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GENERAL SYNTHESIS OF 3-SUBSTITUTED ALKENYL GABA AS POTENTIAL ANTICONVULSANTS

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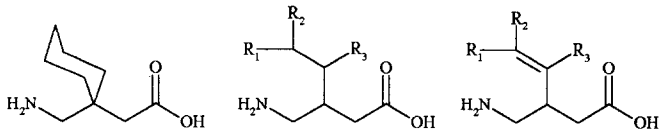
Abstract: stereospecific synthesis of cis and trans 3-substituted vinyl-γ-aminobutyric acid analogs were obtained by either a Claisen rearrangement or a Wittig reaction from common diene precursors.

GABA (4-aminobutyric acid) is the major inhibitory neurotransmitter in mammals.[1] Low levels of GABA in the brain is a major factor linked with epileptic phenomena[2] and the regulation of GABA neurotransmission is the principal mode of action of antiepileptic drugs.[3] Since GABA penetrates poorly the blood brain barrier (BBB) these increase synaptic GABA effect through either stimulation of its synthesis and release (benzodiazepines, valproate) or inhibition of GABA-transaminase (GABA-T) its catabolic enzyme (vigabatrin).[3] The new anticonvulsant agent gabapentin **1** despite its GABA structural similarities does not mimic this neurotransmitter, interfere with its neuronal concentration or bind to its receptors.[4] However **1** is actively transported into the brain through the L aminoacid system[5] and recently a series of 3-alkyl GABA analogs **2** were found to share the same features[6] and in addition increased GABA synthesis by activation of glutamate decarboxylase (GAD).[7] Since some of 3-alkyl GABA are recognized as substrates of GABA-T[8] introduction of a latent reactive function at the 3 position of GABA could lead to mechanism based inhibitors. Therefore 3-alkenyl-GABA analogs **3** should fullfill the criteria of being activated by the enzyme catalysis, by conjugation of the transamination adduct and should be actively transported through the BBB. Since no example of this class of compounds was reported so far it was interesting to have a versatile access to the various substituted analogs **3** to validate this hypothesis.

Scheme 1



1 **2** **3**

A retrosynthetic analysis based on either a Claisen rearrangement or a Wittig reaction lead to substituted 1,4-aminohydroxy-2-butene **4**. This type of synthon could be obtained from the corresponding 1,4-halo-hydroxyderivatives **5** accessible from the dienes **6** by 1,4 addition.[9] In the case of a monosubstituted

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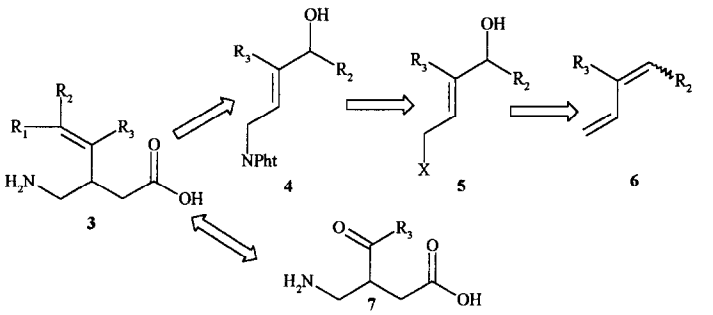
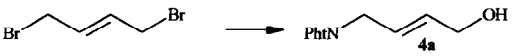
double bond the trans isomer is expected by the thermal reaction, therefore a kineticaly controlled Wittig condensation with a carbonyl derivative **7** should afford the cis isomer. This type of carbonyl compound could be synthesized by ozonolysis of various **3**. The choice of a phthalimido function to protect the primary amine was made based on both its thermal and acidic stability, necessary during the sequence.

Scheme 2



The starting material **4a** for 3-vinyl GABA (**3a**,R_1=R_2=R_3=H) is readily obtained by sequential substitution of 1,4-dibromo-2-butene by potassium phthalimide and sodium acetate in 60% overall yield as shown below:

Scheme 3



The mono and disubstituted precursors **5** were obtained by treatment of the dienes **6** with N-bromosuccinimide in glacial acetic acid, followed by ester hydrolysis in acidic conditions. Essentially 1,4 addition was observed at room temperature and the 1,2 adduct was scarcely detected. Moderate yields were observed due to the partial polymerisation of starting material during the course of the reaction (12 to 24 h). This approach afforded mono and disubstituted methyl or ethyl derivatives as shown in table 1:

Scheme 4

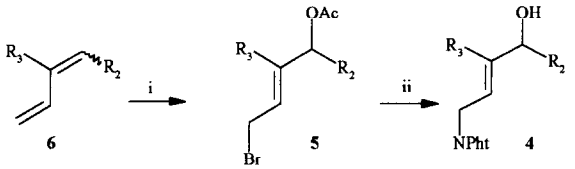
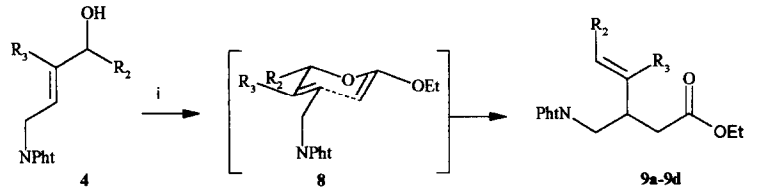


Table 1:	**5a**	**4a**	**5b**	**4b**	**5c**	**4c**
R_2	Me		Et		Me	
R_3	H		H		Me	
%	88	45	75	40	57	45

i: NBS, AcOH, RT.
ii: a) KNPht, DMF, RT;
b) EtOH, cat.TsOH, RT.

The various allyl alcohols **4** were then heated at reflux in ethyl or methyl orthoacetate with acidic catalysis and continual distillation of the liberated alcohol. Only the E isomer **9** was detected, obtained by the rearrangement of the thermodynamically favoured chair trans-equatorial transition state, but etherification of the starting alcohol (15 to 20%) was observed with the more hindred analogs. Better yields are obtained with the ethyl reagent, presumably due to its higher boiling point allowing a faster completion of the rearrangement (table 2) (entries **9a** to **9d**).

Scheme 5

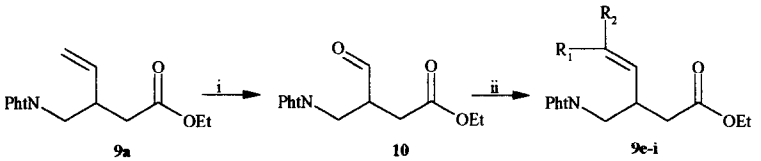


4 8 9a-9d

i: $CH_3(OEt)_3$, ε $PrCO_2H$, Δ.

The synthesis of ω-disubstituted or cis-mono derivatives **9** (**e** to **i**) was achieved by a Wittig reaction on aldehyde **10** obtained by ozonolysis of **9a** in high yield. A complete stereospecific kinetic control was observed for the formation of the cis-mono substituted compounds and the trans isomer was almost undetectable. Since this control came first, moderate yields were observed as shown in table 2 (entries **9e** to **9i**):

Scheme 6



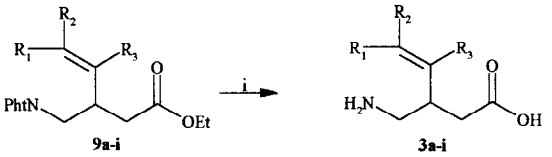
9a 10 9e-i

i: O_3,-78°C, CH_2Cl_2, 88%. ii: $Ph_3P{=}CR_1R_2$, THF, -78°C.

Table 2:	9a	9b	9c	9d	9e	9f	9g	9h	9i
R_1	H	H	H	H	Me	Et	Pr	iPr	Me
R_2	H	Me	Et	Me	H	H	H	H	Me
R_3	H	H	H	Me	H	H	H	H	H
%	80	30	27	68	34	29	39	47	51

The hydrolysis of the ester and the phthalimido group in **9**, carried out either by prolonged acidic hydrolysis (A) or sequential treatment by acid then methylhydrazine (B), afforded the free amino acids **3** in moderate yields after recristallisation in ethanol-water as shown in table 3:

Scheme 7

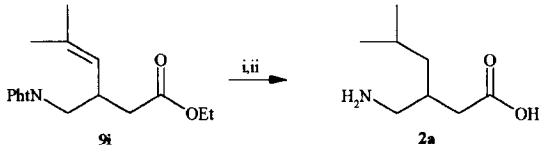


9a-i 3a-i

i: A: H_2SO_4 3N, Δ, 60 h or B: a) H_2SO_4 3N, Δ, 12 h b) $MeNHNH_2$, EtOH, RT, 60 h

This synthetic route could also gave access to the saturated derivative by hydrogenation, as illustrated by the synthesis of the reference compound 3-isobutyl GABA **2a** ($R_1 = R_2 = Me$ R_3=H):[6]

Scheme 8



9i 2a

i: H_2, 2 atm, EtOH, Pd/C; ii: HCl 6N, reflux 24 h, 20% overall yield.

Table 3:

							δ (ppm) ; (J, (Hz))			
	R_1	R_2	R_3	i	Yield %	Mp °C	R_1	R_2	R_3	Hc_3
3a	H	H	H	A	29	156	2H, m 5.35		1H, m 5.75	1H, m 2.8
3b	H	Me	H	B	30	167.5	1H, m 5.45 (15)	3H, dd 1.55	1H, m 5.5 (15)	1H, m 2.4-2.6
3c	H	Et	H	B	39	178	1H, m 5.57 (16)	2H, m 1.75 3H, t 0.75	1H, m 4.97 (16)	1H, m 2.53
3d	H	Me	Me	B	40	175.5	1H, m 5.35	3H, m 1.4	3H, m 1.45	1H, m 2.62
3e	Me	H	H	A	23	185	3H, d 1.65 (3.5)	1H, m 5.75 (11)	1H, m 5.20 (11)	1H, m 3.15
3f	Et	H	H	B	45	158	CH_3 CH_2 t, 3H m,2H 1.0 2.15	dd, 1H 5.75 (10.8)	dd, 1H 5.15 (10.8)	m, 1H 3.12
3g	nPr	H	H	B	35	hygro.	t, 3H, 0.87 m, 2H, 1.42 m, 2H, 2.10	m, 1H 5.72 (11)	m, 1H 5.17 (11)	m, 1H 3.05
3h	iPr	H	H	B	25	183	$(CH_3)_2$ CH dd6H m,1H 0.95 2.62	dd, 1H 5.55 (11)	dd, 1H 5.02 (11)	m, 1H 3.15
3i	Me	Me	H	B	38	171.5	s, 3H 1.80	s, 3H 1.65	d, 1H 4.95 (3.5)	m, 1H 3.07

The biological properties of these new class of compounds were evaluated on two purified enzymes of the GABA metabolic cascade: GAD and GABA-T as decribed.[10] None of the compounds **3** shown a significant activation of GAD up to 2.5 mM when **2a** increased it by 50% at this concentration. On the other hand only **3a** inhibited GABA-T irreversibly ($t_{1/2}$=39 min at 1mM) but to a much less extent than vigabatrin (0.3 min at 1mM).[10]

In conclusion we have developed a general access to 3-substituted-vinyl-GABA from substituted 4-phthalimido-2-buten-1-ol with the stereocontrol of the substituants by either a Claisen or a Wittig reaction[11]. Despite their low activation / inhibitory activities on GAD/GABA-T, a full evaluation of the pharmacological profile of these new GABA derivatives is in progress.

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11. All new compounds 3,4,5 and 9 gave spectroscopic data (FT-IR, 360 MHz ,^{1}H NMR,MS) and elemental analyses (CHN) in agreement with the assigned structures. For experimental details see Serfass, L., PhD thesis 95/STR1/2037. Strasbourg 1995.