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Furanaphin: a novel naphtho[2,3-*c*]furan-4(1*H*)-one derivative from the aphid *Aphis spiraecola Patch*

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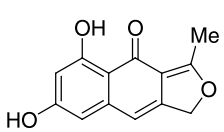
Abstract—A novel naphtho[2,3-*c*]furan-4(1*H*)-one derivative **1**, named furanaphin, was isolated from the aphid *A. spiraecola P*. The structure of the compound was established by a single crystal X-ray analysis of its (*S*)-MTPA ester. Furanaphin was found to have cytotoxicity against HL-60 human tumor cells.

1. Introduction

The extensive investigations of Todd followed by Cameron and their co-workers revealed that a number of aphids produced novel pigments such as xanthoaphins,[1–7] chrysoaphins,[1–9] erythroaphins,[1–5,10–21] protoaphins[1–4,7,9,20,22–31] and so on. Unfortunately, however, their extraordinary work stopped in the early 1980s. Since then hardly any studies of aphid pigments have been reported.[32] Therefore, we started chemical investigations of the pigments found in aphids, having an interest in biological activities and biological meaning for aphids themselves.

We focused at first on *Aphis spiraecola P*. which is a yellowish aphid (max. 1.5 mm long) feeding on *Polygonum cuspidatum* Sieb. et Zucc., since structures of yellowish substances in the aphid had not yet been studied. In our chemical study, a new naphtho[2,3-*c*]furan-4(1*H*)-one derivative, named furanaphin (**1**), together with 6-hydroxymusizin (**2**) was isolated as a yellowish hydrophobic compound. In this paper, we would like to describe the isolation of these compounds, their structure determination, and the cytotoxicity of **1** against HL-60 (leukemia) human tumor cells.



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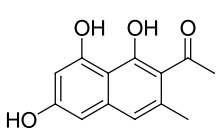

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2. Results and discussion

The aphid *A. spiraecola P*. was collected into a trap by suction with an aspirator in June in Tokushima Prefecture, Japan. The aphid was squashed in ether, and then the ethereal supernatant solution was separated by decantation. The residue was washed with several portions of fresh ether. The combined ethereal solutions were evaporated and subjected to silica-gel column chromatography to afford two yellow pigments **1** and **2**. The less polar compound **2** was identified as 6-hydroxymusizin from chemical and spectroscopic data.[33,34] On the other hand, **1**, isolated as yellow-hued crystals, mp 211–214 °C (dec), is in fact a new natural product, whose infrared spectrum in KBr indicated the presence of hydroxyl (3187 cm^{-1}, br) and intramolecularly-hydrogen-bonded carbonyl (1651 cm^{-1}) groups.

The noise-decoupled ^{13}C NMR spectrum of **1** clearly exhibited 13 carbon resonances, which were classified as one methyl, one methylene, three methines, and eight quaternary carbon atoms using distortionless enhancement by polarization transfer (DEPT) ^{13}C NMR analysis. From these results and the HREIMS (*m*/*z* 230.0570), the molecular formula of **1** was established as $C_{13}H_{10}O_4$. In the ^1H NMR spectrum, two hydroxy protons (14.28 and 9.27 ppm) were observed and the proton resonating at 14.28 ppm was hydrogen-bonded presumably with a carbonyl group. The heteronuclear multiple quantum coherence (HMQC) spectra of **1** (Table 1) revealed the

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Table 1. ^{13}C (150 Hz) and ^{1}H (600 Hz) NMR data of **1** in acetone-d_6

Position	δ_C	δ_H
1	77.5	5.51 (2H, d, *J*=2.6 Hz)
3	184.7	
3a	115.1	
4	184.3	
4a	111.6	
5	167.4	
6	100.5	6.18 (1H, d, *J*=2.2 Hz)
7	164.7	
8	104.7	6.35 (1H, d, *J*=2.2 Hz)
8a	143.9	
9	107.4	6.40 (1H, t, *J*=2.6 Hz)
9a	143.4	
3-CH_3	16.1	2.68 (3H, s)
5-OH		14.28 (1H, s)
7-OH		9.27 (1H, br s)

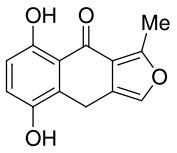
presence of an oxygen-bearing methylene carbon [C 77.5/H 5.51 (2H, d) ppm] and three aromatic and/or olefinic methine carbons [C 100.5/H 6.18 (1H, d) ppm], [C 104.7/H 6.35 (1H, d) ppm], and [C 107.4/H 6.40 (1H, t) ppm]. Furthermore, the carbon signal at 16.1 ppm together with the proton signal at 2.68 (3H, s) ppm hinted at a vinyl methyl group (Table 1), which was located on a particular structure.

The novel structure of **1** was also suggested by the presence of a peculiar olefinic carbon, whose ^{13}C NMR signal was shifted downfield by 184 ppm. That is, although one of the signals at 184.7 or 184.3 ppm can be easily assigned to an ordinary carbonyl carbon, the chemical shift of the other signal must be assigned to an olefinic carbon; this is a highly unusual shift for an olefinic carbon. Moreover, HMBC analysis revealed correlations between the methyl group at 2.68 ppm and carbons at 184.7 and 115.1 ppm. These data implied the existence of a particular α,β-unsaturated carbonyl group. However, it was hard to establish the structure of **1** by spectroscopic means in spite of detailed analyses of 1D and 2D NMR spectra involving $^{1}H-^{1}H$ COSY, NOESY, HMQC, and HMBC measurements.

Hence, **1** was converted to some derivatives (Scheme 1). However, the spectra of the acetate **3** gave very little information on the structure and the generation of **4** puzzled us. Further, no single crystals of **1**, **3** and **4** could be obtained.

Finally, the structure of **1** could be firmly established when a single crystal of (*S*)-MTPA ester **5** suitable for X-ray analysis was fortuitously obtained by the acylation employing (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) with DMAP in CH_2Cl_2.[35] The IR and ^{1}H NMR spectra of **5** suggested that the skeleton of the compound did not change in the reaction sequence. Figure 1 illustrates the molecular structure of **5** with the atomic numbering. Thus, the structure of furanaphin (**1**) was determined to be 5,7-dihydroxy-3-methylnaphtho[2,3-*c*]furan-4(1*H*)-one. In Figure 2, $^{13}C-^{1}H$ long range correlations in the HMBC spectrum of **1** are shown. The unusual carbon signal at 184.7 ppm can be now assigned to the C-3 olefinic carbon, the β-carbon of the carbonyl, bearing an ethereal oxygen atom.[36]

It was surprising that the aphid product **1** was an analogue of MS-444 (**6**), which was isolated from the culture broth of *Micromonosora* sp. and was found to possess inhibitory activity against myosin light chain kinase (IC_{50}=10 μM).[37,38] On the other hand, **6** at 430 μM showed no antimicrobial activity.[37]



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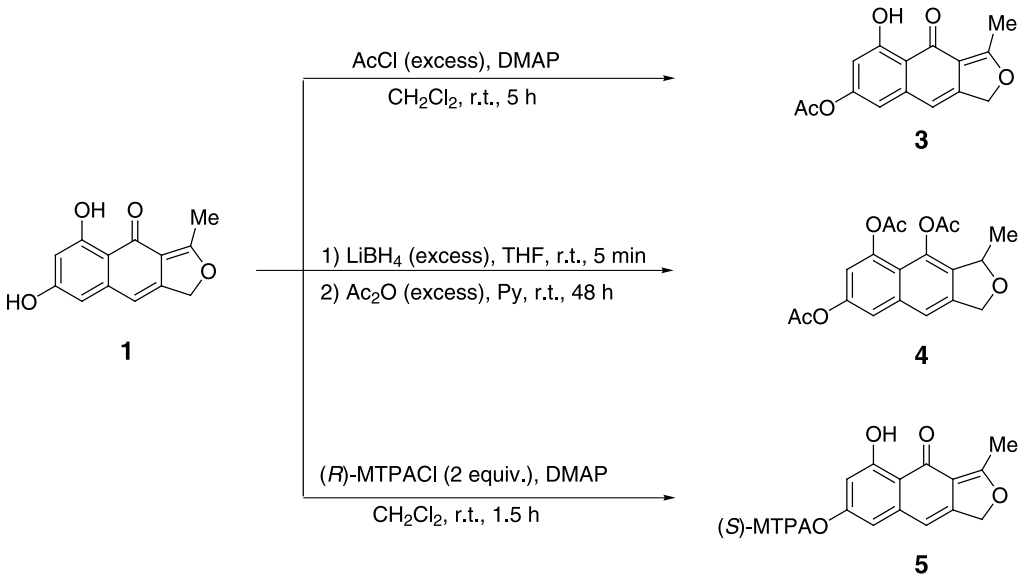
So, it was quite interesting to investigate how the difference of the substitution pattern of hydroxyl groups and the position of the olefin between **1** and **6** influenced biological activities. Hence, first of all, **1** was tested for its cytotoxicity against human promyelocytic leukemia HL-60 cells.[39] The



1 **3** **4** **5**

Scheme 1. Acylation of **1**.

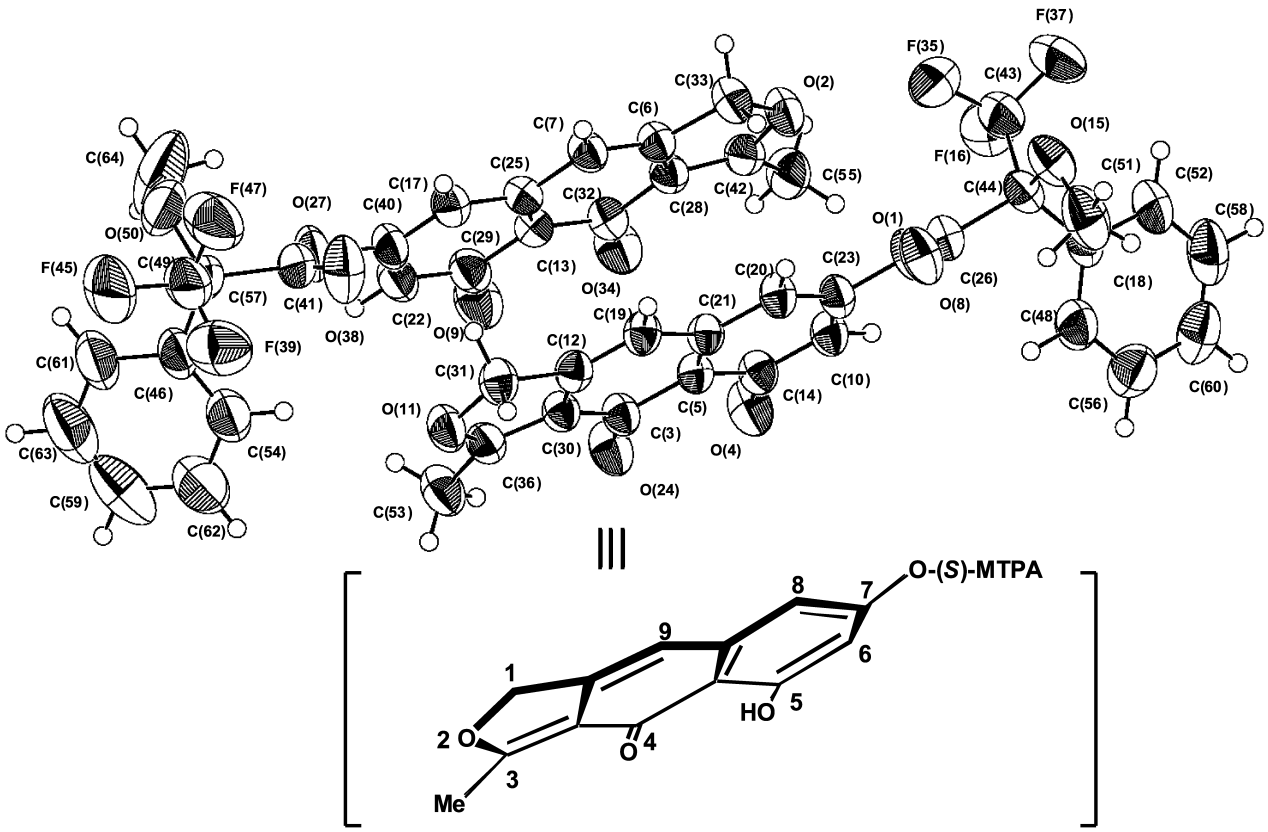


Figure 1. ORTEP structure of **5**.

result was shown in Figure 3, where **1** was found to be active with ED_{50} of 25 μM. This finding encouraged us to continue the investigation of its biological activities including the inhibitory activity against myosin light chain kinase.

3. Conclusion

Thus, **1** is an attractive substance, although we do not know yet the reason why the aphid produces such a novel compound. Further work on the biological activities of **1** and structure determination of other enchanting pigments of aphids is in progress.

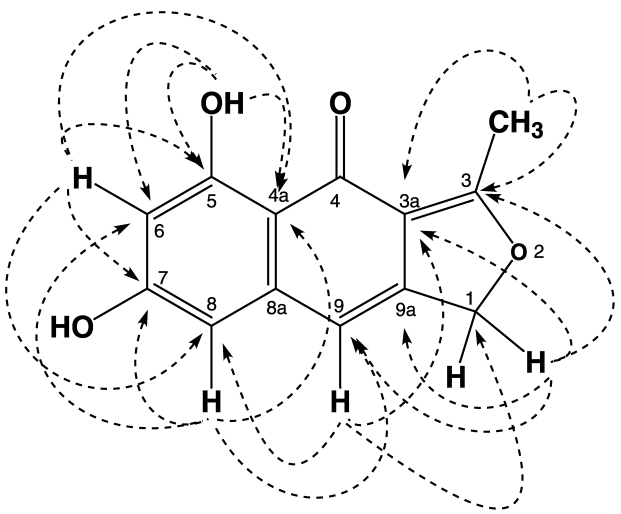
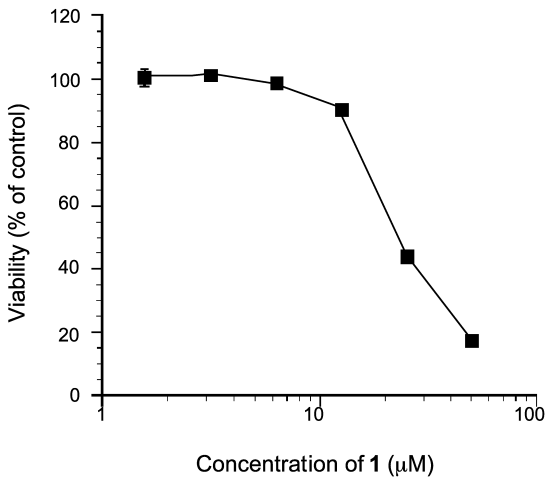


Figure 2. HMBC correlations of **1**.



HL-60 cells were treated with **1** at the indicated concentration for 24 h. Viability of the cells was determined by MTT assay. Data were means ± SD (n= 4).

Figure 3. Cytotoxicity of **1** in HL-60 cells.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-3

apparatus and were uncorrected. IR spectra were measured on a JASCO FT/IR-410 spectrophotometer. UV–visible spectra were measured on a Shimadzu UV-1650pc spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity-600 (600 MHz) with tetramethylsilane as an internal standard in acetone-d_6. ^{13}C NMR spectra were taken on the Varian Unity-600 (150 MHz); chemical shifts were referenced to the residual solvent signal (acetone-d_6: δ_C 29.8 ppm). Signal multiplicities were established by DEPT experiments. Mass spectra including high-resolution mass spectra were recorded on a JOEL JMX AX-500 spectrophotometer. Column chromatography was carried out with Silica gel 60N (Kanto Chemical Co. Inc., 63–210 μm). Acetyl chloride, acetic anhydride, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and pyridine were purchased from Nacalai Tesque Inc. $LiBH_4$ and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) were purchased from Aldrich Chemical Co. Inc. They were used without any purification. THF was distilled from sodium/benzophenone ketyl prior to use.

4.2. Material

The aphid *Aphis spiraecola P.* which were feeding on *Polygonum cuspidatum* Sieb. et Zucc., were collected in June in Tokushima Prefecture, Japan in 2001.

4.3. Extraction and isolation

The aphid (12.7 g) was squashed in diethyl ether, and then the ethereal supernatant solution was separated by decantation. The residue was washed with several portions of fresh ether. The combined ethereal solutions were dried over Na_2SO_4 and were evaporated to give a crude extract (0.69 g). The yellowish residue was subjected to silica-gel column chromatography (36 g) using hexane/AcOEt (3:1–1:3) as eluent to afford two yellow pigments **1** (65.4 mg) and **2** (17.2 mg).

4.3.1. Furanaphin (1). Yellow powder, mp 211–214 °C (dec). UV (CH_3CN) λ_{max} 210 (log ε 4.11), 274 (log ε 4.44), 433 (log ε 4.00) nm. IR (KBr): ν_{max} 3187 (–OH), 1651 (C═O), 1623, 1572, 1484, 1432, 1390 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) and ^{13}C NMR (150 MHz, acetone-d_6) see Table 1. MS (EI) *m/z* 230 (M^+), HRMS (EI) calcd for $C_{13}H_{10}O_4$ (M^+) 230.0579, found 230.0570.

4.3.2. 6-Hydroxymusizin (2). Yellow powder, mp 198.4–204 °C (dec). UV (EtOH) λ_{max} 233 (log ε 4.46), 271 (log ε 4.50), 389 (log ε 4.03) nm. IR (neat): ν_{max} 3349 (–OH), 2925, 1634 (C═O), 1588, 1382, 1154 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ 17.31 (1H, br s), 10.46 (1H, br s), 9.17 (1H, br s), 6.83 (1H, d, *J*=0.6 Hz), 6.53 (1H, d, *J*=2.4 Hz), 6.38 (1H, d, *J*=2.4 Hz), 2.74 (3H, s), 2.59 (3H, d, *J*=1.2 Hz). ^{13}C NMR (75 MHz, acetone-d_6): δ 204.8, 169.7, 162.4, 161.0, 141.1, 135.7, 121.0, 113.4, 108.1, 102.5, 101.9, 31.7, 24.7. MS (EI) *m/z* 232 (M^+), HRMS (EI) calcd for $C_{13}H_{12}O_4$ 232.0735, found 232.0737.

4.3.3. Monoacetate 3. A suspension of **1** (5.3 mg) in CH_2Cl_2 (9 mL) was treated with acetyl chloride (33 μL) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (~5.0 mg). The resulting mixture was stirred at ambient temperature for 4 h and then 8 mL of water was added. The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (4 g, hexane/AcOEt=5:1–1:1) to give 3.8 mg of the ester **3** as a yellow powder, mp 164–166 °C. UV (MeOH) λ_{max} 202 (log ε 4.22), 234 (log ε 4.26), 272 (log ε 4.14) nm. IR (neat): ν_{max} 2922, 1770 (C═O), 1650 (C═O), 1590 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 14.02 (1H, br s), 6.59 (1H, d, *J*=2.2 Hz), 6.52 (1H, d, *J*=2.2 Hz), 6.38 (1H, br t), 5.41 (2H, br d, *J*=1.8 Hz), 2.74 (3H, s), 2.31 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.3, 184.2, 168.8, 165.4, 155.7, 141.7, 141.6, 115.1, 114.9, 109.9, 107.0, 106.5, 76.7, 21.2, 16.5. MS (EI) *m/z* 272 (M^+), HRMS (EI) calcd for $C_{15}H_{12}O_5$ 272.0685, found 272.0655.

4.3.4. Triacetate 4. A solution of **1** (4.1 mg) in THF (3 mL) was treated with $LiBH_4$ (~2 mg) at ambient temperature for 0.1 h and then a saturated aqueous NH_4Cl (2 mL) solution was added. The resulting mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in 3 mL of pyridine and 3 mL of acetic anhydride. The mixture was stirred at ambient temperature for 48 h and then 3 mL of water and 3 mL of AcOEt was added. The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by repeated silica-gel column chromatography (3 g, hexane/AcOEt=3:1, 2.5 g, benzene/AcOEt=7:1) to give 1.6 mg of ester **4** as a white powder, mp 61.8–63.4 °C. IR (neat): ν_{max} 2925, 1770 (C═O), 1371 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54 (1H, s), 7.52 (1H, d, *J*=2.2 Hz), 6.98 (1H, d, *J*=2.2 Hz), 5.37 (1H, q, *J*=6.6 Hz), 5.25 (1H, dt, *J*=12.9, 1.2 Hz), 5.12 (1H, d, *J*=12.9 Hz), 2.40 (3H, s), 2.39 (3H, s), 2.33 (3H, s), 1.51 (3H, d, *J*=6.6 Hz), ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.0, 168.8, 168.5, 147.8, 145.9, 140.8, 138.8, 137.0, 134.8, 118.9, 118.1, 117.3, 116.1, 78.7, 71.4, 21.2, 20.9, 20.3. MS (EI) *m/z* 358 (M^+), HRMS (EI) calcd for $C_{19}H_{18}O_7$ 358.1053, found 358.1034.

4.3.5. (*S*)-MTPA ester 5. To a suspension of **1** (2.0 mg) in CH_2Cl_2 (7 mL) were successively added (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) (3.5 μL) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (~1.0 mg). The resulting mixture was stirred at ambient temperature for 3 h and then was quenched with water (3 mL). The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by silica-gel column chromatography (3 g, hexane/AcOEt=4:1) to give 2.0 mg of ester **5** as yellow plates (AcOEt/hexane), mp 200–203 °C (dec). IR (neat): ν_{max} 1762 (C═O), 1653 (C═O), 1596, 1464, 1370 cm^{-1}. ^{1}H NMR (600 MHz, acetone-d_6): δ 14.37 (1H, s), 7.71 (1H, dd), 7.55–7.59 (3H, m), 6.80 (1H, d, *J*=2.2 Hz), 6.61 (1H, t, *J*=2.2 Hz), 6.54 (1H, d, *J*=2.2 Hz), 5.65 (2H, d, *J*=2.2 Hz), 3.75 (3H, d, *J*=1.1 Hz), 2.77 (3H, s). ^{13}C NMR (150 MHz, acetone-d_6): δ 188.6, 184.8, 166.4, 165.3, 155.4, 144.5, 143.5, 132.7, 130.9, 129.6, 128.1, 125.3, 123.4, 115.9, 115.7, 109.9, 106.8, 105.8, 78.6, 56.3, 16.7. MS (EI) *m/z* 446 (M^+), HRMS (EI) calcd for $C_{23}H_{17}F_3O_6$ 446.0978, found 446.0974.

Table 2. Crystal data and experimental conditions

Chemical formula/formula weight	$C_{23}H_{17}F_3O_6$/446.377
Crystal system/Space group	Triclinic/*P*1
Z	2
a, *b*, *c* (Å)	7.145(4), 7.308(5), 20.095(2)
α (°)	94.238(2)
β (°)	93.703(3)
γ (°)	106.892(2)
V (Å^3)	997.18(12)
D_x (Mg m^{-3})	1.487
Diffractometer	MXC18
Radiation	Mo Kα
λ (Å)	0.71073
μ (Mo Kα) (mm^{-1})	0.125
Crystal description/crystal dimensions (mm^3)	Cube /0.35×0.3×0.2
T (K)	298
θ_{max} (°)	25.80
Range of *h*, *k*, and *l*	$0\leq h\leq 8$, $-8\leq k\leq 8$, $-24\leq l\leq 24$
Reflections: independent/observed	3320/3048
$R(F)(I>3\sigma(I))/wR(F^2)(I>3\sigma(I))$	0.0534/0.1365
S	1.120
$\Delta\rho$ (e Å^{-3})	−0.346, 0.310

4.4. X-ray analysis of 5

The compound **5**, ($C_{23}H_{17}F_3O_6$), FW=446.377, crystallized from AcOEt/hexane in a triclinic system of the space group *P*1. The crystal data and the experimental details are summarized in Table 2. The structure of **5** was solved by the direct method with the program SHELXL97.[40,41] The structure was refined by the full-matrix least squares method with the program maXus.[42] The weighting scheme was $w=1/(\sigma^2(F_o^2)+0.10000F_o^2)$ for **5**. Positions of several hydrogen atoms were obtained on difference maps and those of the others were calculated geometrically. The anisotropic and isotropic temperature factors were applied to non-hydrogen atoms and hydrogen atoms in the final refinement, respectively. The positional parameters of the hydrogen atoms were constrained to have the C–H distances of 0.96 Å. Atomic scattering factors were taken from the International Tables for Crystallography.[43] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 220660. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.5. Cytotoxic activity

HL-60 (human promyelocytic leukemia-60) cells were grown in suspension culture and incubated at 37 °C in RPMI-1640 medium supplemented with 10% FBS and glutamine (2 mM). The cytotoxicity of **1** in HL-60 cells was analyzed by colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay with some modification.[39] HL-60 (1×10^4 cells) were plated on 96-well plates and allowed to adhere at 37 °C in 5% CO_2/95% air for 1 h. Then 50 μL of serial concentration of test compound **1** was added and the cells incubated for 24 h. After 24 h, 10 μL of MTT (5 mg/mL: stock solution) was added and the cells were incubated for an additional 4 h. Following this time the cells were lysed and the dark blue crystals solubilized with 100 μL of 20% sodium dodecyl sulfate in 0.01 N HCl. The optical density (OD) of each well was measured with a microplate spectrophotometer equipped with a 570 nm filter. The results of cytotoxic activity are expressed as ED_{50} (The concentration of compound that inhibited cell line replication by 50%). The ED_{50} of **1** was 25 μM.

Acknowledgements

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