REVIEW

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Steroids: reactions and partial synthesis

James R. Hanson
Department of Chemistry, University of Sussex, Brighton, Sussex, UK BN1 9QJ

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This article reviews the progress in the chemistry of the steroids that was published between January and December 2003. The reactions and partial synthesis of estrogens, androgens, pregnanes, cholic acid derivatives, cholestanes and vitamin D analogues are covered. There are 152 references.

1 Introduction

This review follows the pattern of its predecessor[1] with sections on the chemistry of the major skeletal types of steroids. There has been continued progress in the development of compounds which inhibit stages in steroid metabolism, particularly the C-17(20) lyase, in defining the structural requirements for binding to the steroid receptors and in establishing structure–activity relationships for the neurosteroids that target the $GABA_A$ receptor.

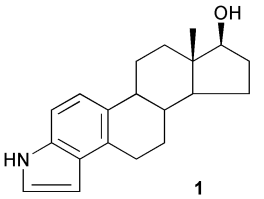
A review of the synthesis, physical and biological properties of enantiomeric steroids has appeared.[2] *Ent*-desmosterol and *ent*-cholesterol have been prepared[3] from *ent*-androst-4-ene-3,17-dione in order to study sterol–lipid interactions. A review has appeared[4] covering the use of transition metal catalysts in steroid synthesis. Although steroid total synthesis is outside the scope of this article, it is worth noting that a new strategy for a convergent steroid synthesis has been described.[5] A review has also appeared[6] covering chemical approaches to the study of transcription, a topic which included steroid examples.

2 Estrogens

The receptor interactions involving anti-estrogens and the role of selective estrogen receptor modulators in medicine has been reviewed.[7] NMR studies on the conformations adopted by estrogen receptor ligands has been reported.[8] 2-Methoxyestradiol has tumour growth inhibitory properties. A new short synthesis has been described[9] based on the oxidation of estradiol bis-THP ether by hydrogen peroxide in the presence of a strong base. An efficient synthesis of estrieno[2,3-*b*]- and [3,4-*c*]-pyrroles **1** by a palladium-catalysed amination has been reported.[10]

Some observations have been made[11] on the hydrolytic behaviour of the ethylene ketals of 5α,10α-epoxy-9(11)-estrenes and their 5α-hydroxy-11β-alkyl counterparts. The X-ray crystal structure of the alkene **2**, obtained from the reduction of the aromatic ring of 13-ethyl-3-ethoxygona-1,3,5(10)-triene-11α,17β-diol, has revealed[12] the presence of products from this reaction with an unusual 10α-hydrogen atom. Some novel estratrienones have been obtained[13] by oxidation at the benzylic C-6 and C-9 positions with *t*-butyl hydroperoxide in the presence of cobalt acetate. Estrogen esters with groups at C-7α, C-11β and C-15α have been used[14] to probe the structural requirements of the estrogen receptor. The synthesis has been reported[15] of a 7α-substituted estradiol–biotin chimera **3** that heterodimerizes the estrogen receptor with a streptavidin protein in a yeast.

The synthesis of a ring B aromatic 13-azasteroid has been described.[16] Although they have a lower binding affinity, some normal and 13-*epi*-D-homoestrone derivatives are recognized by the estrogen receptor.[17] The stereochemistry of the addition reactions to the 16,17-double bond of 3-methoxy-13α-estra-1,3,5(10),16-tetraene has been examined[18] and the conformation of the four 16,17-diols has been established.[19] A stereoselective synthesis of the isomeric *trans* 16-hydroxymethyl-3-methoxy-13α-estra-1,3,5(10)-trien-17-ols (*e.g.* **4**) and their halogenation, has been reported.[20,21] The synthesis and anti-neoplastic activity of 16-arylidene derivatives of estrone, *e.g.* **5**, have been described.[22] Syntheses have been reported of estradiol–adenosine[23] and estradiol–taxol[24] conjugates.



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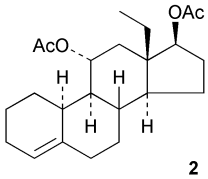

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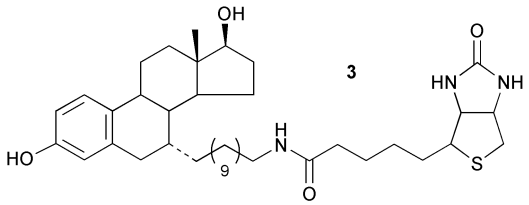

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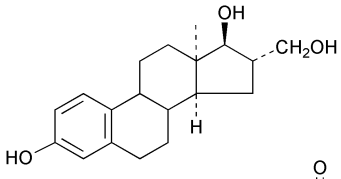

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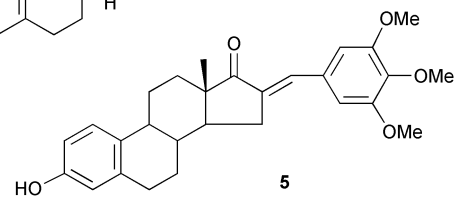

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The modification of ring D of estrone has continued to be of interest in the context of its effects on estrogen metabolism and on the binding of the steroid to the estrogen receptor. Some medium-sized ring D derivatives of estrone, *e.g.* **6**, have been obtained[25] by a combination of intramolecular Heck and Grignard reactions. The sulfamate **7** has been shown[26] to be a potent inhibitor of a steroid sulfatase. The receptor binding activity of 17α-arylestradiols has been examined.[27] The synthesis of ^{11}C labelled compounds in the estradiol series has been reported,[28] while 17α,20*E*/*Z*-[^{125}I]-iodovinyl derivatives of

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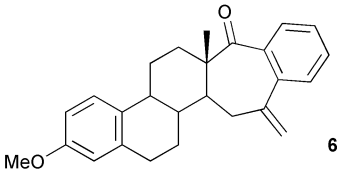
7α-cyanoestradiol[29] and 7α-cyano-19-nortestosterone[30] have been prepared as radioligands for the relevant steroid receptors. Some 4′-substituted cinnamylestradiol derivatives **8** have been evaluated[31] as probes for the estrogen receptor binding domain. Various 17α-substituted estradiolpyridin-2-yl hydrazine complexes with rhenium have also been prepared[32] as potential ligands for labelling the estrogen receptor.

The biomimetic hydroxylation of C-12 to afford **9** using a copper complex and oxygen, with the 17-pyridinyl imine as a directing group, has been examined.[33] Some 17β-estradiol dimers linked *via* an alkyl chain between C-17α have been shown[34] to have cytotoxic activity against human cancer cell lines that are responsive to estrogens.



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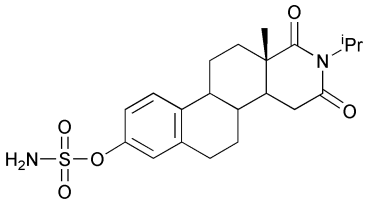

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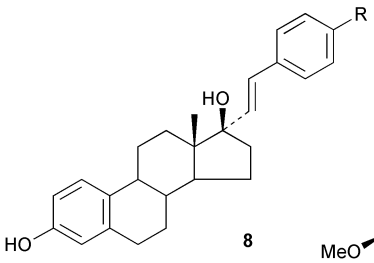

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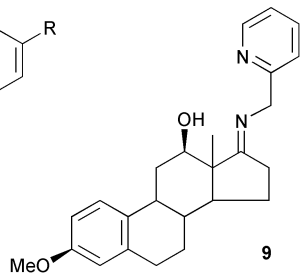

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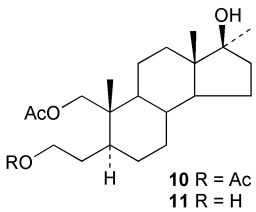
3 Androgens

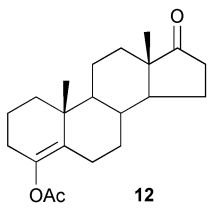
Methods have been reported for the regioselective aminolysis of steroidal 2α,3α-epoxides catalysed by gadolinium triflate[35] and for the preparation of 3β-amino-5α-androstan-17-one.[36] A regioselective *Candida antarctica* lipase catalysed hydrolysis of the diacetate **10** to the mono-ol **11** has provided[37] the basis for a convenient synthesis of the ring A lactone of oxandrolone. The stereochemistry of some reactions of 2-methylene and 2-hydroxymethylene-5α-androstanes has been described.[38,39]



10 R = Ac
11 R = H

The structure–activity relationships of some 3-deoxyandrogens, *e.g.* **12**, as aromatase inhibitors have been evaluated.[40] The nitrone **13** has been examined[41] as a transition state mimic of an enolate intermediate in the formation of 5α-dihydrotestosterone by testosterone 5α-reductase. The oxime ether **14** has been shown[42] to be a novel Na^+,K^+-ATPase inhibitor and this compound may have application in the treatment of heart failure.

Some thermodynamic features of the isomerization of androst-5-ene-3,17-dione to androst-4-ene-3,17-dione have been examined.[43] The microwave-induced enol-acetylation of steroidal ketones has been reported.[44] Some unusual steroidal polyquinane hybrids, *e.g.* **15**, have been described.[45] The proton chemical shifts of androstane amines have been assigned.[46]



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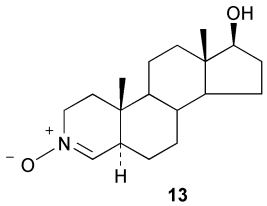

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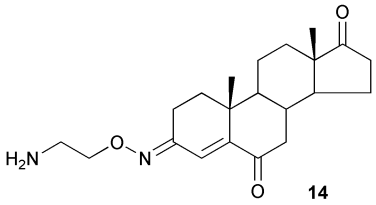

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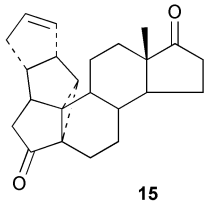

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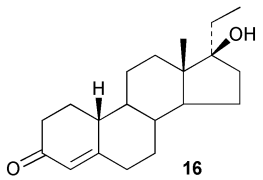
Some structural requirements for binding to the androgen receptor have been determined[47] using some androst-16-enes. The partial syntheses of androst-16-ene-3β,5α-diol and 3β,5α,6β-triol[48] and of some cytostatic ring B lactams[49] have been described. The stereochemical factors affecting the 1,2-addition of Grignard reagents to steroidal unsaturated ketones and the oxidation of 3-hydroxy-3-methyl-Δ^4-steroids have been examined.[50,51]

Androstanes have continued to provide useful substrates for defining the structural requirements for microbiological hydroxylations. Studies on the biotransformation of 3α,17β- and 3β,17α-dihydroxy-5α-androstanes,[52] 4,4-dimethylandrost-5-enes,[53] 5β-methylestr-9-enes,[54] des ring D androstanes,[55] 17-chloroandrosta-4,16-dien-3-one,[56] and 4-formylandrostanes[57] have all been reported. The extent of the double bond migration in the Westphalen rearrangement of des ring D androstenes has been examined.[58]

The syntheses of some equine metabolites of the anabolic steroid, norethandrolone **16**, have been reported.[59] Solvent effects have been shown[60] to play a role in the addition of organolithium reagents to hindered C-11 ketones. The preparation and X-ray crystal structure of 16-acetylandrosta-4,16-diene-3-one **17** has been reported.[61] The conditions for the abnormal Beckmann rearrangement of steroidal C-17 oximes have been optimized[62] for the fragmentation of ring D to form **18**. 16,17-Secosteroids with aminomethylene-2-pyridine structures have been used[63] as chiral ligands for the copper ion activation of oxygen.



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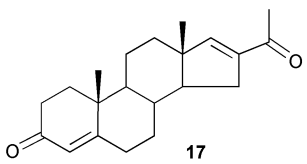

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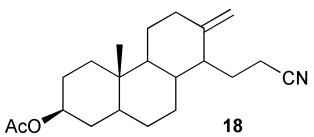

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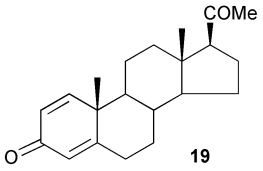
The palladium-catalysed aminocarbonylation of 17-iodoandrost-16-enes[64] in ionic liquids and the X-ray structures of 16-amino-D-homosteroids have been reported.[65] The Cu/Fe-mediated hydrogenation of 17-halo-16-enes in the presence of hydrazine has also been reported.[66]

Androgens containing various 17-azole substituents have been examined as inhibitors of the hydroxylase in the 17(20)-lyase and as potential agents for prostatic cancer therapy.[67,68] Some 5α,13α-D-azasteroids have been prepared[69] as potential precursors of $GABA_A$ receptor modulators. Improvements in the phosphorylation of alcohols with titanium *t*-butoxide as the catalyst have been made[70] using steroidal 17β-alcohols as examples. The synthesis of two new haptens of 16α-hydroxydehydroepiandrosterone has been reported.[71]

4 Pregnanes

Some general patterns have been identified[72] in the wavelength dependence of various photochemical reactions of pregna-1,4-diene-3,20-dione **19**. An efficient process has been developed[73] for the production of the key steroid intermediate, 16-dehydropregnenolone **20**, from diosgenin. A synthesis has been reported[74] of 5,7-dienes related to pregnane-3,17α,20-triols which are abnormal steroid metabolites. Methods have been developed[75] for the synthesis of 6β-hydroxycortisol labelled with stable isotopes. Some pregna-1,4,6-trienones, *e.g.* **21**, have been evaluated[76] as inhibitors of testosterone 5α-reductase. The conjugate addition of *p*-aminothiophenol to pregnane-4,6-dien-3-ones has been observed.[77]



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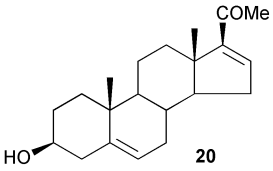

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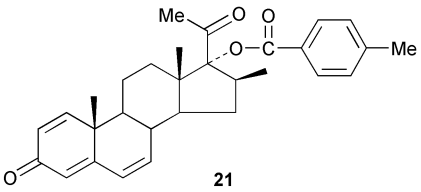

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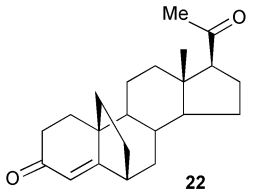
The 6,19-methanoprogesterone **22** has been prepared.[78] Neurosteroids have continued to attract interest. The $GABA_A$ receptor activity of the 6,19-oxidopregnane analogue **23** has been examined.[79] Some other pregnanes with conformationally constrained side chains, *e.g.* **24**, have also been prepared[80] as analogues of neurosteroids with GABA modulatory activity. The synthesis of 11,12-aziridino analogues, *e.g.* **25** of neuroactive steroids has also been reported.[81] Dysfunction of glucocorticoid receptors in the brain has been associated with some neuropsychiatric disorders. Some novel arylpyrazolocorticosteroids have been developed[82] for imaging these receptors.



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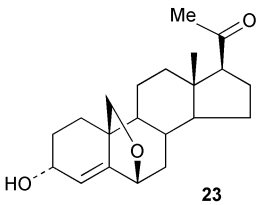

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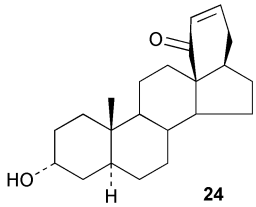

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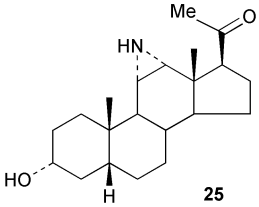
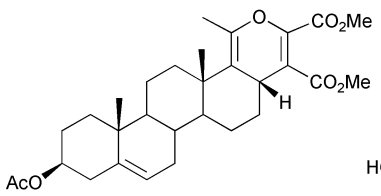


25

16-Dehydropregnenolone acetate has provided the starting material for the preparation of 16β-halo[83] and 16α-methyl[84] derivatives of cyproterone and for the formation of a pyrone **26** by a 4 + 2 cycloaddition.[85]

21,21-Difluoro-3β-hydroxypregna-5,20-diene and the corresponding 5,16,20-triene have been shown[86] to be inhibitors of the 17(20)-lyase. The Grob fragmentation of ring D to give the aldehyde **27**[87] and the base-catalysed cleavage of the dihydroxyacetone side chain of the corticosteroids[88] have been examined. Aerial oxidation of the corticosteroid side chain in the presence of copper acetate has been shown[89] to lead to dimers based on 17,21-acetals. The preparation of 21,21-dimethylprogesterone[90] and the conformation of the side chain of 21-alkylpregnanes[91] have been examined.



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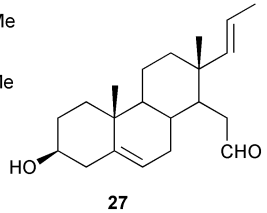

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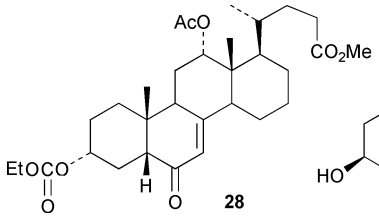
5 Cholic acids

The application of residual dipolar couplings in the NMR spectrum to the assignment of conformation has been explored[92] with sodium cholate. The preparation of fluorinated derivatives of cholic acids has been explored[93] in the context of the synthesis of squalamine analogues. The marine sterol 3β,6α-dihydroxy-5α-cholan-23-one has been synthesized.[94] The conversion of cholic acid to the unsaturated 6-ketone **28**[95] and the synthesis of the lactone **29**[96] have been described.

Metal complexing has been explored[97] as a tool for controlling the self assembly and gelation properties of cholic amide–phenthroline gelating agents. A review has appeared[98] of steroids as the organising components in anion receptors. A cholapod quaternary ammonium salt containing pendant urea groups has been examined[99] in the context of anion recognition. Desoxycholic acid–copper phosphite complexes have been explored[100] as ligands for the enantioselective conjugate addition of diethyl zinc to acyclic enones.



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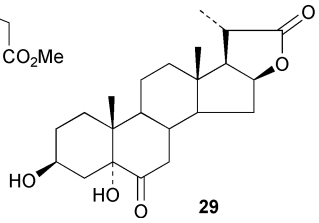

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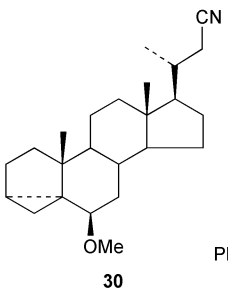
Clathrates based on cholic acid have been used[101] to form complexes with the *o*-, *m*- and *p*-xylenes. The X-ray structure of an inclusion complex between ursodeoxycholic acid and phenanthrene has been described.[102]

The addition of metal cyanides to the *p*-toluenesulfonyl hydrazones of aldehydes has been explored[103] as a method of one-carbon homologation on the steroid side chain, as in the formation of **30**. The properties of a model *trans*-membrane ionophore based on the dimer 3β,6α,7β-trihydroxy-bisnorchol-16-ene 22-terephthalate have been examined.[104] The synthesis of ester-linked lithocholic acid dimers has been reported.[105] Some novel steroidal dendrons have been obtained[106] from 3α-trifluoroacetoxy-5β-cholan-24-oyl chloride and the benzyl ester of 2,2-bis(hydroxymethyl)propionic acid. The complexing properties of some cholane–porphyrin conjugates have been examined.[107] The anti-malarial, anti-mycobacterial and anti-proliferative activity of phenyl-substituted tetraoxanes, *e.g.* **31**, have been examined.[108] The photochemical rearrangement of the C-3 *o*-nitrobenzyl ethers of cholic acid to *o*-nitrosohemiacetals has been observed.[109]



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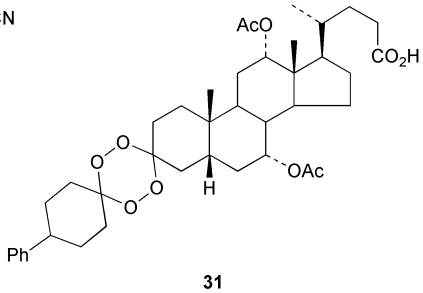

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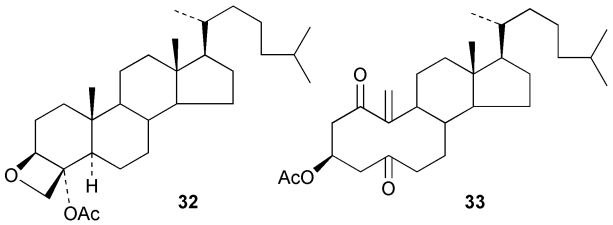
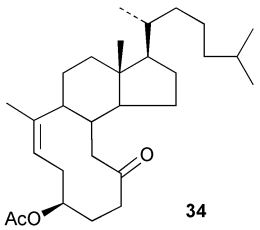
6 Cholestanes

Evidence has been provided[110] for the effect of cholesterol in a membrane on unravelling neighbouring phospholipids by acting as a a rigid hydrophobic template and maximizing the hydrophobic interactions. The interactions of cholesterol with cyclodextrins in solution has been studied[111] by NMR methods.

A formal synthesis of squalamine from desmosterol has been reported.[112] The anti-viral activity of the disulfate of 23,3α-dihydroxy-5α-cholestane has been noted.[113] The reactions of the oxetane **32** have been studied[114] as a model for aspects of taxol chemistry. The oxidative fragmentation of 5α-hydroxy-1-oxo-cholestan-3β-yl acetate to form **33**, and of some 5-hydroxy-B-norcholestan-3β-yl acetates to give 5,10-secosteroids such as **34**, together with their acid-catalysed reactions, have been examined.[115–117]



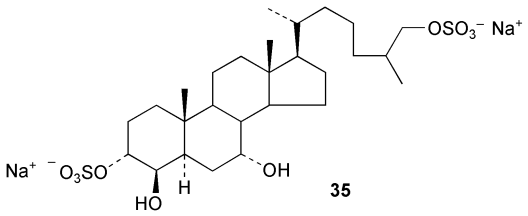


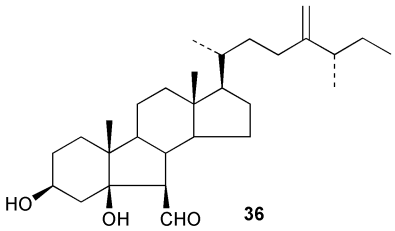
The allylic oxidation of cholesteryl acetate has been examined using *t*-butylhydroperoxide and silica modified with a cobalt alkylphosphonate[118] or copper iodide in acetonitrile.[119] Some further epoxides have been isolated[120] from the autoxidation of isotachysterol. The synthesis of deuteriated samples of 7α- and 26-hydroxycholesterol for use in studying the bile acid pathway has been described.[121]

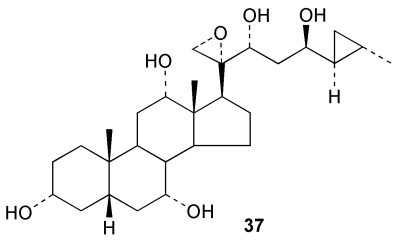
The sperm-activating factor **35** of the ascidian *Ciona intestinalis*, has been synthesized.[122] A synthesis of the follicular fluid meiosis activating sterol, 3β-hydroxy-4,4-dimethyl-5α-cholesta-8,14,24-triene, has been reported[123] in the context of improving *in vitro* fertilization. The synthesis of the B-noraldehyde, orostanal **36**, has attracted interest[124] because it induces apoptosis in HL-60 cells.

A computer program for predicting ^{13}C NMR chemical shifts which takes into account stereochemistry has been applied[125] in the ecdysone series. The brassinolide plant hormones have continued to attract interest with reports on novel methods of constructing the side chain,[126] and the synthesis of B-homo analogues,[127] C-28 homo analogues,[128] and labelled brassinolides.[129] The anti-tumour activity of the marine sterol aragusterol A has provided the stimulus for the synthesis[130] of some analogues, **37**, from cholic acid. The tumour-inhibiting properties of the dimeric steroids of the cephalostatin series has also continued to stimulate synthetic methodology.[131,132] Methyl protodioscin[133] and some rhamnosylated diosgenin glucosides[134] have been synthesized from diosgenin in the course of studies on steroidal cytostatic agents.

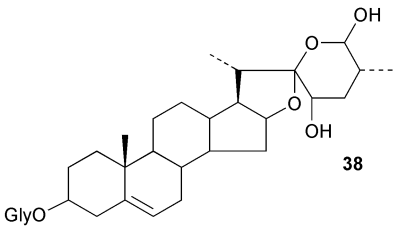
A number of modifications of the spiroketal ring system of the steroidal sapogenins such as diosgenin have been reported including the unusual cleavage of the diol **38** to the

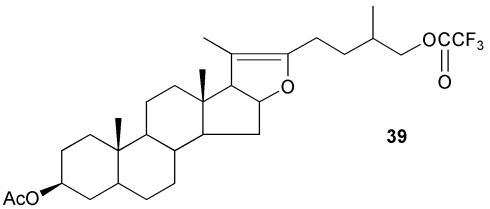


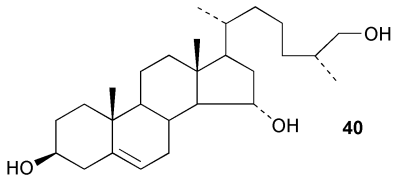


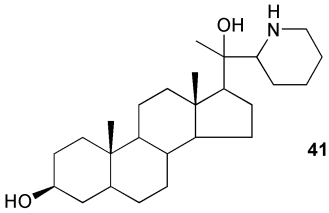


22 → 16-lactone,[135] the formation of C-26 dithioketals[136] and the opening of the spiroketal with trifluoroacetyltrifluoromethanesulfonate to form **39**[137] and the cleavage with boron trifluoride–acetic anhydride.[138] The synthesis of the aglycone of 26-*O*-deacetylpavoninin 5 **40** from diosgenin has been reported.[139] Distinctions between the 25*R* and 25*S* spirostanes have been made[140] using their NMR spectra. The azasterol analogue **41** has been shown[141] to be an inhibitor of the 24-methyl transferase in *Leishmania* species.





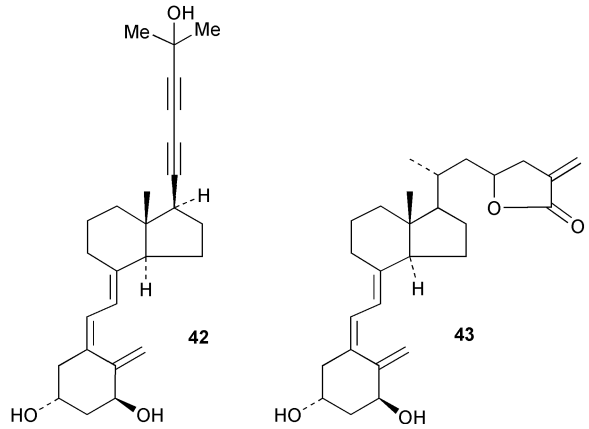




7 Vitamin D

The organic chemistry of vitamin D analogues has been reviewed.[142] 1α,25-Dihydroxyvitamin D_3 (calcitriol) may exert some of its biological activity by binding to a nuclear receptor and initiating gene transcription whilst other effects involving calcium homeostasis may involve interactions with a membrane receptor. The synthesis of analogues modified on rings C and D to differentiate between these binding sites has been reported.[143] The thermal isomerization of vitamin D_3[144] and the photoconversion of 25-hydroxytachysterol to 25-hydroxyprevitamin D_3[145] have been examined.

The rigid acetylenic side chain analogue **42** of calcitriol has been shown[146] to induce vitamin D receptor transcriptional activity whilst 1α-hydroxyvitamin D_3 26 → 23-lactones *e.g.* **43**, have antagonistic activity at the vitamin D receptor.[147,148] Functionalization of C-12 of 1α,25-dihydroxyvitamin D_3 modifies the affinity for the vitamin D receptor. The analogue with a 12-methyl substituent possessed a high affinity for the receptor.[149]



A number of novel hapten derivatives of 1α,25-dihydroxyvitamin D_3 have been prepared.[150] Compounds linked through C-16 expose both ring A and the side chain, to maximize antibody specificity. A number of new strategies for the synthesis of vitamin D analogues have been described.[151,152]

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