Pergamon

Tetrahedron 58 (2002) 6135–6140

TETRAHEDRON

Azepines from the intramolecular Prins cyclization of an aminoderivative of lapachol

Celso A. Camara,[a] Angelo C. Pinto,[a] Maria D. Vargas[b,*] and Julio Zukerman-Schpector[c]

[a]*Centro de Tecnologia, Instituto de Química, Universidade Federal do Rio de Janeiro, Bloco A, Ilha do Fundão, 21945-970 Rio de Janeiro, RJ Brazil*

[b]*Instituto de Química, Universidade Estadual de Campinas, CP 6154, 13083-970 Campinas, SP Brazil*

[c]*Departamento de Química, Universidade Federal de São Carlos, CP 676, 13565-905 Sao Carlos, SP Brazil*

Received 25 February 2002; accepted 18 April 2002

Abstract—Intramolecular Prins reaction of the 2-(2,2-dimethoxyethylamino)-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalene-6,11-dione, an amino derivative of lapachol, under hydrolytic conditions, yielded novel azepines condensed with the naphthoquinone nucleus of lapachol.

1. Introduction

Naphthoquinone derivatives are widespread in nature and their biological and pharmacological activities are of great interest.[1] In particular, lapachol and the related quinones, α and β-lapachones, natural naphthoquinones extracted from a wide range of species from the genus *Tabebuia*, have shown anti-inflammatory,[2] antibacterial,[3] trypanocidal,[4] microbicidal[5] and molluscicidal[6] properties and activity against several types of cancer cells.[7] From the pharmacological point of view, their mechanism of action seems to include cellular toxicity mediated by a redox process.[8] We recently reported the synthesis of new amino and 1-aza-anthraquinone derivatives of lapachol.[9] We wish to report herein the synthesis of novel azepines condensed with the naphthoquinone nucleus of lapachol via an intramolecular Prins reaction[10] on an aminoketal. Seven-membered rings possessing a nitrogen atom are of interest due to their pharmacological activities.[11] Reports in the literature of the synthesis of quinones condensed with seven-membered heterocycles are rare.[12]

2. Results and discussion

Attempts at hydrolyzing compound **1** to the aldehyde derivative **2**, at room temperature, under various conditions were unsuccessful (Scheme 1). Upon heating the reaction mixture, however, a number of unexpected products were obtained, amongst which compounds **3** and **4** were separated by CC on silica gel and obtained in 42 and 8% yields, respectively. These compounds were formed as diastereomeric mixtures (according to NMR spectroscopy, *trans*/*cis* isomers, **3a/3b** ~7:3; **4a/4b** ~4:1) and were fully characterized by analytical and spectroscopic methods (see Table 1). The major diastereoisomer (*trans*) of compounds **3** and **4** (**3a** and **4a**, respectively) were separated by fractional crystallization from CH_2Cl_2/hexane. Compound **3** (**3a/3b**=7:3) was acetylated, using acetic anhydride, pyridine, and catalytic DMAP in CH_2Cl_2, to give the corresponding derivative **5** in 69–78% yield after 24 h at room temperature. According to the NMR spectra, this compound also exists as a diastereomeric mixture (**5a/5b**=7:3). The novel compounds **3**–**5** exhibit a skeleton containing the azepine ring attached to a naphthoquinone nucleus[7c,13] derived from the natural quinone lapachol.

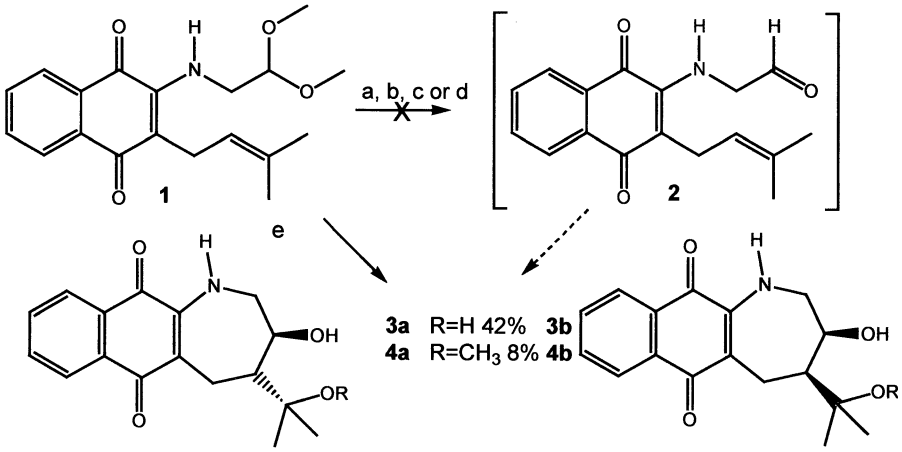
The FTIR spectrum (KBr) of **3** (**3a** and **3b** mixture) showed absorptions at 3613, 3300 and 1602 cm^{-1}, indicating the presence of NH and OH functionalities. The HRMS spectrum of **3** displayed a molecular ion peak at *m*/*z* 301, consistent with the molecular formula $C_{17}H_{19}NO_4$, and the presence of nine degrees of unsaturation. The base peak, at *m*/*z* 225, corresponds to the loss of water and acetone. It also exhibits peaks corresponding to loss of water (*m*/*z* 283) and of an isopropanol unit (*m*/*z* 59).

The ^1H NMR spectrum (see Table 1) of **3a** (500 MHz), $CDCl_3$) exhibits a broad singlet at δ 6.11 compatible with a N–H bond. This N–H signal shows a strong correlation in the COSY spectrum with one of the C-2 methylene hydrogens (at δ 49.5 according to the HMQC). A broad doublet at δ 4.24 (*J*=9.0 Hz), attributed to a CH methine at C-3 (correlated by the HMQC spectrum with a CH signal at δ 73.0), is coupled with H-4 at δ 2.18 (ddd, *J*=11.4, 9.0 and 1.0 Hz)

Keywords: azepine; naphthoquinone; lapachol; Prins reaction; ketal hydrolysis.

* Corresponding author. Fax: +55-19-3788-3023; e-mail: mdvargas@iqm.unicamp.br

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00581-1



Scheme 1. *Reagents and conditions*. (a) *p*-TsOH/THF/H_2O, rt, 2 days; (b) HCl 5% or H_2SO_4 10% MeOH/THF/H_2O, rt, 12 h; (c) BF_3, MeOH/THF/H_2O, rt; (d) $FeCl_3$/THF/H_2O, rt; (e) HCl 10% or H_2SO_4 10% in MeOH/THF/H_2O, reflux 1–2 h.

according to the COSY spectrum; H-3 couples with H-2ax, but not with H-2eq. The H-4 signal is correlated by HMQC to a CH methine at δ 53.5. The COSY spectrum shows also the correlation of H-4 with two signals at δ 2.47 (dd, J=17.0 and 11.4 Hz) and 2.96 (dd, J=17.0 and 1.0 Hz), which are related to a methylene carbon at δ 22.5, as indicated by the HMQC spectrum. These resonances are attributed to the pseudo-axial (H-5ax) and pseudo-equatorial (H-5eq) positions at C-5. H-2ax appears at δ 3.47 as a ddd (J=14.8, 6.9 and 2.0 Hz, with H-2eq, N–H and H-3, respectively). Finally, H-2eq appears at δ 3.87 as a broad doublet (J=14.8 Hz, geminal coupling). The HMBC correlations of compound **3a** (^3J correlations displayed in Table 2) also support the proposed structure containing an azepine nucleus, whose hydrogens were all assigned in the ^{1}H NMR spectrum. Although the NMR spectra do not present all the expected couplings, the *transoid* configuration proposed for isomer **3a** was confirmed by an X-ray diffraction study. In spite of the rather poor diffracting quality of the crystals, due to the presence of a disordered solvent molecule (several peaks non-interpretable in the final difference Fourier map of 2.95 eA^{-3}), the molecular structure was established unequivocally and is shown in Fig. 1.

The ^{1}H NMR spectrum of **3b** shows the CH methine (C-3) more deshielded than that of the corresponding diastereoisomer **3a**, at δ 4.63, as a broad triplet. This signal is coupled with another methine hydrogen at δ 1.91 (ddd, J=10.7, 3.7 and 2.0 Hz), attributed to the C-4 position, more shielded than the corresponding position on diastereoisomer **3a** (δ 2.18). This effect can be attributed to the proximity of the hydroxyl group at C-3. H-4 is also coupled with one of the methylene hydrogens at C-5 (J=10.7 Hz).

The coupling constant values are compatible with the *cisoid* and *transoid* configurations proposed for the **3b** (J=3.7 Hz) and **3a** isomers (J=9.0 Hz), respectively.

The ^{1}H NMR spectrum of **4a** is almost identical to that of **3a**, the only difference being the presence of the peak due to the methoxy group, at δ 3.27. The 1-OMe isopropyl moiety, at *m*/*z* 73, represents the base peak in the HRMS of **4**.

The mechanism of C–C bond formation, to give compounds **3** and **4**, seems to be similar to that of the ene intramolecular reaction between a carbonyl and an alkene.[14] However, in this case the systems are generally 1,7-dienes,[15] with the carbonyl representing the second unsaturation, and the products from the reactions are six- and eight-membered rings.[16] Instead, in our case, the prenyl-double bond and the carbonyl of the incipient aldehyde **2** form a 1,8-diene system. We propose that the formation of **3** and of the analogous compound **4** occurs through a Prins reaction,[17] via nucleophilic attack of H_2O or MeOH at the prenyl double bond, possibly followed by a concerted attack to the protonated carbonyl of **2** (Fig. 2). All reactions gave a reasonable diastereoselectivity, possibly induced by steric hindrance effects of the 4-isopropyl and 3-hydroxyl groups, in spite of the fact that the resulting seven-membered ring of **3** and **4** is less conformationally restricted than a corresponding six-membered ring.

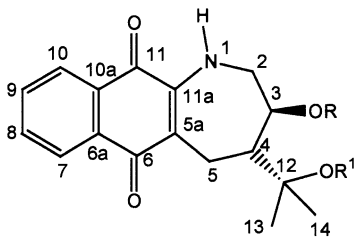
This mechanism is supported by the fact that when the same reaction was carried out in the presence of an excess MeOH and aqueous sulfuric acid at room temperature, compound **4** was obtained in 66% yield (**4a/4b**=4:1).

Anticipating that solvolytic conditions would favor hydrolysis of ketal **1** with the concomitant incorporation of the conjugated nucleophile to give **3**, the reaction of **1** was carried out in concentrated formic acid (88%) and after 2 h, at room temperature, compound **3** (**3a/3b**=7:3) was obtained as the major product (76% yield). Tlc monitoring of this reaction showed that conversion of **1** to **3** was complete after 20–30 min, and suggested that product **3** was produced from the hydrolysis of the corresponding less polar formate ester, whose formation was evidenced by tlc. Indeed, when this reaction was carried out at 0°C, compound **6** (**6a/6b**=7:3) was isolated in 58% yield, together with **3** (17%), according to Scheme 2.

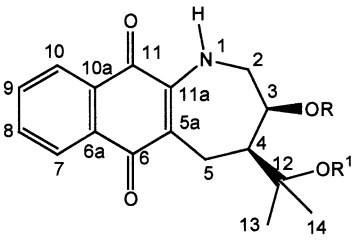
3. Conclusion

The large majority of the modifications carried out so far on the structure of lapachol involve formation of five- or six-membered rings via cyclization of the isoprenyl side chain. In our work, this chain was used with success to construct an

Table 1. ^{1}H NMR data ($CDCl_3$, 500 MHz) of compounds **3**–**6**



3a (R=R^1=H) **3b**
4a (R=H, R^1=CH_3) **4b**
5a (R=$COCH_3$, R^1=H) **5b**
6a (R=H, R^1=CHO) **6b**



	3a	3b	4a	5a	5b	6a	6b
1	6.11 (1H, brs)	5.83 (1H, brt, 7.5)	6.10 (1H, brs)	5,71 (1H, brs)	5.93 (1H, brs)	5.93 (1H, brs)	5.80 (1H, brs)
2_{ax}	3.47 (1H, ddd, 14.8, 6.9, 2.0)	3.54 (2H, brdd, 7.5, 5.1)	3.43 (1H, ddd, 14.4, 6.8, 2)	3.40 (1H, ddd, 14.5, 10.4, 2.5)	3.17 (1H, ddd, 5.0, 4.5, 14.1)	3.58 (1H, ddd, 18.0, 10.7, 3.4)	3.52 (ddd, 14.5, 8.2, 4.0)
2_{eq}	3.87 (1H, brd, 14.8)		3.84 (1H, d, 14.4)	3.59 (1H, dd, 14.5, 7.5)	3.74 (1H, dt, 4.5, 4.5, 14.1)	4.04 (brdd, 3.4, 18.0)	3.72 (1H, dt, 14.5, 8.1, 8.0)
3	4.24 (1H, brd, 9.0)	4.63 (1H, dt, 5.1, 5.1, 3.7)	4.17 (1H, d, 8.4)	4.53 (1H, ddd, 10.0, 7.5, 2.5)	3.81 (1H, dt, 4.5, 4.5, 4.0)	5.42 (1H, brdd, 9.0, 3.5)	5.66 (1H, dt, 8.2, 8.0, 3.0)
4	2.18 (1H, ddd, 11.4, 9.0, 1.0)	1.91 (1H, ddd, 10.7, 3.7, 2.0)	2.17 (1H, dd, 11.5, 8.4)	1.99 (1H, dd, 12.0, 10.0)	1.92 (1H, dd, 11.0, 4.0)	2.32 (1H, ddd, 14.3, 8.5, 2.0)	2.18 (1H, dd, 11.5, 3.0)
5_{ax}	2.47 (1H, dd, 17.0, 11.4)	3.27 (1H, brd, 17.2, 2.0)	2.47 (1H, dd, 16.7, 11.5)	n.o.	2.90 (1H, dd, 17.7, 11.0)	2.70 (1H, dd, 17.2, 14.3)	2.77 (1H, dd, 17.5, 11.4)
5_{eq}	2.96 (1H, dd, 17.0, 1.0)	2.87 (1H, dd, 17.2, 10.7)	2.97 (1H, d, 16.7)	3.30 (1H, brd, 16.7)	3.15 (1H, d, 17.7)	3.34 (1H, brdd, 17.2, 2.0)	3.36 (1H, brd, 17.5)
7	8.08 (1H, dd, 7.8, 1.0)	8.07 (1H, dd, 7.8, 1.0)	8.07 (1H, dd, 7.5, 1.0)	8.08 (1H, dd, 7.8, 1.0)	8.10 (1H, dd, 7.8, 1.0)	8.07 (1H, dd, 8.0, 1.0)	8.07 (1H, dd, 8.0, 1.0)
8	7.70 (1H, dt, 7.8, 7.8, 1.0)	7.68 (1H, dt, 7.8, 7.8, 1.0)	7.68 (1H, dt, 7.5, 7.5, 1.0)	7.70 (1H, dt, 7.8, 7.8, 1.0)	7.70 (1H, dt, 7.8, 7.8, 1.0)	7.68 (1H, dt, 8.0, 8.0, 1.0)	7.71 (1H, dt, 8.0, 8.0, 1.0)
9	7.59 (1H, dt, 7.8, 7.8, 1.0)	7.59 (1H, dt, 7.8, 7.8, 1.0)	7.59 (1H, dt, 7.5, 7.5, 1.0)	7.61 (1H, dt, 7.8, 7.8, 1.0)	7.61 (1H, dt, 7.8, 7.8, 1.0)	7.59 (1H, dt, 8.0, 8.0, 1.0)	7.61 (1H, dt, 8.0, 8.0, 1.0)
10	8.01 (1H, dd, 7.8, 1.0)	7.99 (1H, dd, 7.8, 1.0)	8.08 (1H, dd, 7.5, 1.0)	8.05 (1H, dd, 7.8, 1.0)	8.05 (1H, dd, 7.8, 1.0)	8.00 (1H, dd, 8.0, 1.0)	8.00 (1H, dd, 8.0, 1.0)
13	1.30 (3H, s)	1.39 (3H, s)	1.20 (3H, s)	1.30 (3H, s)	1.34 (3H, s)	1.29 (3H, s)	1.30 (3H, s)
14	1.42 (3H, s)	1.46 (3H, s)	1.29 (3H, s)	1.33 (3H, s)	1.41 (3H, s)	1.31 (3H, s)	1.34 (3H, s)
R	~2.0 (1H, brs)	~2.6 (1H, brs)	4.59 (1H, brs)	2.05 (3H, s)	2.05 (3H, s)		
R1	4.25 (1H, brs)	4.32 (1H, brs)	3.27 (3H, s)			8.07 (1H, s)	8.14 (1H, s)

Compound **4b** was identified in the spectrum of the mixture **4a/4b** (4:1), but its chemical shifts and coupling constants were not assigned.

Table 2. Relevant ^{3}J C–H correlations to compound **3a** ($CDCl_3$)

	^{1}H	^{13}C (HMQC, δ)	^{3}J (HMBC)
1	6.11 (1H, brs)		
2_{ax}	3.47 (1H, ddd, 14.8, 6.9, 2.0)	49.5	C4, C11a
2_{eq}	3.87 (1H, brd, 14.8)		
3	4.24 (1H, brd, 9.0)	73.0	C12
4	2.18 (1H, ddd, 11.4, 9.0, 1.0)	53.5	C5a, C13, C14
5_{ax}	2.47 (1H, dd, 17.0, 11.4)	22.5	C3, C6, C11a, C12
5_{eq}	2.96 (1H, dd, 17.0, 1.0)		
5a		115.4	
6		182.6	
6a		133.3	
7	8.08 (1H, dd, 7.8, 1.0)	126.3	C6, C9, C10a
8	7.70 (1H, dt, 7.8, 7.8, 1.0)	134.5	C6a, C10
9	7.59 (1H, dt, 7.8, 7.8, 1.0)	132.0	C7, C10a
10	8.01 (1H, dd, 7.8, 1.0)	125.9	C8, C11
10a		130.1	
11		181.3	
11a		148.7	
12		75.5	
13	1.30 (3H, s)	24.0	C4, C14
14	1.42 (3H, s)	30.9	C4, C13

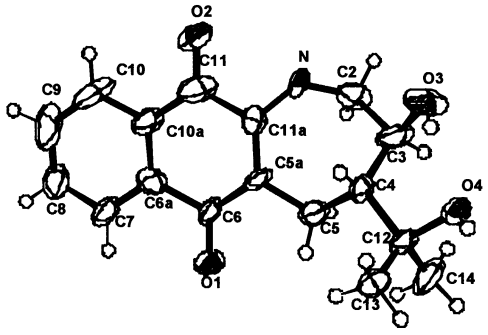


Figure 1. ORTEP drawing of the molecular structure of compound **3a**; thermal ellipsoids were drawn to the 50% probability.

azepine ring in compounds **3** and **4**, which were obtained in relatively good yields. This approach can be explored for the synthesis of other rings, providing that the 2-position of lapachol is substituted accordingly. To our knowledge, this is the first report of an intramolecular Prins reaction of a quinone derivative to give an azepine ring.

4. Experimental

4.1. General

Melting points are uncorrected and were determined on a Thomas–Hoover capillary apparatus. Column chromatography was performed on silica gel G60 (70–230 mesh, ASTM, Merck). Thin-layer chromatography was performed

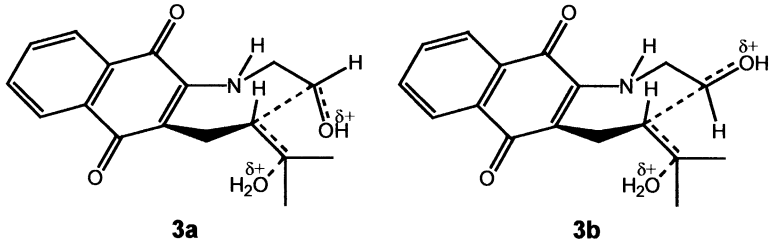
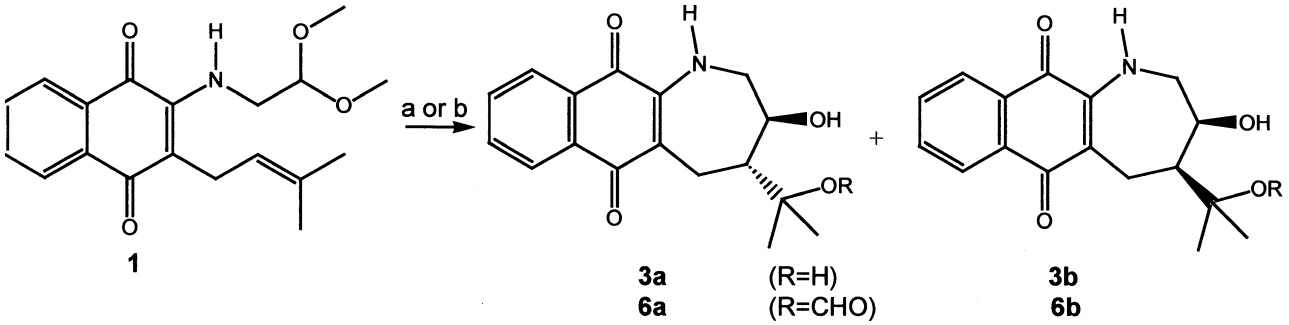


Figure 2. Proposed activation states leading to the formation of **3a** and **3b**.



Scheme 2. *Reagents and conditions*. HCO_2H 88%, 2 h (a) rt: **3** (76%); (b) 0°C: **3** (17%) + **6** (58%), see text.

Table 3. ^{13}C NMR (125 MHz, $CDCl_3$) of compounds **3**–**6**

	3a	3b[a]	4a[a]	5a	5b	6a	6b
2	49.5	49.4	49.2	50.1	50.1	46.2	46.7
3	73.0	70.4	73.0	72.2	76.8	73.8	71.8
4	53.5	48.4	53.5	46.4	46.9	52.2	48.7
5	22.5	18.4	22.2	17.9	18.0	21.1	20.0
5a	115.4	118.3	115.3	118.0	118.4	114.9	118.2
6	182.6	183.3	182.4	183.0	183.2	182.4	183.0
6a	133.3	133.4	133.4	133.0	133.2	133.3	133.1
7	126.3	126.6	126.3	126.3	126.4	126.4	126.4
8	134.5	134.7	134.4	134.4	134.4	134.6	134.5
9	132.0	132.3	132.0	132.0	132.3	132.0	132.2
10	125.9	126.1	125.9	125.8	126.0	125.9	125.9
10a	130.1	130.3	130.2	130.1	130.2	130.0	130.1
11	181.3	181.8	181.3	181.7	181.7	181.3	181.7
11a	148.7	149.4	148.6	148.9	149.4	148.5	148.4
12	75.5	74.7	73.1	74.0	75.3	72.8	72.5
13	24.0	28.5	17.9	22.8	23.3	26.8	27.7
14	30.9	29.4	23.7	28.8	28.7	28.1	28.5
R				21.0	22.0		
				171.1	171.2		
R^1			52.4			160.5	160.2

[a] 50 MHz; compound **4b** was identified in the spectrum of the mixture **4a/4b** (4:1).

on 0.2 mm plates (Merck) and visualized with short wavelength UV light. ^1H NMR and ^{13}C NMR spectra (Tables 1–3) were recorded on a Bruker ACF-200, Bruker AMX-300 or Varian I-NOVA-500 spectrometers. All attributions were carried out with HOMOCOSY, HMBC and HMQC experiments. Values reported for coupling constants are first order. High-resolution mass spectra were obtained by electron impact (70 eV) on a VG Autospec spectrometer. Compound **1** is obtained from the displacement reaction of 2-methoxylapachol with the corresponding 2,2-dimethoxyaminoacetaldehyde[9] (Table 3).

4.1.1. 3-Hydroxy-4-(1-hydroxy-1-methylethyl)-2,3,4,5,6,11-hexahydro-1*H*-naphtho[2,3-*b*]azepine-6,11-dione (3). To a stirred solution of **1** (200 mg, 0.61 mmol) in 10 mL of methanol was added a mixture of 10 mL of tetrahydrofuran and 10 mL of 10% H_2SO_4 solution. The resulting light red solution was refluxed gently for 1 h, and the reaction mixture turned deep red colored. Sodium bicarbonate saturated solution was added to neutralize the reaction mixture, which was extracted with ethyl acetate (3×15 mL). The combined organic fractions were dried over Na_2SO_4 to yield a red oil. Flash chromatography (SiO_2) with 20% EtOAc/hexane gave 77 mg of **3** (r_f=0.16 in 42%) as a red oil (crystals of **3a** from CH_2Cl_2/hexane, mp 173–5°C). IR (**3**, KBr, ν_{max}, cm^{-1}) 3613, 3300, 2973, 2935, 1670, 1602, 1565, 1502, 1373, 1274. MS (rel. int.) *m/z* 59 (35), 77 (29), 225 (100), 243 (30), 254 (14), 268 (12), 283 (11), 301 (M^+, 7). HRMS found: 301.0755; calcd for $C_{17}H_{19}NO_4$: 301.1314. Compound **4** (15 mg, 8%) was also obtained (r_f=0.28, crystals of **4a** from CH_2Cl_2/hexane, mp 92–3°C). IR (**4**, KBr, ν_{max}, cm^{-1}) 3430, 3331, 3067, 2979, 2967, 2918, 2837, 1669, 1607, 1572, 1489, 1338, 1268, 1075, 727. MS (rel. int.) *m/z* 43 (7), 73 (100), 225 (19), 243 (56), 254 (6), 266 (5), 283 (6), 300 (1), 315 (M^+, 4). HRMS found: 315.1470; calcd for $C_{18}H_{21}NO_4$ 315.1470.

4.1.2. 4-(1-Hydroxy-1-methylethyl)-6,11-dioxo-2,3,4,5,6,11-hexahydro-1*H*-naphtho[2,3-*b*]azepin-3-yl acetate (5). To a mixture of pyridine (0.2 mL) were added Ac_2O (0.2 mL) and a few crystals of DMAP in 10 mL of CH_2Cl_2. After adding 30 mg (0.1 mmol) of compound **3**, the resulting mixture was stirred for 24 h, after which time tlc inspection of the reaction mixture showed no more starting material. The mixture was then extracted sequentially with a 5% cupric sulfate aqueous solution, brine and water (3×10 mL each). The organic phase was dried over Na_2SO_4, and submitted to SiO_2 flash chromatography using 20% EtOAc/hexane, furnishing 26.7 mg of the 3-acetoxyazepin derivative **5** as a diastereomeric mixture (7:3) in 78% yield (r_f=0.45). Red solid; crystals of **5a** from CH_2Cl_2/hexane, mp 143–5°C. IR (**5**, KBr, ν_{max}, cm^{-1}) 3354, 3074, 2975, 2932, 2923, 1731, 1668, 1606, 1573, 1490, 125. MS (rel. int.) *m/z* 59 (18), 225 (100), 250 (11), 285 (3), 343 (M^+, 5). HRMS found: 343.1419; calcd for $C_{19}H_{21}NO_5$ 343.1419.

4.1.3. 1-(3-Hydroxy-6,11-dioxo-2,3,4,5,6,11-hexahydro-1*H*-naphtho[2,3-*b*]azepin-4-yl)-1-methylethyl formate (6). Compound **1** (329 mg, 1 mmol) was dissolved in 5 mL of 88% formic acid and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was neutralized with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate (3×20 mL). The combined extracts were dried over Na_2SO_4 and concentrated, furnishing 228 mg (76%) of **3** after flash chromatography (20% EtOAc/hexane). Under the same conditions described above, but at 0°C, the following products were obtained: **3** (51 mg, 17%) and formate **6** (diastereomeric mixture **6a/6b**=7:3; 194 mg, 59%) as a red solid (crystals of **6a** from CH_2Cl_2/hexane, r_f=0.39, mp 142°C,). IR (**6**, KBr, ν_{max}, cm^{-1}) 3529, 3406, 2980, 2939, 1700, 1663, 1601, 1568, 1489, 1337, 1260, 1170. HRMS found: 329.1263; calcd for $C_{18}H_{19}NO_5$ 329.1263.

4.1.4. 3-Hydroxy-4-(1-methoxy-1-methylethyl)-2,3,4,5,6,11-hexahydro-1*H*-naphtho[2,3-*b*]azepine-6,11-dione (4). To a stirred solution compound **1** (250 mg, 0.76 mmol) in 15 mL of MeOH were added 5 mL of 10% H_2SO_4. After refluxing for 45 min, the reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (SiO_2) using AcOEt/hexane afforded **4** as a red solid (158 mg, 66%); crystals of **4a** from CH_2Cl_2/hexane, mp 92°C).

Acknowledgements

The authors thank FAPERJ, FAPESP, CNPq and FUJB for financial support. CAC thanks Dr M. G. Carvalho (ICE-UFRRJ) for the use of facilities and to Drs S. J. Garden and C. R. Kaiser (IQ-UFRJ) for useful discussions.

References

1. (a) Salmon-Chemin, L.; Buisine, E.; Yardley, V.; Kohler, S.; Debreu, M.; Landry, V.; Sergheraert, C.; Croft, S. L.; Krauth-Siegel, R. L.; Davioud-Charvet, E. *J. Med. Chem.* **2001**, *44*, 548. (b) Chenna, P. H. D.; Benedetti-Doctorovich, V.; Baggio,

R. F.; Garland, M. T.; Burton, G. *J. Med. Chem.* **2001**, *44*, 2486.
2. De Almeida, E. R.; Da Silva Filho, A. A.; Dos Santos, E. R.; Lopes, C. A. C. *J. Ethnopharmacol.* **1990**, *29*, 239.
3. (a) Schulze, W.; Gutsche, W.; Wohlrabe, K.; Tresselt, D.; Horn, G.; Fleck, W. *Pharmazie* **1986**, *41*, 99. (b) Bakola-Christianopoulou, M. N.; Ecateriniadou, L. B.; Sarris, K. J. *Eur. J. Med. Chem. Chim. Ther.* **1986**, *21*, 385. (c) Sharma, P. K.; Rohatagi, B. K.; Khanna, R. N. *Acta Chim. Hung.* **1985**, *120*, 163.
4. De Moura, K. C. G.; Emery, F. S.; Neves-Pinto, C.; Pinto, M. C. F. R.; Dantas, A. P.; Salomão, K.; Castro, S. L.; Pinto, A. V. *J. Braz. Chem. Soc.* **2001**, *12*, 325 and references therein.
5. Oliveira, C. G. T.; Miranda, F. F.; Ferreira, V. F.; Freitas, C. C.; Rabello, R. F.; Carballido, J. M.; Corrêa, L. C. D. *J. Braz. Chem. Soc.* **2001**, *12*, 339 and references therein.
6. Dos Santos, A. F.; Ferraz, P. A. L.; Pinto, A. V.; Pinto, M. C. F. R.; Goulart, M. O. F.; Santana, A. E. G. *Int. J. Parasitol.* **2000**, *30*, 1199.
7. (a) Suzuki, M.; Matsumoto, T.; Ohsaki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1987**, *35*, 3658. (b) Tandon, V. K.; Vaish, M.; Khanna, J. M.; Anand, N. *Arch. Pharm. (Weinheim Ger.)* **1990**, *323*, 383. (c) Khalil, M. A.; Habib, N. S. *Arch. Pharm. (Weinheim Ger.)* **1990**, *323*, 471. (d) Antonello, C.; Uriarte, E.; Palumbo, M. *Arch. Pharm. (Weinheim Ger.)* **1988**, *321*, 513.
8. De Abreu, F. C.; Ferraz, P. A. L.; Goulart, M. O. F. *J. Braz. Chem. Soc.* **2002**, *13*, 1.
9. Camara, C. A.; Pinto, A. C.; Rosa, M. A.; Vargas, M. D. *Tetrahedron* **2001**, *57*, 9569.
10. (a) Tomösközi, I.; Gruber, L.; Baitz-Gáts, E. *Tetrahedron* **1992**, *48*, 10345. (b) Hu, Y.; Skalitzky, D. J.; Richnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. (c) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Corwva, R.; Price, R. *Tetrahedron* **1981**, *37*, 3927.
11. (a) Martinez, R.; Espinoza, R. C.; Toscano, R. A.; Cogordan, J. A.; Arellano, M. R. *J. Heterocycl. Chem.* **1996**, *33*, 715. (b) Taylor, E. C.; Dowling, J. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 453. (c) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J. *J. Med. Chem.* **1987**, *30*, 1433. (d) Laatsch, H.; Ernst, B. P.; Hoffmann, D. *Liebigs Annu. Org. Bioorg. Chem.* **1995**, 1773. (e) Kunick, C. *Arch. Pharm. (Weinheim Ger.)* **1991**, *324*, 579. (f) Link, A.; Kunick, C. *J. Med. Chem.* **1998**, *41*, 1299.
12. Valderrama, J. A.; Pessoa-Mahana, H.; Tapia, R. *J. Heterocycl. Chem.* **1992**, *29*, 1177.
13. For related systems with seven-membered rings on quinones, see: (a) Bleeker, C.; Kunick, C. *Pharmazie* **1999**, *54*, 645. (b) Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1966**, *7*, 2361. (c) Dunn, J. P.; Muchowski, J. M.; Nelson, P. H. *J. Med. Chem.* **1981**, *24*, 1097. (d) Misiti, D.; Moore, H. W.; Folkers, K. *Tetrahedron Lett.* **1965**, 1071. (e) Kita, Y.; Takada, T.; Ibaraki, M.; Gyoten, M.; Mihara, S.; Fujita, S.; Tohma, H. *J. Org. Chem.* **1996**, *61*, 223. (f) Misiti, D.; Moore, H. W.; Folkers, K. *Tetrahedron* **1966**, *22*, 1201.
14. Achmatowicz, O.; Białecka-Florjańczyk, E. *Tetrahedron* **1996**, *52*, 8827.
15. Noguchi, M.; Yamada, H.; Takamura, S. *Eur. J. Org. Chem.* **2000**, 1489.
16. Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994.
17. Kocovsky, P.; Ahmed, G.; Srogl, J.; Malkov, A. V.; Steele, J. *J. Org. Chem.* **1999**, *64*, 2765.