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Stereoselective 5-*exo-trig* radical cyclization in the enantioselective synthesis of Pregabalin

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Abstract—A practical stereoselective 5-*exo-trig* radical cyclization procedure was developed in order to prepare enantiomerically pure GABA derivative precursors (4-alkyl-pyrrolidin-2-ones). This procedure allows much more rapid access to optically pure GABA derivatives, such as the powerful antiepileptic agent (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (Pregabaline).

Pregabalin **1** ((*S*)-(+)-3-aminomethylhexanoic acid) is a novel and potent anticonvulsant agent for the treatment of epilepsy and pain.[1] Its biological activity is comparable to that of Gabapentin **2**.[2] Pregabalin was originally obtained along with its opposite *R* enantiomer,[3] however, it was found that this mixture of enantiomers did not posses pharmacological activity after animal tests.[1a] Thus several enantioselective routes to obtain the desired *S* enantiomer have been achieved, not only at industrial level[3,4] but also at academic level[1a] (Fig. 1).

Recently, we reported an accessible method for the synthesis of GABA derivatives **3** and **4**.[5] The 5-*exo-trig* radical cyclization reaction of optically pure allylic amides **5** to give diastereoisomeric pyrrolidinones **6** and **7** was employed as the key reactions.[6] Under the classical free radical condition reactions (Bu_3SnH/AIBN/in refluxing benzene or lauroyl peroxide (DLP) in refluxing benzene), the radical cyclization step was not stereoselective at all.[5–7] However, the presence of the α-phenylethylamine group[8] as chiral auxiliary in the framework of the pyrrolidinones **6** and **7** made it possible to isolate each of the diastereoisomers by column chromatography, which eventually resulted in the isolation of the GABA derivatives **3** and **4** (Scheme 1).

We now report a stereoselective 5-*exo-trig* radical cyclization version of the reaction showed in Scheme 1, and

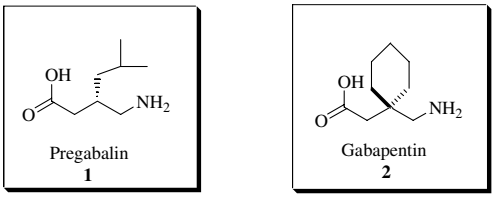
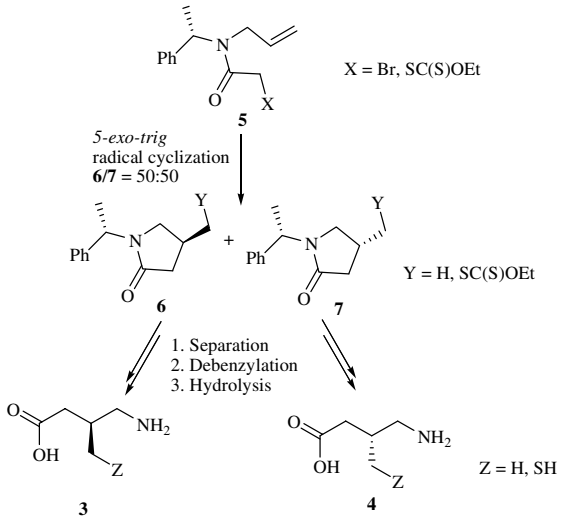


Figure 1. GABA derivatives as potent anticonvulsants.



Scheme 1. The synthesis of GABA derivatives **3** and **4** applying the 5-*exo-trig* radical cyclization as the key reaction.

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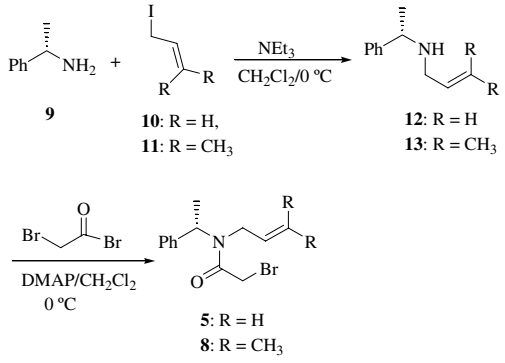
its application to the enantioselective synthesis of the powerful anticonvulsant agent, Pregabalin **1**.

Since the free radical reaction conditions depicted in Scheme 1 were carried out at high temperatures (refluxing solvent temperatures, within 80–100 °C), the absence of diastereoselectivity during the cyclization reaction was actually expected.[5–7] Furthermore, recent studies have shown that the stereoselectivity of free radical cyclization is greatly enhanced as a result of the use of a combination of low temperatures and Lewis acids.[9] Additionally, the use of chiral auxiliaries such as oxazolidinones, sulfoxides, chiral esters and carbohydrates have been also investigated for stereoselective radical cyclization reactions.[10]

Thus, we decided to find optimal reaction conditions for the radical cyclization reaction in order to achieve improved stereoselective outcome. In this sense, we choose to explore lower temperatures and Lewis acid catalysts with the expectation that by controlling the amide electron delocalization between the nitrogen and carbonyl group, the nature of the conformational energy of the transition state of the cyclization reaction can be altered, and thus produce one pyrrolidinone in excess. Having this in mind, and because the chiral auxiliary is not highly oxygenated (there are not multiple sites for chelation), we thought that common Lewis acids such as $BF_3{\cdot}OEt_2$ and $TiCl_4$ may work properly.

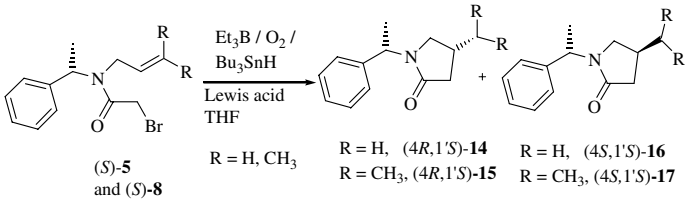


Scheme 2. Synthesis of chiral allylic amides **5** and **8**.

The desired chiral auxiliaries (*S*)-**5** and (*S*)-**8** for the 5-*exo-trig* radical cyclization study were readily prepared following the literature procedure as summarized in Scheme 2.[5] Treatment of (*S*)-α-methylbenzylamine **9** with allyl iodine **10** or dimethylallyl iodine **11** in the presence of triethylamine furnished secondary amines (*S*)-**12** and (*S*)-**13**, which were then converted to allylic amides (*S*)-**5** and (*S*)-**8** by the treatment with bromoacetyl bromide and DMAP (Scheme 2).

The radical precursors (*S*)-**5** and (*S*)-**8** were next subjected to reductive radical reaction conditions using $Bu_3SnH/BEt_3/O_2$/Lewis acids at different temperatures and in THF. As we anticipated, the presence of Lewis acids at lower temperature indeed dramatically enhance the stereoselectivity to give (4*S*,1′*S*)-pyrrolidin-4-ones as the major diastereoisomers (entries 6–9). Thus, using $BF_3{\cdot}OEt_2$ and $TiCl_4$ as the Lewis acids, 91:9 and 86:14 diatereoisomeric ratios were achieved, respectively, at −78 °C (entries 9 and 7). However, with $MgBr_2$, $EtAlCl_2$ and TMSOTf, the reaction was neither stereoselective nor effective (entries **5**, **10** and **11**).[11] This is interesting because the $MgBr_2$ has been successfully used in a number of stereoselective free radical cyclization reactions.[9d,i,10a,d,e] When no Lewis acids were used, no diastereoselectivity was observed even at −78 °C (Table 1, entries 1–4).

Table 1. Stereoselective tin-mediated radical cyclization



Entry	R	Temperature (°C)	Lewis acid	Yield[a] (%)	Ratio[b]	
					(4*R*,1′*R*)-**14** (4*R*,1′*R*)-**15**	(4*S*,1′*S*)-**16** (4*S*,1′*S*)-**17**
1	H	rt	None	78	53	47
2	H	−78	None	81	57	43
3	Me	rt	None	78	55	45
4	Me	−78	None	82	54	46
5	H	−78	$MgBr_2$	77	42	58
6	H	−78	$TiCl_4$	68	15	85
7	Me	−78	$TiCl_4$	74	14	86
8	H	−78	BF_3OEt_2	75	10	90
9	Me	−78	BF_3OEt_2	84	9	91
10	H	−78	$EtAlCl_2$	N.R.	—	—
11	H	−78	TMS-triflate	N.R.	—	—

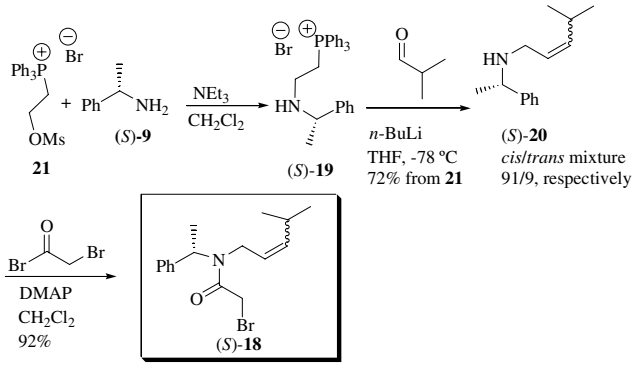
[a] Isolated yields.
[b] Determined ratios by ^1H NMR.

The absolute configurations for all the pyrrolidin-4-ones were correlated with those previously reported in the literature.[5,6,11]

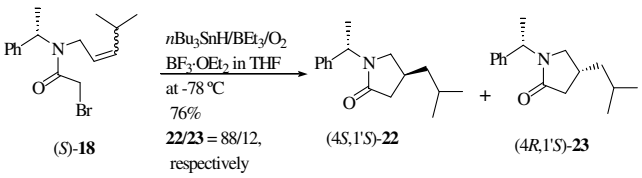
Having established the effectively stereoselective 5-*exo*-*trig* radical cyclization protocol for the synthesis of optically pure pyrrolidin-4-ones, we next proceeded to synthesize the desired chiral auxiliary (*S*)-**18**, which is the precursor for the enantioselective synthesis of Pregabalin **1**. A different route had to be developed to synthesize chiral amide (*S*)-**18** from that for the preparation of chiral amides (*S*)-**5** and (*S*)-**8**. This new strategy consists of the application of a Wittig olefination reaction between the chiral phosphonium salt (*S*)-**19** and the isobutyraldehyde followed by N-acylation of amine (*S*)-**20**.

Chiral phosphonium salt (*S*)-**19** was prepared by the reaction of (*S*)-phenylethylamine **9** and mesylate-phosphonium salt **21** in the presence of triethylamine (Scheme 3). It is worth noting that only one column chromatography purification was necessary for the preparation of allylic amide (*S*)-**20** from (*S*)-**9** and **21**.

Chiral allylic amide (*S*)-**18** was then subjected to stereoselective 5-*exo*-*trig* radical cyclization with the best reaction conditions shown in Table 1 (entries 8 and 9) and gave (4*S*,1′*S*)-4-isopropylpyrrolidinone **22** in good yield and stereoselectivity (Scheme 4).



Scheme 3. Synthesis of chiral allylic amide (*S*)-**18**.

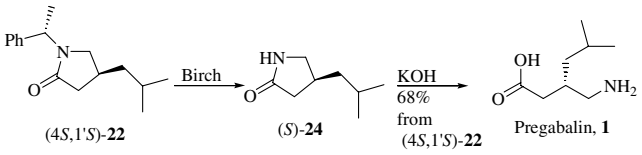


Scheme 4. Synthesis of the pyrrolidinone precursor of the Pregabalin.

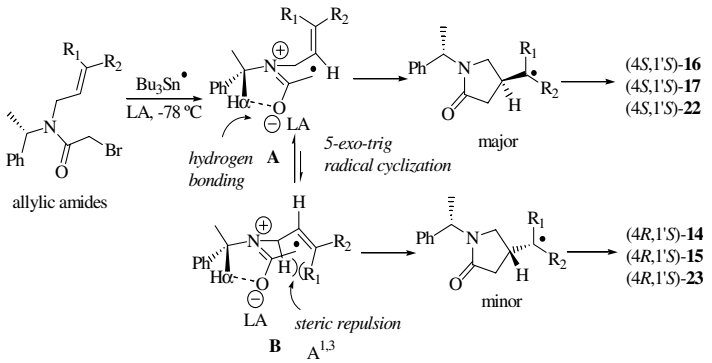
A model explaining the stereo outcome of the reaction is outlined in Scheme 5. In this model, the N–C bond of the amide is considered as a formal double bond, which is obviously favored by the presence of the Lewis acid. Therefore, chairlike transition states for the 5-*exo*-*trig* radical cyclization (**A** and **B**) are proposed. Both, structures **A** and **B** can be locked by a weak Hα–O=C hydrogen bonding interaction to give conformationally restrained structures for cyclization.[12] Furthermore, molecular models suggest that **B** may be slightly disfavored by allylic 1,3-strain ($A^{1,3}$) to produce the minor pyrrolidin-4-ones (see Scheme 5).

With optically pure pyrrolidinone (4*S*,1′*S*)-**22** in hand, we completed the enantioselective synthesis of Pregabalin **1**. Thus, removal of the benzyl group of (4*S*,1′*S*)-**22** was achieved by using Birch reduction to afford (*S*)-4-isobutyl-pyrrolidin-2-one (*S*)-**24** in good yield, which was then submitted to basic hydrolysis to give enantiomerically pure Pregabalin **1** (up to 98% ee); $[\alpha]_D$ +9.6 (*c* 1.0, H_2O) (Lit.[3] $[\alpha]_D$ 10.1, *c* 1.1, H_2O) Scheme 6.

In conclusion, the development of a practical stereoselective 5-*exo*-*trig* radical cyclization protocol of allylic amides allowed us to rapidly access to optically pure GABA derivatives. The enantioselective synthesis of Pregabalin was successfully achieved by using this method. Additionally, with chiral phosphonium salt (*S*)-**19** in



Scheme 6. Completion of the synthesis of Pregabalin.



Scheme 5. Radical cyclization models.

hand, a number of chiral amides with different side chains can be prepared for the synthesis of different optically pure GABA derivatives. Thus, the preparation of a library of GABA derivatives will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.054.

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