Molecules **2000**, *5*, 82-88

molecules
ISSN 1420-3049
http://www.mdpi.org

A High-Yielding Synthesis of the Naturally Occurring Antitumour Agent Irisquinone

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Received: 2 November 1999 / Accepted: 12 January 2000 / Published: 18 January 2000

Abstract: A short, high-yielding synthesis of the antitumour agent irisquinone (**1**) is described. The key steps are the palladium catalysed coupling reaction of dec-9-yn-1-ol with iodide (**2**) to form alkyne (**3**) and the Fremy's salt oxidation of phenol (**7**).

Keywords: Irisquinone; antitumour; Chinese medicine.

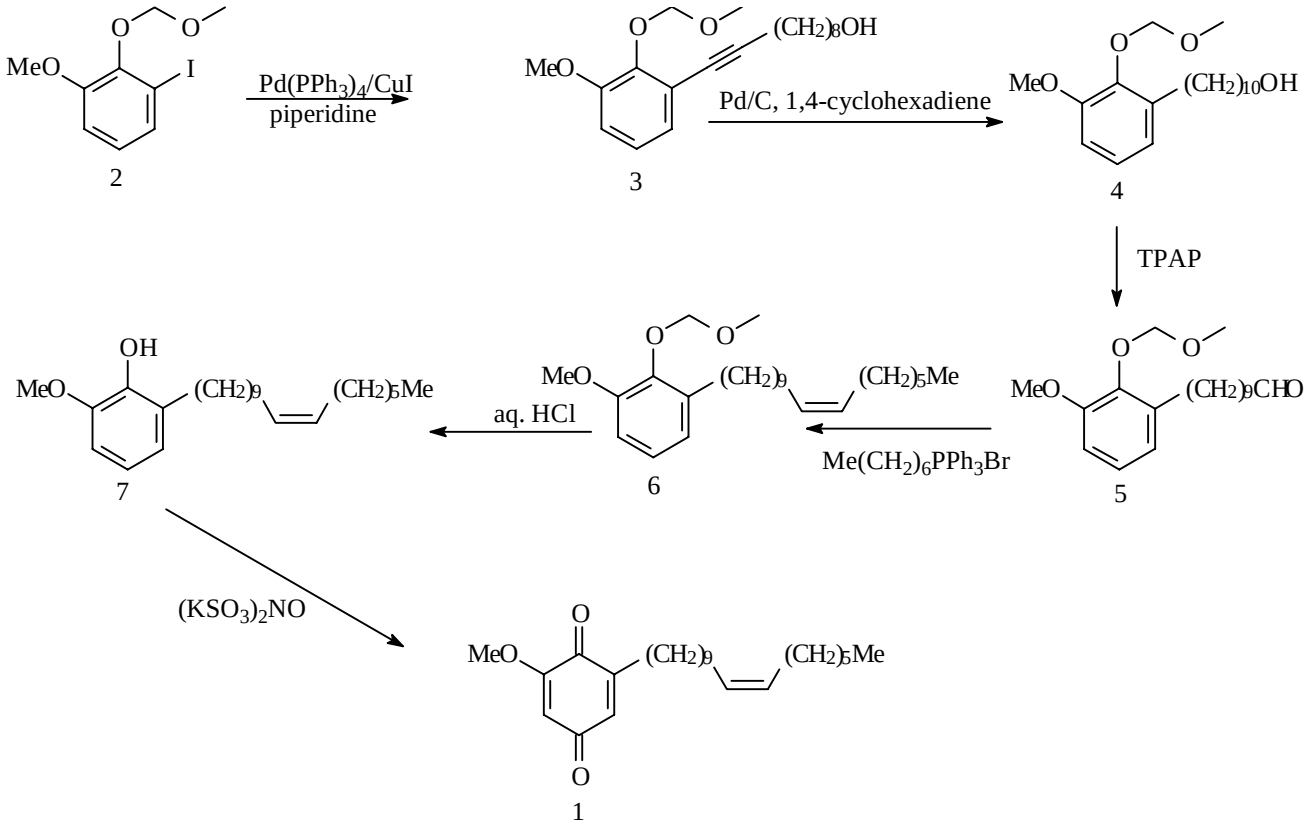
Introduction

The seeds of *Iris pallasi* (*Iridaceae*) have been used in Chinese folk medicine for the treatment of various malignancies and for the treatment of metrorrhagia and vaginal discharge [1]. Irisquinone (**1**) has been isolated as an active principle [2] from the seed oil of *I. pallasi* and this 1,4-benzoquinone is effective against cervical carcinoma, lymphosarcoma, hepatoma and Ehrlich ascites carcinoma (EAC) in mice [2, 3]. Irisquinone (**1**) damages nuclei of cells and inhibits [3] mitosis in cancer cells. Respiration of P388 cells is significantly inhibited by irisquinone (**1**) and mitochondrial damage to EAC cells has been noted [4]. Furthermore, levels of cyclic guanosine monophosphate have been shown to increase [5] in plasma of tumour bearing mice after treatment with this quinone (**1**). These results suggest that the antitumour action of irisquinone (**1**) is likely to be different from that of other cytotoxic

agents. There are several syntheses of irisquinone (**1**) described [6 – 9] in the literature. However the best yield reported [6] was 25% over seven steps. In order to study its mechanism of action, our laboratories required a good supply of irisquinone (**1**). Herein is described a short, high-yielding synthesis of irisquinone (**1**).

Results and Discussion

Dec-9-yn-1-ol was prepared from commercially available dec-2-yn-1-ol by the acetylene Zipper reaction [10] and the aryl iodide (**2**) was prepared by a literature method [11]. Various palladium catalysed coupling reactions of iodide (**2**) with dec-9-yn-1-ol were tried to optimise the yield of alkyne (**3**) using different bases, co-catalysts, solvents and temperatures [12 – 18]. The method of Alami [19] using 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI and piperidine as both base and solvent afforded the alkyne (**3**) in 98% yield.



Scheme 1. Synthesis of irisquinone.

Reduction of this alkyne (**3**) with 1,4-cyclohexadiene and palladium on carbon using a *transfer hydrogenation* process [20] afforded the fully saturated alcohol (**4**) in quantitative yield. Swern oxidation of alcohol (**4**) using activated DMSO afforded aldehyde (**5**) in only 21% yield. However, oxidation

with tetrapropylammonium perruthenate (TPAP) [21] afforded the desired aldehyde (**5**), after column chromatography on silica in virtually quantitative yield after 10 minutes reaction. This aldehyde (**5**) proved to be unstable and was reacted as soon as it was prepared with *n*-heptyltriphenylphosphonium bromide. This reaction afforded exclusively the *Z*-olefin (**6**) in excellent yield. Removal of the methoxymethyl protecting group from olefin (**6**) using dilute hydrochloric acid afforded the phenol (**7**) in quantitative yield. Salcomine catalysed oxidation of phenols has previously been used [22] to prepare 1,4-benzoquinones. However, in our laboratory, salcomine oxidation of phenol (**7**) afforded the desired irisquinone (**1**) in varying yields of 30-60%. Also oxidation of phenol (**7**) with molecular oxygen in the presence of benzyltrimethylammonium hydroxide [23] failed to produce the desired benzoquinone (**1**) in satisfactory yield. Fremy's salt oxidation [24] of this phenol (**7**), however, produced irisquinone (**1**) in excellent yield (87%)(Scheme 1).

The above synthesis of irisquinone (**1**) was attained from aryl iodide (**2**) in six steps in an overall yield of 70%. The general methodology described can be utilised to synthesise a range of alkyl or alkenyl substituted benzoquinones in excellent yield. The biological activities of irisquinone (**1**) and analogues will be reported in a subsequent paper.

Experimental

Synthetic intermediates were used as received from Aldrich Chemical Company or Lancaster Synthesis. NMR spectra were determined on a Bruker AC300 (at 300 MHz) NMR spectrometer in $CDCl_3$ and are expressed in δ values relative to tetramethylsilane. Coupling constants (*J*) are measured in Hz. Infra-red spectra were recorded on a Perkin Elmer 1710 FT spectrometer and are expressed in cm^{-1}. UV-Vis spectra were determined on a Varian Cary 1 UV-VIS spectrophotometer. Melting points are uncorrected. Electron impact mass spectra were determined using a VG Trio 2 or a Kratos MS25 mass spectrometer at an ionisation energy of 70 eV.

*10-[3'-Methoxy-2'-(methoxymethoxy)phenyl]dec-9-yn-1-ol (**3**)*

To a stirred solution of the aryl iodide (**2**) (108 mg, 0.367 mmol), copper (I) iodide (10 mol%, 10 mg, 55 μmol), *tetrakis*(triphenylphosphine) palladium (0) (5 mol%, 20 mg, 17 μmol) in piperidine (1 ml) was added dec-9-yn-1-ol (2.3 eq., 13l mg, 0.85 mmol) in piperidine (1ml) under an atmosphere of argon. The reaction mixture was shaken vigorously for 5 min, stirred for a further 25 min at room temperature, hydrolysed with saturated aqueous ammonium chloride (10 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with brine (3 x l0 ml), dried over anhydrous magnesium sulfate, filtered and concentrated to yield an orange/yellow oil (231 mg). The crude mixture was eluted on silica gel with petrol:ethyl acetate (7:3) to yield the title alkynol (**3**) (253 mg, 98%) as a pale orange oil. ν_{max} (film) 3407(OH). δ_H: 6.90 (2 H, m, Ar-H-4', H-5'); 6.80 (1 H, dd, *J* 6 and 4, Ar-H-6'); 5.20 (2 H, s, O-CH_2-O); 3.80 (3 H, s, Ar-OCH_3); 3.60 (3 H, s, -$OCH_2OC\underline{H}_3$); 3.58 (2

H, t, *J 7*, H-l), 2.40 (2 H, t, *J* 8, H-8), 1.40 (12 H, m, Hs-2 - 7). *m/z* (El) 320 (M^+, 25%), 277 (25), 262 (25), 183 (40), 81 (60), 69 (100), 55 (40). [Found: *m/z* 320.1988 (M^+). $C_{19}H_{28}O_4$ requires 320.1988]

*10-[3'-Methoxy-2'-(methoxymethoxy)phenyl]decan-l-ol (**4**)*

To a stirred solution of the alkynol (**3**) (3.85 g, 12.0 mmol) in absolute ethanol (50 ml) was added 1,4-cyclohexadiene (20 eq., 23 ml, 240 mmol). The solution was cooled to 0°C and Pd/C 10% (1.2 eq., 3.85 g, 14 mmol) was added very carefully in small portions. The suspension was stirred under an atmosphere of argon at room temperature for 1 h, filtered through Celite and the filtrate concentrated to yield the title alcohol (**4**) (3.88 g, 99.8%) as a colourless oil. ν_{max} (film) 3471 (OH). δ_H: 6.95 (1 H, t, *J* 8, Ar-H-5'); 6.83 (1 H, dd, *J* 8 and 2, Ar-H-4'); 6.75 (1 H, dd, *J* 8 and 2, Ar-H-6'); 5.10 (2 H, s, $-OCH_2-O$); 4.85 (1 H, s, -OH), 3.80 (3 H, s, $Ar-OCH_3$); 3.55 (3 H, s, $-OCH_2O\underline{C}H_3$); 3.54 (2 H, t, *J 7*, H-l), 2.65 (2 H, t, *J* 8, H-10), 1.70-1.20 (16 H, bm, Hs-2 -9). *m/z* (EI) 324 (M^+, 10%) 292 (20), 262 (45), 150 (65), 137 (100), 45(50).

*10-[3'-Methoxy-2'-(methoxymethoxy)phenyl]decan-l-al (**5**)*

To a stirred suspension of the alcohol (**4**) (859 mg, 2.65 mmol), 4-methylmorpholine-N-oxide (1.5 eq., 542 mg, 4.63 mmol) and activated powdered 4A molecular sieves (1.54 g, 500 mg/mmol) in anhydrous dichloromethane (7 ml) was added, in one portion, tetrapropylammonium perruthenate (VII), (5 mol%, 54.2 mg, 0.154 mmol). The reaction mixture was stirred under argon for 10 min and filtered through a short pad of silica eluting with ethyl acetate to yield the title aldehyde (**5**) (830 mg, 97%) as a pale yellow oil. ν_{max} (film) 1725 (C=O). δ_H: 9.67 (1 H, t, *J*, 3, CHO); 6.95 (1 H, t, *J* 8, Ar-H-5'); 6.83 (1 H, dd, *J* 8 and 2, Ar-H-4'); 6.75 (l H, dd, *J* 8 and 2, Ar-H-6'); 5.10 (2 H, s, $-OCH_2O$); 3.80 (3 H, s, $Ar-OCH_3$); 3.55 (3 H, s, $-OCH_2O\underline{C}H_3$); 2.65 (2 H, t, *J* 8, H-10); 2.35 (2 H, m, H-2), 1.60-1.20 (14 H, bm, Hs-3 - 9). *m/z* (EI) 322 (M^+, 35%) 137 (45), 85 (50), 83 (75), 44 (100).

*1-[(Z)Heptadec- l0'-enyl]-3-methoxy-2-(methoxymethoxy)benzene (**6**)*

To a stirred suspension of *n*-heptyltriphenylphosphonium bromide (2 eq, 548 mg, 1.24 mmol) in 1,4-dioxane (2 ml) was added a solution of potassium *t*-butoxide (139 mg, 1.24 mmol) in 1,4-dioxane (l ml) under argon. After 30 min stirring at room temperature, a solution of aldehyde (**5**) (200 mg, 0.62 mmol) in 1,4-dioxane (0.5 ml) was added. After stirring for a further hour, the solution was quenched with saturated aqueous ammonium chloride (10 ml). The aqueous solution was extracted with diethyl ether (3 x 10 ml) and the combined ethereal extracts were washed with water (3 x 10 ml), brine (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was filtered and concentrated to yield a crude mixture as a brown oil (505 mg). This oil was eluted on silica with hexane:ether (9:1) to yield the title (*Z*)-alkene (**6**) (213 mg, 85%) as a pale brown syrup. δ_H: 6.95 (1 H, t, *J* 8, Ar-H-5'); 6.83 (1 H,

dd, *J* 8 and 2, Ar-H-4'); 6.75 (1 H, dd, *J* 8 and 2, Ar-H-6'), 5.35 (2 H, t, *J* 4.7, H-10', H-11'); 5.10 (2 H, s, -OCH_2O); 3.80 (3 H, s, Ar-OCH_3); 3.60 (3 H, s, $OCH_2OC\underline{H}_3$); 2.65 (2 H, t, *J* 8, H-1'); 2.00 (4 H, m, H-9', H- l 2'); 1.60 (2 H, m, H- l6'); 1.40-1.20 (20 H, bm, Hs-2'-8', H-13', H- 14', 11-15'); 0.90 (3 H, m, H-17'). *m/z* (EI) 404 (M^+; 20%) 391 (20), 263 (100), 137 (40), 106 (35), 55 (40).

*2-[(Z)Heptadec-10'-enyl]-6-methoxyphenol (***7***)*

To a stirred solution of the alkene (**6**) (483 mg, 1.l9 mmol) in *i*-propanol/ THF (1:1, 10 ml) was added 2 M HCl (4 ml). The solution was stirred at room temperature for 1 h and was extracted with dichloromethane (3 x 25 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 x 25 ml), brine (3 x 25 ml), dried over anhydrous magnesium sulfate, filtered and concentrated to yield the title phenol (**7**) (427 mg, 99.8%) as a colourless oil. ν_{max} (film) 3565 (OH). δ_H: 6.80 (3 H, m, Ar-H-3', H-4', H-5'); 5.70 (1 H, s, Ar-OH); 5.35 (2 H, t, *J* 4.7, H-10', H- 1l'); 3.90 (3 H, s, Ar-OCH_3); 2.65 (2 H, t, *J* 8, H-1'); 2.00 (4 H, m, H-9', H-12'); 1.60 (2 H, m, H-16'); 1.40-1.20 (20 H, m, Hs-2'-8', H13', H-14', H-15'); 0.90 (3 H, m, H-17'). *m/z* (EI) 360 (M^+, 35%) 137 (l00).

*2-[(Z)Heptadec-10'-enyl]-6-methoxybenzo-1,4-quinone, Irisquinone (***1***)*

To a stirred mixture of $NaH_2PO_4.H_2O$ (7.4 eq., 644 mg, 4.67 mmol) in water (200 ml), containing Aliquat 336 (1.25 eq, 0.361 ml, 0.79 mmol), was added the phenol (**7**) (227 mg, 0.631 mmol) in dichloromethane (13 ml). Potassium nitrosodisulfonate (Fremy's salt) (2.5 eq, 423 mg, 1.58 mmol) was added and the mixture shaken vigorously until a colour change to yellow became permanent. The organic layer was collected and the aqueous layer extracted with dichloromethane (3 x 5 ml). The combined organic extracts were washed with water (3 x 5 ml), brine (3 x 5 ml), dried over anhydrous magnesium sulfate, filtered and concentrated to yield the crude quinone (213 mg). The product was eluted on silica gel eluting using petrol:ethyl acetate (3:2) to yield the title quinone (**1**) (205 mg, 87%) as yellow crystals from EtOH; m.p. 42-42.5°C (lit. mp [25] 42.5-43.5°C). ν_{max} (film) 1685 (C=O), 1652 (C=O), 1598 (C=C). λ_{max} 267 nm (15,500) and 363 (980). δ_H: 6.50 (1 H, dt, *J* 2 and 1, H-3); 5.90 (1 H, d, *J* 2, H-5); 5.35 (2 H, t, *J* 4.7, H-10', H-11'); 3.90 (3 H, s, Ar-OCH_3); 2.40 (2 H, t, *J 7*, H-1'); 2.00 (4 H, m, H-9', H-l2'); 1.60 (2 H, m, H-16'); 1.40-1.20 (20 H, m, Hs-2' - 8', H-13', H-14', H-15'); 0.90 (3 H, m, H-17'). (Found: C, 76.94; H, 10.27. $C_{24}H_{38}O_3$ requires C, 76.96; H, 10.23%). *m/z* (EI) 374 (M^+, 40%) 153 (100), 109 (20).

Acknowledgements: This work was supported by the Cancer Research Campaign and the Medical Research Council (UK). Drs Simon Moore and Xiu-guo Zhang are acknowledged for experimental work and advice.

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Sample availability: samples are available from the authors.