# Catalytic Enantioselective Synthesis of the Phosphodiesterase Type IV Inhibitor (*R*)-(-)-Rolipram *via* Intramolecular C-H Insertion Process

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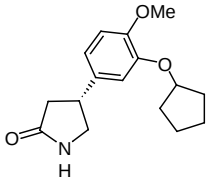
**Abstract:** A new route to the phosphodiesterase type IV inhibitor (*R*)-(-)-rolipram (**1**) has been developed, wherein the key step relies on enantioselective intramolecular C-H insertion of *N*-alkyl-*N*-4-nitrophenyl-α-methoxycarbonyl-α-diazoacetamide **7** catalyzed by chiral dirhodium(II) complex. The dirhodium(II) carboxylate, $Rh_2$(*S*-BPTTL)$_4$, incorporating *N*-benzene-fused-phthaloyl-(*S*)-*tert*-leucinate as a bridging ligand has proven to be the catalyst of choice for this process, providing the desired 2-pyrrolidinone **8** in 88% ee.

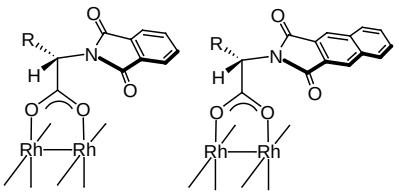
**Key words:** (*R*)-(-)-rolipram, phosphodiesterase inhibitor, enantioselective synthesis, chiral dirhodium(II) catalyst, C-H insertion

Rolipram, (±)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, originally developed as an antidepressant by Schering AG has been shown to be a potent and selective inhibitor of phosphodiesterase type IV (PDE IV),[1] one of the cyclic adenosine 3',5'-monophosphate (cAMP)-specific phosphodiesterases.[2] Inhibition of PDE IV is rapidly becoming recognized as a promising therapeutic target for the treatment of a number of disorders such as asthma,[3] atopy,[4] and multiple sclerosis.[5] While the therapeutic use of rolipram is hampered by nausea and emetic side effects,[6] rolipram has been not only used as a research tool in determining PDE IV isozymes in disease state and second messenger pathways but also chosen as a starting point for subsequent structural modification.[7] It has recently been disclosed that the (*R*)-(-)-enantiomer (**1**) of rolipram is primarily responsible for the pharmacological effects.[8] It is therefore not surprising that (*R*)-(-)-rolipram (**1**) as the prototypical agent has elicited considerable attention from synthetic chemists.[9]



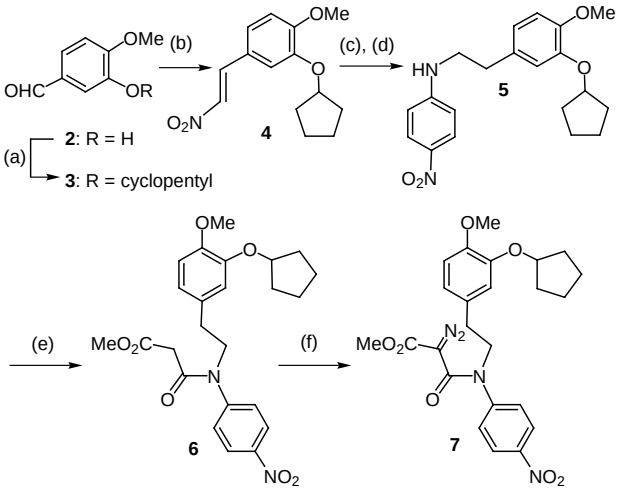

(*R*)-(-)-rolipram (**1**)

Numerous strategies have been developed to achieve asymmetric syntheses of **1**, including conjugate addition of the chiral enolate of Evans' *N*-acetyloxazolidinones to β-nitrostyrene,[10] conjugate addition of an arylcopper reagent to Meyers' chiral α,β-unsaturated bicyclic lactam[11] or a modified pyroglutamate,[12] conjugate addition of cyanide to the chiral α,β-unsaturated oxazoline,[13] palladium-catalyzed, diastereoselective substitution of allylic carbonate by dimethyl malonate,[14] a Claisen rearrangement process with the transfer of chirality,[9] enantioselective deprotonation of 3-substituted cyclobutanone using chiral lithium amide.[15] However, a catalytic enantioselective synthesis of **1** has not yet been addressed. In this respect, we have recently given a protocol for enantioselective construction of 4-substituted 2-pyrrolidinones (up to 82% ee) *via* a site-selective C-H insertion catalyzed by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], $Rh_2$(*S*-PTTL)$_4$.[16] In order to demonstrate a synthetic potential of this catalytic methodology, we have now explored a new route to **1**.




R = Bn: $Rh_2$(*S*-PTPA)$_4$ $Rh_2$(*S*-BPTPA)$_4$
R = Me: $Rh_2$(*S*-PTA)$_4$ $Rh_2$(*S*-BPTA)$_4$
R = *i*-Pr: $Rh_2$(*S*-PTV)$_4$ $Rh_2$(*S*-BPTV)$_4$
R = *t*-Bu: $Rh_2$(*S*-PTTL)$_4$ $Rh_2$(*S*-BPTTL)$_4$

Toward this end, we selected *N*-2-(3-cyclopentyloxy-4-methoxyphenyl)ethyl-*N*-4-nitrophenyl-α-methoxycarbonyl-α-diazoacetamide **7** as a carbene precursor on the basis of our recent finding that the *N*-4-nitrophenyl substituent plays a dual role as a nitrogen protecting group as well as a site-control element.[16] The synthesis of **7** was implemented as shown in Scheme 1. *O*-Alkylation of commercially available isovanillin (**2**) with cyclopentyl bromide and $K_2CO_3$ in DMF followed by a Knoevenagel condensation of **3**[13] with nitromethane in the presence of ammonium acetate[17] provided *trans*-β-nitrostyrene **4**[18] in 72% yield. Reduction of **4** with $LiAlH_4$ followed by condensation with the 4-fluoronitrobenzene[19] afforded 4-nitroaniline **5** in 60% yield. *N*-Acylation of **5** with methyl 3-chloro-3-oxopropionate in the presence of *N*,*N*-dimethylaniline and subsequent diazo transfer using 4-acetamidobenzenesulfonyl azide[20] and DBU[21] furnished α-diazoacetamide **7** in 88% yield.




*Reagents and conditions*: (a) cyclopentyl bromide, $K_2CO_3$, DMF, 60 °C, 12 h, 91%; (b) $MeNO_2$, $NH_4OAc$, reflux, 3 h, 79%; (c) $LiAlH_4$, THF, reflux, 1.5 h; (d) 4-fluoronitrobenzene, $Na_2CO_3$, EtOH, sealed tube, 150 °C, 12 h, 60% (2 steps); (e) $MeO_2CCH_2COCl$, $Me_2NC_6H_5$, $CH_2Cl_2$, 0 °C, 2 h, 97%; (f) 4-acetamidobenzenesulfonyl azide, DBU, MeCN, 0 °C, 3 h, 91%.

**Scheme 1**

With the effectiveness of $Rh_2$(*S*-PTTL)$_4$ as a catalyst previously identified through a closely related C-H insertion,[16] we first examined cyclization of **7** with the aid of 2 mol % of $Rh_2$(*S*-PTTL)$_4$ (Table 1, entry 1). The reaction in $CH_2Cl_2$ proceeded smoothly to give the 2-pyrrolidinone derivative **8**, $[\alpha]_D^{25}$ +5.72 (*c* 1.06, $CHCl_3$), in 75% yield, with no trace of the 2-azetidinone derivative. The enantioselectivity in this reaction was determined to be 78% ee by $^1$H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent. As might be expected from the precedent, the preferred absolute configuration at the insertion site was established as *R* by transformation of **8** into **1** (*vide infra*). In a comparative experiment with **7**, we then reexamined the other chiral dirhodium(II) carboxylates previously screened, $Rh_2$(*S*-PTPA)$_4$, $Rh_2$(*S*-PTA)$_4$, and $Rh_2$(*S*-PTV)$_4$, derived from *N*-phthaloyl-(*S*)-phenylalanine, alanine, and valine, respectively (entries 2-4). While a consistent sense of enantioselection was observed in all cases, poor enantioselectivities observed with them simply provided confirmation that $Rh_2$(*S*-PTTL)$_4$ characterized by a bulky *tert*-butyl group proved to be by far the best choice. At this point, we were intrigued by the feasibility of enhancement of the enantioselectivity by means of the recently developed catalysts,[22] $Rh_2$(*S*-BPTTL)$_4$, $Rh_2$(*S*-BPTPA)$_4$, $Rh_2$(*S*-BPTA)$_4$, and $Rh_2$(*S*-BPTV)$_4$, derived from *N*-benzene-fused-phthaloyl-(*S*)-*tert*-leucine, phenylalanine, alanine, and valine, respectively (entries 5-8).[23] Indeed, we found that this class of catalysts characterized by an extension of the phthalimido wall with one more benzene ring improved the enantioselectivities while the same sense of enantioselection as above was observed in every case. In particular, 88% ee with $Rh_2$(*S*-BPTTL)$_4$ was the highest achievement (entry 5).

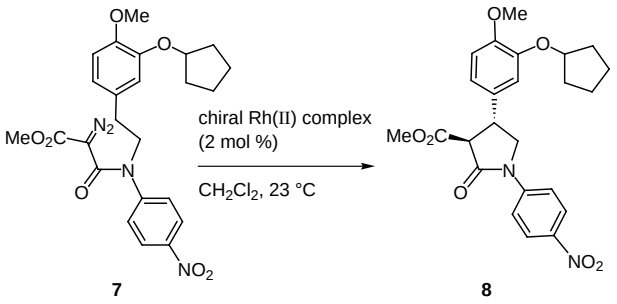
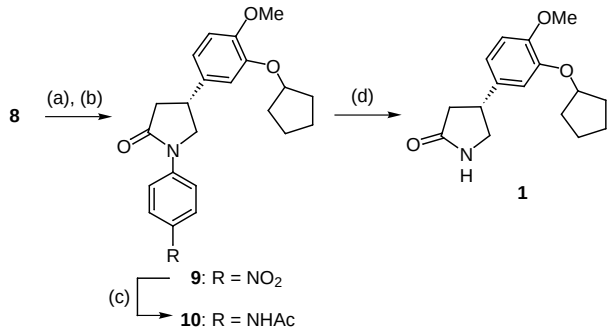



**Table 1** Enantioselective C-H insertion reaction of α-diazoacetamide **7** catalyzed by chiral dirhodium(II) complexes

| | | | 2-pyrrolidinone **8** | |
|---|---|---|---|---|
| entry | Rh(II) complex | time (h) | yield[a] (%) | ee[b] (%) |
| 1 | $Rh_2$(*S*-PTTL)$_4$ | 4 | 75 | 78 |
| 2 | $Rh_2$(*S*-PTPA)$_4$ | 8 | 81 | 33 |
| 3 | $Rh_2$(*S*-PTA)$_4$ | 6 | 71 | 35 |
| 4 | $Rh_2$(*S*-PTV)$_4$ | 4 | 71 | 35 |
| 5 | $Rh_2$(*S*-BPTTL)$_4$ | 8 | 74 | 88 |
| 6 | $Rh_2$(*S*-BPTPA)$_4$ | 6 | 80 | 47 |
| 7 | $Rh_2$(*S*-BPTA)$_4$ | 8 | 78 | 48 |
| 8 | $Rh_2$(*S*-BPTV)$_4$ | 8 | 76 | 41 |

[a] Isolated yield. [b] Determined by $^1$H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent.

With highly optically active 2-pyrrolidinone **8** secured, we then proceeded to the elaboration of the target molecule, which also determined the preferred absolute configuration at the insertion site (Scheme 2). Demethoxycarbonylation of **8** of 88% ee, $[\alpha]_D^{24}$ +9.75 (*c* 1.47, $CHCl_3$), under Krapcho conditions[24] furnished 4-substituted 2-pyrrolidinone **9**, mp 98-99 °C, $[\alpha]_D^{26}$ +29.1 (*c* 1.10, $CHCl_3$), as pale yellow plates in 97% yield. Upon one recrystallization from $CH_2Cl_2$-hexane, there was produced an optically pure sample, mp 99-102 °C, $[\alpha]_D^{25}$ +34.0 (*c* 1.00, $CHCl_3$) in 71% yield, the homochirality of which was confirmed by HPLC on Daicel Chiralpak AD.[25] One-pot conversion of the nitro group into the acetamido group was effected under the influence of iron powder in boiling acetic acid[26] to give acetanilide **10**, mp 120-121 °C, $[\alpha]_D^{25}$ +28.4 (*c* 1.30, $CHCl_3$) as colorless needles in 86% yield. Prior to an oxidative removal of the 4-acetamidophenyl group with ceric (IV) ammonium nitrate (CAN),[27] concern arose over the compatibility of 3-cyclopentyloxy-4-methoxyphenyl group in **10** with the reaction conditions, since CAN was reported to oxidize 1,2-dimethoxybenzene to give a complex mixture of products.[28] Thus, we were gratified to find that treatment of **10** with CAN in aqueous MeCN at 0 °C uneventfully afforded **1**, mp 130-133 °C, $[\alpha]_D^{25}$ -31.1 (*c* 1.08, MeOH) [lit.[8] mp 131-133 °C, $[\alpha]_D^{24}$ -31.0 (*c* 0.5, MeOH)], in 71% yield.




*Reagents and conditions*: (a) NaCl, aq. DMSO, 160 °C, 2 h, 97%; (b) recrystallization 71%; (c) Fe, AcOH, reflux, 2 h, 86%; (d) $Ce(NH_4)_2(NO_2)_6$ (2.5 eq), aq. MeCN, 0 °C, 1 h, 71%.

**Scheme 2**

In summary, we have achieved the first catalytic enantioselective synthesis of (*R*)-(-)-rolipram from isovanillin with an overall yield of 12% for the ten-step sequence, wherein the effectiveness of the catalytic methodology has been increased with the advent of $Rh_2$(*S*-BPTTL)$_4$. The present protocol does not require sophisticated conditions such as exclusion of moisture and oxygen as well as low reaction temperatures, thus providing great potential for a facile access to its novel analogues for biological and pharmacological investigations.

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(23) Typical procedure for enantioselective intramolecular C-H insertion reaction (Table 1, entry 5): Bis(tetrahydrofuran) adduct of $Rh_2$(*S*-BPTTL)$_4$ (6.4 mg, 0.004 mmol) was added in one portion to a stirred solution of **7** (100 mg, 0.21 mmol) in $CH_2Cl_2$ (2 mL) at 23 °C. The mixture was stirred at this temperature for 8 h and the solvent was removed *in vacuo*. The greenish residue was purified by column chromatography (silica gel 10 g, 3:1→2:1 hexane/EtOAc) to provide **8** (70 mg, 74%) as yellow amorphous; $[\alpha]_D^{24}$ +9.75 (*c* 1.47, $CHCl_3$); IR (film) ν 1738, 1715, 1595 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.55-1.63 (m, 2H), 1.79-1.93 (m, 6H), 3.80 (s, 3H), 3.82 (s, 3H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.91 (t, *J* = 9.0 Hz, 1H), 4.02 (ddd, *J* = 8.1, 9.0, 10.0 Hz, 1H), 4.26 (dd, *J* = 8.1, 9.0 Hz, 1H), 4.76 (tt, *J* = 3.2, 5.8 Hz, 1H), 6.80-6.87 (m, 3H), 7.82 (d, *J* = 9.3 Hz, 2H), 8.21 (d, *J* = 9.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 24.0 ($CH_2$), 32.7 ($CH_2$), 40.7 (CH), 53.0 ($CH_3$), 53.4 ($CH_2$), 56.0 ($CH_3$), 57.2 (CH), 80.5 (CH), 112.3 (CH), 113.7 (CH), 118.7 (CH), 119.0 (CH), 124.6 (CH), 130.4 (C), 143.7 (C), 143.9 (C), 147.9 (C), 149.7 (C), 168.6 (C), 168.7 (C); MS (EI) *m/z* (rel. int. %) 454 ($M^+$, 18), 386 (30), 328(100); HRMS *m/z* 454.1737 [$M^+$, calcd for $C_{24}H_{26}N_2O_7$ 454.1740]. The enantiomeric excess was determined to be 88% on the basis of $^1$H NMR spectrum ($CDCl_3$) taken with 100 mol % of Eu(hfc)$_3$ which exhibited the methoxy signals of the 3*S*,4*R* and 3*R*,4*S* enantiomers at δ 4.01 and 3.92, respectively.
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