

Steroids: partial synthesis in medicinal chemistry

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This article reviews the progress in the chemistry of the steroids that was published between January and December 2005. The reactions and partial synthesis of estrogens, androgens, pregnanes, bile acid derivatives, cholestanes and vitamin D analogues are covered. There are 139 references.

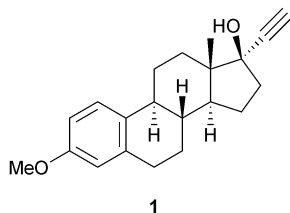
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1 Introduction

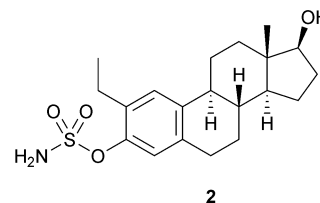
This review follows the pattern of its predecessors¹ with sections on the major skeletal types of steroids. Reviews have appeared on steroid hormone receptors² and on the chemistry and structural biology of the androgen receptor.³ A series of review articles on progesterone and progestins in human pregnancy and breast cancer have appeared in the *Journal of Steroid Biochemistry and Molecular Biology*.⁴ A review of the range of substrates containing two double-bond equivalents and a carbonium ion source which undergo the generalized dienol–benzene rearrangement of ring A has appeared.⁵ The illegal use of anabolic steroid hormones has prompted studies on the preparation of labelled analogues and on the development of analytical strategies for their detection and that of their metabolites.⁶

2 Estrogens

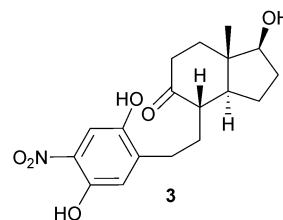
The thermodynamics of cytoplasmic steroid/nuclear receptor interactions has been compared⁷ to that of interactions with membrane receptors using estradiol as a substrate. The metabolism of estradiol and estrone to polar products by human tissue and cytochrome P₄₅₀ isoforms has been reviewed.⁸ The microbial transformation of mestranol **1** by *Cunninghamella elegans*, which involved hydroxylation at C-6 β and C-12 β , has been described.⁹



An improved synthesis of 3-aminoestrone by a Pd(0)-catalysed Buchwald–Hartwig amination of estrone triflate with benzophenone imine has been reported.¹⁰ The conditions for the regioselective phenolic or carbinol glycosidation of estradiol have been defined.¹¹ Some estradiol is transported between its site of biosynthesis and the target organ as the 3-*O*-sulfate. The estrogen 3-*O*-sulfamate **2** has been shown to affect this and to be a potential anti-cancer agent for hormone-dependent breast cancer.¹²



Interest in the catechols related to the estrogens has been stimulated by the implication of the corresponding quinones in mutagenic interactions with DNA. The synthesis of the 2,3- and 3,4-catechols, by oxidation of estrone and estradiol with iodoxybenzoic acid followed by reduction of the quinones, has been reported.^{13,14} The loss of deoxyribose from N-7 deoxyguanosine adducts of the estradiol 3,4-quinone has been studied¹⁵ in the context of its mutagenicity. The oxidative cleavage of the 9,10-bond of 2-nitroestradiol to give **3** in the presence of hydrogen peroxide and peroxidase has been observed.¹⁶

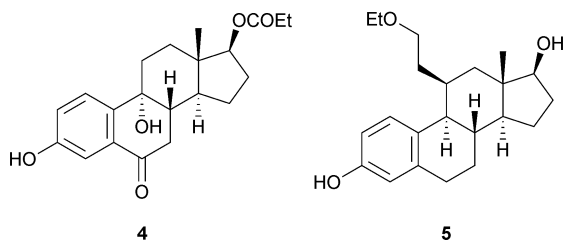


Structure–activity relationships of 2-, 4- and 6-substituted estrogens as aromatase inhibitors have been explored.¹⁷ 6 α -Phenylestrone was a particularly powerful inhibitor. The interesting observation has been made¹⁸ that the epoxidation of estr-5(10)-ene-3,17-dione with perphthalic acid gave the β -epoxide as the major product rather than the α -epoxide.

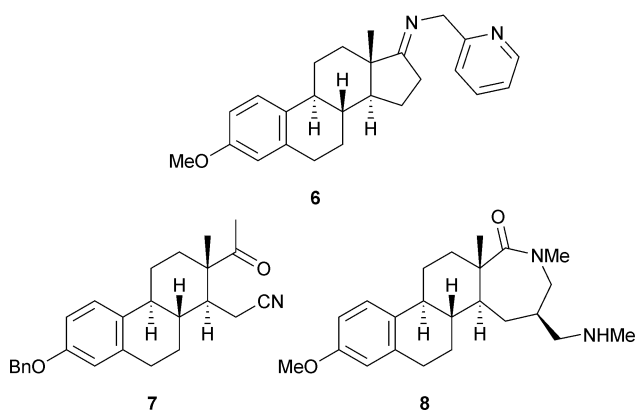
The synthesis and estrogenic activity of some 6,9-disubstituted estradiol derivatives such as **4** has been reported.¹⁹ The introduction of non-polar short-chain substituents at C-11 β has resulted²⁰ in compounds, exemplified by **5**, which possess anti-estrogenic

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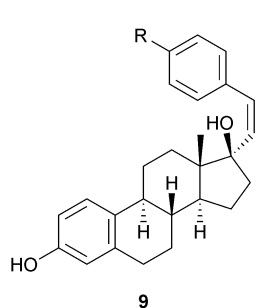
activity. This is reminiscent of the anti-progestational effect of substituents at C-11, exemplified by mifepristone. The synthesis of 11β -perfluorohexylestradiol has been described²¹ in the context of binding studies to the estrogen receptor. Total syntheses of 11-thia and 3-aza-11-thia-1,3,5(10)-trienes have been published.²²



17-(2-Iminomethyl)pyridino-steroids (e.g. **6**) form copper complexes which have been shown²³ to mediate the C-12 β hydroxylation of steroids with molecular oxygen. There was an unexpected 12 β -chlorination when the reaction was carried out in dichloromethane. The Beckmann fragmentation of a 17 β -hydroxy-17 α -methyl-16-oxime led²⁴ to the cleavage of ring D and the formation of the 17-methyl-16,17-secoestra-1,3,5(10)-trien-16-nitrile **7**. The anti-estrogenic activity of these derivatives has been examined. Stereoselective syntheses of aza-D-homo and aza-D-dihomo steroids in the estrone series, affording compounds such as **8**, have been described.^{25,26}

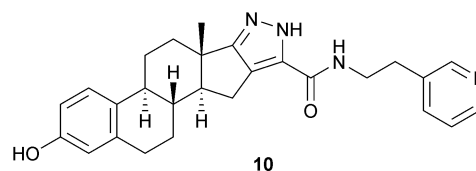


Estradiol derivatives conjugated with different amino acids have been prepared and their binding affinity to the estrogen receptor has been measured.²⁷ The synthesis of a series of (17 α ,20Z)-4-substituted phenylalkenes **9** as ligands for the estrogen receptor α -hormone binding domain has been reported.²⁸ The conformation of estrane 17-acetals has been determined²⁹ by X-ray crystallography.



The 17 β -hydroxy dehydrogenase enzyme system regulates the bioavailability of some estrogens and androgens. 16-Substituted

estrogen derivatives such as **10** have been shown^{30,31} to be potent inhibitors of this system. This inhibition reduces estrogen levels and can promote the regression of tumours that are hormone-dependent. Some estradiol-adenosine hybrids have been designed³² to inhibit this system.

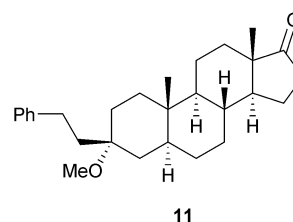


A combined Sonogashira coupling and Wittig olefination has been introduced³³ as a means of adding substituents to C-16 and C-17. The preparation of some benzothieno- and benzofurano-annulated estranes have been described.³⁴ The synthesis of estrogenic carriers for cytotoxic platinum(II) fragments has been examined³⁵ in the context of the chemotherapy of hormone-dependent cancers.

3 Androgens

Studies have continued on steroidal aromatase inhibitors based on androstenedione. Examination³⁶ of the structure-activity relationships of steroids modified on rings A and D has indicated that the binding pocket of the active site of aromatase requires planarity in the region of the A/B rings, whilst the structure of ring D is also critical. However, 2 α -halogeno and 2 α -alkylandrostenedione analogues are quite active as aromatase inhibitors.³⁷ The anti-proliferative activity of some 10-hydroxy-ring A dienone rearrangement products has been examined.³⁸ The absence of a deuterium isotope effect has been noted³⁹ in the oxidative reactions of [19,19-²H₂]-19-hydroxy-3-deoxyandrogens by placental aromatase. This parallels observations made previously with the natural substrate. The formation of 19-norsteroids by *in situ* demethylation of endogenous steroids in stored urine samples has been noted.⁴⁰ This observation has significance in the testing of athletes' samples for steroid hormone abuse.

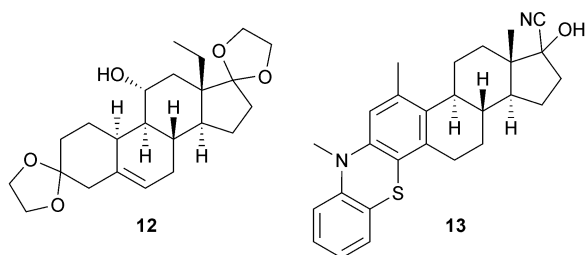
Inhibition of the type 3 steroid 17 β -dehydrogenase is important in the context of androgen-specific diseases. Androsterone derivatives with a 3 β -substituent and a 3 α -ether, e.g. **11**, have been shown⁴¹ to be potent inhibitors of this system. The glucuronidation of androstane alcohols using an iodosugar and an imidate donor has been reported.⁴² A convenient synthesis of C-4- and C-6-aryl-substituted steroids by a Suzuki-Miyaura cross-coupling reaction based on the bromo analogues has been reported.⁴³



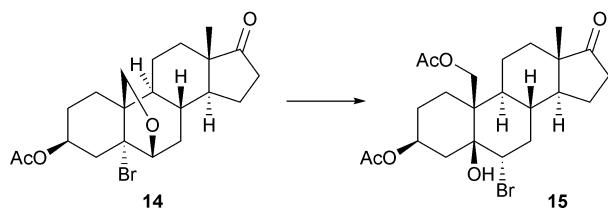
The conditions for the hydrazine hydrate reductive cleavage of α,β -epoxyketones have been modified⁴⁴ to allow the isolation of β -hydroxyketones. The stereochemistry of the Grignard addition to the carbonyl group of 4,5-epoxy-3-ketones has been shown⁴⁵ to be determined by the stereochemistry of the epoxide. The

alkyl group at C-3 became attached to the steroid on the same face as the epoxide. It is possible that the stereochemistry of the addition was determined by an initial co-ordination of the magnesium of the Grignard reagent to the epoxide oxygen. 3 α ,17 β -Dihydroxy-5 α -androstane is a testosterone metabolite which may act as a potential GABA_A receptor modulatory neurosteroid. An HPLC-MS assay has been devised⁴⁶ to detect this steroid in plasma. 3 β -Chloroandrost-5-en-17-one has been obtained⁴⁷ by chlorination of the corresponding 3 β -hydroxy- Δ^5 steroid with anhydrous ferric chloride in a reaction which proceeds *via* the homoallylic carbonium ion.

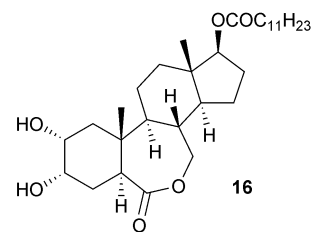
X-Ray crystallographic studies on the product of ketalization of 13 β -ethyl-11 α -hydroxygon-5-ene-3,17-dione have shown⁴⁸ that an inversion of configuration took place at C-10 during the course of the reaction to give **12**. A benzothiazol-[4,3-*b*]-estratriene **13** has been obtained⁴⁹ as a by-product from the reaction of androsta-1,4-dien-3,17-dione and 2-(methylamino)benzenethiol and boron trifluoride etherate.



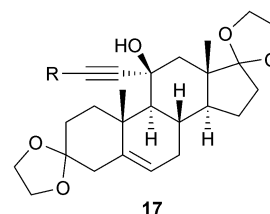
The ring opening of a 5 α -bromo-6,19-epoxysteroid **14** with boron trifluoride etherate in acetic anhydride has been shown⁵⁰ to give **15** by a rearrangement of the bromine to C-6 α . The mechanism is reminiscent of that involved in the isomerization of diaxial cholestane 5 α ,6 β -dibromides to diequatorial 5 β ,6 α -dibromides. The metabolism of 19-norandrostenedione by human hepatocytes has been shown⁵¹ to involve hydroxylation at C-6 β and reduction at C-3 and C-5, affording products such as 6 β -hydroxy-19-nortestosterone, and 3 α ,6 β -dihydroxy- and 3 β ,6 β -dihydroxy-5 α -estrane-17-one. This work was carried out in the context of evaluating urinary metabolic profiles in the detection of steroid abuse by athletes.



The synthesis of androstane brassinosteroid analogues with C-17 β ester groups, *e.g.* **16**, has afforded⁵² some bioactive products. The allylic oxidation of androst-5-enes at C-7 has continued to attract interest, with new methods based on the bismuth trichloride catalysed oxidation with *tert*-butyl hydroperoxide⁵³ and a copper bromide catalysed substitution using *tert*-butyl perbenzoate⁵⁴ being reported. The human metabolites of dehydroisoandrosterone include the 7 β -hydroxy derivative, which has been shown to have neuroprotective effects.⁵⁵ Both the C-7 α and C-7 β alcohols are typical microbial hydroxylation products, and they have now been obtained⁵⁶ using *Mucor racemosus*.

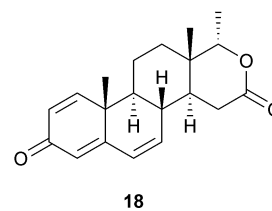


Although the stereochemistry of a neighbouring hydroxyl group can determine the stereochemistry of epoxidation of an alkene, the α - rather than β -stereochemistry of epoxidation of the 9(10)-double bond during the chromium trioxide oxidation of 3 β ,6 β -dihydroxy-5 β -methyl-19-norandrost-9(10)-enes has been observed.⁵⁷ The synthesis of 9 α -chloro- and 9 α -bromoandrostanes has been described.⁵⁸ The introduction of C-11 alkyl substituents can modify the biological properties of steroids. In the context of synthesizing such compounds, the interesting observation has been made⁵⁹ that the radical deoxygenation of the oxalate of the ethynyl alcohol **17** gave the 11 β -ethynyl derivative, despite the diaxial interactions that were introduced.



In the microbiological hydroxylation of C-4- and C-17 α -substituted testosterone derivatives by *Fusarium culmorum*, the presence of a C-17 α alkyl group has been shown⁶⁰ to favour hydroxylation at C-12 β and C-15 α as well as at C-6 β . The hydroxylation of 17 α -methyltestosterone by *Penicillium notatum* also occurred⁶¹ at C-15 α . The microbiological hydroxylation of 17 α -ethynyl- and 17 α -ethyl-steroids such as ethisterone by *Cephalosporium aphidicola* has been examined.⁶² Metabolites of dehydroisoandrosterone are now believed to possess immunomodulatory effects and to have neuroactive effects in the brain. Since C-16 α hydroxylation is a known mammalian metabolic step, derivatives of 16 α -hydroxydehydroisoandrosterone with an additional 7-oxo or 7-hydroxy substituent have been prepared⁶³ in this context.

The synthesis and anti-aromatase activity of some ring D lactones, *e.g.* **18**, has been reported.^{64,65} The chromatographic data of some oximes of substituted androstenes has been rationalized⁶⁶ in terms of their lipophilicity. A ring D pentadeuterio-3'-hydroxystanozol has been prepared⁶⁷ for use as an internal standard in doping analysis. An ELISA method for the screening of 17 α -alkyl anabolic steroid metabolites has been developed⁶⁸ for the detection of anabolic steroid abuse in horse racing.



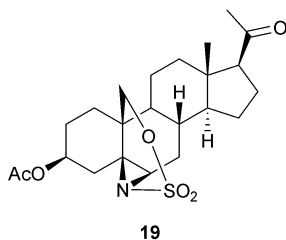
A new approach to the synthesis of finasteride from androstenedione has been reported.⁶⁹ Linear oligoesters of 3 β -hydroxyandrost-5-ene-17 β -carboxylic acid have been prepared⁷⁰ as gelators. A complex cytotoxic marine sterol, xestobergsterol A, has been synthesized from dehydroepiandrosterone.⁷¹ The chemistry and biology of wortmannin, which binds to the ATP site in regulatory kinases, has been reviewed.⁷²

4 Pregnanes

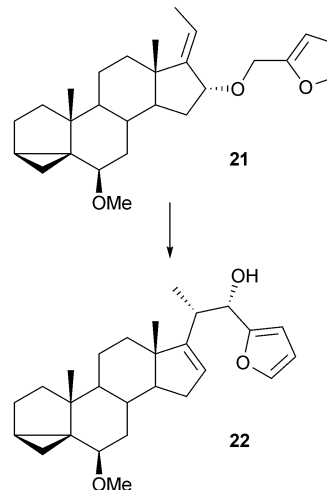
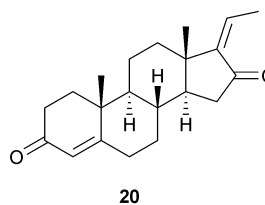
The role of pregnanes as neurosteroids has continued to attract interest. The sensitivity of the analysis by LC-MS methods of stress-induced changes in neurosteroid levels in rat brains has been enhanced⁷³ by the derivatization of pregnenolone and progesterone with 2-nitro-4-trifluoromethylphenylhydrazine. The synthesis of 6-aza-allopregnanolone by the Beckmann rearrangement of the *E*-oxime of a 6-oxo-*B*-norpregnane derivative has been reported.⁷⁴ However, it was only weakly active in binding to the GABA_A receptor. The effect of methyl substituents at C-6 and C-7 on the GABA modulatory and anaesthetic action of 3 α -hydroxy-5 α - and 5 β -pregnan-20-ones has been examined.⁷⁵ Only a C-6 β methyl group was tolerated. The effects of 17 β -conformational constraints on the modulation of GABA_A receptors by these neurosteroids has also been examined.⁷⁶

A concise method for the preparation of [6,7-²H₂]-cortisone has been described.⁷⁷ The metabolites of the anti-androgenic ring A lactone, 17 α -acetoxy-6-chloro-2-oxa-4,6-pregnadiene-3,20-one (osaterone acetate) have been identified.⁷⁸ Urinary markers for the detection of the oral administration of pregnanes in drug abuse have been described.⁷⁹ The microbial transformation of pregnenolone⁸⁰ and prednisone⁸¹ by *Cunninghamella elegans* has been examined.

The synthesis of pregnanes with a 6,19-sulfur or a 6,19-sulfamidate bridge (*e.g.* **19**) has been reported^{82,83} in the context of their potential application as immunomodulatory agents. Remote functionalization methods based on the photolysis of 11 α -hydroxy steroids have been used⁸⁴ to create a C-1-C-11 oxygen bridge in the pregnane series.



Molecular modeling studies have been made⁸⁵ of the binding of the *E* and *Z* 17(20)-isomers of guggulsterone **20** to the farnesoid X receptor in the context of their biological activity. The Wittig rearrangement of (*E*)-17(20)-ethylidene-16 α -furfuryloxy ethers (*e.g.* **21** \rightarrow **22**) has been examined⁸⁶ in the context of the construction of the steroid side chain. The crystal structure of a 20*R*-cyanosilylated pregnene has been described.⁸⁷ The biological activity of some progesterone derivatives as testosterone 5 α -reductase inhibitors for the treatment of prostate disease has been reported.^{88,89} Some further heterocyclic pregnane derivatives have been described.^{90,91}

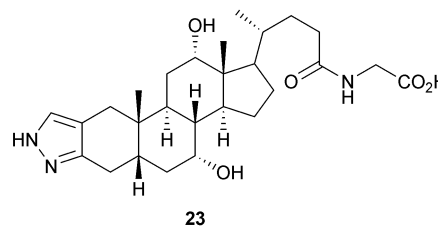


Methods for attaching 2-keto sugars to ring A diols in order to synthesize the gomphosides have been reported.⁹² The partial synthesis of some cardenolides has been explored⁹³ in the context of their anti-tumour activity. The microbiological hydroxylation of resibufogenin by *Mucor polymorphosporus*⁹⁴ and of bufalin by *Cunninghamella blakesleana*⁹⁵ has been reported.

5 Bile acids

Further methods for the regioselective modification of cholic acids in order to differentiate between oxygen functions at C-3, C-7 and C-12 have been explored.^{96,97} Partial syntheses of methyl 3 $\alpha,7\alpha,12\alpha$ -triamino-5 β -cholan-24-oate⁹⁸ and methyl 11 α -amino-3 $\alpha,7\alpha$ -diacetoxy-12-oxo-5 β -cholan-24-oate⁹⁹ from readily available cholic acid derivatives have been reported. A shark metabolite, scymnol, has been prepared¹⁰⁰ from cholic acid.

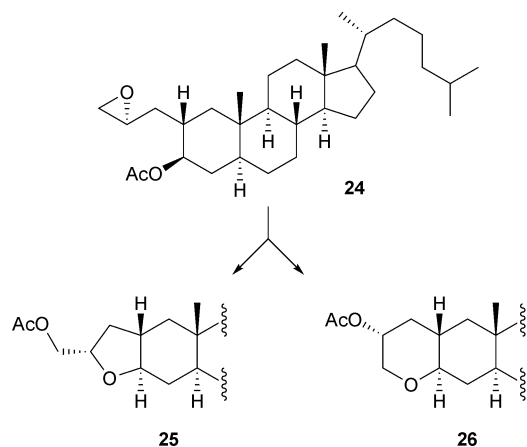
The properties of modified cholic acids as molecular tweezers¹⁰¹ and as transport agents (*e.g.* **23**)¹⁰² have been explored. The binding of bile acids to L- and D-tryptophan-modified β -cyclodextrins has been examined.¹⁰³



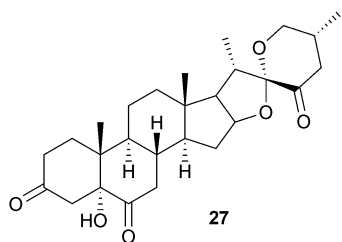
6 Cholestanes

A method for the gram-scale purification of stigmasterol has been outlined.¹⁰⁴ The stereochemistry of the reductive amination of 3-keto steroids has been examined¹⁰⁵ in the context of the

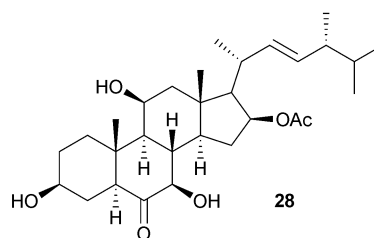
preparation of squalamine analogues. A number of biologically active families of steroids contain 2,3-diols. A new method for the synthesis of 2 β ,3 β -diols from the 2-alkene, using iodine and ceric ammonium nitrate in acetic acid, has been reported.¹⁰⁶ The regioselective enzymatic acylation¹⁰⁷ and oxidative cleavage of these diols with lead tetra-acetate¹⁰⁸ has been examined. Tetrahydropyran formation by rearrangement of the epoxy ester (**24** \rightarrow **25**, **26**) has been explored¹⁰⁹ in the context of model studies on the formation of marine polyether toxins. Further studies have been reported^{110,111} on the behaviour of organic free radicals based on cholesteryl esters. The stereochemistry of the electrochemical bromination of cholest-5-enes in different solvents has been examined.¹¹² Further reports on the epoxidation of cholesterol derivatives have appeared.¹¹³



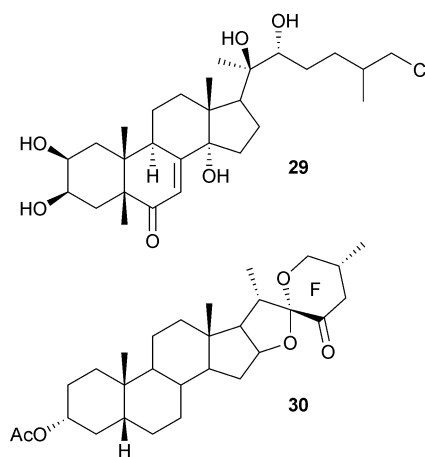
The brassinosteroid activity of some 5 α -hydroxy-6-ketones derived from stigmasterol and from spirostanes, *e.g.* **27**, has been examined.^{114,115} The anti-microbial activity of oxygenated derivatives of cholesterol has been explored,¹¹⁶ particularly against resistant strains of *Candida albicans*. The conformation of the nine-membered ring of B-nor-5,10-seco steroids has been determined¹¹⁷ by NMR and X-ray methods.



The preparation of transition-state analogues of sterol 24-methyl transferase has been studied¹¹⁸ in the context of preparing potential anti-parasitic agents. The preparation of 25*R* and 25*S* steroids functionalized on C-26 has been described¹¹⁹ in the context of biosynthetic studies on the bile acids. 23-Oxa analogues of the OSW-saponins have been prepared¹²⁰ as part of studies on their potential anti-tumour activity. The synthesis of the steroid **28** and the evaluation of its neurotrophic activity has been reported.¹²¹

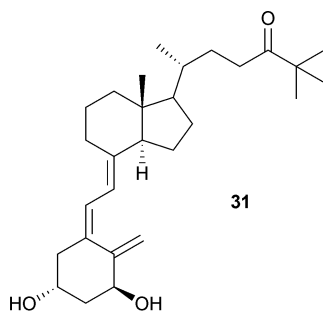


The synthesis and insect-moulting activity of the C-25 epimeric 26-haloponasterones, *e.g.* **29**, have been reported.¹²² An extensive review of NMR data has provided¹²³ the basis for assigning the stereochemistry of the 27-methyl group in the furostane steroidal saponins. Hecogenin has been used¹²⁴ as a carrier for the *N,N*-bis(2-chloroethyl)aminocinnamic acid moiety in cancer chemotherapy. The contraction of ring F of 23-oxo-3-*epi*-smilagenin acetate **30** induced by iodosobenzene has been observed.¹²⁵ A facile conversion of the steroidal alkaloid 23-hydroxyspirosolane, which is obtained from tomatoes, into 3 β ,16 β -dihydroxypregnan-20-one has been reported.¹²⁶ Further studies have been made¹²⁷ on the synthesis of parts of the cephalostatins from readily available spirostanes. The synthesis from diosgenin of a shark-repellant steroid, pavoninin **4**, has been achieved.¹²⁸ Microbiological methods for the removal of sugars from steroidal saponins have been reported.¹²⁹



7 Vitamin D

The ability of calcidiol (25-hydroxyvitamin D₃) to inhibit cell growth and control cell differentiation and proliferation, together with the association between vitamin D₃ levels and a reduced risk of prostate cancer, has attracted considerable interest.¹³⁰ Syntheses of a number of vitamin D analogues including 17-*epi*-calcitriol,¹³¹ derivatives of 1 α ,25-dihydroxy-19-norvitamin D₃ bearing substituents at C-2,^{132,133} and other ring A analogues,^{134,135} have been reported. The effect of modifications of the side chain have continued to be explored. Some highly anti-proliferative low calcemic ketones, *e.g.* **31**, have been prepared.¹³⁶ Modification of the side chain of calcitriol can affect the resistance of human HL-60 promyelocytic leukemia cells to drug-induced apoptosis.¹³⁷ The effect of the conformation of the side chain on binding to the vitamin D receptor has been explored^{138,139} with various conformationally restricted analogues.



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