Pergamon

*Tetrahedron Letters*, Vol. 38, No. 1, pp. 153-154, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02240-X

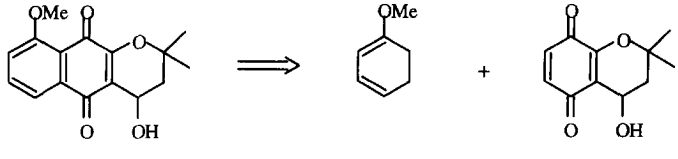
# Synthesis of 3,4-Dihydro-4-hydroxy-9-methoxy-2*H*-naphtho[2,3-b]thiopyranoquinone

Ricardo A. Tapia,*[a] Miriam C. Gárate,[a] Jaime A. Valderrama,[a] Paul R. Jenkins,[b] John Fawcett[b] and D R. Russell[b]

[a]Facultad de Química. Pontificia Universidad Católica de Chile. Casilla 306, Santiago 22. Chile.
[b]Department of Chemistry, The University, Leicester LE1 7RH, UK.

***Abstract***: A convergent synthesis of naphtho[2,3-b]thiopyranoquinone **6** has been accomplished wherein the key step is the Alder-Rickert reaction between the benzothiopyranoquinone **5** and 1-methoxy-1,3-cyclohexadiene. Copyright © 1996 Elsevier Science Ltd

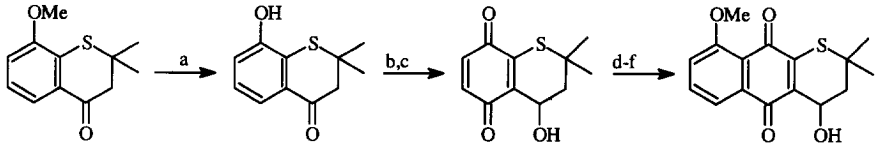
Naturally occurring naphtho[2,3-b]pyranoquinones have been attracting attention in synthetic organic chemistry,[1] since such compounds exhibit interesting biological properties.[2] Recently we described a new and convergent route to naphthopyranoquinones through an Alder-Rickert reaction of the benzopyranoquinone **2** with 1,3-dienes.[3] Using this method, the racemic synthesis of the new cytotoxic quinone **1** isolated from *Mansoa alliacea*[4] , and some aza-analogues using 1-methoxy-1,3-cyclohexadiene and 1-aza-1,3-dienes respectively were reported.[5,6] As part of our continuing search for more compounds with useful biological activity we report herein the synthesis of the sulfur bioisoster **6**.




**1** **2**

The starting point for the synthesis was the known Michael addition of 2-methoxybenzenethiol to 3-methyl-2-butenoic acid and Friedel-Craft cyclization of the resultant 3-methyl-3-phenylthiobutanoic acid with polyphosphoric acid to obtain thiochromanone **3**.[7] The hydrolysis of **3** with hydrobromic acid, reduction of the ketone **4** with lithium aluminum hydride and oxidation with potassium nitrosodisulfonate (Fremy's salt) afforded benzothiopyranoquinone **5** in 46% yield.[8] The reaction of quinone **5** with 1-methoxy-1,3-cyclohexadiene in methanol at room temperature gave a mixture of diastereoisomers, which upon enolization with sodium hydride, oxidation with silver(I) oxide and aromatization by heating in xylenes afforded

naphtho[2,3-b]thiopyranoquinone **6** in 40% yield.[9] The product showed a proton spectrum similar to **1**, but the definitive proof of the structure of **6** was deduced by X-Ray crystal analysis (Figure 1).




**Scheme 1**. Reagents: a) HBr/AcOH, 84%; b) $LiAlH_4$/THF, 92%; c) $K_2S_2O_6$/MeOH-$H_2ONO$, 60%; d) 1-methoxy-1,3-cyclohexadiene/MeOH; e) NaH/THF; $Ag_2O$/THF; f) 135 °C, 40% (from **5**)

**Acknowledgements**

We are grateful to FONDECYT (Research Grant 1930436) for financial support of this work and CONICYT and The British Council for a fellowship to M.G.

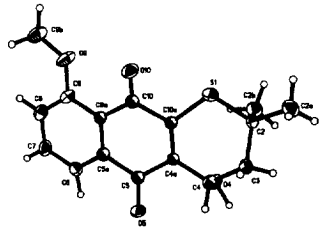


**Figure 1**: X-Ray structure for compound **6**

**References and Notes**

1. a) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.*, **1989**, 111, 7668-7670. b) Brade, W.; Vasella, A. *Helv. Chim. Acta*, **1989**, 72, 1649-1657. c) Oliveira, A. B.; Ferreira, D. T.; Raslan, D. S. *Tetrahedron Lett.* **1988**, 29, 155-158 d) Hahashi, T.; Smith, F. T.; Lee, K-H. *J. Med. Chem.*, **1987**, 30, 2005-2008.
2. Berdy, J. Handbook of Antibiotic Compounds; Vol III, CRC Press: Florida, 1980; pp. 221-279
3. Saitz, C.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* **1992**, 22, 955-960.
4. Itokawa, H.; Matsumoto, K.; Morita, H.; Takeka, K. *Phytochemistry*, **1992**, 31, 1061-1062.
5. Tapia, R.; Valderrama, J. A.; Quintanar, C. *Heterocycles*, **1994**, 38, 1797-1804.
6. Zuloaga, F.; Tapia, R.; Quintanar, C. J. Chem. Soc. Perkin Trans. 2, **1995**, 939-943.
7. Tércio, J.; Catani, V.; Comaseto, J. V. *Synthesis* **1987**, 149-153.
8. Data for compound **5**: m.p. 64-66 °C; IR 3400 (OH), 1645 and 1620 (C=O) $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$): 1.41 (3 H, s, $CH_3$), 1.50 (3 H, s, $CH_3$), 2.07 (2 H, m, $CH_2$), 3.64 (1 H, broad s, OH), 4.96 (1 H, t, 6.5 Hz, CH), 6.72 (1 H, d, J 10.1 Hz, 6-H or 7-H), 6.80 (1 H, d, J 10.1 Hz, 7-H or 6-H); $\delta_C$ (50.3 MHz, $CDCl_3$): 29.5, 29.8, 42.8, 43.1, 63.5, 133.9, 136.3, 137.8, 147.5, 183.9, 185.0; Found: C: 59.17, H: 5.21, S: 14.32, required for $C_{11}H_{12}O_3S$: C: 58.90, H: 5.39, S: 14.30.
9. Data for compound **6**: m.p. 176-178 °C; IR 3400 (OH), 1645 and 1620 (C=O) $cm^{-1}$;$\delta_H$ (250 MHz, $CDCl_3$): 1.41 (3 H, s, $CH_3$), 1.51 (3 H, s, $CH_3$), 2.10 (2 H, m, $CH_2$), 4.00 (3 H, s, $OCH_3$), 4.01 (1 H, broad s, OH), 5.10 (1 H, t, 6.6 Hz, CH), 7.25 (1 H, dd, J 8.2 and 1.0 Hz, 8-H), 7.67 (1 H, t, J 8.2 Hz, 7-H), 7.75 (1 H, dd, J 8.2 and 1.0 Hz, 6-H); $\delta_C$ (62.9 MHz, $CDCl_3$): 29.4, 29.9, 42.7, 42.9, 56.5, 64.1, 117.4, 119.4, 134.2, 134.3, 135.5, 152.6, 159.9, 180.7, 182.6; Found: C: 63.12, H: 5.36, S: 10.44, required for $C_{16}H_{16}O_4S$: C: 63.14, H: 5.30, S: 10.53. Crystal structure details: triclinic, *P*1, $a$ = 8.217 (2), $b$ = 9.695 (2), $c$ = 10.034 (3) Å; $\alpha$ = 111.43°, $\beta$ = 95.51°, $\gamma$ = 104.07°, V = 706.5 (3) $Å^3$, Z = 2, $D$ = 1.431 $g/cm^3$, $F$ (000) = 320, $T$ = 293 K.

*(Received in UK* 1 *November* 1996; *accepted* 15 *November* 1996)