JOC*Note*

Synthesis of 4-Aryl-2-pyrrolidones and β-Aryl-γ-amino-butyric Acid (GABA) Analogues by Heck Arylation of 3-Pyrrolines with Arenediazonium Tetrafluoroborates. Synthesis of (±)-Rolipram on a Multigram Scale and Chromatographic Resolution by Semipreparative Chiral Simulated Moving Bed Chromatography

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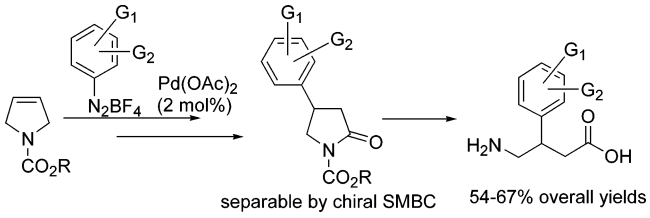

We report herein a new, practical, and economic synthesis of the phosphodiesterase inhibitor Rolipram on a multigram scale as well as the synthesis of new 4-aryl pyrrolidones and β-aryl-γ-amino butyric acids (GABA derivatives) employing an efficient Heck−Matsuda arylation of 3-pyrroline with aryldiazonium tetrafluoroborates. Racemic Rolipram was resolved into its enantiomers using chiral simulated moving bed chromatography having the low-cost microcrystalline cellulose triacetate as a chiral stationary phase.

Pyrrolidin-2-ones encompass a wide variety of physiologically active compounds that also work as precursors for the synthesis of γ-amino butyric acids (GABA analogues).[1] Several analogues of the neurotransmitter GABA display important pharmacological and therapeutic functions on the central nervous system.[2]

Rolipram **1**, or (*R*,*S*)-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one, was initially developed as an antidepressant drug and commercialized in Europe by Schering AG.[3] It is a potent and selective inhibitor of phosphodiesterase IV (PDE4), the main enzyme regulating the concentration of the secondary messenger, cyclic adenosine-3′,5′-monophosphate (cAMP). Cleavage of the phosphodiester bridge of cAMP blocks the action of this secondary messenger and consequently the cascade of biochemical events leading to inflammatory processes.[4] The action of PDE4 is also related to a number of pathological processes in the central nervous system (CNS) such as multiple sclerosis, coronary failure, asthma, pulmonary diseases, and diabetes, among others.[5]

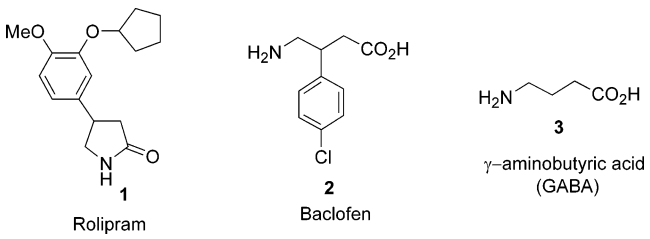

FIGURE 1. Structures of Rolipram, Baclofen, and GABA

Despite a number of synthetic approaches to Rolipram in the literature,[6] this compound is a very expensive one, limiting its use in pharmacological studies.[7] Both enantiomers of Rolipram are active toward PDE4 with the (*R*)-(−) isomer being the most active one.[6c,k] In view of the importance of Rolipram as a potential drug and as a pharmacological probe, a general approach to Rolipram and new derivatives is highly desirable. Moreover, due to the close chemical correlations of Rolipram to the important neurotransmitter γ-amino butyric acid **3** (GABA) and, in particular, to $GABA_B$ receptor agonists such as Baclofen **2** (used to treat spasms caused by spinal cord injuries), a route designed for the preparation of Rolipram could also be amenable to the preparation of new GABA derivatives.

Herein, we report on a new route to the efficient synthesis of Rolipram **1** on a multigram scale, as well as the synthesis of new Rolipram and Baclofen analogues. The route features a Heck−Matsuda arylation of a simple 3-pyrroline with a diazonium salt as the key step.[8]

The first stages of the synthesis were directed to the preparation of the aryldiazonium salt **7** on a multigram scale, from the cheap and commercially available 5-nitro-2-methoxyphenol **4**. Phenol **4** was readily converted into the cyclopentyl ether **5** with cyclopentyl bromide in acetone,[6b] in 98% yield (> 98% of purity by capillary GC).

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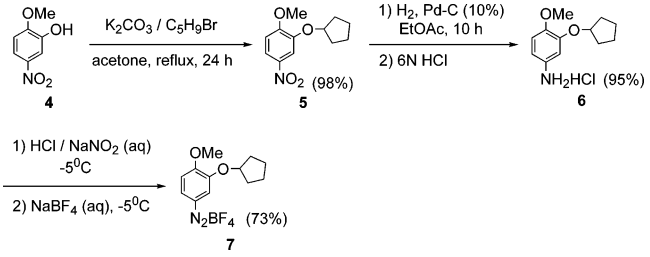
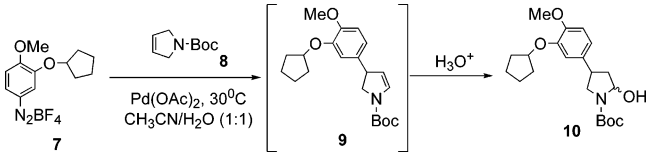
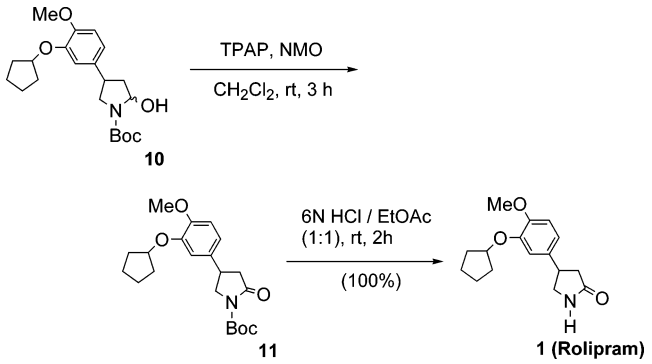
SCHEME 1. Synthesis of the Aryldiazonium Tetrafluoroborate 7



SCHEME 2. Heck−Matsuda Reaction Coupling the Pyrrolidine Ring to the Aromatic Moiety



SCHEME 3. Synthesis of Rolipram 1 from the Heck−Matsuda Adduct 10



Ether **5** was next subjected to catalytic hydrogenation (H_2, Pd−C, EtOAc, 10 h), followed by filtration through Celite and acidification with 6 M HCl to provide the pure aniline hydrochloride **6** in 95% yield. Acidification with HCl caused precipitation of the ammonium salt, which helped to improve the yields. Moreover, purification of the hydrochloride **6** was unnecessary; washing the crude hydrochloride **6** with CH_2Cl_2 resulted in a white solid of high purity. The hydrochloride **6** was then transformed into the aryldiazonium tetrafluoroborate **7** using a standard procedure, as indicated in Scheme 1, in 73% yield after recrystallization.

Next, the *N*-Boc-3-pyrroline **8** (prepared in 82% yield according to the protocol of Grubbs)[9] was submitted to a Heck−Matsuda arylation with the aryldiazonium tetrafluoroborate salt **7** in the presence of 2 mol % $Pd(OAc)_2$ in CH_3CN/H_2O (1:1, v/v).[8b] The reaction proceeded rapidly (30−45 min) to furnish lactamol **10**, which was isolated and used in the next step without further purification (Scheme 2). Under the Heck−Matsuda conditions, the primary product of the Heck arylation was the endocyclic enecarbamate **9**, which quickly underwent hydrolysis due to the acidity of the reaction medium, to provide lactamol **10**.[10]

The crude lactamol **10** was then oxidized with catalytic tetrapropylammonium perruthenate (TPAP), with *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant in CH_2Cl_2, to give lactam **11** (66% yield from **7**).[11] Oxidation employing either pyridinium chlorochromate (PCC) in CH_2Cl_2 or *o*-iodoxybenzoic acid (IBX) in EtOAc[12] led to lactam **11** in comparable yields (60−63%). Finally, acidic hydrolysis of lactam **11** with 6 M HCl in ethyl acetate at room temperature provided racemic Rolipram **1** in quantitative yield (Scheme 3). The physical and spectroscopic data of Rolipram **1** were in excellent agreement with those reported in the literature.[6]

Following the protocol described above, racemic Rolipram was synthesized in six steps from commercially available 5-nitro-2-methoxyphenol **4** in an overall yield of 45% (average of 87−88% yields per step).[13]

The Heck−Matsuda approach was flexible enough to allow the synthesis of the unreported γ-amino butyric acids (GABA) analogues **13** and **14**. Thus, basic hydrolysis of lactam **11** with LiOH in THF using Grieco's conditions[14] produced N-protected γ-amino acid **12** in 85% yield. Removal of the Boc protecting group occurred smoothly with 6 M HCl/EtOAc (1:1) at room temperature to provide the desired γ-amino butyric acid hydrochloride **13** in quantitative yield. The temperature of acidic hydrolysis significantly affects the type of product obtained. Thus, lactam **11** was hydrolyzed at 95 °C with 6 M HCl for 12 h to cleanly furnish the hydrochloride **14** in 84% yield. On the other hand, when hydrolysis of lactam **11** was carried out under acidic conditions at reflux, a hard-to-separate mixture of the γ-amino butyric

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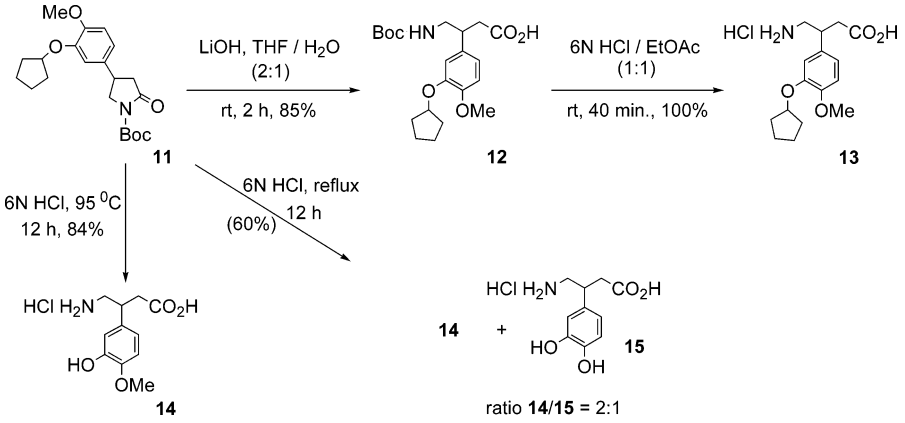
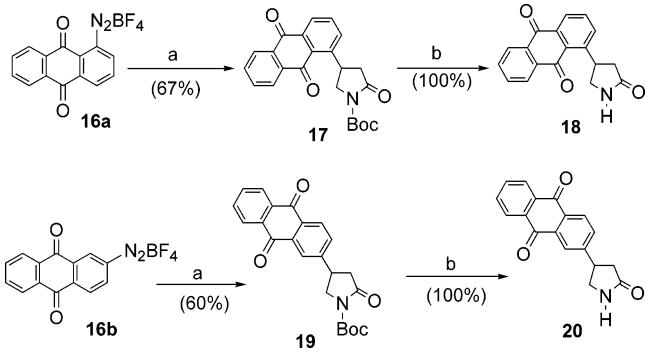
SCHEME 4. Conversion of the 4-Arylpyrrolidin-2-one 11 into New GABA Derivatives



SCHEME 5. Synthesis of 4-(9,10-Dioxo-9,10-dihydro-anthracenyl)-pyrrolidin-2-ones 18 and 20[a]



[a] Reagents and Conditions: (a) (1) $Pd(OAc)_2$, **8**, CH_3CN/H_2O; (2) PCC, CH_2Cl_2, rt, 3 h. (b) 6 N HCl/EtOAc (1:1), rt, 2 h.

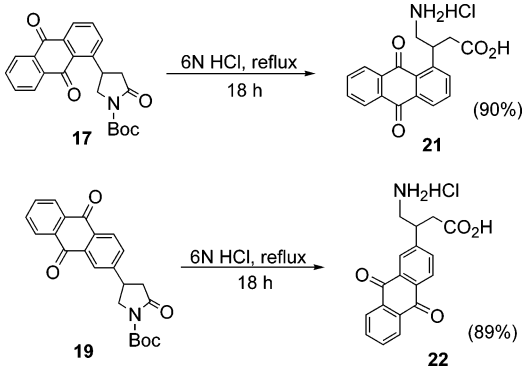
acid hydrochlorides **14/15** was obtained in 60% yield, in a ratio of ~2:1, as determined by ^1H NMR in D_2O (Scheme 4).

Due to our interest in new 4-arylpyrrolidones we additionally obtained the unreported 4-(9,10-dioxo-9,10-dihydro-anthracenyl)-pyrrolidin-2-ones **18** and **20** in excellent overall yields (67 and 60% yields, respectively) from the 9,10-dioxo-9,10-dihydro anthracenyl diazonium salts **16a** and **16b**, as shown in Scheme 5. The corresponding anthracenyl diazonium salts were obtained following Milner's procedure.[15]

Acidic hydrolysis of lactams **17** and **19** produced the expected γ-amino butyric acid hydrochlorides **21** (90%) and **22** (89%), respectively (Scheme 6).

Semipreparative Simulated Moving Bed Chromatography. The SMB Chromatography is an automated, continuous, and multicolumn chromatographic system, which has reduced solvent consumption, time-consumption, and purification costs.[16] This technique simulates movement of the chromatographic packing material, or bed, against the liquid phase and allows a continuous recovery of the desired compound. In this process, the solvent and the binary mixture of compounds (racemate) to be resolved are injected into and withdrawn from a ring of chromatographic columns, at periodic and simultaneous switching points between the columns in the direction of the desorbent flow.

SCHEME 6. Hydrolysis of Pyrrolidinones 17 and 19 to the Anthracenyl GABA Derivatives



Recently, there has been increasing interest in the pharmaceutical sector in the synthesis of single enantiomers of chiral drugs.[17] As part of an ongoing project to associate continuous simulated moving bed chromatography (SMBC) to organic synthesis, the racemic Rolipram (1 g scale) prepared as described herein was resolved into its enantiomers by means of a semipreparative chiral simulated moving bed chromatographic unit composed of eight semipreparative columns having microcrystalline cellulose triacetate (MCTA)[6c] as a chiral stationary phase. The SMBC was performed with ethanol as an eluent and with a feed concentration of 4.0 g/L to provide enantiomerically enriched (*R*)-(−)-**1** (>88% ee) as determined by analytical HPLC analysis on a Kromasil Chiral TBB column and (*S*)-(+)-**1** (>68% ee), with good recoveries. After a single recrystallization of the compound obtained in the raffinate stream in EtOAc/Hex, the enantiomer (*R*)-(−)-**1** was obtained with more than 96% enantiomeric excess (Fig. 1 in Supporting Information).

In summary, we report a new, practical, and economic synthesis of the phosphodiesterase inhibitor Rolipram on a multigram scale as well as the synthesis of new 4-aryl pyrrolidones and β-aryl-γ-amino butyric acids (GABA derivatives) employing an efficient Heck−Matsuda arylation of 3-pyrroline with aryldiazonium tetrafluoroborates. We successfully separated racemic Rolipram into its enantiomers using a "locally built" Chiral SMB chromatographic unit composed of eight semipreparative columns containing the low-cost MCTA as a chiral

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stationary phase. (*R*)-(−)-Rolipram was obtained in >96% ee after a single recrystallization of the material separated in the raffinate stream.

Experimental Section

1-(*tert*-butoxycarbonyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-ol (10). To a solution of *N*-*tert*-butoxycarbonyl-3-pyrroline **8** (6.0 g, 35.46 mmol) in 160 mL of CH_3CN/H_2O (1:1) was added the diazonium salt **7** (7.23 g, 23.62 mmol), followed by addition of $Pd(OAc)_2$ (110 mg, 2 mol %). The reaction medium was stirred for 45 min at 30 °C. The reaction was monitored by nitrogen evolution and by the precipitation of Pd(0). The mixture was diluted with EtOAc (∼250 mL), transferred to a separatory funnel, and extracted with saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to give **10** as a dark colored oil, which was used in the next step without further purification. TLC: R_f = 0.38 and 0.66 (EtOAc/Hex = 1:1) phosphomolybdic acid; IR (film, NaCl, crude oil) ν (cm^{-1}): 3452, 2966, 2870, 2835, 1693, 1516, 1392, 1257, 1165, 1126, 1011, 879.

1-(*tert*-Butoxycarbonyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one (11). To a solution of 8.916 g of the crude lactamol **10** (∼23.6 mmol) in 180 mL of CH_2Cl_2 were added 830 mg (2.36 mmol, 10 mol %) of tetrapropylammonium perruthenate and 5.44 g (47.25 mmol) of *N*-methyl-morpholine-*N*-oxide. The reaction mixture was vigorously stirred at room temperature. After 3 h, the crude mixture was filtered through a pad of silica gel (approximately 6 cm of SiO_2 in a 5 cm i.d. column) and washed with CH_2Cl_2. The solvent was evaporated in vacuum, and the residue was flash chromatographed on silica gel (EtOAc/hexane 10−20%) to provide 5.86 g (66% yield over two steps) of lactam **11** as a white solid. Mp: 81−83 °C. TLC: R_f = 0.64 (EtOAc/Hex = 1:1) phosphomolybdic acid. IR (film, NaCl) ν (cm^{-1}): 2962, 2873, 1786, 1751, 1712, 1516, 1365, 1315, 1261, 1153, 1018. ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 6.86−6.73 (m, 3H), 4.76 (m, 1H), 4.13 (dd, J = 8.1 and 10.2 Hz, 1H), 3.83 (s, 3H), 3.65 (dd, J = 8.8 and 10.2 Hz, 1H), 3.46 (m, 1H), 2.87 (dd, J = 8.8 and 17.6 Hz, 1H), 2.67 (dd, J = 9.5 and 17.6 Hz, 1H), 2.04−1.74 (m, 6H), 1.70−1.43 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 172.8, 149.7, 149.1, 147.7, 132.7, 118.5, 113.5, 112.1, 82.9, 80.5, 56.0, 53.3, 40.5, 36.0, 32.8, 28.0, 24.0. MS: *m/z* (rel intensity) = 375 (17) $[M]^{+\bullet}$, 207 (100), 150 (83), 135 (15), 57 (52). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.05; H, 7.70; N, 3.78. HRMS *m/z* calcd for $C_{21}H_{29}NO_5$, 375.20457; found, 375.20451.

4-(3-Cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one (Rolipram, 1). Lactam **11** (4.85 g, 12.92 mmol) was dissolved in 50 mL of 6 M HCl/EtOAc (1:1). After stirring at room temperature for 2 h, the solution was diluted with 80 mL of EtOAc/H_2O (3:1) and transferred to a separatory funnel and the layers were separated. The organic layer was washed with water, saturated Na_2CO_3 solution, and brine and then dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuum to give 3.55 g (100% yield) of Rolipram **1** as a white solid. Mp: 130.5−131.5 °C (lit.[3] 130−132 °C). TLC: R_f = 0.21 (EtOAc) phosphomolybdic acid. IR (film, NaCl) ν (cm^{-1}): 3201, 3093, 2958, 2873, 1678, 1585, 1516, 1265, 1238, 1165, 1138, 1030, 818. IR (KBr) ν (cm^{-1}): 3437, 3201, 3097, 2943, 2912, 2831, 1701, 1516, 1250, 1146, 1003, 814. ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 6.91−6.65 (m, 4H), 4.78 (m, 1H), 3.83 (s, 3H), 3.76 (apparent t, J = 8.8 Hz, 1H), 3.62 (apparent m, 1H), 3.39 (dd, J = 7.3 and 8.8 Hz, 1H), 2.72 (dd, J = 8.8 and 16.8 Hz, 1H), 2.48 (dd, J = 8.8 and 16.8 Hz, 1H), 2.01−1.74 (m, 6H), 1.72−1.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 177.6, 148.9, 147.7, 134.4, 118.6, 113.7, 112.0, 80.5, 56.1, 49.8, 40.0, 38.2, 32.8, 24.0. MS: *m/z* (rel intensity) = 275 (25) $[M]^{+\bullet}$, 207 (87), 150 (100), 135 (24). HRMS *m/z* calcd for $C_{16}H_{21}NO_3$, 275.15214; found, 275.15212.

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Supporting Information Available: Chromatographic analysis of (*R*)-(−)-Rolipram, experimental details and spectroscopic characterization for compounds **1**, **5**−**7**, **10**−**14**, **14**/**15**, and **7**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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