m, 1H, CHOSi), 5.25 (d, J = 12.7 Hz, 1H, CH_2Ph), 5.29 (d, J = 12.7 Hz, 1H, CH_2Ph), 5.38 (dd, J = 7.2, 1.5 Hz, 1H, NCH), 7.26–7.35, 7.42–7.44 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 3040 cm^{-1}, 1714. MS; m/z (%): 334 (1) [M-OCH_3]$^+$. $C_{19}H_{31}NO_4Si$ (365.55).

*6.1.41. Ethyl (2*R*,4*R*)-1-benzyloxycarbonyl-4-(tert-butyl)dimethylsilyloxypyrrolidine-2-acetate [(2*R*,4*R*)-**20**] and ethyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-(tert-butyl)dimethylsilyloxypyrrolidine-2-acetate [(2*S*,4*R*)-**20**]*

To a solution of 3.00 (8.2 mmol) of a mixture of (2*R*,4*R*)-**19** and (2*S*,4*R*)-**19** and 8.60 g (purity: 61%, 32.8 mmol) of 1-ethoxy-1-(trimethylsilyloxy)ethene in 83 ml of CH_2Cl_2, 2.43 g (17.2 mmol) of $BF_3{\cdot}Et_2O$ was added at –78 °C. The reaction was quenched after 4 h using 66.7 ml (48.3 mmol) of aq. 5% K_2CO_3. The organic layer was separated, dried ($MgSO_4$) and concentrated. Purification by CC (n-heptane/EtOAc, 88:12). Separation of the diastereomers by prep. HPLC (n-heptane/EtOAc, 88:12; 12 ml min^{-1}; t_R = 32.7 min [(2*R*,4*R*)-**20**], 27.0 min [(2*S*,4*R*)-**20**]). Analytical HLPC (n-heptane/EtOAc, 88/12; 1.3 ml min^{-1}; ds [(2*R*,4*R*)-**20**/(2*S*,4*R*)-**20**] = 87:13; t_R = 12.0 min [(2*R*,4*R*)-**20**], 9.5 min [2*S*,4*R*)-**20**].

(2*R*,4*R*)-**20**: Yield: 2.72 g (79%); colorless oil. $[\alpha]_D^{20}$ = +13.0 (c =1.02, EtOAc). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.13 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.94 (s, 9H, $C(CH_3)_3$), 1.25 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.04 (dt, J = 13.5, 2.4 Hz, 1H, CH_2CHCH_2COO), 2.32 (ddd, J = 13.5, 8.1, 5.4 Hz, 1H, CH_2CHCH_2COO), 2.91 (dd, J = 15.1, 9.6 Hz, 1H, CH_2COO), 3.18 (dd, J = 15.1, 4.0 Hz, 1H, CH_2COO), 3.50 (ddd, J = 11.4, 2.9, 1.1 Hz, 1H, NCH_2), 3.82 (dd, J = 11.4, 5.4 Hz, 1H, NCH_2), 4.14–4.22 (m, 2H, CH_2CH$_3$), 4.43–4.53 (m, 2H, CHOSi and NCH), 5.26 (s, 2H, CH_2Ph), 7.24–7.45 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 1738 cm^{-1}, 1704. MS; m/z (%): 422 (36) [M + 1]$^+$. $C_{22}H_{35}NO_5$ (421.61).

(2*S*,4*R*)-**20**: Yield: 314 mg (9%); colorless oil. $[\alpha]_D^{20}$ = –40.3 (c =1.00, EtOAc). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.06 (s, 6H, 2 $SiCH_3$), 0.90 (s, 9H, $Si(CH_3)_3$), 1.24 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.06–2.12 (m, 1H, CH_2CHCH_2COO), 2.22–2.28 (m, 1H, CH_2CHCH_2COO), 2.62 (dd, J = 15.1, 8.5 Hz, 1H, CH_2COO), 3.08 (dd, J = 15.1, 2.2 Hz, 1H, CH_2COO), 3.62 (dt, J = 11.3, 2.2 Hz, 1H, NCH_2), 3.69 (br. d, J = 11.3 Hz, 1H, NCH_2), 4.17 (q, J = 7.0 Hz, 2H, CH_2CH$_3$), 4.50–4.56 (m, 2H, NCH and CHOSi), 5.23 (d, J = 12.9 Hz, 1H, CH_2Ph), 5.27 (d, J = 12.9 Hz, 1H, CH_2Ph), 7.25–7.43 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 1735 cm^{-1}, 1705. MS; m/z (%): 422 (72) [M + 1]$^+$. $C_{22}H_{35}NO_5$ (421.61).

*6.1.42. Ethyl (2*R*,4*R*)-1-benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetate [(2*R*,4*R*)-**21**]*

To a solution of 90 mg (0.21 mmol) of (2*R*,4*R*)-**20** in 2 ml of THF, 0.26 ml (1.0 M in THF, 0.26 mmol) of TBAF was added. After 4.5 h. at r.t. 2.0 ml of 0.1% K_2CO_3 was added. The organic layer was separated, dried (Na_2SO_4), and evaporated. Purification by CC (iPr$_2$O/EtOH, 95:5). Yield: 58 mg (88%); colorless oil. $[\alpha]_D^{22}$ = +23.4 (c = 0.7, EtOAc). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 1.24 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.09 (dtd, J = 13.8, 3.1, 1.3 Hz, 1H, CH_2CHCH_2COO), 2.39 (ddd, J = 13.8, 8.4, 5.6 Hz, 1H,

CH_2CHCH$_2$COO), 2.60 (s, 1H, OH), 2.93 (dd, J = 15.4, 9.2 Hz, 1H, CH$_2$COO), 3.17 (dd, J = 15.4, 4.1 Hz, 1H, CH$_2$COO), 3.57 (ddd, J = 11.8, 2.9, 1.3 Hz, 1H, NCH$_2$), 3.83 (dd, J = 11.8, 5.4 Hz, 1H, NCH$_2$), 4.17 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 4.41–4.48 (m, 1H, NCH), 4.54–4.58 (m, 1H, CHOH), 5.25 (s, 2H, CH_2Ph), 7.25–7.45 (m, 5H, H$_{aromat}$). IR: $\tilde{\nu}$ = 3442 cm^{-1}, 1731, 1682. MS; *m/z* (%): 308 (93) [M + 1]$^+$. $C_{16}H_{21}NO_5$ (307.35).

*6.1.43. Methyl (2*S*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylate [(2*S*,4*R*)-**22a**]*

According to GP1 from 50 mg (0.30 mmol) of KI, 454 mg (1.50 mmol) of **RBr** (R = **a**) [11,21], 274 mg (1.0 mmol) of (2*S*,4*R*)-**11** and 691 mg (5.0 mmol) of K_2CO_3 in 8 ml of acetone. Yield: 273 mg (52%); colorless oil. $[\alpha]_D^{20}$ = –53.3 (c = 0.6, EtOAc). ^{1}H NMR (CDCl$_3$): δ = 2.03 (ddd, J = 13.7, 7.6, 3.1 Hz, 1H, NCHCH_2), 2.19 (dd, J = 13.7, 7.6 Hz, 1H, NCHCH_2), 2.30 (q, J = 7.5 Hz, 2H, NCH$_2$CH_2), 2.41 (dd, J = 10.1, 3.6 Hz, 1H, NCH_2CHOH), 2.62 (dt, J = 12.2, 7.5 Hz, 1H, NCH_2CH$_2$), 2.82 (dt, J = 12.2, 7.5 Hz, 1H, NCH_2CH$_2$), 3.33 (dd, J = 10.1, 5.5 Hz, 1H, NCH_2CHOH), 3.53 (t, J = 7.6 Hz, 1H, NCH), 3.67 (s, 3H, OCH$_3$), 4.40–4.45 (m, 1H, CHOH), 6.07 (t, J = 7.5 Hz, 1H, =CHCH$_2$), 7.15–7.38 (m, 10H, H$_{aromat}$). IR: $\tilde{\nu}$ = 3418 cm^{-1}, 1738. MS; *m/z* (%): 352 (67) [M + 1]$^+$. $C_{22}H_{25}NO_3$ (351.45).

*6.1.44. Methyl (2*R*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylate [(2*R*,4*R*)-**22a**]*

According to GP1 from 50 mg (0.30 mmol) of KI, 936 mg (3.09 mmol) of **RBr** (R = **a**) [11,21], 549 mg (3.00 mmol) of (2*R*,4*R*)-**11**, 2.07 g (15.0 mmol) of K_2CO_3 in 12 ml of acetone. Yield: 432 mg (41%); colorless oil. $[\alpha]_D^{20}$ = +45.4 (c = 1.00, EtOAc). ^{1}H NMR (CDCl$_3$): δ = 1.92 (ddt, J = 14.2, 3.6, 1.5 Hz, 1H, NCHCH_2), 2.30 (q, J = 7.5 Hz, 2H, NCH$_2$CH_2), 2.29–2.37 (m, 1H, NCHCH_2), 2.58 (dd, 1H, J = 9.9, 4.0 Hz, NCH_2CHOH), 2.63 (dt, J = 12.0, 7.5 Hz, 1H, NCH_2CH$_2$), 2.81 (dt, J = 12.0, 7.5 Hz, 1H, NCH_2CH$_2$), 3.00 (dt, J = 9.9, 1.5 Hz, 1H, NCH_2CHOH), 3.26 (dd, J = 9.9, 3.6 Hz, 1H, NCH), 3.70 (s, 3 H, OCH$_3$), 4.23–4.26 (m, 1H, CHOH), 6.08 (t, J = 7.5 Hz, 1H, =CHCH$_2$), 7.16–7.40 (m, 10H, H$_{aromat}$). IR: $\tilde{\nu}$ = 3424 cm^{-1}, 1732. MS; *m/z* (%): 352 (100) [M + 1]$^+$. $C_{22}H_{25}NO_3$ (351.45).

*6.1.45. Methyl (2*S*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*S*,4*R*)-**22c**]*

According to GP1 from 50 mg (0.30 mmol) of KI, 682 mg (1.49 mmol) of **RBr** (R = **c**) [11,22], 273 mg (1.49 mmol) of (2*S*,4*R*)-**11**, 680 mg (6.85 mmol) of K_2CO_3 in 6 ml of acetone. Yield: 414 mg (53%); colorless oil. $[\alpha]_D^{22}$ = –24.5 (c = 0.55, EtOH). ^{1}H NMR (CDCl$_3$): δ = 2.00–2.07 (m, 1H, NCHCH_2), 2.16 (ddt, J = 13.6, 7.2, 3.3 Hz, 1H, NCHCH_2), 2.57 (dd, J = 10.2, 3.4 Hz, 1H, NCH_2CHOH), 2.83 (m, 1H, NCH_2CH$_2$), 2.95 (m, 1H, NCH_2CH$_2$), 3.20 (t, J = 6.1 Hz, 2H, NCH$_2$CH_2), 3.38 (dd, J = 10.2, 5.4 Hz, 1H, NCH_2CHOH), 3.64–3.66 (m, 1H, NCH), 3.65 (s, 3H, COOCH$_3$), 3.78 (s, 9H, ArOCH_3), 4.40–4.44 (m, 1H, CHOH), 6.83–6.79 (m, 6H, H$_{aromat}$), 7.29–7.33 (m, 6H, H$_{aromat}$). IR: $\tilde{\nu}$ = 3418 cm^{-1}, 1740. MS (ESI$^+$); *m/z* (%): 522 [M + 1]$^+$ (1). $C_{30}H_{35}NO_7$ (521.61).

*6.1.46. Methyl (2*R*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*R*,4*R*)-**22c**]*

According to GP1 from 42 mg (0.25 mmol) of KI, 1.14 g (2.50 mmol) of **RBr** (R = **c**) [11,22], 458 mg (2.50 mmol) of (2*R*,4*R*)-**11**, 1.73 g (12.5 mmol) of K_2CO_3 in 12 ml of acetone. Yield: 429 mg (33%); colorless oil. $[\alpha]_D^{20}$ = +30.8 (c = 1.45, EtOH). ^{1}H NMR (CDCl$_3$): δ = 1.88–1.93 (m, 1H, NCHCH_2), 2.32 (ddd, J = 14.2, 10.0, 5.9 Hz, 1H, NCHCH_2), 2.67 (dd, J = 9.9, 4.1 Hz, 1H, NCH_2CHOH), 2.79 (dt, J = 12.4, 6.0 Hz, 1H, NCH_2CH$_2$), 2.94 (dt, J = 12.4, 6.0 Hz, 1H, NCH_2CH$_2$), 3.03 (s, 1H, OH), 3.06 (dt, J = 9.9, 1.4 Hz, 1H, NCH_2CHOH), 3.12–3.21 (m, 2H, NCH$_2$CH_2), 3.38 (dd, J = 10.0, 3.9 Hz, 1H, NCH), 3.66 (s, 3H, COOCH$_3$), 3.77 (s, 9H, ArOCH_3), 4.20–4.24 (m, 1H, CHOH), 6.78–6.82 (m, 6H, H$_{aromat}$), 7.28–7.32 (m, 6H, H$_{aromat}$). IR: $\tilde{\nu}$ = 3444 cm^{-1}, 1732. MS (ESI$^+$); *m/z* (%): 522 (1). $C_{30}H_{35}NO_7$ (521.61).

*6.1.47. (1*S*,4*S*)-5-(4,4-Diphenylbut-3-en-1-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-3-one [(1*S*,4*S*)-**23a**]*

According to GP4 from 195 mg (0.578 mmol) of (2*S*,4*R*)-**7a** and 304 mg (1.160 mmol) of Ph$_3$P, 151 mg (0.867 mmol) of DEAD in 10 ml of THF; reaction time: 13 h. Yield: 157 mg (85%); colorless crystals, m.p. 85–86 °C (n-heptane/acetone = 4:1). $[\alpha]_D^{21}$ = –60.7 (c = 0.84, EtOH). ^{1}H NMR (CDCl$_3$): δ = 1.85 (dd, J = 10.5, 1.6 Hz, 1H, NCHCH_2), 1.92–2.08 (m, 1H, NCHCH_2), 2.15 (dd, J = 10.6, 1.2 Hz, 1H, NCH_2CHO), 2.17–2.31 (m, 2H, NCH$_2$CH_2), 2.43 (dt, J = 11.8, 6.6 Hz, 1H, NCH_2CH$_2$), 2.68 (dt, J = 11.8, 7.1 Hz, 1H, NCH_2CH$_2$), 3.22 (dd, J = 10.6, 0.9 Hz, 1H, NCH_2CHO), 3.48 (br. s, 1H, NCH), 4.78 (br. s, 1H, NCH$_2$CHO), 6.02 (t, J = 7.3 Hz, 1H, =CHCH$_2$), 7.09–7.30 (m, 10H, H$_{aromat}$). IR: $\tilde{\nu}$ = 1766 cm^{-1}. MS; *m/z* (%): 320 (100) [M + 1]$^+$. $C_{21}H_{21}NO_2$ (319.40).

*6.1.48. Methyl (2*R*,4*S*)-4-acetoxy-1-(4,4-diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylate [(2*R*,4*S*)-**24a**]*

According to GP4 from 120 mg (0.352 mmol) of (2*R*,4*R*)-**22a**, 134 mg (0.513 mmol) of Ph$_3$P, 243 µl (38–40% in PhCH$_3$, 0.513 mmol) of DEAD, 29 mg (0.510 mmol) of AcOH in 5 ml of THF; reaction time: for 6 h; purification by CC (n-heptane/EtOAc, 3:1) and prep. HPLC (n-heptane/EtOAc, 75:25; 12 ml min^{-1}; t_R = 37.8 min). Yield: 92 mg (69%); colorless oil. $[\alpha]_D^{20}$ = +43.1 (c = 1.02, EtOAc). ^{1}H NMR (CDCl$_3$): δ = 2.02 (s, 3H, CH$_3$COO), 2.12 (ddd, J = 13.9, 7.5, 2.9 Hz, 1H, NCHCH_2), 2.25–2.33 (m, 3H, NCHCH_2 and NCH$_2$CH_2), 2.50 (dd, J = 10.8, 3.3 Hz, 1H, NCH_2CHO), 2.59 (dt, J = 12.0, 7.6 Hz, 1H, NCH_2CH$_2$), 2.79 (dt, J = 12.0, 8.0 Hz, 1H, NCH_2CH$_2$), 3.43 (dd, J = 10.8, 6.2 Hz, 1H, NCH_2CHO), 3.49 (t, J = 7.5 Hz, 1H, NCH), 3.68 (s, 3H, COOCH$_3$), 5.17–5.22 (m, 1H, NCH$_2$CHO), 6.06 (t, J = 7.4 Hz, 1H, =CHCH$_2$), 7.14–7.38 (m, 10H, H$_{aromat}$). IR:

$\tilde{\nu}$ = 1738 cm^{-1}, 1718. MS; *m/z* (%): 394 (64) $[M + 1]^+$. $C_{24}H_{27}NO_4$ (393.48).

*6.1.49. Methyl (2*R*,4*S*)-4-acetoxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxy-late [(2*R*,4*S*)-**24c**]*

According to GP4 from 100 mg (0.192 mmol) of (2*R*,4*R*)-**22c** and 79 mg (0.290 mmol) of Ph_3P, 139 µl (38–40% in toluene, 0.288 mmol) of DEAD, 13 mg (0.220 mmol) of AcOH in 3.5 ml of THF; reaction time: 4 h; purification by CC (*n*-heptane/acetone, 3:1) and prep. HPLC (*n*-heptane/EtOAc, 60:40; 12 ml min^{-1}; t_R = 32.1 min). Yield: 60 mg (56%); colorless oil. $[\alpha]_D^{20}$ = +21.3 (*c* = 1.10, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3H, CH_3COO), 2.12 (ddd, *J* = 13.9, 7.5, 3.0 Hz, 1H, NCHCH_2), 2.27 (dt, *J* = 13.9, 7.5 Hz, 1H, NCHCH_2), 2.64 (dd, *J* = 11.0, 3.3 Hz, 1H, NCH_2CHO), 2.79 (dt, *J* = 12.6, 6.2 Hz, 1H, NC$H_2$$CH_2$), 2.89–2.94 (m, 1H, NC$H_2$$CH_2$), 3.19 (t, *J* = 6.2 Hz, 2H, NCH_2CH_2), 3.48 (dd, *J* = 11.0, 6.2 Hz, 1H, NCH_2CHO), 3.59 (t, *J* = 7.5 Hz, 1H, NC*H*), 3.67 (s, 3H, $COOCH_3$), 3.78 (s, 9H, ArOCH_3), 5.17–5.21 (m, 1H, NCH_2C*H*O), 6.78–6.81 (m, 6H, H_{aromat}), 7.29–7.32 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 1738 cm^{-1}, 1732. $C_{32}H_{37}NO_8$ (563.65).

*6.1.50. Methyl (2*S*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-**25a**]*

According to GP1 from 81 mg (0.410 mmol) of (2*S*,4*R*)-**12**, 129 mg (0.426 mmol) of **RBr** (R = **a**) [11,21], 228 mg (1.65 mmol) of K_2CO_3 and 10 mg of KI; reaction time: 3 d. Yield: 89 mg (59%); colorless oil. $[\alpha]_D^{20}$ = –72.8 (*c* = 0.87, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.83 (ddd, *J* = 13.6, 8.4, 7.0 Hz, 1H, CH_2CHCH_2COO), 1.93 (ddd, *J* = 13.6, 7.0, 3.1 Hz, 1H, CH_2CHCH_2COO), 2.16 (dd, *J* = 10.1, 4.4 Hz, 1H, NCH_2CHOH), 2.19–2.33 (m, 3H, CH_2COO and NCH_2CH_2), 2.39 (ddd, *J* = 12.0, 8.8, 4.9 Hz, 1H, NC$H_2$$CH_2$), 2.58 (dd, *J* = 15.0, 4.2 Hz, 1H, CH_2COO), 2.81 (dt, *J* = 12.0, 7.3 Hz, 1H, NC$H_2$$CH_2$), 3.02–3.09 (m, 1H, NCH), 3.29 (dd, *J* = 10.1, 6.0 Hz, 1H, NCH_2CHOH), 3.62 (s, 3H, OCH_3), 4.29–4.35 (m, 1H, C*H*OH), 6.06 (t, *J* = 7.2 Hz, 1H, =C*H*CH_2), 7.14–7.37 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 1738 cm^{-1}. MS; *m/z* (%): 366 (57) $[M + 1]^+$. $C_{23}H_{27}NO_3$ (365.47).

*6.1.51. Methyl (2*S*,4*R*)-1-[4,4-di(3-methylthien-2-yl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-**25b**]*

According to GP1 from 94 mg (0.480 mmol) of (2*S*,4*R*)-**12**, 156 mg (0.480 mmol) of **RBr** (R = **b**) [10,23], 330 mg (2.40 mmol) of K_2CO_3 and 11 mg of KI in 3 ml of acetone; reaction time: 3 d; purification by CC (*n*-heptane/acetone, 3:1). Yield: 80 mg (41%); slight yellow oil. $[\alpha]_D^{20}$ = –84.6 (*c* = 1.00, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.83 (ddd, *J* = 13.5, 8.3, 7.1 Hz, 1H, CH_2CHCH_2COO), 1.95 (ddd, *J* = 13.5, 7.1, 3.2 Hz, 1H, CH_2CHCH_2COO), 2.00 (s, 3H, thienyl-CH_3), 2.03 (s, 3H, thienyl-CH_3), 2.16–2.32 (m, 4H, NCH_2CHOH, CH_2COO and NCH_2CH_2), 2.41 (ddd, *J* = 11.9, 8.2, 5.0 Hz, 1H, NC$H_2$$CH_2$), 2.62 (dd, *J* = 15.0, 4.0 Hz, 1H, CH_2COO), 2.83 (dt, *J* = 11.9, 8.2 Hz, 1H, NC$H_2$$CH_2$), 3.05–3.12 (m, 1H, NCH), 3.33 (dd, *J* = 10.2, 6.1 Hz, 1H, NCH_2CHOH), 3.65 (s, 3H, OCH_3), 4.32–4.37 (m, 1H, C*H*OH), 6.04 (t, *J* = 7.3 Hz, 1H, =C*H*CH_2), 6.75 (d, *J* = 5.1 Hz, 1H, SC=CH), 6.83 (d, *J* = 5.1 Hz, 1H, SC=CH), 7.04 (d, *J* = 5.1 Hz, 1H, SCH=), 7.20 (d, *J* = 5.1 Hz, 1H, SCH=). IR: $\tilde{\nu}$ = 3410 cm^{-1}, 1738. MS; *m/z* (%): 406 (46) $[M + 1]^+$. $C_{21}H_{27}NO_3S_2$ (405.57).

*6.1.52. Methyl (2*S*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*S*,4*R*)-**25c**]*

According to GP1 from 195 mg (1.00 mmol) of (2*S*,4*R*)-**12**, 457 mg (1.00 mmol) of **RBr** (R = **c**) [11,22], 690 mg (5.00 mmol) of K_2CO_3 and 16 mg of KI in 3 ml of acetone. Yield: 210 mg (39%); colorless oil. $[\alpha]_D^{20}$ = –28.2 (*c* = 1.00, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.81 (ddd, *J* = 13.5, 8.4, 7.0 Hz, 1H, CH_2CHCH_2COO), 1.95 (ddd, *J* = 13.5, 7.0, 3.1 Hz, 1H, CH_2CHCH_2COO), 2.23 (dd, *J* = 15.0, 9.1 Hz, 1H, CH_2COO), 2.32 (dd, *J* = 10.4, 4.4 Hz, 1H, NCH_2CHOH), 2.56–2.66 (m, 2H, CH_2COO and NC$H_2$$CH_2$), 2.93 (dt, *J* = 12.6, 6.3 Hz, 1H, NC$H_2$$CH_2$), 3.10–3.20 (m, 3H, NC*H* and NCH_2CH_2), 3.36 (dd, *J* = 10.4, 5.8 Hz, 1H, NCH_2CHOH), 3.63 (s, 3H, $COOCH_3$), 3.77 (s, 9H, ArOCH_3), 4.33–4.38 (m, 1H, C*H*OH), 6.78–6.82 (m, 6H, H_{aromat}), 7.30–7.34 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 3444 cm^{-1}, 1735. $C_{31}H_{37}NO_7$ (535.64).

*6.1.53. Methyl (2*S*,4*R*)-1-[3-(carbazol-9-yl)-1-propyl]-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-**25d**]*

According to GP1 from 166 mg (0.847 mmol) of (2*S*,4*R*)-**12**, 406 mg (purity: 70%, 0.85 mmol) of **RBr** (R = **d**) [24], 574 mg (1.240 mmol) of K_2CO_3 in 3.5 ml of acetone. Yield: 170 mg (57%); yellowish oil. $[\alpha]_D^{20}$ = –51.0 (*c* = 1.05, EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.89 (ddd, *J* = 13.6, 8.2, 7.0 Hz, 1H, CH_2CHCH_2COO), 1.94–2.11 (m, 3H, CH_2CHCH_2COO and 2H of CHNCH_2CH_2), 2.17–2.24 (m, 2H, CH_2COO and NCH_2CHOH), 2.38 (ddd, *J* = 12.0, 7.1, 4.7 Hz, 1H, CH_2NCH), 2.50 (dd, *J* = 15.0, 4.9 Hz, 1H, CH_2COO), 2.78 (dt, *J* = 12.0, 7.9 Hz, 1H, CH_2NCH), 3.05–3.11 (m, 1H, NCH), 3.40 (dd, *J* = 10.2, 6.0 Hz, 1H, NCH_2CHOH), 3.61 (s, 3H, OCH_3), 4.30 (dt, *J* = 14.9, 7.4 Hz, 1H, CH_2-carbazole), 4.37–4.43 (m, 2H, C*H*OH and CH_2-carbazole), 7.23 (t, *J* = 7.4 Hz, 2H, H_{aromat}), 7.41 (br. d, *J* = 7.9 Hz, 2H, H_{aromat}), 7.44–7.47 (m, 2H, H_{aromat}), 8.10 (br. d, *J* = 7.9 Hz, 2H, H_{aromat}). IR: $\tilde{\nu}$ = 3417 cm^{-1}, 1732. MS; *m/z* (%): 367 (100) $[M + 1]^+$. $C_{22}H_{26}N_2O_3$ (366.46).

*6.1.54. (1*S*,5*S*)-6-(4,4-Diphenylbut-3-en-1-yl)-2-oxa-6-azabicyclo[3.2.1]octane-3-one [(1*S*,5*S*)-**26a**]*

According to GP4 from 97 mg (0.270 mmol) of (2*S*,4*R*)-**8a** and 112 mg (0.411 mmol) of Ph_3P in 5 ml of THF, 198 µl (38–40% in toluene, 0.410 mmol) of DEAD; reaction time: 4 h; purification by CC (*n*-heptane/acetone, 3:1) and prep. HPLC (*n*-heptane/EtOAc, 1:1; 12 ml min^{-1}; t_R = 35.8 min). Yield: 65 mg (76%); colorless crystals, m.p. 72–74 °C. $[\alpha]_D^{20}$ = +4.6 (*c* = 1.00, EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.98 (br. s, 2H, CH_2CHCH_2COO), 2.26 (q, *J* = 7.3 Hz, 2H, NCH_2CH_2), 2.43 (dd, *J* = 18.6, 3.7 Hz, 1H, CH_2COO),

2.67–2.78 (m, 3H, CH_2COO and NCH_2CH_2), 2.95 (d, J = 11.9 Hz, 1H, NCH_2CHO), 3.06 (dd, J = 11.9, 3.7 Hz, 1H, NCH_2CHO), 3.37–3.41 (m, 1H, NCH), 4.84–4.86 (m, 1H, NCH$_2$CHO), 6.09 (t, J = 7.3 Hz, 1H, =CHCH$_2$), 7.15–7.39 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 1732 cm^{-1}. MS; *m/z* (%): 334 (100) [M + 1]$^+$. $C_{22}H_{23}NO_2$ (333.43).

*6.1.55. (1S,5S)-6-[4,4-Di(3-methylthien-2-yl)but-3-en-1-yl]-2-oxa-6-azabicyclo[3.2.1]octane-3-one [(1S,5S)-**26b**]*

According to GP4 from 111 mg (0.284 mmol) of (2*S*,4*R*)-**8b** and 154 mg (0.568 mmol) of Ph_3P in 6 ml of THF, 269 μl (38–40% in toluene, 0.570 mmol) of DEAD; reaction time: 4 h; purification by CC (*n*-heptane/acetone, 3:1) and prep. HPLC (*n*-heptane/EtOAc, 35:65; 12 ml min^{-1}; t_R = 42.7 min). Yield: 74 mg (70%); colorless oil. $[\alpha]_D^{22}$ = +6.9 (*c* = 1.00, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.97–2.00 (m, 2H, CH_2CHCH$_2$COO), 2.00 (s, 3H, thienyl-CH_3), 2.03 (s, 3H, thienyl-CH_3), 2.28 (q, J = 7.3 Hz, 2H, NCH$_2$CH_2), 2.45 (dd, J = 18.7, 3.7 Hz, 1H, CH_2COO), 2.68–2.81 (m, 3H, CH_2COO and NCH_2CH$_2$), 2.97 (br. d, J = 11.9 Hz, 1H, NCH_2CHO), 3.06 (dd, J = 11.9, 3.7 Hz, 1H, NCH_2CHO), 3.38–3.41 (m, 1H, NCH), 4.85–4.87 (m, 1H, NCH$_2$CHO), 6.06 (t, J = 7.3 Hz, 1H, =CHCH$_2$), 6.76 (d, J = 5.2 Hz, 1H, SC=CH), 6.84 (d, J = 5.2 Hz, 1H, SC=CH), 7.05 (d, J = 5.2 Hz, 1H, SCH=), 7.21 (d, J = 5.2 Hz, 1H, SCH=). IR: $\tilde{\nu}$ = 1738 cm^{-1}. MS; *m/z* (%): 374 (32) [M + 1]$^+$. $C_{20}H_{23}NO_2S_2$ (373.53).

*6.1.56. (1S,5S)-6-{2-[Tris(4-methoxyphenyl)methoxy]-1-ethyl}-2-oxa-6-azabicyclo[3.2.1]octane-3-one [(1S,5S)-**26c**]*

According to GP4 from 96 mg (0.18 mmol) of (2*S*,4*R*)-**8c** and 97 mg (0.37 mmol) of Ph_3P in 4 ml of THF, 174 μl (38–40% in toluene, 0.37 mmol) of DEAD; reaction time: 4 h; purification by CC (*n*-heptane/acetone, 3:1) and prep. HPLC (*n*-heptane/EtOAc, 8:2; 12 ml min^{-1}; t_R = 32.4 min). Yield: 43 mg (46%); colorless oil. $[\alpha]_D^{20}$ = +2.4 (*c* = 0.55, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.99 (br. s, 2H, CH_2CHCH$_2$COO), 2.47 (dd, J = 18.6, 3.5 Hz, 1H, CH$_2$COO), 2.82–2.88 (m, 3H, CH_2COO, NCH_2CH$_2$ and NCH_2CHO), 3.07 (d, J = 12.0 Hz, 1H, NCH_2CHO), 3.14–3.18 (m, 3H, NCH_2CH$_2$ and NCH$_2$CH_2), 3.48–3.51 (m, 1H, NCH), 3.78 (s, 9H, ArOCH_3), 4.85–4.87 (m, 1H, NCH$_2$CHO), 6.79–6.83 (m, 6H, H_{aromat}), 7.28–7.32 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 1737 cm^{-1}. $C_{30}H_{33}NO_6$ (503.59).

*6.1.57. (1S,5S)-6-[3-(Carbazol-9-yl)-1-propyl]-2-oxa-6-azabicyclo[3.2.1]octane-3-one [(1S,5S)-**26d**]*

According to GP4 from 142 mg (0.403 mmol) of (2*S*,4*R*)-**8d** and 212 mg (0.806 mmol) of Ph_3P in 8 ml of THF, 383 μl (38–40% in toluene, 0.810 mmol) of DEAD; reaction time: 3 h; purification by CC (*n*-heptane/acetone, 3:2) and prep. HPLC (*n*-heptane/EtOAc, 2:8; 16.5 ml min^{-1}; t_R = 36.0 min). Yield: 55 mg (41%); colorless oil. $[\alpha]_D^{20}$ = +6.2 (*c* = 0.97, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.95–2.07 (m, 4H, CH_2CHCH$_2$COO and CHNCH$_2$CH_2), 2.41–2.51 (m, 2H, CH_2COO and CH_2NCH), 2.58–2.64 (m, 1H, CH_2NCH), 2.73–2.79 (m, 1H, CH$_2$COO), 3.00 (br. d, J = 11.8 Hz, 1H, NCH_2CHO), 3.06 (dd, J = 11.8, 3.5 Hz, 1H, NCH_2CHO), 3.28–3.31 (m, 1H, NCH), 4.36–4.49 (m, 2H, CH_2-carbazole), 4.8–4.91 (m, 1H, NCH$_2$CHO), 7.21–7.26 (m, 2H, H_{aromat}), 7.41–7.48 (m, 4H, H_{aromat}), 8.09–8.12 (m, 2H, H_{aromat}). IR: $\tilde{\nu}$ = 1738 cm^{-1}. MS; *m/z* (%): 335 (100) [M + 1]$^+$. $C_{21}H_{22}N_2O_2$ (334.42).

*6.1.58. (2S,4R)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2S,4R)-**28**]*

According to GP3 from 312 mg (1.06 mmol) of (2*S*,4*R*)-**27** [20]. Yield: 290 mg (98%); colorless oil. $[\alpha]_D^{20}$ = –61.2 (*c* = 1.22, MeOH). Analytical data were identical with those given in the literature {Ref. $[\alpha]_D^{20}$ = –62.4 (*c* = 3, MeOH)} [19a].

*6.1.59. (2R,4R)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2R,4R)-**28**]*

According to GP3 from 86 mg (0.28 mmol) of (2*R*,4*R*)-**21**, 0.57 ml (0.57 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 23 h. Yield: 75 mg (91%); colorless oil. $[\alpha]_D^{20}$ = +17.2 (*c* = 1.41, MeOH). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.11–2.17 (m, 1H, CH_2CHCH$_2$COO), 2.37–2.46 (m, 1H, CH_2CHCH$_2$COO), 3.04 (dd, J = 15.8, 8.9 Hz, 1H, CH$_2$COO), 3.28 (dd, J = 15.8, 3.1 Hz, 1H, CH$_2$COO), 3.59–3.67 (m, 1H, NCH$_2$), 3.79–3.85 (m, 1H, NCH$_2$), 4.44–4.51 (m, 1H, NCH), 4.57–4.62 (m, 1H, CHOH), 5.27 (s, 2H, CH_2Ph), 7.25–7.46 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 3296 cm^{-1}, 1716. MS (EI, 70 eV); *m/z* (%): 279 (5) M$^+$. $C_{14}H_{17}NO_5$ (279.30).

*6.1.60. (2S,4S)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2S,4S)-**28**]*

According to GP3 from 98 mg (0.38 mmol) of (1*S*,5*S*)-**29**, 0.77 ml (0.77 mmol) of aq. 1.0 M NaOH in 8.3 ml of MeOH; reaction time: 4 d. Yield: 98 mg (94%); colorless oil. $[\alpha]_D^{20}$ = –17.6 (*c* = 1.03, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**27**. $C_{14}H_{17}NO_5$ (279.30).

*6.1.61. (2R,4S)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2R,4S)-**28**]*

According to GP3 from 73 mg (0.22 mmol) of (2*R*,4*S*)-**32**, 0.89 ml (0.89 mmol) of aq. 1.0 M NaOH in 9.1 ml of MeOH; reaction time: 3 d. Yield: 60 mg (98%); colorless oil. $[\alpha]_D^{20}$ = +59.6 (*c* = 1.05, MeOH). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.10–2.20 (m, 1H, CH_2CHCH$_2$COO), 2.36–2.44 (m, 1H, CH_2CHCH$_2$COO), 2.72 (dd, J = 15.6, 8.2 Hz, 1H, CH$_2$COO), 3.20 (dd, J = 15.6, 3.8 Hz, 1H, CH$_2$COO), 3.70 (dd, J = 11.5, 4.4 Hz, 1H, NCH$_2$), 3.79 (d, J = 11.5 Hz, 1H, NCH$_2$), 4.53–4.62 (m, 2H, CHOH and NCH), 5.25 (s, 2H, CH_2Ph), 7.24–7.45 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 3423 cm^{-1}, 1704. MS; *m/z* (%): 280 (44) [M + 1]$^+$. $C_{14}H_{17}NO_5$ (279.30).

*6.1.62. Benzyl (1S,5S)-3-oxo-2-oxa-6-azabicyclo[3.2.1]-octane-6-carboxylate [(1S,5S)-**29**]*

According to GP4 from 290 mg (1.04 mmol) of (2*S*,4*R*)-**28**, 491 mg (1.87 mmol) of Ph_3P in 25 ml of THF, 886 µl (38–40% in $PhCH_3$, 1.9 mmol) of DEAD; reaction time: 7 h; purification by CC (*n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 55:45:1.0; 12 ml min^{-1}; t_R = 53.8 min). Yield: 191 mg (70%); colorless oil. $[\alpha]_D^{20}$ = –63.4 (*c* = 1.22, $CHCl_3$). ^1H NMR ($C_6D_5NO_2$, 120°C): δ = 2.19 (br. s, 2H, CH_2CHCH_2COO), 2.70–2.77 (m, 1H, CH_2COO), 3.04 (br. d, *J* = 18.5 Hz, 1H, CH_2COO), 3.67–3.71 (m, 1H, NCH_2), 3.88 (d, *J* = 12.2 Hz, 1H, NCH_2), 4.52 (br. s, 1H, NCH), 5.06 (br. s, 1H, NCH_2CHO), 5.24 (br. s, 2H, CH_2Ph), 7.25–7.44 (m, 5H, H_{aromat}). IR: $\tilde{\nu}$ = 1747 cm^{-1}, 1709. MS; *m/z* (%): 262 (100) $[M + 1]^+$. $C_{14}H_{15}NO_4$ (261.28).

*6.1.63. Ethyl (2R,4R)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetate [(2R,4R)-**30a**]*

According to GP1 from 92 mg (0.440 mmol) of (2*R*,4*R*)-**13**, 132 mg (0.439 mmol) of **RBr** (R = **a**) [11,21], 298 mg (2.160 mmol) of K_2CO_3 and 10 mg of KI in 2.7 ml of acetone. Yield: 115 mg (69%); colorless oil. $[\alpha]_D^{20}$ = +58.9 (*c* = 0.85, EtOAc). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.20 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.69 (ddt, *J* = 14.3, 6.1, 1.7 Hz, 1H, CH_2CHCH_2COO), 2.16 (dd, *J* = 10.0, 4.2 Hz, 1H, NCH_2CHOH), 2.23–2.33 (m, 3H, NCH_2CH_2 and NCH_2CH_2), 2.37 (ddd, *J* = 14.3, 9.2, 6.5 Hz, 1H, CH_2CHCH_2COO), 2.43 (dd, *J* = 15.3, 7.8 Hz, 1H, CH_2COO), 2.62 (dd, *J* = 15.3, 3.3 Hz, 1H, CH_2COO), 2.63–2.70 (m, 2H, NCH and OH), 2.80–2.90 (m, 1H, NCH_2CH_2), 2.99 (d, *J* = 10.0 Hz, 1H, NCH_2CHOH), 4.05–4.15 (m, 3H, CHOH and CH_2CH_3), 6.05–6.09 (m, 1H, $=CHCH_2$), 7.14–7.37 (m, 10H, H_{aromat}). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.2 (CH_3), 28.8 (NCH_2CH_2), 38.8 (CH_2COO), 40.9 (1 C, CH_2CHCH_2COO), 53.3 (NCH_2CH_2), 59.5 (NCH), 60.4 (OCH_2CH_3), 62.1 (NCH_2CHO), 70.1 (CHOH), 127.0, 127.1 (2 C, C_{aromat}), 127.3 ($=CHCH_2$), 128.2, 128.3 (4 C, C_{aromat}), 129.9 (4 C, C_{aromat}), 140.0 (2 C, $C=CHCH_2$), 142.5 142.7 (2 C, C_{aromat}), 172.3 (COO). IR: $\tilde{\nu}$ = 3415 cm^{-1}, 1731. MS; *m/z* (%): 380 (82) $[M + 1]^+$. $C_{24}H_{29}NO_3$ (379.50).

*6.1.64. Ethyl (2R,4R)-1-[4,4-di(3-methylthien-2-yl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetate [(2R,4R)-**30b**]*

According to GP1 from 92 mg (0.440 mmol) of (2*R*,4*R*)-**13**, 143 mg (0.439 mmol) of **RBr** (R = **b**) [10,23], 298 mg (2.160 mmol) of K_2CO_3 and 10 mg of KI in 2.7 ml of acetone. Yield: 95 mg (52%); yellow oil. $[\alpha]_D^{20}$ = +69.8 (*c* = 0.80, EtOAc). ^1H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.69 (ddt, *J* = 14.3, 6.1, 1.7 Hz, 1H, CH_2CHCH_2COO), 1.99 (s, 3H, thienyl-CH_3), 2.04 (s, 3H, thienyl-CH_3), 2.20 (dd, *J* = 10.0, 4.1 Hz, 1H, NCH_2CHOH), 2.25–2.40 (m, 4H, NCH_2CH_2, CH_2CHCH_2COO and NCH_2CH_2), 2.43 (dd, *J* = 15.4, 7.8 Hz, 1H, CH_2COO), 2.52 (br. s, 1H, OH), 2.62–2.72 (m, 2H, NCH and CH_2COO), 2.81–2.92 (m, 1H, NCH_2CH_2), 3.01 (br. d, *J* = 10.0 Hz, 1H, NCH_2CHOH), 4.05–4.18 (m, 3H, CHOH and 2H of CH_2CH_3), 6.03–6.07 (m, 1H, $=CHCH_2$), 6.75 (d, *J* = 5.2 Hz, 1H, SC=CH), 6.84 (d, *J* = 5.2 Hz, 1H, SC=CH), 7.04 (d, *J* = 5.2 Hz, 1H, SCH=), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=). IR: $\tilde{\nu}$ = 3433 cm^{-1}, 1732. MS; *m/z* (%): 420 (29) $[M + 1]^+$. $C_{22}H_{29}NO_3S_2$ (419.60).

*6.1.65. Ethyl (2R,4R)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2R,4R)-**30c**]*

According to GP1 from 136 mg (0.608 mmol) of (2*R*,4*R*)-**13**, 278 mg (0.608 mmol) of **RBr** (R = **c**) [11,22], 420 mg (3.040 mmol) of K_2CO_3 and 15 mg of KI in 4 ml of acetone. Yield: 175 mg (52%); colorless oil. $[\alpha]_D^{20}$ = +22.5 (*c* = 1.65, EtOAc). ^1H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.69 (ddt, *J* = 14.2, 6.2, 1.7 Hz, 1H, CH_2CHCH_2COO), 2.29 (dd, *J* = 10.1, 4.2 Hz, 1H, NCH_2CHOH), 2.38 (ddd, *J* = 14.2, 9.5, 6.6 Hz, 1H, CH_2CHCH_2COO), 2.41–2.48 (m, 2H, NCH_2CH_2 and CH_2COO), 2.64 (dd, *J* = 15.8, 3.4 Hz, 1H, CH_2COO), 2.70–2.77 (m, 1H, NCH), 2.96 (dt, *J* = 12.6, 6.3 Hz, 1H, NCH_2CH_2), 3.05 (br. d, *J* = 10.1 Hz, 1H, NCH_2CHOH), 3.12 (dt, *J* = 9.5, 5.8 Hz, 1H, NCH_2CH_2), 3.19 (dt, *J* = 9.5, 6.1 Hz, 1H, NCH_2CH_2), 3.77 (s, 9H, $ArOCH_3$), 4.01–4.14 (m, 2H, CH_2CH_3), 4.13–4.18 (m, 1H, CHOH), 6.79–6.82 (m, 6H, H_{aromat}), 7.30–7.33 (m, 6 H, H_{aromat}). IR: $\tilde{\nu}$ = 3440 cm^{-1}, 1731. $C_{32}H_{39}NO_7$ (549.66).

*6.1.66. Ethyl (2R,4R)-1-[3-(carbazol-9-yl)-1-propyl]-4-hydroxypyrrolidine-2-acetate [(2R,4R)-**30d**]*

According to GP1 from 122 mg (0.528 mmol) of (2*R*,4*R*)-**13**, 279 mg (purity: 70%, 0.53 mmol) of **RI** (R = **d**) [25] and 400 mg (2.910 mmol) of K_2CO_3 in 3 ml of acetone. Yield: 8.2 g; yellow oil [purity: 70% (w/w); I/Cl = 1.6:1 (mol/mol), determined by ^1H NMR].Yield: 193 mg (87%); colorless oil. $[\alpha]_D^{20}$ = +56.8 (*c* = 0.96, EtOAc). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.74 (ddt, *J* = 14.3, 6.2, 1.7 Hz, 1H, CH_2CHCH_2COO), 1.99–2.14 (m, 2H, $CHNCH_2CH_2$), 2.21 (dd, *J* = 10.0, 4.1 Hz, 1H, NCH_2CHOH), 2.23–2.29 (m, 1H, CH_2NCH), 2.38–2.46 (m, 2H, CH_2CHCH_2COO and CH_2COO), 2.56 (dd, *J* = 15.6, 3.6 Hz, 1H, CH_2COO), 2.64–2.71 (m, 1H, NCH), 2.84 (ddd, *J* = 15.9, 8.7, 7.3 Hz, 1H, CH_2NCH), 3.11 (br. d, *J* = 10.0 Hz, 1H, NCH_2CHOH), 4.07–4.17 (m, 2H, CH_2CH_3), 4.19–4.23 (m, 1H, CHOH), 4.28–4.35 (m, 1H, CH_2-carbazole), 4.42–4.49 (m, 1H, CH_2-carbazole), 7.25 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 2H, H_{aromat}), 7.44 (br. d, *J* = 8.0 Hz, 2H, H_{aromat}), 7.49 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 2H, H_{aromat}), 8.12 (br. d, *J* = 8.0 Hz, 2H, H_{aromat}). IR: $\tilde{\nu}$ = 3427 cm^{-1}, 1732. MS; *m/z* (%): 381 (27) $[M + 1]^+$. $C_{23}H_{28}N_2O_3$ (380.49).

*6.1.67. Ethyl (2R,4S)-4-acetoxy-1-(4,4-diphenylbut-3-en-1-yl)pyrrolidine-2-acetate [(2R,4S)-**31a**]*

According to GP4 from 50 mg (0.13 mmol) of (2*R*,4*R*)-**30a** and 52 mg (0.20 mmol) of Ph_3P in 2 ml of THF, 94 µl (38–40% in toluene, 0.20 mmol) of DEAD and 11 mg

(0.18 mmol) of AcOH; reaction time: 23 h; purification (*n*-heptane/EtOAc, 3:1) and prep. HPLC (*n*-heptane/EtOAc, 75:25; 12 ml min^{-1}; t_R = 37.8 min). Yield: 40 mg (72%); colorless oil. $[\alpha]_D^{20}$ = +57.9 (*c* = 0.98, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.89 (ddd, *J* = 13.9, 9.0, 7.6 Hz, 1H, CH_2CHCH_2COO), 2.01 (s, 3H, CH_3COO), 2.06 (ddd, *J* = 13.9, 6.6, 2.6 Hz, 1H, CH_2CHCH_2COO), 2.17–2.40 (m, 5H, NCH_2CHO, NCH_2CH_2, CH_2COO and NCH_2CH_2), 2.61 (dd, *J* = 15.0, 4.2 Hz, 1H, CH_2COO), 2.80–2.87 (m, 1H, NCH_2CH_2), 2.97–3.04 (m, 1H, NCH), 3.42 (dd, *J* = 10.8, 6.4 Hz, 1H, NCH_2CHO), 4.05–4.17 (m, 2H, CH_2CH_3), 5.06–5.11 (m, 1H, NCH_2CHO), 6.06 (t, *J* = 7.2 Hz, 1H, =$CHCH_2$), 7.14–7.38 (m, 10H, H_{aromat}). IR: $\tilde{\nu}$ = 1740 cm^{-1}, 1732. MS; *m/z* (%): 422 (46), $[M + 1]^+$. $C_{26}H_{31}NO_4$ (421.54).

*6.1.68. Ethyl (2*R*,4*S*)-4-acetoxy-1-[4,4-di(3-methylthien-2-yl)but-3-en-1-yl]pyrrolidine-2-acetate [(2*R*,4*S*)-**31b**]*

According to GP4 from 117 mg (0.279 mmol) of (2*R*,4*R*)-**30b** and 108 mg (0.419 mmol) of Ph_3P in 4 ml of THF, 199 μl (38–40% in toluene, 0.420 mmol) of DEAD and 24 mg (0.400 mmol) of AcOH; reaction time: 3 h; purification by CC (*n*-heptane/EtOAc, 4:1) and prep. HPLC (*n*-heptane/EtOAc, 75:25; 12 ml min^{-1}; t_R = 27.3 min). Yield: 81 mg (63%); colorless oil. $[\alpha]_D^{20}$ = +86.8 (*c* = 0.94, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.87 (ddd, *J* = 13.9, 9.0, 7.6 Hz, 1H, CH_2CHCH_2COO), 2.00–2.09 (m, 10H, CH_2CHCH_2COO, CH_3COO and 2 × thienyl-CH_3), 2.18–2.42 (m, 5H, NCH_2CHO, NCH_2CH_2, CH_2COO and NCH_2CH_2), 2.63 (dd, *J* = 15.1, 4.2 Hz, 1H, CH_2COO), 2.83 (dt, *J* = 11.5, 8.1 Hz, 1H, NCH_2CH_2), 2.97–3.05 (m, 1H, NCH), 3.44 (dd, *J* = 10.8, 6.4 Hz, 1H, NCH_2CHO), 4.12 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 5.06–5.11 (m, 1H, NCH_2CHO), 6.02 (t, *J* = 7.2 Hz, 1H, =$CHCH_2$), 6.75 (d, *J* = 5.1 Hz, 1H, SC=CH), 6.83 (d, *J* = 5.1 Hz, 1H, SC=CH), 7.05 (d, *J* = 5.1 Hz, 1H, SCH=), 7.20 (d, *J* = 5.1 Hz, 1H, SCH=). IR: $\tilde{\nu}$ = 1738 cm^{-1}, 1732. MS; *m/z* (%): 462 (12) $[M + 1]^+$. $C_{24}H_{31}NO_4S_2$ (461.64).

*6.1.69. Ethyl (2*R*,4*S*)-4-acetoxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*R*,4*S*)-**31c**]*

According to GP4 from 147 mg (0.267 mmol) of (2*R*,4*R*)-**30c** and 105 mg (0.401 mmol) of Ph_3P in 5 ml of THF, 190 μl (38–40% in toluene, 0.400 mmol) of DEAD and 19 mg (0.320 mmol) of AcOH; reaction time: 2 h; purification by CC (*n*-heptane/acetone, 3:1) and prep. HPLC (*n*-heptane/EtOAc, 60:40; 12 ml min^{-1}; t_R = 32.1 min). Yield: 50 mg (32%); colorless oil. $[\alpha]_D^{20}$ = +23.4 (*c* = 1.51, EtOAc). ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.86 (ddd, *J* = 13.9, 9.1, 7.4 Hz, 1H, CH_2CHCH_2COO), 2.01 (s, 3H, CH_3COO), 2.06 (ddd, *J* = 13.9, 6.6, 2.6 Hz, 1H, CH_2CHCH_2COO), 2.21 (dd, *J* = 15.1, 9.1 Hz, 1H, CH_2COO), 2.34 (dd, *J* = 10.9, 4.4 Hz, 1H, NCH_2CHO), 2.48–2.55 (m, 1H, NCH_2CH_2), 2.65 (dd, *J* = 15.1, 4.1 Hz, 1H, CH_2COO), 2.90–2.97 (m, 1H, NCH_2CH_2), 3.03–3.18 (m, 3H, NCH and NCH_2CH_2), 3.46 (dd, *J* = 10.9, 6.3 Hz, 1H, NCH_2CHO), 3.78 (s, 3H, $ArOCH_3$), 4.06–4.14 (m, 2H, CH_2CH_3), 5.06–5.12 (m, 1H, NCH_2CHO), 6.78–6.82 (m, 6H, H_{aromat}), 7.29–7.33 (m, 6H, H_{aromat}). IR: $\tilde{\nu}$ = 1733 cm^{-1}. $C_{34}H_{41}NO_8$ (591.70).

*6.1.70. Ethyl (2*R*,4*S*)-4-acetoxy-1-[3-(carbazol-9-yl)-1-propyl]pyrrolidine-2-acetate [(2*R*,4*S*)-**31d**]*

According to GP4 from 110 mg (0.289 mmol) of (2*R*,4*R*)-**30d** and 152 mg (0.578 mmol) of Ph_3P in 4 ml of THF, 269 μl (38–40% in toluene, 0.580 mmol) of DEAD and 26 mg (0.430 mmol) of AcOH; reaction time: 3 h; purification by CC (*n*-heptane/acetone, 4:1) and prep. HPLC (*n*-heptane/EtOAc, 60:40; 12 ml min^{-1}; t_R = 34.2 min). Yield: 104 mg (85%); colorless oil. $[\alpha]_D^{20}$ = +43.6 (*c* = 1.04, EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.93–2.12 (m, 7H, CH_2CHCH_2COO, $CHNCH_2CH_2$ and CH_3COO), 2.19 (dd, *J* = 15.0, 8.6 Hz, 1H, CH_2COO), 2.29 (dd, *J* = 10.8, 4.3 Hz, 1H, NCH_2CHO), 2.32–2.35 (m, 1H, CH_2NCH), 2.48 (dd, *J* = 15.0, 4.4 Hz, 1H, CH_2COO), 2.77 (dt, *J* = 12.1, 7.8 Hz, 1H, CH_2NCH), 3.00–3.05 (m, 1H, NCH), 3.53 (dd, *J* = 10.8, 6.3 Hz, 1H, NCH_2CHO), 4.08 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.29–4.35 (m, 1H, CH_2-carbazole), 4.37–4.43 (m, 1H, CH_2-carbazole), 5.14–5.18 (m, 1H, NCH_2CHO), 7.21–7.25 (m, 2H, H_{aromat}), 7.41–7.42 (m, 2H, H_{aromat}), 7.45–7.48 (m, 2H, H_{aromat}), 8.09–8.11 (m, 2H, H_{aromat}). IR: $\tilde{\nu}$ = 1737 cm^{-1}, 1732. MS; *m/z* (%): 423 (100) $[M + 1]^+$. $C_{25}H_{30}N_2O_4$ (422.53).

*6.1.71. Ethyl (2*R*,4*S*)-1-benzyloxycarbonyl-4-formyloxypyrrolidine-2-acetate [(2R,4S)-**32**]*

According to GP4 from 106 mg (0.345 mmol) of (2*R*,4*R*)-**21** and 135 mg (0.517 mmol) of Ph_3P in 5 ml of THF, 245 μl (38–40% in toluene, 0.720 mmol) of DEAD; reaction time: 16 h; purification by CC (*n*-heptane/acetone, 3:1) and prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 78:22:0.8; 12 ml min^{-1}; t_R = 22.7 min). Yield: 92 mg (80%); colorless oil. $[\alpha]_D^{20}$ = +36.4 (*c* = 1.64, $CHCl_3$). ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 1.21–1.26 (m, 3H, CH_2CH_3), 2.25–2.33 (m, 1H, CH_2CHCH_2COO), 2.41–2.49 (m, 1H, CH_2CHCH_2COO), 2.64–2.72 (m, 1H, CH_2COO), 3.04–3.10 (m, 1H, CH_2COO), 3.75–3.80 (m, 1H, NCH_2), 3.89 (d, *J* = 12.1 Hz, 1H, NCH_2), 4.13–4.20 (m, 2H, CH_2CH_3), 4.45–4.52 (m, 1H, NCH), 5.26 (s, 2H, CH_2Ph), 5.45–5.49 (m, 1H, NCH_2CHO), 7.27–7.36, 7.40–7.44 (m, 5H, H_{aromat}), 8.03 (s, 1H, HCOO). IR: $\tilde{\nu}$ = 1728 cm^{-1}, 1705. MS; *m/z* (%): 308 (79). $C_{17}H_{21}NO_6$ (335.36).

6.2. Biological test

6.2.1. Preparation of subcellular membrane suspensions

Two subcellular membrane pellets, termed bfcP2B (from bovine frontal cortex)[a] and bbsP2C (from bovine brain stem)[b], respectively, were prepared according to literature [20]. Their suspensions were prepared and measured as described by Bradford [26]. cfcP2B (from calf frontal cortex)[c] and cbsP2C (from calf brain stem)[d], pfcP2B (from porcine frontal cor-

tex)[e] and pbsP2C (from porcine brain stem)[f] were applied alternatively instead of bfcP2B and bbsP2C, respectively.

6.2.2. Inhibition of GAT-1 mediated GABA-uptake

Aliquots of about 50–100 μg protein bfcP2B (alternatively cfcP2B or pfcP2B) were preincubated with 10 μM aminooxyacetic acid and a test compound in 200 μl of buffer (119 mM NaCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.7 mM KCl, 11 mM glucose and 25 mM Tris–HCl pH 7.2) for 10 min at 37 °C. 25 μl of 12.5 nM [^{3}H] GABA and 25 μl of 250 nM GABA were added and the sample was incubated at 37 °C for 4 min. The incubation was terminated by filtration in a Brandel M-24R Harvester through Whatman GF/C filters, which had been immersed in 0.9% NaCl for 1 h. The filters were washed with 0.9% NaCl (4 × 2 ml) and then measured in 3 ml of Rotiszint Eco Plus by the use of a Packard TriCarb 1600 Counter. Specific uptake was defined as difference between entire uptake and non-specific uptake, which was determined with identical samples lacking NaCl.

6.2.3. Inhibition of GAT-3 mediated GABA-uptake

Aliquots of about 50–100 μg protein bbsP2C (alternatively cbsP2C or pbsP2C) were preincubated with 10 μM aminooxyacetic acid, 10 μM NNC-711 and a test compound in 200 μl of buffer (119 mM NaCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.7 mM KCl, 11 mM glucose and 25 mM Tris–HCl pH 7.2) for 10 min at 37 °C. Next, 25 μl of 50 nM [^{3}H] GABA and 25 μl of 1 μM GABA were added and the sample was incubated for 4 min at 37 °C. The subsequent procedure was the same as described above in Section 6.2.2.

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