Tetrahedron Letters,Vol.30,No.36,pp 4783-4786,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

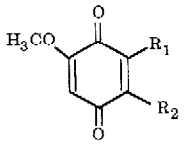
THE SYNTHESIS OF IRISQUINONE

Ronald S. Michalak, David R. Myers,
Jack L. Parsons*, Prabhakar A. Risbood
Starks Associates, Inc., 1280 Niagara Street, Buffalo, New York 14213

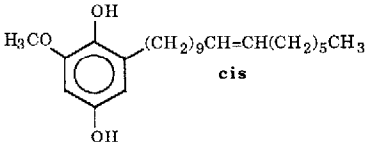
Rudiger D. Haugwitz, V. L. Narayanan
Division of Cancer Treatment, National Cancer Institute,
Bethesda, MD 20892

Abstract: Irisquinone 1 has been synthesized for the first time to investigate its use as a potential radiosensitizer. The key step in its synthesis involves the regioselective lithiation of a phenol ether. The cis-double bond has been confirmed via ^{1}H NMR spectroscopy. Its saturated side chain derivative 2 and its dihydro derivative 5 have also been prepared.

Irisquinone, 1, a benzoquinone derivative isolated from Iris pallasii Fisch. var. chinensis Fisch.[1] and from Iris pseudacorus[2], was synthesized for the first time to confirm the structure proposed[2] and to investigate its potential as a radiosensitizer.[3] The biological activities of the structurally related irisoquin[4] 3, and maesanin[5] 4 have been reported earlier. During this study, compounds 2 and 5 were also prepared.



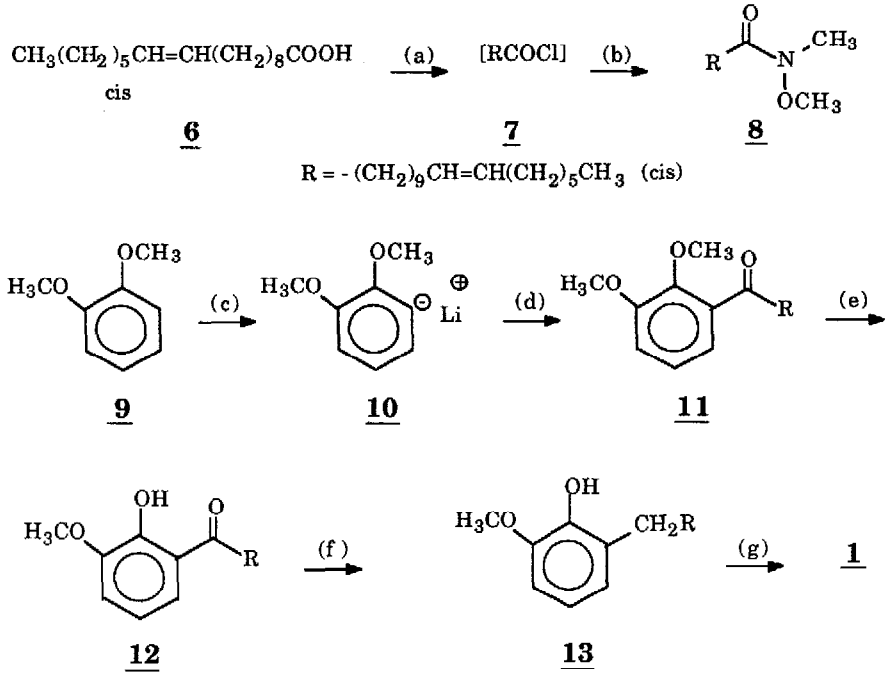
1 R_1 = cis-$(CH_2)_9CH{=}CH(CH_2)_5CH_3$
R_2 = H
2 R_1 = $-(CH_2)_{15}CH_3$
R_2 = H
3 R_1 = $(CH_2)_{17}CH_3$
R_2 = -OH
4 R_1 = cis-$(CH_2)_9CH{=}CH(CH_2)_3CH_3$
R_2 = -OH



5

The synthesis plan for irisquinone was based on the regiospecific lithiation[6] of a phenol ether which in turn would be reacted with a carbonyl derivative of the cis-side chain. Eventually, N-methoxy-N-methyl-10-cis-

heptadecenamide 8 and Li-veratrole 10 became the reactants of choice. Selective demethylation of 11 with boron trichloride followed by a Clemmensen reduction of ketone 12 and, finally, oxygenation of 13 completed the synthesis of 1 (Scheme I).



Scheme 1

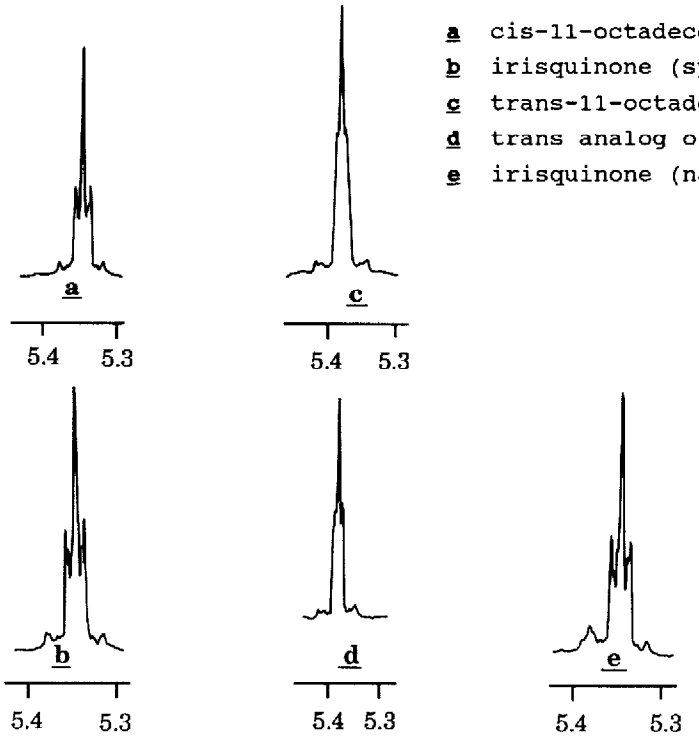
(a) oxalyl chloride; (b)N,O-dimethylhydroxylamine HCl, py; (c) n-butyl lithium, tetramethylethylenediamine (TMEDA); (d) compound 8; (e) boron trichloride; (f) Zn-Hg amalgam; (g) salcomine, oxygen, DMF.

A heated (50°C) benzene solution of 10-cis-heptadecenoic acid[8] was reacted with oxalyl chloride under argon, followed by removal of solvents in vacuo and azeotropic removal of residual oxalyl chloride with benzene to give 10-cis-heptadecenoyl chloride 7 in 95% yield. This acid chloride was then reacted with an excess of N,O-dimethylhydroxylamine HCl[7] in ethanol free chloroform containing pyridine to yield N-methoxy-N-methyl-10-cis-heptadecenamide 8 in 98% yield.

Veratrole 9 and n-butyl lithium were reacted in the presence of TMEDA in dry ether, initially at reflux, and then at room temperature to form the dimethoxyphenyl lithium reagent 10[6], which was not isolated, but instead, was directly added via syringe to a stirred solution of amide 8 in dry THF. Work up with HCl/EtOH, ether, and saturated NaCl, followed by azeotropic removal of excess veratrole with water, drying, and silica gel chromatography (EtOAc:hexane, 1:4) yielded 1-(cis-10-heptadecenoyl)-2,3-dimethoxy benzene 11, (67%). The aryl

ketone 11 was selectively demethylated with boron trichloride to yield 2-(cis-10-heptadecenoyl)-6-methoxyphenol 12 (88%) as a pale yellow oil, after chromatography on silica gel (EtOAc:hexane, 1:4). This ketone 12 was reduced under Clemmensen conditions (Zn/Hg, 6N HCl, toluene, reflux, 2h) to yield 2-(cis-10-heptadecenyl)-6-methoxyphenol 13, the penultimate product, in 27% yield[10] after silica gel chromatography (EtOAc:hexane, 1:9). Oxidation of this phenol 13 with oxygen gas in the presence of salcomine[11], followed by careful chromatography on silica gel (EtOAc:hexane, 1:5) and recrystallization from hexane yielded irisquinone[12,13] 1 in 66% yield, as a pale yellow solid, m.p. 43°-44 C. This material was spectrally indistinguishable from the crystalline solid isolated from plant material. The trans-isomer was prepared in analogous fashion by substituting 10-trans-heptadecenoic acid[8], for the cis-isomer. Spectral data for both are in full support of the cis-assignment for 1 and consistent with literature data[14] for similar olefin moieties.

500 MHZ ^{1}H NMR OF VINYL REGION OF IRISQUINONE, trans-IRISQUINONE, and MODELS



a cis-11-octadecenoic acid
b irisquinone (synthetic)
c trans-11-octadecenoic acid
d trans analog of irisquinone
e irisquinone (natural product)

Acknowledgement: We would like to thank Dr. Y. W. Lee, Research Triangle Institute, for an authentic sample of irisquinone and Drs. T. S. Strike and H. Stone for supplying us with initial radiosensitizing data. This work was funded by the National Cancer Institute, Contract N01-CM-67798.

References:

1) Wu, S.-J; Yang Q.-Z; Hua Hsueh Pao, (1980), 38, 156; (Chem. Abstr. 93, 128739K).

2) Seki, K.; Kaneko, R.; Chem.Ind. (London) (1975), 349.

3) (a) Wang, S.; Liu, R.; Li, D.; Li, W.; Tianjin Yiyao, (1981), 9, 300; (Chem. Abstr., 97, 51901e). (b) Zhang, Y.; Fan, G.; Xia, S.; Fushe Yanjiu Yu Fushe Gongyi Xuebao, (1985), 3, 39; (Chem. Abstr. 104, 105163z). (c) Wang, S.; Chin. J. Clin. Oncol. (China); (1987), 14, 88; ibid., (1986), 13, 241. (d) Mao, H. ibid., (1987), 14, 78, 84. (e) Zizheng, H. ibid., (1987), 14, 75, 81. (f) Dehua, L. ibid., (1987), 14, 67, 73. (g) Lixun, Z., ibid., (1987), 14, 69.

4) Wong, S.-M.; Pezzuto, J. M.; Fong, H. H. S.; Farnsworth, N. R.; J. Pharm. Sci. (1985), 74, 1114.

5) Kubo, I.; Kim, M.; Ganjian, I.; Kamikawa, T.; Yamagiwa, Y.; Tetrahedron, (1987), 43, 2653.

6) Gilman, H; Swiss, J.; Cheney, L. C.; J. Am. Chem. Soc., (1940), 62, 1963.

7) We would like to thank Dr. Howard McPherson of Starks Associates, Inc. for bringing to our attention the following procedure: Nahm, S.; Weinreb, S. M., Tetrahedron Lett., (1981), 22, 3815.

8) Cis- and trans-10-heptadecenoic acids, and other cis- and trans-fatty acids used, are commercially available from "Nu-Chek-Prep, Inc.", Elysian, MN, USA. These compounds were studied by ^{1}H NMR (500 MHz) to establish cis- and trans-splitting and multiplicity.

9) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N.; Tetrahedron Lett., (1966), 4153.

10) Isolated yields of 50% were achieved in subsequent reactions by using a Morton flask for improved mixing. These reactions were worked up prior to completion when a typical TLC (silica gel, EtOAc/hexane 1:9) showed product and starting material (~70:30), an unidentified baseline spot, and several trace byproducts which were not identified.

11) van Dort, H. M.; Geursen, H. J.; Recl. Trav. Chim. Pays-Bas, (1967), 86, 520.

12) Analysis calc'd. for $C_{24}H_{38}O_3$, C, 76.96; H, 10.23; found C, 77.01; H, 10.27. ^{1}H-NMR (500 MHz) ($CDCl_3$): δ 6.48 (d, 1H, H at C_5); 5.87 (d, 1H, H at C_3); 5.35 (m, 2H, -CH=CH-); 3.81 (s, 3H, $-OCH_3$); 2.42 (m, 2H, "Ar"-CH_2); 2.01 (m, 4H, allylic -CH_2); 1.49 (m, 2H, "Ar"-CH_2CH_2); 1.27 (m, 20H, -CH_2); 0.88 t, 3H, -CH_3). High resolution mass spectrum calc'd for $C_{24}H_{38}O_3$ = 374.2821; found 374.2823 ^{13}C-NMR ($CDCl_3$) δ ppm 187.84, 182.25, 158.69, 147.48, 132.79, 129.91, 129.83, 107.04, 56.37, 43.47 and other methylene carbons.

13) Compound 2 was prepared in analogous fashion substituting palmitic acid for 10-cis-heptadecenoic acid. Compound 5 was obtained from the $NaBH_4$ reduction of 1.

14) Frost, D. J.; Gunstone, F. D.; Chem. Phys. Lipids, (1975), 15, 53.

(Received in USA 22 February 1989)