# First synthesis of (±)-vertilecanin A

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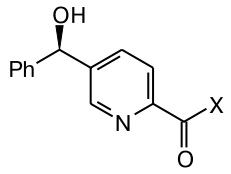
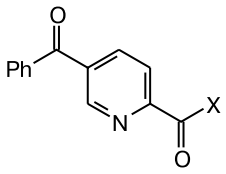
5-[(Hydroxy)(phenyl)methyl]pyridine-2-carboxylic acid ((±)-vertilecanin A) was prepared from nicotinic acid in four steps with an overall yield of 29%.

**Key words:** vertilecanin A, phenopicolonic acid, nicotinic acid, insecticides.

Five phenopicolonic acid analogs **1—5** named vertilecanins have recently[1] been isolated from solid substrate fermentation cultures of *Verticilium lecanii*. The most abundant component (–)-vertilecanin A (**1**) was reported to possess insecticidal activity against *Helicoverpa zea*.



**1—4**



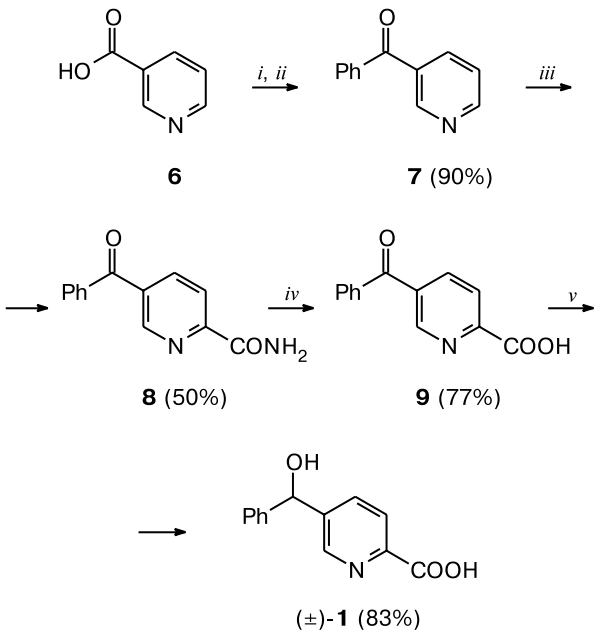
**5**

**1:** X = OH (vertilecanin A)
**2:** X = OMe (vertilecanin A methyl ester )
**3:** X = $HNCH_2CO_2H$ (vertilecanin B)
**4:** X = $HNCH_2CO_2Me$ (vertilecanin B methyl ester)
**5:** X = $HNCH_2CO_2Me$ (vertilecanin C)

Our retro-synthetic analysis showed that vertilecanin A (**1**) can easily be synthesized from nicotinic acid (**6**). Herein we report the first synthesis of (±)-vertilecanin A from acid **6** in four steps (Scheme 1).

The first step of the synthesis was the preparation of 3-benzoylpyridine (**7**) from nicotinic acid (**6**) according to a known procedure.[2] For this purpose, acid **6** was chlorinated with $SOCl_2$ to form acid chloride, which was used for the acylation of benzene in the presence of $AlCl_3$ according to the Friedel—Crafts reaction. The resulting 3-benzoylpyridine (**7**) was converted to carboxamide **8** as described earlier.[3] Hydrolysis of carboxamide **8** to acid **9** was the most critical step in the synthesis. Conventional acidic or basic conditions for the hydrolysis of carboxamide **8** were ineffective. $Ti^{IV}$-catalyzed hydrolysis[4] of carboxamide **8** gave acid **9** in good yield. In the last step, the carbonyl group of compound **9** was reduced with $NaBH_4$ to give (±)-vertilecanin A (**1**). The physical and spectral properties of (±)-**1** are in good agreement with those of an authentic sample.

**Scheme 1**



**Reagents and conditions:** *i*. $SOCl_2$. *ii*. $C_6H_6$, $AlCl_3$, reflux. *iii*. $FeSO_4 \cdot 7H_2O$, $H_2SO_4$, $Bu^tOOH$, $HC(O)NH_2$. *iv*. $TiCl_4$, HCl, dioxane, reflux. *v*. $NaBH_4$, MeOH, then $H_2O$.

Thus, with relatively little effort we achieved the synthesis of (±)-vertilecanin A in four steps from commercially available nicotinic acid in an overall yield of 29%. We suppose that this synthetic approach can be a versatile methodology for the preparation of different phenopicolonic acid derivatives.

## Experimental

**5-Benzoylpyridine-2-carboxylic acid (9).** A solution of $TiCl_4$ (0.280 g, 1.5 mmol) in water (1.3 mL) and then 1 *M* HCl (15 mL) were added to a solution of pyridinecarboxamide **8** [2,3] (3.00 g,

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13.3 mmol) in a water—dioxane (1 : 9) mixture (13 mL, ~1 *M* $H_2O$). The reaction mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was poured onto 30 g of ice. The organic components were extracted with AcOEt (3×30 mL), and the extract was dried with $Na_2SO_4$. After the solvent was removed, acid **9** was obtained in a yield of 2.34 g (77%) as white crystals, m.p. 128—130 °C (from $CHCl_3$). $^1$H NMR (200 MHz, $CDCl_3$), δ: 9.73 (br.s, 1 H, COOH); 9.07 (br.s, 1 H, H(6)); 8.37 (br.d, A part of AB system, 1 H, H(3) or H(4), $J_{3,4}$ = 8.1 Hz); 8.32 (dd, B part of AB system, 1 H, H(3) or H(4), $J_{3,4}$ = 8.1 Hz, $^4J$ = 1.8 Hz); 7.82 (dm, 2 H, H arom., $J$ = 7.7 Hz); 7.73—7.64 (m, 1 H, H arom.); 7.54 (tm, 2 H, H arom., $J$ = 7.7). $^{13}$C NMR (50 MHz, $CDCl_3$), δ: 193.5, 163.7, 149.2, 148.4, 139.4, 136.8, 136.0, 133.9, 130.1, 128.9, 123.7. IR (KBr), ν/cm$^{-1}$: 3063, 3026, 2873, 2624, 1713, 1665, 1597, 1579, 1476, 1448, 1384, 1246, 1122, 1033. Mass spectrum, $m/z$ ($I_{rel}$ (%)): 184.0 [$M^+ - CO_2$] (12), 182.9 [$M^+ - CO_2$] (100), 181.9 [$M^+ - CO_2H$] (42), 105.9 (16), 104.9 (72), 77.9 (18), 76.8 (46).

**(±)-5-[(Hydroxy)(phenyl)methyl]pyridine-2-carboxylic acid (vertilecanin A) (1).** A solution of ketone **9** (0.5 g, 2.2 mmol) in MeOH (10 mL) was added dropwise at 0 °C to a magnetically stirred suspension of $NaBH_4$ (0.1 g, 2.7 mmol) in MeOH (30 mL). After the addition was completed, the mixture was stirred at room temperature for 12 h. Then MeOH was distilled off under reduced pressure, and water (10 mL) was added. The organic components were extracted with AcOEt (3×30 mL), and the extracts were dried with $Na_2SO_4$. Removal of the solvent and recrystallization from MeOH gave (±)-vertilecanin A as colorless crystals (0.420 g, 83%), m.p. 155—157 °C (*cf.* Ref. 1 for (–)-**1**: m.p. 155—157 °C). $^1$H NMR (400 MHz, acetone-$d_6$), δ: 8.75 (br.s, 1 H, H(6)); 8.11 (d, A part of AB system, 1 H, H(3), $J_{3,4}$ = 8.1 Hz); 8.06 (dd, B part of AB system, 1 H, H(4), $J_{3,4}$ = 8.1 Hz, $J_{3,6}$ = 1.8 Hz); 7.47 (br.d, 2 H, $J$ = 7.3 Hz); 7.35 (br.t, 2 H, $J$ = 7.3 Hz); 7.27 (br.t, 1 H, $J$ = 7.3 Hz); 6.06 (s, 1 H, CH—OH). $^{13}$C NMR (100 MHz, acetone-$d_6$), δ: 164.8, 147.4, 146.1, 145.4, 144.3, 135.8, 128.7, 127.8, 126.7, 123.9, 73.0.

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