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

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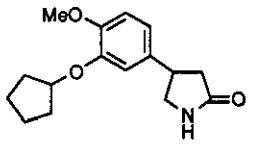
*Abstract* — Enantioselective synthesis of the antidepressant (*R*)-(-)-rolipram (**1**) has been achieved by using an enantioselective deprotonation of the cyclobutanone derivative as a key step.

Recently we developed[1] a novel procedure for the chiral synthesis of γ-butyrolactones in high enantiomeric excess by using an enantioselective deprotonation[2] 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



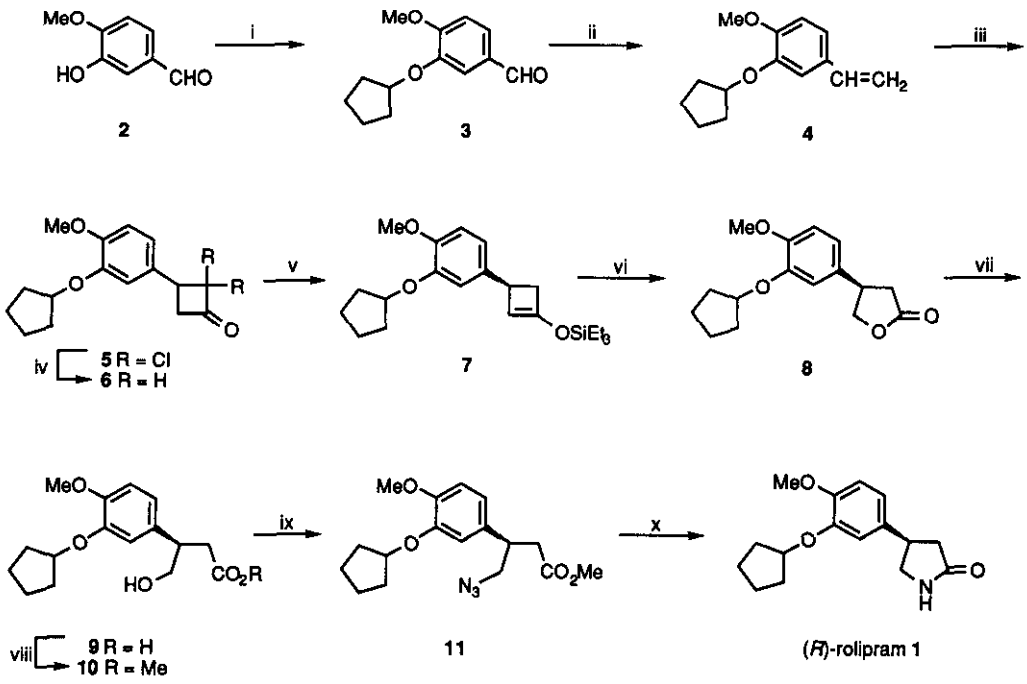

rolipram

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, $K_2CO_3$, DMF, 100°C; ii $Ph_3PCH_3Br$, *n*-BuLi, THF, 0°C; iii, $CCl_3COCl$, $POCl_3$, Zn-Cu, THF, room temperature; iv, Zn, AcOH, reflux; v, (*R*,*R*')-α,α'-dimethyldibenzylamine, *n*-BuLi, TESCl, THF, -100°C; vi, 1) $O_3$, MeOH, -78°C, 2) $NaBH_4$, MeOH, room temperature, 3) 2N-HCl, room temperature; vii, 1) 3N-KOH, room temperature, 2) 15%-HCl; viii, $CH_2N_2$, $Et_2O$, 0°C; ix, DEAD, $Ph_3P$, DPPA, THF, 0°C; x, Mg, MeOH, room temperature.

We previously observed[1] that the use of lithium (*S*,*S*')-α,α'-dimethyldibenzylamide[12] 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'-dimethyldibenzylamide[12] 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° (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° (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 azodicarboxylate[13] in THF at 0°C in 97% yield. Finally reduction of the azide (**11**) with magnesium turning in methanol[14] 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° (c=0.1, MeOH), lit.,[10b] $[\alpha]_D$ -31.0° (MeOH); lit.,[10c] $[\alpha]_D$ -19.5° (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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