

## An Efficient and Practical Total Synthesis of Sauristolactam

Jung-Nyoung Heo,\* Tae Jeong Kim, and Joa Kyum Kim

Medicinal Chemistry Research Center, Korea Research Institute of Chemical Technology, Daejeon 305-600, Korea

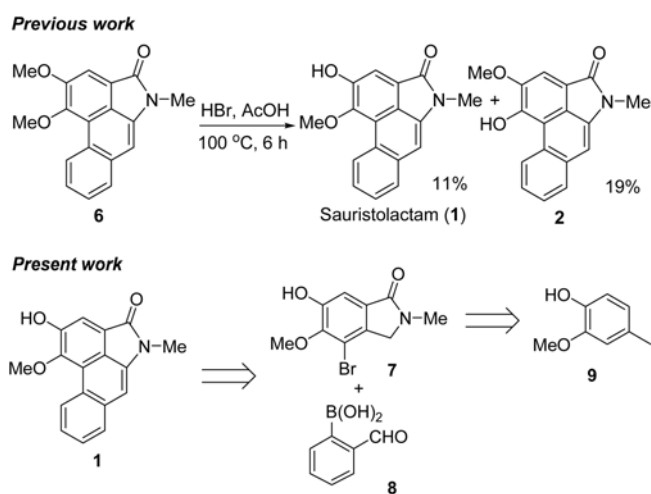
\*E-mail: heojn@kRICT.re.kr

Received September 25, 2011, Accepted October 11, 2011

**Key Words :** Sauristolactam, Phenanthrene lactam, Suzuki-Miyaura coupling, Cascade reaction

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.<sup>1</sup> As illustrated in Figure 1, sauristolactam, one of the members of structurally related aristolactams **2-5**, is comprised of a phenanthrene lactam scaffold.<sup>2</sup> Due to its unique structures and promising biological properties, the aristolactam family continues to attract considerable interest from many organic and medicinal chemists.<sup>3</sup> 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 ( $IC_{50} = 4.1 \mu M$ ).<sup>4</sup> In addition, sauristolactam exhibited inhibitory activity of osteoclast differentiation against mouse RAW264.7 monocyte/macrophage cells for the potential treatment of osteoporosis.<sup>5</sup> 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.<sup>6</sup>

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).<sup>7</sup> Therefore, we envisaged a new synthetic approach which involved distinction between hydroxy and methoxy groups from the

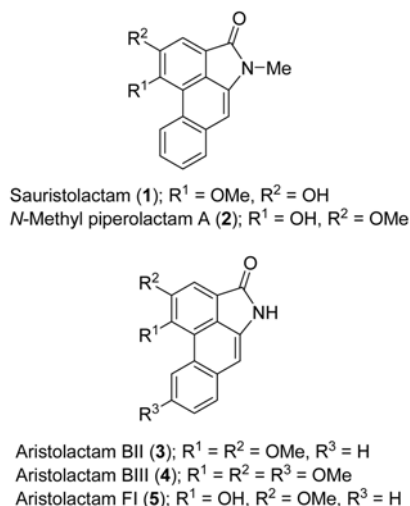


**Scheme 1.** Previous and present synthetic strategies for sauristolactam.

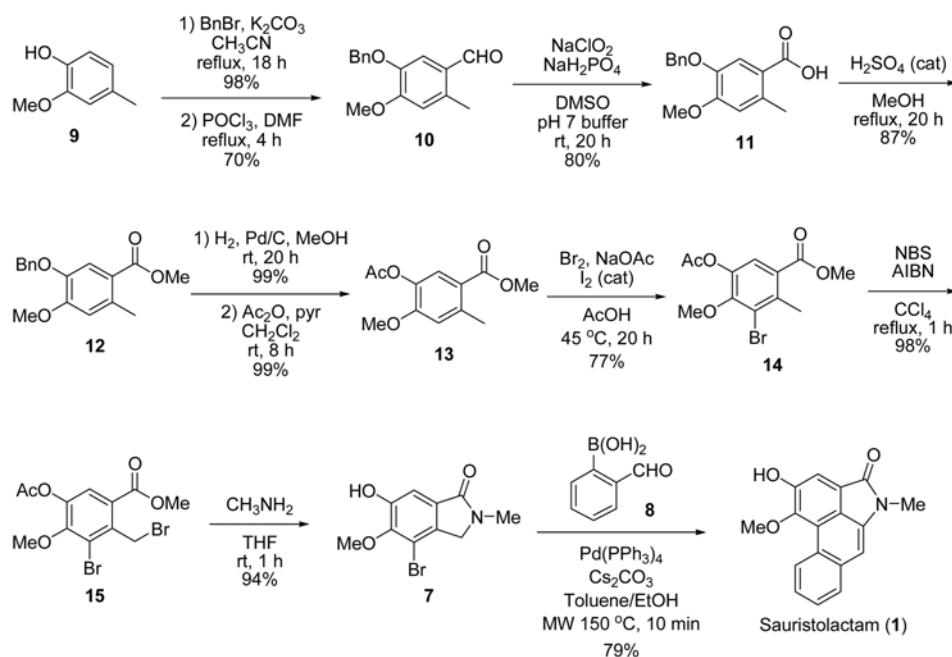
beginning. Herein, we report an efficient and practical route to sauristolactam, starting from 2-methoxy-4-methylphenol (**9**), by employing a Suzuki-Miyaura coupling/aldol condensation cascade reaction as a key step (Scheme 1).<sup>8</sup>

The requisite benzoic acid **11** was readily prepared from 2-methoxy-4-methylphenol (**9**) in three steps by following modified literature procedures (Scheme 2).<sup>9</sup> 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 debenzoylation, which led to the formation of undesired products, including methyl 2-bromo-3-hydroxy-4-methoxy-6-methylbenzoate.<sup>10</sup> Therefore, we decided to switch the protecting group from benzyl to acetyl, which is more compatible under acidic bromination conditions. The debenzoylation 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.<sup>11</sup> Then, benzoate **14** was subjected to benzylic bromi-



**Figure 1.** Representative members of phenanthrene lactam alkaloids.



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  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{Cs}_2\text{CO}_3$  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 ( $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra) of the synthetic material were in good agreement with the literature data.<sup>1,6,7</sup>

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  $\text{CH}_3\text{CN}$  was added  $\text{K}_2\text{CO}_3$  (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  $\text{H}_2\text{O}$  and extracted with EtOAc (3  $\times$  50 mL). The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , and concen-

trated *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%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{POCl}_3$  (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:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{NaH}_2\text{PO}_4$  (2.4 g, 19.9 mmol) in pH 7 buffer (15 mL). Then a solution of aq. 80%  $\text{NaClO}_2$  (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.  $\text{NaHCO}_3$ . The aqueous layer was extracted with ether and acidified to pH 2–3 with conc.  $\text{HCl}$ . The precipitates were collected *via* Buchner funnel and dissolved in  $\text{CH}_2\text{Cl}_2$ . The resulting solution was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to give benzoic acid **11** (7.2 g, 80% yield) as a white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 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<sub>2</sub>SO<sub>4</sub> (0.5 mL). The mixture was refluxed for 20 h and solvents were removed under reduced pressure. The residue was treated with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aq. NaHCO<sub>3</sub> solution. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, 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: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>, 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): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>, 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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, 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: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>, 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<sub>2</sub> (0.1 g). The mixture was allowed to warm to 45 °C and Br<sub>2</sub> (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<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, 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: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.59 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.68 (s, 3H), 2.35 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>+2, 11), 316 (M<sup>+</sup>, 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<sub>4</sub> 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<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, 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: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>+2, 11), 316 (M<sup>+</sup>, 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<sub>2</sub>O, 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<sub>2</sub>O 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<sub>4</sub>, 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: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40 (s, 1H), 4.22 (s, 2H), 3.98 (s, 3H), 3.19 (s, 3H); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>) 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<sup>+</sup>+2, 100), 271 (M<sup>+</sup>, 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<sub>3</sub>)<sub>4</sub> (34 mg, 4 mol %), and Cs<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub>) to afford 163 mg of sauristolactam (**1**) in 79% yield as a gray solid: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) 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);  $^{13}\text{C}$  NMR (75.5 MHz, DMSO- $d_6$ )  $\delta$  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 ( $\text{M}^+$ , 100), 264 (61), 236 (44), 180 (37), 152 (25), 139 (30).

**Acknowledgments.** We thank the Korea Research Institute of Chemical Technology (SI-1106) and MKE/KEIT (10035256, Development of new insecticides for crop protection) for the financial support.

### References

1. Rao, K. V.; Reddy, G. C. S. *J. Nat. Prod.* **1990**, *53*, 309–312.
2. (a) Kumar, V.; Poonam; Prasad, A. K.; Parmar, V. S. *Nat. Pro. Rep.* **2003**, *20*, 565–583. (b) Bentley, K. W. *Nat. Prod. Rev.* **2006**, *23*, 444–463.
3. (a) Couture, A.; Deniau, E.; Grandclaoudon, P.; Lebrun, S. *Synlett* **1997**, 1475–1477. (b) Couture, A.; Deniau, E.; Grandclaoudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128–3132. (c) Rys, V.; Couture, A.; Deniau, E.; Grandclaoudon, P. *Eur. J. Org. Chem.* **2003**, 1231–1237. (d) Rys, V.; Couture, A.; Deniau, E.; Lebrun, S.; Grandclaoudon, P. *Tetrahedron* **2005**, *61*, 665–671. (e) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432–1437. (f) Benesch, L. B.; Bury, P.; Guillaneux, D.; Houldsworth, S.; Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 961–964. (g) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 4075–4082. (h) Atanes, N.; Castedo, L.; Guitian, E.; Saa, C.; Saa, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984–2988. (i) Estévez, J. C.; Estévez, R. J.; Guitian, E.; Villaverde, M. C.; Castedo, L. *Tetrahedron Lett.* **1989**, *30*, 5785–5786.
4. (a) Choi, Y. L.; Kim, J. K.; Choi, S.-U.; Min, Y.-K.; Bae, M.-A.; Kim, B. T.; Heo, J.-N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3036–3040. (b) Couture, A.; Deniau, E.; Grandclaoudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557–3559.
5. (a) Lee, S.-U.; Choi, Y. H.; Kim, Y. S.; Min, Y. K.; Rhee, M.; Kim, S. H. *Int. Immunopharmacol.* **2010**, *10*, 298–303. (b) Kim, M. H.; Choi, Y. L.; Heo, J.-N.; Min, Y. K.; Kim, S. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 2047–2050.
6. Kim, S. R.; Sung, S. H.; Kang, S. Y.; Koo, K. A.; King, S. H.; Ma, C. J.; Lee, H.-S.; Park, M. J.; Kim, Y. C. *Planta Med.* **2004**, *70*, 391–396.
7. Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett.* **2008**, *10*, 3543–3546.
8. (a) Kim, Y. H.; Lee, H.; Kim, Y. J.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2008**, *73*, 495–501. (b) Choi, Y. L.; Yu, C.-M.; Kim, B. T.; Heo, J.-N. *J. Org. Chem.* **2009**, *74*, 3948–3951.
9. (a) Le, T. N.; Van, H. T. M.; Lee, S.-H.; Choi, H. J.; Lee, K. Y.; Kang, B. Y.; Cho, W.-J. *Arch. Pharm. Res.* **2008**, *31*, 6–9. (b) Ptaszek, M.; McDowell, B. E.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 4328–4331. (c) Lista, L.; Manini, P.; Napolitano, A.; Pezzella, A.; d'Ischia, M. *Steroids* **2006**, *71*, 670–673.
10. The use of  $\text{Br}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  for 1 h resulted in only 32% yield of the desired product. Other conditions included  $\text{Br}_2/\text{NaOAc}$  in  $\text{AcOH}$ : Nicolaou, K. C.; Sasmal, P. K.; Xu, H.; Namoto, K.; Ritzén, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4225–4229.
11. Martin, P. *Helv. Chim. Acta* **1989**, *72*, 1554–1582.