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Synthesis of Vertilecanin C and Two New Derivatives of Vertilecanin A via Nicotinic Acid

Serpil DEMİRCİ, Süleyman GÖKSU*, Murat BOZTAŞ
Ferhan TÜMER* and Hasan SEÇEN
Department of Chemistry, Faculty of Arts and Sciences, Atatürk University,
25240 Erzurum-TURKEY
e-mail: sgoksu@atauni.edu.tr

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Vertilecanin C and 2 new phenyl-substituted derivatives of vertilecanin A were synthesized. Lithiation of 5-benzoylpicolinamide with BuLi at –78 °C followed by treatment with methyl bromoacetate gave vertilecanin C [methyl 2-(3-benzoylpicolinamido)acetate], a natural product. Vertilecanin A type phenopicolinic acid derivatives were synthesized starting from nicotinic acid in 4 steps. Chlorination of nicotinic acid with $SOCl_2$ followed by treatment with anisole in the presence of $AlCl_3$ gave (4-methoxyphenyl)(pyridin-3-yl)methanone. The Minisci reaction of the ketone afforded 5-(4-methoxybenzoyl)picolinamide. $TiCl_4$-catalyzed acidic hydrolysis of the picolinamide gave 5-(4-methoxybenzoyl)picolinic acid, from which 5-(hydroxy(4-methoxyphenyl)methyl)picolinic acid was obtained by selective reduction with $NaBH_4$. The same reaction sequence performed with toluene instead of anisole afforded 5-(hydroxy(p-tolyl)methyl)picolinic acid.

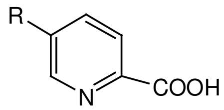
Key Words: Vertilecanin A, Vertilecanin C, diarylketones, Nicotinic acid.

Introduction

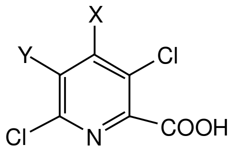
Picolinic acid and its derivatives are known as important organic compounds for humans and animals. Picolinic acid (**1**) itself plays a significant role in carrying metal ions in the human body and in animals.[1] Calcium, magnesium, and potassium salts of picolinic acid are used as food and beverage supplements to improve the nutritive capacity of food stuffs and beverages.[2] 5-Alkylpicolinic acids **2-5**, which are known as hypotensive agents, are reported to have strong inhibitory effects on dopamine β-hydroxylase.[3] Phenopicolinic acid **6**, originally isolated from cultures of a *Paecilomyces* sp., is a dopamine β-hydroxylase inhibitor and shows antihypertensive activity.[4] Halogen- containing picolinic acids **7-8** have been widely used as herbicides in agriculture and are potential contaminants of groundwater.[5] The need for new sources of environmentally friendly pesticides and fungi displaying a 'broad spectrum' of parasitic abilities has

*Corresponding authors

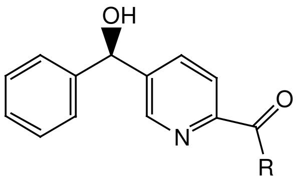
been increasing. For this purpose, Soman et al. isolated 5 new fungal metabolites, the vertilecanins **9-13**, from solid–substrate fermentation cultures of *Verticillium lecanii.* While **10-13** did not have insecticidal or antifungal activity, the most abundant component, vertilecanin A (**9**), displayed insecticidal activity against *Helicoverpa zea* (a corn butterfly) and showed antibacterial activity against *Bacillus subtilis* (ATCC 6051).[6]



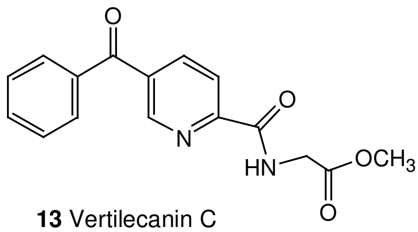
1 R=H, Picolinic acid
2 R=Me
3 R=Et
4 R=*iso*-Propyl
5 R=*n*-Butyl, Fusaric Acid
6 R=*p*-Hydroxybenzyl, Phenopicolinic acid



7 X=Y=H, Clopyralid
8 X=NH_2, Y=Cl, Picloram



9 R=OH, Vertilecanin A
10 R=OCH_3
11 R=$NHCH_2CO_2H$, Verrtilecanin B
12 R=$NHCH_2CO_2CH_3$

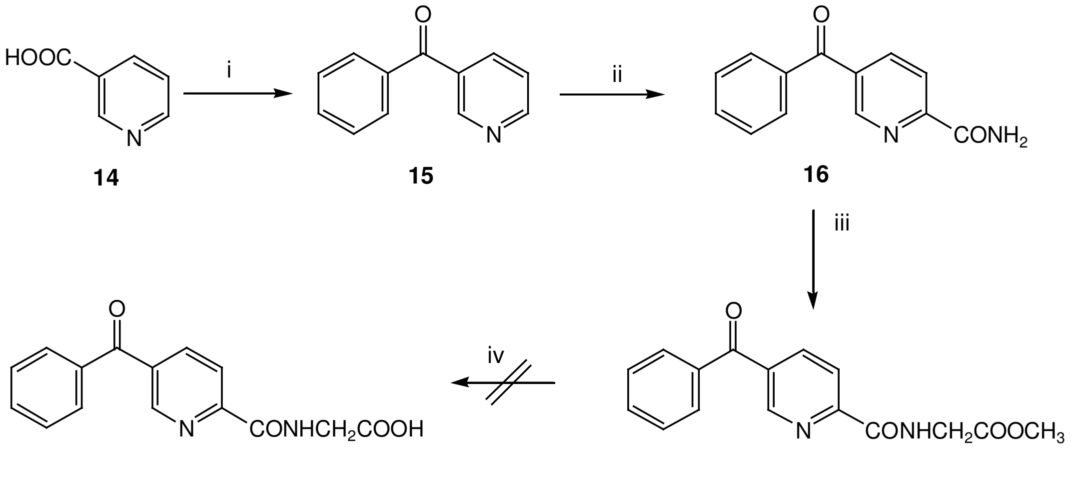


13 Vertilecanin C

Recently, we described a methodology[7] for the preparation of vertilecanin A starting from nicotinic acid in 4 steps with an overall yield of 29%. As a part of this ongoing project, we now report the first synthetic preparation of vertilecanin C and 2 phenyl-substituted derivatives of vertilecanin A.

Results and Discussion

The first step for synthesis of vertilecanin C (**13**) was the preparation of 3-benzoylpyridine (**15**)from nicotinic acid by following the literature procedure.[8] Nicotinic acid was chlorinated with $SOCl_2$ followed by treatment with benzene in the presence of $AlCl_3$ to give 3-benzoylpyridine (**15**). 3-Benzoylpyridine was converted to carboxamide **16** by following the procedure described by Langhals et al.[9] The most critical step in the synthesis was the alkylation of the amide with a suitable alkylating reagent. Lithiation of carboxamide **16** at –78 °C with BuLi followed by treatment with methyl 2-bromoacetate readily gave vertilecanin C (**13**). We considered that a chemoselective hydrolysis of the ester group of **13** followed by a chemoselective reduction of the keto group should afford vertilecanin B (**11**). For the chemoselective hydrolysis of the ester group, different acidic or basic hydrolysis procedures were applied. Unfortunately, all these methods failed to give the carboxylic acid **17** but instead the amide bond hydrolyzed to form 5-benzoylpicolinic acid[7] (Scheme 1). Therefore, although vertilecanin C was synthesized from nicotinic acid in 3 steps with an overall yield of 37%, conversion of vertilecanin C to vertilecanin B failed.



Scheme 1. (i) $SOCl_2$, then C_6H_6, $AlCl_3$, reflux, 90%; (ii) $FeSO_4.7H_2O$, H_2SO_4, t-BuOOH, $HC(O)NH_2$, 50%; (iii) THF, BuLi, –78 °C; then $BrCH_2COOCH_3$, 82% (iv) (a) K_2CO_3, MeOH, (b) KOH, MeOH, H_2O; (c) HCl, H_2O, MeOH.

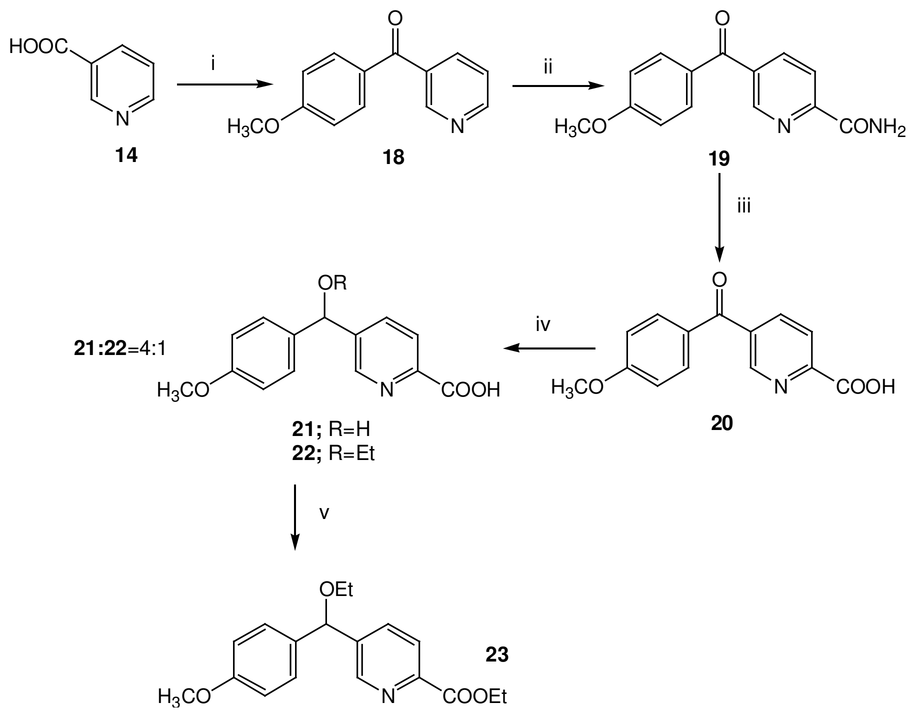
In the second part of this work, we aimed to synthesize phenyl-substituted derivatives of vertilecanin A. For this purpose, the Friedel-Crafts acylation of nicotinic acid was performed with anisole and toluene. The chlorination of nicotinic acid (**14**) with $SOCl_2$ followed by treatment with anisole afforded the nicotinyl ketone **18**. Ketone **18** was converted to the corresponding carboxyamide **19** by the known Minisci procedure.[9] Fisher et al. have reported the Ti(IV) catalyzed mild hydrolysis or alcoholysis of amides.[10] Following this procedure, $TiCl_4$-catalyzed hydrolysis of carboxyamide **19** gave carboxylic acid **20** in a good yield. A surprising result in the chemoselective reduction of the keto group of **20** was the formation of the ether **22** as a side product (**21:22**= 4:1 according to ^{1}H-NMR spectra). Because of the insolubility of the carboxylic acid **20** in MeOH, this reaction was performed in EtOH. Therefore, we wanted to elucidate the reaction mechanism for the formation of **22**. The mixture of compounds **21** and **22** was converted to the ester derivative (**23**) by refluxing in EtOH in the presence of pTSA. The formation of the etheric ester **23** as a sole product implies that the reaction proceeds via an S_N1 mechanism because of the electron-donor effect of 4-OMe on the phenyl ring.

The reaction sequence shown in Scheme 3 is similar to those in Schemes 1 and 2, except for the products formed in the Minisci reaction of ketone **24**. This reaction gave isomeric carboxyamides **25** and **26** in a ratio of 1:1. After separation, these carboxyamides were converted to the corresponding carboxylic acids **27** and **28**. Selective reduction of the keto-carboxylic acid **27** with $NaBH_4$ gave the corresponding hydroxy-carboxylic acid **29**, a vertilecanin A analogue.

In summary, using nicotinic acid (**14**) as a key compound, we achieved the first total synthesis of vertilecanin C (**13**), a natural product. We also described the synthesis of 2 new phenyl substituted analogues of vertilecanin A, which can be used for further chemical and biological purposes.

Experimental

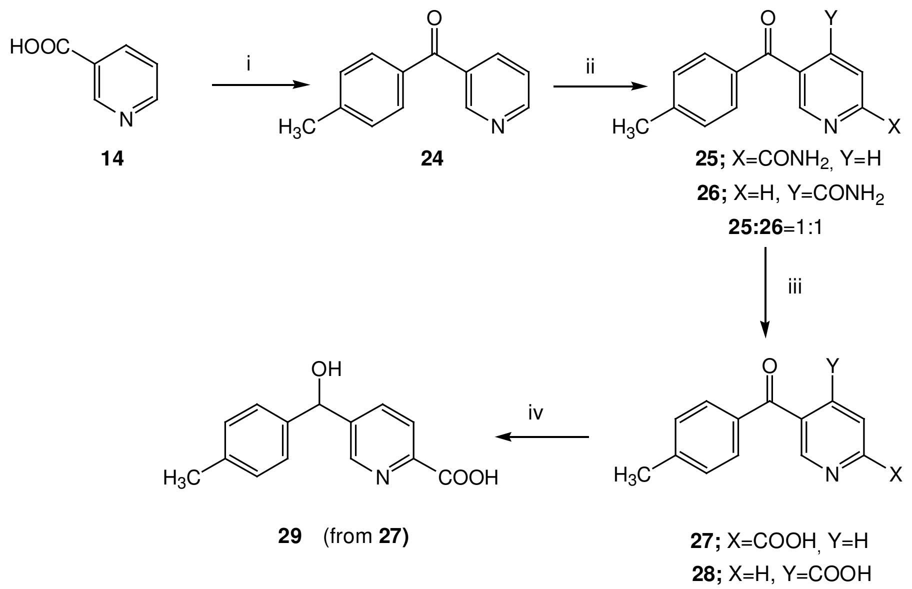
General. Solvents were purified and dried by standard procedures before use. Melting points were determined on a Büchi 539 capillary melting apparatus and are uncorrected. Infrared spectra were obtained



Scheme 2. (i) $SOCl_2$, then anisole, $AlCl_3$, 60-70 °C, 47%[a]; (ii) $FeSO_4.7H_2O$, H_2SO_4, t-BuOOH, HC(O)NH_2, 60%[a]; (iii) $TiCl_4$, HCl, dioxane, reflux, 60%[a] (iv) $NaBH_4$, EtOH, then H_2O, 84%[b] (v) EtOH, pTSA, reflux, 77%.

[a]yield after recrystallization

[b]total yield



Scheme 3. (i) $SOCl_2$, then toluene, $AlCl_3$, 60-70 °C, 45%[a]; (ii) $FeSO_4.7H_2O$, H_2SO_4, t-BuOOH, HC(O)NH_2, 46%[b]; (iii) $TiCl_4$, HCl, dioxane, reflux, 60% for **27**, 66% for **28** (iv) $NaBH_4$, MeOH, then H_2O, 49%.

[a]yield after recrystallization

[b]total yield

from KBr or film on a Mattson 1000 FT-IR spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on 400 (100) or 200 (50) MHz Varian spectrometers; δ in ppm. Elemental analyses were carried out with a Leco CHNS-932 instrument. EIMS spectra were recorded on a Thermo-Finnigan and Perkin-Elmer Clarus 500 GC/MS analyzer. Column chromatography was performed on silica gel 60 (70-230 mesh ASTM). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, 60 F254 analytical aluminum plates.

Phenyl-3-pyridinylmethanone (**15**). The ketone **15** was synthesized from nicotinic acid (**14**) following a well described literature procedure[8] (90% yield). mp 44-46 °C (solidified); Lit.[8] liquid. The ^{1}H-NMR data and ^{13}C-NMR data are in agreement with the data given in the literature.[9]

5-Benzoyl-pyridine-2-carboxamide (**16**). The 5-benzoyl-pyridine-2-carboxamide (**16**) was synthesized from phenyl-3-pyridinylmethanone (**15**) according to the literature procedure described by Langhals et al.[9] (50%). mp 144-146 °C (from EtOAc-hexane); Lit.[9] mp 147-155 °C. The ^{1}H-NMR and ^{13}C-NMR are in agreement with the literature.[9]

(+/-)-Vertilecanin C [methyl 2-(5-benzoylpicolinamido)acetate](13). A solution of carboxamide **16** (0.60 g, 2.6 mmol) dissolved in THF (25 mL) was cooled to −78 °C. At the same temperature and under N_2 atmosphere, 1.8 mL of n-BuLi (1.6 M, 2.9 mmol) was added dropwise and the mixture was stirred for 1 h. To the reaction mixture was added methyl bromoacetate (0.45 g, 2.7 mmol) and the temperature was raised to rt. The mixture was stirred for 12 h at rt. After removal of THF at reduced pressure, 1 mL of H_2O was added and the organic phase was extracted with CH_2Cl_2 (3 × 40 mL). Combined organic phases were washed with water (2 × 5 mL) and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on a short Al_2O_3 column (15 g) eluting with hexane-$CHCl_3$ (70:30; 50:50; 30:70) gave vertilecanin C (**13**) as a colorless oil (0.65 g, 82%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.95 (d, 1H, H-C(6), $J_{4,6}$=2.0 Hz); 8.52 (bt, 1H, NH, $J_{NH,CH2}$=5.5 Hz); 8.32 (A part of AB system, d, 1H, H-C(3), $J_{3,4}$=8.1 Hz); 8.23 (B part of AB system, dd, 1H, H-C(4), $J_{3,4}$=8.1 Hz; $J_{4,6}$=2.0 Hz), 7.81 (quasi d, 2H, H-C(2′) and H-C(6′), J=8.1 Hz); 7.70-7.49 (m, 3H, H-C(3′), H-C(4′), H-C(5′)), 4.30 (d, 2H, CH_2, $J_{NH,CH2}$=5.5 Hz), 3.80 (s, 3H, OCH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 194.1 (*C*O, ketone); 169.9 (*C*O, ester); 163.7 (*C*O, amide); 151.5 (C(2)); 149.3 (C(6)); 138.5 (C(4)); 136.5 (C(1′)); 135.4 (C(5)); 133.5 (C(4′)); 130.0 (C(2′/6′)); 128.7 (C(3′/5′)); 121.9 (C(3)); 52.3 (O*C*H_3); 41.3 (*C*H_2). EIMS (m/z, %) 298 (M^+, 33) 266 (M^+-CH_3OH, 46), 239 (M^+-$C_2H_3O_2$), 210 (M^+-$NHCH_2COOMe$, 58), 182 (M^+-$CONHCH_2COOMe$, 68), 105 ($C_6H_3NO^+$, 80).^{1}H-NMR data, ^{13}C-NMR data, and EIMS data are in agreement with data given for the natural product **13**.[6]

4-Methoxyphenyl-3-pyridinylmethanone (**18**). The literature procedure[8] described for the synthesis of phenyl-3-pyridinylmethanone (**15**) was applied to nicotinyl chloride by using anisole instead of benzene to give 4-methoxyphenyl-3-pyridinylmethanone (**18**) (47%). mp 92-94 °C (from CH_2Cl_2-hexane); lit.[11] mp 95-96 °C from cyclohexane. The ^{1}H-NMR data and ^{13}C-NMR data are in agreement with the data given in the literature.[9]

5-(4-Methoxy-benzoyl)-pyridine-2-carboxamide (**19**). 5-(4-methoxy-benzoyl)-pyridine-2-carboxamide (**19**) was synthesized from 4-methoxyphenyl-3-pyridinylmethanone (**18**) according to the literature procedure[9] (60%). mp 213-215 °C (from EtOAc-hexane); Lit.[9] mp 217 °C. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.87 (bs, 1H, H-C(6)); 8.29 (bs, 2H, NH_2); 8.25 (A part of AB system, dd, 1H, H-C(4), $J_{3,4}$=8.1 Hz, $J_{4,6}$=2.0 Hz); 8.19 (B part of AB system, d, 1H, H-C(3), $J_{3,4}$=8.1 Hz) 7.83 (AA′ part of AA′BB′ system, quasi d, 2H, H-C(2′) and H-C(6′), J=8.8 Hz); 7.13 (BB′ part of AA′BB′ system, quasi d, 2H, H-C(3′) and H-C(5′), J=8.8 Hz); 3.89 (s, 3H, OCH_3). The ^{1}H-NMR data are in agreement with the data given in the lit.[9] ^{13}C-NMR (50 MHz, DMSO-d_6): δ 194.2 (*C*O, ketone); 167.1 (*C*ONH_2); 165.4 (C(4′)); 154.0 (C(2));

150.3 (C(6)); 140.0 (C(4)); 137.3 (C(5)); 134.2 (C(2′/6′)); 130.5 (C(1′)); 123.4 (C(3)); 116.0 (C(3′/5′)); 57.5 (O*C*H_3).

5-(4-Methoxy-benzoyl)-pyridine-2-carboxylic acid (20). The hydrolysis procedure[7] described for 5-benzoylpicolinamide (**16**) was applied to **19** to give picolinic acid **20** (60%). White solid. mp 192-194 °C (solidified). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.92 (bs, 1H, H-C(6)); 8.20 (m, 2H, H-C(3) and H-C(4)); 7.81 (AA′ part of AA′XX′ system, quasi d, 2H, H-C(2′) and H-C(6′), J=8.7 Hz); 7.12 (XX' part of AA′XX′ system, quasi d, 2H, H-C(3′) and H-C(5′), J=8.7 Hz); 3.87 (s, 3H, OCH_3). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 194.2 (*C*O, ketone); 167.4 (*C*OOH); 165.5 (C(4′)); 152.1 (C(2)); 151.0 (C(6)); 139.8 (C(4)); 137.7 (C(5)); 134.2 (C(2′/6′)); 130.4 (C(1′)); 126.1 (C(3)); 116.0 (C(3′/5′)); 57.5 (O*C*H_3). EIMS (m/z, %): 257.2 (M^+, 16); 213.2 (M^+-CO_2, 32); 135.1 ($MeOC_6H_4CO^+$,100); 107.0 ($MeOC_6H_4^+$, 17); 92.1 ($C_6H_4O^+$, 20); 77.1 ($C_5H_3N^+$, 26).

Reduction of ketone 20 with $NaBH_4$. The reduction procedure described for the synthesis of (+/−)-vertilecanin A[7] was applied to 5-(4-methoxy-benzoyl)-pyridine-2-carboxylic acid (**20**) in EtOH to give 5-[hydroxy-(4-methoxy-phenyl)-methyl]-pyridine-2-carboxylic acid (**21**). This reaction gave an inseparable mixture of corresponding alcohol **21** and ether **22** in a ratio of 4:1 as a white solid (the total yield of the mixture was 84%). Only the alcohol **21** could be characterized from ^{1}H-NMR spectrum of the product mixture.

5-[Hydroxy-(4-methoxy-phenyl)-methyl]-pyridine-2-carboxylic acid (**21**). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.87 (bs, 1H, H-C(6)); 8.60 (d, 1H, H-C(3), $J_{3,4}$=8.1 Hz); 8.47 (bd, 1H, H-C(4), $J_{3,4}$=8.1 Hz); 7.33 (AA′ part of AA′XX′ system, quasi d, 2H, H-C(2′) and H-C(6′), J=8.7 Hz); 6.92 (XX' part of AA′XX′ system, quasi d, 2H, H-C(3′) and H-C(5′), J=8.7 Hz); 6.03 (bs, OH); 5.49 (s, 1H, H-C(OH)); 3.77 (s, 3H, OCH_3).

5-[Ethoxy-(4-methoxy-phenyl)-methyl]-pyridine-2-carboxylic acid ethyl ester (**23**). To a stirred solution of **21** and **22** (4:1) (0.50 g, 1.90 mmol) in EtOH (25 mL) was added p-toluene sulfonic acid (70 mg) and the reaction mixture was refluxed for 24 h. The reaction mixture was allowed to cool to rt and the solvent was removed by evaporation. The residue was dissolved in EtOAc (50 mL) and washed with saturated Na_2CO_3 solution (3 × 10 mL). After drying of the organic layer over Na_2SO_4, the solvent was evaporated. The filtration of the residue from silica gel (10 g) with 1:5 EtOAc-hexane gave 5-[ethoxy-(4-methoxy-phenyl)-methyl]-pyridine-2-carboxylic acid ethyl ester (**23**) as a colorless oil (0.46 g, 77%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.75 (d, 1H, H-C(6), $J_{4,6}$=2.1 Hz); 8.11 (A part of AB system, d, 1H, H-C(3), $J_{3,4}$=8.1 Hz); 7.85 (B part of AB system, dd, 1H, H-C(4), $J_{3,4}$=8.1 Hz, $J_{4,6}$=2.1 Hz); 7.26 (AA′ part of AA′XX′ system, quasi d, 2H, H-C(2′) and H-C(6′), J=8.7 Hz); 6.88 (XX' part of AA′XX′ system, quasi d, 2H, H-C(3′) and H-C(5′), J=8.7 Hz); 5.44 (s, 1H, H-C-OEt); 4.47 (q, 2H, OCH_2 of ester, J=7.1 Hz); 3.78 (s, 3H, OCH_3); 3.61-3.42 (m, 2H, OCH_2 of ether); 1.44 (t, 3H, CH_3, J=7.1 Hz); 1.28 (t, 3H, CH_3, J=7.0 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 167.1 (*C*OOEt); 161.6 (C(4′)); 150.6 (C(6)); 149.2 (C(2)); 144.2 (C(5)); 137.0 (C(4)); 135.0 (C(1′)); 130.4 (C(2′/6′)); 126.8 (C(3)); 116.2 (C(3′/5′)); 82.7 (*C*HOEt); 66.6 (*C*H_2, ester); 63.8 (*C*H_2, ether); 57.3 (O*C*H_3); 17.3 (*C*H_3); 16.4 (*C*H_3). Anal. Calcd. for $C_{18}H_{21}NO_4$ (315.36): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.42; H, 6.58; N, 4.55. EIMS (m/z, %): 315.8 (M^+, 1); 270.8 (M^+-OCH_2CH_3, 14); 242.0 (M^+-$COOCH_2CH_3$, 6); 178.6 (M^+-$MeOC_6H_4/C_2H_6$,10); 165.6 ($PyrCOOEt^+$, 61); 137.5 ($MeOC_6H_4CHOH^+$, 65); 135.5 ($MeOC_6H_4CO^+$, 38); 109.5 (50); 94.5 (47); 77.3 ($C_5H_3N^+$, 100).

p-Tolyl-3-pyridinylmethanone (**24**). The literature procedure[8] described for the synthesis of phenyl-3-pyridinylmethanone (**15**) was applied to nicotinyl chloride by using toluene instead of benzene to give p-tolyl-3-pyridinylmethanone (**24**) (45%). mp 75-76 °C (from CH_2Cl_2-hexane); lit.[12] mp 78.0-78.5 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.91 (bs, 1H, H-C(2)); 8.73 (bd, 1H, H-C(6), $J_{5,6}$=4.9 Hz); 8.02 (dt, 1H, H-C(4), $J_{4,5}$=8.1 Hz, $J_{2,4}$=$J_{4,6}$=1.8 Hz); 7.66 (AA′ part of AA′XX′ system, quasi d, 2H, H-C(2′) and H-C(6′), J=7.9 Hz); 7.39 (dd, 1H, H-C(5), $J_{4,5}$=8.1 Hz, $J_{5,6}$=4.9 Hz); 7.24 (XX' part of AA′XX′ system, quasi d, 2H, H-C(3′) and H-C(5′), J=7.9 Hz); 2.38 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 196.4 (*C*O, ketone); 154.5 (C(2)); 152.7 (C(6)); 146.0 (C(4′)); 139.0 (C(4)); 136.0 (C(3) or C(1′)); 135.5 (C(3) or C(1′)); 132.2 (C(2′/6′)); 131.2 (C(3′/5′)); 125.2 (C(5)); 23.6 (*C*H_3).

The Minisci reaction of p-tolyl-3-pyridinyl methanone (**24**). To a stirred solution of pyridin-3-yl-p-tolyl-methanone (**24**) (8.00 g, 40.6 mmol) in formamide (10 mL) was added concentrated H_2SO_4 (4 mL) under N_2 at 0 °C. After the addition of $FeSO_4.7H_2O$ (22.70 g, 81.6 mmol) in one portion, t-BuOOH (70%, 9.1 mL, 65.8 mmol) was added dropwise in 1 h under N_2 at the same temperature. The reaction mixture was stirred at the same temperature for 1 h then at rt for 7 h. The reaction mixture was cooled to 0 °C, and to this mixture was added a solution containing H_2O (16.2 mL), KOH (22.74 g, 406 mmol), and citric acid (28.06, 146 mmol). This mixture was poured into a separatory funnel containing ice (100 g), and then dilute NaOH was added (pH 12). The mixture was extracted with EtOAc (3 × 60 mL). The organic layer was dried over Na_2SO_4. The removal of the solvent gave a mixture of 5-(4-methyl-benzoyl)-pyridine-2-carboxamide (**25**) and 3-(4-methyl-benzoyl)-isonicotinamide (**26**) in a ratio of 1:1 (4.5 g, total yield 46%). Recrystallization of the mixture from EtOH gave 5-(4-methyl-benzoyl)-pyridine-2-carboxamide (**25**) as a white solid (1.50 g, 15%). Recrystallization of the residue from EtOAc-hexane gave 3-(4-methyl-benzoyl)-isonicotinamide (**26**) as a white solid (1.00 g, 10%).

5-(4-Methyl-benzoyl)-pyridine-2-carboxamide (**25**). mp 203-205 °C (from EtOH). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.89 (dd, 1H, H-C(6), $J_{4,6}$=2.0, $J_{3,6}$=0.9 Hz); 8.31 (bs, 1H, H-NH); 8.28 (A part of AB system, dd, 1H, H-C(4), $J_{3,4}$=8.0, $J_{4,6}$=2.0 Hz); 8.20 (B part of AB system, 1H, H-C(3), $J_{3,4}$=8.0, $J_{3,6}$=0.9 Hz); 7.86 (bs, 1H, H-NH); 7.76-7.72 (AA′ part of AA′XX′ system, quasi d, 2H, H-C(2′) and H-C(6′), J=8.0 Hz); 7.44-7.40 (XX' part of AA′XX′ system, quasi d, 2H, H-C(3′), H-C(5′), J=8.0 Hz); 2.44 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 195.4 (*C*O, ketone); 167.1 (*C*ONH$_2$); 154.2 (C(2)); 150.5 (C(6)); 146.0 (C(4′)); 140.3 (C(4)); 136.9 (C(5)); 135.3 (C(1′)); 131.9 (C(2′/6′)); 131.2 (C(3′/5′)); 123.5 (C(3)); 23.0 (*C*H_3). Anal. Calcd. for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66. Found: C, 70.05; H, 5.13; N, 11.70. EIMS (m/z, %): 240.2 (M^+, 26); 225.2 (M^+-CH_3, 35); 223.2 (M^+-NH_3, 20); 197.2 (M^+-CONH, 37); 195.2 (M^+-$CONH_3$, 15); 168.2 (5); 149.1 (8); 119.0 ($MeC_6H_4CO^+$, 100); 91.1 (60).

3-(4-Methyl-benzoyl)-isonicotinamide (**26**). mp 179-181 °C (from EtOAc-hexane). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.61 (s, 1H, H-NH); 8.75 (d, 1H, H-C(6), $J_{5,6}$=4.8 Hz); 8.64 (d, 1H, H-C(2), $J_{2,5}$=1.1 Hz); 7.65 (dd, 1H, H-C(5), $J_{5,6}$=4.8, $J_{2,5}$=1.1 Hz); 7.43-7.38 (AA′ part of AA′XX′ system, dm, 2H, H-C(2′) and H-C(6′), J=8.0 Hz); 7.21-7.15 (XX' part of AA′XX′ system, dm, 2H, H-C(3′) and H-C(5′), J=8.0 Hz); 7.12 (s, 1H, H-NH); 2.30 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 195.0 (*C*O, ketone); 168.5 (*C*ONH$_2$); 152.0 (C(2) or C(6)); 146.7 (C(4′)); 146.6 (C(2) or C(6)); 140.0 (C(3) or C(4)); 139.8 (C(3) or C(4)), 139.2 (C(1′)); 130.7 (C(2′/6′)); 127.2 (C(3′/5′)); 118.5 (C(5)); 22.4 (*C*H_3). Anal. Calcd. for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66. Found: C, 70.02; H, 4.88; N, 11.78. EIMS (m/z, %): 240.8 (M^+, 2); 225.7 (M^+-CH_3, 2); 197.6 (3); 194.5 (2); 167.7 (1); 149.6 (5); 119.5 ($MeC_6H_4CO^+$,100); 91.4 (90), 65.3 (45).

5-(4-Methyl-benzoyl)-pyridine-2-carboxylic acid (**27**). The procedure described for hydrolysis of 5-benzoylpicolinamide (**16**)[7] was applied to carboxyamide **25** to give carboxylic acid **27**. 60% yield. White crystal. mp 143-145 °C (from EtOH). ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 8.94 (d, 1H, H-C(6), $J_{4,6}$=1.5 Hz); 8.28 (m, 2H, H-C(3) and H-C(4)), 7.73 (d, 2H, H-C(2′) and H-C(6′), J=8.3 Hz); 7.38 (d, 2H, H-C(3′) and H-C(5′), J=8.3 Hz); 2.45 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ 193.9 (*C*O, ketone); 165.7 (*C*OOH); 150.2 (C(2)); 149.6 (C(6)); 145.0 (C(4′)); 138.8 (C(4)); 136.5 (C(5)); 133.8 (C(1′)); 130.2 (C(2′/6′)); 129.4 (C(3′/5′)); 124.6 (C(3)); 20.5 (*C*H$_3$). Anal. Calcd. for $C_{14}H_{11}NO_3$ (241.24): C, 69.70; H, 4.60; N, 5.81. Found: C, 69.58; H, 4.69; N, 5.92. EIMS (m/z, %): 241.2 (M^+, 17); 226.2 (M^+-CH_3, 25); 197.2 (M^+-CO_2, 24); 182.2 (M^+-CH_3/CO_2, 12); 168.2 (3); 150.1 (5); 119.0 ($MeC_6H_4CO^+$, 100); 91.1 (55).

3-(4-Methyl-benzoyl)-isonicotinic acid (**28**). The procedure described for hydrolysis of 5-benzoyl-picolinamide (**16**)[7] was applied to carboxyamide **26** to give carboxylic acid **28**. 66% yield. White crystal. mp above 270 °C (from EtOH); Lit.[13] mp 299 °C. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.89 (d, 1H, H-C(6), $J_{5,6}$=5.1 Hz); 8.67 (s, 1H, H-C(2)); 7.85 (d, 1H, H-C(5), $J_{5,6}$=5.1 Hz); 7.55 (d, 2H, H-C(2′) and H-C(6′), J=7.9 Hz); 7.31 (d, 2H, H-C(3′) and H-C(5′), J=7.9 Hz); 3.50 (bs, 2H, NH_2 signal overlapped with CD_3OD-H_2O); 2.35 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, CD_3OD): δ 194.9 (*C*O, ketone); 166.6 (*C*OOH); 152.4 (C(2) or C(6)); 148.9 (C(2) or C(6)); 144.9 (C(4′)); 138.6 (C(1′)); 135.6 (C(4) or C(3)); 135.0 (C(4) or C(3)); 130.1 (C(2′/6′)); 129.9 (C(3′/5′)); 123.5 (C(5)); 21.9 (*C*H$_3$). EIMS (m/z, %): 241.2 (M^+, 7); 197.2 (M^+-CO_2, 19); 182.2 (M^+-CH_3/CO_2, 7); 150.1 (6); 119.1 ($MeC_6H_4CO^+$, 100); 91.1 (40).

5-(Hydroxy-p-tolyl-methyl)-pyridine-2-carboxylic acid (**29**). The reduction procedure described for the synthesis of (+/−)-vertilecanin A[7] was applied to **27** to give 5-(hydroxy-p-tolyl-methyl)-pyridine-2-carboxylic acid (**29**). 49% yield. White solid. mp 174-176 °C (from MeOH-Et_2O). ^{1}H-NMR (200 MHz, DMSO-d$_6$): δ 8.66 (bs, 1H, H-C(6)); 8.14 (A part of AB system, d, 1H, H-C(3), $J_{3,4}$=8.0 Hz); 8.03 (B part of AB system, dd, 1H, H-C(4), $J_{3,4}$=8.0, $J_{4,6}$= 1.8 Hz); 7.28 (AA′ part of AA′BB′ system, quasi d, 2H, J=8.1 Hz); 7.17 (BB′ part of AA′BB′ system, quasi d, 2H, J=8.1 Hz); 5.90 (s, 1H, CH(OH)); 4.94 (bs, 2H, COOH and OH overlapped with DMSO-H_2O); 2.32 (s, 3H, CH_3). ^{13}C-NMR (50 MHz, DMSO-d$_6$): δ 168.9 (*C*O, ketone); 149.9 (C(6)); 149.5 (C(2)); 148.1 (C(5)); 143.4 (C(1′) or C(4′)); 140.6 (C(1′) or C(4′)); 139.4 (C(4)); 132.1 (C(3′/5′)); 129.6 (C(2′/6′)); 127.8 (C(3)); 76.0 (*C*HOH); 22.9 (*C*H$_3$). Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.86; H, 5.15; N, 5.85. EIMS (m/z, %): 243.8 (M^+, 2); 228.7 (M^+-CH_3, 2); 199.7 (M^+-CO_2, 2); 167.7 (M^+-CH_3/OH/CO_2, 2), 150.6 (7); 139.6 (2); 128.6 (5); 124.5 (25); 123.5 (34); 119.5 ($MeC_6H_4CO^+$, 32); 106.5 (Pyr-3-CO^+, 38); 93.4 ($PhCH_3^+H$, 100); 91.4 (90); 78.4 (45), 77.4 (64).

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