Notes

A Concise Synthesis of Fusaric Acid and (*S*)-(+)-Fusarinolic Acid†

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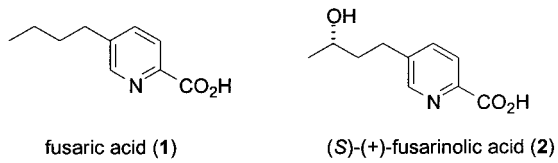
Introduction

The 5-substituted-2-picolinic acids such as fusaric acid (**1**) and (*S*)-(+)-fusarinolic acid (**2**) are a class of alkaloid natural products with important biological activities (Figure 1).[1] In particular, fusaric acid (**1**) was shown to be a potent inhibitor of dopamine β-hydroxylase in vitro and in vivo and displayed notable antihypertensive activity.[2] Fusaric acid also exhibited marked antitumor activity on human colon adenocarcinoma cell lines LoVo, SW48, SW480, and SW742, as well as human mammary adenocarcinoma cell line MDA-MB-468.[3] Other biological activities of fusaric acid and its derivatives include neurogenic,[4] wilting,[5] and herbicidal activities,[6] which were summarized in a recent review article.[7]

To facilitate the biological investigation, a number of synthetic approaches to fusaric acid (**1**) and its analogues, including (*S*)-(+)-fusarinolic acid (**2**), have been developed.[8] The target structures were either established by construction of the pyridine ring via the Diels−Alder type reactions[8a,b,d] or by elaboration of substituted pyridine templates.[8a,e−i] Despite the rather simple structures of compounds **1** and **2**, the reported syntheses generally consisted of 5−10 steps. Most of them employed harsh reaction conditions, low-temperature operations, and undesirable reagents such as SeO_2,[8f] $KMnO_4$,[8g,i] NH_2-NH_2,[8c] and Mg amalgam,[8g] which are not suitable for large-scale synthesis.

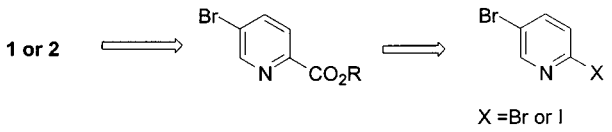


fusaric acid (**1**) (*S*)-(+)-fusarinolic acid (**2**)

Figure 1.

The objective of this study was to develop a concise and practical synthesis of these natural products and their analogues to facilitate further pharmaceutical evaluations. This has led us to devise a flexible synthetic strategy, which employs the 2,5-dihalopyridine as a template (Scheme 1). We envisioned that the sequential coupling at C(2) and C(5) positions of the pyridine ring would enable us to establish a unified and flexible route to a range of fusaric acid derivatives. In this paper, we wish to describe a concise synthesis of fusaric acid and (*S*)-(+)-fusarinolic acid with a selective carbonylation reaction of 2,5-dihalopyridine as the key step.

Scheme 1



Results and Discussion

We first examined the possibility to use the commercially available 2,5-dibromopyridine (**3**, Table 1) as the template. The carbonylation reaction of 2,5-dibromopyridine was previously reported to provide 5-bromopyridine-2-carboxylic acid methyl ester (**4**) in 65% yield after chromatography but the formation of diester (**5**) was not mentioned.[9] We repeated these experiments and noticed that diester (**5**) was an unavoidable byproduct under these reaction conditions. Presumably the diester was formed through the further carbonylation of the monoester via a sequential mechanism.[10] In a typical reaction, a mixture of compounds **4** and **5** was obtained in a ratio of ~6:1 at 88% conversion (Table 1, entry 1). Isolation of the desired monoester from the mixture of monoester, diester and unreacted starting material entailed tedious chromatography, thus resulting in low synthetic efficiency. When $Pd(PPh_3)_2Cl_2$ was used as the

† Dedicated to Professor Satoru Masamune for his enormous contributions to organic chemistry.

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(9) Chambers, R. J.; Marfat, A. *Synth. Commun.* **1997**, 515.

(10) Diester formation (10%) was also observed in the $Pd(PPh_3)_2Cl_2$ mediated carbonylative *ester* formation from 2,5-dibromo-3-methylpyridine: Wu, G. G.; Wong, Y.-S.; Poirier, M. *Org. Lett.* **1999**, *1*, 745.

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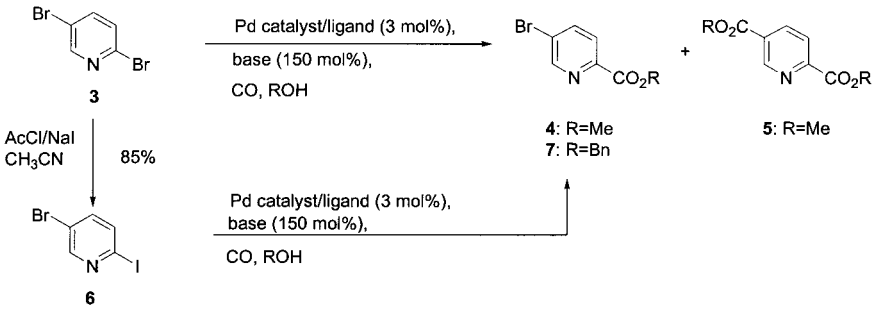
Table 1.



entry	X	ROH	conditions	time (h)	mono/di	isolated yield (mono) (%)
1	Br	MeOH	$Pd(OAc)_2$/dppf[a]/TEA/CH_3CN/CO(60 psi)/60 °C	8	6:1[b]	63
2	Br	MeOH	$Pd(PPh_3)_2Cl_2$/TEA/CH_3CN/CO(60 psi)/60 °C	15	24:1	(50)[c]
3	Br	MeOH	$Pd(PPh_3)_2Cl_2$/TEA/CH_3CN/CO(60 psi)/60 °C	48	14:1	(75)[c]
4	Br	MeOH	$Pd(OAc)_2$/2,2′-dipyridyl/DBU/toluene/CO(60 psi)/65 °C	46	mono only	(<5)[c]
5	I	MeOH	$Pd(OAc)_2$/dppf[a]/TEA/CH_3CN/CO(60 psi)/60 °C	6	mono only	70
6	I	MeOH	$Pd(OAc)_2$/2,2′-dipyridyl/DBU/toluene/CO(60 psi)/65 °C	46	mono only	(10)[c]
7	I	MeOH	$Pd(PPh_3)_2Cl_2$/TEA/CH_3CN/CO(60 psi)/60 °C	15	mono only	97
8	I	$PhCH_2OH$	$Pd(PPh_3)_2Cl_2$/TEA/CH_3CN/CO(60 psi)/60 °C	15	mono only	93

[a] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [b] Ratio at 88% conversion. [c] Conversion measured by ^{1}H NMR.

catalyst, the reaction was much slower and proceeded to only 50% conversion after 15 h (**4**:**5** = 24:1, entry 2). Prolonged heating led to the formation of more diester (**4**:**5** = 14:1 at 75% conversion, entry 3). Recently, Wu et al. reported that 2,2′-dipyridyl was an effective ligand for the selective carbonylative *amide* formation from 2,5-dibromo-3-methylpyridine.[10] Unfortunately, this system was not successful when it was applied to the carbonylative *ester* formation from 2,5-dibromopyridine and the conversion was less than 5% even after 46 h (entry 4). This result was not surprising considering that the carbonylative amide formation is usually more facile than the corresponding ester formation due to the better nucleophilicity of amines than alcohols.[10]

To avoid the diester byproduct and to achieve a better yield in the carbonylative ester formation reactions, we turned our attention to 5-bromo-2-iodopyridine (**6**, Table 1). Despite its obvious advantages and potential utility, this compound has not been employed in organic synthesis and it was only briefly mentioned in one report.[11] This compound was prepared in very low yield (~30%) by treatment of 2,5-dibromopyridine with refluxing HI, but no experimental details or characterizations were given. To secure the synthetic availability and to explore the reactivity of this compound, we first developed an efficient synthesis of 5-bromo-2-iodopyridine (**6**) via a selective substitution reaction. Thus, when 2,5-dibromopyridine (**3**) was heated with AcCl/NaI in refluxing CH_3CN,[12] the iodo-bromo exchange occurred exclusively at the C(2) position to furnish compound **6** in crystalline form in 85% yield without the need for chromatography.

The results of the carbonylation reaction with 5-bromo-2-iodopyridine (**6**) are summarized in Table 1. The progress of the reaction and the product ratios were assessed by ^{1}H NMR analysis of the crude reaction mixtures. In all cases, no diester formation was observed. When 1,1′-bis(diphenylphosphino)ferrocene (dppf) was used as the supporting ligand, the starting material was completely consumed within 6 h to provide compound **4** in 70% isolated yield, along with some unidentified byproducts. Attempts to use 2,2′-dipyridyl as the ligand resulted in sluggish reactions (~10% conversion after 46 h). To our delight, the use of $Pd(PPh_3)_2Cl_2$ as the catalyst dramatically improved the performance of the reaction and pure monoester **4** was isolated with remarkable ease in 97% yield (entry 7). It appeared that the use of an iodide at the C(2) position not only enhanced the rate of the first carbonylation reaction at the C(2) position but also helped slow the subsequent carbonylation at the C(5) position, thus avoiding the diester formation. More detailed mechanistic studies are underway to understand this interesting observation. The benzyl ester **7** was obtained in 93% yield by using similar reaction conditions (entry 8), and it was conveniently employed in the synthesis of fusaric acid (**1**) and (*S*)−(+)-fusarinolic acid (**2**). The benzyl ester was chosen for our synthesis because this group can be easily removed by heterogeneous hydrogenolysis, which would allow the isolation of the polar and highly water soluble final products (**1** and **2**) via a simple filtration.[13]

The bromo substituent at the C(5) position of the pyridine ring served as a convenient handle to attach a variety of appendages via transition metal mediated cross-coupling reactions. Thus, compound **7** was readily coupled with BuZnCl (generated in situ from BuMgBr and $ZnCl_2$) under the catalysis of $Pd(PPh_3)_2Cl_2$ to give the intermediate **8** (Scheme 2).[14] Removal of benzyl group by hydrogenolysis completed the synthesis of fusaric acid (**1**).

For the synthesis of (*S*)-(+)-fusarinolic acid (**2**), the palladium-catalyzed coupling of compound **7** with the commercially available (*S*)-(−)-3-butyn-2-ol (**9**) provided

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(12) Corcoran, R. C.; Bang, S. H. *Tetrahedron Lett.* **1990**, *31*, 6757.

(13) In a previously reported synthesis (see ref 8a), isolation of compound **2** from the aqueous solution required continuous liquid−liquid extraction due to its high solubility in water.

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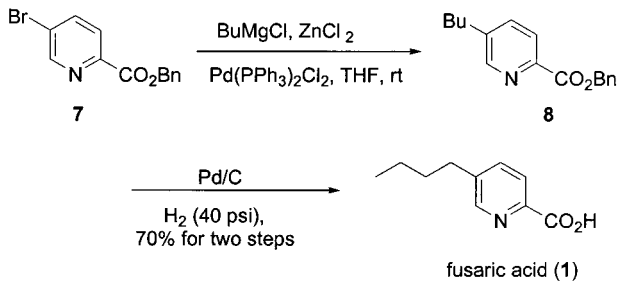
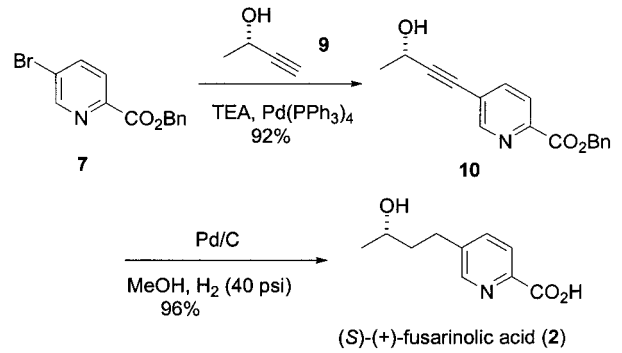
Scheme 2



Scheme 3



compound **10** smoothly in 92% yield (Scheme 3).[15] The simultaneous hydrogenolysis of benzyl ester and the triple bond over Pd/C furnished (*S*)-(+)-fusarinolic acid (**2**) in excellent yield.[16] As expected, the use of a heterogeneous hydrogenation reaction in the last step of our synthesis simplified isolation of the extremely polar and water-soluble final products, thus avoiding the need for the continuous solvent−aqueous extraction that was encountered in a previously reported synthesis.[8a]

Conclusion

In summary, we have developed an expedient synthesis of naturally occurring alkaloids fusaric acid and (*S*)-(+)-fusarinolic acid, which represents the most efficient synthesis of these compounds to date (four steps with overall yields of 55% and 70%, respectively). This synthesis is based on a unified and flexible strategy using 5-bromo-2-iodopyridine (**6**) as a template and is readily applicable to analogue synthesis. The carbonylative *ester* formation of compound **6** was found to occur exclusively at the C(2) position of the pyridine ring under the catalysis of $Pd(PPh_3)_2Cl_2$ to afford the monoester in excellent yield, without the complication of the diester formation. In addition, we reported a greatly improved synthesis of 5-bromo-2-iodopyridine, which makes this compound an attractive and more available template for organic and materials synthesis.[11a]

Experimental Section

General Procedures. All reactions were performed in oven-dried glassware under argon with magnetic stirring. All commercial reagents were used as received. Flash chromatography was performed using 230−400 mesh silica gel.

5-Bromo-2-iodopyridine (6). 2,5-Dibromopyridine (**3**, 100 g, 0.42 mol) was suspended in acetonitrile (500 mL) at room temperature. Sodium iodide (94 g, 0.63 mol) and acetyl chloride (45 mL, 0.63 mol) were added. The reaction was refluxed for 3 h and was quenched with aqueous K_2CO_3 solution to pH = 8. Ethyl acetate (1.5 L) was added to extract the organic materials. The organic layer was washed with saturated aqueous $NaHSO_3$ solution (500 mL) and brine (500 mL), dried over $MgSO_4$, and concentrated to give a mixture of **6** and **3** (90:10). Re-subjection of this crude material to the same conditions pushed the reaction to completion. The same workup provided compound **6**[11a] as light brown crystals (102 g, 85%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (s, 1H), 7.60 (d, J = 8.26 Hz, 1H), 7.44 (d, J = 8.25 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 140.7, 136.5, 121.5, 115.6; mp 112.5−113.5 °C; HRMS calcd for the $[M + 1]^+$ 283.8572, found 283.8568.

Carbonylation Reaction with 5-Bromo-2-iodopyridine: 5-Bromopyridine-2-carboxylic Acid Methyl Ester (4).[9,17] To a solution of compound **6** (0.5 g, 1.76 mmol) in CH_3CN (6 mL) in an autoclave were added TEA (0.37 mL, 2.64 mmol), MeOH (2 mL), and $Pd(PPh_3)_2Cl_2$ (37 mg, 0.05 mmol). The autoclave was sealed, purged with CO twice, and pressured at 60 psi. The reaction mixture was stirred vigorously and heated at 60 °C for 15 h before it was concentrated to give an oil which was subjected to flash chromatography (30% ethyl acetate/hexanes) to yield compound **4** (369 mg, 97%): mp 99.5−100.5 °C (lit.[9] mp 96−97 °C; lit.[17] mp 100−101 °C).

5-Bromopyridine-2-carboxylic Acid Benzyl Ester (7).[9] This compound was synthesized similarly in 93% yield: mp 89.0−90.0 °C (lit.[9] mp 86−88 °C).

Benzyl 5-*n*-Butylpyridine-2-carboxylate (8). To a solution of BuMgCl (2 M/THF, 1.37 mL, 2.73 mmol) in anhydrous THF (8 mL) at room temperature was added $ZnCl_2$ (1 M/ether, 3.0 mL, 3.0 mmol). After the reaction mixture was stirred for 15 min, $Pd(PPh_3)_2Cl_2$ (48 mg, 0.068 mmol) was added followed by the bromide **7** (400 mg, 1.37 mmol). The reaction mixture was stirred at room temperature for 15 h before it was carefully quenched with HCl (1 N) to pH = 6. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and used directly as crude in the next step. Flash chromatography provided compound **8** in pure form as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (d, J = 1.63 Hz, 1H), 8.05 (d, J = 7.98 Hz, 1H), 7.61 (dd, J = 2.21, 7.98 Hz, 1H), 7.48 (d, J = 8.18 Hz, 2H), 7.36 (m, 3H), 5.45 (s, 2H), 2.68 (t, J = 7.56 Hz, 2H), 1.62 (m, 2H), 1.37 (m, 2H), 0.93 (t, J = 7.32 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 150.2, 145.6, 142.2, 136.5, 135.8, 128.6, 128.5, 128.3, 125.0, 67.3, 32.9, 32.7, 22.2, 13.8; HRMS calcd for the $[M + 1]^+$ 270.1494, found 270.1489.

Fusaric Acid (1).[8a] The crude **8** from above reaction was dissolved in MeOH (5 mL) followed by the addition of Pd/C (10 wt %, 70 mg). The reaction mixture was shaken under hydrogen (40 psi) at room temperature for 4 h. Filtration of the reaction mixture afforded the crude product, which was purified by recrystallization from CH_2Cl_2 and hexanes to yield fusaric acid (**1**) (170 mg, 70% for two steps from **8**). ^{1}H NMR and ^{13}C NMR of the synthetic material were identical to those reported for the natural product:[8a] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (s, 1H), 8.14 (d, J = 7.56 Hz, 1H), 7.75 (d, J = 7.44 Hz, 1H), 2.73 (t, J = 7.20 Hz, 2H), 1.60−1.70 (m, 2H), 1.35−1.45 (m, 2H), 0.95 (t, J = 7.30 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 147.9, 143.1, 145.0, 138.4, 124.2, 32.9, 32.8, 22.2, 13.8.

Benzyl 5-(3-Hydroxy-but-1-ynyl)pyridine-2-carboxylate (10). To a solution of the alkyne **9** (0.57 g, 8.1 mmol), bromide **7** (1.58 g, 5.4 mmol), and TEA (1.1 mL, 8.1 mmol) in anhydrous THF (35 mL) was added $Pd(PPh_3)_4$ (312 mg, 0.27 mmol). The reaction mixture was heated at 70 °C for 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (100 mL × 2). The crude material was purified by flash column chromatography (20% ethyl acetate/hexanes) to yield **10** (1.4 g, 92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (d, J = 1.64 Hz, 1H), 8.07 (d, J = 8.00 Hz, 1H), 7.82 (dd, J = 2.00, 8.10 Hz, 1H), 7.48 (m, 2H), 7.36 (m, 3H), 5.45 (s, 2H),

(15) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

(16) Spectroscopic properties of synthetic materials (**1** and **2**) were identical to those reported for the natural products. ^{1}H NMR spectrum of the Mosher ester derived from compound **10** revealed only one diastereomer, thus confirming the stereochemical integrity of the stereogenic center.

(17) Campbell, A. D.; Chooi, S. Y.; Deady, L. W.; Shanks, R. W. *Aust. J. Chem.* **1971**, *24*, 385.

4.79 (m, 1H), 2.10 (br.s, 1H), 1.57 (d, $J = 6.60$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 153.5, 153.4, 147.5, 140.9, 136.7, 130.0, 129.9, 129.8, 125.9, 124.8, 99.4, 81.2, 69.1, 59.8, 25.3; mp 80.5−81.5 °C; $[\alpha]^{25}_D = -14.0°$ (*c* 0.5, MeOH); HRMS calcd for the $[M + 1]^+$ 282.1130, found 282.1147.

(*S*)-Fusarinolic Acid (2).[8a] To a solution of **10** (752 mg, 2.68 mmol) in MeOH (10 mL) was added Pd/C (10 wt %, 75 mg). The reaction mixture was shaken under hydrogen (40 psi) for 6 h. Filtration of the reaction mixture and concentration of the filtrate afforded the final product **2**[8a] (500 mg, 96%). ^{1}H NMR and ^{13}C NMR of the synthetic material were identical to those reported for the natural product:[8a] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (d, $J = 1.6$ Hz, 1H), 7.94 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 4.30−4.80 (br s, 1H), 3.53−3.61 (m, 1H), 2.62−2.82 (m, 2H), 1.60−1.67 (q, $J = 6.2$ Hz, 2H), 1.08 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.2, 149.5, 146.9, 144.2, 140.0, 126.3, 67.7, 41.1, 30.2, 23.7; $[\alpha]^{25}_D = +19.5°$ (*c* 1.5, MeOH) [lit.[8a] $[\alpha]^{25}_D$ +20.5° (*c* 1.05, MeOH)].

Supporting Information Available: ^{1}H NMR spectra for compounds **6**, **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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