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Dirhodium catalyzed intramolecular enantioselective C–H insertion reaction of *N*-cumyl-*N*-(2-*p*-anisylethyl)diazoacetamide: synthesis of (−)-Rolipram

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Abstract—Cumyl(2,2-dimethyl-benzyl) was used as an *N*-protecting group for intramolecular C–H insertion reaction of α-diazoacetamide. Excellent chemoselectivity (>98:2) in C–H insertion over the aromatic addition of *N*-cumyl-*N*-(2-*p*-anisylethyl)-diazoacetamide was obtained with Rh_2[(4*S*)-MEOX)]$_4$ catalyst in moderate enantioselectivity (53% ee). The reaction was successfully applied in the synthesis of (−)-Rolipram in 15% total yield.
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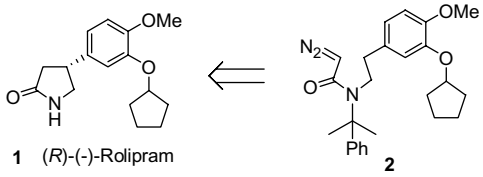
1. Introduction

The intramolecular enantioselective C–H insertion reaction of α-diazo carbonyl compounds catalyzed by chiral dirhodium(II) complexes is well recognized for the construction of both stereogenic carbocyclic and heterocyclic compounds in an efficient fashion.[1] For example, isodeoxypodophyllotoxin and enterolactone were synthesized according to this method.[2] Apart from enantioselectivity, regioselectivity has remained a major challenge in the construction of heterocycles. In the case of *N*-protected diazoacetamide, the reaction of diazo carbon to the *N*-protecting group usually occurs and makes the regioselectivity issue more complicated. It is well documented that the regioselectivity depends highly on the substituents of the diazo carbon as well as the *N*-protecting group on the amide moiety.[3] Many *N*-protecting groups, such as *t*-butyl, phenyl, 4-nitrophenyl, 4-methoxyphenyl, benzhydryl, bis(trimethylsilylmethyl), etc.,[3b,c,4] have been used with varying degrees of success. We have previously reported that cumyl (2,2-dimethyl-benzyl) is a good *N*-protecting group for intramolecular C–H insertion of α-diazoacetamide to give the γ-lactam in high regioselectivity.[5] In addition, it was found that the cumyl protecting group can be easily removed from the five-membered γ-lactam product. Herein, we report the application of this method for the preparation of (−)-Rolipram **1** (Scheme 1).



Scheme 1.

In the family of functionalized γ-lactam, Rolipram, (±)-4-(3-cyclopentyloxyl-4-methoxylphenyl)-2-pyrrolidinone, has been shown to be a potent and selective inhibitor of phosphodiesterase type IV (PDE IV).[6] As a consequence Rolipram, which was initially developed as an anti-depressant by Schering AG, has great potential as an anti-inflammatory.[7] Although both enantiomers are active, the (*R*)-isomer has recently proven to be the most active one. Due to the importance of (*R*)-Rolipram, several stereoselective syntheses have already been reported.[8] For example, Hashimoto et al. reported a high enantioselective and regioselective synthesis of (*R*)-Rolipram from intramolecular C–H insertion of diazoacetoacetamide with an electron withdrawing functional group attached to the diazo carbon.[8i] However,

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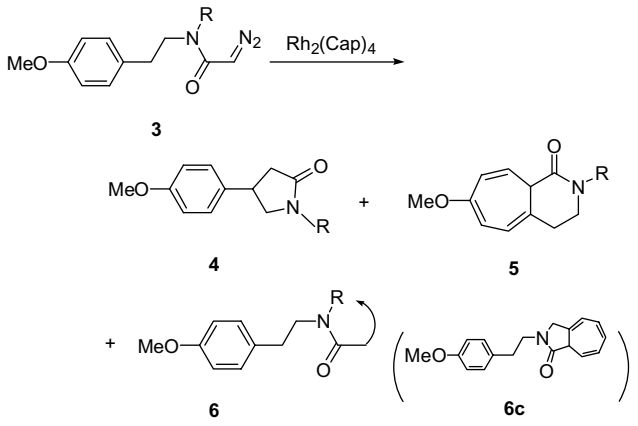
the diazo compound is less reactive towards dirhodium catalysts due to the attachment of the electron withdrawing group. An additional step was implemented to remove the group. The high activity of *N*-cumyl-α-diazoacetamide encouraged us to investigate its application in synthesis of (*R*)-(−)-Rolipram **1**.

2. Results and discussion

2.1. Intramolecular C–H insertion reaction of *N*-2-*p*-anisylethyl diazoacetamide

p-Anisylethyl diazoacetamides **3** were used as model substrates while searching for conditions with the best regio- and enantioselectivity of the C–H insertion reaction. We began by looking at the reaction of *N*-cumyl-*N*-(2-*p*-anisylethyl)-diazoacetamide **3a** with 1 mol % catalyst $Rh_2(cap)_4$ [dirhodium(II) tetra(caprolactamate)] in refluxing dichloromethane. C–H insertion product γ-lactam **4a** was obtained in 73% yield. A major side reaction was the aromatic cycloaddition, although no β-lactam or side product from the attacking *N*-cumyl group was found (Scheme 2, Table 1). Deprotection of γ-lactam **4a** was easily achieved with CF_3COOH to give γ-lactam **7** in 95% yield (Scheme 3). In contrast, a similar selectivity was obtained with *N*-*tert*-butyl diazoacetamide **3b**. The result is in agreement with that reported by Padwa et al. earlier with **3b**.[9] The disadvantage of using **3b** is the difficulty in removing the *tert*-butyl protecting group while maintaining the lactam ring. When benzyl was used as the *N*-protecting group, the yield of γ-lactam **4c** decreased to 40%. Attack of the benzyl group occurred to give a side product **6c** in 27% yield. This is in contrast with the result from **4a**, no such side reaction occurred on the cumyl phenyl group. It is likely that the conformation of the carbenoid intermediate from **4a** favors the one that the cumyl group is placed away from the carbenoid carbon due to steric reasons (Scheme 4).

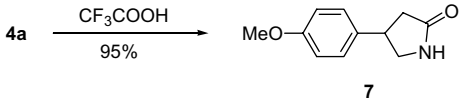


Scheme 2.

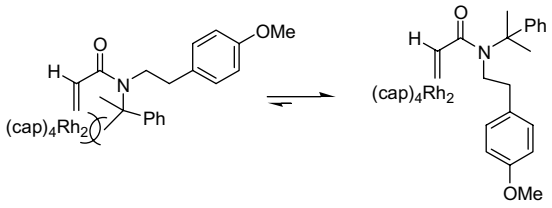
Table 1. Regioselection in intramolecular C–H insertion reaction of diazoacetamides **3a–c** catalyzed by 1 mol % $Rh_2(cap)_4$

Compound	R	Yield (%) of **4**[a]	Yield (%) of **5**[a]
3a	Cumyl	73	10
3b	*t*-Butyl	71	11
3c	Benzyl	40	Trace

[a] Isolated yield after column chromatography.



Scheme 3.



Scheme 4.

A series of representative chiral dirhodium catalysts such as those shown in Figure 1 were examined for asymmetric C–H insertion, with the results shown in Table 2. We can see that rhodium(II) carboxylates gave poor chemoselectivity and low enantioselectivity. Improved chemoselectivity was observed with the Rh_2[(5*S*)-MEPY]$_4$ catalyst. When Rh_2[(4*S*)-MEOX]$_4$ was employed, excellent chemoselectivity (**4a**:**5a** > 98:2) was obtained with moderate enantioselectivity (47% ee of **4a**). The absolute configuration of the insertion product from the Rh_2[(4*S*)-MEOX]$_4$ catalyst was established as ***S*** by comparison of the specific rotation of **7** with the literature {$[\alpha]_D^{25} = +20.7$ (*c* 0.95, MeOH) [(*R*)-4-phenyl-2-pyrrolidinone, $[\alpha]_D^{25} = -37.8$ (*c* 0.95, MeOH)]}.[10]

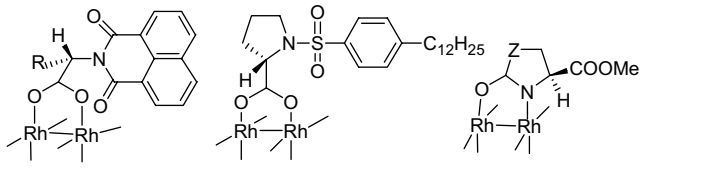


Figure 1. Chiral catalysts used for diazo decomposition of **2a**.

Table 2. Product distribution from catalytic diazo decomposition of diazoacetamide **3a** in refluxing CH_2Cl_2

Entry	Catalyst	**4a**:**5a**[a]	Yield (%) of **4a**[b]	Ee (%) of **4a**[c]	Configuration
1	Rh_2[(*S*)-DOSP]$_4$	47:53	36	3	*R*
2	Rh_2[(*S*)-NTTL]$_4$	58:42	25	2	*R*
3	Rh_2[(*S*)-NTPA]$_4$	53:47	36	13	*R*
4	Rh_2[(5*S*)-MEPY]$_4$	87:13	53	18	*S*
5	Rh_2[(4*S*-MEOX]$_4$	>98:2	72	47	*S*

[a] Determined by ^{1}H NMR of crude reaction mixture.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC using a chiral OD column.

Table 3. Intramolecular C–H insertion of diazoacetamide **3a** catalyzed by Rh_2[(4*S*)-MEOX]$_4$

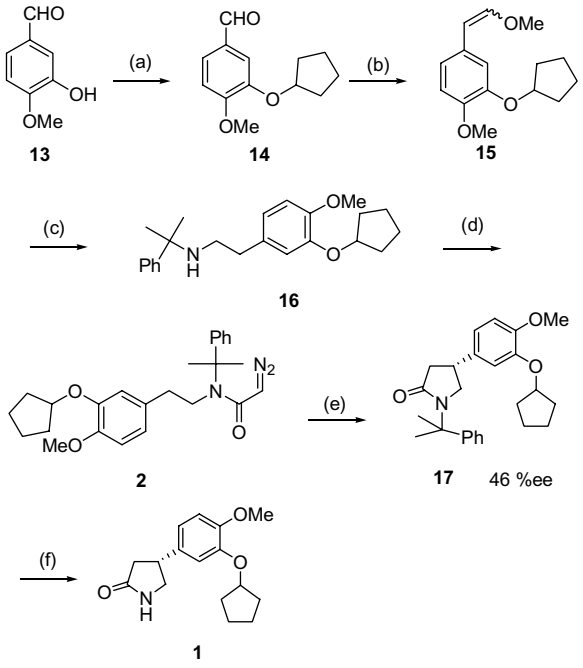
Entry	Solvent	Temp (°C)	Yield (%) of **4a**[a]	Ee (%) of **4a**[b]
1	CH_2Cl_2	Reflux	72	47
2	CH_2Cl_2	20	76	52
3	CH_2Cl_2	0	69	52
4	$(CH_2Cl)_2$	20	74	37
5	Toluene	20	71	47
6	THF	40	69	41
7	Et_2O	Reflux	73	46
8	Dioxane	40	70	54

[a] Isolated yield after column chromatography.
[b] Determined by HPLC using a chiral OD column.

We have previously reported that the solvent has a profound effect on the enantioselectivity for C–H insertion of *N*-(benzyloxyethyl)-*N*-(*tert*-butyl)-diazoacetamide.[11] Several solvents were examined with varying reaction temperatures (Table 3). However, both solvent and temperature have limited effect on the yield and enantioselectivity in this particular case. The results are listed in Table 3. The best ee was 54% in dioxane. In the meantime, the catalyst efficiency was examined by decreasing the catalyst loading. With the catalyst Rh_2[(4*S*)-MEOX]$_4$ loading of 0.1 mol %, 68% isolated yield and 44% ee was obtained.

2.2. Synthesis of (−)-Rolipram

With the conditions in hand, the present method was applied to the synthesis of (*R*)-Rolipram (Scheme 5). To this end, carbene precursor **2** was prepared from the commercially available isovanillin **13** as shown in Scheme 5. *O*-Alkylation of **13** with cyclopentyl bromide in DMF gave **14** in 91% yield. Wittig reaction of **14** with reagent Ph_3PCH_2OMeCl in the present of LDA provided a mixture of enol methyl ether **15** in 96% yield. Hydrolysis of **15** with HCl (12 M) in $CHCl_3$ and followed by reductive amination with cumylamine afforded **16** in 58% yield. Diazoacetamide **2** was formed in 72% yield through diketene condensation/diazo transfer/acetyl cleavage. Cyclization of **2** in CH_2Cl_2 with 1 mol % of Rh_2[(4*R*)-MEOX]$_4$ proceeded smoothly to afford the desired γ-lactam **17** in 64% yield and 46% ee. Removal of the cumyl group from **17** furnished the desired (*R*)-(−)-Rolipram **1**in 65% yield, mp 129–132 °C, $[\alpha]_D^{25} = -17.8$ (*c* 0.6, MeOH) {lit., mp 131–133 °C, $[\alpha]_D^{25} = -31.0$ (*c* 0.5, MeOH)}. Upon two recrystallizations from CH_2Cl_2–*n*-hexane, the ee value was increased to 88%.[12]



Scheme 5. Reagents and conditions: (a) K_2CO_3, DMF, cyclopentyl bromide, 91%; (b) Ph_3PCH_2OMeCl, LDA, −78 °C, 96%; (c) $CHCl_3$, HCl (12 M), cumylamine, CH_3OH, $NaBH_4$, 58%; (d) diketene, THF, *p*-ABSA, DBU, THF, LiOH, H_2O, 72%; (e) Rh_2(4*R*-MEOX)$_4$, CH_2Cl_2, 64%; (f) CF_3COOH 65%.

3. Conclusion

In summary, excellent chemoselectivity and moderate enantioselectivity were achieved from intramolecular C–H insertion of *N*-cumyl-*N*-*p*-anisylethyl diazoacetamide. This efficient method has been successfully applied to the synthesis of (*R*)-(−)-Rolipram.

4. Experimental

4.1. General

Melting points were determined on a digital melting point apparatus and were uncorrected. NMR spectra were recorded on a Brucker-300 MHz spectrometer. HRMS spectra were recorded on TOF EI. Dichloromethane, 1,2-dichloroethane and toluene were distilled over calcium hydride. Solvents THF, Et_2O, and dioxane were distilled over sodium.

4.2. General procedure for the rhodium(II) catalyzed C–H insertion of 3a and 3c

Procedure A: To a solution of the catalyst (1 mol %) in the indicated solvent (10 mL) at reflux was added diazoacetamide in the same solvent (6 mL) via a syringe pump over 1 h. After addition of the diazoacetamide was complete, the reaction solution was stirred for an additional 15 min. The solvent was removed under reduced pressure. Products were purified through silica-gel column chromatography.

Procedure B: To a solution of catalyst (1 mol %) in the indicated solvent (10 mL) at room temperature was added the diazoacetamide in the same solvent (6 mL) in one portion. After the reaction was complete, the solvent was removed under reduced pressure and products purified through silica-gel column chromatography.

4.2.1. 4-*p*-Anisyl-1-cumylpyrrolidin-2-one 4a. (Procedure B, 73%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.14 (m, 5H), 7.06 (d, J = 6.7 Hz, 2H), 6.78 (d, J=6.7 Hz, 2H), 3.70 (s, 3H), 3.63 (dd, J = 9.3, 7.7 Hz 1H), 3.40–3.34 (m, 1H), 3.26 (dd, J = 9.3, 7.6 Hz, 1H), 2.67 (dd, J = 16.5, 8.5 Hz, 1H), 2.48 (dd, J = 16.5, 9.1 Hz, 1H), 1.88 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 158.6, 146.6, 134.2, 128.4, 127.8, 126.7, 125.0, 114.2, 59.1, 55.3, 54.2, 40.6, 36.7, 28.0, 27.9; HRMS(EI) calcd for $C_{20}H_{23}NO_2$ $(M)^+$: 309.1729. Found: 309.1725.

4.2.2. 3-Cumyl-9-methoxy-3-azabicyclo[5.4.0]undeca-6,8,10-trien-2-one 5a. (Procedure B, 9.5%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.18 (m, 5H), 6.04 (d, J = 10.0 Hz, 1H), 5.92 (d, J = 6.5 Hz, 1H), 5.74 (d, J = 6.5 Hz, 1H), 5.62 (dd, J = 10.0, 5.6 Hz, 1H), 3.66 (s, 3H), 3.44–3.41 (m, 2H), 2.77 (d, J = 5.6 Hz, 1H), 2.56–2.52 (m, 2H), 1.81 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 159.6, 148.2, 128.6, 128.5, 126.4, 124.7, 124.6, 122.9, 118.4, 103.6, 63.1, 55.0, 48.0, 45.8, 32.2, 28.5, 28.4; HRMS(EI) calcd for $C_{20}H_{23}NO_2$ $(M)^+$: 309.1729. Found: 309.1725.

4.2.3. 4-*p*-Anisyl-1-benzylpyrrolidin-2-one 4c. (Procedure A, 39.8%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H), 7.07 (d, J = 6.7 Hz, 2H), 6.28 (d, J = 6.7 Hz, 2H), 4.50 (dd, J = 3.4, 3.4 Hz, 2H), 3.76 (s, 3H), 3.62–3.49 (m, 2H), 3.22 (dd, J = 9.2, 6.9 Hz, 1H), 2.58 (dd, J = 17.9, 8.5 Hz, 1H), 2.13 (dd, J = 17.9, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 158.6, 136.4, 134.3, 128.8, 128.3, 127.8, 127.7, 114.2, 55.3, 54.0, 46.6, 39.1, 36.5; HRMS(EI) calcd for $C_{18}H_{19}NO_2$ $(M)^+$: 281.1416. Found: 281.1407.

4.2.4. 3-(2-*p*-Anisylethyl)-3-azabicyclo[5.3.0]deca-5,7,9-trien-2-one 6c. (Procedure A, 27.1%); yellow solid; mp 130–132 ° C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.48–6.46 (m, 2H), 6.19–6.09 (m, 2H), 5.22 (dd, J = 9.5, 3.8 Hz, 1H), 4.08 (br s, 2H), 3.80 (s, 3H), 3.61 (t, J = 7.2 Hz, 2H), 3.04 (br s, 1H), 2.84 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 158.4, 130.6, 130.4, 129.9, 129.7, 129.4, 126.9, 120.7, 119.4, 114.1, 55.3, 51.6, 49.4, 44.2, 32.9; HRMS(EI) calcd for $C_{18}H_{19}NO_2$ $(M)^+$: 281.1416. Found: 281.1423.

4.3. Synthesis of 4-*p*-anisyl-pyrolidin-2-one 7

The γ-lactam **4a** (120 mg, 0.4 mmol) was added to CF_3COOH (2 mL) at room temperature and stirred for 5 h before the solvent was removed under reduced pressure. Silica-gel column chromatography yielded **7** (73 mg, 95.3%). White solid; mp 125–128 °C; $[\alpha]_D^{25}$ = +20.7 (c 0.95, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.48 (br s, 1H), 3.81–3.62 (m, 5H), 3.37 (dd, J = 9.1, 7.2 Hz, 1H), 2.71 (dd, J = 17.0, 8.8 Hz, 1H), 2.46 (dd, J = 17.0, 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 158.8, 134.2, 127.9, 114.4, 55.5, 49.9, 39.8, 38.2; HRMS(EI) calcd for $C_{11}H_{13}NO_2$ $(M)^+$: 191.0946. Found: 191.0952.

4.4. Synthesis of (*R*)-(−)-Rolipram

4.4.1. 3-Cyclopentyloxyl-4-methoxylbenzaldehyde 14. See Ref. 8g.

4.4.2. *N*-[2-(3-Cyclopentyloxyl-4-methoxylphenyl)-ethyl]-*N*-cumylamide 16. To a solution of Ph_3PCH_2OMeCl in THF (40 mL) at −78 °C was added LDA (10 mL, 1.5 M in THF). The reaction mixture was slowly warmed up to room temperature. After 0.5 h, the deep brown reaction mixture was cooled to −78 °C again. A solution of aldehyde **14** (2.20 g, 10 mmol) in THF (10 mL) was added slowly then warmed up to room temperature and stirred overnight, after which water (70 mL) was added. The mixture was then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure and silica-gel column chromatograph (PE/EA = 40:1) gave a mixture enol **15** (2.40 g, 96%). (*E*)-*1-Methyoxyl-2-(3-cyclopentyloxyl-4-methoxylphenyl)-ethylene* **15a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (d, J = 12.9 Hz, 1H), 6.82–6.78 (m, 3H), 5.79–5.75 (d, J = 12.9 Hz, 1H) 4.82–4.80 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 1.93–1.82 (m, 8H). (*Z*)-*1-Methyoxyl-2-(3-cyclopentyloxyl-4-methoxylphenyl)-ethylene* **15b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.32 (m, 3H), 6.08–6.05 (d, J = 7.0 Hz, 1H), 5.18–5.16 (d, J = 7.0 Hz, 1H), 4.82–4.80 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 1.61–1.59 (m, 8H).

Compound **15** (2.40 g) was dissolved in $CHCl_3$ (20 mL) and then concentrated hydrochloride acid (20 mL) added. After stirring at room temperature for 1 h, water (40 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$, then brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a yellow oil that was used directly in next step. To the resulting yellow oil, cumylamide (1.76 g, 13 mmol), and MeOH (30 mL) were added and the resulting solution stirred for 30 min. After the solution was cooled to 0 °C, $NaBH_4$ (0.76 g, 20 mmol) was added in several portions over 1 h. The reaction was warmed to ambient temperature and stirred over-

night. After careful quenching with saturated NH_4Cl solution, the mixture was concentrated in vacuum. The residue was dissolved in H_2O (60 mL), and the solution was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and silica-gel column chromatograph ($CHCl_3$/CH_3OH = 3:1) purification yielded amide **16** as colorless oil (3.42 g, 58% yield). ^1H NMR (300 MHz, $CDCl_3$) 7.28–7.18 (m, 5H), 6.80–6.65 (m, 3H), 4.71 (m, 1H), 3.83 (s, 3H), 2.66 (t, J = 6.1 Hz, 2H), 2.57 (t, J = 6.1 Hz, 2H), 1.91–1.58 (m, 9H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 142.9, 147.7, 132.7, 128.2, 126.2, 125.7, 120.8, 115.8, 112.2, 80.4, 56.3, 55.8, 44.4, 36.4, 32.9, 29.6, 24.2; HRMS(EI) calcd for $C_{23}H_{31}NO_2$ $(M)^+$: 353.2355. Found: 353.2348.

4.4.3. *N*-Cumyl-*N*-[2-(3-cyclopentyloxyl-4-methoxylphenyl)-ethyl]-diazoacetamide 2. To amide **16** (0.389 g, 1.1 mmol) in THF (20 mL) was added diketene (0.26 mL, 0.278 g, 3.3 mmol) at room temperature and the resulting solution stirred overnight. Solvent was removed under reduced pressure and silica-gel column chromatograph (PE/EA = 5:1) purification yielded a yellow oil (0.416 g). The resulting yellow oil was added to THF (20 mL) followed by 4-acetamidobenzene sulfonylazide (0.291 g, 1.2 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.18 mL, 1.2 mmol), and the resulting solution stirred at rt for 12 h. Aqueous lithium hydroxide (0.185 g, 4.4 mmol) in water (10 mL) was added to this mixture, and the resulting orange-brown mixture stirred vigorously for 5 h. The reaction mixture was diluted with ethyl acetate (60 mL) and the organic layer washed with water (2×30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a red-brown oil. Silica-gel column chromatography (PE/EA = 7:1) purification yielded a yellow oil **2** (0.334 g, 72.0% overall yield from the amine **16**). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.24 (m, 5H), 6.84–6.75 (m, 3H), 4.78 (m, 1H), 4.54 (s, 1H), 3.83 (s, 3H), 3.71 (t, J = 8.2 Hz, 2H), 2.95 (t, J = 8.2 Hz, 2H), 1.96–1.59 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 149.0, 148.7, 147.9, 131.6, 128.9, 126.8, 124.7, 120.7, 115.9, 112.4, 80.6, 61.3, 56.3, 49.8, 47.2, 37.1, 32.9, 30.1, 24.1; HRMS (ESI) calcd for $C_{25}H_{31}N_3O_3$ $(M+H)^+$: 422.2438. Found: 422.2450.

4.4.4. (4*R*)-(−)-4-(3-Cyclopentyloxyl-4-methoxylphenyl)-1-cumylpyrrolidin-2-one 17. To a solution of Rh_2[(4*R*)-MEOX]$_4$ (3 mg, 1 mol %) in CH_2Cl_2 (10 mL) at reflux was fast added the diazoacetamide **2** (137 mg, 0.325 mmol) in CH_2Cl_2 (6 mL). The reaction was complete in about 1 h. Solvent was removed under reduced pressure and then silica-gel column chromatography purification yielded pyrrolidinone **17** (82 mg, 64%). $[\alpha]_D^{25} = -8.7$ (c 1.08, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 5H), 6.83–6.73 (m, 3H), 4.76 (m, 1H), 3.83 (s, 3H), 3.37 (dd, J = 7.6, 9.1 Hz, 1H), 3.46–3.32 (m, 2H), 2.77 (dd, J = 16.6, 8.4 Hz, 1H), 2.57 (dd, J = 16.6, 8.7 Hz, 1H), 1.91–1.60 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 149.3, 148.0, 146.7, 134.9, 128.5, 126.8, 125.1, 118.9, 114.1, 112.3, 80.7, 59.2, 56.3, 54.3, 40.7, 37.0, 33.0, 28.1, 28.0, 24.1; HRMS(EI) calcd for $C_{25}H_{31}NO_3$ $(M)^+$: 393.2304. Found: 393.2300.

4.4.5. (*R*)-(−)-Rolipram 1. To pyrrolidinone **17** (35 mg, 0.09 mmol) was added CF_3COOH (2 mL) at room temperature and the resulting solution was stirred for 5 h. Saturated $NaHCO_3$ (20 mL) was added thereafter. The solution was extracted with EtOAc (3×15 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure and silica-gel column chromatograph ($CHCl_3$/CH_3OH = 25:1) purification yielded (*R*)-(−)-Rolipram **1** (16 mg, 65%) as white solid, mp 129–132 °C; $[\alpha]_D^{25} = -17.8$ (c 0.6, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 6.84–6.76 (m, 3H), 6.60 (br s, 1H), 4.77 (m, 1H), 3.83 (s, 3H), 3.78–3.57 (m, 2H), 3.38 (dd, J = 9.0, 7.5 Hz, 1H), 2.71 (dd, J = 16.9, 8.8 Hz, 1H), 2.47 (dd, J = 16.9, 8.9 Hz, 1H), 1.92–1.59 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 149.4, 148.1, 134.7, 119.0, 114.0, 112.4, 80.8, 56.3, 49.9, 40.2, 38.3, 33.0, 24.2; HRMS(ESI) calcd for $C_{16}H_{21}NO_3$ $(M+H)^+$: 276.1594. Found: 276.1599.

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