by evaporation under reduced pressure. The residue was fractionally distilled. Compound V in 1.86 g, 57% yield, was obtained. ^{1}H NMR ($CDCl_3$) δ: 1.04 (m, 2H), 1.29 (d, 3H, J=7 Hz), 2.02 (d, 4H, J=6.9 Hz), 2.95 (m, 1H), 3.48 (s, 3H), 3.51 (s, 3H), 3.56 (s, 6H), 4.42 (t, 1H, J=1.3 Hz), 6.94-6.97 (m, 1H), 7.08-7.15(m, 2H). ^{13}C NMR ($CDCl_3$) δ: 15.01, 15.59, 22.78, 24.99, 34.09, 50.76, 50.98, 51.04, 124.19, 127.24, 129.15, 136.68, 139.17, 146.68. IR (neat) ν: 3030, 2950, 2800, 2170 (vs, Si-H), 1605, 1560, 1480, 1450, 1190, 1100(br), 955, 835(br), 795, 660 cm^{-1}. MS m/e (relative intensity): 326 (M^+, 69), 309 (34), 294[(M-CH_3OH)$^+$, 48], 283 (35), 276 (52), 262(37), 247 (34), 221(M^+-SiH$(OMe)_2CH_2$, 71), 204 (40), 189 (79), 162 (37), 129 (29), 121 (92), 91 [$(SiH(OMe)_2)^+$, 85], 83 (100), 79 (29). Elemental Anal. Cacld. for $C_{15}H_{26}Si_2O_4$: C, 55.19; H, 8.03. Found: C, 55.40; H, 8.11. Compound V was containing 3,4-[2'-(dimethoxysilyl)isopropyl]benzo-1,1-dimethoxy-1-silacyclopentene V' in 14% on the base of ^{1}H NMR spectrum.

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Synthesis of Pyrazinopsoralen: A Pyrazine Ring Fused Monofunctional Psoralen Derivative

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An efficient synthesis of 6,8-dioxa-1,4-diazacyclopenta[b]phenanthren-5-one (Pyrazinopsoralen) (**4**) has been carried out by the Suzuki coupling reaction as a key step starting from 5-bromo-6-methoxybenzofuran (**6**) and methyl 2-iodo-3-pyrazinecarboxylate (**8**).

Introduction

Psoralens have a wide range of photobiological properties. They have shown photosensitizing effects in animals and humans and have been used in PUVA (psoralen + UVA: 320-400 nm) photochemotherapy[1~4] for the treatment of psoriasis, vitiligo, mycosis fungoides, and chronic leukemia. They are known to be phototoxic to insects, fungi, viruses, and bacteria.[5~8] Psoralens are also used as powerful tools in nucleic acid research consequences of defined lesions in DNA.[9,10]

Psoralen (Ps, **1**) is the parent structure of a relatively large number of furocoumarins in which the rings are linearly fused (Figure 1). Their biological properties have been attributed to their ability to photoreact with nucleic acids, especially DNA.[11] It appears that the genotoxic effects, as well as the therapeutically important antiproliferative effects, are due mainly to their capacity to induce photoconjugation to DNA. The modification of DNA by psoralens is a two-step process:[12,13] (a) formation of a molecular complex in the ground state; (b) photoconjugation of the complexed psoralen to pyrimidine bases of DNA, particularly thymine.[11] However, undesirable effects involving the photomutagenecity and photocarcino-

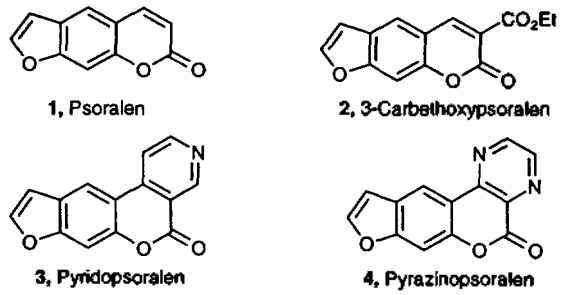
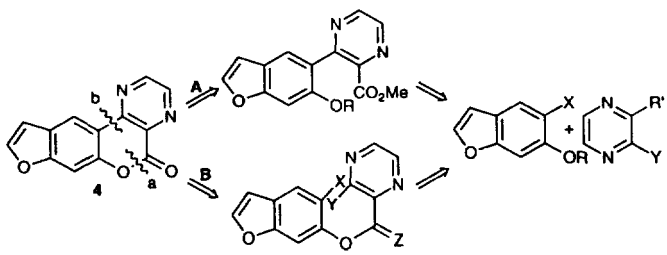


Figure 1

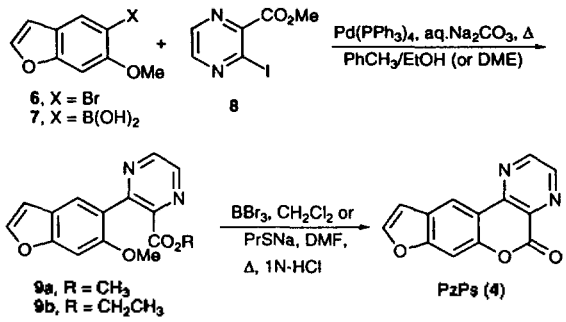
genicity have been observed in many studies,[14] and as a result, a search for new photoreactive and less genotoxic psoralen derivatives has become a main issue.[15]

For this reason, many efforts have been expended to develop furocoumarins which permit only monofunctional photobinding with DNA and thereby diminish undesirable side effects. This has been accomplished by using angular furocoumarins such as 4,5′-dimethylangelicin which does not allow interstrand DNA cross-link for geometric reasons,[16] by blocking the photoreactive α-pyrone double bond with appropriate substituents[17] such as 3-carbethoxypsoralen (3-CPs, **2**), and by annelation of an additional aromatic ring such as pyridopsoralen (PyPs, **3**).[18,19,20] 3-CPs (**2**) has been known to form only 4′,5′-monoadduct with 5,6-double bond of thymine[21] and thymidine[22] because of its bulky carbethoxy substituent. The photoreaction of 3-CPs is proposed to proceed *via* the triplet excited state[23] as evidenced by its high triplet quantum yield (Φ_T>0.35) compared to 8-methoxypsoralen (8-MOP) (Φ_T~0.06). Because of its monofunctional character, it shows little mutagenic and no carcinogenic activity against yeast.[24] However, using of 3-CPs for photosensitizing drug was limited by photo-instability and relative high efficiency of $^1O_2$ formation. PyPs (**3**) can form only 4′,5′-monoadduct with DNA due to the pyridine ring fused at 3,4-double bond[25] and showed lower phototoxic effect. PyPs has relatively low triplet quantum yield (Φ_T~0.02),[26] and the photoreaction of PyPs is thought to proceed *via* its singlet excited state. However, an evidence for the formation of triplet PyPs in DNA-intercalated complex is reported recently.[27] The 365 nm irradiation of PyPs-thymidine and of PyPs-DNA aqueous solution was found to lead to the formation of cyclobutane thymidine dimer, in addition to 4′,5′-monoadduct. The thymine dimer formation proceeds *via* triplet energy transfer from PyPs to thymine because the triplet energy of PyPs is higher than Ps due to pyridine fusion and becomes high enough to transfer energy to thymine, and consequently the thymine dimer production increases significantly. In general, the singlet excited state can react most rapidly at the 4′,5′-furan position, while the triplet state is predicted to react most effectively at the 3,4-pyrone position.[28,29]

This point being very important for an interpretation of various photobiological properties of furocoumarins, it seemed of interest to perform further studies with new monofunctional psoralen derivatives whose structures rule out the possibility of DNA cross-linking. Pyrazinopsoralen (PzPs, **4**) having a fused pyrazine ring on the 3,4 site should be a compound of choice because PzPs is expected to give little genotoxic effect[14] and great proximity effect[30] leading to high triplet state quantum yield. Herein, we describe a simple and convenient synthesis of monofunctional furocoumarin, PzPs.



Scheme 1. Disconnection Approach of PzPs (**4**).

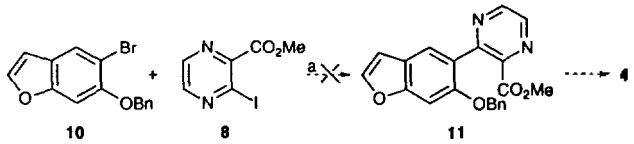


Scheme 2. Synthesis of **4** *via* Suzuki Coupling Reaction.

Several routes were designed to synthesize PzPs. In the course of work directed toward the synthesis of PzPs, the benzofuran moiety can be readily obtained through Worden's procedure[31] and the pyrazine moiety can be prepared from commercially available material.[32] As shown in the retrosynthetic strategy for PzPs in Scheme 1, disconnection of carbon-carbon atoms (path A) reveals a potential palladium-catalyzed cross coupling reaction[33,34] followed by demethylative lactonization and disconnection of the carbon-oxygen atoms (path B) reveals a potential ester formation[35] followed by cyclization of the intermediate using palladium catalyst. We now report the efficient synthesis of PzPs in good yields utilizing palladium catalyst.

Results and Discussion

We have studied the synthesis of the tetracyclic skeleton of PzPs through the palladium-mediated Suzuki coupling reaction[33] followed by demethylative lactonization (Scheme 2). 5-Bromo-6-methoxybenzofuran (**6**) was obtained from 2,4-dihydroxybenzaldehyde by the known procedure.[31a] Treatment of bromobenzofuran **6** with *n*-BuLi followed by trimethoxyborane in tetrahydrofuran (THF) at −78 ℃ readily afforded the corresponding boronic acid **7** in good yields. Methyl 3-amino-2-pyrazinecarboxylate was converted to methyl 3-iodo-2-pyrazinecarboxylate (**8**) through the procedure of Sandmeyer reaction.[36] The desired compound **9** was successfully synthesized by the condensation of boronic acid **7** with methyl carboxylate **8** by the palladium-catalyzed Suzuki coupling.[33] Transesterification accompanied the reaction and **9a** : **9b** was formed in a ratio of 4 : 1 determined by ^{1}H NMR analysis. When boronic acid **7** was treated with

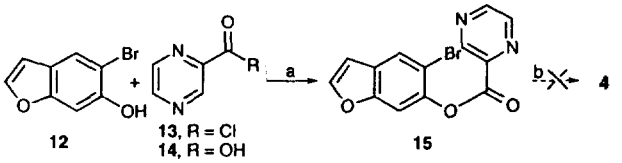


10 **8** **11**

[a]The attempted conditions of Ullmann reaction

10 (mmol)	8 (mmol)	Cu (mmol)	catalyst
1	1	2	none
1	1	2	$Pd(PPh_3)_4$
1	2	4	$Pd(PPh_3)_4$
1	1	2	$Pd(PPh_3)_4 + PPh_3$
1	1	2	$Pd(OAc)_2 + PPh_3$

Scheme 3. Synthetic Approach *via* Ullmann Coupling Reaction[a].



12 **13**, R = Cl; **14**, R = OH **15**

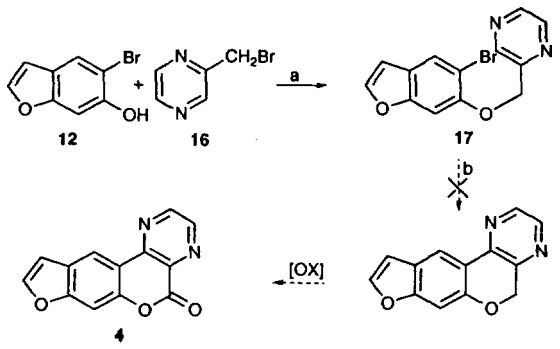
[a]The reaction conditions: (a) (i) K_2CO_3, Me_2CO, or (ii) DCC, DMAP, CH_2Cl_2; (b) $PdCl_2(PPh_3)_2$, DMA, Δ; $PdCl_2(PPh_3)_2$, Et_3N, DMA, Δ; $PdCl_2(PPh_3)_2$, NaOAc, DMA, Δ; or $Pd(OAc)_2$, PPh_3,DMF, Δ.

Scheme 4. Synthetic Approach of **4** *via* Ester Formation[a].

methyl iodocarboxylate **8** under the modified Suzuki cross-coupling condition,[33e] only **9a** was formed in 67% yield. Deprotection of the methyl ether of **9** with boron tribromide in methylene chloride[37] or sodium propanethiolate (*n*-PrSNa) in dimethylformamide[38] (DMF) afforded PzPs (**4**) directly in 53% and 50% three-step overall yield, respectively. The structure was assigned based on the following spectroscopic and mass data: (a) The methyl ether moiety was disappeared in the ^1H NMR spectrum; (b) Two-dimensional ^1H-^{13}C correlation spectrum (in $CDCl_3$) of PzPs (**4**) showed that the vinyl carbon (δ 147.31, 106.84 ppm) and aromatic carbon peaks (δ 149.76, 145.55, 117.58, 100.41 ppm) in the ^{13}C dimension corresponded to the vinyl (δ 7.74, 6.92 ppm) and aromatic protons (δ 8.98, 8.88, 8.80, 7.56 ppm) in the ^1H dimension; (c) The GC/MS spectrum showed molecular ion peak at m/z 238 (M^+, 100%).

We have also investigated the synthesis of the tetracyclic skeleton of PzPs through several other routes: (1) the intermolecular cross Ullmann coupling reaction (Scheme 3);[34] (2) the palladium-catalyzed aromatic coupling by dehydrohalogenation *via* ester-linkage (Scheme 4); and (3) ether-linkage (Scheme 5).[35]

The first attempted route involves an intermolecular cross Ullmann coupling (Scheme 3). The Ullmann biaryl synthesis has been used successfully for the preparation of ester containing biaryls in many previous examples.[34] 6-Benzyloxy-5-bromobenzofuran (**10**), which is available from β-resorcylaldehyde,[31] was chosen as the starting material. The coupling reactions were attempted under various conditions at reflux in the presence of excess copper bronze and a catalytic amount of palladium (0) in DMF. But, neither of these procedures was successful for effecting the coupling, and only reduced reactants were obtained. Probably the ortho substituents of the respective moieties result in a severe steric hindrance to prevent the desired coupling reaction.



12 **16** **17** **4**

[a]The reaction conditions: (a) K_2CO_3, Me_2CO; (b) $PdCl_2(PPh_3)_2$, DMA, Δ; $PdCl_2(PPh_3)_2$, NaOAc, DMA, Δ; or $Pd(OAc)_2$, PPh_3, DMF, Δ.

Scheme 5. Synthetic Approach of **4** *via* Ether Formation[a].

Ames and Opalko reported[35] the synthesis of benzocoumarin *via* intramolecular dehydrohalogenative coupling using a palladium (II) catalyst under a basic condition. Debenzylation[39] of benzyloxy benzofuran **10** gave 5-bromo-6-hydroxybenzofuran (**12**) in 60% yield. 5-Bromobenzofuran-6-yl 2-pyrazinecarboxylate (**15**) was readily prepared either *via* acid chloride **13**[40] or dicyclohexylcarbodiimide (DCC)-mediated method of carboxylic acid **14**.[41] The DCC method is preferred to the acid chloride method in regard to yield and convenience. Synthetic attempts of PzPs (**4**) through palladium catalyzed intramolecular coupling reaction under various reaction conditions using pyrazinecarboxylate (**15**) was not successful and hydrolysis of the ester linkage was mainly observed, probably due to the electron deficiency of pyrazine moiety (Scheme 4).

The third route involved an intramolecular aromatic coupling by dehydrohalogenation *via* ether-linkage (Scheme 5).[35] 2-Bromomethylpyrazine (**16**) was synthesized from 2-methylpyrazine by bromination with *N*-bromosuccinimide (NBS) and a catalytic amount of benzoyl peroxide. 2-(5-Bromobenzofuran-6-yloxymethyl)pyrazine (**17**) was prepared through the coupling of hydroxybenzofuran **12** and bromopyrazine **16** under a basic condition. Intramolecular coupling reaction was studied for the ether **17** under various conditions using palladium (II) catalyst. The desired compound was not produced and only the reactants were recovered.

In conclusion, we have efficiently synthesized PzPs (**4**) through the Suzuki coupling reaction employing palladium catalyst. The synthesized PzPs is expected to give interesting photobiological properties due to high triplet state quantum yield. Studies on photochemical and photobiological activities of the title compound are under progress in this laboratory.

Experimental Section

General Procedures. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AM-500, AM-300, and AM-200 MHz spectrometers. Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS), and ^{13}C re-

sonances were recorded using the 77.0 ppm $CDCl_3$ resonance of the solvent as an internal reference and reported in ppm downfield from TMS. Infrared (FTIR) spectra were recorded on a Bomem MB-100 Series FTIR spectrophotometer. Mass spectra were determined at 70 eV with a Hewlett-Packard 5985A GC/MS spectrometer by the electron impact (EI) method. Melting points were determined in capillary tubes on a Thomas Hoover capillary melting point apparatus.

All reactions were run under a dry nitrogen or argon atmosphere in oven-dried glassware, unless specified otherwise. Reagent grade THF, benzene, and toluene were distilled from sodium benzophenone ketyl under nitrogen immediately prior to use. Reagent grade methylene chloride, toluene, DMF, and 1,2-dimethoxyethane (DME) were distilled under nitrogen from calcium hydride. Bulk grade hexane was distilled prior to use. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used as analytical TLC. Gravity column chromatography and flash chromatography was carried out on silica gel (230-400 mesh from Merck).

6-Methylbenzofuran-5-boronic Acid (7). To a 17 mL THF solution of 5-bromo-6-methoxybenzofuran (**6**) (755 mg, 3.33 mmol) was added 1.6 mL (4.0 mmol) of 2.5 M *n*-BuLi in THF at −78 ℃ under argon atmosphere. The mixture was kept at the temperature for 30 min and treated with $B(OMe)_3$ (1.0 mg, 9.98 mmol),[33b] followed by acidic work-up (5% aqueous hydrochloric acid).[33c] The organic phase was extracted with ethyl acetate, dried over magnesium sulfate, and concentrated by a rotavapor. The residue was recrystallized from ethyl acetate in hexane to give the boronic acid **7** as a solid (594 mg, 93%), mp 156-158 ℃; ν_{max} (NaCl)/cm^{-1} 3236 (BOH), 1619, 1435, 1335, 1195, 1142, 1038 and 1020; δ_H (200 MHz; $CDCl_3$) 8.08 (1H, s, 4-H), 7.53 (1H, d, *J* 2.2, 2-H), 7.04 (1H, s, 7-H), 6.71 (1H, d, *J* 2.2, 3-H) 5.96 (2H, s, 2×OH) and 3.94 (3H, s, OCH_3); δ_C (50 MHz, $CDCl_3$) 162.82 (C), 157.95 (C), 144.42 (CH), 144.23 (C), 129.72 (CH), 121.17 (C), 106.58 (CH), 93.91 (CH), 55.82 (OCH_3) m/z 192 (M^+, 21%), 149 (36), 148 (74), 133 (100), 105 (19) and 62 (52).

Methyl 3-iodopyrazine-2-carboxylate (8). In a 100 mL flask fitted with stirring bar are placed 6.1 mL of concentrated hydrochloric acid and 2 g (13.06 mmol) of methyl 3-aminopyrazine-2-carboxylate. After brief stirring, 4 g of ice water was added and the flask is surrounded by an ice-salt bath. The solution is then diazotized by the dropwise addition with stirring of a solution of 991 mg (14.37 mmol) of sodium nitrite in 2-3 mL of water, the temperature being kept at 0-5 ℃. After stirring the diazotized solution for 15 min, it was slowly poured into a solution of 8.68 g (52.24 mmol) of potassium iodide in 9.2 mL of water. After standing overnight, the heavy dark oil was separated, washed successively with 10% aqueous sodium hydroxide, water, 5% aqueous sodium bisulfate and water, dried over magnesium sulfate and concentrated by a rotavapor. Purification of the residue by column chromatography on silica gel (eluent: 30% ethyl acetate in hexane) gave the pure methyl carboxylate **8** as a colorless solid (860 mg, 25%), mp 30-31 ℃; ν_{max}(NaCl) /cm^{-1} 3030, 2956, 1742, 1550, 1445, 1381, 1298, 1203, 1152 and 1067; δ_H (200 MHz, $CDCl_3$) 8.54 (1H, d, *J* 2.2, 5-H), 8.49 (1H, d, *J* 2.2, 6-H) and 3.99 (3H, s, OCH_3); δ_C (50 MHz, $CDCl_3$) 163.16 (CO), 146.92 (C), 145.29 (CH), 143.70 (C), 141.49 (CH) and 52.87 (CH_3).

Methyl 3-(6-methoxybenzofuran-5-yl)pyrazine-2-carboxylate (9a) and Ethyl 3-(6-methoxybenzofuran-5-yl) pyrazine-2-carboxylate (9b). Method A. To a stirred solution of methyl carboxylate **8** (588 mg, 2.23 mmol) in toluene (22 mL) under nitrogen was successively added tetrakis(triphenylphosphine)palladium(0) (77 mg, 0.067 mmol), aryl boronic acid **7** (470 mg, 2.45 mmol) dissolved in a minimum volume of ethanol, and aqueous sodium carbonate solution (2.2 mL, 2 M in deoxygenated water). The resulting mixture was heated in an oil bath at 110 ℃ with stirring for 8 h, cooled, subjected to filtration. The filtrate was evaporated to dryness *in vacuo* and the residue was treated with brine. The resulting mixture was extracted with methylene chloride, dried over magnesium sulfate, and evaporated to dryness to give products (total 65%) which were purified and isolated by flash chromatography on silica gel (eluent: 30% ethyl acetate in hexane). Methyl carboxylate **9a** (310 mg, 49%), mp 97-98.5 ℃; ν_{max}(NaCl)/cm^{-1} 3116, 2950, 2840, 1736 (CO), 1624, 1473, 1436, 1389, 1306, 1259, 1200, 1144, 1106 and 1027; δ_H (200 MHz, $CDCl_3$) 8.68 (1H, d, *J* 2.4, 5-H), 8.48 (1H, d, *J* 2.3, 6-H), 7.78 (1H, s, 4-H), 7.49 (1H, d, *J* 2.2, 2-H), 6.98 (1H, s, 7-H), 6.68 (1H, d, *J* 2.8, 3-H), 3.76 (3H, s, CH_3) and 3.68 (3H, s, OCH_3); δ_C (50 MHz, $CDCl_3$) 165.96 (CO), 156.46 (C), 154.37 (C), 151.56 (C), 145.45 (CH), 145.34 (C), 144.40 (CH), 140.91 (CH), 123.31 (C), 122.87 (CH), 120.84 (C), 106.56 (CH), 93.89 (CH), 55.12 (OCH_3) and 52.29 (OCH_3); m/z 284 (M^+, 44%), 225 (100), 210 (27), 197 (24), 158 (17), 127 (10) and 102 (11.6); [Found: M^+, 284.0805 (18.3%). $C_{15}H_{12}N_2O_4$ requires M, 284.0797]. Ethyl carboxylate **9b** (107 mg, 16%), mp 111-113 ℃; ν_{max}(NaCl)/cm^{-1} 3115, 2950, 2840, 1732 (CO), 1624, 1473, 1435, 1388, 1315, 1259, 1199, 1144, 1104 and 1025; δ_H (200 MHz, $CDCl_3$) 8.73 (1H, d, *J* 2.2, 5-H), 8.54 (1H, d, *J* 2.4, 6-H), 7.79 (1H, s, 4-H), 7.54 (1H, d, *J* 2.2, 2-H), 7.02 (1H, s, 7-H), 6.73 (1H, d, *J* 2.1, 3-H), 4.24 (2H, q, OCH_2), 3.73 (3H, s, OCH_3) and 1.16 (3H, t, CH_3); δ_C (50 MHz, $CDCl_3$) 165.69 (CO), 156.59 (C), 154.60 (C), 151.83 (C), 145.85 (C), 145.41 (CH), 144.51 (CH), 141.18 (CH), 123.72 (C), 122.89 (CH), 120.92 (C), 106.70 (CH), 93.98 (CH), 61.64 (OCH_2), 55.33 (OCH_3) and 13.88 (CH_3); m/z 298 (M^+, 35%), 239 (16), 225 (100), 210 (25), 197 (28), 158 (13), 127 (7.5) and 102 (7.8); [Found: M^+, 298.0944 (87.9%). $C_{16}H_{14}N_2O_4$ requires M, 298.0954].

Method B. This Suzuki coupling was carried out using the Gronowitz modification.[33e] A mixture of methyl carboxylate **8** (1.26 g, 4.77 mmol), tetrakis(triphenylphosphine)palladium (0) (157 mg, 0.136 mmol), and boronic acid **7** (830 mg, 4.32 mmol) in DME (11 mL) with sodium carbonate (4.3 mL of 2 M in deoxygenated water) was stirred and heated to reflux (85-90 ℃) for 7.5 h until methyl 3-iodopyrazine-2-carboxylate (**8**) was not detectable on TLC. The mixture was cooled to room temperature and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and then purified by flash chromatography on silica gel using 30% ethyl acetate in hexane as eluent to give 823 mg (67%) of methyl carboxylate **9a**. The physical and spectroscopic properties of this product **9a** agreed well with those of method A.

6,8-Dioxa-1,4-diazacyclopenta[b]phenanthren-5-one (Pyrazinopsoralen) (4). Method A. A solution of 1.2 mmol of ester **9a** (or **9b**) in 12 mL of methylene chloride

was added over 5 min to a stirred solution of 7 mL (13.2 mmol) of boron tribromide in 20 mL of methylene chloride at −78 ℃. The reaction was kept at −78 ℃ for 30 min, allowed to warm to 0 ℃ over 30 min, kept at 0 ℃ for 10 min, and then poured into a mixture of ice and concentrated ammonium hydroxide. After the mixture stirred for 30 min, the layers were separated, the aqueous fraction was saturated with sodium chloride and extracted with 60 mL of methylene chloride, and the combined organic extracts were washed with brine. Drying over magnesium sulfate, evaporation, and column chromatography of the residue on silica gel using 40% ethyl acetate in hexane as eluent afforded 242 mg (85%) of PzPs (**4**) as a solid, mp 240-242 ℃ (decomposed); ν_{max}(NaCl)/cm^{-1} 3118, 3066, 3034, 1742 (CO), 1537, 1466, 1385, 1310, 1201, 1152, 1084, and 1014; δ_H (500 MHz, $CDCl_3$) 8.98 (1H, d, *J* 1.9, 2-H), 8.88 (1H, d, *J* 1.7, 3-H), 8.80 (1H, s, 11-H), 7.74 (1H, d, *J* 2.2, 9-H), 7.56 (1H, s, 7-H) and 6.92 (1H, d, *J* 2.1, 10-H); δ_C (125 MHz, $CDCl_3$) 159.15 (CO), 157.23 (C), 150.29 (C), 149.76 (CH), 148.96 (C), 147.31 (CH), 145.55 (CH), 133.13 (C), 125.66 (C), 117.58 (CH), 114.47 (C), 106.84 (CH) and 100.41 (CH); DEPT (90 or 135 deg) methine carbons: 149.77 (2-C), 147.31 (9-C), 145.55 (3-C), 117.57 (11-C), 106.84 (10-C) and 100.41 (7-C); m/z 238 (M^+, 100%), 210 (59), 154 (30) and 127 (21); [Found: M^+, 238.0371 (30.5%). $C_{13}H_6N_2O_3$ requires M, 238.0378].

Method B. To a DMF (0.1 mL) solution of **9a** (34 mg, 0.12 mmol) at 25 ℃ was added a DMF (1 mL) solution of sodium propanethiolate (*n*-PrSNa) prepared by treating propanethiol (65 mL, 0.72 mmol) with sodium hydride (21 mg, 0.48 mmol) at 25 ℃ for 15 min. The reaction mixture was heated at 115 ℃ for 3 h, then cooled to 25 ℃ and acidified (*ca.* pH 4) with 1 N aqueous hydrochloric acid solution after dilution with methylene chloride. The organic phase was separated, dried over magnesium sulfate, concentrated. The residue was purified by column chromatography on silica gel (eluent: 40% ethyl acetate in hexane) to give 23 mg (0.097 mmol, 81%) of PzPs (**4**) as a solid. The spectra of this product were consistent with those of method A.

6-Benzyloxy-5-bromobenzofuran (10). This compound, prepared from β-resorcylaldehyde following the procedure of Worden *et al.*[31] Analytical and spectroscopic data for the compound **10** were as follows: Compound **10**, mp 53-55 ℃; ν_{max}(NaCl)/cm^{-1} 3118, 3064, 3032, 2916, 2869, 1616, 1532, 1458, 1385, 1300, 1190, 1148 and 1027; δ_H (300 MHz, $CDCl_3$) 7.76 (1H, s, 4-H), 7.52 (1H, d, *J* 2.3, 2-H), 7.47-7.30 (5H, m, Ph), 7.09 (1H, s, 7-H), 6.64 (1H, d, *J* 2.17, 3-H) and 5.17 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$) δ 154.61 (C), 152.39 (C), 144.88 (CH), 136.30 (C), 128.53 (CH), 127.90 (CH), 126.99 (CH), 124.57 (CH), 121.94 (C), 107.94 (C), 105.78 (CH), 97.52 (CH) and 71.17 (CH); m/z 304 (MH^{+1}, 2.1%), 302 (2.5), 223 (2.1), 165 (2.0), 92 (7.6) and 91 (100); [Found: M^+, 301.9927 (100%). $C_{15}H_{11}O_2Br$ requires M, 301.9942].

5-Bromo-6-hydroxybenzofuran (12). 6-Benzyloxybenzofuran **10** (1.7 g, 4.66 mmol) was dissolved in 30 mL of absolute ethanol placed in 100 mL flask and immersed in water bath at 25 ℃. A gentle stream of nitrogen was passed through the reaction mixture and thorough sonication (or agitation) was provided. 10% palladium-carbon (1.7 g) was added and followed by the addition of 1,4-cyclohexadiene (4.4 mL, 46.58 mL). The mixture was heated at 50 ℃ for 2 h, then filtered through celite, washed with methylene chloride, and evaporated *in vacuo*. Purification of the residue by column chromatography on silica gel (eluent : 15% diethyl ether in hexane) gave the 5-bromobenzofuran-6-ol (**12**) as a solid (590 mg, 59%), mp 74-76 ℃; ν_{max} (NaCl)/cm^{-1} 3246 (OH), 3104, 3059, 1615, 1536, 1443, 1322, 1279, 1180, 1143, 1112 and 1029; H(300 MHz, $CDCl_3$) 7.67 (1H, s, 4-H), 7.51 (1H, d, *J* 2.2, 2-H), 7.17 (1H, s, 7-H), 6.62 (1H, d, *J* 2.2, 3-H) and 5.54 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 155.09 (C), 149.40 (C), 145.06 (CH), 123.10 (CH), 122.14 (C), 106.09 (C), 105.66 (CH) and 98.81 (CH); m/z 214 (MH^{+1}, 100%), 212 (93), 132 (10.2), 91 (20.6) and 76 (15); [Found: M^+, 211.9501 (100%). $C_8H_5O_2Br$ requires M, 211.9473].

Pyrazine-2-carboxylic Acid 5-Bromobenzofuran-6-yl Ester (15). Method A. 2-Pyrazinecarboxylic acid (3.7 g, 29.81 mmol) was dissolved in benzene (50 mL) and thionyl chloride (6.5 mL, 89.43 mmol) and this mixture was refluxed for 2 h, after which benzene and excess thionyl chloride were distilled off as an azeotrope. The prepared pyrazine-2-carbonyl chloride (**13**) was transferred to a flask containing 50 mL of methylene chloride and the hyrdoxybenzofuran **12** (5.08 g, 23.85 mmol) in 50 mL methylene chloride was added at 0 ℃ under nitrogen atmosphere. The reaction mixture was stirred at 0 ℃ for 1 h, allowed to warm to room temperature, and stirred overnight. The mixture was washed with aqueous $CuSO_4$ solution (2×50 mL), followed by water (50 mL) and brine (2×50 mL). The organic phase was dried over anhydrous magnesium sulfate. The solvent was then evaporated *in vacuo* to give the crude product. The solid was chromatographed with 20% ethyl acetate in hexane to give 7.6 g of ester **15** (23.85 mmol, 80%) as a white solid, mp 132.5-134 ℃; ν_{max}(NaCl)/cm^{-1} 3111, 3040, 2925, 1756 (CO), 1531, 1453, 1278, 1147, 1113, 1089 and 1017; δ_H (300 MHz, $CDCl_3$) 9.55 (1H, d, *J* 1.40, 5-H), 8.88 (1H, s, 3-H), 8.86 (1H, d, *J* 1.42, 6-H), 7.89 (1H, s, 4-H), 7.69 (1H, d, *J* 2.22, 2-H), 7.53 (1H, s, 7-H) and 6.77 (1H, d, *J* 2.22, 3-H); δ_C (75 MHz, $CDCl_3$,) 161.90 (CO), 153.69 (C), 148.32 (CH), 147.08 (CH), 146.93 (CH), 144.79 (CH), 144.35 (C), 142.54 (C), 127.46 (C), 124.72 (CH), 110.21 (C), 107.04 (CH) and 105.99 (CH); m/z 320 (MH^+, 7.3%), 318 (6.8), 240 (22.1), 239 (100), 211 (9.3), 107 (72.3) and 79 (90.1); [Found: M^+, 317.9668 (11.6%). $C_{13}H_7O_3N_2Br$ requires M, 317.9641].

Method B. 2-Pyrazinecarboxylic acid (470 mg, 3.78 mmol) was dissolved to a flask containing the DCC (661 mg, 3.20 mmol) and catalytic amount of 4-dimethylaminopyridine (DMAP) (36 mg, 0.29 mmol) in 15 mL of methylene chloride and hydroxybenzofuran **12** (600 mg, 2.91 mmol) was added in this solution. The mixture was to stir and warm to room temperature for 1 h. The mixture was filtered and the N,N'-dicyclohexylurea (DCU) washed with cold methylene chloride. Flash chromatography (eluent: 20% ethyl-acetate in hexane) yield 857 mg (92%) of desired product **15** as a solid. The physical and spectroscopic properties of method B product agreed with those of method A.

2-(5-Bromo-benzofuran-6-yloxymethyl)-pyrazine (17). A mixture of the 2-methyl pyrazine (1 g, 10.62 mmol), NBS (2.1 g, 11.68 mmol), and benzoyl peroxide (100 mg) dissolved in carbon tetrachloride (50 mL) was refluxed under sunlamp for 2 h. The reaction solution was cooled in an ice-bath and the succinimide was filtered. The solvent was evaporated and the mixture was chromatographed on silica gel in 25% ethyl acetate in hexanes to give 370 mg (20%)

of 2-bromomethylpyrazine (**16**). It was used for next reaction immediately without further purification, δ_H (200 MHz, $CDCl_3$) 8.50 (1H, s, 3-H), 8.32 (1H, d, *J* 2.47, 5-H), 8.27 (1H, d, *J* 2.50, 6-H) and 4.35 (2H, s, CH_2).

To the bromopyrazine **16** (330 mg, 1.92 mmol) and potassium carbonate (350 mg, 2.54 mmol) in dry acetone (10 mL) at room temperature was added hydroxybenzofuran **12** (270 mg, 1.27 mmol) and the mixture was refluxed for 8 h. The mixture was filtered and evaporated the acetone. To the mixture was added ethyl acetate and then aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic fractions were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (eluent; 20% ethyl acetate in hexanes) to afford 338 mg (87 %) of the product **17** as a white solid, mp 133-134 ℃; ν_{max} (NaCl)/cm^{-1} 3106, 3045, 2919, 1617, 1533, 1470, 1445, 1407, 1303, 1198, 1145, 1062 and 1018; δ_H (200 MHz, $CDCl_3$) 8.98 (1H, s, 3-H), 8.50 (2H, s, 5-H and 6-H), 7.72 (1H, s, 4-H), 7.50 (1H, d, *J* 2.1, 2-H), 7.09 (1H, s, 7-H), 6.61 (1H, d, *J* 1.9, 3-H) and 5.24 (2H, s, CH_2); δ_C (50 MHz, $CDCl_3$) 155.01 (C), 153.11 (C), 149.43 (C), 144.72 (CH), 144.70 (CH), 143.61 (CH), 142.60 (CH), 122.82 (CH), 121.31 (C), 109.54 (CH), 108.15 (C), 106.34 (CH) and 30.52 (CH_2); m/z 306 (MH^+, 81%), 304 (92), 225 (39), 208 (39), 197 (62), 169 (61), 168 (78), 140 (39), 118 (55), 114 (54) and 89 (100); [Found: M^+, 303.9837 (11.1%). $C_{13}H_9O_2N_2Br$ requires M, 303.9847].

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Acidities of Benzyltetrahydrothiophenium Halides in Water. A Simple Method of Estimation

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The pK_a values of benzyltetrahydrothiophenium halides **1a-f** in water have been estimated by measuring the absorbances of the solution in aqueous hydroxide ion solution. Assuming that the ratios of the activity coefficients remains close to unity, the absorbance of the solution can be expressed as $A/[SH]_o=(\varepsilon_{SH}+\varepsilon_{S^-}K[OH^-])/(1+K[OH^-])$, where A, $[SH]_o$, K, ε_{SH}, and ε_{S^-} are the absorbance of the solution, the initial concentration of **1a-f**, the equilibrium constant, and the extinction coefficients for SH and S^-, respectively. The ε_{S^-} and K values that best fit with this equation were calculated by a nonlinear regression analysis with a large number of absorbance data determined at different $[OH^-]$ and $[SH]_o$. The pK_a values of the SH were then calculated with the relationship $K_a=-\log K+14$. The validity of this method has been demonstrated by the excellent agreements between the experimental and literature pK_a values of three organic acids. The pK_a values of **1a-f** estimated by this method are in the range of 12.5-15.3 and correlate well with the Hammett equation. The large negative deviation for the pK_a values of **1e** and **1f** from the Hammett plot has been attributed to the extra hydrogen bonding between the phenyl group and water molecules attracted by the hydrophilic substituents.

Introduction

Accurate determination of equilibrium solution acidities becomes difficult when one approaches within about 4 to 5 pK_a units of the solvent because of leveling effects. Although Hammett H^- acidity function has allowed the aqueous acidity scale, which has a practical pK_a range of 0-12, to be extended upward by about 12 pK_a units by employing co-solvents and strong bases, it has certain limitations.[1~5]

In connection with other work, we had to determine the pK_a values of benzyltetrahydrothiophenium halides in water.[6] However, the acidity could not be determined by the acidity function because of the limited solubility of the compounds in the mixed solvents and the short wavelength of the absorption maxima, which renders the accurate measurements of the absorbances difficult except in water. Therefore, it was necessary to estimate the pK_a values in water directly.

For equilibrium between benzyltetrahydrothiophenium halide (SH) and hydroxide in water,

$$SH+OH^- \rightleftarrows S^- + H_2O \quad (1)$$

$$K=[S^-]/[SH][OH^-] \quad (2)$$

Substituting the relationship $A=\varepsilon_{SH}[SH]+\varepsilon_{S^-}[S^-]$ and $[SH]_o=[SH]+[S^-]$ into the equation,

$$A/[SH]_o=(\varepsilon_{SH}+\varepsilon_{S^-}K[OH^-])/(1+K[OH^-]) \quad (3)$$

$$pK_a=-\log K+14 \quad (4)$$

where A and $[SH]_o$ are the total absorbance of the solution and the initial concentration of the benzyltetrahydrothiophenium halide, respectively.[8] In this equation all of the variables except for ε_{S^-} and K can be determined accurately. Therefore, if sufficient number of A at different $[OH^-]$ and $[SH]_o$ is accumulated, both ε_{S^-} and K values that best fit with Eq. (3) can be calculated with a nonlinear regression analysis. The pK_a values of the SH can then be calculated with Eq. (4). We now report that the equilibrium acidity of benzyltetrahydrothiophenium halides **1a-f** in water can be estimated simply by measuring the absorbances of the solution.