A Short Synthesis of γ-Amino Acids from Nitrones; Synthesis of Vigabatrin®

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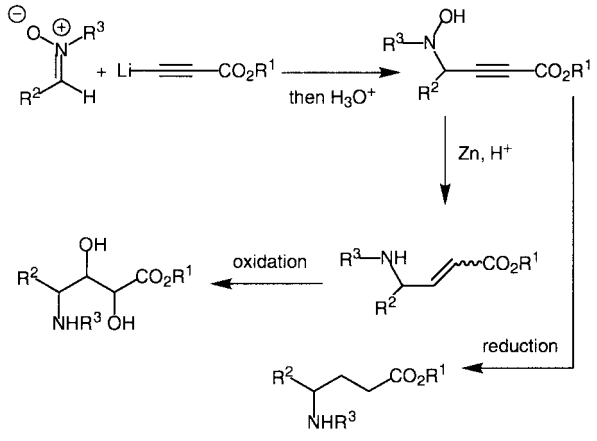
Abstract: Treatment of the γ-*N*-hydroxylamino-α,β-acetylenic esters, obtained by the reaction of nitrones with alkyl 3-lithiopropiolates, with H_2 over Raney nickel, followed by in situ protection of the formed amines, gives *N*-Boc-γ-amino esters. This method has been applied to a synthesis of (*S*) and (*R*)-Vigabatrin®.

Key words: nitrones, γ-amino acids, Vigabatrin,® 3-lithiopropiolates

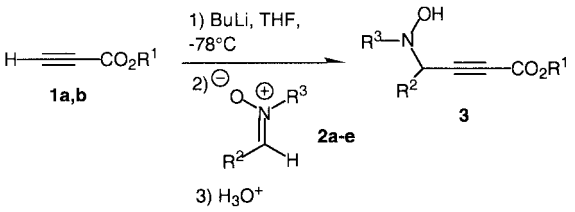
γ-Aminobutyric acid (GABA) is a major neurotransmitter, known to have a beneficial effect against epilepsy. It is degraded by the enzyme GABA-transaminase and when its concentration in the brain falls under a threshold level, epileptic seizures appear.[1] Various GABA-analogs have been synthesized and tested as GABA-transaminase inhibitors, the most important being Vigabatrin® [(*S*)-4-amino-5-hexenoic acid][2] and 4-amino-5-hexynoic acid.[3] In this communication, we present a short synthesis of γ-amino esters, and its application to the synthesis of Vigabatrin® and of its enantiomer.

We have recently reported that the reaction of alkyl 3-lithiopropiolates with nitrones leads to γ-*N*-hydroxyamino-α,β-acetylenic esters (Scheme 1).[4] These compounds are efficient precursors for α,β-ethylenic and α,β-dihydroxy-γ-amino esters.[4-6] We have now found that they can be reduced in one pot into saturated γ-amino esters.



Scheme 1

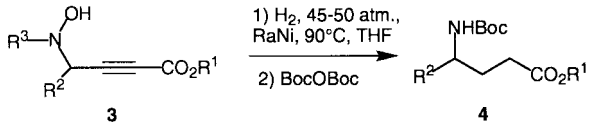
A series of γ-*N*-hydroxyamino-α,β-acetylenic esters were prepared by condensation of the lithiated anion of propiolate esters **1a**,**b** with nitrones **2a-f** at −78 °C in THF (Scheme 2). Yields of isolated *N*-hydroxyamino compounds **3** are summarized in Table 1.



Scheme 2

The direct reduction of γ-*N*-hydroxyamino-α,β-acetylenic esters into saturated amino esters requires the cleavage of the N-O bond and the dihydrogenation of the C≡C triple bond. Furthermore, if R^3 is a benzyl group, it can be expected that the needed reductive conditions will also cleave the N-R^3 bond and liberate the free amine.

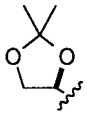
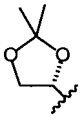
We found that the expected saturated amines were formed when the acetylenic compounds **3** were treated with hydrogen (45−50 atmospheres) over Raney Nickel (Scheme 3). However, as these γ-amino esters can readily undergo self-condensations to lactams or polymerization, we preferred to isolate them as their *N*-Boc protected derivatives **4**. The protection was effected in situ. Compounds **4** were isolated in medium to good yields (Table 2).



Scheme 3

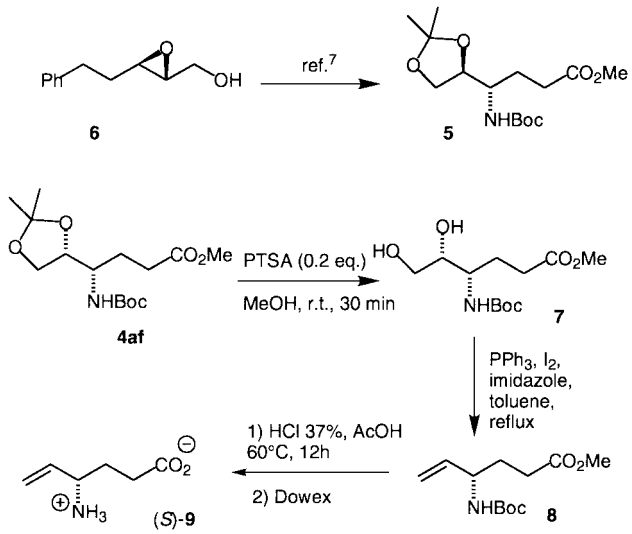
Merino et al.[6] and our team[4] reported that the reaction of lithiopropiolates with α-chiral nitrones is highly stereoselective. This was the case for the reactions presented in entries 6−9 of Table 1. In each case, only one diastereoisomer was obtained. These compounds were attributed a *syn* structure by comparison with Merino's results.[6] Application of the procedure described above to these compounds gave the corresponding Boc-amino esters in good yields (Table 2, entries 6−9). Interestingly, compound **5**, a diastereoisomer of **4af**, has already been described as an intermediate in a synthesis of Vigabatrin®.[7,8] The overall yield of **4ad** from the nitrone **2d** was 68%. The previously

Table 1 Synthesis of Compounds **3**

Entry	Propiolate	R^1	Nitrone	R^2	R^3	Time (h)	Product	Yield (%)
1	**1a**	Me	**2a**	Et	Bn	1.5	**3aa**	69
2	**1b**	Bu^t	**2a**	Et	Bn	3	**3ba**	77
3	**1a**	Me	**2b**	Pr^i	Bn	1	**3ab**	65
4	**1b**	Bu^t	**2b**	Pr^i	Bn	1.66	**3bb**	94
5	**1b**	Bu^t	**2c**	Bu^i	Bn	2.5	**3bc**	60
6	**1a**	Me	**2d**		Bn	1.5	**3ad**[b]	88
7	**1b**	Bu^t	**2d**	–	Bn	1.5	**3bd**[b]	88
8	**1b**	Bu^t	**2e**	–	2,4-DMB[a]	1.5	**3be**[b]	50
9	**1a**	Me	**2f**		Bn	1.5	**3af**[b]	94

[a] 2,4-DMB: 2,4-dimethoxybenzyl.
[b] Only the *syn* isomer was obtained.

reported synthesis of **5**[7] was done in 4 steps and in 45% yield from the epoxy alcohol **6**. Cleavage of the isopropylidene protection followed by reductive elimination of the two hydroxy groups of diol **7** gave the methyl ester of *N*-Boc-(*S*)-Vigabatrin **8**. The deoxygenation was effected by a one pot procedure (PPh_3, I_2, imidazole) which we found more convenient than the two steps protocol used by Pericas et al.[7] Compound **8** was deprotected under acidic conditions to give (*S*)-Vigabatrin **9** (Scheme 4). A similar synthetic sequence starting from nitrone **2d** afforded (*R*)-**9**.



Scheme 4

Mps were obtained with a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded (neat) on a Nicolet Impact 400 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Brucker AC200, AM300, Avance 300 spectrometers or a Varian Unit+500 spectrometer using (unless otherwise stated) $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are in Hz. Mass spectra were carried out on a Nermag R10 mass spectrometer (CI or CDI). Microanalyses were performed by the " Service Central d'Analyse du CNRS".

THF was distilled from sodium-benzophenone and CH_2Cl_2 on CaH_2. Raney Nickel was prepared as described in ref.[9] It was washed four times with H_2O at reflux and then four times with THF before use. Nitrones **2a**–**e** were prepared according to a known procedure.[10] Nitrones **2a**–**d**[4,6,10] were previously known.

(*Z*)-*N*-(1-Deoxy-2,3-*O*-isopropylidene-D-glycero-1-yliden)-2,4-dimethoxybenzylamine *N*-oxide (2e)
Yield: 85%.

Mp: 40–41 °C.

$[\alpha]_D$ +72.5° (*c* 3.2, $CHCl_3$).

IR (NaCl, film): 3100, 2995, 2840, 1615, 1590, 1510, 1470, 1440, 1415, 1380, 1375, 1335, 1295, 1265, 1205, 1160, 1135, 1060, 1035, 930, 850, 755 cm^{-1}.

^1H NMR (500 MHz): δ = 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 3.86 (dd, 1H, *J* = 5.9, 8.6 Hz,

Table 2 Synthesis of Compounds **4**

Entry	Reactant	Time (h)	Product	Yield (%)
1	**3aa**	24	**4aa**	67
2	**3ba**	24	**4ba**	79
3	**3ab**	24	**4ab**	71
4	**3bb**	24	**4bb**	75
5	**3bc**	16	**4bc**	69
6	**3ad**[a]	24	**4ad**[a]	77
7	**3bd**[a]	24	**4bd**[a]	80
8	**3be**[a]	40	**4bd**[a]	65
9	**3af**[a]	24	**4af**[a]	67

[a] *Syn* isomer.

Table 3 Physical and Spectroscopic Data of Compounds **3** and **4**[a]

Product	Mp (°C)	IR (neat) ν (cm^{-1})	^{1}H NMR (300 MHz, 400 MHz or 500 MHz, $CDCl_3$, TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$, TMS) δ	MS (DCI, NH_3 + *i*-C_4H_{12}) *m/z*	$[\alpha]_D$ (*c*, solvent)
3aa[d]	73–74	3485 (NOH), 2235 (C≡C), 1715 (CO_2)	1.01 (t, 3 H, *J* = 7.4, CH_3), 1.65−1.85 (m, 2 H, CH_2), 3.48 (t, 1 H, *J* = 7.4, CHN), 3.79 (s, 3 H, CO_2Me), 3.93 (ABq, 2 H, J_{AB} = 12.8, $\delta_A-\delta_B$ = 56.8, CH_2), 5.53 (s, 1 H, OH), 7.20−7.48 (m, 5 H)	10.7 (CH_3), 25.8 (CH_2), 52.7 (OCH_3), 60.3 (CHN), 61.6 (CH_2Ph), 78.2 and 85.4 (C≡C), 127.6 (CH), 128.4 (CH), 129.6 (CH), 136.7 (C), 153.8 (CO_2)	248 (MH^+), 229 (M^+-H_2O), 217 (MH^+-MeO)	–
3ab[e]	Oil	3475 (NOH), 2230 (C≡C), 1715 (CO_2)	1.02 (d, 3 H, *J* = 6.9, CH_3), 1.06 (d, 3 H, *J* = 6.9, CH_3), 2.00−2.13 [m, 1 H, C<u>H</u>(CH_3)$_2$], 3.20 (d, 1 H, *J* = 8.9, CHN), 3.79 (s, 3 H, OCH_3), 3.95 (ABq, 2H, J_{AB} = 12.8, $\delta_A-\delta_B$ = 105.5, CH_2Ph), 5.01 (br s, 1 H, NOH), 7.22−7.42 (m, 5 H)	19.7 (CH_3), 19.8 (CH_3), 30.5 (CH), 52.6 (CH_3O), 61.8 (CH_2), 65.4 (CH), 78.8 and 85.0 (C≡C), 127.5 (CH), 128.3 (CH), 129.4 (CH), 137.0 (C), 153.9 (CO_2)	262 (MH^+)	–
3ba[d]	92–93	3250 (NOH), 2225 (C≡C), 1705 (CO_2)	1.05 (t, 3 H, *J* = 7.4, CH_3), 1.52 (s, 9 H, *t*-Bu), 1.82−1.89 (m, 2 H, CH_2), 3.58 (t, 1 H, *J* = 7.4, CHN), 3.99 (ABq, 2 H, J_{AB} = 13.0, $\delta_A-\delta_B$ = 79.0, CH_2Ph), 4.59 (s, 1 H, NOH), 7.27−7.41 (m, 5 H)	10.8 (CH_3), 26.0 (CH_2), 28.0 [($\underline{C}H_3$)$_3$C], 60.4 (CHN), 61.8 (CH_2Ph), 79.9, 82.4 and 83.4 [$\underline{C}(CH_3)_3$ and C≡C], 127.5 (CH), 128.4 (CH), 129.4 (CH), 137.1 (C), 152.5 (CO_2)	290 (MH^+), 274, 272, 250, 234	–
3bb[f]	114	3480 (NOH), 2235 (C≡C), 1715 (CO_2)	1.04 (d, 3 H, *J* = 6.8, CH_3), 1.07 (d, 3 H, *J* = 7.2, CH_3), 1.52 (s, 9 H, *t*-Bu), 1.97−2.20 [m, 1 H, C<u>H</u>(CH_3)$_2$], 3.23 (d, 1 H, *J* = 8.9, CHN), 3.98 (ABq, 2 H, J_{AB} = 13.0, $\delta_A-\delta_B$ = 58.6, CH_2Ph), 4.74 (br s, 1 H, NOH), 7.21−7.43 (m, 5 H)	19.8 [($\underline{C}H_3$)$_2$C], 28.0 [($\underline{C}H_3$)$_3$C], 30.6 (CH), 61.9 (CH_2), 65.5 (CH), 80.6, 81.8 and 83.3 [$\underline{C}(CH_3)_3$ and C≡C], 127.4 (CH), 128.4(CH), 129.3 (CH), 137.1 (C), 152.5 (CO_2)	304 (MH^+), 248	–
3bc[f]	Oil	3420 (NOH), 2230 (C≡C), 1720 (CO_2)	0.89 (d, 3 H, *J* = 6.5, CH_3), 0.91 (d, 3 H, *J* = 6.5, CH_3), 1.40−2.02 (m, 3 H, CH and CH_2), 1.52 (s, 9 H), 3.74 (psuedo t, 1 H, *J* = 7.2 and 7.8, CHN), 3.98 (ABq, 2 H, J_{AB} = 13.0, $\delta_A-\delta_B$ = 48.7, CH_2Ph), 4.63 (s, 1 H, NOH), 7.22−7.45 (m, 5 H)	22.2 (CH_3), 22.4 (CH_3), 24.9 [($\underline{C}H_3$)$_3$C], 28.3 (CH), 41.3 (CH_2), 56.9 (CHN), 61.7 (CH_2), 79.8, 82.6 and 83.3 [$\underline{C}(CH_3)_3$ and C≡C], 127.5 (CH), 128.4 (CH), 129.4 (CH), 137.0 (C), 152.5 (CO_2)	318 (MH^+)	–
3ad[f]	Oil	3405 (NOH), 2235 (C≡C), 1725 (CO_2)	1.33 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 3.76 (M of ABMX, d, 1 H, *J* = 6.9, CH), 3.81 (s, 3 H, MeO), 4.01 (ABq, 2 H, J_{AB} = 12.5, $\delta_A-\delta_B$ = 50, CH_2Ph, 4.06 (AB of ABMX, 2 H, J_{AB} = 8.9, J_{AM} = 5.5, J_{BM} = 6.2, CH_2O), 4.44 (X of ABMX, psuedo q, 1 H, J_{obs} = 5.8 and 13, CHO), 5.60 (s, 1 H, NOH), 7.20−7.46 (m, 5 H)	25.5 (CH_3), 26.6 (CH_3), 52.9 (CH_3O), 60.6 (CH), 62.6 (CH_2), 67.1 (CH_2), 75.3 (CH), 79.5 and 81.6 (C≡C), 109.9 [(CH_3)$_2\underline{C}$], 127.9 (CH), 128.6 (CH), 129.6 (CH), 135.7 (C), 153.4 (CO_2)	320 (MH^+)	–46.3 (1.3, $CHCl_3$)[b]
3bd[g]	Oil	3400 (NOH), 2235 (C≡C), 1705 (CO_2)	1.34 (s, 6 H, 2CH_3), 1.50 (s, 9 H, *t*-Bu), 3.77 (M of ABMX, d, 1 H, *J* = 5.0, CH), 4.05 (ABq, 2 H, J_{AB} = 12.7, $\delta_A-\delta_B$ = 134.3, CH_2Ph), 4.06 (AB of ABMX, 2 H, J_{AB} = 8.9, J_{AM} = 5.9, J_{BM} = 6.2, CH_2), 4.40 (X of ABMX, psuedo q, 1 H, J_{obs} = 6.2 and 12.8, CHO), 4.97 (s, 1 H, NOH), 7.23−7.38 (m, 5 H)	25.6 (CH_3), 26.6 (CH_3), 28.0 [($\underline{C}H_3$)$_3$C], 60.6 (CH), 62.5 (CH_2), 67.2 (CH_2), 75.3 (CH), 78.6, 81.2 and 83.7 [$\underline{C}(CH_3)_3$ and C≡C], 109.9 [(CH_3)$_2\underline{C}$], 127.8 (CH), 128.5 (CH), 129.6 (CH), 135.8 (C), 152.1 (CO_2)	362 (MH^+), 344, 239, 220	–41 (1.0, $CHCl_3$)
3be[d]	46–47	3495 (NOH), 2240 (C≡C), 1705 (CO_2)	1.26 (s, 6 H, 2CH_3), 1.44 (s, 9 H, *t*-Bu), 3.71 (s, 3 H, CH_3O), 3.73 (s, 3 H, CH_3O), 3.70−3.77 (m, 1 H, CHN), 3.97 (ABq, 2 H, J_{AB} = 13, $\delta_A-\delta_B$ = 33.6, CH_2Ph), 3.92−3.97 (m, 1 H, CH_2O), 4.00−4.06 (m, 1 H, CH_2O), 4.28 (psuedo q, 1 H, CHO), 6.00 (s, 1 H, NOH), 6.34−6.36 (m, 2 H), 7.16−7.20 (m, 1 H)	25.7 (CH_3), 26.5 (CH_3), 28.0 [($\underline{C}H_3$)$_3$C], 56.6 (2 CH_3O), 57.8 (CH_2), 60.5 (CH_2), 67.2 (CH_2), 79.3, 81.0 and 83.4 [$\underline{C}(CH_3)_3$ and C≡C], 98.5 (CH), 104.1 (CH), 109.5 [(CH_3)$_2\underline{C}$], 116.4 (C), 132.4 (CH), 152.2 (CO_2), 159.1 (C), 160.1 (C)	422 (MH^+), 151	–47.7 (1.5, $CHCl_3$)

Table 3 (continued)

Product	Mp (°C)	IR (neat) ν (cm^{-1})	^{1}H NMR (300 MHz, 400 MHz or 500 MHz, $CDCl_3$, TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$, TMS) δ	MS (DCI, NH_3 + *i*-C_4H_{12}) *m/z*	$[\alpha]_D$ (*c*, solvent)
4aa[d]	39–40	3360 (NH), 1740 and 1690 (2 CO_2)	0.92 (pst, 3 H, *J* = 7.2 and 7.5, CH_3), 1.26-1.97 (m, 4 H, 2 CH_2), 1.44 (s, 9 H, *t*-Bu), 2.38 (t, 2 H, *J* = 7.5, CH_2), 3.38–3.60 (m, 1 H, CHN), 3.67 (s, 3 H, MeO), 4.28 (d, 1 H, *J*=9.2, NH)	10.0 (CH_3), 28.2 [($\underline{C}H_3)_3C$], 28.3 (CH_2), 29.9 (CH_2), 30.6 (CH_2), 51.3 (CH_3O), 51.6 (CH), 78.6 [$(CH_3)_3\underline{C}$], 155.6 ($NHCO_2$), 173.8 (CO_2)	246 (MH^+), 207, 190, 146, 116	–
4ab[f]	64–65	3350 (NH), 1730 and 1695 (2 CO_2)	0.89 (d, 3 H, *J* = 6.9, CH_3), 0.91 (d, 3 H, *J* = 6.9, CH_3), 1.43 (s, 9 H, *t*-Bu), 1.50–1.96 (m, 3 H, CH and CH_2), 2.38 (t, 2 H, *J* = 7.5, CH_2), 3.30–3.54 (m, 1 H, CHN), 3.68 (s, 3 H, MeO), 4.30 (d, 1 H, *J* = 9.6, NH)	17.7 (CH_3), 18.9 (CH_3), 27.5 (CH_2), 28.3 [($\underline{C}H_3)_3C$], 31.1 (CH_2), 32.5 (CH), 51.5 (CH_3O), 55.3 (CHN), 78.8 [$(CH_3)_3\underline{C}$], 155.9 ($NHCO_2$), 174.1 (CO_2)	260 (MH^+), 204, 160, 128, 116	–
4ba[f]	66-–67	3340 (NH), 1730 and 1690 (2 CO_2)	0.91 (pst, 3 H, *J* = 7.2 and 7.5, CH_3), 1.35–1.90 (m, 4 H, 2 CH_2), 1.44 (s, 9H, *t*-Bu), 1.45 (s, 9 H, *t*-Bu), 2.28 (t, 2 H, *J* = 7.5, CH_2), 3.30–3.60 (m, 1 H, CHN), 4.32 (d, 1 H, *J* = 9.2, NH)	10.1 (CH_3), 28.0 [($\underline{C}H_3)_3C$], 28.3 [($\underline{C}H_3)_3C$], 28.5 (CH_2), 29.7 (CH_2), 32.2 (CH_2), 51.7 (CH), 78.7 [$(CH_3)_3\underline{C}$], 80.1 [$(CH_3)_3\underline{C}$], 155.7 ($NHCO_2$), 172.9 (CO_2)	288 (MH^+), 232, 193, 176, 130, 114, 102	–
4bb[f]	62–63	3345 (NH), 1710 and 1695 (2 CO_2)	0.88 (d, 3 H, *J* = 6.9, CH_3), 0.91 (d, 3 H, *J* = 6.9, CH_3), 1.40–1.90 (m, 3 H, CH and CH_2), 1.43 (s, 9 H, *t*-Bu), 1.45 (s, 9 H, *t*-Bu), 2.28 (pst, 2 H, *J* = 7.2 and 7.5, CH_2), 3.30–3.51 (m, 1 H, CHN), 4.33 (d, 1 H, *J* = 11.0, NH)	17.8 (CH_3), 18.9 (CH_3), 27.2 (CH_2), 28.1 [($\underline{C}H_3)_3C$], 28.4 [($\underline{C}H_3)_3C$], 32.6 (CH and CH_2), 55.5 (CHN), 78.9 [$(CH_3)_3\underline{C}$], 80.2 [$(CH_3)_3\underline{C}$], 156.0 ($NHCO_2$), 173.1 (CO_2)	302 (MH^+), 277, 246, 190, 128, 102	–
4bc[f]	50–52	3350(NH), 1730 and 1695 (2 CO_2)	0.91 (d, 6 H, *J* = 6.5, $2CH_3$), 1.15–1.35 (m, 2 H, CH_2), 1.35–1.90 (m, 3 H, CH and CH_2), 1.43 (s, 9 H, *t*-Bu), 1.44 (s, 9 H, *t*-Bu), 2.27 (pst, 2 H, *J* = 7.2 and 7.5, CH_2), 3.48-3.76 (m, 1 H, CHN), 4.23 (d, 1 H, *J*=9.6, NH)	22.3 (CH_3), 23.0 (CH_3), 24.9 (CH), 28.1 [($\underline{C}H_3)_3C$], 28.4 [($\underline{C}H_3)_3C$], 31.0 (CH_2), 32.2 (CH_2), 45.2 (CH_2), 48.5 (CHN), 78.8 [$(CH_3)_3\underline{C}$], 80.1 [$(CH_3)_3\underline{C}$], 155.6 ($NHCO_2$), 173.0 (CO_2)	316 (MH^+), 260, 221, 204, 158, 142, 102	–
4ad[g]	62–63	3370 (NH), 1740 and 1705 (2 CO_2)	1.31 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.41 (s, 9 H, *t*-Bu), 1.80–1.91 (m, 2 H, CH_2), 2.40 (t, 2 H, *J* = 7.5, CH_2CO_2), 3.63 (pst, 1 H, *J* = 7.5 and 7.9, CH_2O), 3.61–3.72 (m, 1 H, CHN), 3.65 (s, 3 H, MeO), 3.98 (dd, 1 H, *J* = 6.8, 9.1, CH_2O), 4.12 (t, 1 H, *J* = 6.3, CHO), 4.63 (d, 1 H, *J* = 9.8, NH)	25.0 (CH_3), 26.2 (CH_3), 28.3 [($\underline{C}H_3)_3C$], 28.7 (CH_2), 30.7 (CH_2), 50.2 (CH), 51.6 (CH_3O), 66.3 (CH_2), 77.4 (CH), 79.5 [$(CH_3)_3\underline{C}$], 109.2 [$(CH_3)_2\underline{C}$], 156.1 ($NHCO_2$), 173.6 (CO_2)	318 (MH^+), 279, 262, 218, 116	+38.6 (1.02, $CHCl_3$)[c]
4bd[g]	78–79	3420 (NH), 1725 and 1700 (2 CO_2)	1.31 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.41 (s, 9 H, *t*-Bu), 1.42 (s, 9 H, *t*-Bu), 1.74–1.85 (m, 2 H, CH_2), 2.29 (t, 2 H, *J* = 7.5, CH_2), 3.60–3.70 (m, 1 H, CHN), 3.63 (dd, 1 H, *J* = 7.2, 8.2, CH_2O), 3.97 (dd, 1 H, *J* = 6.7, 8.2, CH_2O), 4.11 (psuedo t, 1 H, *J* = 5.9 and 6.5, CHO), 4.63 (d, 1 H, *J* = 9.7, NH)	25.0 (CH_3), 26.2 (CH_3), 28.1 [($CH_3)_3C$], 28.3 [($\underline{C}H_3)_3C$], 28.5 (CH_2), 32.1 (CH_2), 50.1 (CH), 66.3 (CH_2), 77.4 (CH), 79.4 and 80.3 [$(CH_3)_3\underline{C}$], 109.1 [$(CH_3)_2\underline{C}$], 156.1 ($NHCO_2$), 172.6 (CO_2)	360 (MH^+), 304, 248, 102	+34 (0.55, $CHCl_3$)

[a] Satisfactory microanalyses obtained: C ± 0.42; H, ± 0.31; N ± 0.23 or HRMS obtained (for compounds **3bd** and **4bd**): ± 0.0008 amu.
[b] Similar data obtained for **3af**, $[\alpha]_D$ +44.8° (*c* 1.25, $CHCl_3$).
[c] Similar data obtained for **4af**, $[\alpha]_D$ –34.8° (*c* 1.0, $CHCl_3$).
[d] Data obtained at 300 MHz.
[e] Data obtained at 400 MHz.
[f] Data obtained at 200 MHz.
[g] Data obtained at 500 MHz.

CH_2O), 4.40 (dd, 1H, *J* = 7.1, 8.6 Hz, CH_2O), 4.83 (s, 2H, CH_2Ph), 5.14 (pseudo tq, 1H, *J* = 4.7, 5.9, 7.1 Hz, CHO), 6.47 (d, 1H, *J* = 2.4 Hz, ArH), 6.50 (dd, !H, *J* = 2.4, 8.3 Hz, ArH), 6.74 (d, 1H, *J* = 4.7 Hz, CHN), 7.25 (d, 1H, *J* = 8.3 Hz, ArH).

^{13}C NMR (75.5 MHz): δ = 24.5 (CH_3), 25.5 (CH_3), 54.8 (CH_3O), 54.8 (CH_3O), 62.9 (CH_2), 67.3 (CH_2), 71.6 (CH), 98.2 (CH arom.), 104.2 (CH arom.), 109.0 [$(CH_3)_2C$], 112.5 (C arom.), 132.2 (CH arom.), 137.6 (CHN), 158.4 (C arom.), 161.5 (C arom.).

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.92; H, 7.07; N, 4.79.

γ-*N*-Hydroxyamino-α,β-acetylenic Esters 3; General Procedure
A solution of *n*-BuLi in hexane (1.33−1.6 M, 1.4 mmol) was added to a magnetically stirred solution of alkyl propiolate **1** (1.5 mmol) in dry THF (10 mL) at −78 °C under Ar. The reaction mixture was stirred for 1 h at that temperature and a solution of nitrone **2** (1 mmol) in dry THF (1 mL) was then slowly added. The evolution of the reaction was monitored by TLC (EtOAc). After stirring for 1−3 h at −78 °C, the reaction was quenched with H_2O and was allowed to warm to r.t. The aqueous phase was extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtrated, and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/pentane, 1:9) to yield hydroxylamine **3** (Tables 1, 3).

γ-Amino Esters 4; General Procedure
In a steel reactor were added Raney Nickel (approx. 1 g) as a suspension in anhyd THF (70 mL), γ-*N*-hydroxyamino-acetylenic ester **3** in THF (5 mL) and di-*tert*-butyldicarbonate (1.1 equiv) in THF (5 mL). The reactor was purged with H_2 during 10 min. The mixture was placed under pressure (45−50 atm.), warmed to 90 °C, and stirred for a period of time (16−40 h, Table 2). After removal of the catalyst by decantation and evaporation of THF under reduced pressure, the resulting crude product was purified by column chromatography (silica gel, EtOAc/pentane, 1:9) to yield pure γ-amino esters **4** (Tables 2, 3).

(*R*)-*N*-Boc-4-amino-5-hexenoic Acid Methyl Ester (8)
To a magnetically stirred solution of compound **4af** (177 mg, 0.558 mmol) in MeOH (6 mL) was added *p*-toluene sulfonic acid (21 mg, 0.112 mmol). After 30 min at r.t., sat. $NaHCO_3$ (2 mL) was added and MeOH was eliminated in vacuo. The resulting aqueous solution was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, EtOAc/pentane, 4:1) to afford compound **7** (110 mg, 0.396 mmol, 71% yield) as an oil.

7:

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.44 (s, 9H, *t*-Bu), 1.80−2.00 (m, 2H, CH_2), 2.44 (t, 2H, *J* = 7.5 Hz, CH_2), 2.71 (br s, 1H, OH), 3.12 (br s, 1H, OH), 3.40−3.70 (m, 7H), 4.83 (d, 1H, *J* = 9.9 Hz, NHBoc).

To a magnetically stirred solution of diol **7** (71 mg, 0.26 mmol) in anhyd toluene (10 mL) was added imidazole (71 mg, 1.04 mmol) and Ph_3P (272 mg, 1.04 mmol). The resulting mixture was refluxed and I_2 (66 mg, 0.261 mmol) was added in portions. The mixture was refluxed for 3 h, whereupon it was allowed to cool to r.t. and was treated with I_2 (66 mg, 0.26 mmol) and NaOH (1.4 M, 1.5 mL). After the disappearance of the red solid, H_2O was added to the mixture. The organic phase was washed with an aqueous solution of sodium thiosulfate, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/Et_2O, 9:1) to afford compound **8** (56 mg, 0.229 mmol, 88% yield) as a white solid. The obtained NMR and IR spectra were in agreement with the data reported for *N*-Boc-(*S*)-Vigabatrin methyl ester.[7] $[\alpha]_D$ +12.5° (*c* 1, $CHCl_3$), [Lit.[7]: $[\alpha]_D$ +11.4° (*c* 1, $CHCl_3$)].

(*S*)-Vigabatrin 9
N-Boc-(*S*)-Vigabatrin (35 mg, 0.144 mmol) was stirred into a mixture of glacial HOAc (0.4 mL) and 37% HCl (0.5 mL) at 60 °C for 12 h. The mixture was then concentrated under vacuum and the resulting material was passed through a column of Dowex 50W ion exchange resin (4 g, 50/100 mesh, H^+ form), eluting with H_2O (discarded) and then 2 N NH_4OH. Evaporation of the latter provided (*S*)-Vigabatrin (12 mg, 65% yield). The NMR and IR spectra were in agreement with the literature data.[2]

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