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Total synthesis of psorospermin

Michael K. Schwaebe,* Terence J. Moran and Jeffrey P. Whitten

Department of Medicinal Chemistry, Cylene Pharmaceuticals Inc., 11045 Roselle St. Suite C, San Diego, CA 92121, USA

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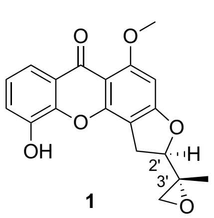
Abstract—The xanthone natural product psorospermin was synthesized in 13 steps with an overall yield of 1.7%. This compound shows potent antineoplastic activity in a variety of cancer cell lines.

Psorospermin **1** is a xanthone natural product first isolated by Kupchan et al. from the bark of the African plant *Psorospermum febrifugum*.[1] The absolute stereochemistry was later determined by Cassady and coworkers[2]. Psorospermin has been of great interest for the past three decades because of it's unique structure and novel antineoplastic properties.[3] Although several publications report efforts toward the total synthesis of both chiral and non-chiral analogs of psorospermin, to date no total synthesis has been achieved.[4] We report the total synthesis of psorospermin, a novel fused tetracyclic xanthone containing two chiral centers and a reactive epoxide.



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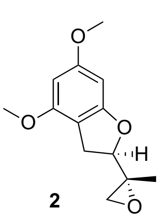

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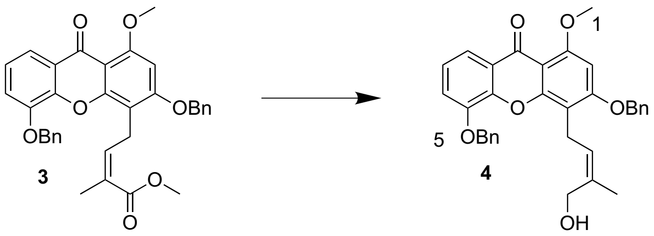
As the two stereocenters are adjacent to each other and one center is highly hindered, we examined a similar route to Cassady and co-workers that utilized a zipper-type reaction as in the synthesis of compound **2**[5]. Our main objective was to develop a scaleable route to provide enough material for preclinical evaluation as a cancer therapeutic.



The natural product, psorospermin, contains the (2′*R*,3′*R*)-stereochemsitry and is set by the stereochemistry of the olefination and the chirality of the epoxidation. This necessitated the selective formation of the *Z*-olefin **3** and its reduction to the allylic alcohol **4** in the presence of a variety of sensitive groups. Additionally, we needed to differentiate the 1- and 5-hydroxys (the 5-hydroxy being more reactive and the 1-hydroxy being more labile) in a manner that enabled selective methylation, protection and deprotection to form the final compound. The synthesis is outlined in Scheme 1.

The synthesis begins with the construction of the xanthone skeleton by the method of Grover et al.[6] Contrary to much of the xanthone literature we found it unnecessary to fuse the zinc chloride prior to the coupling. We found this extra step actually decreases reaction yield because of the insolubility of glass-like fused zinc chloride. To circumvent this step we heated the zinc chloride in $POCl_3$ to 60 °C for 30 min prior to the addition of dimethoxy benzoic acid **5**. We continued to heat for an additional 30 min then added phloroglucinol **6**.

Selective allylation of the 3-hydroxyl followed by methylation of the 1-hydoxyl proceeded smoothly to afford xanthones **8** and **9** in 77% and 95% yields,

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Keywords: Psorospermin; Asymmetric synthesis; Anticancer agent; Xanthone; Natural product.

* Corresponding author. Tel.: +1 8588661605; fax: +1 8588661609; e-mail: mschwaebe@cylenepharma.com

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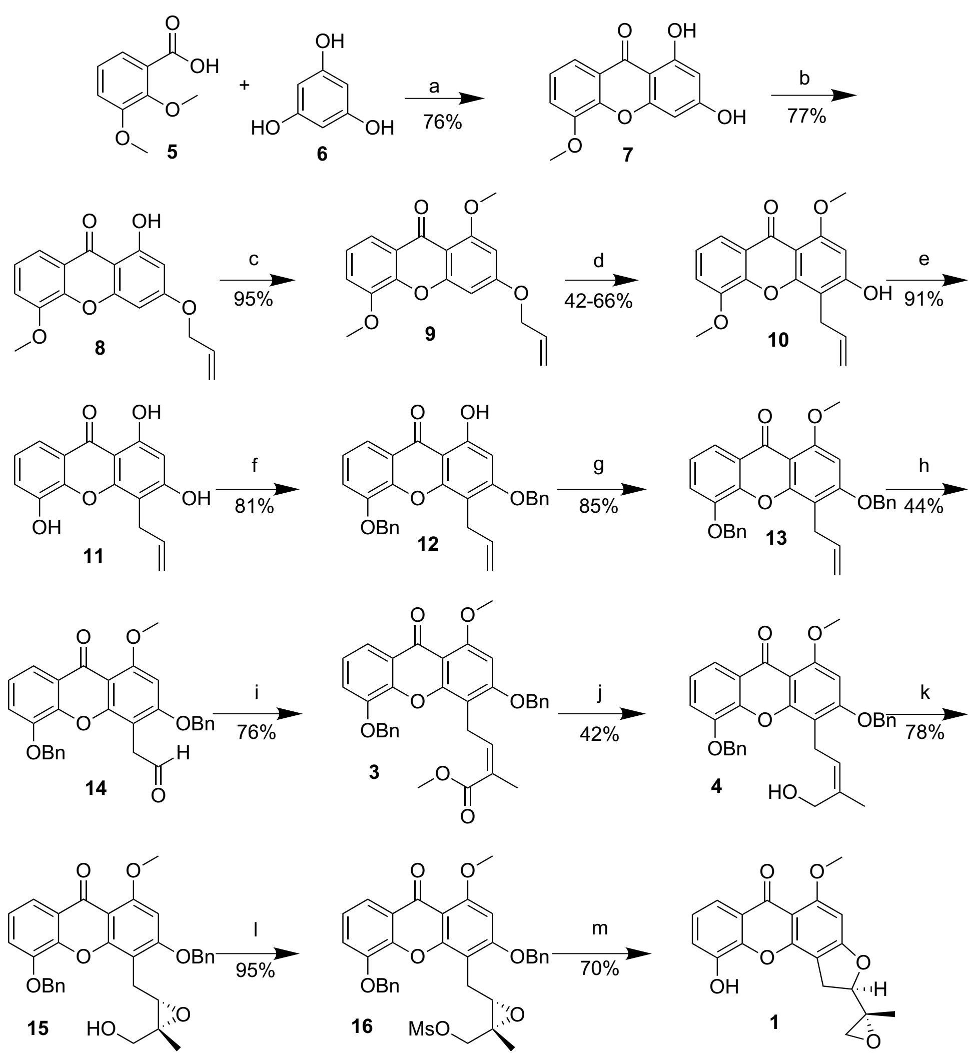

Scheme 1. Reagents: (a) $ZnCl_2$, $POCl_3$; (b) allyl bromide, K_2CO_3; (c) CH_3I, K_2CO_3; (d) mesitylene, 180 °C; (e) BBr_3; (f) benzyl bromide, NaH, DMF; (g) CH_3I, DMF; (h) OsO_4, $NaIO_4$; (i) $(CF_3CH_2O)_2POCHCH_3CO_2Me$, KHMDS, 18-crown-6; (j) DIBALH/CH_2Cl_2; (k) *t*-BUOOH, (−) DIPT, $Ti(i\text{-}Opr)_4$; (l) MsCl, Et_3N; (m) raney nickel/K_2CO_3, ethanol.

respectively. Claisen rearrangement was affected in refluxing mesitylene and the product **10** crystallized out of the reaction mixture upon cooling to room temperature. The use of more polar solvents decreased the ratio of the rearrangement occurring at the 4-position over the 2-position. The addition of even a catalytic amount of a weak base (i.e., potassium carbonate or triethyl amine) results in a significant amount of cyclized material that was identified as the dihydrofuran.

The key to the sequence was whether we could efficiently perform the di-demethylation and subsequent selective 3,5-bis benzylation. Treatment of **10** with boron tribromide at 0 °C cleanly afforded the trihydroxy xanthone **11** in a 91% yield after treatment with ice water and filtration. The bis-benzylation proceeded efficiently to afford the xanthone **12** with only 10% of the tribenzylated material being formed. Methylation of the 1-hydroxyl with methyl iodide proceeded at room temperature with the addition of sodium hydride in DMF in an 85% yield. The use of elevated temperatures with potassium carbonate led to significant amounts of the cyclized dihydrofuran side-product.

As reported in the literature, the choice of solvent for the Johnson–Lemieux oxidation of **13** is critical.[7] Treatment of **13** with catalytic osmium tetroxide and sodium periodate in a 3:1 mixture of dioxane/water afforded the aldehyde **14** in a 44% yield after recrystallization from THF. At elevated temperatures above 40 °C, over-oxidation to the acid became a significant side product. Formation of the *Z*-olefin was efficiently carried out by the method of Still and Gennari.[8] While many other reagents were examined, this method provided a very good yield and *Z*/*E* ratio of products. We found temperature was critical and, although we could add the aldehyde **14** at −85 °C, its solubility demanded the use of copious amounts of THF to dissolve the aldehyde. A better solution was to add the aldehyde **14** as a dry powder all at once at −78 °C. The reaction proceeded smoothly as the solubility of **14** slowly increased without any local exotherm. The result was a consistent, highyielding formation of the olefin in a 10:1 ratio of *Z*/*E*. Pure *Z*-olefin **3** could be obtained by crystallization from ethyl acetate to afford the *Z*-α,β-unsaturated ester **3** in a 76% yield.

The 1,2-reduction of ester **3** was extremely troublesome. After examining a host of reagents and conditions we could only affect the transformation by careful addition of 2.0 equiv of DiBALH in methylene chloride at −78 °C. Even then, it was necessary to separate the product **4** from the residual starting ester **3** and the over-reduced material via silica gel chromatography. This procedure, although less than optimal, afforded the *Z*-allylic alcohol in a 42% yield. Sharpless epoxidation[9] proceeded smoothly with stoichiometric addition of reagents and powdered sieves. The enantioselectivity of the reaction was determined by chiral LC of the 5-methoxy derivative of the final product **1**.[10] Thus, we had our epoxide **15** in a 78% yield with a 70% ee. Formation of the mesylate proceeded routinely to afford the psorospermin precursor **16** in a 95% yield.

The final step involved the selective reduction of the 3- and 5-benzyl protecting groups and a zipper-type cyclization.[11] The key to affecting this transformation was to find a way to reductively cleave both benzyl groups without reduction of the resulting epoxide. When the reduction was carried out with 10% Pd/C in the absence of base, the reaction stalled with the product being absorbed onto the catalyst. In the presence of potassium carbonate, over reduction predominated. An improvement involved the use of 1,4-cyclohexadiene with Pd/Ba_2SO_4 in refluxing methanol. Finally, the use of stoichiometric Raney Nickel with potassium carbonate in a 1:1 mixture of ethyl acetate and ethanol at 60 °C afforded psorospermin in a 70% yield after silica gel chromatography. The ^{1}H NMR spectrum of **1** was in agreement with an authentic sample of psorospermin and showed the characteristic doublets of the 4′ protons at 2.73 and 2.99 ppm ($\Delta\delta$ 0.258).[12,13]

Supplementary data

NMR and LCMS supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.006.

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10. Compound **1** was converted to the 5-methoxy compound for chiral LCMS by treatment of **1** with methyl iodide in the presence of potassium carbonate in acetone. The mixture was evaluated by normal phase chiral chromatography using the Waters 600 pump controller, 2687 dual wave detector and ZQ mass spectrometer. The mobile phase was an isocratic mixture of hexane/isopropanol/1,2-dichloroethane; 30:10:10 at a constant flow of 6.0 mL/min. The stationary phase was a Chirex (S)-VAL and DNAn 250 × 10.0 mm column by phenomenex. The temperature was kept constant at 30 °C with a Waters 600 column heater.
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12. *Spectral data for compound* **1**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (1H, dd, $J = 7.3$, 1.8 Hz), 7.25 (1H, dd, $J = 8.9$, 1.8 Hz), 7.20 (1H, t, $J = 8.3$ Hz), 6.37 (1H, s), 5.61 (1H, s), 4.92 (1H, dd, $J = 9.4$, 7.1 Hz), 3.97 (3H, s), 3.50 (1H, dd, $J = 15$, 10 Hz), 3.31 (1H, dd, $J = 15.3$, 7.2 Hz), 2.99 (1H, d, $J = 4.5$ Hz), 2.73 (1H, d, $J = 5$ Hz), 1.44 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 165.9, 163.3, 154.1, 144.8, 143.8, 123.9, 119.6, 117.4, 106.8, 104.2, 90.1, 87.0, 58.0, 56.6, 51.2, 49.7, 28.9, 16.8; LCMS (254 nm): $R_t = 3.41$ min (100%); EIMS(pos) m/z 341.1 $[M+H]^+$ (100), 363.1 $[M+23]^+$ (17), 271.1 $[M-70+1]^+$ (11).
13. An authentic sample of **1** was obtained from the NCI via Laurence Hurley.