Synthesis of (24*R*)- and (24*S*)-3β, 29-Dihydroxystigmast-7-ene, a Model for the Side Chain of Oogoniol

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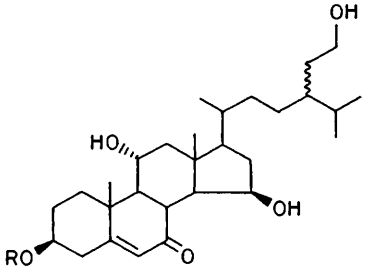
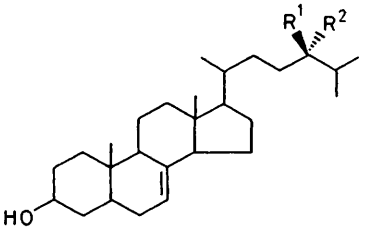
Summary (20*S*)-3β-Acetoxypregn-7-ene-20-carbaldehyde affords stereoselectively (24*R*)- and (24*S*)-3β,29-dihydroxystigmast-7-ene, compounds containing the side chain functionality of oogoniol, through a five step synthesis.

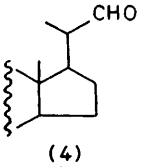
THE oogoniols (**1**) are the second example of steroidal sex hormones to be identified in the plant kingdom. The isolation and structure elucidation of these steroids, apart from the determination of the C-24 chirality, have been reported by McMorris *et al.*[1] Recently a non-stereospecific route for the construction of side chains of oogoniols was reported[1] and two different synthetic pathways were proposed for the introduction of the exact functionalities into the steroid nucleus, starting with compounds containing the cholesterol side chain.[2,3]



(1); R = H, Ac, COEt, or $COCHMe_2$



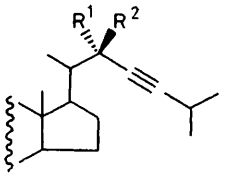
(2); R^1 = H, R^2 = CH_2CH_2OH
(3); R^1 = CH_2CH_2OH, R^2 = H



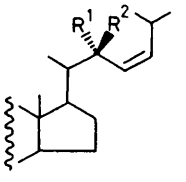
(4)

We report the first stereospecific synthesis of (24*R*)-(**2**) and (24*S*)-3β,29-dihydroxystigmast-7-ene (**3**), two isomeric model steroids, one of which possesses the oogoniol side chain and correct C-24 configuration.

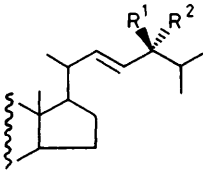
The present synthesis had the objective of first introducing the correct side chain at C-24 and then elaborating the functionalities of the steroid nucleus. (20*S*)-3β-Acetoxypregn-7-ene-20-carbaldehyde[4] (**4**) was chosen as starting material for the elaboration of the side chain, since the main skeletal functions of oogoniol can be introduced *via* the 7-ene unit.[3]



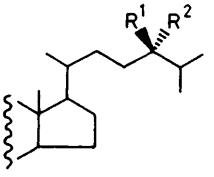
(5); R^1 = H, R^2 = OH
(6); R^1 = OH, R^2 = H



(7); R^1 = H, R^2 = OH
(8); R^1 = OH, R^2 = H



(9); R^1 = H, R^2 = CH_2CO_2Et
(10); R^1 = CH_2CO_2Et, R^2 = H



(11); R^1 = H, R^2 = CH_2CO_2Et
(12); R^1 = CH_2CO_2Et, R^2 = H

The aldehyde (**4**) reacted with 3-methylbutynylmagnesium bromide to give a mixture (85% yield) of two acetylenic alcohols in a 3:2 ratio. The 22*R* configuration was assigned to the more polar, major component (**5**). Precedents for this mode of addition have been reported.[5] In all examples the more polar, major component possesses the 22*R* configuration. Consequently the structure (**6**) was

attributed to the less polar, minor isomer. Half-hydrogenation of the 22*R*-alcohol (**5**) (m.p. 168—170 °C, $[\alpha]_D^{20}$ −9°)† over Lindlar catalyst in EtOAc gave the *cis*-allylic 22*S*-alcohol (**7**), m.p. 153—155 °C, $[\alpha]_D^{20}$ −10°, 100% yield. This was heated in refluxing xylene with ethyl orthoacetate and propionic acid as catalyst to yield, in a Claisen rearrangement, the 24*R*-ester (**9**), m.p. 125—126 °C, $[\alpha]_D^{20}$ −1°, 85% yield. The 24*R* configuration was predetermined for compound (**9**) by the initial configuration at C-22, the *cis*-geometry of the allylic double bond, and the preferred chair geometry of the transition state for the rearrangement.[6]

Hydrogenation of (**9**) over Raney Ni in EtOAc gave the 24*R*-ester (**11**), m.p. 88—90 °C, $[\alpha]_D^{20}$ 5°, 100% yield, which, on treatment with $LiAlH_4$ gave the desired 24*R*-compound (**2**), m.p. 175—176 °C, $[\alpha]_D^{20}$ 0°, 85% yield.

A similar sequence of reactions, with comparable yields, starting with the 22*S*-acetylenic alcohol (**6**) (m.p. 101—103 °C, $[\alpha]_D^{20}$ 4°) led, *via* compounds (**8**), (22*R*, m.p. 167—170 °C, $[\alpha]_D^{20}$ −15°), (**10**), (24*S*, m.p. 118—120 °C, $[\alpha]_D^{20}$ −9°), and (**12**), (24*S*, m.p. 91—92 °C, $[\alpha]_D^{20}$ 3°), to (**3**), (24*S*, m.p. 167—169 °C, $[\alpha]_D^{20}$ 2°).

This high-yield, stereoselective route to (**2**) and (**3**) resolves the problem of the stereospecific construction of the side chain of oogoniol so that the absolute configuration at C-24 can be determined. Even more importantly, application to (**2**) and (**3**) of our synthetic route[3] in the elaboration of the nuclear unit would yield intermediates which would permit evaluation of the structural specificity of the biological activity associated with different functionalities of structure (**1**). In fact it was reported that the intact side chain plays an essential role for significant sex-hormone activity.[2]

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† Satisfactory elemental analyses were obtained for all fully characterized compounds.

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