Steroids: partial synthesis in medicinal chemistry

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Received (in Cambridge, UK) 9th September 2005
First published as an Advance Article on the web 13th December 2005
DOI: 10.1039/b512848j

Covering: January to December, 2004

This article reviews the progress in the chemistry of the steroids that was published between January and December 2004. The reactions and partial synthesis of estrogens, androgens, pregnanes, cholic acid derivatives, cholestanes and vitamin D analogues are covered. There are 127 references.

1 Introduction

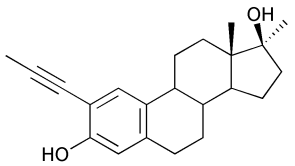
This review follows the pattern of its predecessors[1] with sections on the major skeletal types of steroids. Reviews have appeared on the use of steroids in combinatorial chemistry,[2] on the synthesis and biological activity of cephalostatin analogues,[3] on directing effects in the hydroboration of steroidal alkenes[4] and on the solid phase epoxidation of steroidal alkenes with potassium permanganate and metal salts.[5] The methods that are employed for the identification of anabolic steroids that are abused in sport, have been reviewed.[6] Special issues of the *Journal of Steroid Biochemistry and Molecular Biology* have been devoted to vitamin D[7] and to the role of steroids in prostate cancer and its treatment.[8,9]

2 Estrogens

A number of novel syntheses of the estrane skeleton have been described[10] including an enantioselective synthesis of estrone using a chiral oxazaborolidinium catalyst. A radical cascade cyclization has been used[11] in a new total synthesis of estrone whilst the steroid backbone has been formed[12] by a photo-induced domino-cyclization of silyl enol ethers.

A gas chromatography–mass spectrometric assay of estradiol, catechol estradiols and methoxyestradiol in plasma has been developed[13] whilst isotope dilution GC–MS methods have been used[14] in the detection of estrogens and phytoestrogens in urine. The differentiation of steroid epimers by mass spectrometric methods has been examined.[15] The complete ^{1}H and ^{13}C NMR assignments of some estradiols have been reported.[16]

A molecular dynamics simulation has been used[17] to predict the binding affinities of estrogen analogues to the estrogen receptor. The need for selective targeting of estradiol dependent cancers has been discussed[18] in the context of drug delivery systems for estrogenic hormone antagonists. 2-Methoxyestradiol has tumour growth inhibitory properties. In light of this, the anti-proliferative activity of 2-alkylsulfonyl estrogen derivatives has been examined.[19] A series of 2-methoxyestradiol analogues, *e.g.* **1**, have been prepared[20] in order to study their effects on cell proliferation and cytotoxicity in human cancer cell lines.



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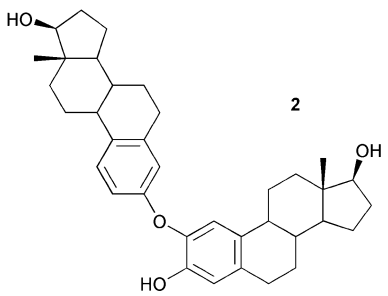
The oxidative coupling of estradiol through the aromatic ring to give **2** using hydrogen peroxide and peroxidase[21] and the bromination of estradiol with *N*-bromosuccinimide[22] have been



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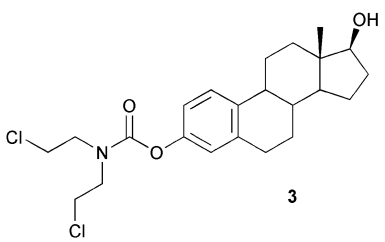

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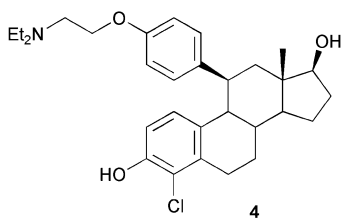

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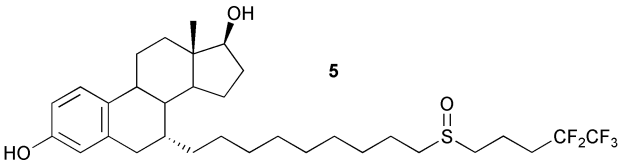
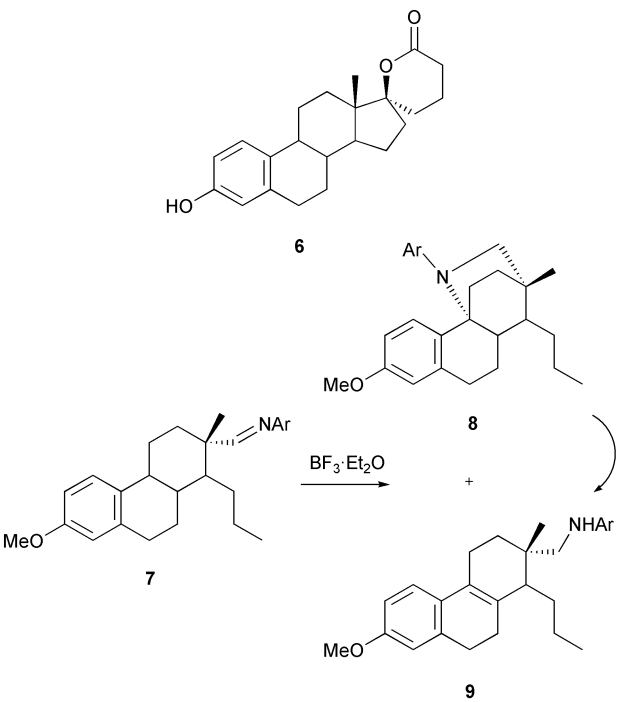
described. The stability of the catechol estrogens in the presence of copper(I) salts has been examined.[23] The anti-cancer agent, estramustane **3** has been synthesized[24] bearing deuterium labels on rings A and D. An industrial synthesis of a 4-chloro-11β-arylestradiol **4** has been described.[25]

The way in which ICI 182780 **5** binds to and regulates the estrogen receptor, has been examined.[26] A further series of estradiol derivatives bearing sulfur containing substituents at the C-7a and C-11β positions have been reported.[27] Some estradiol–taxol® conjugates have been prepared[28] in which the estradiol is linked to the taxol® through the C-11 and C-16 positions.



5

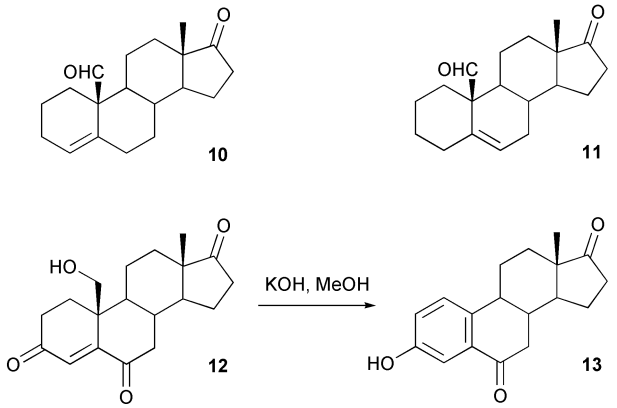
The modification of ring D of the estrogens has continued to be explored in the context of its effects on estrogen metabolism. A number of potential estrogenic inhibitors of the 17β-hydroxysteroid dehydrogenase have been prepared including compounds bearing substituents at C-16[29] and lactones at C-16,[29] *e.g.* **6**.[30] The Mitsunobu inversion of sterically hindered 17β-hydroxy steroids has been examined.[31] An unusual iminium ion induced overall 1,5-hydride shift **7** → **9** has been observed[32] involving a D-*seco* isoquinuclidine **8**.



6 **8** **7** **9**

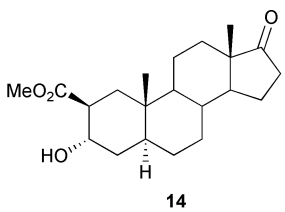
3 Androstanes

Studies on the androgen receptor as a potential target for the treatment of prostate cancer have been reported.[33] The use of anti-androgens in the endocrine treatment of prostate cancer has been discussed.[34] The loss of the androstane 19-methyl group in the aromatase sequence leading to the estrogens, has continued to be a topic of investigation with reports on the synthesis of 19-^{3}H analogues of dehydroepiandrosterone.[35] The determination of the stereochemistry of the reduction of the 19-carbonyl group of the 3-deoxyandrogens **10** and **11** by sodium borohydride has led[36] to the preparation of some 19*R*- and 19*S*-labelled aromatase inhibitors. In both cases the 19*S* isomer predominated in the reduction. It is the 19-pro*R* hydrogen which is lost on the aromatase oxidation to the aldehyde. The cleavage of the C(10)–C(19) bond of oxygenated androst-4-ene-3,6-diones (*e.g.* **12** → **13**) has been examined[37] under various conditions.



10 **11** **12** **13**

The selective carbonylation of 2α,3α-epoxyandrostan-17-one to give 2β-carbomethoxy-3α-hydroxyandrostan-17-one **14** in the presence of a cobalt octacarbonyl catalyst, has been reported.[38] The hydroboration of 3-hydroxy-3-methylandrost-4-enes has been shown[39] to give 4β-hydroxy-3α-methyl-5β(H)-steroids (**15** → **16**) with the elimination of the 3-hydroxyl group irrespective of the stereochemistry at C-3. The β-face selective epoxidation of Δ^5-steroids has continued to be of interest with reports[40] on the use of oxygen in the presence of a silica supported cobalt catalyst. Whereas treatment of 5α,6α-epoxy-3β-methanesulfonoxyandrostan-17-one with hydrobromic acid in glacial acetic acid afforded a 4-methylestratriene by a dienol–benzene rearrangement, the reaction with sulfuric acid led to the product **17** of a Westphalen backbone rearrangement.[41] 3-Chloro-3,5-dienes **18** are easily prepared from the corresponding unsaturated ketones with oxalyl chloride. They have been shown[42] to be oxidized with chromium trioxide to the corresponding Δ^4-3,6-diones in good yield. The synthesis of some 3-hydroxy-3-methyl-6-oxoandrostanes has been reported.[43] The crystal structure has been described[44] of a trifluoroacetate bridged 5,6,7-π-allyl



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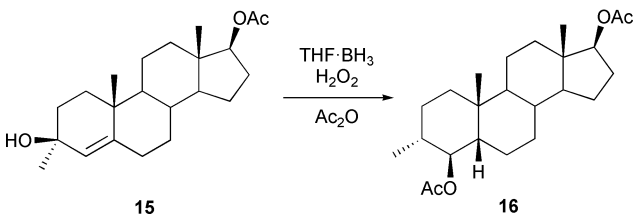
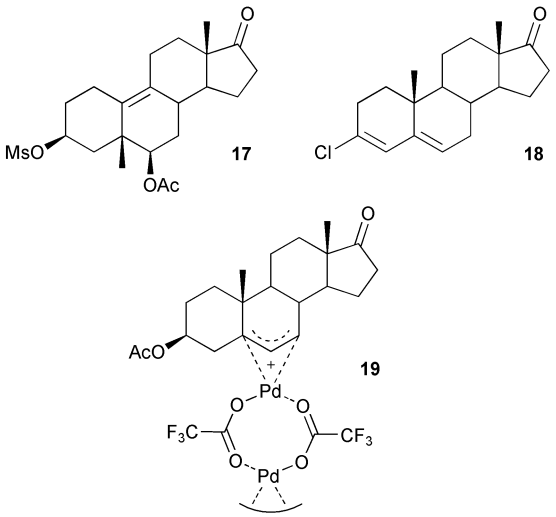
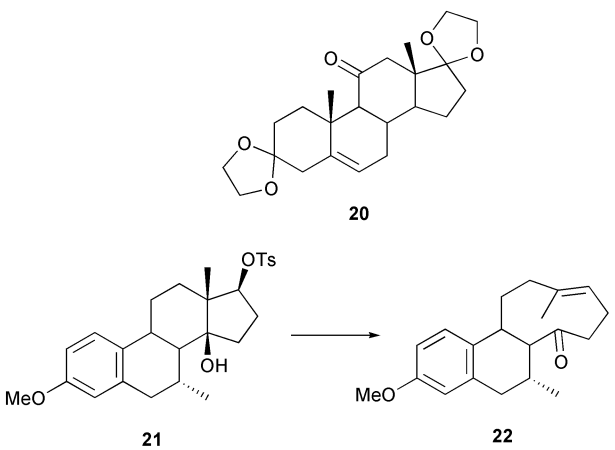


15 **16**

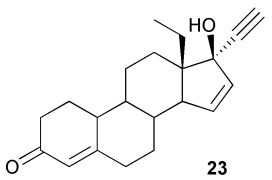
steroid palladium dimer **19** derived from the reaction of 3β-acetoxyandrost-5-en-17-one with palladium(II) trifluoroacetate.



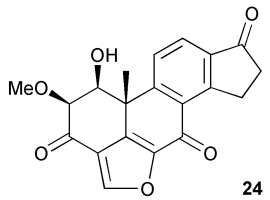
11-Substituted androstanes have continued to attract interest. A cobalt mediated 2 + 2 + 2 cyclization of an allenediyne has been reported[45] to give the 11-aryl steroid skeleton. The reactivity of 11-oxo steroids, *e.g.* **20**, towards organometallic reagents[46] and the radical decomposition of oxalate esters[47] have been examined in the context of preparing 11-substituted derivatives. Further work has been reported on the preparation of 13,14-seco-steroids by the Grob fragmentation of 14α-hydroxy-17β-tosyloxy steroids, **21** → **22**,[48] and by the lead tetra-acetate and iodine oxidation of 14α-hydroxy-17-keto steroids.[49] The reaction of (13*S*)-13-iodo-16β-methoxy-3α,5α-cyclo-13,14-secoandrostan-14,17-dione with hydroxylamine has been examined.[50]



A simple synthesis of gestodene **23** from 18-methylestr-4-ene-3,17-dione has been reported.[51] The detection of 17-alkyl substituted anabolic steroids by liquid chromatography and electrospray tandem mass spectrometry has been examined in relation to the abuse of these steroids.[52] The microbiological hydroxylation of 17-methoxy steroids at C-6 and C-11 by the fungus, *Cephalosporium aphidicola*, has been reported.[53]

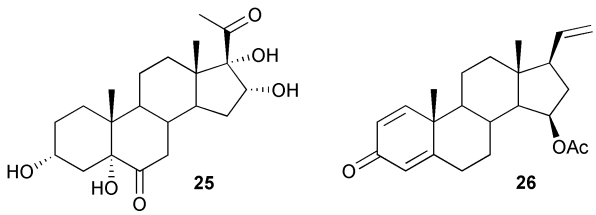


The synthesis of the furanosteroidal antibiotic, viridin **24** has been achieved.[54] The biological activity of a library of viridin and wortmannin analogues as inhibitors of tumour cell growth has been examined.[55]

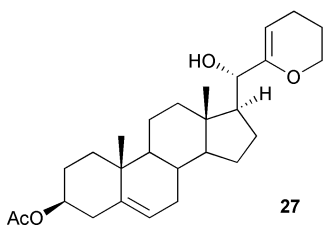


4 Pregnanes

The synthesis and the effect of 3α-amino-5α-pregnan-20-one on the GABA receptor has been studied[56] in the context of the activity of pregnanes as neurosteroids. The synthesis and modification of 3β-steroidal glycosides of 3β,5α,6β-trihydroxypregnan-20-one has been reported.[57] Some 5α-hydroxy-6-ketopregnanes, *e.g.* **25**, have been examined[58] as analogues of brassinosteroid plant growth regulators. 17-Substituted pregnadienes have been prepared[59] as potential inhibitors of testosterone 5α-reductase. An unusual Δ^{20}-pregnene **26** which was obtained[60] from an octacoral, has been shown to be an inhibitor of the mitochondrial respiratory chain.

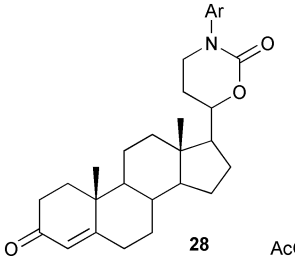


The hydrogenation of a C(20),C(22)-ketene dithioacetal has been used[61] in the stereoselective synthesis of the unnatural C(20*R*) epimer of a C(22) aldehyde. The stereoselective reactions of the 20-dihydropyran **27** have been examined[62] with the object of preparing compounds with modified steroidal side chains.



Steroidal tetrahydroxyoxazineones, *e.g.* **28**, have been examined[63] as inhibitors of testosterone 5α-reductase. A number of heterocyclic steroids have been prepared from dehydropregnenolone acetate and D-secopregnenes including the tetrahydroquinoline analogue **29**.[64,65] The stereoselective addition of pyridyl lithium to a C-22 aldehyde has been reported.[66] The effect of the

modified steroid backbone of 5β-methyl-19-norpregn-9-enes on their biotransformation by *Cephalosporium aphidicola*, has been examined.[67]



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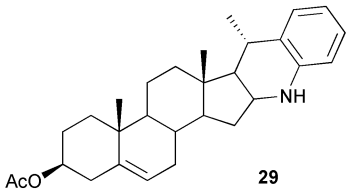

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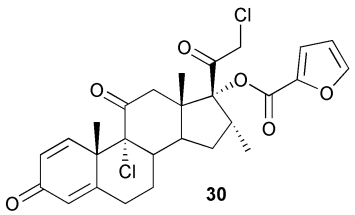
An historical account has been given[68] of the development of the Merck process for the synthesis of cortisone from bile acids. Some novel spironolactone analogues have been detected[69] as impurities in commercial preparations of spironolactone. The flexibility of the progesterone receptor binding pocket has been explored[70] using crystal structures of norethindrone and mometasone furoate **30** complexes. The synthesis and glucocorticoid activity of a series of 17-furoate esters, *e.g.* **31**,[71] and of some C-21 nitroesters of prednisolone,[72] have been explored. The products, including **32**, from the photodegradation of the anti-inflammatory steroid loteprednol etabonate, have been identified.[73]



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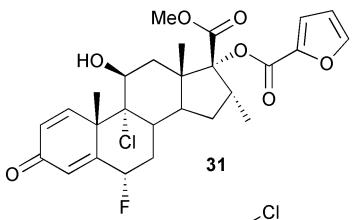

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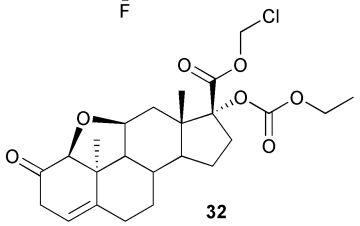
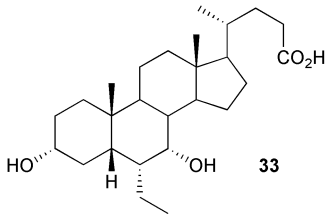


32

The synthesis of the biologically active cardenolides has been reviewed.[74] Bufalin is a bioactive constituent of the Chinese drug Chan-Su, which shows potent anti-cancer activity. A number of cytotoxic bufadienolides have been obtained[75] from bufalin by microbial hydroxylation with *Mucor spinosus.*

5 Bile acids

The partial synthesis of 3α,7α,14α-trihydroxy-5β-cholan-24-oic acid has been described.[76] The C-14α hydroxyl group was introduced by oxidation with dimethyldioxirane. The farnesol X receptor is activated by endogenous bile acids and plays a variety of physiological roles related to the modulation of gene transcription. Some further bile acid analogues based on **33** and derived from chenodeoxycholic acid have been examined[77] in this context. Bile acid conjugates, *e.g.* **34** of mifepristone have been synthesized[78] as liver selective glucocorticoid antagonists for the treatment of type 2 diabetes.



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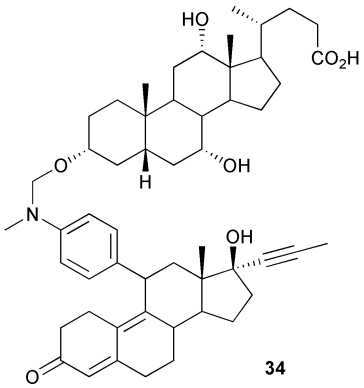
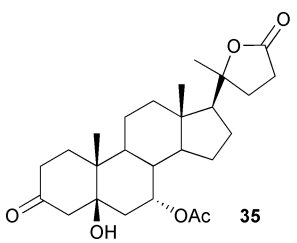


34

The synthesis and X-ray crystal structures have been reported[79–81] of a number of dinorcholane derivatives. The X-ray crystal structure of the monoethyl oxalate ester of 3α-hydroxy-5β-cholan-24-oic acid has been described.[82] Some lithocholic acid derivatives have been synthesized.[83] The hydrogen bonding network of 3-oxo-12α-hydroxy-5β-cholan-24-oic acid has been predicted[84] from X-ray evidence.

The remote functionalization of 3-oxo-bile acids by oxidation with 2,6-dichloropyridine *N*-oxide catalysed by a ruthenium porphyrin has been shown[85] to lead to lactonization at C-20 as in **35**. Conjugates of gadolinium complexes with bile acids have been considered[86] as hepatocyte directed contrast agents for magnetic resonance imaging.

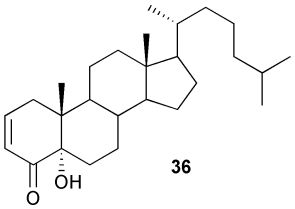


35

6 Cholestanes

A series of gradient enhanced selective NMR experiments have been used[87] to assign the ^{1}H NMR signals of stigmasterol. The synthesis of cholest-1-en-3-one from the 2α-iodo-3-ketone by oxidation of the iodine with per-acid has been described.[88] A series of spirostane analogues of the brassinosteroids have been prepared[89] by the homogeneous potassium permanganate dihydroxylation of 2,3-enes. The oxidation of Δ^2-, $\Delta^{2,4}$- and

$\Delta^{4,6}$-cholestenes with ruthenium tetroxide to form diols and ketols, *e.g.* **36** has been reported.[90]

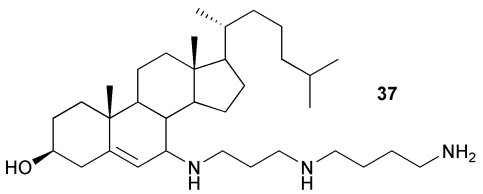


36

Methods for the attachment of glycosyl units at the C-3 of diosgenin have been examined.[91,92] The synthesis of some spirostenols based on diosgenin which prevent β-amyloid induced neurotoxicity has been reported.[93] Cholesterol surrogates containing a benzophenone moiety have been synthesized[94] as potential photo-affinity labels for measuring cellular sterol efflux and HDL formation.

The design of chiral dimesogens containing cholesteryl groups for use in liquid crystals has been reviewed.[95] The ($2\pi + 2\pi$) photo-cycloaddition of cholesteryl cinnamate to methyl phenanthrene-9-carboxylate has been examined[96] in the context of stereoselectivity in the liquid crystalline phase. The dimethylaminobenzoate group linked to cholesterol has been used[97] to examine the microenvironment of gel fibrils by fluorescence methods.

Iron picolinate complexes have been used in the stereoselective allylic 7α-hydroxylation of cholesteryl acetate with oxygen.[98] The antibacterial and cytotoxicity of 7α- and 7β-spermidinyl cholesterol analogues, *e.g.* **37**, has been reported.[99] A 7-hydroxy sterol **38** from a soft coral, has been shown[100] to possess testosterone 5α-reductase inhibitory activity.



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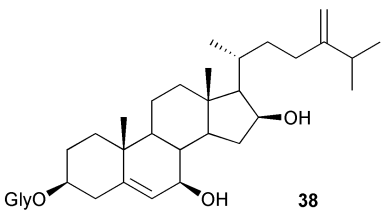

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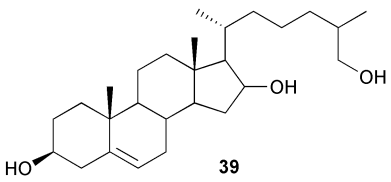
The cytotoxic sterols, 24-methylenecholesta-3β,5α,6β,19-tetraol and 24-methylenecholest-5-ene-3β,7α- and 3β,7β-diols have been synthesized[101,102] from stigmasterol. The 22-spiroketal of diosgenin has been removed[103] by a Clemmensen reduction to afford 3β,16β,26-trihydroxycholest-5-ene, **39**. This methodology has also been used to produce deuteriated samples. The rearrangement of a 23-oxo-spirostane to a 22-oxo-23-spiroketal **40** has been investigated[104] and the structure of the product established by X-ray crystallography.



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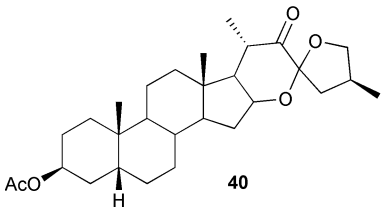

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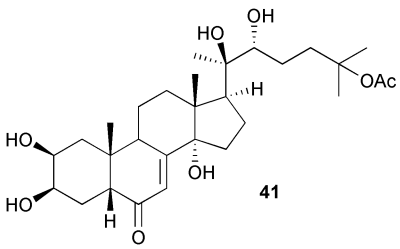
The ecdysone relatives, viticosterone E 41[105] and the 22*R*/*S* epimers of 2α,3α,20,22-tetrahydroxy-5α-cholestan-6-one[106] have been synthesized and the binding of the latter to the ecdysterone receptor has been examined. A number of brassinosteroid relatives have been synthesized and their biological activity evaluated.[107,108] (26,27-$^2H_6$)-Brassinosteroids have been prepared[109] for metabolic studies. The preparation of 1α,25-diacetoxy-3β-hydroxycholesta-4,6-diene **42** from a 5,7-diene has been reported.[110]



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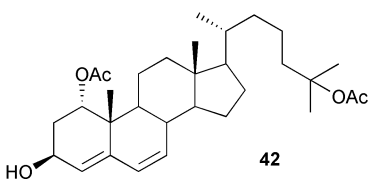
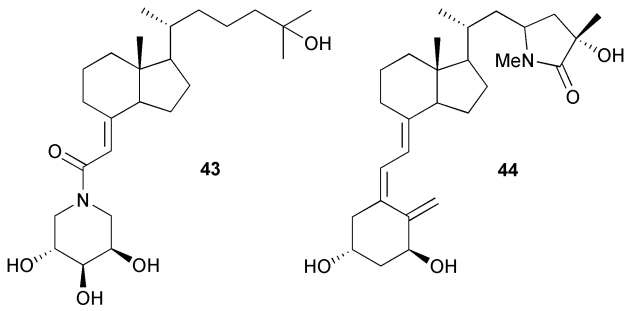


42

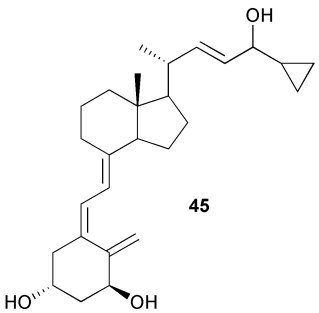
Efficient methods for the separation of lanosterol and dihydrolanosterol from commercial mixtures and for the preparation of epimerically pure derivatives have been described.[111,112]

7 Vitamin D

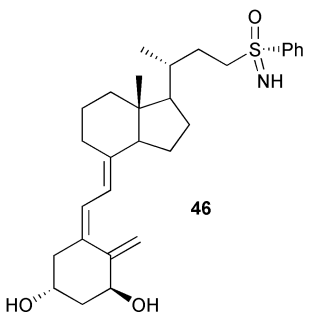
The proceedings of the 12th Vitamin D Workshop have been published.[7] Some new derivatives of 1α,25-dihydroxy-19-norvitamin D_3[113] and 2-methylene analogues[114] have been synthesized and their therapeutic potential has been discussed.[115] Some 2-functionalized analogues of 1α,25-dihydroxyvitamin D_3 have been shown to be[116] potent inducers of cell differentiation and some further 2α-(ω-hydroxyalkoxy)-analogues have also been synthesized.[117] C(3)-Carbamate derivatives of 1α,25-dihydroxyvitamin D_3 showed[118] a low affinity for the vitamin D receptor. The amide analogue **43** has been synthesized.[119] The side chain lactam **44** has been reported[120] to be a vitamin D antagonist.



Calcitriol analogues with two different side chains at C(20) have been synthesized[121] and their use as probes of the vitamin D receptor has been explored.[122] The crystal structure of the vitamin D nuclear receptor liganded with the vitamin D side chain analogue calcipotriol **45**, has been determined[123] in order to provide an insight into the biological activity of these analogues.



24-Sulfone[124] and sulfoxime analogues, *e.g.* **46**[125] of 1α,25-dihydroxyvitamin D_3 have been synthesized. The latter have low calcemic activity and are powerful inhibitors of the 24-hydroxylase involved in the catabolism of vitamin D. A number of other vitamin D derivatives have been synthesized.[126,127]



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