A Total Synthesis of Yellowish Aphid Pigment Furanaphin through Fries Rearrangement Assisted by Boron Trifluoride-Acetic Acid Complex

Taichi Nishimura, Takeki Iwata, Hironori Maegawa, Takeshi Nishii, Masami Matsugasako, Hiroto Kaku, Mitsuyo Horikawa, Makoto Inai, Tetsuto Tsunoda*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan
Fax +81(88)6553051; E-mail: tsunoda@ph.bunri-u.ac.jp

Received: 23.04.2012; Accepted after revision: 22.05.2012

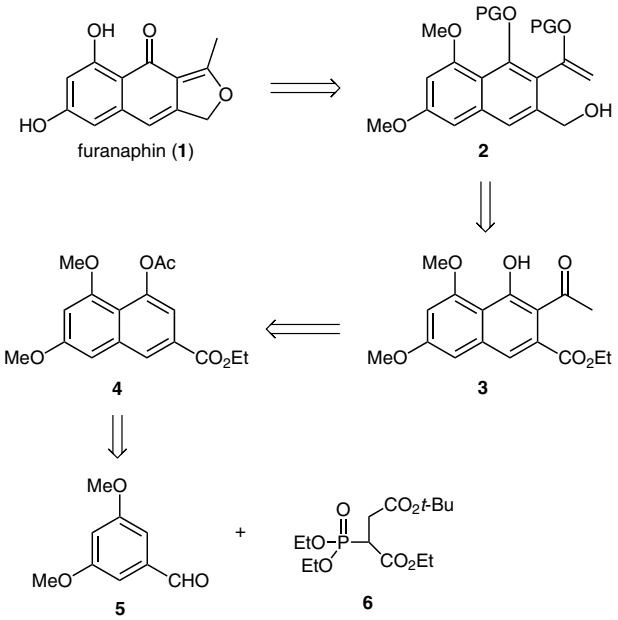
Abstract: The yellowish aphid pigment furanaphin, isolated from *Aphis spiraecola* and possessing cytotoxicity against HL-60 (human promyelocytic leukemia-60) cells, was synthesized by utilizing the Fries rearrangement assisted with a BF_3·2AcOH complex as a key step. It was confirmed that the complex effectively mediated the reaction even though the compounds had an electron-withdrawing substituent.

Key words: dyes, pigments, Fries rearrangement, total synthesis, natural products

Aphids produce novel polyketide pigments such as protoaphins (yellow pigments),[1–7] uroleuconaphines (yellow and red pigments),[8,9] viridaphin A_1 glucoside (green pigment),[10] furanaphin (**1**; yellow pigment having fluorescence),[11] and megouraphin glucosides (yellow pigments having fluorescence).[12] The presence of pigments is important for expressing aphid body color and, presumably, subtle differences in body coloration (color polymorphism) affect predator–prey interactions.[13] Currently, aphid coloration has generated interest from the perspectives of host–endosymbiont and evolutionary–coevolutionary relationships.[14,15] Furthermore, based on their cytotoxic and antibacterial activities, aphid pigments have been proposed to protect aphids from invasive species such as viruses, bacteria, and fungi.[10]

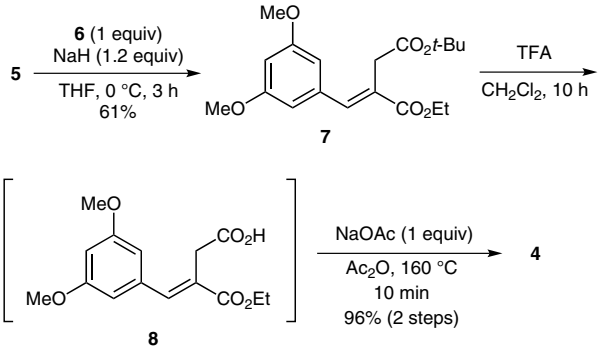
Furanaphin (**1**; Scheme 1) was isolated from *Aphis spiraecola* (max. 1.5 mm long) as a yellowish hydrophobic compound having a unique naphthofuran ring system, which was found to be active (IC_{50} 25 μM) against HL-60 cells.[11] To continue our investigations into the biological activities of **1**, including antiviral, antibacterial, and antifungal activities, an adequate supply of **1** was required. Herein, we report the total synthesis of **1** by utilizing the Fries rearrangement as a key step.

Our retrosynthetic analysis of **1** is illustrated in Scheme 1. Methyl ketone **3** would be used as a key intermediate in the synthesis of **1**. After selective reduction of the ethoxycarbonyl group of **3**, the resulting product **2** was expected to undergo spontaneous cyclization upon acidic treatment to generate the dihydrofuran ring. Fries rearrangement of acetate **4**, which could be afforded by Horner–Wadsworth–Emmons reaction of aldehyde **5** with **6** followed by intramolecular cyclization, would be used to prepare methyl ketone **3**.



Scheme 1 Retrosynthesis of **1**

For the preparation of rearrangement precursor **4** (Scheme 2), according to the method of Rizzacasa,[16] we chose 3,5-dimethoxybenzaldehyde (**5**) as a starting material and converted it into unsaturated ester **7** with *E* geometry at the double bond by the Horner–Wadsworth–Emmons reaction with **6** (61% yield). The *tert*-butyl group of ester **7** was removed by treatment with trifluoroacetic acid (TFA)



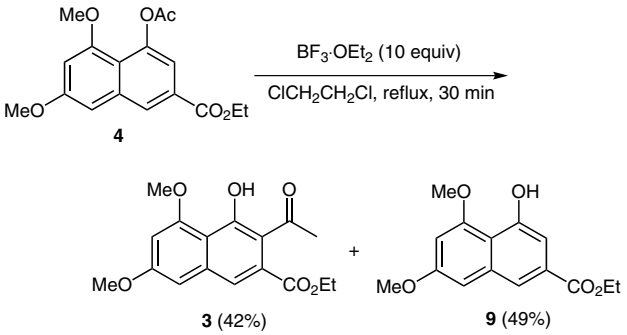
Scheme 2 Preparation of rearrangement precursor **4**

SYNLETT 2012, 23, 1789–1792
Advanced online publication: 29.06.2012
DOI: 10.1055/s-0031-1290429; Art ID: ST-2012-U0349-L

to give carboxylic acid **8**, without purification, which underwent cyclization to afford naphthalene derivative **4** through a mixed acid anhydride, in 96% yield (two steps).

With the desired precursor **4** in hand, we tried the Fries rearrangement[17] of acetate **4** using 10 equiv of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane heated to reflux for 30 min (Scheme 3). Although the desired product **3** was produced, the yield was only 42%, with 49% of hydrolyzed compound **9**.

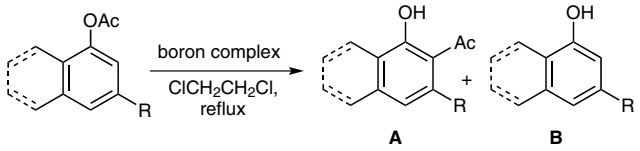
A previous study reported that the efficiency of the Fries rearrangement was decreased by the presence of an electron-withdrawing group.[18] In the course of our studies to refine the yield of the rearrangement, we found that the $BF_3{\cdot}2AcOH$ complex[19] assisted the reaction significantly. To confirm the generality and usefulness of this complex for the Fries rearrangement, we tested several compounds **4** and **10**–**13**. The results, shown in Table 1, compare the outcome of the reaction using this complex to those achieved with $BF_3{\cdot}OEt_2$.

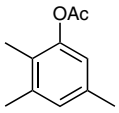
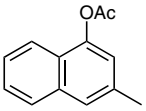
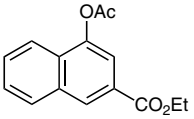
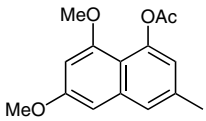
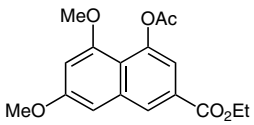


Scheme 3 Fries rearrangement of acetate **4**

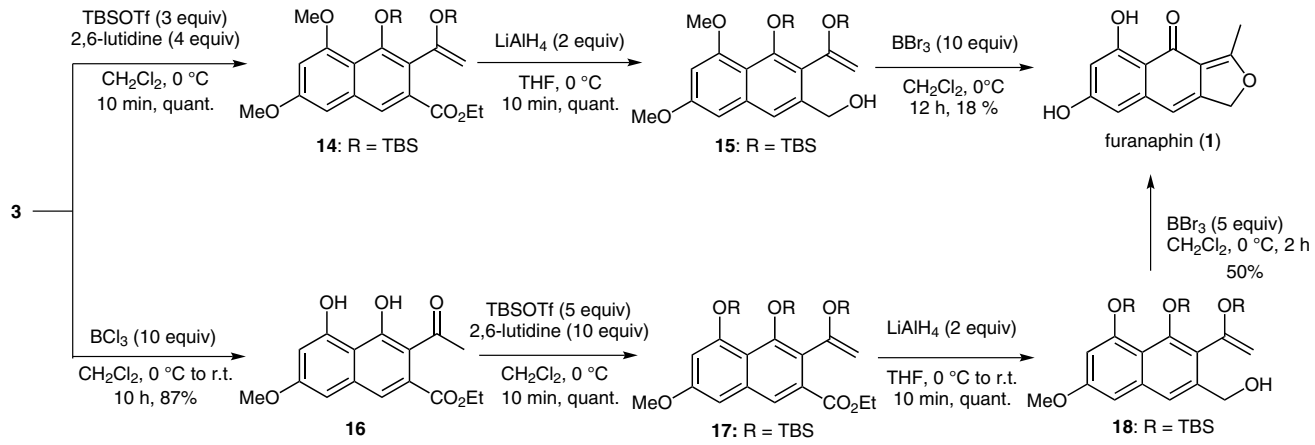
When $BF_3{\cdot}OEt_2$ was employed, we confirmed that the presence of electron-withdrawing groups retarded the efficiency of acyl migration dramatically (compare Table 1, entry 3 vs. entry 5 and entry 7 vs. entry 9), and the yields of the desired reaction products were low to moderate in all cases (entries 1, 3, 5, 7 and 9). In contrast, use of the

Table 1 Optimization of the Fries Rearrangement; Scope of Substrates and Comparison of BF_3 Complexes



Entry	Compounds	Conditions		Yield (%)	
		Boron (equiv)	Time (h)	**A**	**B**
1		$BF_3{\cdot}OEt_2$ (10)	24	34	27
2		$BF_3{\cdot}2AcOH$ (5)	3	92	–
	10				
3		$BF_3{\cdot}OEt_2$ (10)	15	50	44
4		$BF_3{\cdot}2AcOH$ (5)	2	98	–
	11				
5		$BF_3{\cdot}OEt_2$ (10)	24	15	68
6		$BF_3{\cdot}2AcOH$ (10)	12	74	2
	12				
7		$BF_3{\cdot}OEt_2$ (10)	0.5	63	32
8[a]		$BF_3{\cdot}2AcOH$ (10)	1	89	11
	13				
9		$BF_3{\cdot}OEt_2$ (10)	0.5	42	49
10[a]		$BF_3{\cdot}2AcOH$ (10)	0.5	91	8
	4				

[a] In CH_2Cl_2 at reflux.



Scheme 4 Synthesis of furanaphin (**1**)

BF_3·2AcOH complex made a remarkable difference (entries 2, 4, 6, 8 and 10), even for the reactions with substrates having an electron-withdrawing group (entries 6 and 10).

With the desired product **3** obtained in 91% yield (Table 1, entry 10),[20] the hydroxyl and acetyl groups of **3** were protected as a silyl ether and a silyl enol ether (TBSOTf, 2,6-lutidine in CH_2Cl_2), respectively (Scheme 4). Reduction of **14** with $LiAlH_4$ at 0 °C gave alcohol **15** in quantitative yield; subsequent treatment of **15** with BBr_3 cleaved the methyl and silyl ethers and induced spontaneous cyclization under acidic reaction conditions to give furanaphin (**1**) in 18% yield.

As an alternative route, selective cleavage of the methyl ether of **3** was carried out with BCl_3 to give **16**, which was silylated with TBSOTf (5 equiv) in the presence of 2,6-lutidine in CH_2Cl_2 to afford silyl enol ether **17** in quantitative yield. After reduction of **17**, the resulting alcohol **18** was subjected to cleavage of the ether linkages with BBr_3 to give **1**[21] in 50% yield. All spectroscopic data (^1H, ^{13}C NMR, IR, and HRMS) for the synthetic furanaphin (**1**) agreed with those reported previously in the literature.[11]

In summary, we have achieved the total synthesis of furanaphin (**1**) by utilizing the Fries rearrangement as a key step and found that the BF_3·2AcOH complex satisfactorily provided the desired product. Further applications of this reaction and biological activities of **1** are under investigation in our laboratory and will be reported in due course.

Acknowledgment

This work was supported partially by a Grant-in-Aid for Scientific Research (C) from MEXT (the Ministry of Education, Culture, Sports, Science and Technology of Japan). We are also thankful to MEXT-Senryaku, 2008-2012.

References and Notes

(1) Duewell, H.; Human, J. P. E.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *Nature* **1948**, *162*, 759.
(2) Brown, B. R.; Ekstrand, T.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *J. Chem. Soc.* **1952**, 4925.
(3) Cameron, D. W.; Cromartie, R. I. T.; Kingston, D. G. I.; Todd, L. *J. Chem. Soc.* **1964**, 51.
(4) Cameron, D. W.; Chan, H. W.-S.; Kingston, D. G. I. *J. Chem. Soc.* **1965**, 4363.
(5) Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. C* **1966**, 1825.
(6) Bowie, J. H.; Cameron, D. W.; Findlay, J. A.; Quartey, J. A. K. *Nature* **1966**, *210*, 395.
(7) Banks, H. J.; Cameron, D. W. *Aust. J. Chem.* **1972**, *25*, 2199.
(8) Horikawa, M.; Hashimoto, T.; Asakawa, Y.; Takaoka, S.; Tanaka, M.; Kaku, H.; Nishii, T.; Yamaguchi, K.; Masu, H.; Kawase, M.; Suzuki, S.; Sato, M.; Tsunoda, T. *Tetrahedron* **2006**, *62*, 9072.
(9) Horikawa, M.; Tanaka, M.; Kaku, H.; Nishii, T.; Tsunoda, T. *Tetrahedron* **2008**, *64*, 5515.
(10) Horikawa, M.; Hoshiyama, T.; Matsuzawa, M.; Shugyo, T.; Tanaka, M.; Suzuki, S.; Sato, M.; Ito, T.; Asakawa, Y.; Kaku, H.; Nishii, T.; Inai, M.; Takahashi, S.; Tsunoda, T. *J. Nat. Prod.* **2011**, *74*, 1812.
(11) Horikawa, M.; Noguchi, T.; Takaoka, S.; Kawase, M.; Sato, M.; Tsunoda, T. *Tetrahedron* **2004**, *60*, 1229.
(12) Horikawa, M.; Kikuchi, D.; Imai, T.; Tanaka, M.; Kaku, H.; Nishii, T.; Inai, M.; Takahashi, S.; Tsunoda, T. *Heterocycles* **2012**, *85*, 95.
(13) Losey, J. E.; Ives, A. R.; Harmon, J.; Ballantyne, F.; Brown, C. *Nature* **1997**, *388*, 269.
(14) Tsuchida, T.; Koga, R.; Horikawa, M.; Tsunoda, T.; Maoka, T.; Matsumoto, S.; Simon, J.; Fukatsu, T. *Science* **2010**, *330*, 1102.
(15) Moran, N. A.; Jarvik, T. *Science* **2010**, *328*, 624.
(16) (a) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1987**, *40*, 1737. (b) For an alternative synthetic route to **4**, see: Hauser, F. M.; Sengupta, D.; Corlett, S. A. *J. Org. Chem.* **1994**, *59*, 1967.
(17) (a) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1988**, *41*, 1087. (b) Singh, S. B.; Graham, P. L.; Reamer, R. A.; Cordingley, M. G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3143.
(18) Blatt, A. H. *Org. React.* **1942**, *1*, 342.
(19) The Fries rearrangement using the BF_3·2CH_3CO_2H complex was reported. The complex acts as an acyl donor, but the rearrangement of reactants having electron-withdrawing groups was not investigated, see: Davies, J. S. H.; McCrea, P. A.; Norris, W. L.; Ramage, G. R. *J. Chem. Soc.* **1950**, 3206.
(20) **Fries Rearrangement of 4**: To a solution of acetate **4** (104.1 mg, 0.327 mmol) in CH_2Cl_2 (0.5 mL) was added

BF_3·2AcOH (440 μL, 3.16 mmol) under an Ar atmosphere, and the resulting mixture was heated at reflux for 30 min. After addition of H_2O (3 mL) at 0 °C, the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 8:1) to give ethyl 3-acetyl-4-hydroxy-5,7-dimethoxy-2-naphthoate (**3**) in 91% yield as colorless crystals; mp 100–101 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (s, 1 H), 7.75 (d, *J* = 0.4 Hz, 1 H), 6.77 (d, *J* = 2.0 Hz, 1 H), 6.57 (d, *J* = 2.0 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 4.04 (s, 3 H), 3.90 (s, 3 H), 2.65 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7, 166.7, 159.0, 157.7, 152.2, 136.5, 128.4, 122.0, 120.7, 111.9, 100.5, 100.2, 61.5, 56.4, 55.5, 31.8, 14.0. IR (ATR): 3329, 1708, 1624, 1578, 1364, 1250, 1198, 1153, 1111, 1045 cm^{-1}. MS (EI): *m*/*z* (%)= 318 $[M]^+$, 303, 275 (100). HRMS (EI): *m*/*z* calcd for $C_{17}H_{18}O_6$: 318.1103; found: 318.1128.

(21) **Furanaphin (1)**: Orange-yellow needles (MeOH); mp 218–219 °C (MeOH) {Lit[11] 211–214 °C (dec)}. ^{1}H NMR (400 MHz, acetone-d_6): δ = 14.28 (s, 1 H), 9.17 (s, 1 H), 6.40 (dd, *J* = 2.4, 2.4 Hz, 1 H), 6.35 (d, *J* = 2.4 Hz, 1 H), 6.17 (d, *J* = 2.4 Hz, 1 H), 5.51 (d, *J* = 2.4 Hz, 2 H), 2.67 (s, 3 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 184.8, 184.3, 167.4, 164.7, 143.9, 143.5, 115.2, 111.7, 107.4, 104.7, 100.5, 77.6, 16.1. IR (ATR): 3333, 1650, 1569, 1382, 1170, 1153, 1130, 1085, 985, 887, 823 cm^{-1}. MS (EI): *m*/*z* (%) = 231 $[M+H]^+$, 230 (100) $[M]^+$. HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}O_4$: 230.0579; found: 230.0575.

