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TETRAHEDRON: *ASYMMETRY*

# Stereoselective synthesis of cyclobutyl GABA analogues and related compounds from (−)-(*S*)-verbenone

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**Abstract**—The highly stereoselective conjugate addition of nitromethane to α,β-unsaturated cyclobutyl esters derived from (−)-(*S*)-verbenone has been executed to afford the adducts as single stereoisomers in good yields. These products furnish cyclobutyl GABA analogues and γ-lactams which, in turn, can be used as precursors of pyrrolidines. Moreover, both the enantiopure γ-nitro esters and the derived γ-amino esters are potentially useful for incorporation into γ-amino peptidomimetics.


γ-Aminobutyric acid (GABA) has been shown to be an important central nervous system (CNS) neurotransmitter.[1] While GABA itself has not been shown to be useful,[2] many attempts have been made to produce GABAergic drugs and prodrugs. For instance, the prototype GABA agent baclofen has shown a low absorption by CNS,[3] probably due to its high polarity. Nevertheless, the more lipophilic prodrug 3-(*p*-chlorophenyl)pyrrolidine, a biosynthetic precursor of baclofen, is more suitable to cross the blood–brain barrier where conversion to a baclofen-type compound could take place.[4] Other GABAergic agonist recently commercialized is gabapentin (GBP, Neurontin®) which displays important anticonvulsant[5] and analgesic[6] activity as well as other interesting properties. Moreover, several derivatives bearing substituents at the cyclohexane ring, including chiral compounds, have been shown to be useful for the treatment of diabetic retinopathy,[7] and gabapentin-lactam (GBP-L) is neuroprotective in retinal ischemia whereas GBP is not neuroprotective in vivo (Chart 1).[8]

The inclusion of γ-amino acids in γ-peptidomimetics has also attracted much attention owing to the sec-

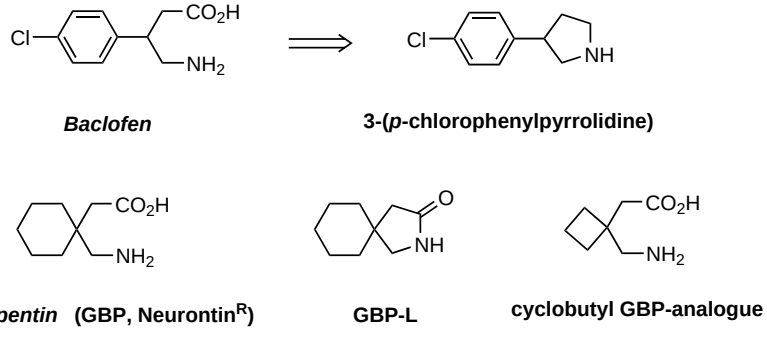


**Chart 1.**

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ondary structures of such compounds, which have been described to be more stable than α-peptides,[9] conferring on them potential usefulness in the development of new therapeutic agents.

The very recent finding that cyclobutyl analogues of gabapentin are useful in the treatment of insomnia[10] prompts us to report our preliminary results on the synthesis of novel chiral cyclobutyl γ-amino acids and related products. In connection with our research program devoted to the synthesis and structural study of new types of amino acids, we describe herein a useful and versatile synthetic approach to these kind of molecules. The synthesis of these compounds is based on the highly stereoselective conjugate addition of nitromethane to cyclobutyl α,β-unsaturated esters derived from (−)-(*S*)-verbenone (95% e.e.) as a source of chirality. Nitro compounds have been used as nucleophiles[11] or as Michael acceptors[12] to prepare γ-amino acid derivatives using intrinsically chiral substrates or chiral auxiliaries to produce enantiomerically pure products. We describe herein our preliminary results in this field showing the scope of the methodology employed to synthesize the title compounds.

Oxidative cleavage of the double bond in (−)-(*S*)-verbenone followed by manipulation of the functional groups led to aldehydes,[13] which were converted into substrates **1**–**4** through Wittig-type condensations with suitable phosphonates or phosphoranes. In this way, both (*Z*)- and (*E*)-isomeric conjugated esters **1**[14] and **2**[15] were prepared. Compounds **3** and **4**[14] were only available as the (*E*)-isomers. Nitromethane did not add to the trisubstituted olefin **4** under the usual conditions. On the contrary, substrates **1**–**3** reacted with nitromethane in the presence of tetrabutylammonium fluoride, in THF at room temperature for 20 h, to afford adducts **5**–**7** as single isomers in 75–80% yields. It is noteworthy that the geometry of the double bond did not influence the π-facial diastereoselection of the nucleophilic addition since the same adduct was obtained from the corresponding (*Z*)- or (*E*)-isomer whose reactivities were similar. The configuration of the newly formed stereogenic center was determined as described below. Reduction of the nitro group was performed by treatment of **5**–**7** with ammonium formate and 10% Pd on charcoal in boiling methanol for 20 h to give the corresponding amino esters in 68–70% yields.[16] The *tert*-butyl nitro ester **6** afforded amino ester **8** which is a promising candidate for incorporation into a γ-peptide by coupling of the amino group. This intermediate is complementary to substrates **5**–**7** bearing a masked amine to be produced in later steps. These compounds can be coupled with other amino acids through the carboxylic acid group after hydrolytic cleavage of the ester-protecting group.

The amino esters resulting from the reduction of nitromethyl esters **5** and **7** reacted further under the reaction conditions to afford the γ-lactams **9** and **10**, respectively. Compound **9** provided crystals suitable for X-ray structural analysis allowing the assignment of the (*S*)-configuration to the stereogenic center created in the addition step (Fig. 1).[17] This configuration can be rationalized by considering the preferential orientation of the attack on the face of the double bond opposite to the *gem*-dimethyl substitution of the cyclobutane. The same induced chirality has been observed in the addition of *N*-benzyl hydroxylamine[14] and in the cycloaddition of diazomethane[18] to the same or closely related substrates (Scheme 1).

The γ-lactams, in turn, can furnish the free amino acids by hydrolysis (6N aqueous HCl, 100°C, 8 h), as shown by the conversion of **9** into **10**, or can be useful as precursors in the synthesis of pyrrolidines, the biosynthetic precursors of GABA analogues.

Thus, the stereoselective conjugate addition of nitromethane to α,β-unsaturated esters derived from (−)-(*S*)-verbenone, is a convenient method for the synthesis of optically active cyclobutyl γ-amino acids and related products. The synthesis of these compounds as well as their biological activities is under active investigation in our laboratory.

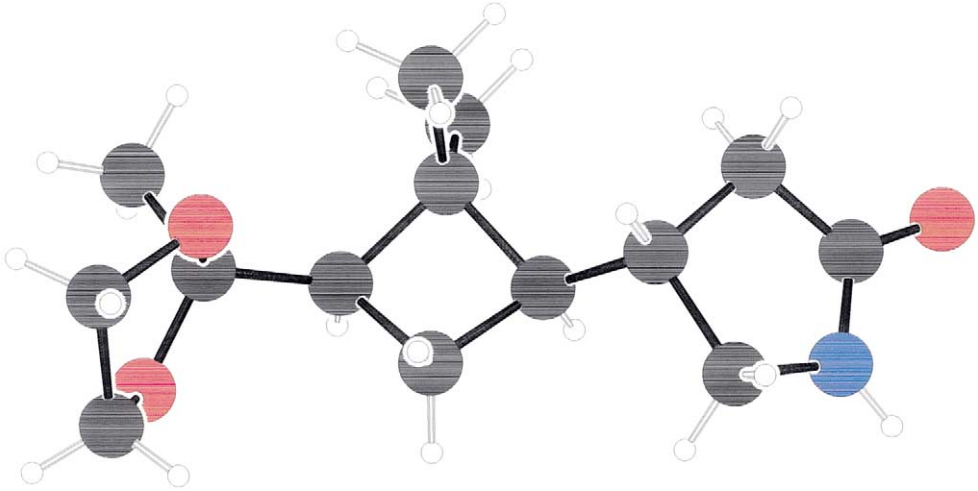
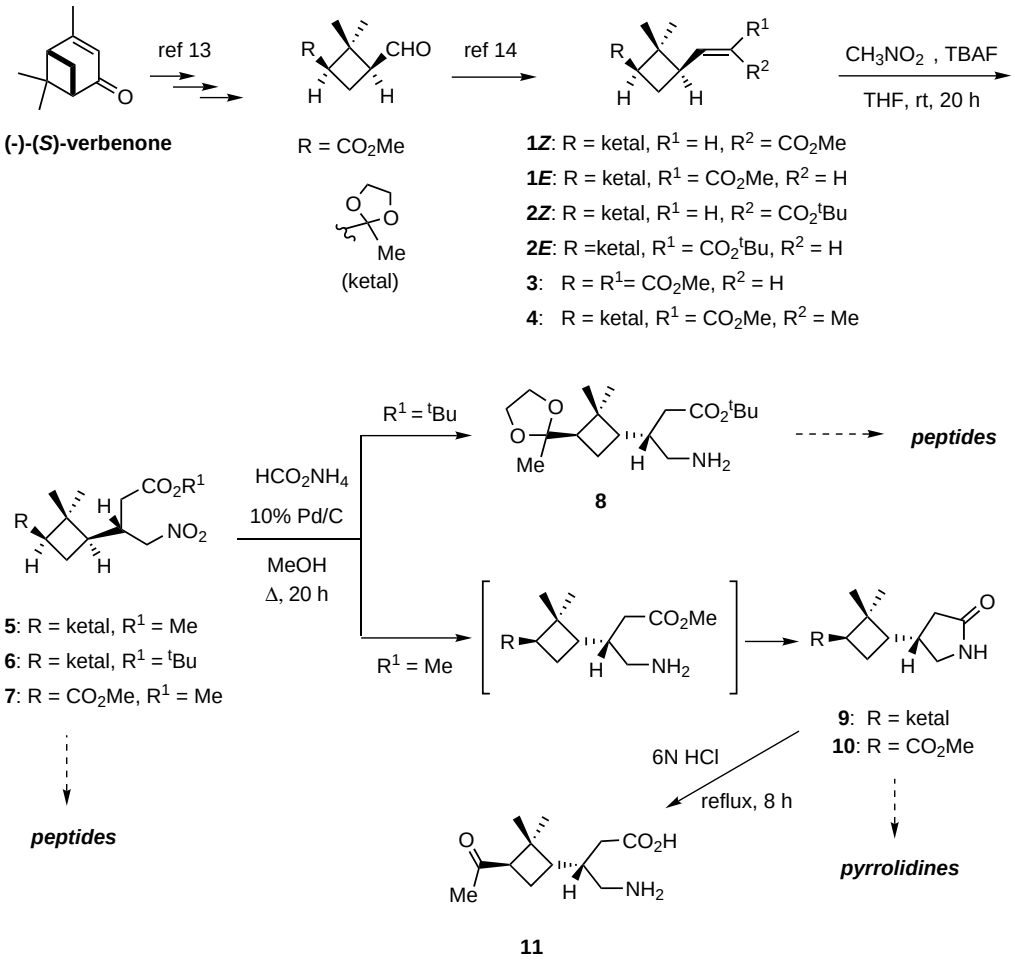


**Figure 1.** Structure of γ-lactam **9** as determined by X-ray structural analysis.




**Scheme 1.**

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15. All new products were identified and fully characterized by their spectroscopic data and physical constants. Selected data follow. Compound **6**: oil, $[\alpha]_D$ −10.6 (*c* 1.23, MeOH); compound **7**: oil, $[\alpha]_D$ −8.75 (*c* 1.60, $CHCl_3$); compound **8**: $[\alpha]_{285}$ −3.3 (*c* 0.90, MeOH); compound **9**: crystals, mp 70–71°C (from acetone), $[\alpha]_D$ −15.4 (*c* 0.65, $CHCl_3$); compound **10**: crystals, mp 108–110°C (from ethanol), $[\alpha]_D$ −17.0 (*c* 1.00, $CHCl_3$). The e.e.s for these compounds was assumed to be 95%, the same as for the verbenone starting material, as determined by $^1H$ NMR after derivatization. Diastereomeric homogeneity was verified from the corresponding $^{13}C$ NMR spectra showing one single set of signals in each case.
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