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SYNTHESIS OF (±)-ROLIPRAM

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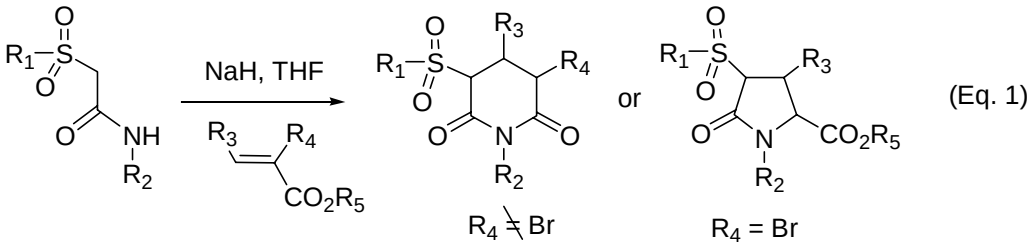
Abstract – A facile synthesis of rolipram *via* stepwise [3+2] annulation and desulfonated hydrolysis was reported. Base-induced coupling/cyclization reactions of α-sulfonylacetamide with (*Z*)-2-bromoacrylic ester yielded three contiguous centers on the pyroglutamate system with *trans-trans* orientation as the one-pot key step.

1. INTRODUCTION

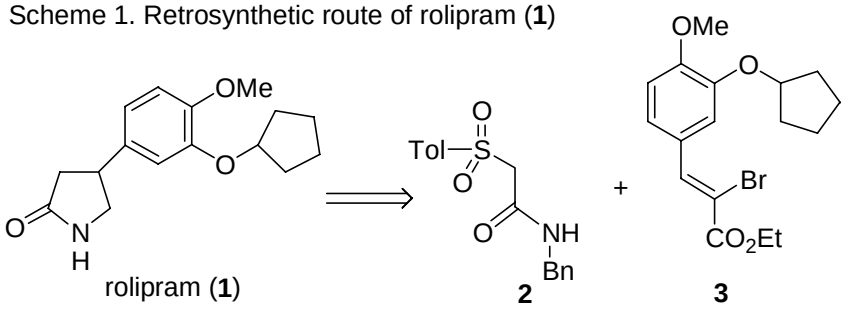
Recently, we reported a facile stepwise [3+3] annulation reaction between different α-sulfonylacetamide derivatives and a series of the α- or β-, aryl- and alkyl-substituted acyclic α,β-unsaturated alkyl esters that lead to corresponding glutarimides (piperidine-2,6-diones) in good yields.[1-12] We have already presented some successful applications for the syntheses of natural products and potential drugs *via* this facile [3+3] annulation. In the α,β-unsaturated esters containing a α-bromo group, the stepwise [3+2] annulation[13-14] with α-sulfonylacetamide was proceeded to produce the pyroglutamic skeleton as shown in Equation 1. Pyroglutamate can serve as key building blocks for the synthesis of a variety of pyrrolidin-2-one ring. We are interested in the generalization of this facile [3+2] route for pyrrolidin-2-one to afford the corresponding 3-aryl substituted derivatives.[15-39]



Pyrrolidin-2-one possesses varied potential pharmaceutical activity and is also valuable intermediate for the synthesis of interesting nitrogen-containing products.[40-45] The preparation of pyrrolidin-2-one is

mainly based on the transformation of pyroglutamate derivatives in all successful routes.[23-39] Among the drugs bearing a pyrrolidin-2-one ring, rolipram (**1**)[46-58] is a potent and selective inhibitor of cyclic-AMP specific phosphodiesterase (*c*AMP, PDE) designated PDE IV, and it is known to bind stereoselectively and with very high affinity to binding sites in brain tissue. Here, we synthesized rolipram (**1**) using the novel and facile [3+2] strategy as the key step. The retrosynthetic analysis for the synthesis of rolipram (**1**) is shown in Scheme 1.

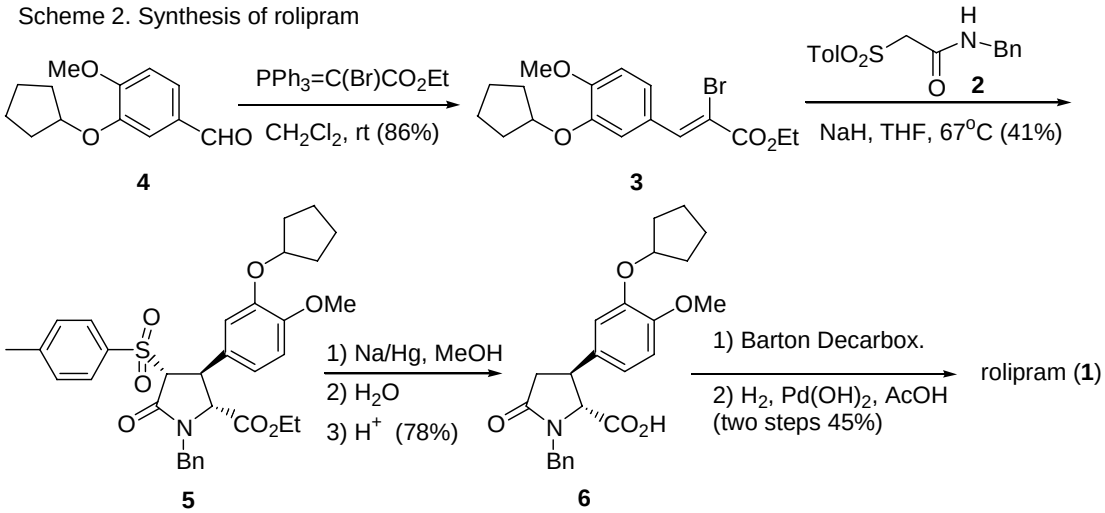
Scheme 1. Retrosynthetic route of rolipram (**1**)



2. RESULTS AND DISCUSSION

Benzylamine was treated with chloroacetyl chloride and triethylamine to produce α-chloroacetamide, which was then treated with *p*-toluenesulfinic acid sodium salt to give α-sulfonylacetamide (**2**) in 85% yield from the two-steps reaction. Treatment of isovanillin with cyclopentyl bromide in K_2CO_3/DMF system yielded the alkylated product (**4**), which on Wittig reaction with $Ph_3P{=}C(Br)CO_2Et$ gave **3**, in 86% yield from **4**. The one-pot synthesis began with the reaction of **2** with **3** (NaH/THF) and proceeded through stereo- and regioselective annulation with the appropriate carbonyl substrate in a [3+2] mode, resulting in the overall formation of single pyroglutamate isomer (**5**) with three contiguous chiral centers (Scheme 2).

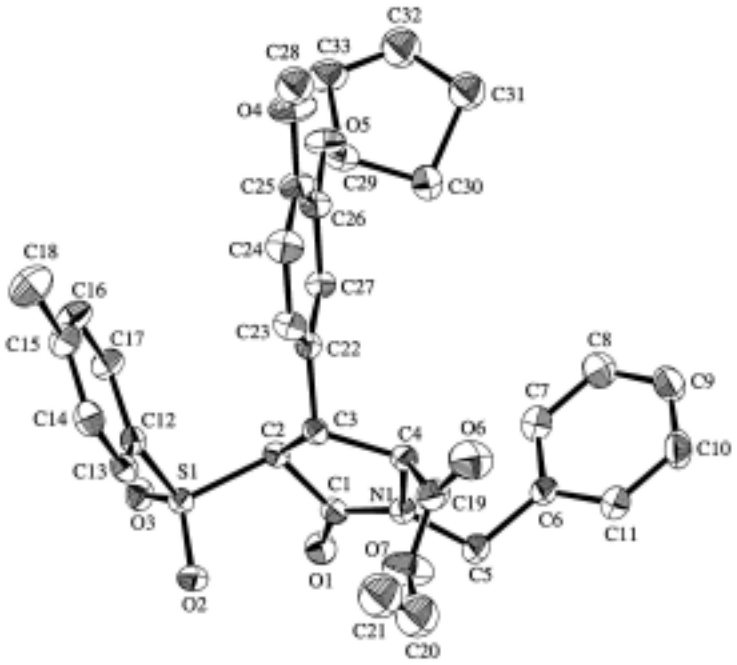
Scheme 2. Synthesis of rolipram



The reaction mechanism of **2** with (*Z*)-**3** presented an outstanding stereoselectivity for the formation of **5** and had already been proposed.[13] Presumably, **3** reacted with dianion (**2**), after 1,4-addition, ring closure by substitution of bromide could then be followed, providing the cyclized **5** with substituents at C_2 and C_3

also C_3 and C_4 in *trans* configuration to each other. The structure of compound (**5**) was determined by single-crystal X-Ray analysis as shown in diagram 1. The one-pot desulfonation and hydrolysis of compound (**5**) was accomplished by treatment of **5** with 6% sodium amalgam (Na/Hg) and sodium phosphate, after addition of water to the resulting mixture and then acidification, to yield acid (**6**) in 78% yield. Barton and coworkers have described a decarboxylation procedure of *N*-protected α-amino acids and peptides wherein the stereochemistry of the reaction molecule is preserved completely.[59] This decarboxylation procedure[20,53,59] was successfully applied to **6**, subsequent debenzylation produced rolipram (**1**). The total yield for the synthesis of racemic rolipram is 12% in five steps from the known aldehyde (**4**).

Diagram 1. X-Ray crystallography of **5**



3. CONCLUSION

In conclusion, we explored a one-pot cycloaddition strategy that is synthetically useful for constructing ethyl pyroglutamate and utilized the method to achieve the synthesis of rolipram.

4. EXPERIMENTAL

4.1. General. THF was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude products were purified using preparative TLC or column chromatography on silica gel. All reported temperatures were uncorrected.

4.2. (*Z*)-2-Bromo-3-(3-cyclopentyloxy-4-methoxyphenyl)acrylic acid ethyl ester (3)

Potassium carbonate (1.67 g, 12.1 mmol) and cyclopentyl bromide (1.3 mL, 12.1 mmol) were successively added to a solution of isovanillin (0.61 g, 4.0 mmol) in DMF (20 mL). The mixture was stirred at 100 ^{o}C for 20 h and the solvent and excess reagent were removed under reduced pressure. Water was added to the residue and the product was extracted with dichloromethane (3 x 20 mL) to give **4** as yellow oil (880 mg). Without further purification, a solution of **4** (880 mg, 4.0 mmol) in dichloromethane (10 mL) was added to a rapidly stirred solution of $Ph_3P{=}C(Br)CO_2Et$ (2.1 g, 5.0 mmol) in dichloromethane (20 mL), then stirred at rt for 5 h. The resulting mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Evaporation of the solvent followed by purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (4/1) produced **3** (1.26 g, 86%) as the oil: IR ($CHCl_3$) 1688, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.83-4.79 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 2.03-1.80 (m, 6H), 1.67-1.59 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.66, 151.84, 147.17, 140.55, 126.17, 125.17, 115.77, 111.07, 110.00, 80.51, 62.60, 55.95, 32.83 (2x), 24.15 (2x), 14.25; HRMS m/z: Calcd for $C_{17}H_{21}O_4Br$ 368.0623. Found 368.0629.

4.3. Ethyl 1-benzyl-3-(3-cyclpentyloxy-4-methoxyphenyl)-4-(4-methylphenylsulfonyl)pyroglutamate (5)

A solution of **2** (303 mg, 1.0 mmol) in THF (30 mL) was carefully added to a rapidly stirred suspension of sodium hydride (124 mg, 3.1 mmol, 60%) in THF (30 mL). After the reaction mixture was stirred at rt for 15 min, a solution of **3** (404 mg, 1.1 mmol) in THF (30 mL) was added. The resulting mixture was stirred for 6 h at refluxed temperature, quenched with 40% NH_4Cl (2 mL) in an ice bath, and concentrated under reduced pressure. Water (20 mL) was added to the crude product, and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried, filtered and evaporated. Evaporation of the solvent followed by purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (4/1) produced **5** as a solid (242 mg, 41%): mp: 167-168 ^{o}C (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29-7.23 (m, 5H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.45 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 5.26 (d, *J* = 14.5 Hz, 1H), 4.47-4.44 (m, 1H), 4.37-4.30 (m, 1H), 4.29-4.24 (m, 3H), 4.00 (d, *J* = 3.0 Hz, 1H), 3.93 (d, *J* = 3.5 Hz, 1H), 3.78 (s, 3H), 2.46 (s, 3H), 1.81-1.73 (m, 6H), 1.58-1.56 (m, 2H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.43, 164.98, 149.62, 148.21, 145.44, 135.11, 134.30, 133.66, 129.65 (2x), 129.47 (2x), 129.03 (2x), 128.87 (2x), 128.18, 118.32, 112.63, 112.11, 80.30, 73.16, 63.87, 62.03, 56.03, 46.57, 41.33, 32.71, 32.66, 24.08, 24.06, 21.75, 14.16; EI-MS m/z (%): 91 (100), 294

(29), 368 (10), 591 (1); HRMS m/z: Calcd for $C_{33}H_{37}NO_7S$ 591.2291. Found 591.2298; Anal. Calcd for $C_{33}H_{37}NO_7S$ C, 66.98; H, 6.30. Found C, 66.72; H, 6.18. Single-crystal X-Ray diagram: crystal of **5** was grown by slow diffusion of ethyl acetate into a solution of **5** in dichloromethane to yield colorless prism. The compound crystallizes in the primitive monoclinic crystal system, space group $P2_1/c$ (#14), a=13.129(3) Å, b=13.405(2) Å, c=18.276(2) Å, β=101.28(1)^o, V=3154.2(9) Å^3, Z=4, d_{calcd}=1.25 g/cm^3, F(000)=1256.00, 2θ range 20(8.8~13.5^o), R= 0.066.

4.4. 1-Benzyl-3-(3-cyclpentyloxy-4-methoxyphenyl)pyroglutamic acid (6)

6% Sodium amalgam (Na/Hg, 300 mg) was added to a solution of **5** (118 mg, 0.2 mmol) and sodium phosphate (71 mg, 0.5 mmol) in methanol (5 mL). The mixture was vigorously stirred for 2 h at rt. Water (2 mL) was added to the residue. The residue was filtered and washed with methanol (2 x 10 mL). The combined layers were concentrated to get the crude product. Water (10 mL) was added to the crude product, and the mixture was extracted with ethyl acetate (3 x 20 mL). The aqueous layer was acidified with 2N HCl (2 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried, filtered and evaporated. Evaporation of the solvent followed by purification of the crude product by column chromatography on silica gel with ethyl acetate/methanol (4/1) produced **6** as a gum (64 mg, 78%): IR ($CHCl_3$) 3320, 1713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (br s, 5H), 6.92 (br s, 1H), 6.37 (br s, 3H), 5.16 (br s, 1H), 4.26 (br s, 1H), 3.91 (br s, 1H), 3.80 (br s, 1H), 3.58 (br s, 3H), 3.47 (br s, 1H), 3.12 (br s, 1H), 2.35 (br s, 1H), 1.61 (br s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.82, 176.37, 148.86, 147.76, 136.22, 135.53, 128.49 (4x), 127.44, 118.64, 112.36, 111.70, 80.08, 68.90, 55.80, 45.91, 40.50, 38.56, 32.56 (2x), 23.99 (2x). EI-MS m/z (%): 91 (100), 296 (5), 341 (1), 409 (1); HRMS m/z: Calcd for $C_{24}H_{27}NO_5$ 409.1889. Found 409.1890.

4.5. 4-(3-Cyclpentyloxy-4-methoxyphenyl)-2-pyrrolidinone (rolipram) (1)

Isobutyl chloroformate (13.6 mg, 0.1 mmol) in THF (2 mL) was added to a solution of **6** (41 mg, 0.1 mmol) and *N*-methylmorpholine (10.2 mg, 0.1 mmol) in THF (5 mL) at -15 ^{o}C. After 5 min, a solution of *N*-hydroxy-2-thiopyridone (15.2 mg, 0.12 mmol) and triethylamine (12.2 mg, 0.12 mmol) in THF (5 mL) was added. The mixture was stirred for 1 h in the dark. The precipitate was removed under nitrogen by suction and washed with THF (2 x 3 mL). After addition of *t*-butylthiol (0.09 mL, 1.0 mmol), the solution was irradiated (100 W) for 1 h at rt. The mixture was diluted with ether (10 mL), washed with 0.5N HCl, brine and water. The organic layer was dried and evaporated. Without further purification, 10% palladium hydroxide on activated carbon (10 mg) as catalyst was added to a solution of the resulting product (22 mg, 60%) in acetic acid (5 mL). Hydrogen was bubbled into the mixture for 10 min, and the mixture was stirred at rt for 18 h. Filtration through a short plug of Celite and washing with ethyl acetate (3 x 10 mL) resulted in the crude product. Purification on silica gel (hexane/ethyl acetate = 1/1) produced **1** (12.4 mg, 75%) as a solid: mp = 133-134 ^{o}C (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, J = 8.0 Hz, 1H),

6.77 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.16 (br s, 1H), 4.79-4.75 (m, 1H), 3.83 (s, 3H), 3.75 (td, *J* = 1.0, 9.5 Hz, 1H), 3.66-3.60 (m, 1H), 3.38 (dd, *J* = 6.0, 9.5 Hz, 1H), 2.71 (dd, *J* = 9.0, 17.0 Hz, 1H), 2.47 (dd, *J* = 9.0, 17.0 Hz, 1H), 1.95-1.80 (m, 6H), 1.65-1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.59, 149.17, 147.88, 134.49, 118.77, 113.78, 112.16, 80.57, 56.12, 49.69, 39.98, 38.01, 32.79 (2x), 24.00 (2x); HRMS m/z: Calcd for $C_{16}H_{21}NO_3$ 275.1521. Found 275.1231. The ^{1}H and ^{13}C NMR spectral data of **1** were in accordance with those reported in the literature.

5. ACKNOWLEDGEMENTS

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