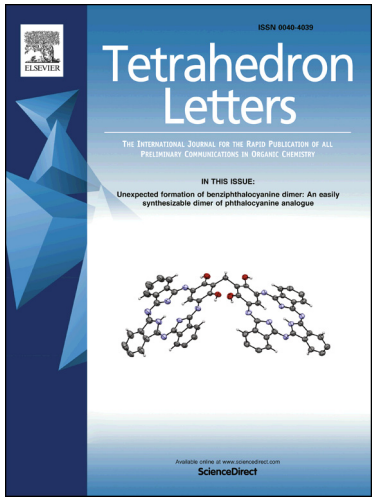

Efficient synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram

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Efficient synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram

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ABSTRACT

A novel, efficient and protecting group free enantioselective synthetic approach of (-)-(*R*)-**1** and (+)-(*S*)-rolipram **2** is described employing the organocatalyzed asymmetric Michael addition, Henry condensation, Wittig olefination and reductive lactamization reactions as key steps.

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] Among them, γ-aminobutyric acid (GABA) and its analogues rolipram (**1**-**2**), brivaracetam **3** and (*S*)-pregabalin **4** are useful division of compounds possessing interesting pharmacological activities (Fig. 1).[2] The rolipram (**1**-**2**) are simple cyclo-GABA derivative possessing a catechol type ring at chiral carbon (C-3).[3] The (±)-rolipram was discovered and developed by Schering AG pharmaceutical company at Berlin, Germany in early 1990[4] and it acts as a selective phosphodiesterase-4 inhibitor and potential antidepressant drug.

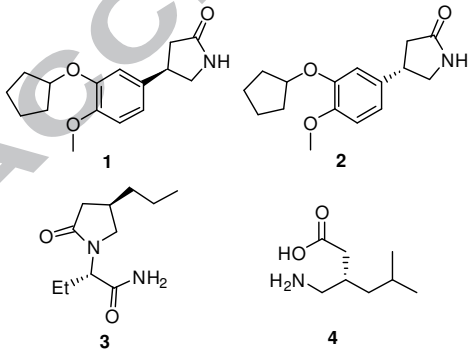


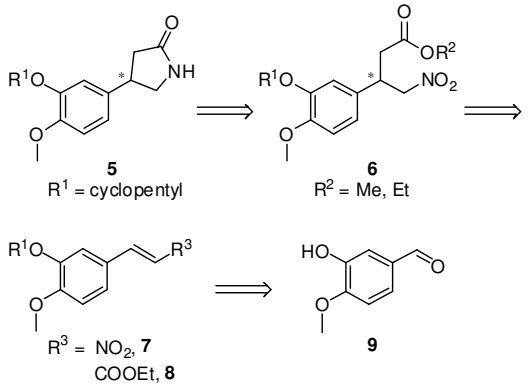
Fig. 1. Some structures of GABA derivatives (**1**-**4**).

The most active enantiomer (*R*)-rolipram **1** 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] The (*R*)-**1** and (*S*)-rolipram **2** have been synthetic target of considerable interest for academia and pharmaceutical industries due to its high antidepressant activity combined with attractive structural features. Various elegant studies and syntheses of (*R*)-**1** and (*S*)-rolipram **2** have been documented in the literature.[11] In 2008, Dixon and co-workers[11f] reported an enantioselective total synthesis of (*R*)-rolipram in six steps employed the bifunctional catalyst mediated asymmetric Michael addition of malonate nucleophiles as key step. Recently, Kobayashi and co-workers[11a] described the continuous flow asymmetric synthesis of (*R*)- and (*S*)-rolipram employed the chiral heterogeneous catalysts as key step. As part of our ongoing research programme directed towards the asymmetric synthesis of biologically active compounds,[12] we became interested in developing a short and efficient route to (*R*)-**1** and (*S*)-rolipram **2** with two different strategies employing the organocatalyzed asymmetric Michael addition, Henry condensation, Wittig olefination and reductive lactamization reactions as the key steps.

Results and Discussion

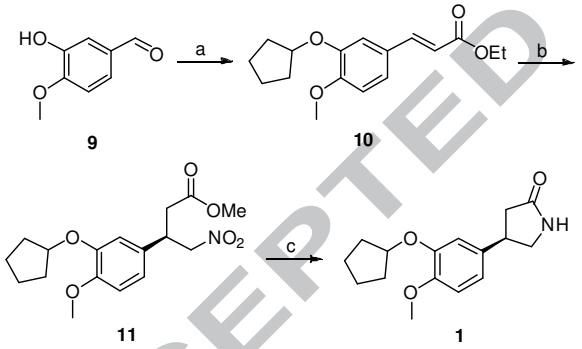
Our synthetic approach for the enantioselective synthesis of pyrrolidone skeleton **5** was envisioned *via* the retrosynthetic route as depicted in Scheme 1. The ester derivative **6** was visualized as a synthetic intermediate from which pyrrolidone **5**, and rolipram (**1**-**2**) could be easily synthesized *via* intramolecular cyclization under hydrogenation conditions. The ester derivative **6** in turn could be synthesized from olefin **7** or **8** by means of (*R*)- and (*S*)-diphenylprolinolsilyl ether mediated asymmetric Michael addition reactions followed by standard organic transformations.

The nitro olefin derivative **7** could be derived from commercially available isovanillin **9** through base catalyzed *O*-alkylation and Henry condensation reaction, whereas olefinic ester **8** could be easily synthesized from isovanillin **9** *via O*-alkylation and 2C-Wittig olefination. Thus, in principle, both the enantiomers of rolipram (**1**-**2**) along with different substitutions at *O*-site could be accessed by two different approaches.



Scheme 1. Retrosynthesis of pyrrolidone skeleton **5**.

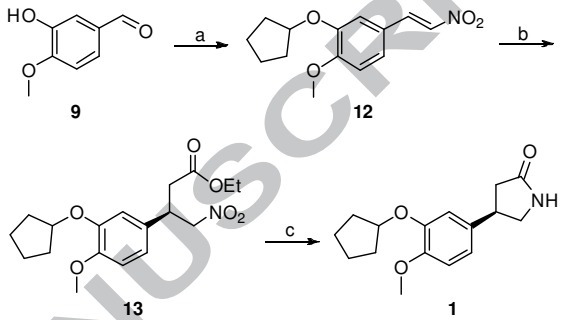
The synthesis of (*R*)-rolipram **1** started with commercially available isovanillin **9** which on treatment with cyclopentylbromide under basic conditions followed by 2C-Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane in THF afforded the *trans*-olefinic ester **10** in 92% yield (Scheme 2). The DIBAL-H reduction of ester **10** at −78 °C to *α*,*β*-unsaturated aldehyde and subsequent asymmetric Michael oxidative esterification[13] with nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether (10 mol%) furnished the nitro aldehyde adduct which on *in situ* treatment with NBS/MeOH furnished the *γ*-nitroester **11** in 78% yield.



Scheme 2. *Reagents and conditions:* (a) (i) cyclopentylbromide, K_2CO_3, DMF, 100 °C, 30 h; (ii) $PPh_3CHCOOEt$, THF, rt, 12 h, 92% (over two steps); (b) (i) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; (ii) (*R*)-diphenylprolinol silyl ether, CH_3NO_2, benzoic acid, MeOH, 16 h, rt; (iii) NBS, 16 h, 4 °C, 78% (over three steps); (c) H_2, Pd/C (10%), Et_3N, EtOAc, rt, 12 h, 92%.

With enantiomerically pure ester **11** in hand, it was then subjected to intramolecular reductive lactamization under 1 atm H_2 pressure in presence of catalytic amount of Pd/C in EtOAc/Et_3N to furnish the (*R*)-rolipram **1** in 92% yield and >99% *ee*[14] {$[\alpha]_D^{25}$ −31.1 (*c* 1.05, CH_3OH), [lit.[11f] $[\alpha]_D^{25}$ −31 (*c* 1.05, CH_3OH)]}. The spectroscopical and physical data of (*R*)-rolipram **1** were found to be in full agreement with the literature data.[11c-f,i-j]

In another approach, the synthesis of (*R*)-rolipram **1** commenced with treatment of the isovanillin **9** with cyclopentylbromide under basic conditions followed by Henry condensation reaction with nitromethane to afford the nitro olefin **12** in 87% yield (Scheme 3).[11f] Asymmetric Michael addition of acetaldehyde to nitro olefin **12** in the presence of catalyst (*R*)-diphenylprolinol silyl ether[15] (10 mol%) in a sealed tube afforded the nitroaldehyde adduct,[16] which on spontaneous oxidation with oxone[17] and subsequent esterification using TMSCl/EtOH[18] successfully furnished the ester derivative **13** in 85% yield. Our next endeavour was to carry out the intramolecular reductive lactamization at the nitro group site. Towards this end, nitroester **13** underwent hydrogenation in the presence of catalytic amount of Pd/C in EtOAc/Et_3N to deliver the target compound (*R*)-rolipram **1** in 93% yield and >99% *ee*[19] {$[\alpha]_D^{25}$ −31.1 (*c* 1.05, CH_3OH), [lit.[11f] $[\alpha]_D^{25}$ −31 (*c* 1.05, CH_3OH)]}. The spectral and physical data of (*R*)-rolipram **1** was found to be in consonance with those reported in the literature.[11c-f,i-j]



Scheme 3. *Reagents and conditions:* (a) (i) cyclopentylbromide, K_2CO_3, DMF, 100 °C, 30 h; (ii) CH_3NO_2, NH_4OAc, 130 °C, 24 h, 87% (over two steps); (b) (i) acetaldehyde, (*R*)-diphenylprolinolsilyl ether, 1,4-dioxane, 4 °C to rt, 18 h; (ii) oxone, DMF, rt, 12 h; (iii) TMSCl, EtOH, rt, 12 h, 85% (over three steps); (c) H_2, Pd/C, Et_3N, EtOAc, rt, 12 h, 93%.

The (*S*)-rolipram **2** was also synthesized in >99% *ee*[20] {$[\alpha]_D^{25}$ +31.8 (*c* 0.6, CH_3OH) [lit.[11j] $[\alpha]_D^{rt}$ +31 (*c* 0.6, CH_3OH)]} following an analogous series of reactions as shown in Scheme 3 using the (*S*)-diphenylprolinol ether catalyst during the asymmetric Michael addition step. The spectral and physical data of (*S*)-rolipram **2** was found to be in accordance with the literature data.[11c-d,j]

In conclusion, we have disclosed a novel, short and protecting group free enantioselective syntheses of (*R*)-**1** and (*S*)-rolipram **2** from commercially available isovanillin as a starting material employing the (*R*)- and (*S*)-diphenylprolinol silyl ether mediated asymmetric Michael addition reaction as key step. The overall yields for the (*R*)-rolipram **1** were 66% (Scheme 2) and 69% (Scheme 3) with two different strategies after three column chromatographic purification steps. The merits of our synthesis are high enantioselectivity (i.e. >99% *ee*) and high yielding reaction steps. The synthetic approach also has significant potential for the variation at *O*-alkyl site to synthesize various *γ*-pyrrolidone derivatives with expected increase in biological activities.

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14) HPLC spectral data of (*R*)-rolipram **1**: The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.668 min, (*S*)-enantiomer: t_r = 36.624 min.

15) (*R*)-Diphenylprolinol silyl ether was prepared from (*R*)-diphenylprolinol and TMSCl using a known procedure; see: Hayashi, Y.; Gotoh, H.; Hayashi. T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

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19) HPLC spectral data of (*R*)-rolipram **1**: The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.768 min, (*S*)-enantiomer: t_r = 36.994 min.

20) HPLC spectral data of (*S*)-rolipram **2:**The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.521 min, (*S*)-enantiomer: t_r = 35.654 min.

Highlights

- Rolipram, an antidepressant drug and suggested for the treatment of multiple sclerosis.
- Protecting group free enantioselective synthesis of rolipram.
- TMS-prolinol mediated asymmetric Michael addition reaction as key step.
- Henry condensation and Wittig olefination reactions.

Graphical Abstract

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Ramandeep Kaur and Satyendra Kumar Pandey*

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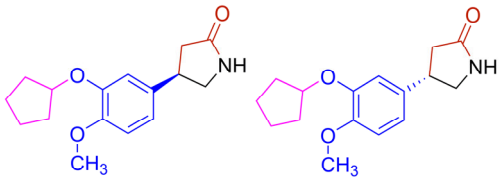

(*R*)-Rolipram (*S*)-Rolipram