

A Simple Synthesis of a Model of the Tetracyclic Bisketal Lactone Mainframe of Saudin

by **Guillermo R. Labadie, Liliana E. Luna, Raquel M. Cravero, and Manuel González-Sierra***

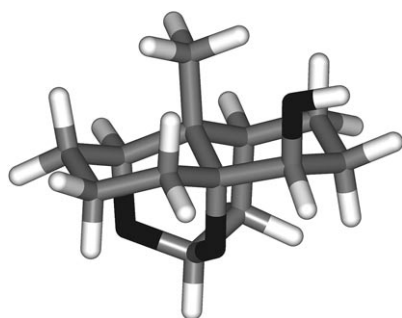
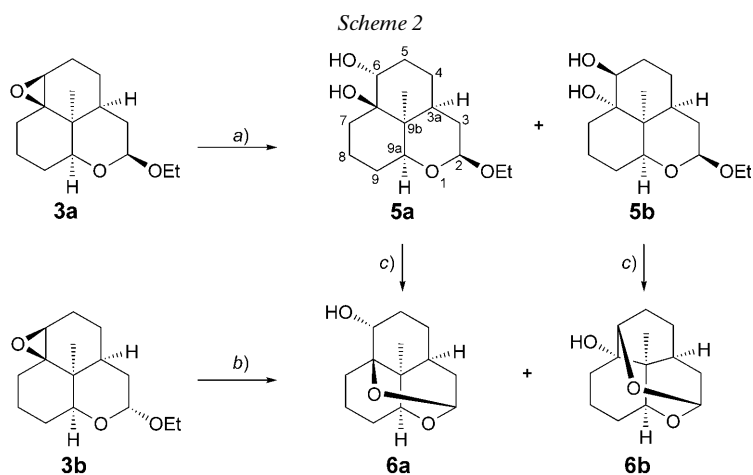
Instituto de Química Orgánica y de Síntesis (IQUIOS-CONICET),
Departamento de Química Orgánica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad
Nacional de Rosario, Suipacha 531, S2002LRK, Rosario, Argentina
(phone/fax: +54-341-4370477; e-mail: gonzalezsierra@iquios.gov.ar)

The partial structure **2** of the bisketal-type, tetracyclic saudin (**1**), an important natural product, was *de novo* synthesized. A key step was the *Jones* oxidation of the epoxide **3**, which gave rise to epoxide-ring opening, followed by acetal hydrolysis, alcohol oxidation, and, finally, intramolecular acetal formation. The resulting key intermediate was finally oxidized to the target lactone **2**.

Introduction. – Saudin (**1**) is a natural product with a bisketal polycyclic skeleton. Its isolation from the leaves of the toxic plant *Cluytia richardiana* was reported in 1985 [1]. It was found to induce hypoglycemia in mice, and could be a new promising lead structure for the development of new agents to treat diabetes [2]. Structurally, compound **1** is a sesquiterpene with a unique rearranged labdane skeleton including seven stereogenic centers, four of them consecutive. Since its isolation, different groups have been interested in its preparation [3–5]. The first total synthesis was reported by *Winkler* and *Doherty* [6]. Later, *Boeckman et al.* [7] published the first enantioselective synthesis of saudin, and also determined its absolute configuration.

During the last years, our group has been working on the preparation of related model compounds [8–10], and the development of new synthetic approaches [11]. Herein, we describe the stereoselective synthesis of the lactone **2** as a simplified model of saudin (**1**) containing the bisketalic oxygenated cage with its seven-membered lactone ring. The fact that saudin (**1**) possesses four consecutive stereogenic C-atoms, *i.e.*, C(1)–C(5)–C(9)–C(16), disposed into a four-ring fashion, make the synthesis of this moiety particularly challenging. Also, the synthesis of compounds that can help to determine the pharmacophoric-group requirements for activity is a key issue, being especially important in cases like saudin (**1**), where the mechanism of action has not been elucidated yet. The high density of functional groups of this natural product adds difficulties to develop plain synthetic procedures to prepare simplified model compounds.

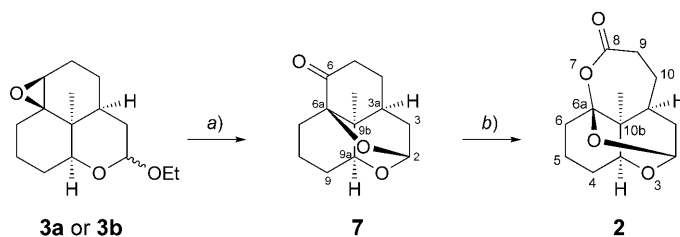
Results and Discussion. – Our strategy for the synthesis of lactone **2** was based on the epoxy-ketal **3** previously obtained in our laboratory [9–11]. This compound can be easily prepared in four steps starting from α -tetralone (**4**; *Scheme 1*). Starting from compounds of type **3**, initial epoxide-ring opening was attempted under acidic condi-

Fig. 1. Calculated structure of **6a**

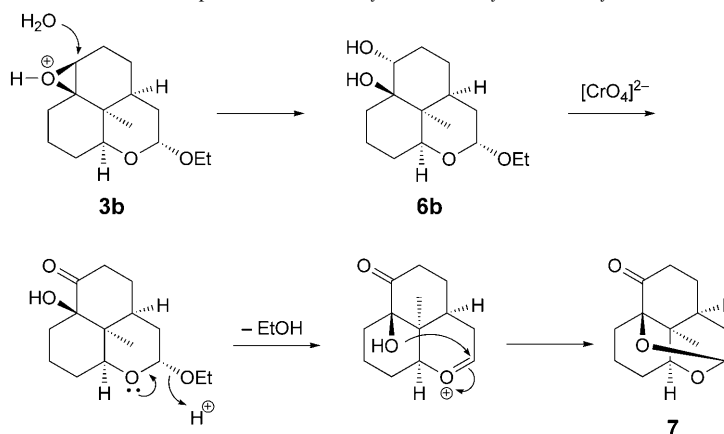
With the impossibility of oxidizing **6a**, and having in mind that epoxide-ring opening seems to be faster than acetal hydrolysis, we considered that, as an alternative, one could accomplish alcohol oxidation before the formation of the cyclic ketal. For the oxidation step under acidic conditions, our first choice was to use *Jones'* reagent [13]. Indeed, under these conditions, the epoxy-ketal **3a** was converted after 2 h to the desired compound **7** (Scheme 3). After isolation and purification, the $^1\text{H-NMR}$ spectrum of **7** showed the lack of the signals of the H-atoms of the epoxide and the ethyl ketal, and appearance of the characteristic signal for the cyclic ketal at $\delta(\text{H})$ 5.21, and of the expected $\text{C}=\text{O}$ resonance at $\delta(\text{C})$ 210 in the $^{13}\text{C-NMR}$ spectrum. Thus, under these conditions, we were able to perform four transformations in a simple one-pot reaction.

Based on our experience, we postulate a mechanism as shown in Scheme 4. The first step probably involves acid-catalyzed epoxide-ring opening. Then, the secondary alcohol is oxidized by chromate to the keto alcohol. Subsequently, the ketal is hydrolyzed and intermolecularly cyclized to **7**. We think that oxidation occurs before ketal hydrolysis, based on the results found for the epoxide-ring opening under acidic conditions shown above, where the ketal was formed and the secondary alcohol could not be oxi-

Scheme 3



a) Jones' reagent, acetone; 72%. b) *m*-CPBA, NaHCO₃, CH₂Cl₂, –20°; 88%.

Scheme 4. Proposed Mechanism for the Transformation of **3b** to **7**

dized. Therefore, it is clear that the epoxide is opened by α -attack of H₂O at C(6a), followed by nucleophilic ring opening without carbocation formation.

With compound **7** at hand, we next explored different ways to form the lactone **2**. As shown in *Scheme 3*, this was finally achieved by regioselective *Baeyer–Villiger* oxidation with *m*-CPBA ('*meta*-chloroperbenzoic acid') in CH₂Cl₂ at –20°, and in the presence of NaHCO₃ [14] to prevent acetal hydrolysis. The reaction proceeded under exclusive formation of **2** in good yield (88%). The structural corroboration of the product was achieved by a full analysis of the ¹³C-NMR spectroscopic data (*Fig. 2*): the signal of C(6a) at δ (C) 81.07 for **7** was shifted to δ (C) 106.7 in **2**; similarly, the signal of the keto C=O group of **7** was shifted from δ (C) 210.0 to 172.7, which is characteristic for a lactone (**2**). The complete assignment of the spectra was accomplished by a combination of 1D- and 2D-NMR experiments. Further, a good correlation was observed between the ¹³C-NMR chemical shifts of **2** and those of the most-significant signal reported for saudin (**1**) [1].

Conclusions. – This paper describes a simple two-step conversion of the epoxide **3** to the tetracyclic lactone **2** under complete stereocontrol in a very efficient way. The key step, *Jones* oxidation, induces four transformations in a one-pot reaction.

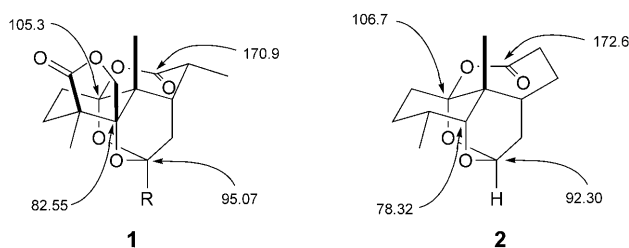


Fig. 2. Comparison of the ^{13}C -NMR chemical shifts (in ppm) of saudin (**1**) and the target compound **2**

We are grateful to *Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET)* for generous financial support. *R. M. C.* and *G. R. L.* are members of the Researcher Career of the *National Research Council of Argentina (CONICET)*.

Experimental Part

General. All solvents were dried and distilled before use. All reactions were carried out under anhydrous conditions in an N_2 atmosphere. TLC: aluminum-foil plates coated with 0.1-mm *Merck silica gel 60 GF₂₅₄*. Column chromatography (CC): *Merck silica gel 60 H*, under a low pressure of N_2 , with increasing AcOEt /hexane gradients. M.p.: *Ernst Leitz* hot-stage microscope; uncorrected. IR Spectra: *Bruker FT I-25* spectrophotometer; in cm^{-1} . ^1H - and ^{13}C -NMR Spectra were recorded at 200.1 and 50.3 MHz, resp., on a *Bruker AC-200-E* spectrometer in CDCl_3 soln.; δ in ppm, J in Hz. 2D-NMR Experiments were run with standard *Bruker* software. High-resolution mass spectrometry (HR-MS) was performed at the UCR Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside, U.S.A. Elemental analyses were performed at *Atlantic Microlab, Inc.*, Georgia, U.S.A.

(2*S*,3*aS*,6*R*,6*aR*,9*aS*,9*bS*)- (**5a**) and (2*S*,3*aS*,6*S*,6*aS*,9*aS*,9*bS*)-2-Ethoxydecahydro-9*b*-methylnaphtho[1,8-*bc*]pyran-6,6*a*(4*H*)-diol (**5b**). To a soln. of **3a** (80 mg, 0.32 mmol) in $\text{THF}/\text{H}_2\text{O}$ 2:1 (8 ml), 6*N* aq. HCl (50 μl) was added, and the mixture was allowed to react overnight. The mixture was neutralized by addition of sat. aq. NaHCO_3 soln. (5 ml), and then extracted with Et_2O (3 \times 3 ml). The combined org. extracts were dried (Na_2SO_4) and evaporated, and the residue was subjected to CC (SiO_2) to provide **5a** (64 mg, 75%) and **5b** (5 mg, 6%).

Data of 5a. Colorless solid. IR (KBr): 3265, 2960, 1410, 1325, 1285, 1270, 1245, 1125, 1060, 1045, 960, 735. ^1H -NMR: 5.40 (s, 6*a*-OH); 4.54 (*dd*, $J = 10.0, 2.7$, H-C(2)); 4.00–3.88 (*m*, 1 H of OCH_2); 3.83 (br. s, H-C(6)); 3.58–3.40 (*m*, 1 H of OCH_2); 3.25 (br. s, H-C(9*a*)); 2.70 (*dt*, $J = 14.4, 2.0$); 2.40–1.50 (*m*, 13 H); 1.23 (*t*, $J = 7.2$, MeCH_2); 1.23 (s, 9*b*-Me). ^{13}C -NMR: 102.6 (C(2)); 34.1 (C(3)); 36.8 (C(3*a*)); 20.8 (C(4)); 25.2 (C(5)); 63.4 (C(6)); 75.6 (C(6*a*)); 32.4 (C(7)); 16.9 (C(8)); 25.9 (C(9)); 82.7 (C(9*a*)); 35.7 (C(9*b*)); 22.9 (9*b*-Me); 64.2 (OCH_2); 15.1 (MeCH_2).

Data of 5b. Yellowish oil. ^1H -NMR: 5.04 (s, 6*a*-OH); 4.54 (*dd*, $J = 10.0, 2.7$, H-C(2)); 4.00–3.85 (*m*, 1 H of OCH_2); 3.58–3.45 (*m*, 1 H of OCH_2); 3.50 (br. s, H-C(6)); 3.24 (br. s, H-C(9*a*)); 2.50–1.40 (*m*, 14 H); 1.23 (*t*, $J = 7.0$, MeCH_2); 1.19 (s, 9*b*-Me).

(2*R*,3*aS*,6*R*,6*aR*,9*aS*,9*bS*)-Decahydro-9*b*-methyl-2,6*a*-epoxynaphtho[1,8-*bc*]pyran-6(4*H*)-ol (**6a**) and (2*R*,3*aS*,6*S*,6*aS*,9*aS*,9*bS*)-Decahydro-9*b*-methyl-2,6*a*-epoxynaphtho[1,8-*bc*]pyran-6*a*(4*H*)-ol (**6b**). Following the procedure mentioned above for the hydrolysis of **3a**, compound **3b** (43 mg, 0.17 mmol) in $\text{THF}/\text{H}_2\text{O}$ 2:1 (3 ml) was treated with 6*N* aq. HCl (20 μl) to provide, after purification by CC, **6a** (22 mg, 60%) and **6b** (10 mg, 10%).

Data of 6a. Colorless oil. IR (film): 2948, 2926, 2884, 1776, 1732, 1460, 1446, 1276, 1240, 1116, 1072, 1022, 998, 918, 904, 720. ^1H -NMR: 5.10 (*ddd*, $J = 3.4, 1.2$, H-C(2)); 3.76 (br. *d*, $J = 4$, H-C(9*a*)); 3.63 (br. *d*, $J = 3$, H-C(6)); 2.60–1.40 (*m*, 14 H); 1.20 (s, 9*b*-Me). ^{13}C -NMR: 90.5 (C(2)); 34.1 (C(3)); 32.3 (C(3*a*)); 21.9 (C(4)); 25.9 (C(5)); 62.2 (C(6)); 77.9 (C(6*a*)); 30.6 (C(7)); 16.1 (C(8)); 26.1 (C(9)); 76.7 (C(9*a*)); 32.7 (C(9*b*)); 19.2 (9*b*-Me). MS: 207 (1, $[\text{M} - \text{OH}]^+$), 182 (55), 105 (100), 77 (61), 51 (29).

Data of 6b. Colorless oil. IR (film): 2930, 2870, 1465, 1440, 1280, 1160, 1120, 1080, 1010, 950, 835, 640. ¹H-NMR: 5.07 (*d*, *J* = 2.6, H–C(2)); 3.62 (*d*, *J* = 3.2, H–C(6)); 3.47 (br. *s*, H–C(9a)); 2.20–1.13 (*m*, 14 H); 1.13 (*s*, 9b-Me). ¹³C-NMR: 90.6 (C(2)); 34.2 (C(3)); 32.9 (C(3a)); 22.1 (C(4)); 24.7 (C(5)); 73.8 (C(6)); 76.7 (C(6a)); 29.4 (C(7)); 15.9 (C(8)); 26.3 (C(9)); 76.2 (C(9a)); 32.2 (C(9b)); 16.4 (9b-Me).

(2*R*,3*aS*,6*aR*,9*aS*,9*bS*)-Decahydro-9*b*-methyl-2,6*a*-epoxynaphtho[1,8-*bc*]pyran-6(6*H*)-one (**7**). To a soln. of **3** (60 mg; 0.24 mmol) in acetone (8 ml) at 0°, Jones' reagent (210 µl) was added dropwise. When the addition was complete, the mixture was maintained at r.t. and stirred until all the starting material had disappeared (*ca.* 90 min according to TLC). Excess reagent was quenched by addition of *i*-PrOH, and then filtered through a pad of Celite (180 mg), and then through a pad of SiO₂, eluting in both cases with AcOEt. The filtrate was concentrated and purified by CC (SiO₂) to afford **7** (39 mg, 72%). IR (film): 2962, 2938, 2876, 1712, 1452, 1342, 1254, 1142, 1118, 1069, 1006, 908, 812, 672. ¹H-NMR: 5.21 (*dd*, *J* = 2.5, 1.5, H–C(2)); 3.85 (*t*, *J* = 2.2, H–C(9a)); 3.20–3.02 (*m*, H–C(7)); 2.33–1.40 (*m*, 12 H); 0.84 (*s*, 9b-Me). ¹³C-NMR: 89.6 (C(2)); 32.7 (C(3)); 32.7 (C(3a)); 24.1 (C(4)); 35.1 (C(5)); 210.0 (C(6)); 81.1 (C(6a)); 27.8 (C(7)); 15.0 (C(8)); 25.7 (C(9)); 75.0 (C(9a)); 37.0 (C(9b)); 16.7 (9b-Me). HR-EI-MS: 222.1259 (*M*⁺, C₁₃H₁₈O₃⁺; calc. 222.1256).

'2,6*a*-Epoxy-10*b*-methyl-perhydro-3,7-dioxacyclohepta(de)naphthalen-8-one' (**2**)¹. To a soln. of **7** (24 mg, 0.11 mmol) in anhyd. CH₂Cl₂ (3 ml) was added solid NaHCO₃ (20 mg, 0.14 mmol) at 0°, and then *m*-CPBA (42 mg, 0.15 mmol) in small portions. After 2 h, the mixture was poured into brine and extracted with CH₂Cl₂ (3 × 5 ml). The combined org. extracts were washed with 1M aq. NaOH soln. and H₂O, dried (Na₂SO₄), and evaporated to afford, after purification by CC, the title compound (23 mg, 88%). Clear oil. IR (film): 2956, 2947, 2834, 1645, 1452, 1347, 1218, 1191, 1064, 1019, 916, 819. ¹H-NMR: 5.30 (br. *s*, H–C(2)); 3.92 (br. *s*, H–C(3a)); 2.92 (*dt*, *J* = 2.8, 14.4, H–C(9)); 2.56 (*ddd*, *J* = 1.4, 5.3, 14.4, H–C(9)); 2.24–1.45 (*m*, 11 H); 1.05 (*s*, 10b-Me). ¹³C-NMR: 92.4 (C(2)); 37.4 (C(1)); 35.7 (C(10a)); 24.4 (C(10)); 34.1 (C(9)); 172.7 (C(8)); 106.8 (C(6a)); 30.1 (C(6)); 16.1 (C(5)); 24.8 (C(4)); 78.4 (C(3a)); 37.6 (C(10b)); 15.24 (10b-Me). HR-EI-MS: 238.1185 (*M*⁺, C₁₃H₁₈O₄⁺; calc. 238.1205). Anal. calc. for C₁₃H₁₈O₄: C 65.53, H 7.61; found: C 65.63, H 7.64.

REFERENCES

- [1] J. S. Mossa, J. M. Cassady, M. D. Antoun, S. R. Byrn, A. T. McKenzie, J. F. Kozlowski, P. Main, *J. Org. Chem.* **1985**, *50*, 916.
- [2] J. S. Mossa, I. A. Muhammed, M. A. Al-Yahya, H. M. Mirza, F. El-Feraly, A. T. McPhail, *J. Nat. Prod.* **1996**, *59*, 224.
- [3] R. K. Boeckman, M. J. Neeb, M. D. Gaul, *Tetrahedron Lett.* **1995**, *36*, 803.
- [4] J. D. Winkler, E. M. Doherty, *Tetrahedron Lett.* **1998**, *39*, 2253.
- [5] U. K. Tambar, T. Kano, B. M. Stoltz, *Org. Lett.* **2005**, *7*, 2413.
- [6] J. D. Winkler, E. M. Doherty, *J. Am. Chem. Soc.* **1999**, *121*, 7425.
- [7] R. K. Boeckman, M. R. Rico-Ferreira, L. H. Mitchell, P. Shao, *J. Am. Chem. Soc.* **2002**, *124*, 121.
- [8] G. R. Labadie, R. M. Cravero, M. Gonzalez-Sierra, *Synth. Commun.* **1996**, *26*, 4671.
- [9] G. R. Labadie, R. M. Cravero, M. Gonzalez-Sierra, *Molecules* **2000**, *5*, 321.
- [10] G. R. Labadie, L. E. Luna, M. Gonzalez-Sierra, R. M. Cravero, *Eur. J. Org. Chem.* **2003**, 3429.
- [11] R. M. Cravero, M. Gonzalez-Sierra, G. R. Labadie, *Helv. Chim. Acta* **2003**, *86*, 2741.
- [12] R. B. Miller, C. G. Gutierrez, *J. Org. Chem.* **1978**, *43*, 1569.
- [13] A. Jones, *J. Chem. Soc.* **1956**, 2456.
- [14] E. Lee, I. Choi, S. Y. Song, *J. Chem. Soc., Chem. Commun.* **1995**, 321.

Received July 14, 2006

¹) Systematic name: (2*R*,3*aS*,7*aS*,10*aS*,10*bS*)-decahydro-10*b*-methyl-2,7*a*-epoxyprano[4,3,2-*ef*][1]benzoxepin-6(6*H*)-one; the anal. data refer to the non-systematic name (see atom numbering in Scheme 3).