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An Efficient and Practical Total Synthesis of Sauristolactam

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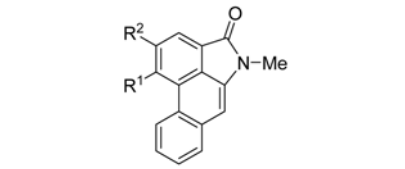
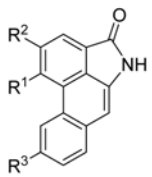
Sauristolactam (**1**) is a naturally occurring alkaloid that was first isolated from the extracts of the aquatic weed *Saururus cernuus* L. (Saururaceae) by Rao and Reddy in 1990.[1] As illustrated in Figure 1, sauristolactam, one of the members of structurally related aristolactams **2-5**, is comprised of a phenanthrene lactam scaffold.[2] Due to its unique structures and promising biological properties, the aristolactam family continues to attract considerable interest from many organic and medicinal chemists.[3] For example, sauristolactam was identified as a potential anticancer agent proven to be active against a variety of tumor cell lines, including HCT-15 colon cancer cell (IC_{50} = 4.1 μM).[4] In addition, sauristolactam exhibited inhibitory activity of osteoclast differentiation against mouse RAW264.7 monocyte/macrophage cells for the potential treatment of osteoporosis.[5] Kim and colleagues reported neuroprotective activity of sauristolactam against glutamate-induced toxicity in primary cultured rat cortical cells *via* the direct inhibition of nitric oxide production.[6]

While we carried out *in vivo* studies, it was necessary to prepare sauristolactam in a multi-gram scale. However, in our previous synthesis of sauristolactam, regioselective mono-demethylation of phenanthrene lactam **6** was not very effective at the final stage, which provided the desired product **1** in only 11% yield (Scheme 1).[7] Therefore, we envisaged a new synthetic approach which involved distinction between hydroxy and methoxy groups from the beginning. Herein, we report an efficient and practical route to sauristolactam, starting from 2-methoxy-4-methylphenol (**9**), by employing a Suzuki-Miyaura coupling/aldol condensation cascade reaction as a key step (Scheme 1).[8]

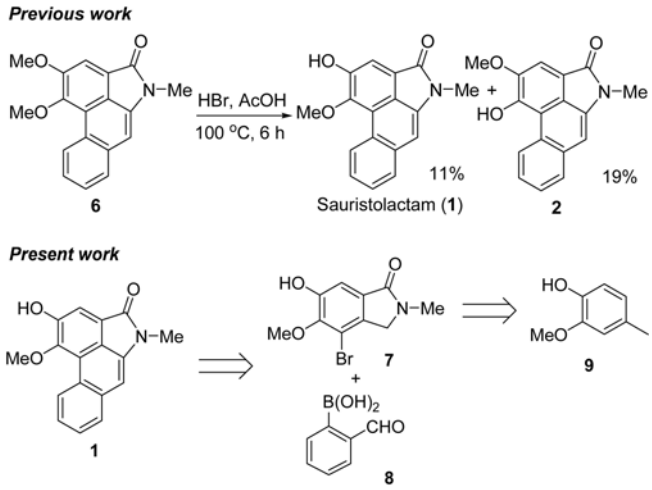


Sauristolactam (**1**); R^1 = OMe, R^2 = OH
N-Methyl piperolactam A (**2**); R^1 = OH, R^2 = OMe



Aristolactam BII (**3**); R^1 = R^2 = OMe, R^3 = H
Aristolactam BIII (**4**); R^1 = R^2 = R^3 = OMe
Aristolactam FI (**5**); R^1 = OH, R^2 = OMe, R^3 = H

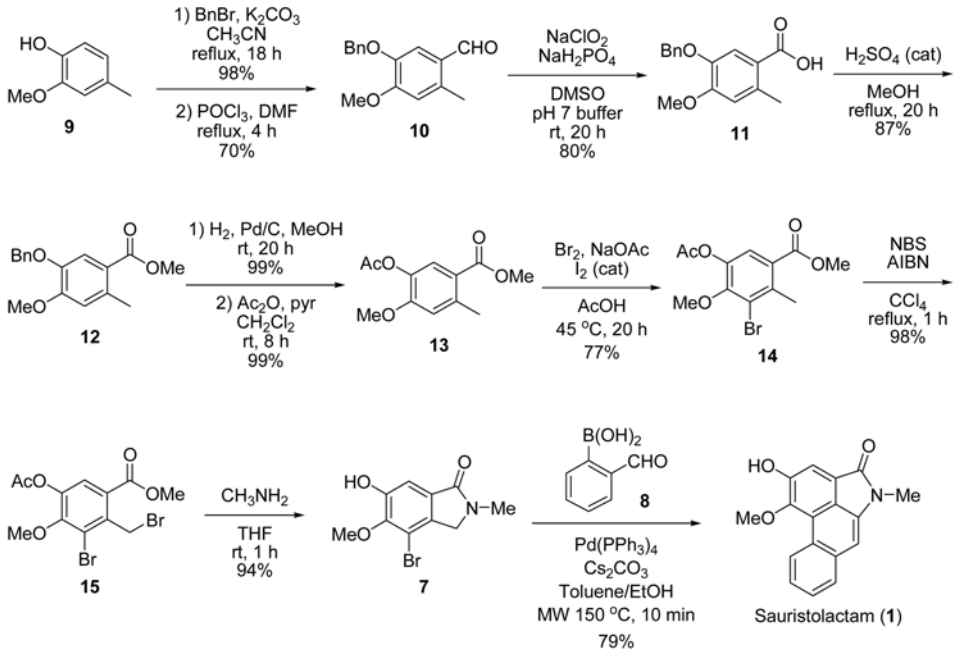
Figure 1. Representative members of phenanthrene lactam alkaloids.



Scheme 1. Previous and present synthetic strategies for sauristolactam.

The requisite benzoic acid **11** was readily prepared from 2-methoxy-4-methylphenol (**9**) in three steps by following modified literature procedures (Scheme 2).[9] Benzylic protection of phenol **9** followed by the Vilsmeier reaction with $POCl_3$/DMF provided benzaldehyde **10**, which was oxidized with $NaClO_2$ in a pH 7 buffer solution to furnish the benzoic acid **11** in over a 10 gram scale.

Benzoic acid **11** was converted into methyl ester **12** in the presence of catalytic H_2SO_4 in 87% yield. We next examined the bromination of **12** under various reaction conditions. However, all attempts proved difficult mainly due to debenzylation, which led to the formation of undesired products, including methyl 2-bromo-3-hydroxy-4-methoxy-6-methylbenzoate.[10] Therefore, we decided to switch the protecting group from benzyl to acetyl, which is more compatible under acidic bromination conditions. The debenzylation of **12** using a Pd-catalyzed hydrogenation, followed by acetylation with acetic anhydride in the presence of pyridine, provided acetyl-protected benzoate **13** in quantitative yield. Indeed, the bromination of **13** with Br_2 in acetic acid proceeded smoothly to obtain the desired product **14** in 77% yield.[11] Then, benzoate **14** was subjected to benzylic bromi-



Scheme 2. Total synthesis of sauristolactam.

nation with NBS/AIBN to allow the generation of benzyl bromide **15** in excellent yield. Subsequent treatment of **15** with excess amounts of methylamine efficiently furnished the target isoindolone **7** in 98% yield, which simultaneously resulted in the removal of the acetyl-protecting group.

With isoindolone **7** in hand, the Suzuki-Miyaura coupling/aldol condensation cascade reaction was carried out under standard conditions for the construction of the phenanthrene lactam scaffold. The reaction of **7** with 2-formylphenylboronic acid (**8**) in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in a mixture of toluene/EtOH (2:1) under microwave irradiation for 10 min at 150 °C successfully provided sauristolactam (**1**) in 79% yield. The spectroscopic data (^1H and ^{13}C NMR spectra) of the synthetic material were in good agreement with the literature data.[1,6,7]

In summary, a practical and efficient total synthesis of sauristolactam has been achieved in 10 steps and 26.2% overall yield, starting from commercially inexpensive 2-methoxy-4-methylphenol (**9**). Notably, the use of the Suzuki-Miyaura coupling/aldol condensation cascade reaction allowed the construction of the phenanthrene lactam core in a one-pot reaction. Studies involving evaluation of *in vivo* efficacy of sauristolactam will be reported in due course.

Experimental Section

5-(Benzyloxy)-4-methoxy-2-methylbenzaldehyde (10). To a solution of phenol **9** (10.0 g, 72.4 mmol) in 145 mL of CH_3CN was added K_2CO_3 (20.0 g, 145 mmol) and benzyl bromide (24.8 g, 145 mmol). The resulting mixture was refluxed for 18 h and the solvent was removed with a rotary evaporator. The residue was treated with H_2O and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to yield 1-(benzyloxy)-2-methoxy-4-methylbenzene (16.2 g, 98%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 2H), 7.29-7.27 (m, 3H), 6.77 (d, J = 8.1 Hz, 1H), 6.72 (s, 1H), 6.63 (d, J = 8.1 Hz, 1H), 5.12 (s, 2H), 3.87 (s, 3H), 2.29 (s, 3H).

To a mixture of $POCl_3$ (40.3 g, 263 mmol) and DMF (19.5 g, 263 mmol) at 0 °C was added 1-(benzyloxy)-2-methoxy-4-methylbenzene (10.0 g, 43.8 mmol). The resulting solution was heated to 80 °C and stirred for 4 h. After being cooled to room temperature, the reaction mixture was poured into ice and extracted with ether. The combined extracts were concentrated *in vacuo* and purified by silica gel flash column chromatography (10% EtOAc/hexanes) to afford benzaldehyde **10** (7.8 g, 70%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.45 (d, J = 7.7 Hz, 2H), 7.40-7.17 (m, 4H), 6.71 (s, 1H), 5.16 (s, 2H), 3.95 (s, 3H), 2.62 (s, 3H).

5-(Benzyloxy)-4-methoxy-2-methylbenzoic Acid (11). To a solution of benzaldehyde **10** (8.5 g, 33.2 mmol) in 50 mL of DMSO at 0 °C was added a solution of NaH_2PO_4 (2.4 g, 19.9 mmol) in pH 7 buffer (15 mL). Then a solution of aq. 80% $NaClO_2$ (15.0 g, 133 mmol) in pH 7 buffer (35 mL) was added to the mixture. The resulting mixture was stirred for 20 h at room temperature and quenched with saturated aq. $NaHCO_3$. The aqueous layer was extracted with ether and acidified to pH 2-3 with conc. HCl. The precipitates were collected *via* Buchner funnel and dissolved in CH_2Cl_2. The resulting solution was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give benzoic acid **11** (7.2 g, 80% yield) as a white solid: ^1H NMR (300MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.41-7.30 (m, 3H), 6.74 (s, 1H), 5.15 (s, 2H), 3.93 (s, 3H), 2.61 (s, 3H); MS (EI) *m/z* 272 (M^+, 100), 256 (8), 199 (6), 181 (9), 163

(6), 149 (8).

Methyl 5-(Benzyloxy)-4-methoxy-2-methylbenzoate (12). To a solution of benzoic acid **11** (1.5 g, 5.5 mmol) in MeOH (10 mL) was added catalytic H_2SO_4 (0.5 mL). The mixture was refluxed for 20 h and solvents were removed under reduced pressure. The residue was treated with CH_2Cl_2 and washed with saturated aq. $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give benzoate **12** (1.37 g) in 87% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.47-7.31 (m, 5H), 6.71 (s, 1H), 5.14 (s, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.4, 152.6, 145.6, 136.9, 135.5, 128.5, 128.0, 127.6, 120.8, 116.4, 114.6, 55.9, 51.6, 21.8; MS (EI) *m/z* 286 (M^+, 36), 255 (7), 195 (7), 163 (8), 135 (10), 91 (100).

Methyl 5-Acetoxy-4-methoxy-2-methylbenzoate (13). To a solution of benzoate **12** (2.8 g, 9.8 mmol) in 50 mL of MeOH was added 10 wt % Pd/C (280 mg). The mixture was stirred for 20 h under hydrogen atmosphere using a balloon. The mixture was filtered through a short pad of Celite and concentrated *in vacuo* to give methyl 5-hydroxy-4-methoxy-2-methylbenzoate (1.9 g, 99% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.68 (s, 1H), 5.41 (s, 2H), 3.93 (s, 3H), 3.85 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.4, 149.3, 143.0, 134.0, 121.7, 116.8, 113.4, 55.9, 51.6, 21.6; MS (EI) *m/z* 196 (M^+, 96), 181 (15), 165 (100), 149 (12), 136 (60).

To a solution of methyl 5-hydroxy-4-methoxy-2-methylbenzoate (1.9 g, 9.7 mmol) in 194 mL of CH_2Cl_2 at 0 °C was added pyridine (1.2 mL, 14.6 mmol). After being stirred for 10 min at 0 °C, acetic anhydride (1.4 mL, 14.6 mmol) was added dropwise to the mixture over 20 min. The mixture was allowed to warm to room temperature, and then stirred for 8 h. The reaction mixture was quenched by adding H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give benzoate **13** (2.3 g) in 99% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.79 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.63 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.0, 166.6, 153.8, 141.0, 137.0, 125.5, 121.2, 115.1, 55.9, 51.6, 22.1, 20.5; MS (EI) *m/z* 238 (M^+, 16), 207 (10), 196 (100), 165 (68), 164 (68), 136 (38).

Methyl 5-Acetoxy-3-bromo-4-methoxy-2-methylbenzoate (14). To a solution of benzoate **13** (1.4 g, 5.9 mmol) in 10 mL of acetic acid was added NaOAc (1.16 g, 14.2 mmol) and I_2 (0.1 g). The mixture was allowed to warm to 45 °C and Br_2 (2.8 g, 17.7 mmol) was added dropwise. The resulting mixture was stirred for 28 h at this temperature and then cooled to room temperature. After quenching with saturated aq. $Na_2S_2O_3$ solution, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give **14** (1.44 g) in 77% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.68 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.7, 166.6, 152.1, 141.5, 139.2, 127.1, 124.7, 123.0, 60.9, 52.3, 20.8, 20.7; MS (EI) *m/z* 318 (M^++2, 11), 316 (M^+, 12), 276 (96), 274 (100), 244 (43), 242 (40), 216 (25), 214 (24).

Methyl 5-Acetoxy-3-bromo-2-(bromomethyl)-4-methoxybenzoate (15). To a solution of benzoate **14** (500 mg, 1.6 mmol) in 5.0 mL of CCl_4 was added *N*-bromosuccinimide (338 mg, 1.9 mmol) and AIBN (26 mg, 0.16 mmol). The mixture was stirred at reflux temperature for 1 h and cooled to room temperature. The precipitate was filtered off and the resulting solution was washed with saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to provide 2-(bromomethyl)benzoate **15** (613 mg) in 98% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 5.19 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 2.36 (s, 3H); MS (EI) *m/z* 318 (M^++2, 11), 316 (M^+, 12), 276 (96), 274 (100), 244 (43), 242 (40), 216 (25), 214 (24).

4-Bromo-6-hydroxy-5-methoxy-2-methylisoindolin-1-one (7). To a solution of 2-(bromomethyl)benzoate **15** (550 mg, 1.4 mmol) in 4.0 mL of THF was added methylamine (3.5 mL of 40 wt % in H_2O, 7.0 mmol). The mixture was stirred at room temperature for 1 h and the solvent was removed by rotary evaporation. The resulting residue was dissolved with EtOAc/H_2O and transferred to a separatory funnel. The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization (EtOAc/hexanes) to provide isoindolin-1-one **7** (370 mg) in 94% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 4.22 (s, 2H), 3.98 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 171.8, 156.8, 152.9, 138.2, 134.4, 117.0, 114.8, 65.3, 56.6, 34.3; MS (EI) *m/z* 273 (M^++2, 100), 271 (M^+, 100), 256 (30), 254 (26), 244 (37), 242 (48), 192 (38), 177 (49).

Sauristolactam (1). To a thick-well borosilicate glass vial (5 mL) was added isoindolin-1-one **7** (200 mg, 0.74 mmol), 2-formylphenylboronic acid **8** (166 mg, 1.1 mmol), $Pd(PPh_3)_4$ (34 mg, 4 mol %), and Cs_2CO_3 (723 mg, 2.2 mmol) sequentially. The mixture was suspended in toluene/EtOH (3.0 mL/1.5 mL). Then, the reaction vial was sealed and placed into a microwave reactor and irradiated at 150 °C for 10 min (Usually, the average microwave power ranged from 60 to 80 W and the internal pressure was 6-8 bars). After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (2% MeOH/CH_2Cl_2) to afford 163 mg of sauristolactam (**1**) in 79% yield as a gray solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ

10.32 (bs, 1H), 9.11 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.60-7.56 (m, 2H), 7.30 (s, 1H), 4.01 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 166.7, 152.2, 148.7, 136.9, 134.6, 129.0, 127.4, 126.8, 126.2, 125.5, 120.92, 120.89, 120.1, 113.5, 103.4, 59.5, 26.1; MS (EI) *m/z* 279 (M^+, 100), 264 (61), 236 (44), 180 (37), 152 (25), 139 (30).

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