Synthesis of the Angular Furanoxanthone, Deoxydehydropsorospermin Methyl Ether (5,10-Dimethoxy-2-isopropenyl-6*H*-furo[2,3-*c*]xanthen-6-one)

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The angular isopropenylfuranoxanthone heterocyclic system, on which the anti-leukemic natural product psorospermin is based, is synthesized by the reaction of cuprous isopropenylacetylide with 4-bromo-1,5-dimethoxy-3-hydroxyxanthone.

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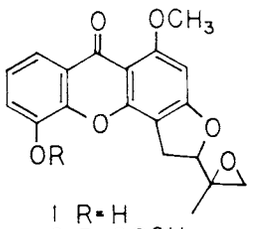
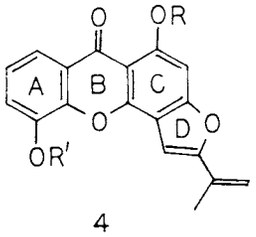
Following the determination [1] that an ethanolic extract of *Psorospermum febrifugum* Sprach. (*Guttiferae*) exhibited significant activity *in vivo* against P-388 lymphocytic leukemia (3PS) in mice and *in vitro* against a cell culture derived from a human epidermoid carcinoma of the nasopharynx (9KB), a recent examination of the biologically active fraction led to the isolation of the anti-leukemic agent which was named psorospermin [2]. The structure **1** proposed for this compound was based almost entirely upon interpretation of the proton magnetic resonance spectrum. An acetate ester **2** and methyl ether derivative **3** were the sole reported derivatives, and paucity of material precluded chemical studies necessary to establish the stereochemistry of the natural product. Failure to obtain a suitable crystal also precluded an X-ray crystallographic structure determination.



1 R=H
2 R=COCH3
3 R=CH3



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We have examined a synthetic approach to the parent heterocyclic skeleton framework, represented by the general formula **4** by which the isopropenylfuran (ring D) fragment is constructed by the reaction of cuprous isopropenylacetylide with a suitably pre-formed *o*-halophenolic xanthone. We have previously used this technique for direct synthesis of the euparinoids [3] (euparin, methoxyeuparin and dehydrotremetone), furanocoumarins [4] (oroselone, arnocoumarin) and intermediates for the natural dibenzofurans (ruscodibenzofuran [5], cannabifuran [6], and dehydrocannabifuran [6].

For the starting material, we chose 1,3-dihydroxy-5-methoxyxanthone (**7**) which bears the requisite oxygen substitution pattern and was readily available by condensation of 2,3-dimethoxybenzoic acid (**5**) and phloroglucinol (**6**) [7]. Since preliminary experiments indicated that bromination of **7** in acetic acid solution afforded little selectivity in product formation, as expected, a less reactive ring-C derivative was sought.

For this purpose, application of the procedure developed by Dimroth [8] for protection of a phenolic function *ortho-* or *peri-* to a carbonyl function by reaction with boron triacetate and acetic anhydride, yielded from **7** the boroacetate **8** as a bright yellow solid. Hydrolysis of this borate ester by boiling with water gave the 3-acetoxy-1-hydroxy-5-methoxyxanthone (**9**) which on methylation (methyl iodide, silver oxide) yielded the dimethyl ether **10**, readily converted to the monohydric phenol **11** by base hydrolysis.

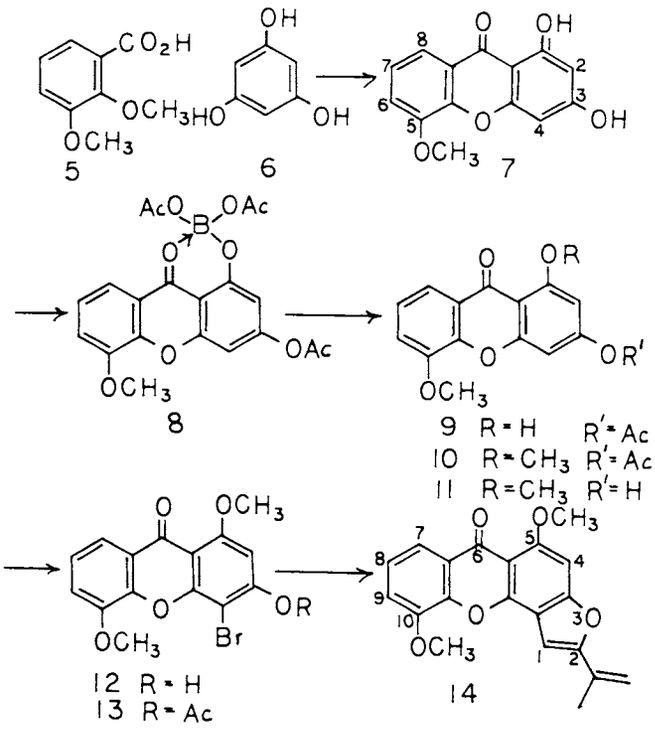
Treatment of **11** with bromine in acetic acid solution gave gratifyingly a single mono-bromo derivative in approximately 90% yield. Examination of the pmr spectrum of this product showed that the characteristic *meta* proton doublet signals of compound **11** (and of **7**, **9** and **10**) attributable to the C-2 and C-4 protons were replaced by a singlet signal, thus establishing that halogen substitution had occurred as hoped in ring C. Distinction between the 2-bromo and desired 4-bromo substituted structure **12** for this product was forthcoming from two independent pmr spectrometric considerations.

Fales and Warren have studied the effect of benzene in causing upfield chemical shifts (from chloroform) of methoxyl groups attached to aromatic rings [9]. In general, aryl methoxyl groups bearing an *ortho* proton undergo upfield shifts of at least 0.3 ppm greater than o,o'-disubstituted methoxyl groups. Since the bromoxanthone, now to be attributed structure **12** had limited solubility for spectrum determination, it was converted to the acetate derivative **13**. In deuteriochloroform solution, this compound exhibited methoxyl signals at δ 3.96 and 3.98 which were diamagnetically shifted to δ 3.24 and 3.37 in hexadeuteriobenzene solution. This comparable shift implied that *both*

methoxyl groups have aryl *ortho* protons and that the bromination product from phenol **11** was the 4-bromo derivative **12** rather than the 2-bromo-isomer in which only one methoxyl group had an *ortho* proton (at C-6).

This conclusion was additionally supported by a nuclear Overhauser enhancement experiment. Irradiation of the methoxyl signal of **13** at δ 3.98 results in a 19% enhancement of the singlet aryl proton signal at δ 6.66, while the double doublet aryl proton signal (at H-8) was unaffected.

Reaction of the *o*-bromophenol **12** with cuprous isopropenylacetylide in pyridine solution gave in over 60% yield the angular furanoxanthone, deoxydehydropsorospermin methyl ether **14**. This pathway, which thus provides regioselectively the angular isopropenylfuranoxanthone framework on which psorospermin is based, was not further pursued when it came to our attention that the phenol **11** had been converted, in unpublished work, to psorospermin methyl ether [10].



EXPERIMENTAL

1,3-Dihydroxy-5-methoxyxanthone (**7**).

A mixture of 2,3-dimethoxybenzoic acid (5.0 g), 1,3,5-trihydroxybenzene (5.78 g), zinc chloride (20 g) and phosphorus oxychloride (50 ml) was heated at 70-72° with stirring for 1.25 hours, then cooled to room temperature and quenched with ice. The resultant red solid precipitate (13.0 g) was extracted with water (Soxhlet apparatus) for 18 hours, and the extract discarded. The dried residue (4.6 g) was then similarly extracted with ethanol (8 days), and evaporation of the extract gave the xanthone as an orange powder (2.28 g) which crystallized from ethanol as long yellow needles, mp 308-310° dec (lit [7]mp >300°; nmr (DMSO-d_6): δ 3.97 (s, OMe), 6.20 (d, J 2.1 Hz, H-2), 6.38 (d, J 2.1 Hz, H-4), 7.33-7.50 (m, H-6 and -7), 7.64 (dd, J 2.5, 7 Hz, H-8) and 12.78 (s, OH).

3-Acetoxy-1-hydroxy-5-methoxyxanthone (**9**).

A mixture of 1,3-dihydroxy-5-methoxyxanthone (1.53 g) and boron triacetate (2 g) in acetic anhydride (15 ml) was heated under reflux for 5 minutes. After cooling to room temperature, the yellow precipitate was collected to give the boroacetate **8** as a bright yellow powder; nmr (DMSO-d_6): δ 1.93 (s, $B(OAc)_2$), 2.31 (s, OAc), 3.90 (s, OMe), 6.62 (d, J 2 Hz, H-2), 6.70 (d, J 2 Hz, H-4), 7.36-7.47 (m, H-6 and -7) and 7.65 (dd, J 3, 8 Hz, H-8). The boroacetate (2.05 g) was added to water (50 ml) and the mixture heated under reflux for 3 hours, then cooled and filtered. The precipitate was washed with water, then dried under reduced pressure to give the acetoxyxanthone (**9**) (1.35 g) which was recrystallized from methanol as light yellow needles, m.p. 192-193°; nmr (DMSO-d_6): δ 2.30 (s, OAc), 3.96 (s, OMe) 6.63 (d, J 2 Hz, H-2), 6.95 (d, J 2 Hz, H-4), 7.34-7.52 (m, H-6 and -7) and 7.69 (dd, J 2, 7 Hz, H-8).

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 63.89; H, 3.97.

3-Acetoxy-1,5-dimethoxyxanthone (**10**).

A mixture of the monoacetoxyxanthone **9** (1.24 g), silver oxide (2.23 g) and methyl iodide (2.49 g) in acetone (17 ml) was heated under reflux for 27 hours, then cooled and filtered. Evaporation of the filtrate under reduced pressure gave the dimethoxyxanthone **10** as a yellow powder (1.32 g) which crystallized from methanol as long slender needles (970 mg), mp 206-206.5°; nmr (deuteriochloroform): δ 2.32 (s, OAc), 3.99 (s, two OMe), 6.57 (d, J 2 Hz, H-2), 6.96 (d, J 2 Hz, H-4), 7.08-7.17 (m, H-6 and -7) and 7.83 (dd, J 2, 7 Hz, H-8).

Anal. Calcd. for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49. Found: C, 64.76; H, 4.61.

1,5-Dimethoxy-3-hydroxyxanthone (**11**).

A mixture of the acetoxydimethoxyxanthone (**10**) (849 mg) and potassium hydroxide (5 g) in methanol (50 ml) was stirred at room temperature for 3 hours, then acidified with acetic acid and diluted with water. The precipitate was collected, washed with water and dried to give the hydroxyxanthone **11** as a white powder (726 mg) which crystallized from methanol as faint yellow small prisms, mp 343-346°; nmr (DMSO-d_6): δ 3.83 (s, OMe), 3.94 (s, OMe), 6.35 (d, J 2.4 Hz, H-2), 6.41 (d, J 2.4 Hz, H-4), 7.22-7.49 (m, H-6 and -7) and 7.56 (dd, J 2.4, 7 Hz, H-8); ms: m/e 272.0682 [Calcd. for $C_{15}H_{12}O_5$: 272.0685].

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.44; H, 4.49.

4-Bromo-1,5-dimethoxy-3-hydroxyxanthone (**12**).

A solution of bromine in acetic acid (1.62 ml of a 0.08 *M* solution) was added dropwise over 30 minutes to a stirred suspension of the hydroxyxanthone **11** (452 mg) in acetic acid (45 ml). Stirring was continued overnight, after which the precipitate was collected and washed with water. The yellow powder (517 mg) was recrystallized from acetic acid to give the 4-bromoxanthone **12** as white feathery needles (447 mg), mp 332-333°; nmr (DMSO-d_6): δ 3.84 (s, OMe), 3.97 (s, OMe), 6.58 (s, H-2), 7.30-7.48 (m, H-6 and -7) and 7.60 (dd, J 2.5, 7 Hz, H-8); ms: m/e 349.9792 [Calcd. for $C_{15}H_{11}O_5Br$: 349.9791].

Anal. Calcd. for $C_{15}H_{11}BrO_5$: C, 53.10; H, 3.16. Found: C, 52.77; H, 3.12.

3-Acetoxy-4-bromo-1,5-dimethoxyxanthone (**13**).

A solution of the bromohydroxyxanthone **12** (64 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was heated under reflux for 30 minutes, then cooled and poured onto ice. The precipitate (64 mg) was collected and recrystallized from methanol to give the acetoxybromoxanthone (**13**) as colourless fine needles, mp 216-217.5°; nmr (deuteriochloroform): δ 2.40 (s, OAc), 3.96 (s, OMe), 3.98 (s, OMe), 6.66 (s, H-2), 7.21-7.27 (m, H-6 and -7) and 7.80 (dd, J 3, 7 Hz, H-8); nmr (hexadeuteriobenzene): δ 3.24 (s, OMe) and 3.37 (s, OMe).

Anal. Calcd. for $C_{17}H_{13}BrO_6$: C, 51.93; H, 3.33. Found: C, 51.93; H, 3.28.

5,10-Dimethoxy-2-isopropenyl-6*H*-furo[2,3-*c*]xanthen-6-one (**14**).

A stirred suspension of cuprous isopropenylacetylide (205 mg), and 4-bromo-1,5-dimethoxy-3-hydroxyxanthone (400 mg) in pyridine (25 ml)

was heated under reflux under nitrogen for 21 hours, then cooled to room temperature and diluted with ether (500 ml). The mixture was set aside at 0° overnight, then filtered through celite. The filtrate was washed with water (3 × 200 ml), aqueous sodium hydroxide (1*N*, 3 × 100 ml), water (3 × 200 ml) and brine (3 × 200 ml). Evaporation of the dried extract gave a solid (319 mg) which was crystallized from acetone to give the angular isopropenylfuranoxanthone **14** as small off-white prisms, mp 183-185°; nmr (deuteriochloroform): δ 2.12 (br s, vinyl Me), 4.02 (s, two OMe), 5.15 (br s, vinyl H), 5.72 (br s, vinyl H), 6.88 (s, H-1 or -4), 6.92 (s, H-4 or -1), 7.12-7.35 (m, H-8 and 9) and 7.78 (dd, J 2.6, 7.1 Hz, H-7); ms: m/e 336.0997 [Calcd. for $C_{20}H_{16}O_5$: 336.0998].

Anal. Calcd. for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.30; H, 4.88.

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