Supplementary Material (ESI) for Chemical Communications

(Electronic Supplementary Information)

One-pot Synthesis of Furocoumarins through Cascade Addition-Cyclization-Oxidation

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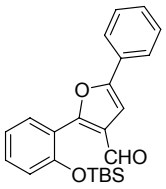
General details :

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm from internal TMS (δ). Melting points (uncorrected) were determined on a Buchi-510 capillary apparatus. High resolution mass spectra were recorded on a Finnigan MAT 95 mass spectrometer (ESI) and a Finnigan-4201 spectrometer (EI). Column chromatography was performed with 200-300 mesh silica gel using flash column techniques. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

General experimental procedures for the synthesis of furocoumarins:

Synthesis of **4**: A solution of of **3** (60 mg, 0.24 mmol), CH_3SO_3H (0.025 mL, 0.38 mmol) and H_2O (0.04 mL, 2.2 mmol) in DMF (1.5 mL) was heated at 90℃ for 0.5 h, and then $CuCl_2$ (67mg, 0.50 mmol) was added. The reaction mixture was stirred at 90℃ for 20 h at the same temperature. After complete consumption of the intermediate as determined by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was washed with water (30 mL × 3) and brine (10 mL) and then dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by column chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 57 mg (89%) of compound **4.**

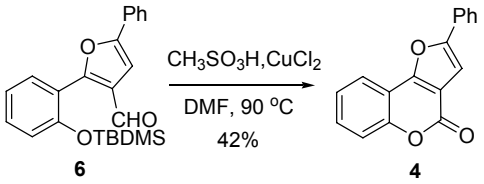
Formation of 6 by protect intermediate D with TBSCl



Compound **6**

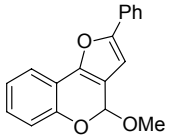
A mixture of **3** (60 mg, 0.24 mmol), CH_3SO_3H (0.025 mL, 0.38 mmol) and H_2O (0.04 mL, 2.2 mmol) in the DMF (2 mL) was stirred at 90□ for 1 h. The mixture was diluted with ethyl acetate (30 mL), and washed with water (30 mL × 3) and brine (10 mL), dried over $MgSO_4$, and evaporated to afford intermediate as a coffee solid. The mixture of this solid, TBDMSCl (41 mg, 1.2 equiv) and imidazole (23 mg, 1.5 equiv) in DMF was stirred for 2 h, diluted with ethyl acetate (30 mL) and washed with water (30 mL × 3) and brine (10 mL). After the organic layer was dried over $MgSO_4$ and concentrated, the residue was purified by flash chromatography (silica gel, 15:1 petroleum ether/ethyl acetate) to afford 72 mg of **6** (80% from **3**) as a colorless colloid. ^{1}H NMR ($CDCl_3$): δ = 9.92 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.53 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.46-7.37 (m, 3H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.16-7.09 (m, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 0.83 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 186.90, 159.27, 154.56, 153.83, 131.53, 129.61, 128.74, 128.25, 125.58, 124.18, 121.64, 120.89, 120.81, 102.66, 25.49, 18.05, -4.55; MS (EI): m/z 378 (M^+, 8), 321 (100), 293 (25), 247 (23); HRMS (EI) m/z calcd for (M^+) $C_{23}H_{26}O_3Si$: 378.1651; found: 378.1651.

Formation of furocoumarin(4) from (6)



A mixture of **6** (27.3 mg, 0.072 mmol), CH_3SO_3H (0.03 mL, 0.46 mmol) and $CuCl_2$ (21.3 mg, 0.158 mmol) in DMF (2 mL) was stirred at 90□ for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), washed with water (30 mL × 3) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. 8 mg of **4** (42%) was obtained after flash chromatograph.

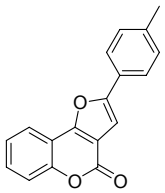
Synthesie of 3-Phenylethynyl-4*H*-benzopyran-4-one (7) using this acid catalyzed method.



Compound **7**[1].

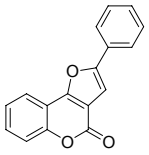
A mixture of **3** (90 mg, 0.37 mmol), CH_3SO_3H (0.038 mL, 0.58 mmol) and CH_3OH (1 mL, 2.2 mmol) in dry DMF (2 mL) was stirred at 90□ for 10 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), washed with water (30 mL × 3) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. 99 mg (97%) of **7** was obtained. ^{1}H NMR ($CDCl_3$): δ = 7.77-7.72 (m, 2H), 7.65 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.45-7.38 (m, 2H), 7.21-7.33 (m, 2H), 7.06-7.12 (m, 2H), 6.74 (s, 1H), 6.34 (s, 1H), 3.56 (s, 3H). The characterization data of 7 is identical with the report in the literature.

Synthesis of substituted furocoumarins



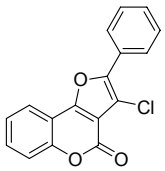
Compound **2a**

Followed the general procedures and purified by flash chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 59 mg of **2a** (89%) as a white solid: m.p. 205-206℃; ^{1}H NMR ($CDCl_3$): δ = 7.95 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.52 (td, *J* = 7.7, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.37 (td, *J* = 7.7, 1.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 158.22, 156.83, 156.51, 152.47, 139.28, 130.38, 129.63, 126.16, 124.47, 124.43, 120.68, 117.28, 112.75, 112.47, 101.81, 21.36; MS (EI): m/z 276 (M^+, 100); Elemental analysis (%) calcd for $C_{18}H_{12}O_3$: C 78.25, H 4.38; found: C 77.92, H 4.38.



Compound **4**[2]

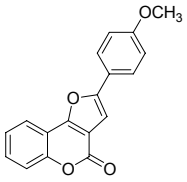
Followed the general procedure and purified by flash chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 57 mg of compound **4** (89%) as a white solid: m.p. 175-176℃; ^{1}H NMR ($CDCl_3$): δ = 7.98 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.58-7.48 (m, 4H), 7.44-7.36 (m, 2H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 158.02, 156.59, 156.35, 152.37, 130.45, 128.99, 128.86, 128.66, 124.43, 124.31, 120.60, 117.17, 112.49, 112.84, 102.42. MS (EI): m/z 262 (M^+, 100); IR (KBr): ν=1734, 1631, 1487, 1425, 1056, 962, 916, 746cm^{-1}; Elemental analysis (%) calcd for $C_{17}H_{10}O_3$: C 77.85, H 3.84; found: C 77.58, H 3.88.



Compound **4a**

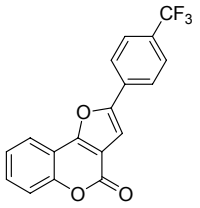
A mixture of **3** (60 mg, 0.24 mmol), CH_3SO_3H (0.025 mL, 0.38 mmol) and H_2O (0.04 mL, 2.2 mmol) and $CuCl_2$ (67 mg, 0.50 mmol) in the DMF (1.5 mL) was stirred at 90□ for 20 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), washed with water (30 mL × 3) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. 22 mg of **4** (35%) and 29 mg of **4a** (40%) was obtained after flash chromatograph (silica gel, 2:1 petroleum ether/CH_2Cl_2). **4a:** ^{1}H NMR ($CDCl_3$): δ = 8.10-8.04 (m, 2H), 7.95 (dd, *J* = 8.0, 1.6 Hz,

1H), 7.61-7.36 (m, 6H). ^{13}C NMR ($CDCl_3$): δ = 156.00, 155.20, 152.39, 149.56, 131.20, 129.24, 128.65, 127.49, 125.36, 124.62, 120.60, 117.13, 111.84, 110.00, 109.92; MS (EI): m/z 296 (M+, 100), 297 (32), 298 (18);



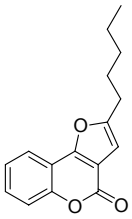
Compound **9a**

Followed the general procedures and purified by flash chromatography (silica gel, 2:1 petroleum ether/ethyl acetate) to afford 51.8 mg of **9a** (74%) as a white solid: m.p. 181-183℃; ^{1}H NMR ($CDCl_3$): δ = 7.95 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.52 (td, *J* = 7.8, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.38 (td, *J* = 7.8, 1.6 Hz, 1H), 7.05 (s, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 160.36, 156.74, 156.31, 152.42, 130.23, 126.08, 124.44, 121.76, 120.57, 117.27, 114.43, 112.79, 112.56, 100.88, 55.35; MS (EI): m/z 292 (M^+, 84), 277 (62), 149 (47), 135 (100); Elemental analysis (%) calcd for $C_{18}H_{12}O_4$: C 73.97, H 4.14; found: C 73.88, H 4.43.



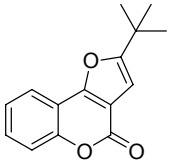
Compound **9b**

Followed the general procedures and purified by flash chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 57 mg of **9b** (72%) as a white solid: m.p. 204-206℃. ^{1}H NMR ($CDCl_3$): δ = 7.98 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.57 (td, *J* = 7.8, 1.6 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.40 (td, *J* = 7.8, 1.6 Hz, 1H), 7.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 157.81, 157.44, 154.78, 152.72, 131.98, 131.10, 130.82, 130.50, 126.04, 126.00, 125.15, 124.69, 124.54, 122.49, 120.86, 117.43, 112.37, 104.64; MS (EI): m/z 330 (M^+, 100); HRMS (EI) m/z calcd for (M^+) $C_{18}H_9F_3O_3$: 330.0504; found: 330.0501.



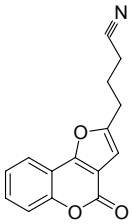
Compound **9c**

Followed the general procedures and purified by flash chromatography (silica gel, 3:1 petroleum ether/CH_2Cl_2) to afford 37 mg of **9c** (60%) as a colorless colloid: ^{1}H NMR ($CDCl_3$): δ = 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.49 (td, *J* = 7.8, 1.7 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.33 (td, *J* = 7.7, 1.7 Hz, 1H), 6.58 (s, 1H), 2.795 (t, *J* = 7.5 Hz, 2H), 1.76 (m, 2H), 1.39 (m, 4H), 0.93 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 159.97, 158.25, 156.31, 152.10, 129.91, 124.20, 120.38, 117.00, 112.75, 111.26, 103.12, 31.05, 27.86, 27.16, 22.19, 13.81; MS (EI): m/z 256 (M^+, 32), 199(100); HRMS (EI) m/z calcd for (M^+) $C_{16}H_{16}O_3$: 256.1099; found: 256.1107.



Compound **9d**

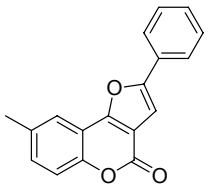
Followed the general procedures and purified by flash chromatography (silica gel, 8:1 petroleum ether/ ethyl acetate) to afford 45 mg of **9d** (77%) as a a white solid: m.p. 132-134℃. ^{1}H NMR ($CDCl_3$): δ = 7.86 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 6.56 (s, 1H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$): δ = 167.56, 158.40, 156.32, 152.16, 129.93, 124.16, 120.44, 117.02, 112.83, 111.04, 100.56, 33.01, 28.67; MS (EI): m/z 242 (M^+, 27), 227(100); HRMS (EI) m/z calcd for (M^+) $C_{15}H_{14}O_3$: 242.0943; found: 242.0947.



Compound **9e**

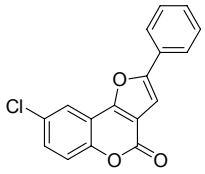
Followed the general procedures and purified by flash chromatography (silica gel, 3:1 petroleum ether/ ethyl acetate) to afford 39 mg of **9e** (64%) as a white solid: m.p.

75-77℃; ^{1}H NMR ($CDCl_3$): δ = 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.52 (td, *J* = 7.8, 1.7 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.35 (td, *J* = 7.7, 1.7 Hz, 1H), 6.69 (s, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.14 (m, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 157.85, 156.80, 156.74, 152.10, 130.33, 124.32, 120.41, 118.70, 116.98, 112.37, 111.04, 104.47, 26.63, 23.44, 16.34; MS (EI): m/z 253 (M^+, 32), 199 (100), 149 (38); HRMS (EI) m/z calcd for (M^+) $C_{15}H_{11}NO_3$: 253.0739; found: 253.0739.



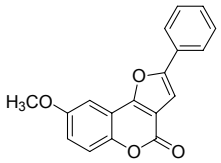
Compound **9f**

Followed the general procedures and purified by flash chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 45 mg of **9f** (72%) as a white solid: m.p. 164-166℃; ^{1}H NMR ($CDCl_3$): δ = 7.78 (d, *J* = 7.6 Hz, 2H), 7.70 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.30 (m, 2H), 7.13 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (100M, $CDCl_3$): δ = 158.29, 156.71, 156.23, 150.63, 134.34, 131.53, 128.95, 128.87, 128.80, 124.33, 120.32, 116.91, 112.21, 112.18, 102.47, 20.85; MS (EI): m/z 276 (M^+, 100); Elemental analysis (%) calcd for $C_{18}H_{12}O_3$: C 78.25, H 4.38; found: C 78.11, H 4.42.



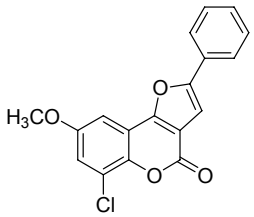
Compound **9g**

Followed the general procedures and purified by flash chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 50 mg of **9g** (70%) as a white solid: m.p. 215-216℃; ^{1}H NMR ($CDCl_3$): δ = 7.93 (d, *J* = 2.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.53-7.37 (m, 5H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 157.53, 157.19, 155.38, 150.77, 130.45, 130.11, 129.39, 129.04, 128.54, 124.57, 120.22, 118.76, 113.68, 113.116, 102.65; MS (EI): m/z 296 (M^+, 100), 297 (32), 298 (18); Elemental analysis (%) calcd for $C_{17}H_9ClO_3$: C 66.82, H 3.06; found: C 68.75, H 3.02.



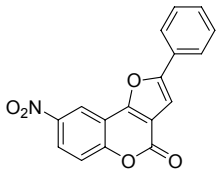
Compound **9h**

Followed the general procedures and purified by flash chromatography (silica gel, 1:1 petroleum ether/CH_2Cl_2) to afford 26 mg of **9h** (37%) as a white solid and 16 mg of byproduct (20%). **9h**: m.p. 170-172℃; ^{1}H NMR ($CDCl_3$): δ = 7.79 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.14 (s, 1H), 7.06 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 158.28, 156.65, 156.48, 156.25, 147.01, 129.08, 128.94, 128.83, 124.47, 118.51, 118.46, 112.85, 112.59, 102.70, 102.65, 55.88; MS (EI): m/z 292 (M^+, 100), 277(26), 249(24); Elemental analysis (%) calcd for $C_{18}H_{12}O_4$: C 73.97, H 4.14; found: C 73.92, H 4.37.



Byproduct

^{1}H NMR ($CDCl_3$): δ = 7.83 (m, 2H), 7.50 (m, 2H), 7.43 (m, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.20 (s, 1H), 7.19 (d, *J* = 2.8 Hz, 1H), 3.93 (s, 3H); MS (EI): m/z 326 (M^+, 100).



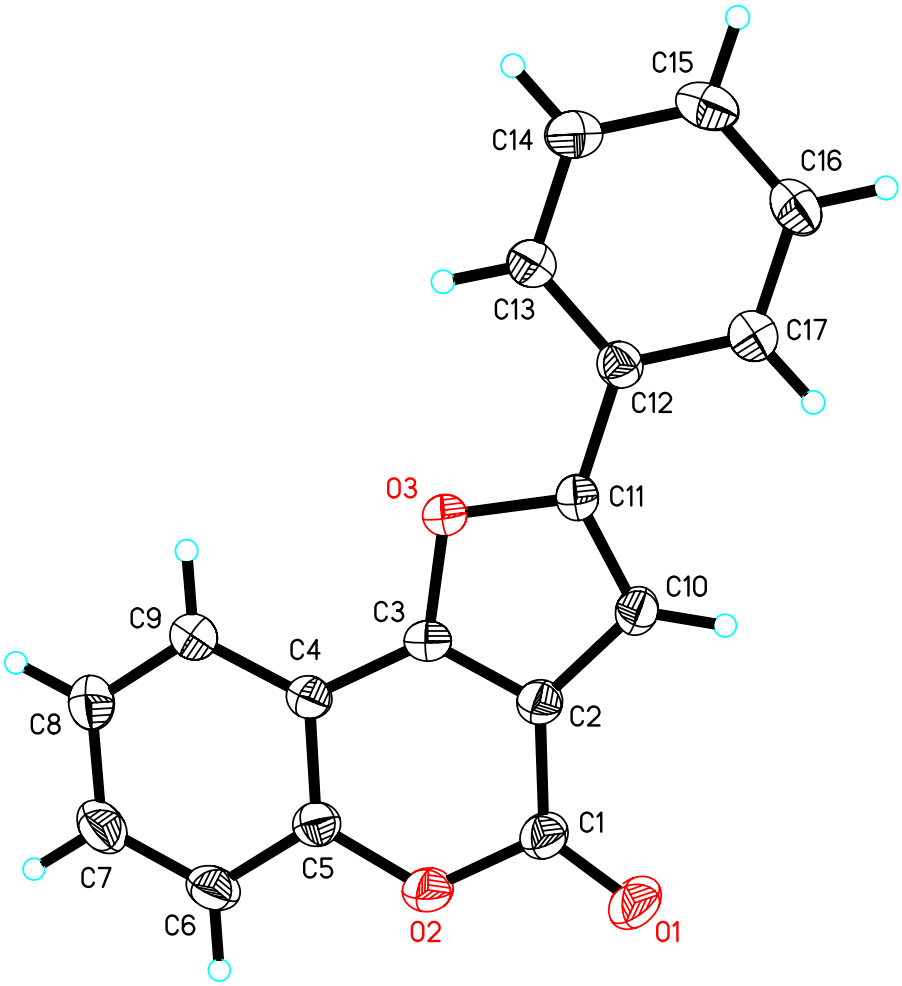
Compound **9i**

After a mixture of **8j** (30 mg, 0.10 mmol), CH_3SO_3H (0.13 mL, 0.20 mmol) and H_2O (0.03 mL, 2.2 mmol) in the DMF (1 mL) was stirred at 90□ for 2 h (until TLC analysis indicate complete conversion), $CuCl_2$(40 mg, 0.30 mmol) was added and the reaction mixture was stirred for 120□ to continue for 40 h. After the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (40 mL), filtered through a short pad of silica, concentrated, and filtered, then washed with

THF and $CHCl_3$ to afford 16 mg (51%) of **9i** as light yellow solid: m.p. 278-280℃; ^{1}H NMR ($CDCl_3$): δ = 8.87 (d, *J* = 2.3 Hz, 1H), 8.39 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.57-7.42 (m, 3H), 7.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 158.23, 156.59, 155.55, 154.97, 144.19, 129.86, 129.22 128.27, 125.16, 124.86, 118.50, 116.98, 113.86, 113.12, 102.71; MS (EI): m/z 307 (M^+, 100), 261(24); HRMS (EI) m/z calcd for (M^+) $C_{17}H_9NO_5$: 307.0481; found: 307.0487.

References

1. T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164;
2. a) S. Tollari, G. Palmisano, S. Cenini, G. Cravotto, G. B. Giovenzana, A. Penoni, *Synthesis*, **2001**, *5*, 735. b) K. Kobayashi, K. Sakashita, H. Akamatsu, K. Tanaka, M. Uchida, T. Uneda, T. Kitamura, O. Morikawa, H. Konishi, *Heterocycles,* **1999,** *51*, 2881.



View of **4.** Ellipsoid probability: 50%.