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A simple enantioselective route toward (*R*)- and (*S*)-Rolipram via anhydride desymmetrization

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ABSTRACT

A highly enantioselective metal-free synthesis of both enantiomers of Rolipram is reported. The key stereoinductive step is a cinchona alkaloid catalyzed opening of a cyclic anhydride prepared from isovanillin, where both enantiomers are available using the same chiral catalyst in two protocols. An extended one-pot Curtius sequence provides the lactam directly from the desymmetrization product after enrichment in high yield and excellent *ee*.

1. Introduction

Rolipram **1**, a cyclic derivate of GABA is a compound possessing antidepressive,[1] antiinflammatory,[2] antipsyhotic,[3] and neuroprotective[4] effects, among others. Biological activity is drawn from the selective inhibition of cAMP-selective phosphodiesterase activity (PDE), and recent animal studies show promise in ameliorating Alzheimer's disease[5] and regeneration of the spinal axon.[6] There is also growing excitement that PDE inhibitors may target multiple aspects of the tumor microenvironment, bearing potential for therapeutical use in the future.[7]

Although Rolipram is commercially available in the racemic form, its enantiomers show different biological activities,[1,8] and a simple method for obtaining both of them in sufficient quantities is desirable. Several asymmetric routes have been reported up to date; the chirality was, for example, induced via addition of arylboronic acids to aminobutenoic acid,[9] ethyl-γ-phthalimidocrotonate,[10] or an α,β-unsaturated γ-lactam;[11] via reduction of γ-phthalimido[12] or azido[13] substituted α,β-unsaturated esters; via carbon–hydrogen insertion;[14] via Michael addition of malonate to nitroolefins[15–18] or nitroalkanes to enals.[19–21]

While excellent ees are obtained using some of the above methods, high-priced metals or complex organocatalysts are typically used in the chirality inducing step. Moreover, to obtain the product in both enantiomeric forms, two chiral modifiers need to be prepared first, which may present a problem at the time if they turn out to be unequally reactive in the synthesis. The pathways mentioned, thus, tend to be impractical for greater production of both enantiomers. On the other hand, Rolipram may be prepared as a racemate on a multigram scale and resolved using the semipreparative simulated moving bed chromatography.[22] To the best of our knowledge, the only published protocol suitable for the larger production of both enantiomers proceeds through the resolution of racemic intermediate.[23]

In addition, we present herein a simple metal-free route toward Rolipram (Fig. 1), whereby both enantiomers are obtained using the same readily available catalyst in two protocols for the selective opening of anhydride **3**.

2. Results and discussion

Anhydride **3** was prepared according to the Smith and Kort protocol,[24] starting with aldehyde **2**. The latter is readily available from isovanillin through a single O-alkylation step in 95% yield.[25] The piperidine catalyzed condensation of **2** with ethylacetoacetate was performed in ethanol, from which the product precipitated. In sequence, hydrolysis with concentrated alkali yielded a glutaric acid intermediate in the form of crystals upon dilution and acidification. If used for the reaction, diluted alkali produces a certain amount of side product[24] that is harder to separate. Treatment of the glutaric acid intermediate with acetic anhydride at reflux allowed for the isolation of anhydride **3** after crystallization in a 60% overall yield from aldehyde **2** (Fig. 2).

The enantioselective desymmetrization of cyclic *meso*-anhydrides[26,27] has already been identified as a convenient method for stereoinduction in the total syntheses of biologically active substances,[28–30] including Pregabalin,[31] Biotin,[32] Baclofen,[33] etc.

Procedures using stoichiometric quantities of natural cinchona alkaloids for the opening of succinic anhydrides at low temperatures was developed by Bolm et al.[34] If a catalytic amount of alkaloid is used at room temperature instead, a drastic reduction of selectivity is observed. Alternatively, a catalytic amount of modified cinchona alkaloids including ethers,[35] ureas or thioureas,[36] and sulfonamides[37] was also found to steer the reaction toward the desired enantiomer.

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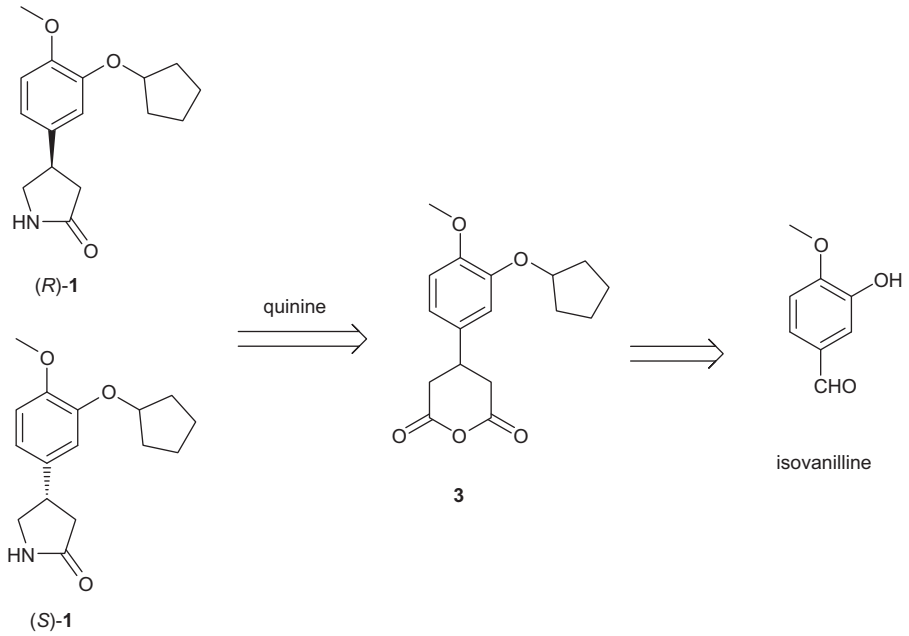

Figure 1. Retrosynthetic analysis of Rolipram **1**.

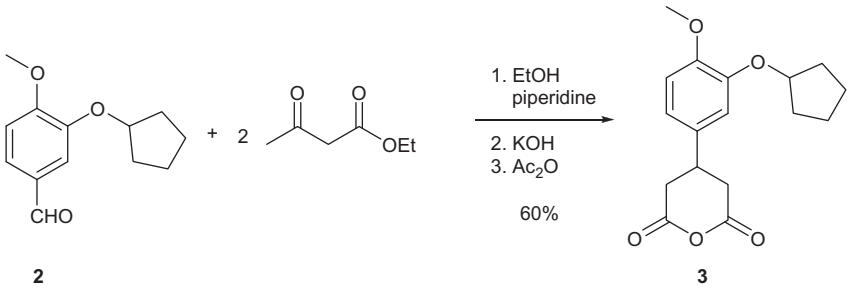

Figure 2. Preparation of anhydride **3**.

In contrast, glutaric anhydrides tend to show different behaviors. While both stoichiometric and catalytic opening with natural alkaloids proceed in moderate enantioselectivity at room temperature, the products formed are of opposite configurations.[38]

Quite recently, we published a work on optimization of the catalytic room temperature protocol using alkaloids as an organic acid salt, showing that the opposite pathway can be further improved to a synthetically useful level.[39] Consequently, both enantiomers of the product were available with the same naturally occurring chiral catalyst, solely by altering the protocol.

On the other hand, modified cinchona alkaloids, if used for the opening of the more demanding glutaric anhydrides (compared to the succinic), produce inferior results with the same catalyst loading,[36] and the resolution of enantiomers may nevertheless be needed in order to reach a satisfactory enantiopurity.

In the case of glutaric anhydrides, especially when both product enantiomers are required in larger quantities, the ease of the protocols utilizing inexpensive natural alkaloids turns out to be advantageous. The latter were our primary choice for anhydride desymmetrization in our synthesis of Rolipram. After opening of **3** with benzyl alcohol, monoester **4** was obtained preferentially when quinine was used as a catalyst in stoichiometric amount. The same catalyst produced the opposite *ent*-**4** if catalytic conditions with xanthene-9-carboxylic acid (X9C) were employed (Fig. 3). In contrast, quinidine, (the pseudoenantiomer of quinine) yielded **4** when used in a catalytic procedure, and *ent*-**4** in a stoichiometric protocol, all with comparable yields and *ee*s. Thus, the availability of both product enantiomers over this pathway was not limited by access to the two chiral catalysts.

Typically, somewhat lower yields of the isolated monoesters are found in anhydride desymmetrizations compared to the conversions.[40] The loss of the products is attributed to the emulsification properties of their salts during the workup which comprises of successive washing of alkaline aqueous monoester solutions with an organic solvent to remove residual alcohol.[31,39] In fact, during the present work, monoester **4** was found to be completely hydrolyzed in 2 h by a 2% carbonate solution. In addition, the room temperature catalytic protocol requires removal of the carboxylic acid additive, which is accomplished by fine tuning the pH down to the point where only the additive remains dissolved. While monoesters **4** and **5** appear as solids, both issues were resolved by a slow addition of the bulk mixture to the buffer solution, after which the product was isolated by filtration. Regeneration of the acid additive was possible by acidification of the residing mother liquor, previously washed with organic solvent.

Thus, after the usual removal of the alkaloid and the solvent, monoesters **4** and **5** were purified, both from the acid and the excess alcohol in a convenient isolation step without product loss. The results of anhydride **3** openings utilizing both the catalytic and stoichiometric protocols are summarized in Table 1.

As both benzyl (Bn) and cinnamyl (Cinn) monoesters are white solids, some enantiomeric enrichment was accomplished by

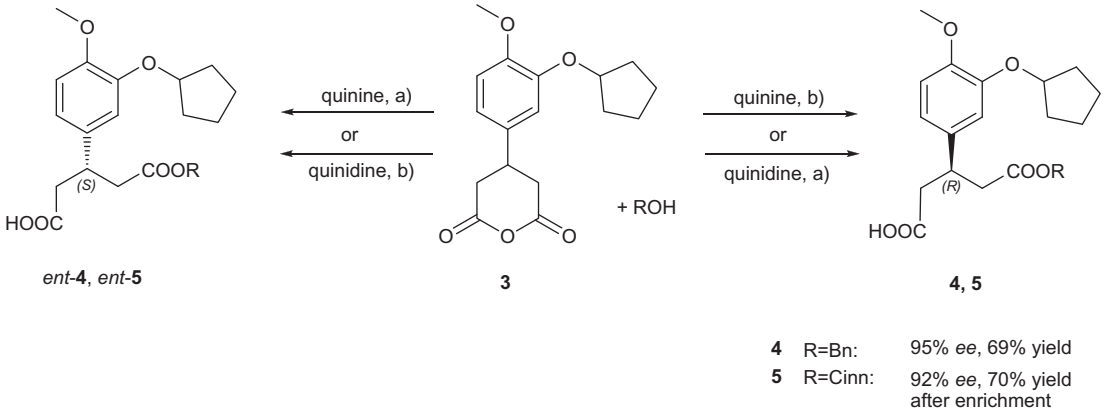

Figure 3. Cinchona catalyzed opening of anhydride **3**. Both product enantiomers are available with the same chiral catalyst. Conditions: (a) alkaloid (0.1 equiv), X9C (0.2 equiv), rt, then resolution with PEA or (b) alkaloid (1.1 equiv), −30 °C, then resolution with PEA.

Table 1
Enantioselective opening of **3** with natural cinchona alkaloids[a]

Entry	Method[b]	R′OH	Temp	Time	Yield (%)	*ee*[d] (%)	Product configuration
1	A(0.1 QD+X)	BnOH	rt	3 days	98	71	(*R*)
2	B(1.1 Q)	BnOH	−30 °C	7 days	94	73	(*R*)
3	A(0.1 Q+X)	BnOH	rt	3 days	94	62	(*S*)
4	B(1.1 QD)	BnOH	−30 °C	7 days	93	68	(*S*)
5	A(0.1 QD+X)	CinnOH	rt	3 days	95	73	(*R*)
6	B(1.1 Q)	CinnOH	−30 °C	3 days	72[c]	74	(*R*)

[a] Reactions were carried out with 10 mmol of anhydride, 0.1 M solution in toluene, and 1.5 equiv of alcohol until complete conversion was reached.
[b] Methods: (A) 0.1 equiv of quinidine (QD) or quinine (Q), 0.2 equiv of xanthene-9-carboxylic acid (X); (B) 1.1 equiv of quinine (Q) or quinidine (QD).
[c] Reaction was quenched after time indicated.
[d] Determined by chiral HPLC.

spontaneous crystallization from 2-propanol. However, the maximum *ee* obtained this way was about 90%. Alternatively, the resolution of (*S*)-phenylethylamine (PEA) salts allowed for the enrichment of benzyl product **4** from 73% *ee* to 95% *ee* by a single crystallization proceeding in a 73% yield from the desymmetrization product (Fig. 3). The enriched monoesters were used in the next step after liberation from the salt.

Various protected unnatural aminoacids[29,31,33,41] are available from succinic or glutaric acid monoesters through the one-pot sequence employing a Curtius rearrangement. The azide initially formed is thermally rearranged into an unstable isocyanate intermediate which reacts with a nucleophile to yield an N-protected aminoester.[42] However, during the deprotection step in a recent Pregabalin synthesis, intramolecular formation of a lactam was observed as an unwanted side reaction of a free amine and a neighboring ester group.[31] In the case of Rolipram, in contrast, the aforementioned pathway toward the lactam becomes more interesting, so a question arises as to whether a cyclization would proceed in the Curtius sequence if the free amine was formed directly. This could be accomplished if aqueous acid was used in the place of a nucleophile to hydrolyze the isocyanate intermediate formed in the rearrangement, followed by loss of carbon dioxide.[43]

Herein we have demonstrated that the cyclization indeed follows the thermal decarboxylation in the same step. In both cases, starting from monoester **4** or **5**, the isolated product was characterized as Rolipram (Fig. 4).

As a result, the need for protection and subsequent deprotection of the amine was avoided. The lactam was produced directly from the enriched monoester in a 51% yield over an extended one pot Curtius sequence without the isolation of unstable intermediates.

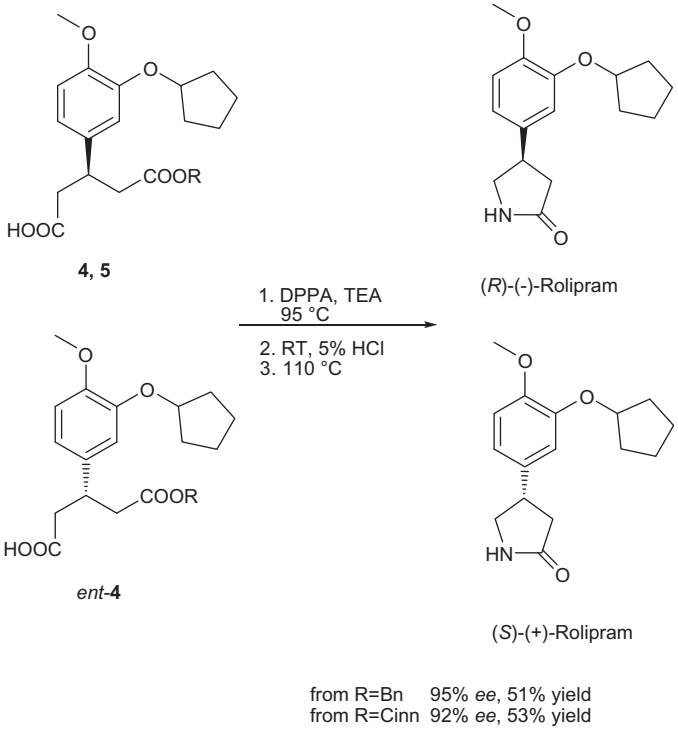

Figure 4. One pot extended Curtius reaction featuring lactam cyclization of **1**.

3. Conclusion

In conclusion, a simple metal-free enantioselective synthesis of both enantiomers of Rolipram has been developed. Chirality was introduced through the desymmetrization of glutaric anhydride **3** catalyzed by a natural cinchona alkaloid. Both enantiomers of the intermediary monoesters were available with a single chiral catalyst in a convenient synthesis starting from isovanillin.

An extended Curtius reaction of the enantiomerically enriched intermediary monoester through a one pot sequence yielded Rolipram of 95% *ee* in 51% yield. All stable intermediates were easily purified; chromatography was not needed except for the isolation of the final product.

4. Experimental

General methods: All reactions were conducted under an argon atmosphere unless otherwise noted. Aldehyde **2** was prepared according to the literature.[25] Triethylamine was dried over KOH prior to use. Toluene was dried in situ by distillation of azeotrope. All other reagents and solvents were purchased from commercial sources and used without purification. Column chromatography was performed on silica gel (silica gel 60, 70–230 mesh, Fluka). ^{1}H and ^{13}C NMR were recorded on a Bruker AV 300 spectrometer. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to TMS. High resolution mass spectrometry (HRMS) was performed on a 4800 Plus MALDI TOF/TOFAnalyzer. Optical rotations were measured using an Optical Activity AA-10 automatic polarimeter. Melting points were determined on a Electrothermal 9100 apparatus in open capillaries and are not corrected.

4.1. 2,4-Diacetyl-3-(3-cyclopentyloxy-4-methoxy-phenyl)-pentanedioic acid diethyl ester

Benzaldehyde **2** (22.32 g, 0.1 mol, 1 equiv) and ethylacetoacetate (27 mL, 0.21 mol, 2.1 equiv) were dissolved in absolute ethanol (100 mL). Piperidine (3 mL) was added and reaction stirred for 2 days at rt. The precipitated product was filtered, washed with ethanol and used in the next step without further purification (34.3 g, 73%).

4.2. 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-pentanedioic acid

The diethyl ester from the previous procedure (47 g, 0.1 mol) was added to a solution of KOH (62 g) in water (50 mL) and ethanol (40 mL). After 4 days stirring at room temperature the brownish mixture was diluted with water (50 mL) and slowly acidified with conc. HCl to pH 1. The crystals were filtered, washed with water and dried over Na_2SO_4 to obtain 24.2 g (74%) of the title compound. Combined mother liquor and washings were extracted with ethyl acetate (2 × 50 mL). Upon drying and evaporation the brownish oily residue was triturated with chloroform (20 mL) to yield an additional 3.8 g (15%) of product. Mp 176.7–177.5 °C. ^{1}H NMR (300 MHz, DMSO, δ): 1.52–1.60 (m, 2H); 1.66–1.74 (m, 4H); 1.81–1.89 (m, 2H); 2.48 (dd, J_1 = 15.5, J_2 = 8.6 Hz, 2H); 2.60 (dd, J_1 = 15.5, J_2 = 6.4 Hz, 2H); 3.26–3.40 (m, 1H); 3.69 (s, 3H); 4.73–4.77 (m, 1H); 6.74 (dd, J_1 = 8.4, J_2 = 2.1 Hz, 1H); 6.80–6.84 (m, 2H); 12.01 (br s, 2H) ppm. ^{13}C NMR (75 MHz, DMSO, δ): 23.95; 32.63; 37.96; 40.80; 55.96; 79.82; 112.60; 115.04; 119.76; 136.20; 147.04; 148.66; 173.37 ppm. ν_{max}(KBr) = 3482, 2965, 2943, 2912, 2834, 2672, 2578, 1704, 1594, 1518, 1427, 1348, 1337, 1313, 1297, 1257, 1240, 1169, 1139, 1032, 992, 943, 853, 810 cm^{-1}; HRMS (MALDI): *m*/*z*: calcd for $C_{17}H_{22}O_6K$ [*M*+*K*$^+$] 361.1049; found: 361.1050.

4.3. 4-(3-Cyclopentyloxy-4-methoxy-phenyl)-dihydro-pyran-2,6-dione 3

The glutaric acid from the previous procedure (2.71 g, 8.42 mmol) was dissolved in acetic anhydride (9 mL). The mixture was heated to 110 °C for 30 min and left to cool down to room temperature. After evaporation, the residue was crystallized from chloroform (4 mL) and diisopropyl ether (25 mL) to achieve 2.39 g (93%) of anhydride **5**. Mp 101.0–101.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.52–1.68 (m, 2H); 1.78–1.98 (m, 6H); 2.83 (dd, J_1 = 17.6, J_2 = 10.9 Hz, 2H); 3.08 (dd, J_1 = 17.6, J_2 = 4.6 Hz, 2H); 3.30–3.42 (m, 1H); 3.83 (s, 3H); 4.71–4.79 (m, 1H); 6.66–6.74 (m, 2H); 6.85 (d, J = 8.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, δ): 24.02; 32.81; 33.61; 37.39; 56.13; 80.74; 112.47; 113.26; 118.07; 131.43; 148.25; 149.89; 165.97 ppm. HRMS (MALDI): *m*/*z*: calcd for $C_{17}H_{20}O_5H$ [*M*+*H*$^+$] 305.1384; found: 305.1378.

4.4. (*R*)-3-(3-Cyclopentyloxy-4-methoxy-phenyl)-pentanedioic acid monobenzyl ester 4

4.4.1. Method A

Quinidine (0.320 g, 0.98 mmol, 0.1 equiv) was dissolved with xanthene-9-carboxylic acid (0.46 g, 2.02 mmol, 0.205 equiv) and anhydride **3** (3 g, 9.8 mmol, 1 equiv) in toluene (98 mL, 0.1 M with respect to the anhydride). Benzyl alcohol (1.5 mL, 1.60 g, 14.8 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 3 days. The reaction was quenched with 5% HCl (100 mL). The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residual white solid was dissolved in MeOH (15 mL) and added dropwise to a stirred phosphate buffer pH 5.4 (2.667 g of $NaH_2PO_4{\cdot}2H_2O$ and 1.167 g of citric acid monohydrate in 150 mL of water). White crystals (4.0 g, 98%) were collected, washed with water and dried. Enantiomeric purity (*ee* 71%) was determined by chiral HPLC (Chiralcel OD, hexane/EtOH/TFA = 95:5:0.1, 280 nm, 1 mL min^{-1}, t_{major} = 17.3 - min, t_{minor} = 19.4 min).

4.4.2. Method B

Benzyl alcohol (1.5 mL, 1.60 g, 14.8 mmol, 1.5 equiv) was added to the solution of anhydride **3** (3 g, 9.8 mmol) and quinine (3.52 g, 1.1 equiv) in toluene (98 mL, 0.1 M with respect to anhydride) cooled to −30 °C,. The reaction was stirred at −30 °C for 7 days and 5% HCl (100 mL) was added. The isolation of the product was performed as in method A. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.53–1.67 (m, 2H); 1.75–1.94 (m, 6H); 2.62–2.84 (m, 4H); 3.34–3.62 (m, 1H); 3.80 (s, 3H); 4.66–4.74 (m, 1H); 5.01 (s, 2H); 6.70–6.78 (m, 3H); 7.16–7.34 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, δ): 24.02; 32.71; 32.75; 37.63; 40.46; 40.70; 55.98; 66.29; 80.28; 112.03; 114.37; 118.97; 128.06; 128.14; 128.46; 134.51; 135.67; 147.52; 148.93; 171.43; 177.07 ppm. ν_{max}(KBr) = 3459, 3038, 2965, 2873, 2842, 2680, 2570, 1736, 1686, 1589, 1514, 1425, 1388, 1357, 1260, 1213, 1166, 1137, 1020, 983, 805, 735 cm^{-1}; HRMS (MALDI): *m*/*z*: calcd for $C_{24}H_{28}O_6Na$ [*M*+*Na*$^+$] 435.1778; found: 435.1781.

4.5. Enantiomeric enrichment of (*R*)-4

A mixture of ester **4** (4.29 g, 10.41 mmol, 73% *ee*) and (*S*)-phenylethylamine (1.33 mL, 1.27 g, 10.41 mmol) was heated in methyl isobutyl ketone (40 mL) and diisopropyl ether (40 mL) until a clear solution was obtained. At 45 °C a few milligrams of seed crystals were added. A crystal slurry was stirred at 45 °C for 1 h and then at rt overnight. Filtration yielded white crystals of amine salt (4.05 g, 73% yield, 95% *ee*).

(*S*)-PEA salt was suspended in toluene (50 mL) and stirred with 5% HCl (30 mL) until a clear solution was obtained. The organic

layer was washed once again with 3% HCl and then with brine. The toluene solution can be used directly in the subsequent reaction; otherwise, evaporation of solvent provided monoester **4** quantitatively. Mp 104.7–106.0 °C. $[\alpha]_D^{25} = +5.2$ (*c* 0.764, CH_2C_2).

4.6. (*R*)-3-(3-Cyclopentyloxy-4-methoxy-phenyl)-pentanedioic acid monocinnamyl ester 5

The product was synthesized according to the method A or method B, with cinnamyl alcohol instead of benzyl alcohol (see Table 1). Enantiomeric purity was determined by chiral HPLC (Chiralcel AS, hexane/EtOH/TFA = 9:1:0.01, 280 nm, 1 mL min^{-1}, t_{minor} = 16.4 min, t_{major} = 19.5 min). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.54–1.64 (m, 2H); 1.76–1.95 (m, 6H); 2.62–2.82 (m, 4H); 3.56–3.64 (m, 1H); 3.78 (s, 3H); 4.66 (d, *J* = 6.4 Hz, 2H); 4.73–4.77 (m, 1H); 6.12–6.20 (m, 1H); 6.56 (d, *J* = 15.9 Hz, 1H); 6.73–6.80 (m, 3H); 7.24–7.38 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, δ): 23.99; 32.73; 32.76; 37.63; 40.47; 40.73; 55.95; 65.03; 80.39; 112.13; 114.53; 119.08; 122.98; 126.57; 128.00; 128.55; 134.10; 134.63; 136.16; 147.56; 149.01; 171.35; 177.21 ppm. ν_{max}(KBr) = 3451, 3057, 2956, 2871, 2836, 2677, 2563, 1731, 1691, 1579, 1431, 1255, 1138, 965, 803 cm^{-1}; HRMS (MALDI): *m*/*z*: calcd for $C_{26}H_{30}O_6Na$ [*M*+*Na*$^+$] 461.1935; found: 461.1939.

4.7. Enantiomeric enrichment of (*R*)-5

A mixture of ester **5** (1.7 g, 3.88 mmol, 73% *ee*) and (*S*)-phenylethylamine (0.49 mL, 0.47 g, 3.88 mmol) was heated in 2-propanol (10 mL) and diisopropyl ether (20 mL) until a clear solution was obtained. At 45 °C, a few milligrams of seed crystals were added. The crystal slurry was stirred at 45 °C for 1 h and then at rt overnight. Filtration yielded white crystals of amine salt (1.57 g, 73% yield, 92% *ee*).

S-PEA salt was suspended in toluene (50 mL) and stirred with 5% HCl (30 mL) until a clear solution was obtained. The organic layer was washed once again with 3% HCl and then with brine. The toluene solution can be used directly in the subsequent reaction; otherwise evaporation of solvent provides monoester **5** quantitatively. Mp 89.4–91.0 °C. $[\alpha]_D^{25} = -7.3$ (*c* 0.41, MeOH).

4.8. (*R*)-(−)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-pyrrolidin-2-one 1

Dry triethylamine (0.60 mL, 4.32 mmol, 1.1 equiv) and diphenylphosphorylazide (0.85 mL, 3.93 mmol, 1 equiv) were added under argon to a solution of optically enriched monoester **4** (1.62 g, 3.93 mmol, 1 equiv, 95% *ee*) in dry toluene (15 mL). The reaction was heated to 90 °C for 30 min and cooled down to room temperature. Dilute hydrochloric acid (5% HCl, 15 mL) was added and the mixture was stirred vigorously overnight. The layers were separated, the organic layer washed with water (15 mL) and left at reflux (110 °C) overnight. Upon cooling down to room temperature, the mixture was washed with 2% Na_2CO_3 (15 mL) and then water (10 mL), and dried over Na_2SO_4. Evaporating the solvent, (*R*)-(−)-Rolipram (548 mg, 51%) was isolated using column chromatography (methanol/dichloromethane 5:95). The enantiomeric purity was determined as 95% (Chiralcel AS, ethanol, 280 nm, 0.8 ml min^{-1}, t_{major} = 10.5 min, t_{minor} = 13.7 min). Compound characterization: white crystals, mp 130.6–131.4 °C (lit.[22] 130.5–131.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.54–1.68 (m, 2H); 1.78–1.98 (m, 6H); 2.47 (dd, 1H, J_1 = 16.8 J_2 = 8.9 Hz, 1H); 2.71 (dd, J_1 = 16.8 Hz, J_2 = 8.9 Hz, 1H); 3.34–3.44 (m, 1H); 3.55–3.69 (m, 1H); 3.71–3.80 (m, 1H); 3.83 (s, 3H); 4.71–4.81 (m, 1H); 6.46 (s, 1H); 6.74–6.86 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, δ): 24.00; 32.82; 38.11; 40.00; 49.75; 56.19; 80.68; 112.38; 114.00; 118.84; 134.64; 147.98; 149.28; 177.74 ppm.

ν_{max}(KBr) = 3200, 3085, 2964, 2870, 2834, 1709, 1688, 1518, 1263, 1238, 1164, 1144, 1029, 816 cm^{-1}; HRMS (MALDI): *m*/*z*: calcd for $C_{16}H_{21}NO_3H^+$ [*M*+*H*$^+$] 276.1594; found 276.1600.

4.9. (*R*)-(−)-Rolipram

$[\alpha]_D^{26} = -29.9$ (*c* 0.586, MeOH) for 95% *ee*, lit.[17] $[\alpha]_D^{25} = -31.0$ (*c* 1.05, MeOH) for >99% *ee*.

4.10. (*S*)-(+)-Rolipram

The product was prepared as the opposite enantiomer in an analogous reaction sequence from anhydride **3**. $[\alpha]_D^{25} = +30.5$ (*c* 0.605, MeOH) for 95% *ee*, lit.[23] $[\alpha]_D^{rt} = +31$ (*c* 0.6, MeOH) for 98.95% *ee*.

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