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An Expedient Route to a Potent Gastrin/CCK-B Receptor Antagonist (+)-AG-041R

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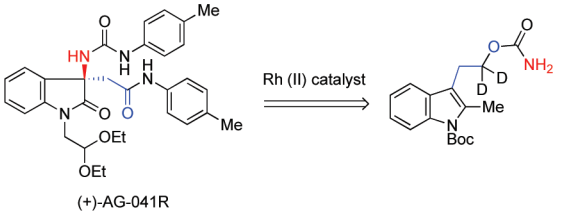
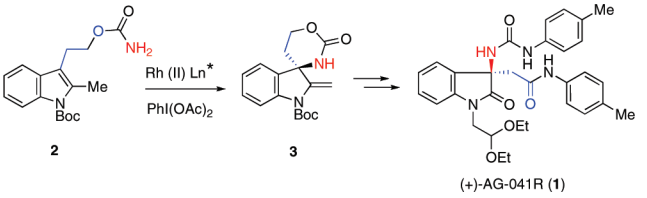


An enantiocontrolled synthesis of (+)-AG-041R (**1**), a potent gastrin/CCK-B receptor antagonist, has been achieved employing a chiral rhodium(II)-catalyzed, oxidative intramolecular aza-spiroannulation as the key step.

Metal nitrenoid complexes in combination with a suitable chiral ligand offer expeditious access to enantiomerically enriched nitrogen-containing motifs.[1,2] During endeavors directed toward the enantiocontrolled synthesis of marine alkaloid chartellines,[3−5] we have developed an efficient route to the spiro β-lactam unit with a chiral quaternary carbon via a strategy involving a highly enantioselective intramolecular asymmetric aza-spirocyclization onto an indole ring catalyzed by a chiral rhodium complex.[6,7] Besides needing to determine the enantioselectivity of the rhodium-catalyzed asymmetric process, the novel array of functionalities within the enantiomerically enriched product inspired us to transform **3** to AG-041R (**1**), the potent gastrin/CCK-B receptor antagonist,[8] featuring the quarternary 3-aminooxindole structure (Scheme 1). We report herein an expedient, asymmetric synthesis of (+)-AG-041 (**1**).

SCHEME 1. Synthetic Plan for AG-041R



Synthesis of the metal nitrenoid precursor **6** was initiated by protection of the known indole **4**[9] with a Boc group followed by reduction with $LiAlD_4$ to afford the alcohol **5** in 90% yield: the introduction of two atoms of deuterium was confirmed to be essential for the efficient promotion of the key spirocyclization[10,11] (Scheme 2). Installation of a carbamate handle was then carried out by a conventional two-step sequence consisting of trichloroacetyl carbamate formation and the subsequent detrichloroacetylation.[12] Oxidative intramolecular aza-spiroannulation[13] in **6** under the action of 7 mol % of Rh_2(*S*-TCPTTL)$_4$[14] with 1.6 equiv of $PhI(OAc)_2$ and 3.0 equiv of MgO[15] afforded **7** in 70% yield with 96% ee, in which the newly constructed quarternary center was unambiguously determined to be *R* by connecting to (+)-AG-041R as described in Scheme 3.

The subsequent transformation was initiated by revealing the oxindole structure via ozonolysis of the exomethylene

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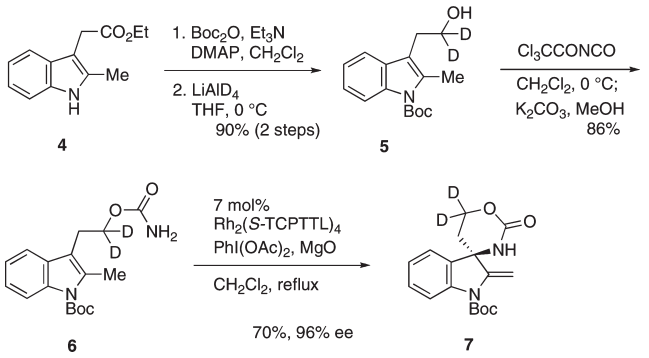
SCHEME 2. Oxidative Asymmetric Intramolecular Aza-spiroannulation Reaction



portion of **7**. The selective and facile cleavage of the cyclic carbamate moiety in **8** was performed by treatment with Boc_2O in the presence of DMAP and Et_3N followed by K_2CO_3 in methanol to give **9** in 74% yield with concomitant deprotection of a Boc group from the indole moiety. The oxidation of the primary alcohol to a carboxylic acid was facilely achieved in a one-pot method employing a catalytic amount of 1-MeAZADO$^+$Cl$^-$ in the presence of $NaClO_2$ in MeCN and CH_3CO_2H/CH_3CO_2Na buffer, which is a method recently developed in our laboratory.[16] The resulting carboxylic acid was converted to methyl ester **10** under CH_2N_2 in methanol in quantitative yield.

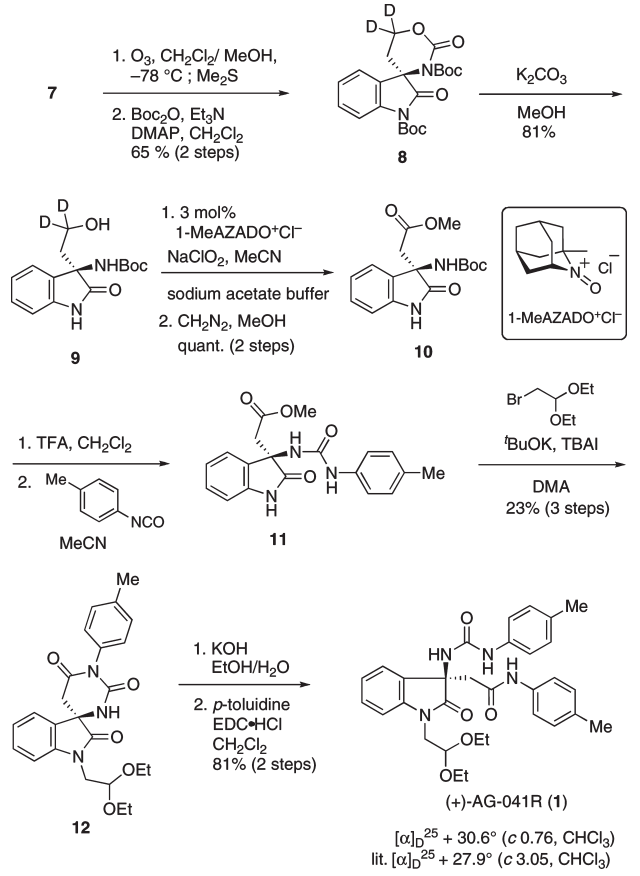
Removal of the Boc group in **10** under acidic conditions followed by treatment with *p*-tolyl isocyanate afforded urea **11**. When **11** was alkylated with bromoacetaldehyde diethyl acetal and potassium *tert*-butoxide, the cyclization between the methyl ester moiety and the urea moiety occurred to produce cyclic urea **12** in 23% yield in three steps. Hydrolysis of **12** was performed using KOH in ethanol/H_2O to furnish the carboxylic acid, which was finally converted to AG-041R (**1**) [[α]$^{25}_D$ +30.6 (*c* 0.76, $CHCl_3$) [lit.[8a] [α]$^{25}_D$ +27.9 (*c* 3.05, $CHCl_3$)]] with *p*-toluidine in the presence of EDC·HCl. The absolute configuration was confirmed as *R* by comparison of the optical rotation value with the literature value.

In conclusion, we have described the stereocontrolled synthesis of (+)-AG-041R via a highly enantioselective oxidative intramolecular aza-spiroannulation reaction catalyzed by a chiral rhodium catalyst. Through the synthesis of (+)-AG-041R, we confirmed that the stereochemistry of the quaternary carbon center was *R* in the Rh_2(*S*-TCPTTL)$_4$-catalyzed reaction. This concise synthesis also provides the possibility of access to other biologically attractive compounds having 3-aminooxindole core.[17]

Experimental Section

(3*R*)-1-*tert*-Butoxy-2-methylenespiro[3*H*-indol-3,6′-[4′,4′-^{2}H2]-[1′,3′]oxazinan-2′-one (7). To a solution of carbamate **6** (1.50 g, 4.68 mmol) in CH_2Cl_2 (468 mL) at rt were added MgO (566 mg, 14.0 mmol), PhI(OAc)$_2$ (2.43 g, 7.49 mmol), and Rh_2(*S*-TCPTTL)$_4$ (589 mg, 0.328 mmol, 7 mol %). The reaction mixture

SCHEME 3. Synthesis of AG-041R



$[\alpha]_D^{25}$ + 30.6° (*c* 0.76, $CHCl_3$)
lit. $[\alpha]_D^{25}$ + 27.9° (*c* 3.05, $CHCl_3$)

was stirred vigorously at reflux for 48 h. The mixture was allowed to cool to rt and filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (1:6 AcOEt/hexane) to give cyclic carbamate **7** as white amorphous solid (1.04 g, 3.28 mmol, 70%): [α]$^{25}_D$ +52.7 (*c* 0.93, $CHCl_3$); IR (neat) 3242, 3120, 2979, 1713, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.6 Hz, 1H), 7.34 − 7.30 (m, 2H), 7.12 (dd, J = 7.4, 7.4 Hz, 1H), 5.82 (d, J = 1.7 Hz, 1H), 5.26 (br, 1H), 5.00 (d, J = 1.6 Hz, 1H), 2.08 (s, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.0, 150.6, 140.2, 132.0, 129.9, 123.9, 122.6, 115.9, 97.2, 83.3, 62.3, 61.6 (br), 35.3, 28.2; MS *m*/*z* 318 (M$^+$), 57 (100); HRMS calcd for $C_{17}H_{18}D_2O_4N_2$ 318.1547, found 318.1538.

1,1′-Di-*tert*-butoxycarbonylspiro[2,3-dihydro-1*H*-indol-3,6′-[4′,4′-^{2}H2][1′,3′]oxazinane]-2,2′-dione (8). Cyclic carbamate **7** (1.134 g, 3.56 mmol) was dissolved in CH_2Cl_2/MeOH (1:1 178 mL). The solution was cooled at −78 °C, and ozone was introduced for 5 min and followed by argon gas for 20 min. To the mixture was added Me_2S (2.62 mL, 35.6 mmol), and the resulting solution was allowed to warm slowly at rt and stirred for overnight. The solution was concentrated in vacuo. To the crude mixture in CH_2Cl_2 (35.6 mL) were added Boc_2O (1.23 mL, 5.34 mmol) and DMAP (43.5 mg, 0.356 mmol, 10 mol %). The reaction mixture was stirred for 10 min. The reaction was poured onto H_2O (50 mL), extracted with AcOEt (2 × 50 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (1:2 AcOEt/hexane) to give amide **8** as a white amorphous solid (980 mg, 2.33 mmol, 65% for 2 steps): [α]$^{29}_D$ +37.2 (*c* 1.19, $CHCl_3$); IR (neat) 2982, 1794, 1733, 1608 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 1H), 7.42 (ddd, J = 1.2, 7.5, 8.2 Hz, 1H), 7.33 (dd, J = 1.2, 7.5 Hz, 1H), 7.24 (ddd, J = 1.0, 7.5,

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7.5 Hz, 1H), 2.34 (d, J = 14.8 Hz, 1H), 2.24 (d, J = 14.8 Hz, 1H), 1.66 (s, 9H), 1.15 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 149.1, 148.8, 148.6, 138.3, 129.8, 129.1, 125.0, 121.4, 115.4, 85.1, 84.9, 63.4, 61.0 (br), 33.6, 27.9, 26.9; MS m/z 420 (M^+), 220 (100); HRMS calcd for $C_{21}H_{24}D_2O_7N_2$ 420.1864, found 420.1862.

(3*R*)-3-*tert*-Butoxycarbonylamino-3-(2-hydroxy[2,2-^{2}H2]ethyl)-2,3-dihydo-1*H*-indol-2-one (9). To a solution of cyclic carbamate **8** (980 mg, 2.33 mmol) in MeOH (23.3 mL) was added K_2CO_3 (64.4 mg, 0.466 mmol) at rt and the mixture stirred for 13 h. The reaction was poured into saturated NH_4Cl (30 mL), extracted with AcOEt (3 × 70 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (2:1 AcOEt/hexane) to give alcohol **9** as a white amorphous solid (554 mg, 1.88 mmol, 81%): $[\alpha]^{25}_D$ +15.9 (c 0.60, $CHCl_3$); IR (neat) 3314, 2979, 1722, 1621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (br, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.18 (dd, J = 7.5, 7.5 Hz, 1H), 7.01 (dd, J = 7.5, 7.7 Hz, 1H), 6.90 (br, 1H), 6.88 (d, J = 7.5 Hz, 1H), 2.10 (d, J = 14.7 Hz, 2H), 1.98 (d, J = 14.7 Hz, 1H), 1.26 (br, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 154.4, 140.4, 131.6 (br), 128.6, 122.7, 122.5, 110.5 (br), 80.4 (br), 62.0 (br), 57.2, 38.6, 28.0 (br); MS m/z 294 (M^+), 147 (100); HRMS calcd for $C_{15}H_{18}D_2O_4N_2$ 294.1547, found 294.1567.

Methyl (3*R*)-(3-*tert*-Butoxycarbonylamino-2-oxo-2,3-dihydro-1*H*-indoyl-3-yl)acetate (10). To a solution of alchol **9** (147 mg, 0.50 mmol) in MeCN (1.6 mL) and CH_3CO_2H/CH_3CO_2Na buffer (pH 4.0, 1.6 mL) were added $NaClO_2$ (80%, 170 mg, 1.50 mmol) and 1-MeAZADO$^+$Cl$^-$[16] (3.0 mg, 15 μmol, 3 mol %) at rt, and the solution stirred for 2 h. The reaction was quenched with 2-methyl-2-butene, water was added, and the resultant solution was extracted with AcOEt (3 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a solution of crude mixture in MeOH (1.0 mL) at 0 °C was added a solution of CH_2N_2 in Et_2O (2.0 mL). The reaction was allowed to warm to rt and stirred for 1 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography (1:2 AcOEt/hexane) to give methyl ester **10** as a white amorphous solid (160 mg, 0.50 mmol, 100% for two steps): $[\alpha]^{29}_D$ +46.5 (c 1.38, $CHCl_3$); IR (neat) 3285, 2979, 1726, 1622 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br, 1H), 7.24−7.19 (m, 2H), 7.00 (dd, J = 7.5, 7.5 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.45 (br, 1H), 3.71 (s, 3H), 2.93 (d, J = 15.1 Hz, 1H), 2.62 (d, J = 15.1 Hz, 1H), 1.30 (br, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 170.3, 153.9, 140.5, 129.9, 129.2, 123.1, 122.6, 110.4, 80.6, 59.5, 52.2, 40.5, 28.0; MS m/z 320 (M^+), 264 (100); HRMS calcd for $C_{16}H_{20}O_5N_2$ 320.1372, found 320.1349.

3-(4-Methoxyphenyl)-1′-(2,2-diethoxyethyl)spiro[5,6-dihydropyrimidin-6,3′;2′,3′-dihydro-1*H*-indoyl]-2,2′,4-trione (12). To a solution of methyl ester **10** (35 mg, 10.9 μmol) in CH_2Cl_2 (1.0 mL) was added TFA (0.112 mL, 1.51 mmol) at 0 °C, and the mixture warmed to rt. The reaction was allowed to warm to rt and stirred for 2 h. The reaction was poured into H_2O (5 mL) and washed with Et_2O (2 × 10 mL), and the aqueous solution was basified with saturated $NaHCO_3$. The basic solution was extracted with $CHCl_3$ (3 × 20 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a solution of crude mixture in MeCN (1.0 mL) was added p-tolyl isocyanate (10.2 μL, 0.120 mmol) at rt. After the reaction was stirred for 1 h, the precipitation was collected, washed with MeCN, and dried under reduced pressure. To a solution of the crude mixture in DMA (1.4 mL) were added potassium *tert*-butoxide (26.7 mg, 21.8 μmol, 2.0 equiv), bromoacetaldehyde diethyl acetal (19.7 μL, 0.131 mmol), tetrabutylammonium iodide (10.1 mg, 27.3 μmol, 25 mol %). The mixture was maintained at 80 °C for 4 h and then cooled to ambient temperature. Saturated NH_4Cl (3 mL) was added and the mixture extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (1:1 AcOEt/hexane) to give cyclic urea **12** as a yellowish oil (15 mg, 34.3 μmol, 23% for 3 steps): $[\alpha]^{24}_D$ +61.3 (c 1.28, $CHCl_3$); IR (neat) 3272, 2977, 1737, 1689, 1614 cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.42−7.38 (m, 2H), 7.30−7.23 (m, 4H), 7.18−7.12 (m, 2H), 5.57 (br, 1H), 4.71 (t, J = 5.3 Hz, 1H), 4.12 (dd, J = 5.3, 14.5 Hz, 1H), 3.39−3.71 (m, 3H), 3.55−3.48 (m, 2H), 3.22 (d, J = 16.4 Hz, 1H), 2.89 (dd, J = 1.7, 16.4 Hz, 1H), 2.39 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 167.1, 154.3, 143.0, 138.6, 132.1, 130.8, 129.9, 128.4, 126.5, 123.7, 123.3, 111.0, 100.2, 63.7, 63.6, 43.6, 39.9, 21.3, 15.3, 15.2; MS m/z 437 (M^+), 103 (100); HRMS calcd for $C_{24}H_{27}O_5N_3$ 437.1951, found 437.1940.

2-[(*R*)-1-(2,2-Diethoxyethyl)-2-oxo-3-(3-*p*-tolylureido)-2,3-dihydro-1*H*-indol-3-yl]-*N*-*p*-tolylacetamide (AG-041R) (1). To a solution of cyclic urea **12** (15 mg, 34.3 μmol) in EtOH/H_2O (10:1, 1.9 mL) at 0 °C was added KOH (4.8 mg, 85.8 μmol), and the mixture was allowed to warm to rt and stirred for 10 h. The reaction was poured onto H_2O (5 mL) and 10% HCl (5 mL), extracted with $CHCl_3$ (2 × 20 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a solution of crude mixture in CH_2Cl_2 (1.0 mL) at 0 °C were added EDC·HCl (8.5 mg, 44.6 μmol, 1.3 equiv) and p-toluidine (4.8 mg, 44.6 μmol, 1.3 equiv) at 0 °C. The mixture was stirred for 40 min at 0 °C. The reaction was poured onto H_2O (5 mL) and 10% HCl (5 mL), extracted with $CHCl_3$ (2 × 20 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (1:1 AcOEt/hexane) to give AG-041R **1** as white crystals (15.2 mg, 27.9 mmol, 81% for 2 steps): mp 100—102 °C; $[\alpha]^{25}_D$ +30.6 (c 0.760, $CHCl_3$); IR (neat) 3319, 2974, 2921, 1698, 1686, 1663, 1608 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.29−7.21 (m, 5H), 7.17 (s, 1H), 7.07−6.96 (m, 6H), 6.89 (d, J=8.2 Hz, 2H), 4.75 (dd, J = 4.6, 5.5 Hz, 1H), 3.97 (dd, J = 5.9, 14.4 Hz, 1H), 3.78 (dd, J = 4.2, 14.5 Hz, 1H), 3.72−3.48 (m, 4H), 2.97 (d, J = 14.7 Hz, 1H), 2.63 (dd, J = 14.7 Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 1.13 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 167.3, 154.0, 142.5, 135.9, 134.7, 134.5, 132.3, 130.0, 129.4, 129.2, 128.8, 122.9, 122.8, 120.7, 119.8, 110.2, 100.6, 63.4, 59.7, 43.9, 43.9, 20.9, 20.7, 15.3; MS m/z 544 (M^+), 103 (100); HRMS calcd for $C_{31}H_{36}O_5N_4$ 544.2686, found 544.2704.

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Supporting Information Available: Experimental details and charachterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.