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Synthesis of Incrustasterols, Two Cytotoxic Polyoxygenated Sponge Steroids#

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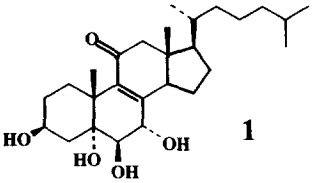
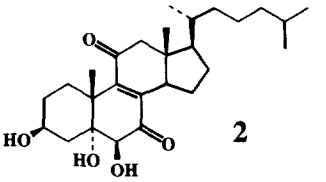
Abstract: *The synthesis of two cytotoxic marine steroids incrustasterol A and B is reported.*

Recently two novel polyoxygenated steroids, incrustasterol A (**1**) and B (**2**)[1], were isolated from the marine sponge *Dysidea incrustans* and their structures, which include a rare 8,9-en-11-one functionality, were determined by interpretation of spectral data. These steroids showed cytotoxicity against human non-small-cell lung carcinoma, human renal carcinoma E39, and human melanoma cell lines[1]. Since very limited amounts of the incrustasterols were isolated from the natural source (18 mg of **1** and 4.5 mg of **2**) we decided to synthesize them as outlined in Scheme I. The key step of the synthesis is the allylic rearrangement of compound **9** which afforded incrustasterol A tetraacetate.



1



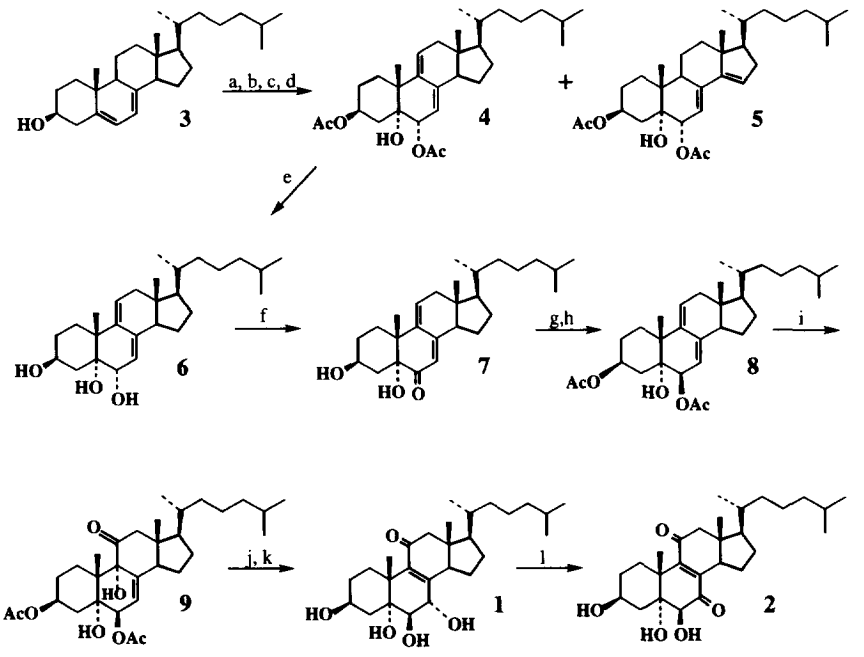
2

5α-Cholest-7,9(11)-diene-3β,5,6α-triol-3,6-diacetate (**4**) was prepared by peracid oxidation of commercially available Δ^7-cholesterol, followed by benzoate hydrolysis, acetylation and dehydrogenation with mercuric acetate[2]. Compound **4** was separated from the minor isomeric $\Delta^{7,14}$ diacetate **5**[3] by careful purification on silica gel. Hydrolysis of **4** with refluxing methanolic potassium hydroxide afforded triol **6** which was oxidised to **7** in satisfactory yield, if compared to the MnO_2 oxidation[2], by a novel procedure using ^{t}BuOOH and catalytic amounts of OsO_4[4]. $LiAlH_4$ reduction, acetylation and RuO_4 oxidation afforded the previously reported compound **9**[5]. Allylic rearrangement of **9** in acidic conditions[6] followed by methanolysis afforded **1**.

Attempted PCC oxidation[7] of **9** in order to directly obtain **2**, as the acetate, was unsuccessful. Incrustasterol B (**2**) was eventually obtained by allylic oxidation of **1** with ^{t}BuOOH and catalytic amounts of OsO_4[4] which afforded **2** in 33% yield, with 40% of recovered starting material. The NMR spectra of the synthetic incrustasterols were identical to those of the corresponding natural compounds[8], although the $[\alpha]_D$ value for incrustasterol B (**2**) differed in sign and magnitude from that reported[8].

#*Dedicated to prof. Luigi Minale in occasion of his 60th birthday*

Scheme I



a. MCPBA / CH_2Cl_2, 0°C; **b.** KOH / MeOH, reflux; **c.** Ac_2O / Pyridine, r.t. (54%, three steps); **d.** $Hg(OAc)_2$ / AcOH / CH_2Cl_2, 48h (**4**: 38% **5**: 7%); **e.** KOH/ MeOH, reflux (95%); **f.** ^tBuOOH / NEt_4OH / OsO_4 / ^tBuOH, 3h (55%);[9] **g.** $LiAlH_4$ / Et_2O (59%); **h.** Ac_2O / Pyridine, r.t. (84%); **i.** RuO_4 / $(CH_3)_2CO$, -70°C, 5h (65%); **j.** TsOH / AcOH / Ac_2O, 6h (59%); **k.** K_2CO_3 / MeOH, 7h, r.t. (70%); **l.** ^tBuOOH / NEt_4OH / OsO_4 / ^tBuOH, 3h (55%, based on recovered starting material).

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8. Incrustasterol A (**1**):$[\alpha]_D$: + 42.9° (c = 0.6, MeOH); lit.[1] + 42.7° (c= 1, MeOH). Incrustasterol B (**2**): $[\alpha]_D$: - 39.2° (c = 0.3, MeOH); lit.[1] + 10.6 (c= 1, MeOH). **2** is quite unstable and decomposes slowly even at -20°; this might account for the discrepancy in the $[\alpha]_D$ values.
9. Allylic oxidation was carried out on 50 mg batches since larger reactions afforded lower yields.

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