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TOTAL SYNTHESIS OF NEW STEROIDS

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Abstract

An asymmetric total synthetic scheme of A-nor steroids is detailed, following a short and flexible approach. This stereoselective procedure is extended to the preparation of a number of novel compounds, including optically active D-homo steroids and A-nor heterocyclic steroids. Several unexpected and potentially useful side-reaction compounds have been identified. Some of these new steroids exhibit promising biological properties which are discussed.

Introduction

In 1975, investigators from the People's Republic of China reported that a significant antifertility activity is associated with anordrin **(1c)**, a substance which is a five - membered ring A steroid called A - nor steroid. About 40 years ago, two sapogenins, called hecogenin **(2)** and tigogenin **(3)**, were isolated from the sisal plant *Agave sisalana* from Mexico. This plant is also widely found in Brazil and East Africa. Recently, the scientists from Shanghai have identified both sapogenins in *Agave americana* from the Kwangtung Province, allowing them to convert these sapogenins to anordrin **(1c)**. Lately, anordrin **(1c)**, as well as other similar nor - steroids have been prepared in our laboratory in a programme sponsored by the World Health Organization (WHO). The antifertility properties have been confirmed by Diczfalusy in Stockholm and Goldzieher in the U.S. These A - nor - steroids form a class of non - natural compounds, with unusual chemical and biological properties. As early as in 1962, Gregory Pincus

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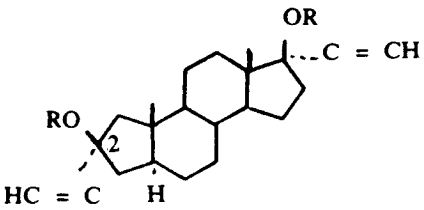

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b, R = Ac
c, R = Pr

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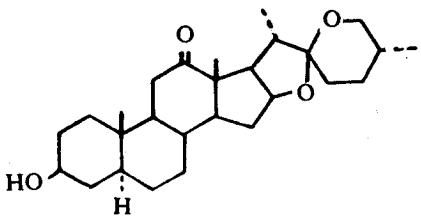

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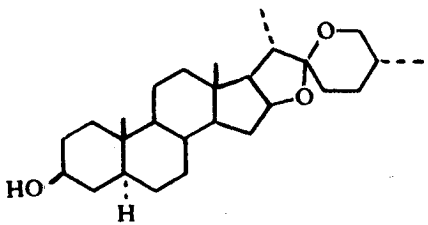

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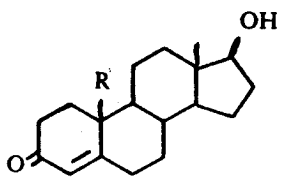

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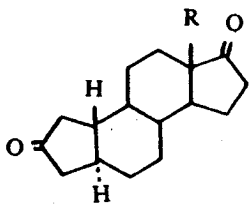

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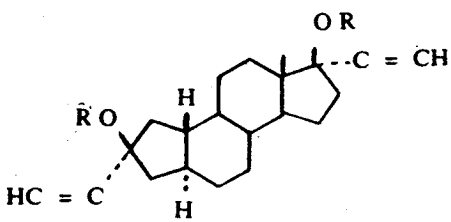

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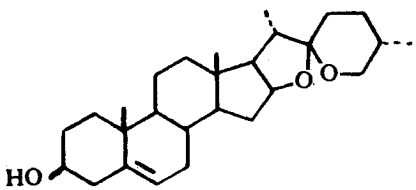
c, R = Pr



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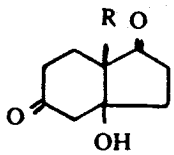


8 a, R = Me
b, R = Et

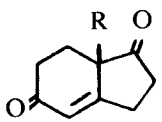
reported the implantation inhibitor activity[1] exhibited by some A - nor - androstanes, initially prepared by Jean Jacques and co - workers[2]. These nor - steroids have seen a considerable revival of interest following recent publications by Gu Zhiping and other Chinese investigators[3]. Various clinical reports have described the use of anordrin administered postcoitally, and the Chinese scientists call it a "vacation pill" or "pill no. 53".

In view of the potent fertility regulation properties reported for anordrin, the stereochemically pure 2β, 17β - diol **(1a)** and the corresponding diacetate **(1b)**, as well as dipropionate (anordrin, **1c**) were prepared from testosterone **(4a)**, by a classical route and the interesting biological properties of anordrin **(1c)** confirmed[4]. As sometimes rather trivial chemical modifications of an active molecule can lead to substantial differences in the biological profile, it was decided to prepare the 19 - nor - counterpart of anordrin by chemical transformations of 19 - nortestosterone **(4b)**, using a known methodology[4]. 19 - Nortestosterone **(4b)**, was converted to the 2,17 - diketo - dinorsteroid **(5a)** by conventional techniques. This was treated with an excess of lithium acetylide - ethylenediamine complex to afford a ca. 3:2 mixture of the 2α - ethynyl compound **(6a)** and its 2β - epimer, separated by preparative thin layer chromatography (TIC). Esterification of the tertiary hydroxyl groups of diol **(6a)** with acetic anhydride furnished the corresponding diacetate **(6b)**. Similarly, treatment of diol **(6a)** with propionic anhydride provided dinordrin **(6c)**[4]. This nor-steroid proved to be about 20 times more potent than anordrin **(1c)**.

Asymmetric Synthesis of Dinordrin

In recent years the field of asymmetric synthesis has grown from a little investigated chapter of organic chemistry to an intensely active research area with potential industrial implications. This report outlines the asymmetric synthesis of a number of novel steroids, emphasizing that spectacular progress has been made in the application of stereochemical principles to organic synthesis.

The attractive biological profile of dinordrin **(6c)** made it desirable to have an easy synthetic approach, as its preparation from naturally occurring sapogenins and sterols is rather lengthy and low yielding. Indeed, more than eighteen steps are involved in the chemical conversion of the readily available sapogenin diosgenin **(7)** to dinordrin **(6c)**, with a total yield not exceeding 4%[5]. In this report we describe a stereo - controlled asymmetric synthesis of dinordrin **(6c)** and some chemically related analogues not readily available by other routes[6].



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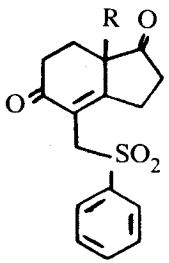
b, R = Et



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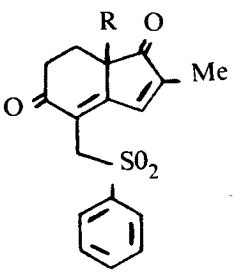

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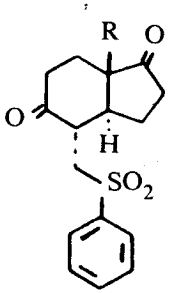
b, R = Et



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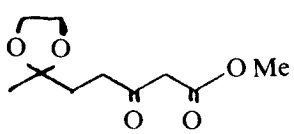
b, R = Et



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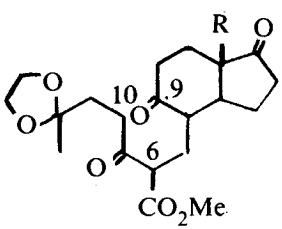
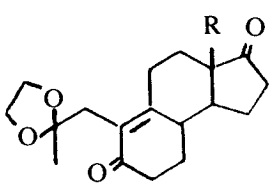
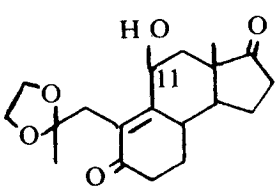


14 a, R = Me
b, R = Et



15 a, R = Me
b, R = ET



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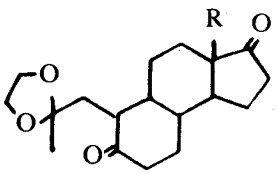
The initial steps of this approach are based on earlier work by Wiechert *et al.*[7] who reported a preparation of the optically active bicyclic indanedione **(8a)**, by aldol cyclization of a prochiral alkylated cyclopentanedione in the presence of (-) - (S) - proline. The indanedione **(8a)** was dehydrated with acid to give the enedione **(9a)**. The bicyclic sulphone **(10a)** was obtained by treatment of optically active (+) 7aβ - methyl - 6H - 7,7a - dihydroindane - 1, 5 - dione **(9a)** with paraformaldehyde and benzenesulphinic acid in tetramethylethylenediamine, along with some of the alkylated dienedione **(11a)** as a by - product. Catalytic hydrogenation[8] of enone **(10a)** in acidic medium, in the presence of palladium on charcoal afforded the fairly labile crystalline sulphone **(12a)**, which was allowed to react with methyl - 6,6 - ethylendioxy - 3 - oxoheptanoate **(13)**, to provide the bicyclic triketoester **(14a)**, possessing all the carbon atoms of the dinordrin steroid skeleton. The keto - ester **(13)**, precursor for the construction of rings A and B, was prepared in two steps from acetylacetone, by reaction with ethyleneglycol, catalyzed with sulphuric acid in a two - phase system. The monoketal wal then condensed with dimethylcarbonate, thus affording the desired ketoester **(13)** in 68% yield.

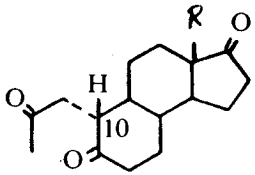
Condensation of the potassium salt of the enolate of the keto - ester **(13)** and the hydrindanedione **(12a)** was achieved in anhydrous toluene solution. The crude product **(14a)** was directly submitted to an annellation reaction to provide the enedione **(15a)** in an over - all yield exceeding 90%. Four steps are involved in this remarkable transformation of compound **(14a)** into **(15a)**, namely ring formation (condensation) between positions 9 and 10, dehydration of the tertiary carbinol, hydrolysis of the ester group and decarboxylation at position 6.

In the course of these reactions a by - product was generally present in the mixture, which could amount to up to 15%. Isolation of this crystalline material, followed by a careful study of its physical properties, including X - ray crystallographic data, allowed to assign the 11β - hydroxystructure **(16)**. This constitutes a potential avenue for the synthesis of 11 - and 12 - substituted oestrane derivatives, as well as a new route for the total synthesis of corticoid molecules.

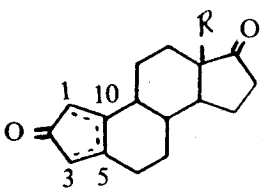
Catalytic hydrogenation of enone **(15a)** in ethanol solution and a trace of triethylamine, in the presence of 5% palladium on charcoal, yielded the saturated dione **(17a)**. A brief exposure of ketal **(17a)** to hydrochloric acid in acetone furnished the trione **(18a)**, with the thermodynamically favoured equatorial configuration for the chain at position 10. The intramolecular cyclization of the tricyclic keto - derivative **(18a)** was achieved by treatment with methanolic potassium hydroxide, affording a 2:1 mixture of $\triangle^{1(10)}$ - **(19a)** and $\triangle^{3(5)}$ - enone **(19b)**, in 75% yield. A drastically different result was obtained when the cyclization of **(18a)** was attempted in acidic medium, which produced the bridged steroid **(20)**[9] in 84% yield.



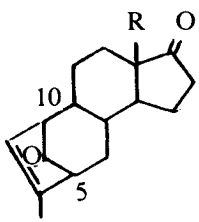
17 a, R = Me
b, R = Et



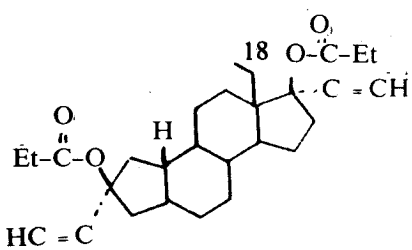
18 a, R, = Me
b, R = Et



19 a, $\triangle^{1(10)}$, R = Me
b, $\triangle^{3(5)}$, R = Me
c, $\triangle^{3(5)}$, R = Et
d, $\triangle^{1(10)}$, R = Et



20 a, R = Me
b, R = Et



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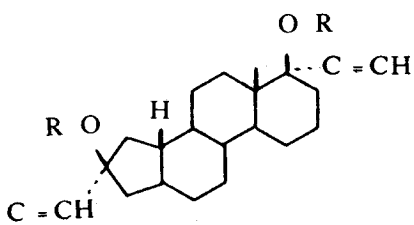
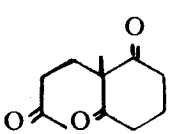


22 a, R = H
b, R = Pr



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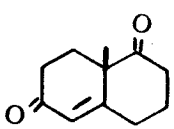

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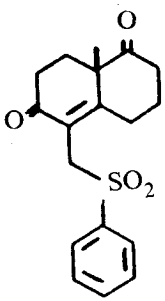
Lithium in ammonia reduction of the mixture of double bond isomers **(19)** provided the A - nor - oestrane - 2,17 - dione **(5a)**, shown to be identical with an authentic sample[4]. Ethynylation at position 2 and 17 of the diketone **(5a)** was achieved by addition of lithium acetylide - ethylenediamine complex, thus affording a mixture of isomeric 2 - ethynyl derivatives separated by preparative TLC. Esterification with propionic anhydride of the alcohol **(6a)** then afforded dinordrin **(6c)** in the optically active form[6].

Synthesis of Dinordrin Analogues

Parallel to our effort to construct the A - nor - steroid skeleton and to gain access to dinordrin, work was also carried out aimed at the synthesis of some analogues, including 18 - homo - dinordrin **(21)** and D - homo - dinordrin **(22b)**. Thus, the known 4 - methylenesulphone 7aβ - ethyl - 6H - 7,7a - dihydroindane - 1,5 - dione **(10b)**[7] was submitted to the above reaction sequence. The alkylated diene - dione **(11b)** was again isolated as a by - product. The tricyclic intermediate **(15b)** prepared by the above route, was reduced catalytically to generate the saturated dione **(17b)**, which on treatment with acid gave the corresponding trione **(18b)**. Cyclization of ring A was accomplished in methanolic sodium hydroxide. The $\triangle^{3(5)}$ - enone **(19c)** and its $\triangle^{1(10)}$ - isomer **(19d)** were obtained. The isomeric mixture was reduced with lithium in liquid ammonia to afford the A - nor - 18 - homo - diketo - steroid **(5b)**, then converted into 18 - homo - dinordrin **(21)** by conventional techniques[4].

Since few synthetic schemes for A - nor - D - homo - steroids have been reported[10], it was contemplated to apply the above route for the preparation of such D - homo - steroids. When this total synthetic scheme was extended to D - homo - dinordrin **(22b)**, substantial differences were noted in the chemical behaviour of intermediates, emphasizing that the chemical properties observed in one series cannot necessarily be extrapolated to another. The Wieland - Miescher ketone **(24)** was prepared in the optically active form from the prochiral triketo - intermediate **(23)**, by cyclization in the presence of (-) - (S) - proline in DMF solution. Although almost quantitative optical yields were obtained in the preparation of the dihydroindane - 1,5 - diones, [6,7] in the present case the ketone **(24)** was only obtained with an optical yield of about 85%. The diketone **(24)** had to be recrystallized several times to improve its optical purity[11].

The enedione **(24)** was converted to the corresponding sulphone **(25)** by treatment with paraformaldehyde and sodium benzenesulphinate.[6,7]. Catalytic hydrogenation of the double bond in enone **(25)** was achieved in acidic ethanol solution, in the presence of palladium on charcoal. These conditions led to a mixture of the desired *trans* - **(26a)** and *cis* - **(26b)** decalones, separated by fractional crystallization.



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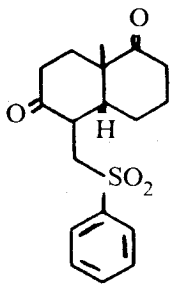
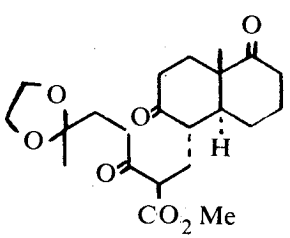


26 a, α H
b, β H



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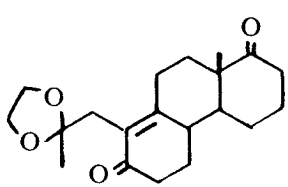

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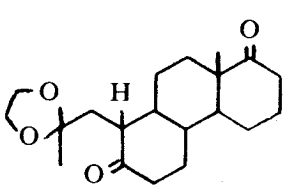

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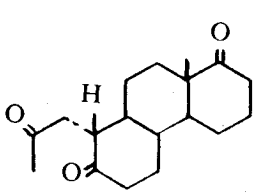

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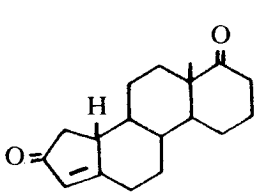

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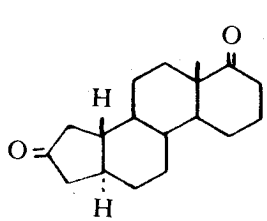

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As in the case of dinordrin **(1c)**, the β - keto ester **(13)**[11] was reacted with sulphone **(26a)** to afford the intermediate **(27)**, which was cyclized into the tricyclic compound **(28)**. Catalytic reduction of the double bond in enone **(28)** in ethanol solution and a trace of triethylamine, in the presence of 5% palladium on charcoal, yielded the saturated dione **(29)** almost quantitatively. Exposure of the ketal group to hydrochloric acid in acetone furnished the trione **(30)** in 90% overall yield from **(28)**. These conditions gave the thermodynamic product **(30)** with the equatorial configuration for the chain at C - 10. Cyclization of the tricyclic ketoderivative **(30)** into the $\triangle^{3(5)}$ - enone **(31)** was achieved in 80% yield on treatment with potassium - t - butoxide in toluene solution. It is interesting to note that in this series no $\triangle^{1(10)}$ - isomer was detected after cyclization, thus indicating that the enone **(31)**, the kinetic product, is fairly stable. Lithium in ammonia reduction of the enone **(31)** readily provided the expected A - nor diketo - steroid **(32)**.

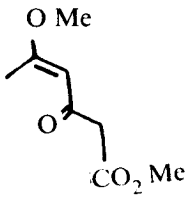
Ethynylation at positions 2 and 17 of the diketone **(32)** was achieved by addition of potassium acetylide in THF solution, thus affording a *ca.* 1:1 mixture of isomeric 2 - ethynyl derivatives separable by column chromatography. The 2β - hydroxy derivative **(22a)** was obtained as a cystalline compound, which was esterified to provide the D - homo - homologue **(22b)** of dinordrin.

The above total synthetic approach is short, flexible and easy to perform, thus constituting an useful approach to this unusual class of biologically important A - nor steroids. It is noteworthy that the cyclization reaction of the intermediates **(14)** and **(27)**, followed by catalytic reduction of enones **(15)** and **(28)**, acid hydrolysis of the ketal, ring A closure and Birch reduction of the cyclopentenones afforded the diones **(5)** and **(32)** with the correct stereochemistry at all asymmetric centers.

Synthesis of Novel Heterocyclic Steroids

It was then contemplated to adapt the above described total synthetic scheme to the preparation of ring A heterocyclic analogues, because only few papers report the synthesis of steroids containing an hetero - atom in ring A[12].

The initial step of the synthesis required condensation of the known sulphone **(12a)**[6,7] with the keto - ester **(33)**, prepared from 2,4 - pentanedione in two steps[13]. In an initial approach, the enol ether group of intermediate **(34)** was hydrolyzed before ring closure and decarboxylation, which led to cyclization and formation of ring B, but also achieved hydrolysis of the ester, decarboxylation and cleavage of the β - diketo - grouping, thus furnishing the known enedione **(35)**. The problem of cleavage of the β - diketone was circumvented by effecting the conversion of intermediate **(34)** to the desired enetrione **(38)** stepwise. Thus, compound **(34)** was first subjected to base treatment with methanolic potassium hydroxide, which achieved saponification of the ester grouping followed by decarboxylation, providing trione **(36)**. The enol ether



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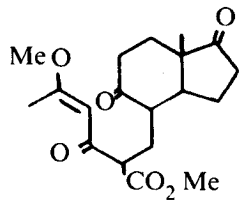

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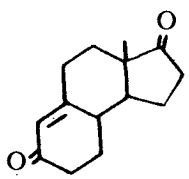
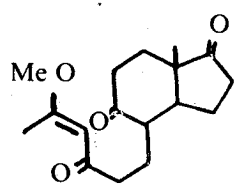
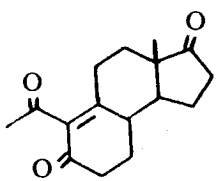


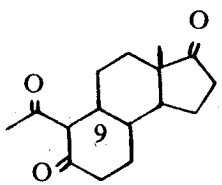
35



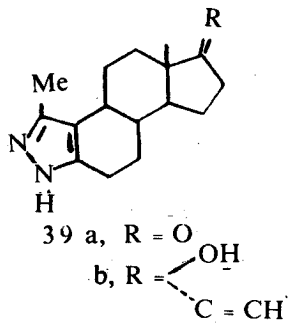
36



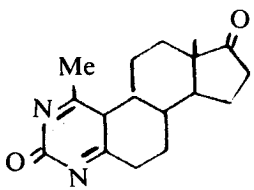
37



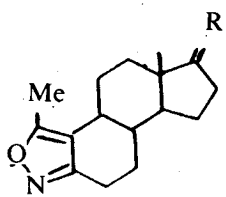
38 a, 9α H
b, 9β H



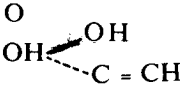
39 a, R = O
b, R =



40



41 a, R = O
b, R = OH



functionality in compound **(36)** was then hydrolyzed with hydrochloric acid in acetone solution, providing directly the expected enone **(37)** in 52% over - all yield from the triketoester **(34)**. It is worth emphasizing that the intramolecular condensation of intermediate **(34)** took place under substantially different conditions from those used for the synthesis of natural steroids[7] and the above mentioned A - nor - steroids [6,11].

The cross - conjugated enetrione **(37)** proved to be fairly unstable, probably prone to oxidation into phenolic materials, in the presence of air. Catalytic hydrogenation of the enetrione **(37)** in ethanol solution under neutral conditions and pressure, in the presence of 5% palladium on charcoal, gave an 8:5 mixture of isomeric 9 α - **(38a)** and 9 β - **(38b)** triones, separated by column chromatography. It is interesting to note that, contrary to the observations made in other series,[6,7,11] the catalytic reduction of enone **(37)** was not stereoselective, perhaps due to the crossconjugated enedione system.

The triketone **(38a)** is the key intermediate which was used for the preparation of the novel heterocyclic steroids reported in this work. On the one hand, reaction of trione **(38a)** with 95% hydrazine hydrate in refluxing ethanol[13] afforded selectively the 1 - methyl - 2,3 - diaza - steroid derivative **(39a)**, in 90% yield. Surprisingly, the 17 - ketone was not affected under these conditions. Treatment of the 17 - keto group in **(39a)** with lithium acetylide then provided the 17 α - ethynyl steroid **(39b)**.

On the other hand, reaction of the keto - derivative **(38a)** with urea in absolute ethanol afforded the pyrimidone steroid **(40)** as a pale yellow crystalline material, whose structure is supported by its physical properties.

Finally, when trione **(38a)** was reacted with hydroxylamine hydrochloride in aqueous ethanol solution at 70°, the steroidal isoxazole **(41a)** was obtained in 83% yield. Ethynylation of the keto group in compound **(41a)** also provided the corresponding 17α - ethynyl carbinol **(41b)** in good yield[13].

It is noteworthy that the heterocyclic steroids **(39a)** and **(41a)** could be obtained in high yield, in spite of the potential competitive formation of the 17 - hydrazone and oxime. This seems to be attributed to the reactivity of the keto - group located at position 5 which must be higher than at C - 17. Moreover, the quasi exclusive formation of the steroidal benzisoxazole **(41a)** is unexpected, since a mixture of isomers could have been anticipated.

Preliminary testing indicates that compounds **(39a)**, **(39b)**, **(41a)** and **(41b)** do not show a significant increase in uterine weight after administration at different levels. However, in the rat compounds **(39a)** and **(41b)** show a high affinity for androgen binding protein (ABP), and it is known that ligands that bind with high affinity to ABP but do not interact with the androgen receptor are potential inhibitors of male fertility[14]. Further work is currently under way involving structural modifications susceptible to increase the unusual biological profile associated with these heterocyclic steroids.

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บทคัดย่อ

ได้แสดงแผนภูมิการสังเคราะห์ A - nor steroids โดยใช้วิธีการที่สั้นและดัดแปลงได้ง่าย วิธีการซึ่ง stereoselective นำมาใช้ได้ในการเตรียมสารใหม่หลายตัวรวมทั้ง optically active D - homo steroids และ A - nor heterocyclic steroids ได้สารอีกหลายตัว จากปฏิกิริยาข้างเคียงโดยไม่ได้คาดไว้ก่อน ซึ่งอาจเป็นประโยชน์ สเตรอยด์ใหม่นี้บางตัวมีคุณสมบัติทางชีววิทยาซึ่งจะได้ชี้แจง