

**CHIRAL SYNTHESIS OF PHOSPHODIESTERASE INHIBITOR,
(*R*)-(-)-ROLIPRAM, BY MEANS OF ENANTIOSELECTIVE
DEPROTONATION STRATEGY[†]**

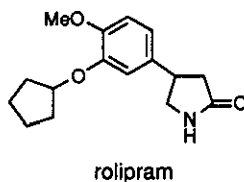
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Abstract — Enantioselective synthesis of the antidepressant (*R*)-(-)-rolipram
(1) has been achieved by using an enantioselective deprotonation of the
cyclobutanone derivative as a key step.

Recently we developed¹ a novel procedure for the chiral synthesis of γ -butyrolactones in high enantiomeric excess by using an enantioselective deprotonation² of the corresponding cyclobutanone derivatives as a key step. This methodology has been successfully employed in the chiral synthesis of physiologically active natural products.³ Here we report a further application of this synthetic strategy to the synthesis of the

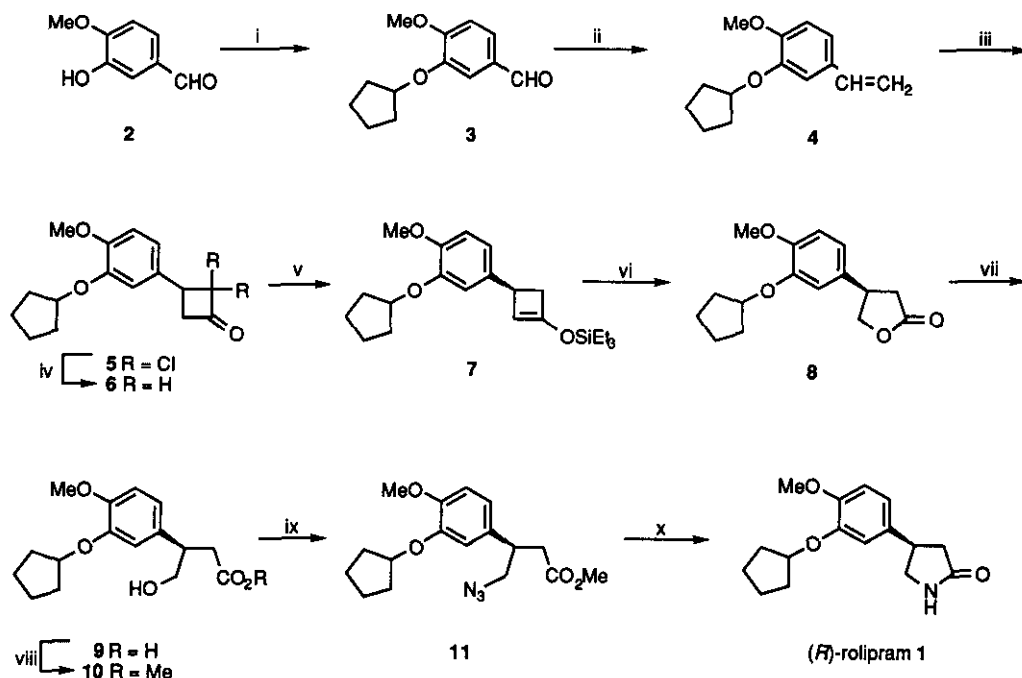


antidepressant rolipram, 4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one, which is known to be the selective, prototypical inhibitor of the calcium-independent, low K_m cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase (PDE)⁴⁻⁶ designated PDE IV.^{7,8} Since the pharmacological activity of

rolipram depends on the absolute configuration,⁹ we investigated the enantioselective synthesis of the more effective enantiomer (*R*)-(-)-**1**.¹⁰

The starting cyclobutanone (**6**) was prepared as follows.

Treatment of isovanillin (**2**) with cyclopentyl bromide in *N,N*-dimethylformamide (DMF) in the presence of potassium carbonate at 100°C afforded the alkylated product (**3**), which on the Wittig reaction with triphenylphosphonium methylide gave the olefin (**4**), in 89% overall yield from **2**. [2+2] Cycloaddition of the olefin (**4**) with trichloroacetyl chloride and phosphoryl chloride in tetrahydrofuran (THF) in the presence of zinc-copper couple,¹¹ followed by dechlorination of the dichlorocyclobutanone (**5**) with zinc powder in refluxing acetic acid provided the desired cyclobutanone derivative (**6**) in 36% yield from **4**.



Scheme Reagents and conditions: i, cyclopentyl bromide, K₂CO₃, DMF, 100°C; ii, Ph₃PCH₃Br, *n*-BuLi, THF, 0°C; iii, CCl₃COCl, POCl₃, Zn-Cu, THF, room temperature; iv, Zn, AcOH, reflux; v, (*R,R*)-α,α'-dimethyldibenzylamine, *n*-BuLi, TESCl, THF, -100°C; vi, 1) O₃, MeOH, -78°C; 2) NaBH₄, MeOH, room temperature; 3) 2N-HCl, room temperature; vii, 1) 3N-KOH, room temperature; 2) 15%-HCl; viii, CH₂N₂, Et₂O, 0°C; ix, DEAD, Ph₃P, DPPA, THF, 0°C; x, Mg, MeOH, room temperature.

We previously observed¹ that the use of lithium (*S,S'*)-α,α'-dimethyldibenzylamide¹² as the chiral base for the enantioselective deprotonation of 3-substituted cyclobutanone, followed by trapping of the resulting enolate with trialkylchlorosilane, resulted in the formation of (*S*)-silyl enol ether. To synthesize the more

effective (*R*)-(-)-enantiomer of rolipram, the cyclobutanone (**6**) was treated with lithium (*R,R'*)- α,α' -dimethyldibenzylamide¹² at -100°C in THF and the resulting enolate was trapped by triethylsilyl chloride to afford the silyl enol ether (**7**) in 48% yield together with the recovered starting material (38%). Although the enantiomeric excess of the silyl enol ether (**7**) could not be determined at this stage, it was further converted into the γ -lactone (**8**), $[\alpha]_D -32.4^\circ$ ($c=0.6$, CHCl_3), by ozonolysis, followed by sodium borohydride reduction of the ozonide in 62% overall yield. Hydrolysis of the γ -lactone (**8**) with 3*N* potassium hydroxide and subsequent treatment of the resulting carboxylic acid (**9**) with diazomethane in ether furnished the hydroxy ester (**10**), $[\alpha]_D -11.7^\circ$ ($c=0.6$, CHCl_3), in 98% overall yield. The enantiomeric excess of **10** was determined to be >95% by comparison of the nmr spectrum (270 MHz) of its Mosher ester with that of the racemate. This result would support that the enantioselective deprotonation of the cyclobutanone (**6**) would also proceed in high enantiomeric excess.

To complete the synthesis, the alcohol (**10**) was converted into the azide (**11**) by using diphenylphosphoryl azide, triphenylphosphine, and diethyl azodicarboxylate¹³ in THF at 0°C in 97% yield. Finally reduction of the azide (**11**) with magnesium turning in methanol¹⁴ under argon afforded (-)-rolipram (**1**), mp 130-132°C (lit.,^{10b} 131-133°C; lit.,^{10c} 126-128°C), in quantitative yield, whose spectroscopic data including its specific optical rotation, $\{[\alpha]_D -30.2^\circ$ ($c=0.1$, MeOH), lit.,^{10b} $[\alpha]_D -31.0^\circ$ (MeOH); lit.,^{10c} $[\alpha]_D -19.5^\circ$ (MeOH)}, were identical with those reported.^{10b,c}

Thus we could disclose the novel chiral synthesis of phosphodiesterase inhibitor (*R*)-(-)-rolipram, by employing an enantioselective deprotonation of the cyclobutanone derivative as a key step, and this strategy would be applicable to the enantioselective synthesis of the other clinically important compounds.

REFERENCES AND NOTES

- † This paper is dedicated to the memory of the late Professor Yoshio Ban.
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