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Synthesis of Mirasorvone, a Defensive Steroid from the Sunburst Diving Beetle (*Thermonectus marmoratus*)

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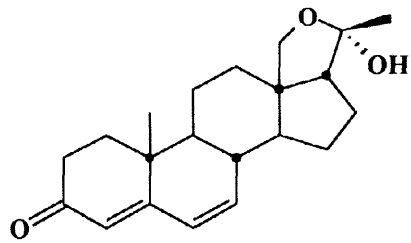
Abstract: The structure and stereochemistry of mirasorvone, an 18-oxygenated pregnane from the defensive prothoracic glands of the sunburst diving beetle, *Thermonectus marmoratus*, has been confirmed by synthesis and single-crystal X-ray diffraction analyses.

Mirasorvone, an insect defensive steroid, is the chief component of the milky fluid produced by the defensive prothoracic glands of the sunburst diving beetle, *Thermonectus marmoratus*.[1] This steroid was characterized as the hemiketal **1** based on an analysis of extensive spectroscopic data.[1] To the best of our knowledge, this is the first 18-oxygenated steroid to be isolated from an insect source. In order to confirm the structure and stereochemistry of mirasorvone, as well as to make available sufficient material for a study of its behavioral and physiological activities, we have carried out the synthesis of **1** described in this report.



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The synthetic route to mirasorvone (**1**) is outlined in Scheme 1. 3β-Acetoxypregn-5-ene-20β-ol (**2**) was prepared by reduction of the commercially available pregnenolone acetate with sodium borohydride in THF and methanol (1:1) in 85% yield.[2] Irradiation of **2** in the presence of iodine, freshly recrystallized lead tetraacetate,

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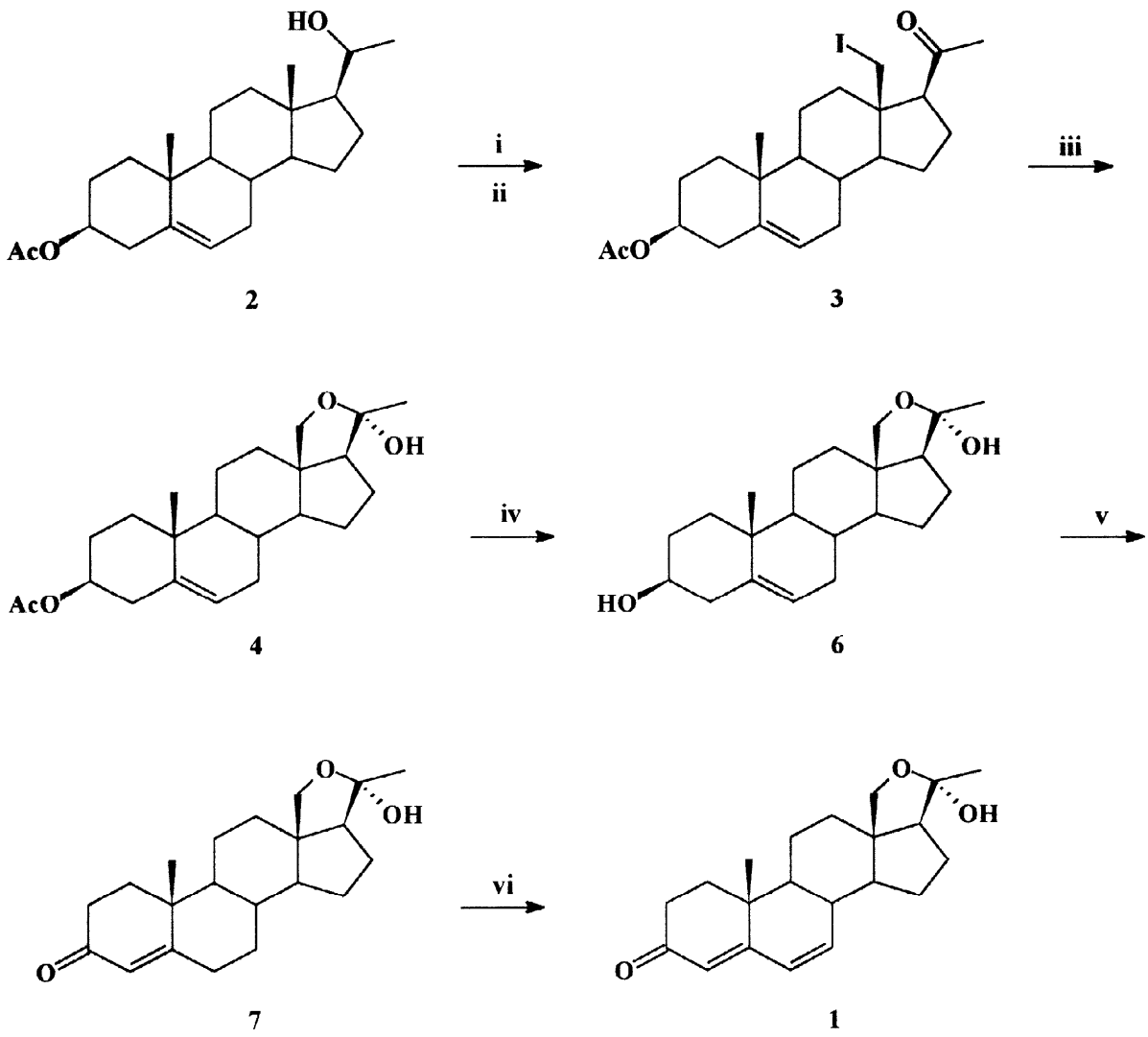
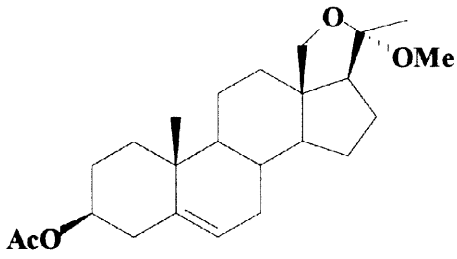


Scheme 1

Reagents and conditions: i. $Pb(OAc)_4$, I_2, $CaCO_3$, cyclohexane, *hv*, reflux; ii. CrO_3, H^+, acetone, 0°C, 10 min., 50% from **2**; iii. AgOAc, 1,4-dioxan, H_2O (9:1), 65°C, 12h, 92%; iv. 10% NaOH, MeOH, r.t., 30 min., 95%; v. $Al(OPr^i)_3$, N-methyl-4-piperidone, PhMe, reflux, 5h, 72%; vi. chloranil, *tert*-butanol, reflux, 30 min., 54%.

and dried calcium carbonate in cyclohexane, using a 500 w-tungsten lamp,[3,4] was carried out until the iodine color had disappeared (*ca.* 25 min.). The reaction mixture was immediately quenched and worked up to afford a residue of 3β-acetoxy-18-iodopregn-5-ene-20β-ol, which was oxidized (without purification) with Jones reagent to give the unstable 3β-acetoxy-18-iodopregn-5-ene-20-one (**3**) in 50% yield. Reaction of the iodoketone **3** with silver acetate in aqueous dioxane[3] provided the 18, 20-hemiketal **4** in 92% yield, m.p. 157-158°C, $[\alpha]_D$ = -16° (c, 0.2, $CHCl_3$)[lit.[5] m.p. 158-161°C], while silver-ion-promoted solvolysis in methanol

gave the corresponding 18,20-epoxy-20α-methoxy derivative **5**, m.p. 174-176°C, $[\alpha]_D$ = +22.6° (c, 0.3, $CHCl_3$)[lit.[4] m.p. 171.5-175°C]. The configuration of **5** at C-20 was established by X-ray diffraction analysis[6] (Fig. 1). Another X-ray diffraction analysis[6] showed that the 18,20-hemiketal **4** also crystallizes in the 18,20-epoxy-20α-hydroxy form (Fig. 2).



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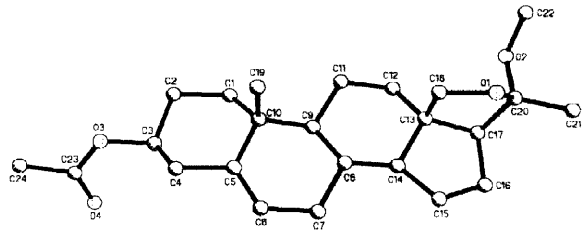


Fig. 1: X-ray crystallographic structure of **5**

Alkaline hydrolysis of the 3β-acetate **4** afforded the 3β-alcohol **6** in 95% yield, m.p. 116-118°C, $[\alpha]_D$ = +50°(c, 1.3, $CHCl_3$). A Keana-Reich modification of the Oppenauer oxidation[4,7] of the alcohol **6** with aluminum isopropoxide and N-methyl-4-piperidone in dry toluene provided the enone **7** in 72% yield, m.p. 160-161°C, $[\alpha]_D$ = +158° (c, 0.3, $CHCl_3$){lit.[4] m.p. 154-156°C; lit.[8] m.p. 164-165°C, $[\alpha]_D$ = +157°; lit.[9] m.p. 159-160°C, $[\alpha]_D$ = +159°}. Finally, dehydrogenation of the enone **7** with chloranil in *tert*-butanol[10] gave the target mirasorvone (**1**) in 54% yield, m.p. 138-142°C, $[\alpha]_D$ = +180° (c, 0.1, $CHCl_3$). The 20α-hydroxy configuration of the hemiketal **1**, assigned on the basis of NMR spectroscopic data,[1] seems to be generally preferred by these 18-hydroxy-20-ketopregnane derivatives, since the analogous structures **4**, **5**, and **7**[6] also possess this stereochemistry (Fig. 1-3).

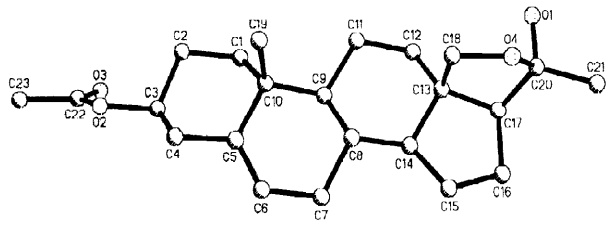


Fig. 2: X-ray crystallographic structure of **4**

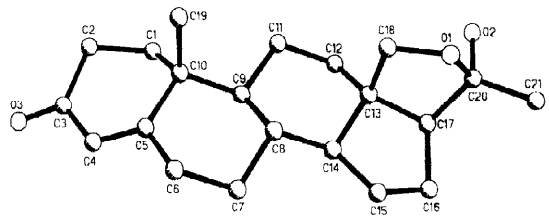
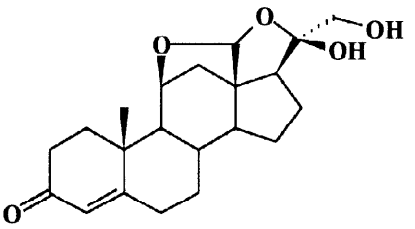


Fig. 3: X-ray crystallographic structure of **7**

The only steroidal hemiketal closely related to mirasorvone whose C-20 configuration has been definitively determined appears to be aldosterone (**8**), "the most potent regulator of electrolyte excretion and ... vital ... to innumerable life processes."[11] Interestingly, aldosterone has a configuration at C-20 opposite to that of mirasorvone.[11,12]



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6. The crystal of **4** was in the orthorhombic system with space group $P2_12_12_1$ and the unit cell dimensions were determined as a = 6.4045(13), b = 9.958(2), c = 32.484(7) Å, $\alpha = \beta = \gamma = 90°$, V = 2071.9(7) Å^3, Z = 4; **5** was in the orthorhombic system with space group $P2_12_12_1$ and the unit cell dimensions were determined as a = 6.6010(13), b = 12.444(3), c = 26.377(5) Å, $\alpha = \beta = \gamma = 90°$, V = 2166.7(7) Å^3, Z = 4; **7** was in the orthorhombic system with space group $P2_12_12_1$ and the unit cell dimensions were determined as a = 6.3360(13), b = 11.419(2), c = 25.230(5) Å, $\alpha = \beta = \gamma = 90°$, V = 1825.4(6) Å^3, Z = 4. All atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.
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12. This is paper no. 154 in our series, *Defense Mechanisms of Arthropods*; paper no. 153 is F. Schröder *et al.*, *Science* (submitted).