Total synthesis of Norepinephrine Reuptake Inhibitor, Rolipram: A review

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Abstract:

γ-aminobutyric acid (GABA) and its analogues rolipram , brivaracetam and (S)-pregabalin are useful division of compounds possessing interesting pharmacological activities. The present review represented the synthesis rolipram employed the bifunctional catalyst mediated asymmetric Michael addition of malonate nucleophiles, desymmetrization of glutaric anhydride and the chiral heterogeneous catalysts as key step.

Introduction:

Chirally branched pyrrolidones are among the most bioactive heterocyclic compounds in organic chemistry due to their ubiquitous structural motifs in natural and unnatural products with varied biological activity.[1] The rolipram (**1-2**) are simple cyclo-GABA derivative possessing a catechol type ring at chiral carbon (C-3).[2] The (±)-rolipram was discovered and developed by Schering AG pharmaceutical company at Berlin, Germany in early 1990[3] and it acts as a selective phosphodiesterase-4 inhibitor and potential antidepressant drug. The most active enantiomer (*R*)-rolipram **1** (Fig. 10)[4] is an advanced novel class of effective antidepressant drug with additional possible emetic,[5] which act as selective inhibitor for cardiac cyclic AMP phosphodiesterase, present in brain tissue and mainly effective for the PDE4B and subtype of PDE4.[6] Additionally, (*R*)-rolipram **1** has also been proposed as a antiinflammatory,[7] immunosupressant,[7] putative antiparkinsonian,[8] neuroprotective,[9] antipsychotic[10] and has been suggested for the treatment of multiple sclerosis.[10]

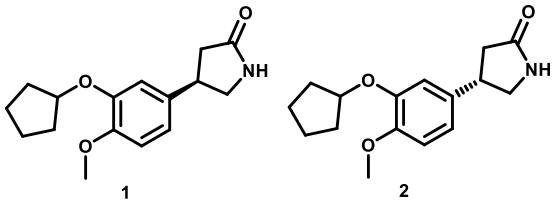
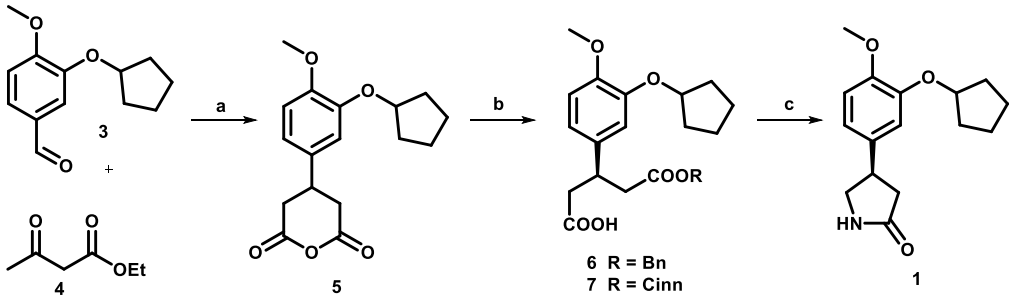


Figure 10. Some structures of GABA derivatives (**1-2**).

Synthesis of (*R*)-1 and (*S*)-rolipram 2:

Hamersak, Z. (2013)[11c]

Z. Hamersak and co-workers reported the enantioselective synthesis of (*R*)-**1** and (*S*)-rolipram **2** by cinchona alkaloid catalyzed opening of cyclic anhydride (desymmetrization of glutaric anhydride) as key step (Scheme 42). The aldehyde intermediate **3** was obtained from commercially available isovanillin *via O*-alkylation with cyclopentylbromide in 95% yield. The aldehyde **3** on condensation with ethylacetoacetate **4** followed by hydrolysis with concentrated alkali afforded the glutaric acid intermediate which on subsequent treatment with acetic anhydride furnished the anhydride **5** in 93% yield. The quinine mediated opening of anhydride **5** with benzyl alcohol or cinnamyl alcohol furnished ester **6** in 98% yield or **7** in 95% yield, respectively. The corresponding ester on treatment with DPPA afforded the azide derivative which was thermally rearranged into an unstable isocyanate intermediate and reacts with a nucleophile to afford *N*-protected aminoester followed by thermal decarboxylation to furnish the cyclized product (*R*)-rolipram **1** in 51% yield. The synthesis of (*S*)-rolipram **2** was performed by following an analogous series of reactions as described in Scheme 42.

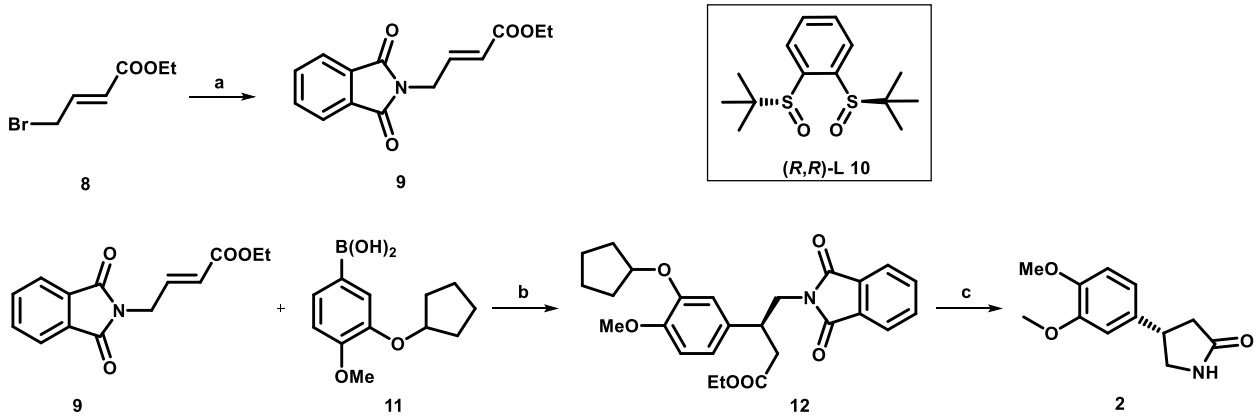


Scheme 42. *Reagents and conditions*: (a) i) piperidine, EtOH, rt, 2 days, 73%; ii) KOH, H_2O:EtOH, rt, 4 days, 74%; iii) Ac_2O, 110 ^oC, 30 min, 93%; (b) quinine, BnOH or CinnOH, rt, 3 days, 98% for **6** and 95% for **7**; (c) DPPA, Et_3N, toluene, 90 ^oC, 30 min, 51%.

Liao, J. (2011)[11d]

J. Liao and co-workers reported the total synthesis of (*S*)-rolipram **2** employed the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to ethyl-γ-phthalimidocrotonate by using bis-sulfoxide ligands as key step (Scheme 43). The (*E*)-ethyl-4-bromobut-2-enoate **8** on treatment with phthalimide potassium salt afforded the ethyl-γ-phthalimidocrotonates **9** in excellent yield. The compound **9** which on treatment with 3-cyclopentoxy-4-$MeOC_6H_3$-boronic acid **11** in the presence of ligand (*R,R*)-L **10** furnished the phthalimide intermediate **12** in 85% yield. The ester

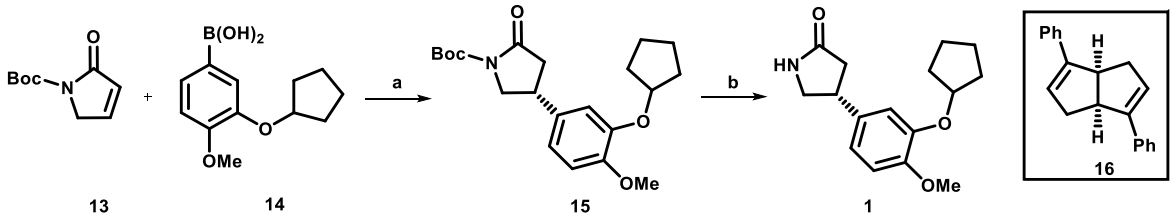
derivative **12** on phthalimide deprotection with hydrazine hydrate and cyclization under basic conditions afforded the target compound (*S*)-rolipram **2** in 78% yield.



Scheme 43. *Reagents and conditions*: (a) Potassium phtahlimide, DMF, rt, 12 h, 90%; (b) [(*R*,*R*)L**10**-RhCl]$_2$ (2.5 mol%), CH_2Cl_2:H_2O, KOH (50 mol%), 40 ^oC, 1.5 h, 85%; (c) i) NH_2NH_2, THF, 0 ^oC-rt, 5 h; ii) Et_3N, toluene, reflux, 20 h, 78% (over two steps).

Lin, G. Q. (2011)[11e]

G. Q. Lin and co-workers described the asymmetric synthesis of (*R*)-rolipram **1** employed the rhodium/diene-catalyzed asymmetric addition of arylboronic acids to α,β-unsaturated γ-lactams (Scheme 44). The boronic acid derivative **14** on enantioselective addition to lactam **13** in the presence of rhodium complex **16** afforded the *N*-Boc protected lactam derivative **15** in 98% yield with 99% ee (after single crystallization). The compound **15** on *N*-Boc deprotection with TFA furnished the final compound (*R*)-rolipram **1** in quantitative yield.



Scheme 44. *Reagents and conditions*: (a) [RhCl(C_2H_4)$_2$]$_2$/**16** (3 mol% Rh), toluene/H_2O, Et_3N, 60 ^oC, 98%; (b) TFA, CH_2Cl_2, 0 ^oC-rt, quantitative.

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References:

1. a) Dias, R. M. P.; Momo, P. B.; Burtoloso, A. C. B. *Tetrahedron* **2017**, *73*, 3720; (b) Matviiuk, T.; Madacki, J.; Mori, G.; Orena, B. S.; Menendez, C.; Kysil, A.; Andre-Barres, C.; Rodriguez, F.; Kordulakova, J.; Mallet-Ladeira, S.; Voitenko, Z.; Pasca, M. R.; Lherbet, C.; Baltas, M. *Eur. J. Med. Chem*. **2016**, *123*, 462.
2. (a) Belliotti, T. R.; Capiris, T.; Ekhato, V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Melzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Zhi-Su, T.; Weber, M. L.; Wustrow, D. J. *J. Med. Chem.* **2005**, *48*, 2294; (b) Costantino, G.; Macchiarulo, A.; Guadix, A. E.; Pellicciari, R. *J. Med. Chem.* **2001**, *44*, 1827.
3. Zhu, J.; Mix, E.; Winblad, B. *CNS Drug Reviews* **2001**, *7*, 387.
4. (a) Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 870; (b) Mulzer, J. *J. Prakt. Chem.* **1994**, *336*, 287.
5. Heaslip, R. J.; Evans, D. Y. *Eur. J. Pharmacol.* **1995**, *286*, 281.
6. Day, J. P., Lindsay, B.; Riddell, T.; Jiang, Z.; Allcock, R. W.; Abraham, A.; Sookup, S.; Christian, F.; Bogum, J.; Martin, E. K.; Rae, R. L.; Anthony, D.; Rosair, G. M.; Houslay, D. M.; Huston, E.; Baillie, G. S.; Klussmann, E.; Houslay, M. D.; Adams, D. R. *J. Med. Chem.* **2011**, *54*, 3331.
7. (a) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097; (b) Sekut, L. ; Yarnall, D.; Stimpson, S. A.; Noel, L. S.; Bateman, F. R.; Clark, R. L.; Brackeen, M. F.; Menius J. A.; Conolly, K. M. *Clin. Exp. Immunol.* **1995**, *100*, 126.
8. Casacchia, M.; Meco, G.; Castellana, F.; Bedini, L.; Cusimano, G.; Agnoli, A. *Pharmacol. Res. Commun.* **1983**, *15*, 329.
9. Kato, H.; Araki, T.; Itoyama, Y.; Kogure, K. *Eur. J. Pharmacol.* **1995**, *272*, 107.
10. Maxwell, C. R.; Kanes, S. J.; Abel, T.; Siegel, S. J. *Neuroscience* **2004**, *129*, 101