A Concise Synthesis of Furostifoline by Tetrabutylammonium Fluoride-Promoted Indole Ring Formation

Akito YASUHARA,* Naoyuki SUZUKI, and Takao SAKAMOTO

Graduate School of Pharmaceutical Sciences, Tohoku University, Aobaku, Sendai 980–8578, Japan.
Received September 18, 2001; accepted October 20, 2001

Furostifoline, a furo[3,2-*a*]carbazole alkaloid, was synthesized in 10% overall yield in four steps from 2-acetyl-3-bromofuran. The key step of this synthesis was the 2-substituted indole formation with tetrabutylammonium fluoride (TBAF) from 2-(2-propenyl)-3-((2-ethoxycarbonylamino)phenylethynyl)furan, which was easily prepared from ethyl 2-ethynylphenylcarbamate with 3-bromo-2-(2-propenyl)furan by the Sonogashira reaction.

Key words total synthesis; furostifoline; indole; tetrabutylammonium fluoride

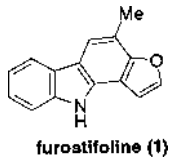
The furo[3,2-*a*]carbazole alkaloid, furostifoline (**1**), was isolated in 1990 from *Murrata euchrestitolia* by Furukawa and his group.[1] Furostifoline was the first carbazole alkaloid exhibiting a furo[3,2-*a*]carbazole framework. Several synthetic organic groups were interested in its unprecedented framework and pharmacological potential.[2,3a] The first total synthesis of **1** was reported by Knölker and Fröhner using their convergent iron-mediated formation of carbazole,[4] and three other syntheses of **1** were achieved.[3] Soós and coworkers reported a five-step synthesis of **1** from bromocresole using the ring formation of carbazole through the nitrene intermediate as a key reaction.[3a] Hibino[3b] and Beccalli[3d] developed an benzofuran ring formation by intramolecular photocyclization and electrocyclization, leading to the preparation of **1**. Recently, Hibino and his group reported the synthesis of **1** by the allene-mediated electrocyclic reaction of 2-furyl-3-propargylindole derivative.[3c]

We reported a cyclization reaction of 2-ethynylanilines with tetrabutylammonium fluoride (TBAF) gives the corresponding 2-substituted indoles in good yields (Chart 2).[5] The method has wide usage for the synthesis of indoles having multi-functional groups, because the 2-ethynylanilines are easily prepared by the Sonogashira reaction from 2-haloanilines for which many synthetic methods have been reported (*i.e.* by *ortho*-lithiation of *N*-protected anilines with alkyllithium[6]) and the cyclization reaction with TBAF proceeds without affecting many functional groups. Now we report a concise synthesis of **1** using the cyclization with TBAF from 2-ethynylanilines as a key reaction.

At the first step, isopropenyl-2-(3-bromo)furan (**3**) was prepared by the Wittg reaction of 2-acetyl-3-bromofuran with methyltriphenylphosphonium bromide and butyllithium in 82% yield. Then, the Sonogashira reaction[7] of **3** with ethyl 2-ethynylphenylcarbamate gave 2-(isopropenyl)-3-[(2-ethoxycarbonylamino)phenylethynyl]furan (**5**) in 79% yield, as shown in Chart 3.

We also reported that a palladium-catalyzed cross-coupling reaction of *N*-(2-iodophenyl)methanesulfonamide with terminal alkynes gives the corresponding 2-substituted indoles instead of ethynylanilines[8] (Chart 2). In order to use this one-step palladium-catalyzed indole synthesis from 2-haloanilines, we tried to prepare 3-trimethylsiliylethynyl-2-(isopropenyl)furan (**6**) using the Sonogashira reaction of **3** with trimethylsilylacetylene (TMSA). However, the reaction at 100 °C for 14 h gave a complex mixture that was not separable by column chromatography. We surmised that the low reactivity of **3** with TMSA for the Sonogashira reaction required high reaction temperature and extended reaction time, and the conditions caused self-condensation of TMSA and decomposition of **3** in the presence of the palladium catalyst. On the other hand, an ethyl ethynylphenylcarbamate–DMF (*N*,*N*-dimenylformamide) solution was dropped to the mixture of **3**, DMF and the palladium catalyst at refluxing temperature for 1 h to give **5** in good yield. The reaction conditions avoid the self-condensation of the terminal acetylene to obtain **5**, but it was difficult to adopt these conditions for the Sonogashira reaction of **3** with TMSA because of the low boiling point of TMSA.

The TBAF-promoted cyclization reaction of **5** gave a mixture of 2-[(isopropenyl)furanyl]indole (**7**) and 3-(2-aminophenyl)ethynyl-(isopropenyl)furan (**8**), and the mixture was easily separated by silica gel column chromatography in 47% and 33% yield, respectively. Compound **5** was reproduced by the protection of **8** with ethyl chloroformate in 76% yield. Finally, intramolecular photocyclization (high-pressure Hg lamp) of **7** with a catalytic amount of I_2 in toluene led directly to furostifoline (**1**) in 24% yield. Although **1** was ob-



furostifoline (1)

Chart 1

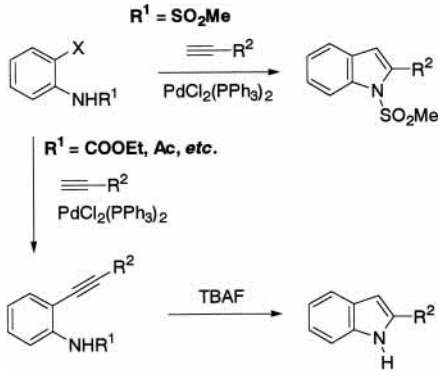


Chart 2

* To whom correspondence should be addressed. e-mail: yasuhara@mail.pharm.tohoku.ac.jp

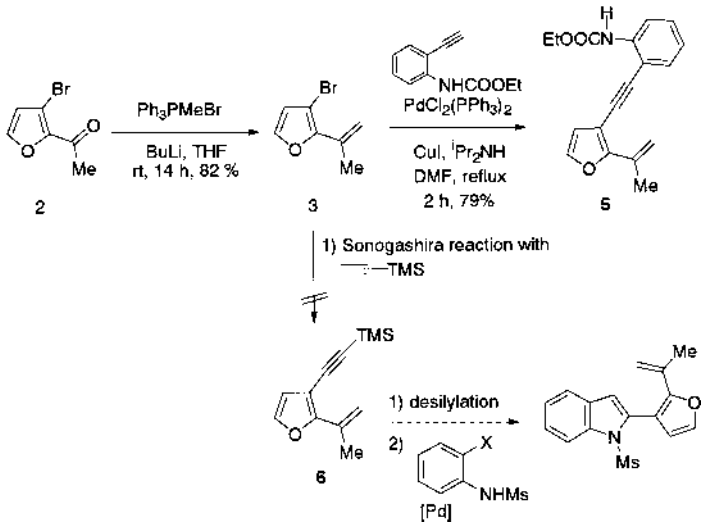


Chart 3

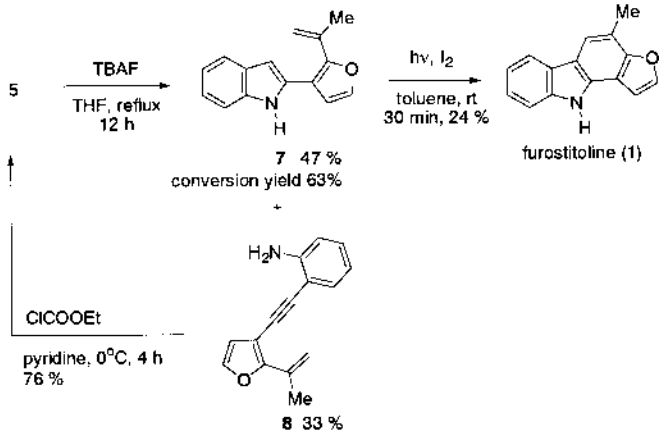


Chart 4

tained as only one product in the reaction mixture of the photocyclization, some insoluble matter was founded. So we supposed that the photocyclization caused the polymerization of **7** and gave **1** in only 24% yield. The spectral data of our synthetic furostifoline are in full agreement with those described by Furukawa for the natural product (UV, IR, ^{1}H-NMR, MS).

In conclusion, our synthesis provides furostifoline in 4 steps and 10% overall yield based on 2-acetyl-3-bromfurane using our synthetic method of 2-substituted indole with TBAF as a key reaction.

Experimental

Melting point and boiling point are uncorrected. IR spectra were taken on a Shimadzu FT-IR 8400 spectrophotometer. ^{1}H-NMR spectra were recorded on Varian Gemini 200 (300 MHz) spectrometers. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as an internal reference. UV spectrum was recorded on Shimadzu UV-3100PC instrument. MS and high-resolution (HR)-MS were recorded on JMS-DX303 and JMS-AX500 instruments.

Isopropenyl-2-(3-bromo)furan (3) A mixture of methyltriphenylphosphonium bromide (2.49 g, 6.89 mmol), BuLi (1.43 M hexane solution, 5.0 ml, 6.98 mmol), and tetrahydrofuran (THF) (20 ml) was stirred for 1 h at room temperature under Ar atmosphere. 2-Acetyl-3-bromofuran[9] (0.86 g, 4.65 mmol) in THF (20 ml) was added to the mixture. The mixture was stirred for 14 h, filtrated and concentrated under reduced pressure. Water (50 ml) was added to the residue and extracted with Et_2O (50 ml×3). The ethereal layer was washed with brine (100 ml×2). The residue obtained from the ethereal extract was purified by silica gel column chromatography (hexane). The product was purified by distillation. Colorless liquid (0.71 g, 82%). bp 70—80 °C (90 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 5.15 (1H, s), 5.73 (1H, s), 6.43 (1H, d, J=1.9 Hz), 7.28 (1H, d, J=1.9 Hz). MS *m/z* 188, 186 (M^+). HR-MS *m/z*: 185.9705 (Calcd for $C_7H_7{}^{79}BrO$: 185.968), 187.9657 (Calcd for $C_7H_7{}^{81}BrO$: 187.9660).

3-[(2-Ethoxycarbonylamino)phenylethynyl]-2-isopropenylfuran (5) After ethyl 2-ethnylphenylcarbamate[10] (564 mg, 2.98 mmol) in DMF (5.0 ml) was added to a mixture of **3** (462 mg, 2.48 mmol), $PdCl_2(PPh_3)_2$ (174 mg, 0.25 mmol), CuI (47 mg, 0.25 mmol), diisopropylamine (6 ml), and DMF (15 ml) at refluxing temperature for 1 h, the mixture was refluxed for 1 h. Et_2O (100 ml) was added to the mixture, and washed with brine (100 ml×2). The residue obtained from the extract was purified by silica gel column chromatography (hexane). Yellow viscous oil (580 mg, 79%). IR (neat) cm^{-1}: 3404, 2210, 1740. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz), 2.25 (3H, s), 4.25 (2H, q, J=7.1 Hz), 5.17 (1H, s), 5.84 (1H, s), 6.53 (1H, d, J=1.9 Hz), 7.01 (1H, dt, J=1.1, 7.4 Hz), 7.03—7.36 (3H, m), 7.46 (1H, dd, J=1.6, 8.2 Hz), 8.16 (1H, d, J=8.2 Hz). MS *m/z* 295 (M^+). HR-MS *m/z*: 295.1232 (Calcd for $C_{18}H_{17}NO_3$: 295.1208).

Cyclization Reaction of 5 with TBAF A mixture of **5** (283 mg, 0.96 mmol), 1 M TBAF–THF solution (3 ml, 2.88 mmol), and THF (20 ml) was refluxed for 12 h, and the mixture was concentrated under reduced pressure. Water (50 ml) was added to the residue and extracted with AcOEt (50 ml×3). The AcOEt layer was washed with brine (50 ml×3). The residue obtained from the extract was purified by silica gel column chromatography (AcOEt : hexane=1 : 20).

2-(2-Isopropenylfuran-3-yl)indole (**7**): Yellow viscous oil (101 mg, 47%). IR (neat) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 5.21 (1H, s), 5.49

(1H, s), 6.58 (1H, d, J=1.6 Hz), 6.59—6.60 (1H, m), 7.07—7.20 (2H, m), 7.33 (1H, d, J=7.4 Hz), 7.39 (1H, d, J=1.6 Hz), 7.59 (1H, d, J=7.4 Hz), 8.32 (1H, br). MS m/z 223 (M^+). HR-MS m/z: 223.0977 (Calcd for $C_{15}H_{13}NO$: 223.0997).

3-(2-Aminophenylethynyl)-2-isopropenylfuran (**8**): Pale yellow viscous oil (70 mg, 33%). IR (neat) cm^{-1}: 3445, 3381, 2206. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 4.22 (2H, br), 5.13 (1H,s), 5.88 (1H, s), 6.49 (1H, d, J=1.9 Hz), 6.68—6.73 (2H, m), 7.13 (1H, dt, J=1.6, 6.6 Hz), 7.30—7.33 (2H, m). MS m/z 223 (M^+). HR-MS m/z: 223.1012 (Calcd for $C_{15}H_{13}NO$: 223.0997).

The Protection of 8 with Ethyl Chloroformate A mixture of **8** (28 mg, 1.26 mmol), ethyl chloroformate (164 mg, 1.51 mmol), and pyridine (5 ml) was stirred for 3 h at room temperature, and concentrated. Water (50 ml) was added to the residue, and extracted with Et_2O (50 ml×3). The ethereal layer was washed with $CuSO_4 \cdot 5H_2O$ (50 ml×2) and water (100 ml×2). The residue obtained from the extract was purified by silica gel column chromatography (hexane) to give **5** as a yellow viscous oil (283 mg, 76%).

Furostifoline (1)[1] A mixture of **7** (23 mg, 0.10 mmol), a catalytic amount of I_2, and toluene (10 ml) was irradiated for 30 min. The residue obtained from the mixture was purified by silica gel column chromatography (AcOEt : hexane=1 : 20). Colorless prisms from hexane (5.6 mg, 24%). mp 175—176 °C (lit.[4b] 174—175 °C). IR (KBr) cm^{-1}: 3406, 1457, 1442, 1360, 1308, 1159, 1043, 878, 746, 735. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (3H, s), 7.00 (1H, d, J=2.2 Hz), 7.23—7.28 (1H, m), 7.38 (1H, t, J=8.2 Hz), 7.49 (1H, d, J=8.2 Hz), 7.73 (1H, d, J=2.2 Hz), 7.77 (1H, s), 8.06 (1H, d, J=8.2 Hz), 8.28 (1H, br). UV λ (MeOH) nm: 260, 278, 295, 322, 334. MS m/z 221 (M^+). HR-MS m/z: 221.0851 (Calcd for $C_{15}H_{11}NO$: 221.0841).

References

1) Ito C., Furukawa H., *Chem. Pharm. Bull.*, **38**, 1548—1550 (1990).
2) Timári G., Soós T., Hajós G., Messmer A., Nacsa J., Molnár J., *Bioorg. Med. Chem. Lett.*, **6**, 2831—2836 (1996).
3) *a*) Soós T., Timári G., Hajós G., *Tetrahedron Lett.*, **40**, 8607—8609 (1999); *b*) Hagiwara H., Choshi T., Fujimoto H., Sugino E., Hibino S., *Chem. Pharm. Bull.*, **46**, 1948—1949 (1998); *c*) Hagiwara H., Choshi T., Nobuhiro J., Fujimoto H., Hibino S., *ibid.*, **49**, 881—886 (2001); *d*) Beccalli E. M., Clerici F., Marchesini A., *Tetrahedron*, **54**, 11675—11682 (1998).
4) *a*) Knölker H. J., Fröhner W., *Tetrahedron Lett.*, **37**, 9183—9186 (1996); *b*) *Idem*, *Synthesis*, **2000**, 2131—2136.
5) Yasuhara A., Kanamori Y., Kaneko M., Numata A., Kondo Y., Sakamoto T., *J. Chem. Soc.*, *Perkin Trans. 1*, **1999**, 529—534.
6) Snieckus V., *Chem. Rev.*, **90**, 879—933 (1990).
7) Sonogashira K., Ohda Y., Hagihara N., *Tetrahedron Lett.*, **1975**, 4467—4470.
8) Sakamoto T., Kondo Y., Iwashita S., Nagano T., Yamanaka H., *Chem. Pharm. Bull.*, **36**, 1305—1308 (1988).
9) Koyanagi J., Yamamoto K., Nakayama K., Tanaka A., *J. Heterocycl. Chem.*, **32**, 1289—1291 (1995).
10) Shin K., Ogasawara K., *Synlett*, **1995**, 859—860.