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An update on the stereoselective synthesis of γ -amino acids

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ABSTRACT

This review outlines the most recent papers describing the stereoselective synthesis of γ -amino acids. In this update, the γ -amino acids have been classified according to the type of compounds, position and number of substituents, and depending on the type of substrate, acyclic, carbocyclic or azacyclic derivatives, following in the first case an order related to the strategy used, whereas in the second and third cases the classification is based on the ring size.

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Contents

1. Introduction	1000
2. Stereoselective synthesis of acyclic γ -amino acids	1000
2.1. α -Substituted and α,α -disubstituted γ -amino acids	1000

Abbreviations: ABO, 2,7,8-trioxabicyclo[3.2.1]octane; Ac, acetyl; ACPECA, 4-aminocyclopent-2-ene-1-carboxylic acid; AHPPA, 4-amino-3-hydroxy-5-phenylpentanoic acid; AMCP, 2-(aminomethyl)-cyclopentanecarboxylic acid; APCH, 2-(1-aminopropyl)cyclohexanecarboxylic acid; APTS, (3-aminopropyl)triethoxysilane; ATCAS, 4-amino(methyl)-1,3-thiazole-5-carboxylic acids; BBB, blood–brain-barrier; 9-BBN, 9-borabicyclo[3.3.1]nonane; BGT-1, mammalian betaine transporter; BINAP, 2,2-bis(diphenylphosphino)-1,1-binaphthyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; CACP, *cis*-3-aminocyclopentane-1-carboxylic acid; CAL, *Candida antarctica*; CAMP, *cis*-2-aminomethylcyclopropane-1-carboxylic acid; CAN, cerium ammonium nitrate; Cbz, carbobenzyloxy; CDI, *N,N*-carbonyldiimidazole; Cinn, cinnamyl; CPME, cyclopentyl methyl ether; CPP, 3-amino-4-difluoromethylenecyclopentanecarboxylic acid; DABCO, 1,4-diazabicyclo[2.2.2]octano; Dap, dolaproine; DBAD, di-*tert*-butyl azodicarboxylate; DBF, dibromoformaldehyde; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DCR, diaza-cope rearrangement; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; d.e., diastereoisomeric excess; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DIB, (diacetoxyiodo)benzene (also BAIB); DIBAL-H, diisobutylaluminum hydride; DIEA, diisopropyl ethylamine; Dil, dolaisoleucine; DIPEA, diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DME, dimethyl ether; DME, dimethoxyethane; DMF, *N,N*-dimethylformamide; DMP, 2,2-dimethoxypropane; DMP, Dess–Martin–Periodinane; DMSO, dimethyl sulfoxide; DPPA, diphenylphosphoryl azide; d.r., diastereoisomeric ratio; E, entgegen (opposite, *trans*); e.e., enantiomeric excess; Fmoc, 9-fluorenylmethoxycarbonyl; GABA, γ -aminobutyric acid; GABA-AT, γ -aminobutyric acid aminotransferase; GABA-T, γ -aminobutyric acid transaminase; GABOB, γ -amino- β -hydroxybutyric acid; HBTU, *N,N,N'*, *N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate *O*-(benzotriazol-1-yl)-*N,N,N'*, *N'*-tetramethyluronium hexafluorophosphate; HMPA, hexamethylphosphoramide; HOBT, 1-hydroxybenzotriazole; HWE, Horner–Wadsworth–Emmons; *hpen*, (*R,R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane; HPLC, high performance liquid chromatography; HLAP, horse liver acetone powder; IBX, 2-iodoxybenzoic acid; IPA, isopropyl alcohol; Ipc₂BAl, allyldiiso-2-caranylborane; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide; LiTMP, lithium 2,2,6,6-tetramethylpiperidide; MAHT, malonic acid half thioester; MBA, methylbenzylamine; *m*-CBPA, *m*-chloroperoxybenzoic acid; MMAH, 3-methoxy-5-methyl-4-(methylamino) hexanoic acid; MMPP, magnesium monoperoxyphthalate; MNBA, 2-methyl-6-nitrobenzoic anhydride; MSA, methanesulfonic acid; MsCl, methanesulfonyl chloride; MTBE, *tert*-butyl ether; MW, microwave; NaHDMS, sodium bis(trimethylsilyl)amide; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphonate; NBS, *N*-bromosuccinimide; NFI, *N*-fluorobenzenesulfonamide; NMM, *N*-methylmorpholine; NMO, 4-methylmorpholine *N*-oxide; Ns, *p*-nitrobenzenesulfonyl; OYE, Old Yellow Enzyme; PDC, pyridinium dichromate; PhMe, toluene; PhthN, phthalimido; PMHS, polymethylhydrosiloxane; PIFA, [bis(trifluoroacetoxy)iodo]benzene; PLAP, Porcine Liver Acetone Powder; PLP, pyridoxal phosphate; PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; PPTS, pyridinium *p*-toluenesulfonic acid; PTC, phase transfer catalyst; Py, pyridine; rt, room temperature; SAAs, sugar amino acids; ω -TABG, ω -transaminase from *Burkholderia graminis*; TAc, trichloroacetamide; TACP, *trans*-3-aminocyclopentane-1-carboxylic acid; TAMP, *trans*-2-aminomethylcyclopropane-1-carboxylic acid; ω -TAPO, ω -transaminase from *Polaromonas* sp.; TBAB, tetra-*n*-butylammonium bromide; TBAF, tetra-*n*-butylammonium fluoride; TBAI, tetra-*n*-butylammonium iodide; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBDPS, *tert*-butyldiphenylsilyl; TBME, *tert*-butyl methyl ether; TBS, *tert*-butyldimethylsilyl (also TBDMS); TBSOTf, *tert*-butyldimethylsilyl trifluoromethanesulfonate; *t*-Bu, *tert*-butyl; TCCA, trichloroisocyanuric acid; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; TMS, trimethylsilylchloride; TMSBr, trimethylsilylbromide; TMSCl, trimethylsilylchloride; TMSCN, trimethylsilylcyanide; TMSOTf, trimethylsilyl trifluoromethanesulfonate; TBSOTf, *tert*-butyldimethylsilyl trifluoromethanesulfonate; Ts, *p*-toluenesulfonyl; TBTA, *tert*-butyl 2,2,2-trichloroacetimidate; TIPS, triisopropylsilyl (alcohol protection); TMDS, 1,1,3,3-tetramethyldisiloxane; Tris, 2-amino-2-(hydroxymethyl)-1,3-propanediol.

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2.2.	β -Substituted and β,β -disubstituted γ -amino acids	1002
2.3.	β -Hydroxysubstituted γ -amino acids	1019
2.4.	γ -Substituted γ -amino acids	1021
2.5.	Polysubstituted γ -amino acids	1028
2.5.1.	α,β -Disubstituted γ -amino acids	1028
2.5.2.	α,γ -Disubstituted γ -amino acids	1029
2.5.3.	β,γ -Disubstituted γ -amino acids	1031
2.5.4.	α,β,γ -Trisubstituted γ -amino acids	1033
3.	Stereoselective synthesis of cyclic γ -amino acids	1034
3.1.	Synthesis of $C_{\alpha,\beta}^3$ derivatives	1034
3.2.	Synthesis of $C_{\beta,\gamma}^3$ derivatives	1039
3.3.	Synthesis of $C_{\alpha,\beta}^4$ derivatives	1040
3.4.	Synthesis of $C_{\beta,\gamma}^4$ derivatives	1040
3.5.	Synthesis of $C_{\alpha,\gamma}^5$ derivatives	1041
3.6.	Synthesis of $C_{\alpha,\beta}^5$ derivatives	1041
3.7.	Synthesis of $C_{\alpha,\gamma}^5$ derivatives	1042
3.8.	Synthesis of $C_{\alpha,\beta}^6$ derivatives	1045
3.9.	Synthesis of $C_{\beta,\gamma}^6$ derivatives	1046
3.10.	Synthesis of $C_{\alpha,\gamma}^6$ derivatives	1047
4.	Stereoselective synthesis of azacyclic γ -amino acids	1048
4.1.	Synthesis of N, C_{α}^5 derivatives	1048
4.2.	Synthesis of N, C_{β}^5 derivatives	1048
4.3.	Synthesis of N, C_{γ}^6 derivatives	1050
5.	Conclusions	1051
	Acknowledgements	1051
	References	1052

1. Introduction

γ -Aminobutyric acid **1** (GABA), is the major inhibitory neurotransmitter in the mammalian central nervous system modulated by three types of receptors: GABA_A, GABA_B and GABA_C,¹ and plays a significant role in several brain disorders including epilepsy,² neuropathic pain,³ depression and anxiety,⁴ migraine,⁵ Parkinson's disease,⁶ Alzheimer's disease⁷ and Huntington's chorea.⁸ However, the administration of GABA orally or intravenously is not an efficient therapy due to its low lipophilicity, and its very poor ability to cross the blood–brain barrier (BBB).⁹ Consequently, the synthesis of more lipophilic GABA derivatives capable of crossing the blood–brain barrier, which would inhibit the GABA transaminase (GABA-T), the enzyme that degrades GABA,¹⁰ has been the target of a great number of studies. For example, the first major agonist of the GABA_B receptor is the Baclofen **2** (Lioresal®), which was originally designed as a lipophilic analogue of GABA that would display enhanced permeability through the blood–brain barrier.¹¹ It has been found that the (*R*)-enantiomer is substantially more active than the (*S*)-enantiomer and is used as a muscle relaxant and antispastic agent,¹² whereas Arbaclofen placarbil **3** serves as a pro-drug of (*R*)-Baclofen, which was developed to enhance oral absorption compared to the parent compound.^{13,14} (*R*)-Phenibut **4**, is another agonist at the GABA_B receptor,¹⁵ and has been used as psychotropic, anticonvulsant, antidepressant and antineuropathic drug.^{16,17} (*S*)-Pregabalin **5** (Lyrica®) is used for the treatment of epilepsy, neuropathic pain, antihyperalgesic and generalized anxiety disorders.¹⁸ (*S*)-Vigabatrin **6** (Sabril®), is another potent irreversible inhibitor of GABA-T and is used in cases where classic antiepileptics are ineffective,¹⁹ and has been shown to be effective in the treatment of addiction.²⁰ Gabapentin **7** (Neurontin®), an achiral β,β -disubstituted GABA analogue, is commercialized for the treatment of several cerebral disorders diseases, principally for the treatment of peripheral neuropathic pain (Fig. 1).²¹ Additionally, the γ -amino acids represent great potential as building blocks for the synthesis of γ -peptides²² and heterogeneous backbone foldamers.²³

The therapeutic potential of GABA derivatives in enantiomerically pure form has prompted organic chemists to report numerous

procedures for their stereoselective synthesis, and the purpose of this review is to describe a summary of the most relevant procedures reported during the last few years. It is important to take into account that a summary of procedures was already reported in early 2007,²⁴ and hence this report specially covers the new strategies or methodologies trying to focus the subject in an advantageous classification that can be useful to specialized readers on this area, covering only the years from 2007 until early 2016. In this update the γ -amino acids have been classified according on the type of compounds, position and number of substituents, and depending on the type of substrate, acyclic, carbocyclic or azacyclic derivatives, following in the first case an order related to the strategy used, whereas in the second and third cases the classification will be based on the ring size.

2. Stereoselective synthesis of acyclic γ -amino acids

2.1. α -Substituted and α,α -disubstituted γ -amino acids

The approach reported for the diastereoselective and enantioselective synthesis of α -substituted and α,α -disubstituted γ -amino acids is the reaction between appropriate enolates as nucleophiles with bromoacetonitrile or the corresponding nitroethylene and *N*-

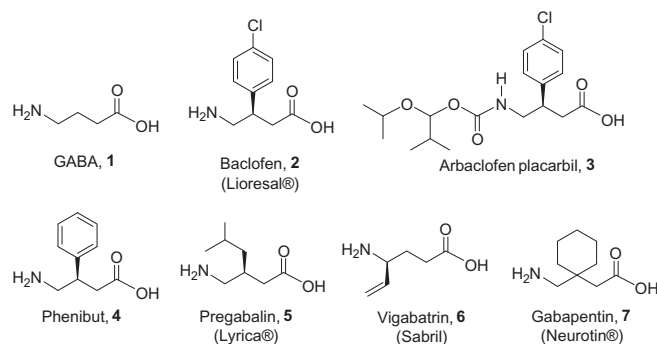


Figure 1. Structure of GABA and pharmaceutical analogues.

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