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***

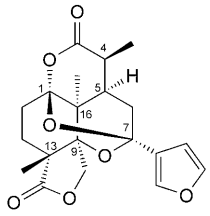
Instituto de Química Orgánica y de Síntesis (IQUIOS-CONICET),
Departamento de Química Orgánica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK, Rosario, Argentina
(phone/fax: +54-341-4370477; e-mail: gonzalezsierra@iquios.gov.ar)

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**.

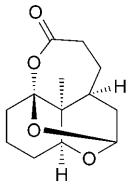
Introduction. – Saudin (**1**) is a natural product with a bisketal polycyclic skeleton. Its isolation from the leaves of the toxic plant *Cluytia richardiana* was reported in 1985 [1]. It was found to induce hypoglycemia in mice, and could be a new promising lead structure for the development of new 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-



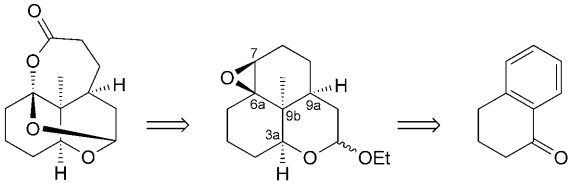
(–)-Saudin (**1**)



2

tions. This reaction was performed with 6M HCl in THF/H_2O, which gave different results, depending on the relative configuration at C(2) of the starting ketal. When compound **3a** was submitted to hydrolysis, a mixture of the corresponding 6α,6aβ- and 6β,6aα-diols **5a** and **5b** was obtained in a ratio of 12.5 : 1, respectively, with a yield of 81% (*Scheme 2*). When the same reaction conditions were applied to the α-ketal **3b**, a mixture of the tetracyclic ketals **6a**/**6b** in a 2.3 : 1 ratio was obtained, in this case with a yield of 85%.

Scheme 1. *Retrosynthetic analysis of the target compound* **2**

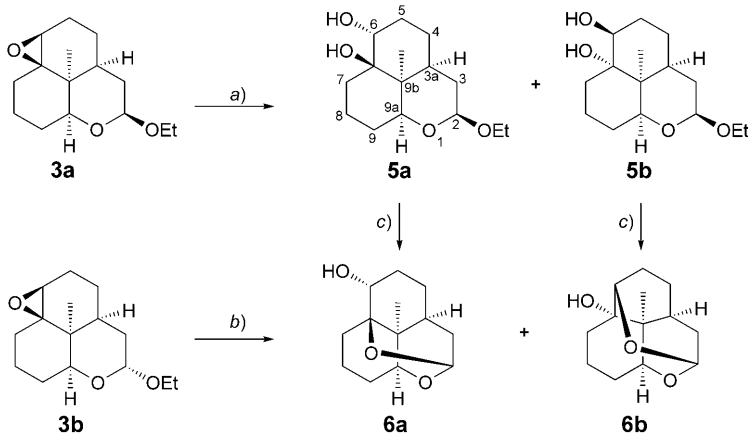


2 **3** **4**

It appears that after initial epoxide-ring opening, the diol cyclizes under acid catalysis to form the corresponding ketals. To demonstrate this hypothesis, we tested whether compounds **6a** and **6b** would be obtained as products of an intramolecular ketalization of the diols **5a** and **5b**, respectively (*Scheme 2*). The reaction was performed by stirring a solution of the alcohols in toluene in the presence of TsOH (=4-methylbenzenesulfonic acid) as catalyst at room temperature for 2 d [8]. Indeed, the expected ketals were quantitatively obtained in both cases, which corroborated how these compound are produced. The observation that none of the cyclic acetals were formed when the hydrolysis was performed with the β-acetal suggests that the reaction with the α-acetal might be assisted by an intramolecular ketalization.

The synthesis continued with different attempts to oxidize the alcohol **6a** to the corresponding ketone. A large variety of reagents and conditions were tested, such as CrO_3, AcOH, r.t., overnight [12]; pyridinium dichromate, CH_2Cl_2, r.t., 24 h; or *Jones* reagent, acetone, 0° [13]. In all cases, the starting material was fully recovered, showing the high stability of the ketal function even under harsh conditions. A careful examination of this caged structure, as confirmed later by molecular modeling (*Fig. 1*), showed an extreme conformational rigidity that, together with a 1,3-diaxial interaction, could hinder the approach of reagents, thus preventing alcohol oxidation.

Scheme 2



a) 6M HCl, THF/H_2O, 40°; 81%. *b*) 6M HCl THF/H_2O, 40°; 85%. *c*) TsOH, toluene, 2 d; quant.

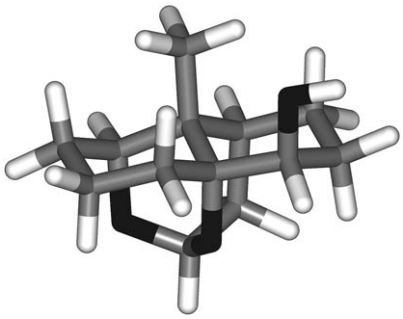
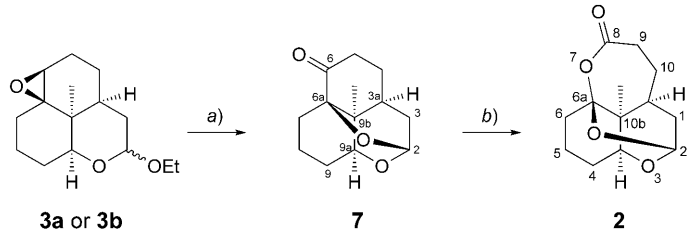


Fig. 1. *Calculated structure of* **6a**

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}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 δ(H) 5.21, and of the expected C=O resonance at δ(C) 210 in the ^{13}C-NMR spectrum. Thus, under these conditions, we were able to perform four transformations in a simple one-pot reaction.

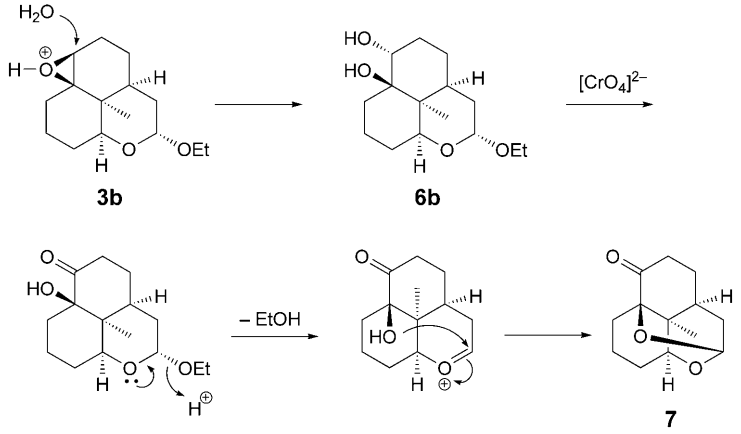
Based on our experience, we postulate a mechanism as shown in *Scheme 4*. The first step probably involves acid-catalyzed epoxide-ring opening. Then, the secondary alcohol is oxidized by chromate to the keto alcohol. Subsequently, the ketal is hydrolyzed and intermolecularly cyclized to **7**. We think 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, $NaHCO_3$, CH_2Cl_2, $-20°$; 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 H_2O 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 CH_2Cl_2 at $-20°$, and in the presence of $NaHCO_3$ [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 ^{13}C-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 ^{13}C-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.

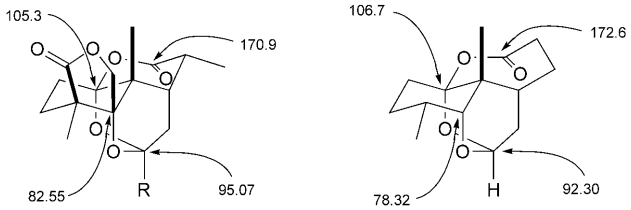


Fig. 2. *Comparison of the* ^{13}*C-NMR chemical shifts* (in ppm) *of saudin* (**1**) *and the target compound* **2**

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Experimental Part

General. All solvents were dried and distilled before use. All reactions were carried out under anh. conditions in an N_2 atmosphere. TLC: aluminum-foil plates coated with 0.1-mm *Merck* silica gel *60 GF*$_{254}$. 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}. ^{1}H- 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*,3a*S*,6*R*,6a*R*,9a*S*,9b*S*)-* (**5a**) *and (2*S*,3a*S*,6*S*,6a*S*,9a*S*,9b*S*)-2-Ethoxydecahydro-9b-methylnaphtho[1,8-*bc*]pyran-6,6a(4*H*)-diol* (**5b**). To a soln. of **3a** (80 mg, 0.32 mmol) in THF/H_2O 2:1 (8 ml), 6N 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 (3×3 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. ^{1}H-NMR: 5.40 (*s*, 6a-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(9a)); 2.70 (*dt*, *J* = 14.4, 2.0); 2.40–1.50 (*m*, 13 H); 1.23 (*t*, *J* = 7.2, *Me*CH_2); 1.23 (*s*, 9b-Me). ^{13}C-NMR: 102.6 (C(2)); 34.1 (C(3)); 36.8 (C(3a)); 20.8 (C(4)); 25.2 (C(5)); 63.4 (C(6)); 75.6 (C(6a)); 32.4 (C(7)); 16.9 (C(8)); 25.9 (C(9)); 82.7 (C(9a)); 35.7 (C(9b)); 22.9 (9b-Me); 64.2 (OCH_2); 15.1 (*Me*CH_2).

Data of **5b**. Yellowish oil. ^{1}H-NMR: 5.04 (*s*, 6a-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(9a)); 2.50–1.40 (*m*, 14 H); 1.23 (*t*, *J* = 7.0, *Me*CH_2); 1.19 (*s*, 9b-Me).

*(2*R*,3a*S*,6*R*,6a*R*,9a*S*,9b*S*)-Decahydro-9b-methyl-2,6a-epoxynaphtho[1,8-*bc*]pyran-6(4*H*)-ol* (**6a**) *and (2*R*,3a*S*,6*S*,6a*S*,9a*S*,9b*S*)-Decahydro-9b-methyl-2,6-epoxynaphtho[1,8-*bc*]pyran-6a(4*H*)-ol* (**6b**). Following the procedure mentioned above for the hydrolysis of **3a**, compound **3b** (43 mg, 0.17 mmol) in THF/H_2O 2:1 (3 ml) was treated with 6N 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. ^{1}H-NMR: 5.10 (*ddd*, *J* = 3.4, 1.2 , H–C(2)); 3.76 (br. *d*, *J* = 4 , H–C(9a)); 3.63 (br. *d*, *J* = 3 , H–C(6)); 2.60–1.40 (*m*, 14 H); 1.20 (*s*, 9b-Me). ^{13}C-NMR: 90.5 (C(2)); 34.1 (C(3)); 32.3 (C(3a)); 21.9 (C(4)); 25.9 (C(5)); 62.2 (C(6)); 77.9 (C(6a)); 30.6 (C(7)); 16.1 (C(8)); 26.1 (C(9)); 76.7 (C(9a)); 32.7 (C(9b)); 19.2 (9b-Me). MS: 207 (1, $[M - OH]^+$), 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. ^{1}H-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). ^{13}C-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*,3a*S*,6a*R*,9a*S*,9b*S*)-Decahydro-9b-methyl-2,6a-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 SiO_2, eluting in both cased with AcOEt. The filtrate was concentrated and purified by CC (SiO_2) to afford **7** (39 mg, 72%). IR (film): 2962, 2938, 2876, 1712, 1452, 1342, 1254, 1142, 1118, 1069, 1006, 908, 812, 672. ^{1}H-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). ^{13}C-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^+, $C_{13}H_{18}O_3^+$; calc. 222.1256).

'*2,6a-Epoxy-10b-methyl-perhydro-3,7-dioxacyclohepta(*de*)naphthalen-8-one*' (**2**)[1]). To a soln. of **7** (24 mg, 0.11 mmol) in anh. CH_2Cl_2 (3 ml) was added solid $NaHCO_3$ (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 CH_2Cl_2 (3 × 5 ml). The combined org. extracts were washed with 1M aq. NaOH soln. and H_2O, dried (Na_2SO_4), 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. ^{1}H-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). ^{13}C-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^+, $C_{13}H_{18}O_4^+$; calc. 238.1205). Anal. calc. for $C_{13}H_{18}O_4$: C 65.53, H 7.61; found: C 65.63, H 7.64.

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[1]) Systematic name: (2*R*,3a*S*,7a*S*,10a*S*,10b*S*)-decahydro-10b-methyl-2,7a-epoxypyrano[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*).