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Preparation of Novel Lipophilic GABA Analogues Containing Cyclopropane Rings via Cyclopropanation of *N*-Silylated Unsaturated Amines

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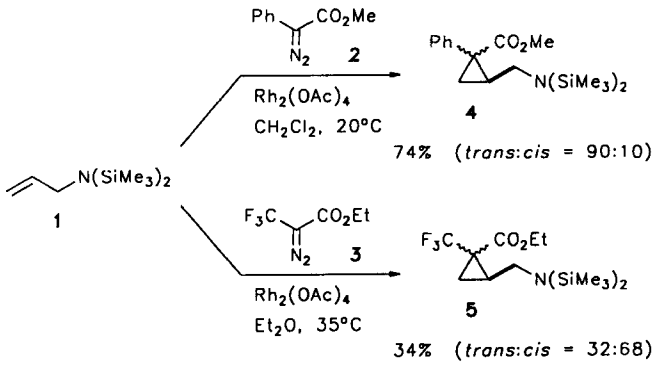
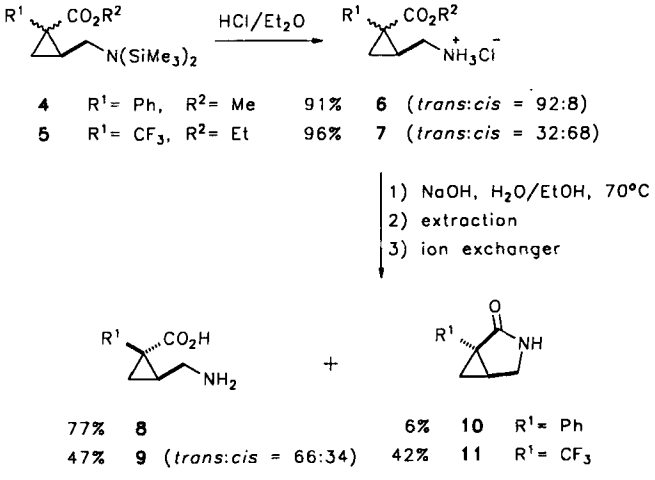
Abstract. Novel lipophilic γ-amino acids **8** and **9** analogous to GABA containing cyclopropane rings are synthesized by Rh(II)-catalyzed reaction of diazo compounds **2** and **3** with *N,N*-bis(trimethylsilyl)allylamine (**1**) and subsequent hydrolysis. In addition, routes are described leading to the vinylogous GABA analogue **15** and to the unusual tricyclic γ-amino acid **20**.

Analogues of the important inhibitory neurotransmitter γ-aminobutyric acid (GABA) are compounds of high pharmacological interest [1]. Recently we succeeded in the synthesis of cyclopropyl and cyclopropenyl substituted GABA analogues via rhodium acetate catalyzed reactions of β,γ-unsaturated, *N*-silylated amines such as **1** and methyl diazoacetate [2, 3]. Here we report on the synthesis of GABA analogues with rigid conformations and substitution patterns which enhance the lipophilicity of these amino acids. This property is considered decisive for their potential as pharmaceuticals [4–9]. To achieve this goal we have extended our previous synthetic route by varying the diazo component or the *N*-silylated amine. The reaction of methyl phenyldiazoacetate (**2**) [10] or ethyl trifluoromethyldiazoacetate (**3**) [11], respectively, with *N,N*-bis(trimethylsilyl)allylamine (**1**) [2] under Rh(II) catalysis afforded the cyclopropane derivatives **4** and **5**.



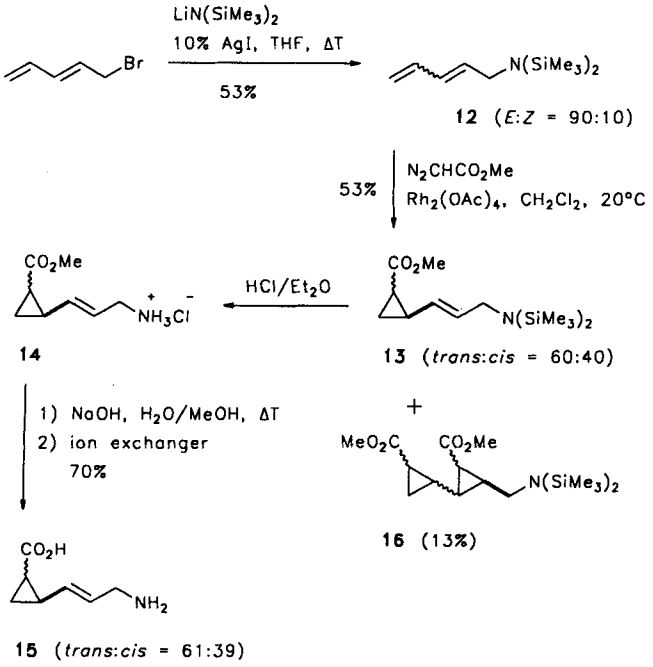
Diazo compound **2** reacted with remarkable diastereoselectivity (*trans:cis* = 90:10) in 74 % yield, while the CF_3-substituted diazo component **3** and **1** gave by far lower selectivity (*trans:cis* = 32:68) and yield (34 %) (*trans* and *cis* always refer to the aminomethyl and carboxylic substituent). It is noteworthy that the reaction of **3** only proceeded smoothly in refluxing diethylether, and it is the only case on which the *cis*-isomer was formed in excess. The stereochemical assignment of **4** and **5** by NMR spectroscopy was not unambiguous. However, the stereochemistry was ascertained for products obtained after desilylation and hydrolysis (vide infra).

For liberation of the amino acids **8** and **9**, desilylation was performed with saturated HCl/diethylether at room temperature. The hydrochlorides **6** and **7** obtained in excellent yield were exposed to alkaline conditions (aqueous NaOH, 70 °C). This treatment finally led to instantaneous formation of γ-lactams from *cis*-configurated precursors and to the formation of the desired γ-amino carboxylates from *trans*-configurated starting materials [2].

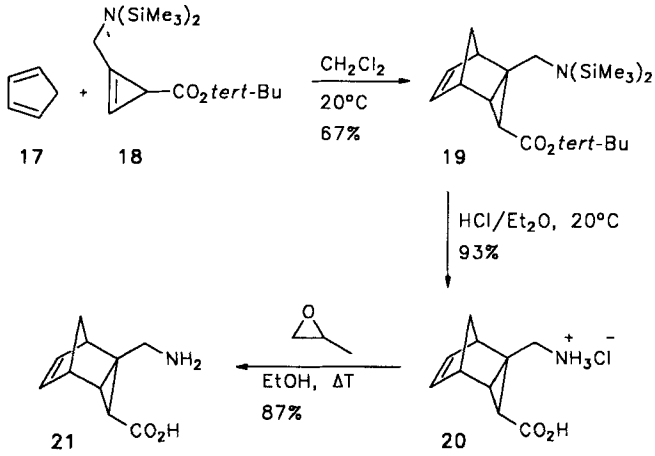


The lactams were easily separated by extraction of the alkaline reaction mixture. The amino acids were liberated and isolated after ion exchanger treatment. The mild reaction conditions employed allowed to utilize the different stability of amides or lactams and carboxylic esters towards hydrolysis. In most cases, we exclusivly obtained *trans*-configurated amino acids. The CF_3-group in lactam **11**, however, seems to activate the carboxylic function in a way sufficient for partial hydrolysis under the applied reaction conditions to provide *cis*-**9**. This was the only example were we obtained more amino acid than expected considering the content of *trans*-configurated esters. All γ-amino acids described in this paper show a rather low tendency to crystallize. They usually occur as hydrates (compare with reference [12]) which slowly lose the crystal water while being heated in vacuo.

The vinylogous GABA analogue **15** was obtained in a similar reaction sequence via **13** and **14** starting from *N*-silylated pentadienylamine **12** and methyl diazoacetate. Compound **12** was accessible as a mixture of *E*/*Z*-isomers (90/10) from pentadienylbromide [13] by employing Murai's [14] AgI-catalyzed substitution reaction with lithiated hexamethyldisilazane. The cyclopropanation occurred with remarkably high regioselectivity and we isolated only products derived from cycloaddition to the δ,ε-double bond of *E*-**12**. In addition to **13** bisadduct **16** was obtained in 13 % yield as byproduct. Unambiguous assignment by NMR data was not possible for **16** due to the multitude of occurring diastereomers. Not unexpectedly [2] the *trans*/*cis*-selectivity for formation of **13** is rather low (60/40).



An additional access to lipophilic GABA analogues consists in the smooth and diastereoselective [4 + 2] cycloaddition of cyclopropene derivative **18** to cyclopentadiene. As previously reported, *N*-silylated propargylamine [15] can be cyclopropenated in surprisingly high yield with methyl and *tert*-butyl diazoacetate in the presence of $Rh_2(OAc)_4$ [3]. *tert*-Butyl ester **18** reacted with cyclopentadiene to give only one of four diastereomers of the tricyclic compound **19** in satisfactory yield. The configuration of this cycloadduct was elucidated from ^{1}H-NMR data (COSY-spectra and NOE-experiments) in analogy to the closely related methyl ester [3]. Use of *tert*-butyl esters **18** and **19** was crucial for the synthesis of GABA analogue **21** which is only accessible under acidic conditions via hydrochloride **20**. Tricyclic γ-amino acid **21** was liberated in excellent yield by heating the corresponding hydrochloride with propene oxide in ethanol [16]. Starting with the methyl ester analogue of **19** we obtained only a tetracyclic γ-lactam during hydrolysis under alkaline conditions [3].



The presented examples demonstrate that the route via cyclopropanation or cyclopropenation of *N*-silylated unsaturated amines offers a very versatile access to conformationally rigid lipophilic amino acids analogous to GABA, thus offering new possibilities for additional studies concerning structure-activity relationships and the biological activity of these compounds [17, 18].

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Experimental

^{1}H NMR and ^{13}C NMR spectra were measured as $CDCl_3$ $SO(CD_3)_2$, or D_2O solutions at 300 and 75.5 MHz. *J* values are given in Hz. IR spectra were measured with KBr pellets or films. The melting points are uncorrected. Boiling points correspond to the temperature in the oven of a bulb-to-bulb distillation apparatus (Kugelrohr oven). All solvents were dried by standard methods. The experiments were carried out under exclusion of moisture.

General Procedure (A) for the Cyclopropanation of N-Silylated Unsaturated Amines

1 equivalent of *N*-silylated unsaturated amine was mixed with

1.5 mol-% of $Rh_2(OAc)_4$ (1 mol-% with regard to the diazo component) and dichloromethane (1 ml/5 mmol). To this suspension a solution of 1.5–2 equivalents of diazo component in dichloromethane (1 ml/5 mmol) was slowly added (3–4 h) while stirring vigorously at room temperature. After stirring for an additional hour at room temperature, the reaction mixture was concentrated in vacuo. A small amount of NEt_3 (0.05 ml/mmol amine) was added to the resulting crude product, before it was filtrated over neutral alumina (activity III; 2 g/mmol amine) with *n*-pentane. The solvent was removed under reduced pressure and the residue was distilled in a Kugelrohr apparatus.

Methyl 2-[N,N-bis(trimethylsilyl)aminomethyl]-1-phenyl-1-cyclopropanecarboxylate (**4**)

7.81 g (38.8 mmol) of allylamine **1**, 10.3 g (58.5 mmol) of diazo component **2**, and 0.227 g (0.514 mmol) of $Rh_2(OAc)_4$ were reacted according to general procedure **A**. Bulb-to-bulb distillation (110 °C/0.01 Torr) afforded 10.0 g (74 %) of **4** (*trans:cis* = 90:10) that slowly turned into a colourless wax-like solid (m.p. 32–35 °C). ^1H NMR ($CDCl_3$): δ 7.39–7.13 (m, 5H), 3.56*, 3.55 (2s, 3H), 3.32* (dd, *J* = 15, 3, 0.1H), 3.06 (br.d, *J* = 14.5, 0.9H), 2.95* (dd, *J* = 15, 8, 0.1H), 1.88–1.70 (m, 2.9H), 1.37* (dd, *J* = 9, 4, 0.1H), 1.31 (dd, *J* = 6.5, 4, 0.9H), 0.15*, 0.06 (2s, 18H). ^{13}C NMR ($CDCl_3$): δ 174.3, 172.4* (2s), 140.8*, 135.5, 130.8, 129.9, 129.0*, 128.1*, 127.0, 126.9* (2s, 6d), 52.1, 51.9* (2q), 46.3, 43.9* (2t), 35.1*, 33.4 (2s), 33.2*, 31.1 (2d), 22.4, 22.2* (2t), 2.2 (q). * refers to the minor diastereoisomer. IR (film) 3050–2840 (C-H), 1720 (C=O), 1250 (Si-C). Anal. Calcd. for $C_{18}H_{31}NO_2Si_2$ (349.6): C, 61.84; H, 8.94; N, 4.01. Found: C, 61.78; H, 8.76; N, 3.91.

Ethyl 2-[N,N-bis(trimethylsilyl)aminomethyl]-1-trifluoromethyl-1-cyclopropanecarboxylate (**5**)

5.96 g (29.6 mmol) of allylamine **1**, 2.18 g (12.0 mmol) of diazo component **3**, and 0.053 g (0.120 mmol) of $Rh_2(OAc)_4$ were reacted in refluxing diethylether instead of dichloromethane according to general procedure **A**. Bulb-to-bulb distillation (80 °C/0.08 Torr) afforded 1.47 g (34 %) of **5** (*trans:cis* = 32:68). ^1H NMR ($CDCl_3$): δ 4.29–4.17 (m, 2H), 3.30* (br.d, *J* = 15, 0.32H), 3.10, 2.84–2.78 (m_c, m, 1.68H), 1.62–1.14 (m, 5.68H), 1.73* (dd, *J* = 9, 4, 0.32H), 0.11 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 168.2*, 166.6 (2s), 124.8*, 124.4 (2q, *J** = 274, *J* = 273), 61.7 (t), 43.1*, 42.9 (2t), 32.2, 31.7* (2q, *J* = *J** = 34), 32.8*, 29.3 (2d), 19.6*, 18.5 (2t), 14.0 (q), 2.0 (q). * refers to the minor diastereoisomer. IR (film) 3000–2840 (C-H), 1730 (C=O), 1245 (Si-C). Anal. Calcd. for $C_{14}H_{28}F_3NO_2Si_2$ (355.5): C, 47.30; H, 7.94; N, 3.94. Found: C, 47.66; H, 7.78; N, 3.61.

General Procedure (B) for the Desilylation with HCl-Saturated Diethylether

After dissolving the *N*-silylated cyclopropane derivate in diethylether (1 ml/mmol) a saturated solution of dry HCl in diethylether (1–2 ml/mmol) was slowly added at room temperature. The corresponding hydrochlorides commonly immediately precipitated. The reaction mixture was stirred for an additional hour at room temperature and the products were isolated by filtration or by removal of volatile components in vacuo. If necessary the crude products were recrystallized from ethanol/diethylether (1/2).

Methyl 2-aminomethyl-1-phenyl-1-cyclopropanecarboxylate hydrochloride (**6**)

1.24 g (calculated yield 91 %; compound still contained 15 mol-% EtOH according ^1H NMR) of **6** [*trans:cis* = 92:8; m.p. 188–190 °C (dec.)] was obtained from 1.89 g (5.41 mmol) of **4** (*trans:cis* = 90:10) by following general procedure **B**. A second recrystallization afforded pure *trans*-**6** [m.p. 192–194 °C (dec.)]. ^1H NMR [$SO(CD_3)_2$] *trans*-**6**: δ 8.32 (br.s, 3H), 7.31 (s, 5H), 3.53 (s, 3H), 2.93 (dd, *J* = 12.5, 4.5, 1H), 2.14–2.07 (m, 1H), 1.72 (dd, *J* = 12.5, 10.5, 1H), 1.60 (dd, *J* = 8.5, 5, 1H), 1.51 (dd, *J* = 6, 5, 1H). ^{13}C NMR [$SO(CD_3)_2$]: δ 173.2 (s), 134.8, 131.2, 128.4, 127.6 (s, 3d), 52.4 (q), 39.4 (t), 33.6 (s), 23.8 (d), 20.1 (t). IR (KBr) 3300–2800 (N-H, C-H), 1715 (C=O). Anal. Calcd. for $C_{12}H_{16}ClNO_2$ (241.7): C, 59.63; H, 6.67; N, 5.80. Found: C, 59.22; H, 6.84; N, 5.55.

Ethyl 2-aminomethyl-1-trifluoromethyl-1-cyclopropanecarboxylate hydrochloride (**7**)

0.053 g (96 %) of **7** [*trans:cis* = 32:68; m.p. 122-125 °C (dec.)] was obtained from 0.079 g (0.222 mmol) of **5** (*trans:cis* = 32:68) by following general procedure **B**. ^1H NMR [$SO(CD_3)_2$]: δ 8.48 (br.s, 3H), 4.31–4.13 (m, 2H), 3.23* (dd, *J* = 13, 4, 0.32H), 3.14 (dd, *J* = 13, 6, 0.68H), 2.91 (dd, *J* = 13, 8, 0.68H), 2.76* (m_c, 0.32H), 2.13 (m_c, 1H), 1.72–1.55 (m, 1H), 1.23, 1.20* (2d, *J* = 7, 3H). ^{13}C NMR [$SO(CD_3)_2$]: δ 166.7*, 165.6 (2s), 124.6*, 124.2 (2q, *J** = *J* = 273), 62.3, 62.1 (2t), 36.7*, 36.4 (2t), 30.8, 30.7* (2q, *J* = *J** = 33), 24.4*, 21.9 (2d), 17.7*, 16.9 (2t), 13.9 (q). * refers to the minor diastereoisomer. IR (KBr) 3400–2500 (N-H, C-H), 1730 (C=O), 1140, 1120 (C-F). Anal. Calcd. for $C_8H_{13}ClF_3NO_2$ (247.6): C, 38.81; H, 5.29; N, 5.66. Found: C, 38.60; H, 5.16; N, 5.58.

General Procedure (C) for the Liberation of Amino Acids

The hydrochlorides of the alkyl aminomethyl cyclopropanecarboxylates were dissolved in a mixture of 1N NaOH and methanol (1/1; 4 ml/mmol ester) and heated to 60–70 °C for 20 minutes. Methanol was removed under reduced pressure and the aqueous solution was extracted with dichloromethane (3 × 2–3 ml/mmol) and ethyl acetate (2 × 2–3 ml/mmol). The combined organic phases were dried with Na_2SO_4 and the solvents were removed in vacuo thus affording the γ-lactams derived from the *cis*-configurated precursors in pure form. For further purification the lactams were recrystallized from ethyl acetate. – The aqueous reaction mixture was concentrated under reduced pressure. The residue was dissolved in a small amount of water and the amino acids were liberated by treatment with an ion exchanger resin (3–4 g Lewatit S 100 or Amberlite IR 120/mmol amino acid; 1N NH_3-solution as eluent). After removal of solvents the amino acids were obtained as sticky yellow solids which were recrystallized.

trans-2-Aminomethyl-1-phenyl-1-cyclopropanecarboxylic acid (**8**) *and 1-phenyl-3-azabicyclo[3.1.0]hexane-2-one* (**10**)

1.17 g (4.84 mmol) of **6** (*trans:cis* = 92:8) was treated according to general procedure **C** thus affording 0.048 g (5.7 %) of γ-lactam **10** (m.p. 68–70 °C) and 0.901 g of crude **8** (without isolation of the hydrochloride **6**, lactam **10** was obtained in 7.0 % yield with respect to **4**). 0.379 g of crude **8** was recrystallized from water/ethanol (1/1) leading after 3 h drying at

50 °C/0.05 Torr to 0.312 g (77 % calculated yield) of **8** as a hydrate [m.p. 224–227 °C (dec.)]. ^{1}H NMR (D_2O) **8**: δ 7.40–7.30 (m, 5H), 3.04 (m_c, 1H), 1.99–1.92 (m, 2H), 1.54, 1.26 (2br.s, 2H). ^{13}C NMR (D_2O) **8**: δ 184.1 (s), 140.5, 133.6, 131.3, 130.0 (s, 3d), 44.0 (t), 39.2 (s), 25.2 (d), 20.9 (t). IR (KBr) 3600–2800 (O-H, N-H, C-H), 1620 (C=O). Anal. Calcd. for $C_{11}H_{13}NO_2$ x 0.5 H_2O (200.2): C, 65.99; H, 7.05; N, 7.00. Found: C, 66.24; H, 7.00; N, 7.15. – ^{1}H NMR ($CDCl_3$) **10**: δ 7.42–7.23 (m, 5H), 6.94 (br.s, 1H), 3.62 (dd, *J* = 10.5, 5.5, 1H), 3.37 (br.d, *J* = 10.5, 1H), 2.20 (m_c, 1H), 1.53 (dd, *J* = 8, 4.5, 1H), 1.14 (t, *J* = 4.5, 1H). ^{13}C NMR ($CDCl_3$) **10**: δ 178.6 (s), 136.1, 128.8, 128.4, 127.1 (s, 3d), 43.2 (t), 33.6 (s), 22.7 (d), 19.2 (t). IR (KBr) 3220 (N-H), 3120–2800 (C-H), 1675, 1660 (C=O). Anal. Calcd. for $C_{11}H_{11}NO$ (173.2): C, 76.28; H, 6.40; N, 8.09. Found: C, 75.87; H, 6.46; N, 7.78.

cis/trans-2-Aminomethyl-1-trifluoromethyl-1-cyclpropanecarboxylic acid (**9**) *and 1-trifluoro-methyl-3-azabicyclo[3.1.0]hexane-2-one* (**11**)

1.02 g (4.12 mmol) of **7** (*trans:cis* = 32:68) was treated according to general procedure **C** thus affording 0.288 g (42 %) of γ-lactam **11** (m.p. 93–95 °C; m.p. 96–98 °C after recrystallization) and 0.393 g (47 %) of **9** (*trans:cis* = 66:34) as a hydrate [anhydrous *cis/trans*-**9**: m.p. 267–268 °C (dec.) after recrystallization from H_2O/MeOH/THF and 5 h drying at 50–70 °C/0.04 Torr]. ^{1}H NMR (D_2O) *cis/trans*-**9**: δ 3.38 (dd, *J* = 13.5, 6.0, 0.66H), 3.18 (m_c, 1.34H), 1.82 (m_c, 1H), 1.63 (m_c, 0.66H), 1.54* (dd, *J* = 9.5, 5.5, 0.34H), 1.39 (m_c, 1H). ^{13}C NMR (D_2O) *cis/trans*-**9**: δ 176.3, 174.5* (2s), 128.5, 128.0* (2q, *J* = *J** = 273), 41.5*, 40.9 (2t), 36.6*, 35.3 (2q,*J** = 32, *J* = 30), 25.2, 21.4* (2d), 18.5, 17.3* (2t). IR (KBr) 3500–2500 (O-H, N-H, C-H), 1650 (C=O), 1205 (C-F). Anal. Calcd. for $C_6H_8F_3NO_2$ (183.1): C, 39.36; H, 4.40; N, 7.65. Found: C, 39.08; H, 4.28; N, 7.37. – ^{1}H NMR ($CDCl_3$) **11**: δ 7.32 (br.s, 1H), 3.56 (dd, *J* = 11, 5.5, 1H), 3.31 (br.d, *J* = 11, 1H), 2.36 (m_c, 1H), 1.57 (dd, *J* = 8.5, 5.5, 1H), 1.08 (br.t, *J* = 5, 1H). ^{13}C NMR ($CDCl_3$) **11**: δ 172.0 (s), 123.7 (q, *J* = 274), 42.5 (t), 30.8 (q, *J* = 37), 19.5 (d), 14.9 (t). IR (KBr) 3230 (N-H), 3150–2800 (C-H), 1690 (C=O), 1140 (C-F). Anal. Calcd. for $C_6H_6F_3NO$ (165.1): C, 43.65; H, 3.66; N, 8.48. Found: C, 43.70; H, 3.61; N, 8.52.

1-[N,N-bis(trimethylsilyl)amino]-2,4-pentadiene (**12**)

The reaction of 17.4 g (108 mmol) of hexamethyldisilazane, 30 ml (72.1 mmol) of 2.4 M *n*-BuLi solution in *n*-hexane, 10.6 g (72.1 mmol) of *E*-1-bromo-2,4-pentadiene and 1.69 g (7.20 mmol) of AgI in 40 ml of dry THF was performed according to reference [14]. After 60 h at 60–70 °C the reaction mixture was filtered through a sintered glass plug which contained a pad of Celite, the solvents were removed under reduced pressure and the residue was distilled in vacuo (102 °C/34 Torr) thus affording 8.64 g (53 %) of **12** (*E:Z* = 90:10). ^{1}H NMR ($CDCl_3$) *E*-**12**: δ 6.35 (dt, *J* = 17, 10, 1H), 6.18–6.06 (m, 1H), 5.65 (dt, *J* = 15, 5, 1H), 5.13 (dd, *J* = 17, 1, 1H), 5.00 (dd, *J* = 10, 1, 1H), 3.52 (dd, *J* = 5, 1, 1H), 0.12 (s, 18H). ^{13}C NMR ($CDCl_3$) *E*-**12**: δ 137.4, 136.9, 129.9 (3d), 115.2 (t), 46.4 (t), 2.0 (q). – ^{1}H NMR ($CDCl_3$) *Z*-**12**: δ 6.58 (dtd, *J* = 17, 11, 1, 1H), 5.88 (m_c, 1H), 5.34 (dt, *J* = 11, 6, 1H), 5.23–4.96 (m, hidden by *E*-**12** signals, 2H), 3.65 (dd, *J* = 6, 1, 1H), 0.12 (s, 18H). ^{13}C NMR ($CDCl_3$) *Z*-**12**: δ 136.8, 132.1, 127.0 (3d), 117.4 (t), 42.3 (t), 2.0 (q). IR (film) 2960–2840 (C-H), 1600 (C=C), 1245 (C-Si). Anal. Calcd. for $C_{11}H_{25}NSi_2$ (227.5): C, 58.08; H, 11.08; N, 6.16. Found: C, 58.38; H, 11.25; N, 6.00.

Methyl 2-[3'-N,N-bis(trimethylsilyl)amino-E-1'-propenyl]-1-cyclopropanecarboxylate (**13**) *and methyl 2-[N,N-bis(trimethylsilyl)aminomethyl]-3-(2'-methoxycarbonyl-cyclopropyl)-1-cyclopropanecarboxylate* (**16**)

10.5 g (46.1 mmol) of **12** (*E:Z* = 90:10), 10.0 g (100 mmol) of methyl diazoacetate and 0.305 g (0.690 mmol) of $Rh_2(OAc)_4$ was treated according to general procedure **A**. Bulb-to-bulb distillation at 80–130 °C/0.02 Torr afforded in the first fraction 8.98 g of colourless oil that consisted of 85 % of **13** (*trans:cis* = 60:40; 53 % calculated yield) and of 15 % of **16** (9 % calculated yield). In the second fraction (170 °C/0.02 Torr) we obtained 0.619 g (4 %) of pure **16**. Careful redistillation of the first fraction at 80 °C/0.02 Torr afforded pure **13** in low yield.

^{1}H NMR ($CDCl_3$) **13**: δ 5.59–5.35 (m, 1.4H), 5.04 (ddt, *J* = 15.3, 8.3, 1.7, 0.6H), 3.63, 3.61* (2s, 3H), 3.39–3.34 (m, 2H), 2.00–1.83 (m, 1.4H), 1.53 (m_c, 0.6H), 1.30 (dt, *J* = 9, 4.5, 0.6H), 1.22–1.10 (m, 0.8H), 0.88 (ddd, *J* = 8.6, 6.3, 4.5, 0.6H), 0.03 (s, 18H); the signals were assigned by means of NOE experiments. ^{13}C NMR ($CDCl_3$) **13**: δ 174.0, 172.2* (2s), 135.0*, 133.7, 128.6, 126.0* (4d), 51.6, 51.5* (2q), 46.3*, 46.1 (2t), 24.5, 23.7*, 21.3, 20.4* (4d), 15.5, 13.8* (2t), 1.9 (q). * refers to the minor diastereoisomer. IR (film) 3100–2840 (=C-H, C-H), 1725 (C=O), 1245 (C-Si). Anal. Calcd. for $C_{14}H_{29}NO_2Si_2$ (299.6): C, 56.13; H, 9.76; N, 4.68. Found: C, 56.37; H, 9.75; N, 4.21. ^{1}H NMR ($CDCl_3$) **16**: δ 3.68–3.62 (7s, 6H), 2.98–2.38, (m, 2H), 1.77–0.63 (m, 7H), 0.11–0.05 (6s, 18H). ^{13}C NMR ($CDCl_3$) **16**: δ 173.9–171.8 (8s), 51.6, 51.5 (2q), 47.4–42.6 (5t), 35.5–18.6 (35d), 15.9–12.6 (8t), 2.6–1.9 (4q); unambiguous assignment of signals was not possible. IR (film) 3000–2840 (C-H), 1720 (C=O), 1250 (C-Si). Anal. Calcd. for $C_{17}H_{33}NO_4Si_2$ (371.6): C, 54.94; H, 8.95; N, 3.77. Found: C, 55.13; H, 9.09; N, 3.69.

Methyl 2-(3'-amino-E-1'-propenyl)-1-cyclopropanecarboxylate hydrochloride (**14**)

1.62 g (5.41 mmol) of a mixture (*trans*-**13**:*cis*-**13**:**16** = 62:34:4) was treated according to general procedure **B**. Removal of volatile components in vacuo afforded 1.04 g (100 %) of crude **14** (*trans:cis* = 65:35) as a highly viscous, colourless oil. The crude product was used without further purification. ^{1}H NMR ($CDCl_3$): δ 8.02 (br.s, 3H), 5.77–5.31 (m, 2H), 3.52, 3.49* (2s, 3H), 3.63–3.21 (m, 2H), 1.93–1.68, 1.51, 1.15, 1.06, 0.83 (m, 4m_c, 4H). ^{13}C NMR ($CDCl_3$): δ 173.0, 172.0* (2s), 137.7, 134.6*, 122.5*, 121.2 (4d), 51.7*, 51.5 (2q), 41,1*, 41.0 (2t), 23.8, 22.9*, 21.7, 20.5* (4d), 15.8, 14.8* (2t).

2-(3'-Amino-E-1'-propenyl)-1-cyclopropanecarboxylic acid (**15**)

0.965 g (5.03 mmol) of crude **14** was reacted according to general procedure **C** thus leading to 0.692 g (86 %) of crude **15** (*trans:cis* = 61:39) as a pale yellow hydrate (estimated purity >90 % according to ^{1}H NMR). 0.351 g of the crude product was dissolved in hot methanol and precipitated with diethylether. Filtration and drying in vacuo (4–5 h at 50–70 °C/0.02 Torr) afforded 0.262 g (70 % calculated yield) of **15** x 0.25 H_2O [m.p. 225–227 °C (dec.)]. ^{1}H NMR (D_2O) **15**: δ 5.76–5.64 (m, 1.39H), 5.50 (dd, *J* = 15.5, 8.5, 0.61H), 3.55–3.53 (m, 2H), 1.93–1.83 (m, 1.39H), 1.54 (ddd, *J* = 9, 5.5, 4, 0.61H), 1.24–1.13 (m, 1.39H), 0.95 (ddd, *J* = 8.5, 5.5, 4.5, 0.61H). ^{13}C NMR (D_2O) **15**: δ 184.4, 182.7* (2s), 142.3, 139.9*, 124.1*,

122.4 (4d), 43.7*, 43.5 (2t), 27.3, 27.1*, 25.7, 23.6* (4d), 17.3, 15.6* (2t). * refers to the minor diastereoisomer. IR (KBr) 3600–2400 (O-H, N-H, =C-H, C-H), 1670 (C=O), 1645 (C=C). Anal. Calcd. for $C_7H_{11}NO_2$ x 0.25 H_2O (145.7): C, 57.71; H, 7.96; N, 9.61. Found: C, 57.55; H, 7.90; N, 9.39.

tert-Butyl 2-[N,N-bis(trimethylsilyl)aminomethyl]tricyclo-[3.2.1.$O^{2,4}$]oct-6-ene-3-carboxylate (**19**)

1.29 g (4.12 mmol) of **18** was dissolved in 5 ml dichloromethane, 4.00 g (60.5 mmol) of cyclopentadiene was added and the mixture was stirred for 10 h at room temperature. Removal of volatile components under reduced pressure and distillation in vacuo (150–160 °C/0.02 Torr) afforded 1.05 g (67 %) of **19** that slowly turned into a wax-like solid (m.p. 52–54 °C). ^{1}H NMR ($CDCl_3$): δ 5.89 (m_c, 2H), 3.41, 3.32 (2d, J = 15.5, 2H), 3.17 (br.s, 1H), 2.91 (br.s, 1H), 1.90, 1.85 (2m_c, 2H), 1.53–1.30 (m, 2H), 1.41 (s, 9H), 0.11 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 170.3 (s), 133.6 (d), 132.6 (d), 80.1 (s), 61.6 (t), 46.4 (d), 43.5 (d), 42.7 (t), 38.6 (d), 33.8 (s), 28.2 (q), 28.1 (d), 2.5 (q). IR (KBr) 3070 (=C-H), 3000-2860 (C-H), 1720 (C=O), 1260, 1250 (C-Si). Anal. Calcd. for $C_{20}H_{37}NO_2Si_2$ (379.7): C, 63.27; H, 9.82; N, 3.69. Found: C, 63.49; H, 9.75; N, 3.66.

2-(Aminomethyl)tricyclo[3.2.1.$O^{2,4}$]oct-6-ene-3-carboxylic acid hydrochloride (**20**)

0.799 g (2.10 mmol) of **19** was dissolved in 8 ml diethylether, 10 ml of HCl saturated diethylether was added and the mixture was stirred for 24 h at room temperature. Filtration of the precipitate and careful washing with diethylether afforded 0.420 g (93 %) of pure **20** [m.p. 213–215 °C (dec.)]. ^{1}H NMR [$SO(CD_3)_2$]: δ 12.4 (br.s, 1H), 8.23 (br.s, 3H), 5.95 (s, 2H), 3.56–3.23 (m, 3H), 2.97 (br.s, 1H), 1.89 (m_c, 2H), 1.54 (d, J = 7.2, 1H), 1.50 (d, J = 2.7, 1H). ^{13}C NMR [$SO(CD_3)_2$]: δ 171.3 (s), 133.6 (d), 132.3 (d), 61.7 (t), 47.2 (d), 43.2 (d), 38.5 (t), 35.0 (d), 30.4 (s), 27.8 (d). IR (KBr) 3300–2100 (O-H, N-H, =C-H, C-H), 1710 (C=O), 1610 (C=C). Anal. Calcd. for $C_{10}H_{14}ClNO_2$ (215.7): C, 55.68; H, 6.54; N, 6.49. Found: C, 55.57; H, 6.55; N, 6.61.

2-(Aminomethyl)tricyclo[3.2.1.$O^{2,4}$]oct-6-ene-3-carboxylic acid (**21**)

0.261 g (1.21 mmol) of hydrochloride **20** was dissolved in 5 ml of dry ethanol. The solution was refluxed for 1 h after the addition of 1.5 ml propeneoxid. The resulting precipitate was isolated by filtration of the cold reaction mixture and careful washing with ethanol and diethylether. Drying in vacuo (3–4 h at 50–70 °C/0.02 Torr) afforded 0.189 g (87 %) of pure (according to ^{1}H NMR) **21** [m.p. 211–214 °C (dec.)]. The crude product was recrystallized from ethanol/water and dried in vacuo. ^{1}H NMR (D_2O): δ 5.97 (m_c, 2H), 3.49 (s, 2H), 3.02 (br.s, 1H), 1.96 (br.s, 1H), 1.83 (d, J = 6.5, 1H), 1.70–1.65 (m, 2H). ^{13}C NMR (D_2O): δ 152.6 (s), 136.2 (d), 134.8 (d), 63.9 (t), 50.3 (d), 46.0 (d), 44.7 (t), 42.1 (d), 30.9 (s), 28.9 (d). IR (KBr) 3200–2400 (O-H, N-H, =C-H, C-H), 1640 (C=O), 1625 (C=C). Anal. Calcd. for $C_{10}H_{13}NO_2$ x 0.1 H_2O (181.0): C, 66.35; H, 7.35; N, 7.74. Found: C, 66.14; H, 7.31; N, 7.67.

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[18] Compounds **8** and **10** did not show anticonvulsive effects. In addition, these amino acid derivates and compound **20** did not inhibit benzodiazepin receptor, GABA A-receptor and GABA transaminase. We are grateful to Dr. K. Unverfehrt (Arzneimittelwerke Dresden) for organizing these biological tests

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