Stereoselective Synthesis of Steroid Side-chains

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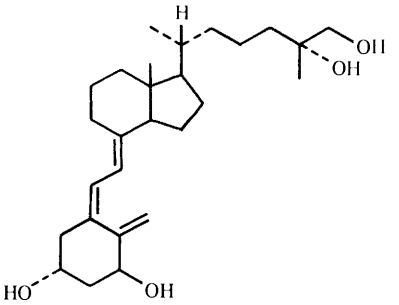
1 Introduction

The discovery of interesting steroids with modified side-chains (Figure 1), such as the vitamin D metabolites,[1,2] withaferin-A[3,4] and other withanolides with anti-tumour activity,[5,5a] the insect moulting hormones,[6,6a] the plant growth promoters brassinolide,[7,7a] castasterone[8] and dolicholide,[8a] the sex stimulating steroids antheridiol[9] and oogoniol[10,11] of the watermould *Achlya*, and all types of marine steroids,[12] has stimulated the search for stereoselective syntheses of steroid side-chains.

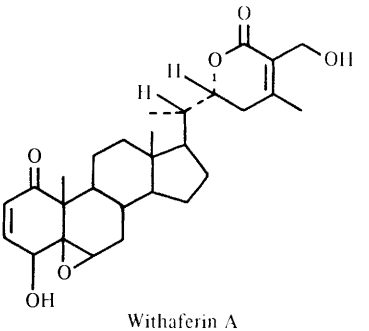
An added incentive has been the development of efficient microbiological methods for the production of androsta-1,4-diene-3,17-dione, androst-4-ene-3,17-dione, and 9α-hydroxyandrost-4-ene-3,17-dione. These processes have made 17-keto-steroids available as starting materials for the preparation of cortico-steroids.[13]

Earlier work in this field was reviewed in 1972 by Oliveto[14] and again in

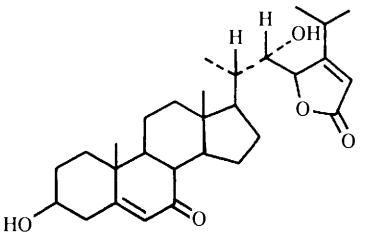
[1] H. F. de Luca and H. K. Schnoes, *Annu. Rev. Biochem.*, 1976, **45**, 631.
[2] H. Jones and G. Rasmussen. *Prog. Chem. Org. Natural Prod.*, 1980, **39**, 64.
[3] A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 1968, 962.
[4] M. Hirayama, K. Gamoh, and N. Ikekawa, *Tetrahedron Lett.*, 1982, **23**, 4725.
[5] I. Moriguchi and K. Komatsu. *Eur. J. Med. Chem.*, 1981, **16**, 19.
[5a] M. Hirayama, K. Gamoh, and N. Ikekawa, *Chem. Lett.*, 1982, 491.
[6] R. Lafont, P. Beydon, G. Sommé-Martin, and C. Blais, *Steroids*, 1980, **36**, 185.
[6a] P. Cherbas, D. A. Trainor, R. J. Stonard, and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 1982, 1307.
[7] M. D. Grove, G. F. Spencer, W. K. Rohwedder, N. Mandava, J. F. Worley, J. D. Warthen, jun., G. L. Steffens, J. L. Flippen-Anderson, and J. C. Cook, *Nature*, 1979, **281**, 216.
[7a] M. Sakakibara, K. Okada, Y. Ichikawa, and K. Mori, *Heterocycles*, 1982, **17**, 301.
[8] T. Yokota, M. Arima, and N. Takahashi, *Tetrahedron Lett.*, 1982, **23**, 1275.
[8a] T. Yokota, J. Baba, and N. Takahashi, *Tetrahedron Lett.*, 1982, **23**, 4965.
[9] G. P. Arsenault, K. Biemann, A. W. Barksdale, and T. C. Morris, *J. Am. Chem. Soc.*, 1968, **90**, 5635.
[10] T. C. McMorris, S. R. Schow, and G. R. Weihe, *Tetrahedron Lett.*, 1978, 335.
[11] J. R. Wiersig, N. Waespe-Sarcevic, and C. Djerassi, *J. Org. Chem.*, 1979, **44**, 3374.
[12] C. Djerassi, *Pure Appl. Chem.*, 1981, **53**, 873.
[13] M. G. Wovcha, F. J. Antosz, J. C. Knight, L. A. Kominek, and T. R. Pyke, *Biochem. Biophys. Acta*, 1978, **531**, 308.
[14] E. P. Oliveto, in 'Organic Reactions in Steroid Chemistry,' ed. J. Fried and J. A. Edwards, Van Nostrand Reinhold Company, New York, 1972, Vol. II, chapter 11.



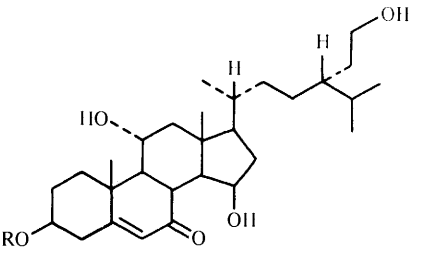
1,25,26-Trihydroxyvitamin D3



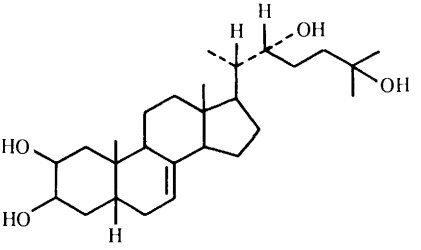
Withaferin A



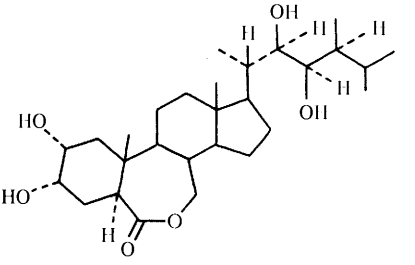
Antheridiol



Oogoniol



α-Ecdysone



Brassinolide

Figure 1 *Steroids with modified side-chains*

1978 by Piatak and Wicha.[15] The *Solanum*,[16] *Veratrum*, and *Buxus*[17] alkaloids, as well as the cardenolides[18] have also been reviewed extensively. Hardly any synthetic work has been reported on the sapogenins.[19] In the present review we limit discussion to the major principles of side-chain stereoselective syntheses as illustrated in the recent literature (1978—September 1982).

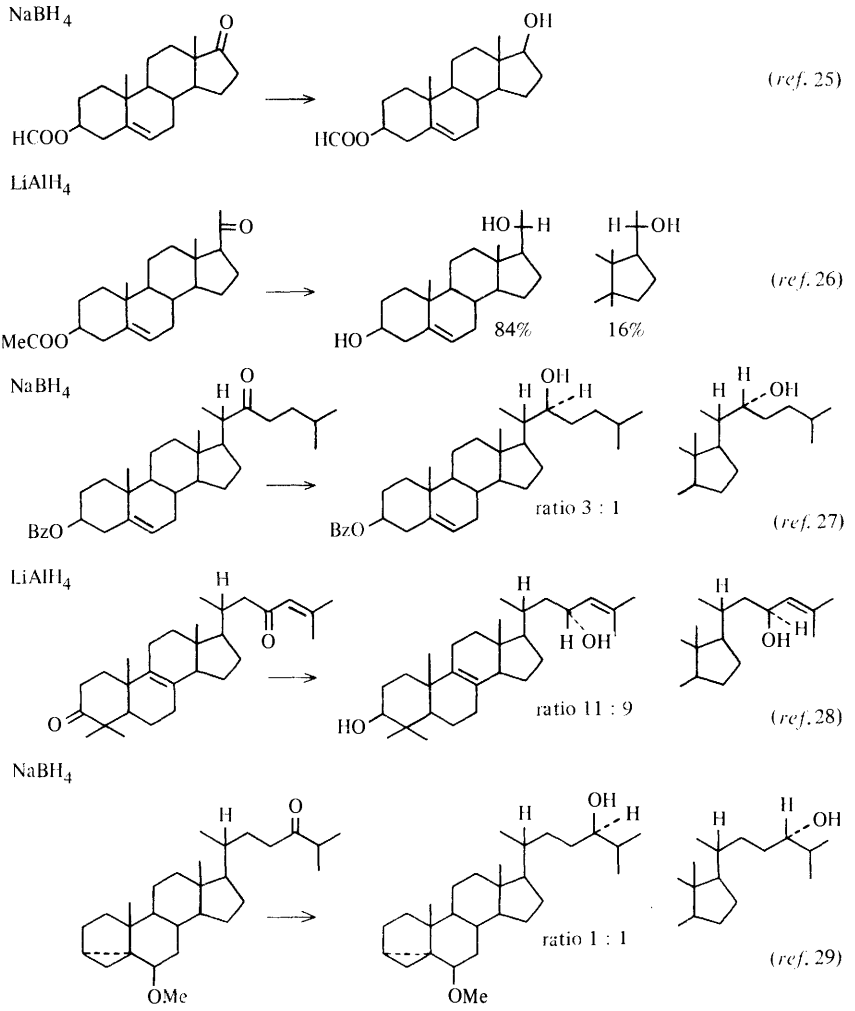
The notation of the stereochemistry of the side-chain is a difficult problem in a review of this nature. The Cahn, Ingold, and Prelog notation[20] is precise but priorities sometimes change with differences in substitution. For example, both α-ecdysone and brassinolide are 22*R*-hydroxy-steroids although they have opposite configuration. The Fischer–Plattner–Fieser–Fieser convention[21] does not suffer from this disadvantage but confusion has arisen through the introduction of the van Nes convention,[22] which unfortunately uses that same αβ-designation. Thus, brassinolide is 22α,23α- using the van Nes convention[23] but $22\alpha_F,23\beta_F$- using the Fischer convention. In this review the Fischer convention will be used where necessary and indicated by the subscript F (Fischer), in line with earlier suggestions.[24]

2 Strategy

As illustrated in Scheme 1, reactions of the 17-keto-group can be highly stereoselective with the effect diminishing as we proceed along the flexible side-chain to C-20 and C-22, and disappearing in the 23- and 24-keto-steroids. Consequently, chiral centres can be introduced by diastereoselective reactions, but at C-22 part of the specificity is lost. The availability of 3-hydroxypregn-5-ene-20-carboxaldehyde as a cheap technical product has, however, encouraged its use as a starting material, despite the need to separate the mixture of isomers formed.

The use of chiral reagents, although little explored in this area, can be complementary. Schönemann and van Vliet[30] studied the reduction of 3-methoxyestra-1,3,5(10)-trien-17-one with the chiral complexes of (+)- or (−)-

[15] D. M. Piatak and J. Wicha, *Chem. Rev.*, 1978, **78**, 199.
[16] H. Ripperger and K. Schreiber, in 'The Alkaloids,' ed. R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, Vol. 19, p. 81.
[17] J. Tomko and Z. Votický, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1973, Vol. 14, p. 1.
[18] P. G. Marshall, in 'Rodd's Chemistry of Carbon Compounds,' 2nd edition, Elsevier Publishing Company, Amsterdam, 1970, IID, p. 360.
[19] J. Elks, in 'Rodd's Chemistry of Carbon Compounds,' 2nd edition, Elsevier Publishing Company, Amsterdam, 1971, IIE, p. 1.
[20] R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 385.
[21] L. Fieser and M. Fieser, 'Steroids,' Reinhold Publishing Corporation, New York, 1959, p. 337.
[22] W. R. Nes, *Adv. Lipid Res.*, 1977, **15**, 233.
[23] M. J. Thompson, N. B. Mandava, W. J. Meudt, W. R. Lusby, and D. W. Spaulding, *Steroids*, 1981, **38**, 567.
[24] L. F. Fieser and M. Fieser, *Tetrahedron*, 1960, **8**, 360.
[25] H. J. Ringold, B. Löhen, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 1956, **78**. 816.
[26] D. C. Ayres and R. Sawday, *J. Chem. Soc.* (*B*), 1967, 581.
[27] E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, 1969, **34**, 103.
[28] N. Entwistle and A. D. Pratt, *Tetrahedron*, 1969, **25**, 1449.
[29] J. Zielinski, H. Li, and C. Djerassi, *J. Org. Chem.*, 1982, **47**, 620.
[30] K. H. Schönemann and N. P. van Vliet, personal communication.



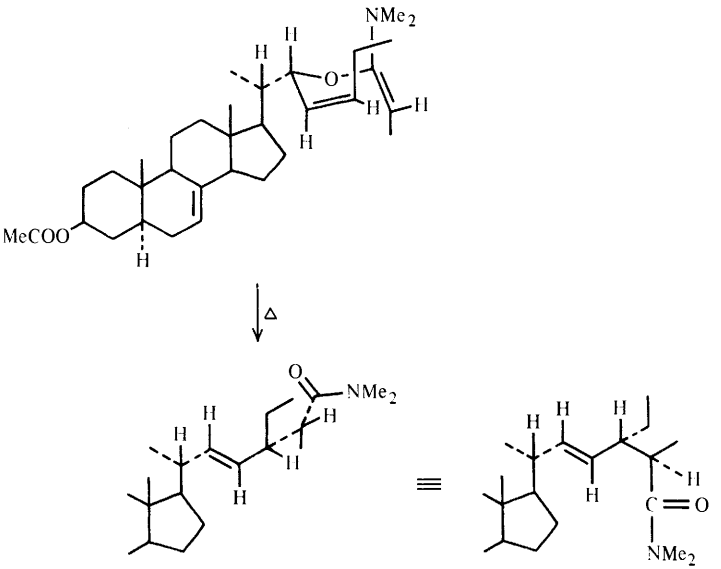
Scheme 1

(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol.[31] The effect was small. The complex with the (+)-alcohol shifted the 17β:17α ratio of the 3-methoxyestra-1,3,5(10)-trien-17-ols from the usual 97:3 to 93:7, whereas the complex with the (−)-alcohol gave a 99:1 mixture. On the other hand, Ishiguro *et al.*[32] achieved reduction of a 24-keto-steroid to 24-hydroxy-steroids with

[31] S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 1870.
[32] M. Ishiguro, N. Koizumi, M. Yasuda, and N. Ikekawa, *J. Chem. Soc., Chem. Commun.*, 1981, 115.

95% enantiomeric purity with complexes of $LiAlH_4$, ethanol, and 2,2'-dihydroxy-1,1'-binaphthyl.

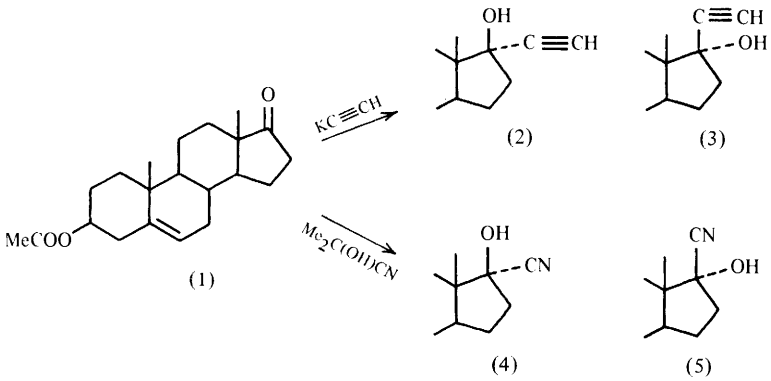
Other possible methods of introducing the desired chirality are through condensation with a chiral fragment[32a-36] and by chirality transfer from another centre through reactions with a rigid transition-state, such as the Claisen rearrangement (Scheme 2).[37,38]



Scheme 2

Syntheses Starting from 17-Ketones.—The least hindered approach of the nucleophilic reagent is from the α-side. Consequently, reactions under kinetic conditions, with a transition-state close to the starting compound, yield mainly 17α-substituted-17β-hydroxy-steroids. For example, ethynylation of 3β-acetoxyandrost-5-en-17-one (1) with potassium acetylide in t-butanol yields the 17α-ethynyl-17β-hydroxy-steroid (2) with only 0.3% of the isomer (3).[39] Under equilibrating conditions somewhat more of the 17β-ethynyl-17α-hydroxy-isomers are formed.[40]

[32a] P. J. Kocienski, B. Lythgoe, and D. A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1978, 834.
[33] H. Takayama, M. Ohmori, and S. Yamada, *Tetrahedron Lett.*, 1980, **21**, 5027.
[33a] S. Yamada, M. Ohmori, H. Takayama, T. Suda, and Y. Takasaki. *Chem. Pharm. Bull.*, 1981. **29**, 1187.
[34] J. J. Partridge, S. J. Shiuey, N. K. Chadha, E. G. Baggiolini. J. F. Blount, and M. R. Uskoković, *J. Am. Chem. Soc.*, 1981, **103**, 1253.
[35] S. Yamada, K. Nakayama, and H. Takayama, *Tetrahedron Lett.*, 1981, **22**, 2591.
[36] S. Yamada, K. Nakayama, and H. Takayama, *Chem. Pharm. Bull.*, 1981. **29**, 2393.
[37] W. Sucrow and B. Girgersohn, *Chem. Ber.*, 1970, **103**. 750.
[38] W. Sucrow, B. Schubert, W. Richter, and M. Slopianka, *Chem. Ber.*, 1971, **104**, 3689.
[39] T. Reichstein and C. H. Meystre, *Helv. Chim. Acta*, 1938, **22**, 728.
[40] R. M. Konojia, G. O. Allen, J. M. Killinger, and J. L. McGuire, *J. Med. Chem.*, 1979, **22**, 1538.

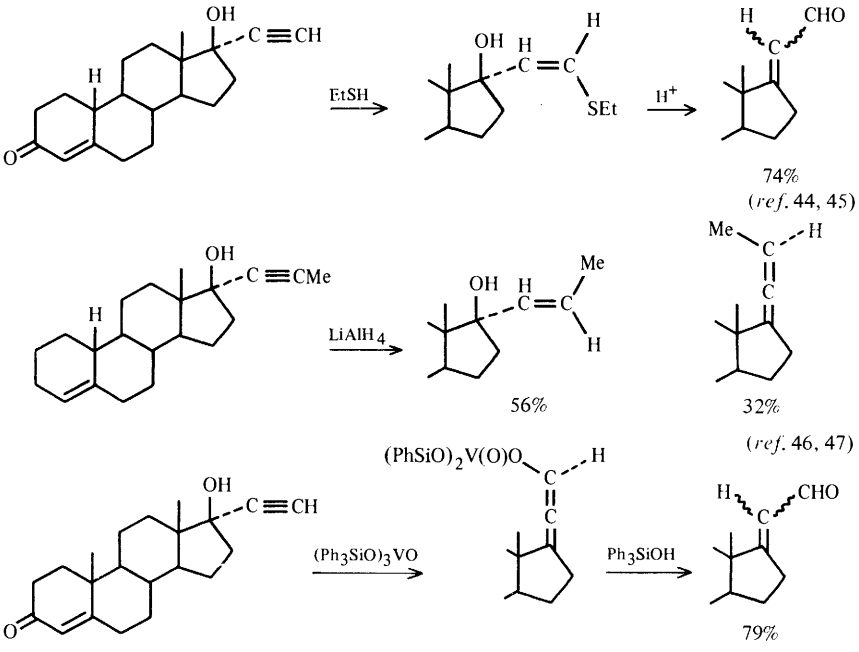


Scheme 3

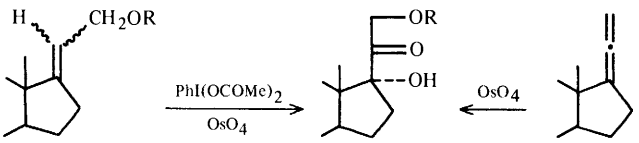
Teichmüller showed that the reaction of 17-keto-steroids with acetone cyanohydrine in aqueous alcohol at pH 8.5—9 yields, after a short reaction time, the 17α-cyano-17β-hydroxy-steroid (4) as the kinetic product. By using a high concentration and longer reaction times the less soluble 17β-cyano-17α-hydroxy-steroid (5) was obtained in 98% yield.[41-43] The 17β-cyano-17α-hydroxy-steroid (5) can be converted, after protection of the 17-hydroxy-group as an ether, into a 17α-hydroxy-20-keto-steroid using a Grignard reaction.

The 17α-ethynyl-17β-hydroxy-steroids are important starting materials. Reaction of a nucleophile at the 21-position may result in *trans* addition to the acetylenic bond or in allene formation. The pregn-17-en-21-als can, after reduction to the 21-ols and acetylation, be oxidized stereoselectively to give the dihydroxyacetone side-chain characteristic for the corticosteroids.[49] The oxidation of an allene with OsO_4 to give this side-chain has also been described.[50] The yield was only 53% however. An interesting variation is based on the unsaturated sulphoxide–sulphenate rearrangement[51] (Scheme 6). Its overall yield was 63%. Other examples of the use of this rearrangement can be found in the synthesis of 3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene-20-carbaldehyde,[52] 3β-

[41] G. Teichmüller, 9th Conference on Isoprenoids, Prague, 1981.
[42] G. Teichmüller, G. Haessler, K. Barnikoloc, G. Grinenko, and E. Dolginowa, GDR patent 147669.
[43] J. C. Gasc and L. Nédélec, *Tetrahedron Lett.*, 1971, 2005.
[44] K. Ponsold and W. Schade, *Z. Chem.*, 1975, **15**, 148.
[45] K. Ponsold and W. Schade, GDR patent 112124.
[46] L. A. van Dijck, K. H. Schönemann, and F. J. Zeelan, *Recl. Trav. Chim. Pays-Bas*, 1969, **88**, 254.
[47] C. J. Elsevier, J. Meijer, H. Westmijze, P. Vermeer, and L. A. van Dijck, *J. Chem. Soc., Chem. Commun.*, 1982, 85.
[48] G. L. Olson, K. D. Morgan, and G. Saucy, *Synthesis*, 1976, 25.
[49] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, 1955, **77**, 4436.
[50] M. Biollaz, W. Haefliger, E. Velarde, P. Crabbé, and J. H. Fried, *Chem. Commun.*, 1971, 1322.
[51] V. V. van Rheenen and K. P. Shephard, *J. Org. Chem.*, 1979, **44**, 1582.
[52] B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, 1975, **94**, 4018.



Scheme 4

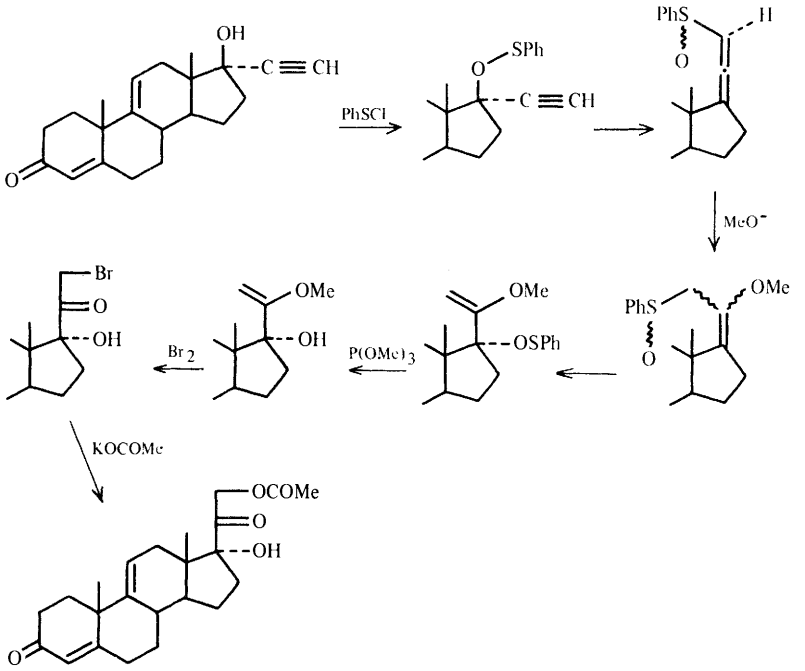


Scheme 5

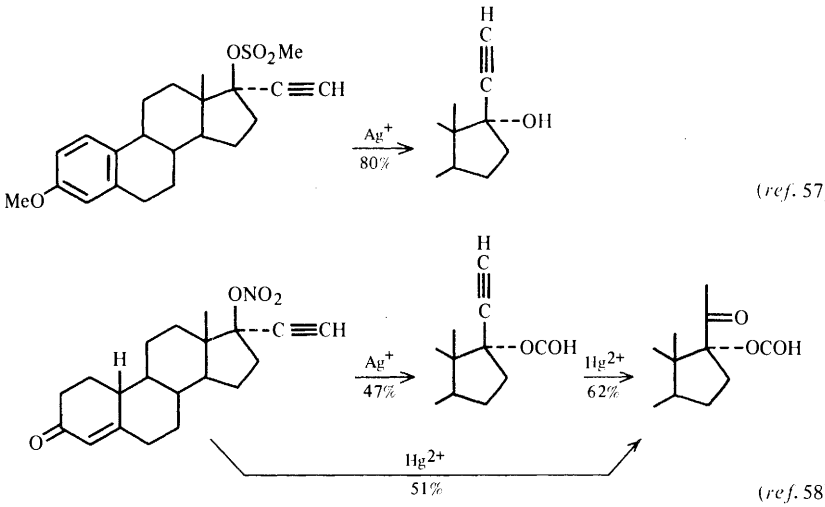
ethoxy-21-methylpregna-5,17(20),20-triene,[53] cholesterol,[54] 25-hydroxycholesterol,[54] and 20,22β_F-dihydroxycholesterol (Scheme 21).[55]

Despite the ready occurrence of these rearrangements of 17-esters[56] it proved possible, with proper choice of ester, nucleophile, catalyst, and solvent, to achieve nucleophilic substitution with inversion of the side-chain. Methanesulphonate esters could be replaced by an hydroxy-group using Ag^+ and tetrahydrofuran-

[53] G. Neef, U. Eder, and A. Seeger, *Tetrahedron Lett.*, 1980, **21**, 903.
[54] M. Ohmori, S. Yamada, H. Takayama, and K. Ochi, *Tetrahedron Lett.*, 1982, **23**, 4709.
[55] K. S. Kyler and D. S. Watt, *J. Org. Chem.*, 1981, **46**, 5182.
[56] W. R. Benn, *J. Org. Chem.*, 1968, **33**, 313.



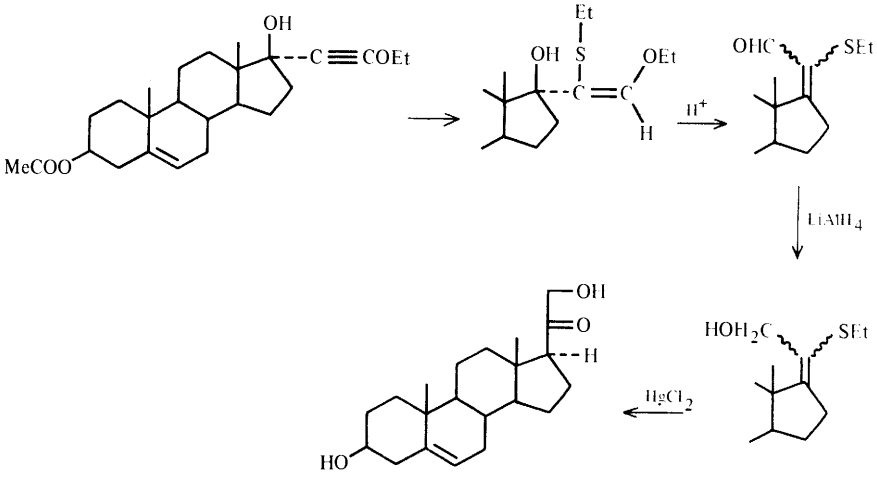
Scheme 6



Scheme 7

water,[57] and nitrate esters by formate using Ag^+ and formic acid in hexamethylphosphortriamide[58] (Scheme 7).

Free-radical addition of thiols to an ethoxyethynylsteroid was studied by Sperna Weiland and Arens.[59] The addition product was rearranged to the enal, reduced, and converted into the ketol in 47—51% overall yield.

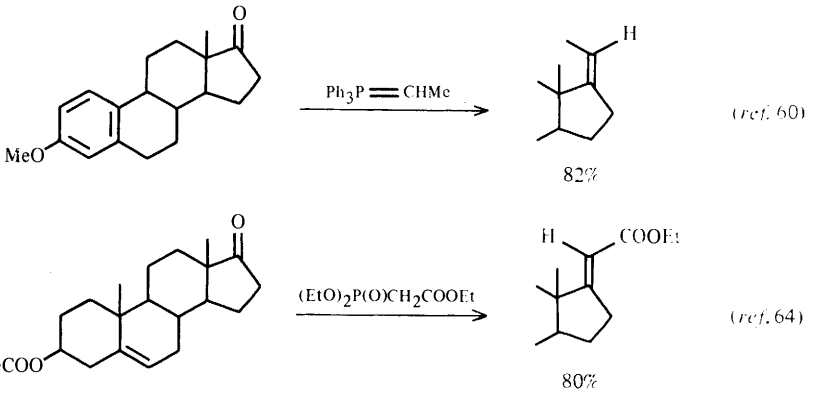


Scheme 8

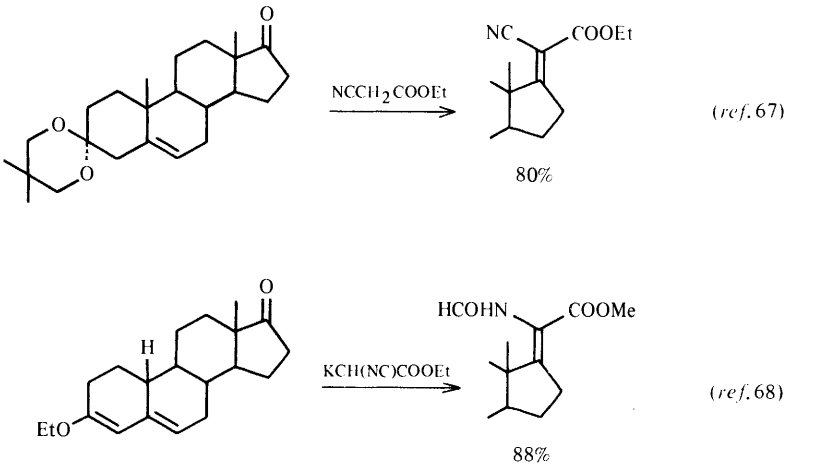
Wittig Reactions and Aldol Condensations of 17-Keto-steroids.—Reaction of 17-keto-steroids with non-stabilized ylides yields mainly the *Z*-alkenes,[60-62] whereas reaction of stabilized ylides leads to the more stable *E*-isomers.[63-66]

Aldol condensations of steroidal 17-ketones with other ketones result mainly in the formation of 16-substituted steroids, consequently for the elaboration of 17-ketones into pregnanes or sterols only Knoevenagel condensations with esters can be used.[67-70]

[57] H. Westmijze, H. Kleyn, P. Vermeer, and L. A. van Dijck, *Tetrahedron Lett.*, 1980, **21**, 2665.
[58] H. Hofmeister, K. Annen, H. Laurent, and R. Wiechert, *Chem. Ber.*, 1978, **111**, 3086.
[59] H. Sperna Weiland and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1960, **79**, 1293.
[60] A. M. Kubriner and E. P. Oliveto, *J. Org. Chem.*, 1966, **31**, 24.
[61] S. Danishefsky, K. Nagasawa, and N. Wang, *J. Org. Chem.*, 1975, **40**, 1989.
[62] C. Y. Byon and M. Gut, *J. Org. Chem.*, 1980, **45**, 4404.
[63] M. L. Raggio and D. S. Watt, *J. Org. Chem.*, 1976, **41**, 1873.
[64] J. Wicha, K. Bal, and S. Piekut, *Synth. Commun.*, 1977, **7**, 215.
[65] J. Wicha and K. Bal, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1282.
[66] W. Nagata and Y. Hayaze, *J. Chem. Soc.* (*C*), 1969, 460.
[67] G. Haffer, U. Eder, G. Neef, G. Sauer, and R. Wiechert, *Chem. Ber.*, 1978, **111**, 1533.
[68] U. Schöllkopf and K. Hantke, *Chem. Ber.*, 1976, **109**, 3964.
[69] L. Nédélec, V. Torelli, and M. Hardy, *J. Chem. Soc., Chem. Commun.*, 1981, 775.
[70] G. Neef, U. Eder, A. Seeger, and R. Wiechert, *Chem. Ber.*, 1980, **113**, 1184.



Scheme 9

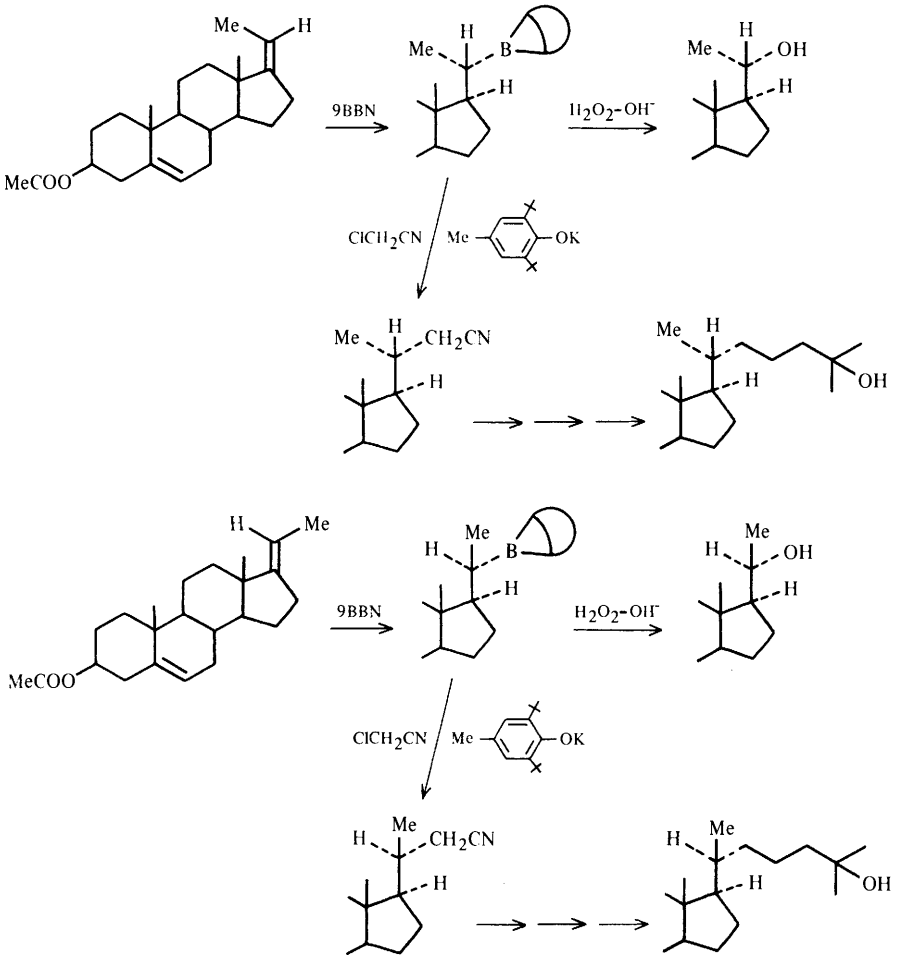


Scheme 10

Scheme 11

In the last example[70] the aldol was isolated and dehydrated in a separate step. This compound can also be prepared *via* a Reformatsky-type reaction using ethyl trichloroacetate, zinc, and diethylchloro-aluminum to give the methyl 20-chloropregnenoate, which is then treated with sodium methoxide.[71]

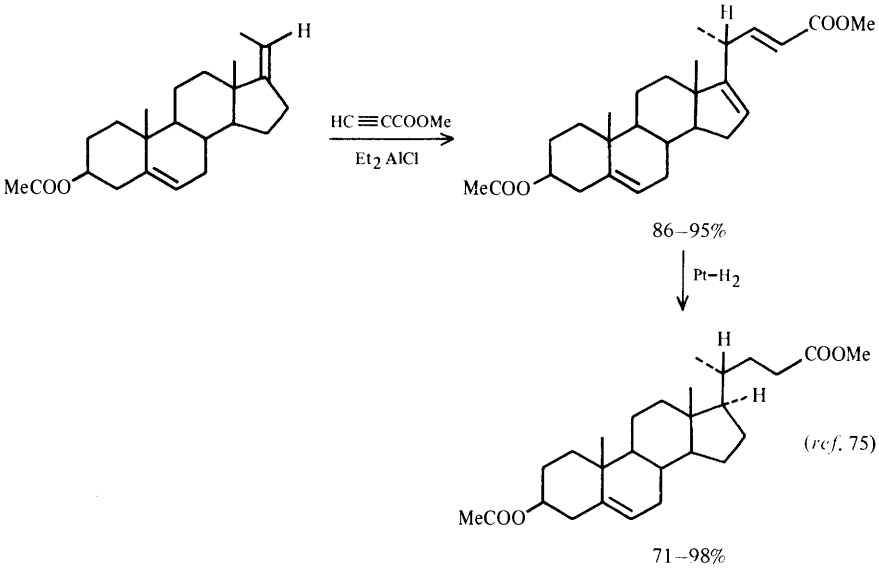
The use of 1-[(isocyanomethyl)sulphonyl]-4-methylbenzene (TOSMIC) as a potential route to progesterone and derivatives *via* 17-cyano-steroids was disappointing in that it yielded a mixture of isomers at position-17.[72]



Scheme 12

[71] A. R. Daniewski and W. Wojciechowska, *J. Org. Chem.*, 1982, **47**, 2993.
[72] J. R. Bull and W. R. Tuinman, *Tetrahedron*, 1975, **31**, 2151.

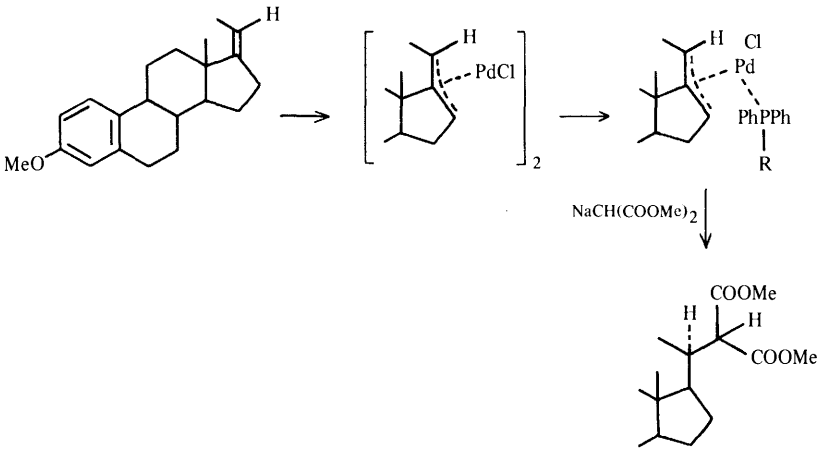
Reactions of 17(20)-Pregnenes.—The ethylidene derivatives are useful intermediates. Selective hydroboration with 9-borabicyclo[3.3.1]nonane proceeds in a stereoselective manner from the α-side. The borane derivatives can then be treated with alkaline hydrogen peroxide to give the alcohols or with chloroacetonitrile to give cyano-steroids.[73,74] Ene reactions also proved possible without touching the 5(6)-double bond.[75–79] The use of (π-allyl)Pd complexes for



Scheme 13

synthesis of the steroid side-chain was explored by Trost and Verhoeven.[80] Following activation of the complex with a phosphorus ligand, alkylation was possible but the product obtained had unnatural stereochemistry at C-20, resulting from a *trans* approach to the α-substituted Pd group. A product with a natural configuration at C-20 was obtained using alkenylzirconium reagent,

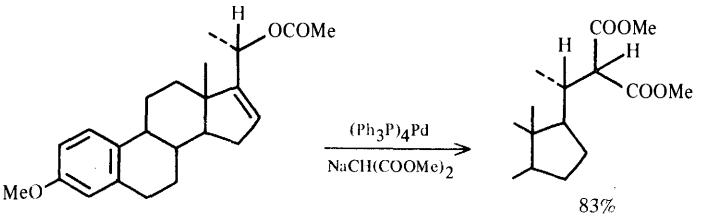
[73] M. M. Midland and Y. C. Kwon, *J. Org. Chem.*, 1981, **46**, 229.
[74] M. M. Midland and Y. C. Kwon, *Tetrahedron Lett.*, 1982, **23**, 2077.
[75] W. G. Dauben and T. Brookhart, *J. Am. Chem. Soc.*, 1981, **103**, 237.
[76] A. D. Batcho, D. E. Berger, M. R. Uskoković, and B. B. Snider, *J. Am. Chem. Soc.*, 1981, **103**, 1293.
[77] A. D. Batcho, D. E. Berger, S. G. Davoust, P. M. Wovkulich, and M. R. Uskoković, *Helv. Chim. Acta*, 1981, **64**, 1682.
[78] E. G. Baggiolini, J. A. Jacobelli, B. M. Hennessy, and M. R. Uskoković, *J. Am. Chem. Soc.*, 1982, **104**, 2495.
[79] W. G. Dauben and T. Brookhart, *J. Org. Chem.*, 1982, **47**, 3921.
[80] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435.



Scheme 14

which is known to give a *cis* approach. In this case, however, the regioselectivity was poor.[81-83]

Another disadvantage of these reactions is the need to use stoicheiometric amounts of expensive palladium salts. Both problems were overcome when it was discovered that allylic acetates could be alkylated following complex formation with catalytic amounts of Pd^0 complexes.[80,84] This reaction sequence was used to synthesize 5α-cholestanone and ecdysone. Another application of

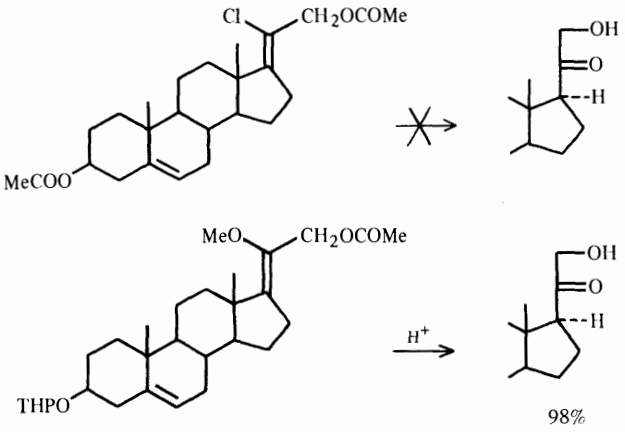


Scheme 15

this Pd-catalysed reaction is the synthesis of 24-hydroxycholesterol derivatives from Δ^{23}-22-acetoxycholesterol derivatives.[85]

The 20-alkylation of *E*-15β,16β-oxidopregna-5,17(20)-dien-3-ol dimethyl-t-butylsilylether is also determined by the steric preference for α-face approach.[86]

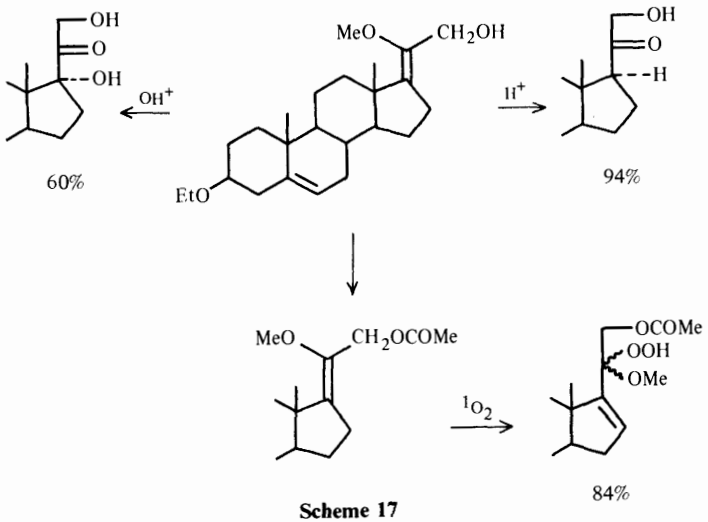
[81] J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, 1980, **102**, 7381.
[82] Y. Hayasi, M. Riediker, J. S. Temple, and J. Schwartz, *Tetrahedron Lett.*, 1981, **22**, 2629.
[83] M. Riediker and J. Schwartz, *Tetrahedron Lett.*, 1981, **22**, 4655.
[84] B. M. Trost and Y. Matsamura, *J. Org. Chem.*, 1977, **42**, 2036.
[85] S. Takatsuto, M. Ishiguro, and N. Ikekawa, *J. Chem. Soc., Chem. Commun.*, 1982, 258.
[86] J. P. Marino and H. Abe, *J. Am. Chem. Soc.*, 1981, **103**, 2907.



(*ref.* 71)

Scheme 16

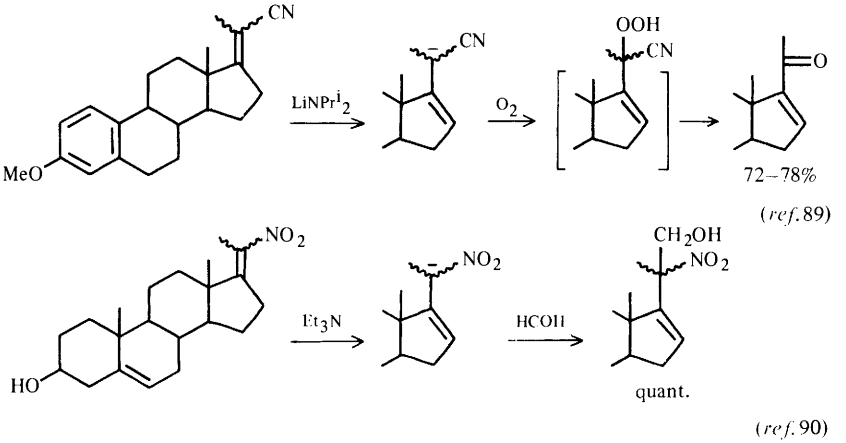
The reactivity of the 17(20) double bonds depends strongly on the substituents. Electron-withdrawing groups deactivate this bond towards electrophilic substitution (Scheme 16). In practice a high reactivity of the 17(20) double bond is necessary to prevent reaction with other double bonds in the molecule. For that reason it is best that α,β-unsaturated esters are first reduced to alcohols before carrying out substitutions at the double bond. Recent work has been concentrated on finding routes to good activating groups. For example, Neef *et al.*[70] explored



Scheme 17

the use of enol ethers (Scheme 17). The use of enamides was explored by Barton *et al.*[87,88] and by Nédélec *et al.*[69]

Reactions of Carbanions at Position-20.—Electron-withdrawing groups at the 20-position promote the formation of carbanions at the 20-position, through hydrogen abstraction, and this opens up a series of synthetic possibilities (Scheme 18).[89,90] The nitro-group of the last mentioned compound in Scheme 18, for example, could be reduced to the oxime and then hydrolysed to the 20-ketone.

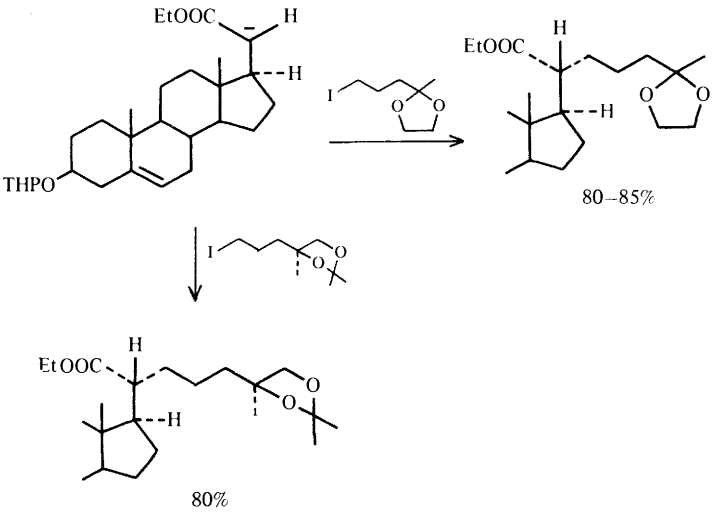


Scheme 18

The anions can also be generated when no double bond is present.[90] Raggio and Watt[63] and Haffer *et al.*[67] used the anionic oxidation to convert 20-cyano-pregnanes into 20-ketopregnanes. A high stereoselectivity was found for the alkylation of the pregnenals[91] and the pregnenoates,[65] leading to products with the configuration of the natural sterols. The high stereoselectivity was retained when a chiral centre was present in the alkyl chain and this made possible a stereoselective synthesis of both 25*S*,26- and 25*R*,26-dihydroxycholecalciferol.[34,92]

Reactions of the 20-Carbonyl Group.—The stereochemistry of reactions of functional groups on a flexible side-chain is dependent on conformational preferences. Since these may vary with different substituents, stereochemical guidelines of a general nature can not be defined.

[87] D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1981, 774.
[88] D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *Nouv. J. Chim.*, 1982, **6**, 295.
[89] R. R. Wroble and D. S. Watt, *J. Org. Chem.*, 1976, **41**, 2939.
[90] D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1982, 551.
[91] Y. Letourneux, G. Büjüktür, M. T. Ryzlak, A. K. Banerjee, and M. Gut, *J. Org. Chem.*, 1976, **41**, 2288.
[92] J. J. Partridge, S. J. Shuey, N. K. Chadha, E. G. Baggiolini, B. M. Hennessy, M. R. Uskoković, J. L. Napoli, T. A. Reinhardt, and R. L. Horst, *Helv. Chim. Acta*, 1981, **64**, 2138.



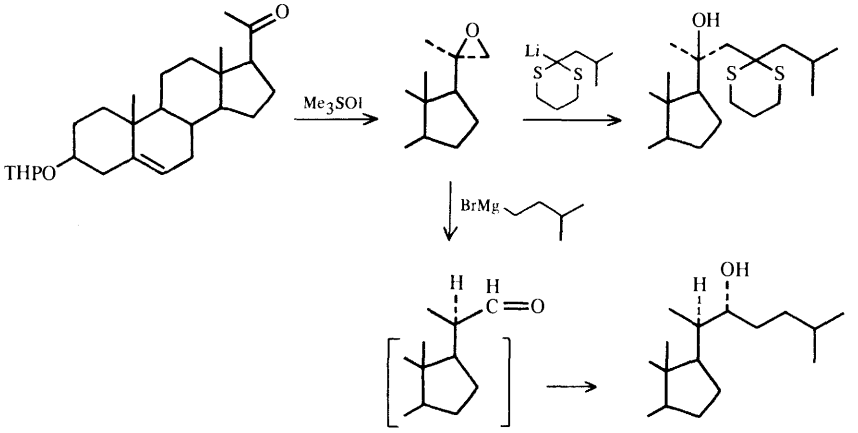
Scheme 19

For example, whereas Grignard-type additions to unsubstituted 20-ketones[93,94] and 20-aldehydes[95] yield mixtures with some preference for products resulting from approach from the $20\alpha_F$-side, Makino *et al.*[96,97] found that reaction of labelled MeMgI with a 17α-hydroxy-20-keto-steroid gave 99% of the *S*-isomer ($20\alpha_F$-approach) but with a 16α,17α-epoxy-20-keto-steroid yielded 93% of the *R*-isomer ($20\beta_F$-approach).

In contrast to Grignard reagents, high stereoselectivity was reported for the addition of dimethylsulphoxonium methylide, to give the 20*R*-oxide.[98] A 20*R*-oxide could also be synthesized *via* stereoselective addition of methylselenomethyllithium.[99] These oxides react in the normal fashion with 2-lithio-2-isobutyl-1,3-dithiane but rearrange into 20-iso-21-aldehydes during Grignard reactions or by treatment with Lewis acids. This opened a route to 20-isosterols.[98–100]

High stereoselectivity was achieved by Kyler and Watt[55] (Scheme 21). Enolization of the 20-ketone was, however, a competing side-reaction so that the yield was only moderate. As shown in Scheme 21, the product was converted into the dianion and *C*-alkylated with high stereoselectivity, although *O*-alkylation was a competing reaction. After removal of the silyl group, with inversion

[93] W. R. Nes and T. E. Varkey, *J. Org. Chem.*, 1976, **41**, 1652.
[94] M. Koreeda, N. Koizumi, and B. A. Teichler, *J. Chem. Soc., Chem. Commun.*, 1976, 1035.
[95] V. Pouzar and R. Havel, *Collections*, 1981, **46**, 2758.
[96] Y. Osawa, T. Makino, K. Shibata, C. M. Weeks, and W. L. Duax, *J. Chem. Soc., Chem. Commun.*, 1976, 991.
[97] T. Makino, K. Shibata, D. C. Rohrer, and Y. Osawa, *J. Org. Chem.*, 1978, **43**, 276.
[98] M. Koreeda and N. Koizumi, *Tetrahedron Lett.*, 1978, 1641.
[99] J. R. Schauder and A. Krief, *Tetrahedron Lett.*, 1982, **23**, 4389.
[100] W. Sucrow and M. van Nooy, *Liebigs Ann. Chem.*, 1982, 1897.



Scheme 20

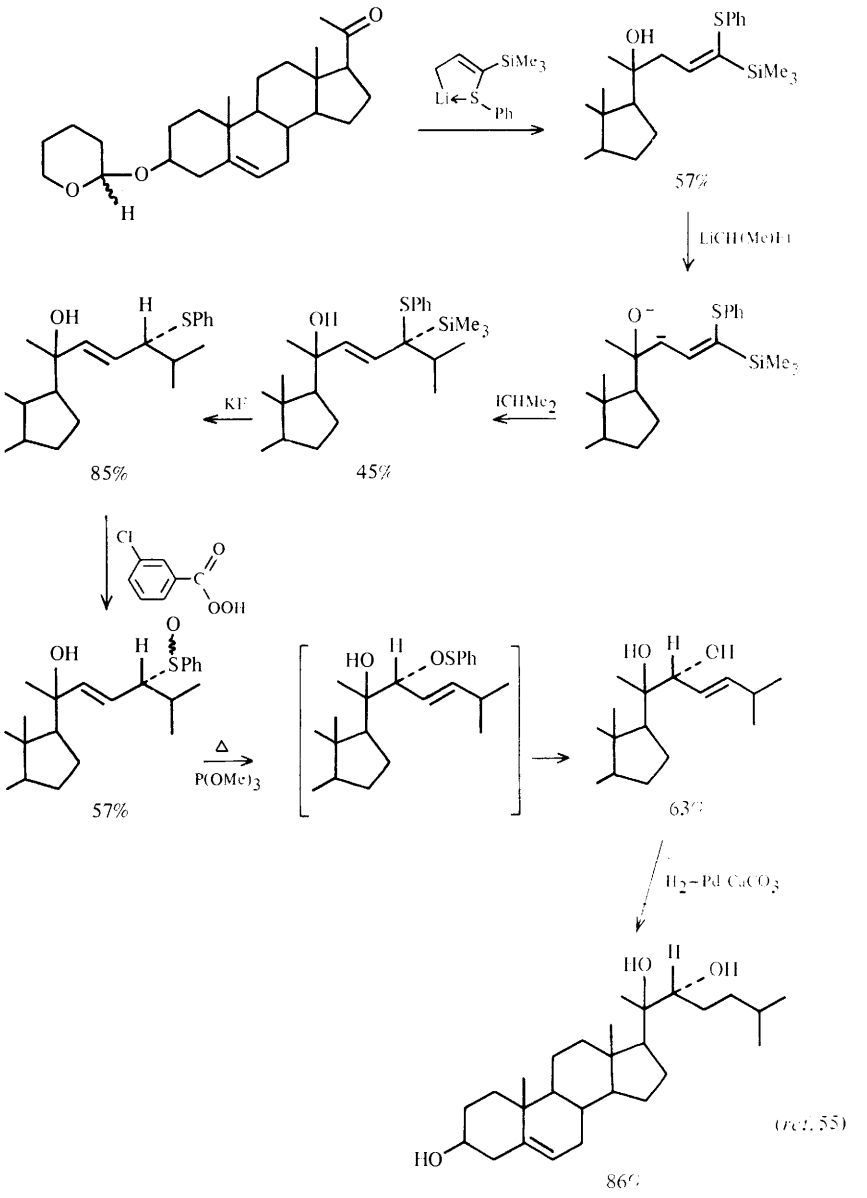
of configuration at C-24, the sulphide was oxidized to sulphoxide and subjected to [2,3]sigmatropic rearrangement, as discussed earlier in this review. Reduction of the sulphinate ester, selective hydrogenation, and removal of the protecting group at C-3 gave dihydroxycholesterol.

An approach to ecdysone side-chain synthesis used the coupling of 2-lithio-5-methylfuran with 20-keto-steroids, followed by dehydration to the 20-pregnene, which could then be hydrogenated to the 20*S*-steroid.[100a] These reactions proceeded with a remarkable selectivity.

Wittig Reactions.—Wittig reactions of 3β-hydroxypregn-5-en-20-one with non-stabilized ylides have been noted to give solely the *E*-isomer.[101-104] Selective catalytic hydrogenation then yields a mixture of the 20*R*- and 20*S*-isomers in a ratio that is strongly dependent on the exact hydrogenation conditions (50—90% 20*R*).[101-105]

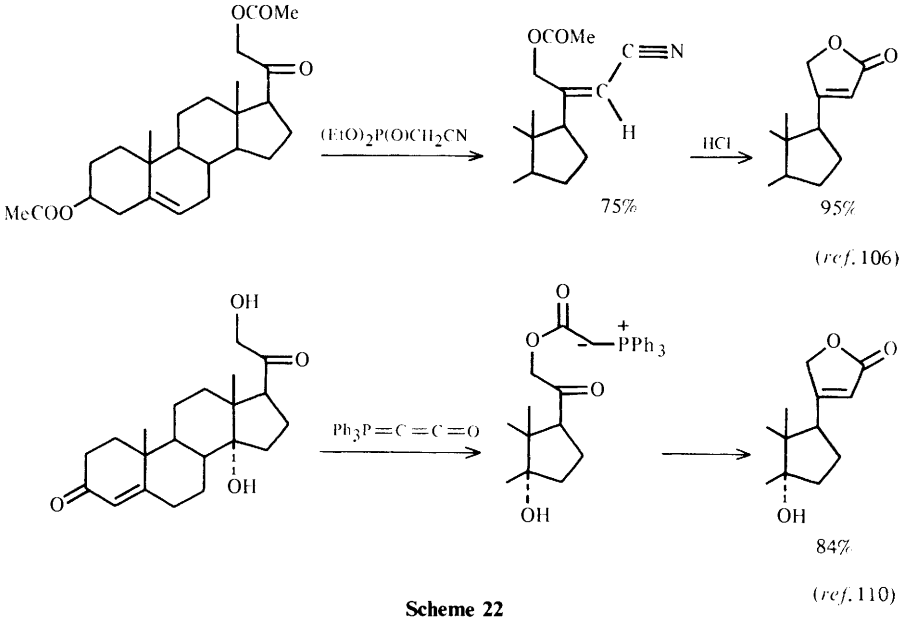
The reaction with stabilized ylides has been explored, mainly with the aim of producing the side-chain of the cardenolides. Reaction of 3,21-diacetoxypregn-5-en-20-one with diethyl cyanomethylenephosphonate gives a high yield of the *E*-isomer, which can be converted by saponification into the lactone.[106,107]

[100a] T. Kametani, M. Tsubuki, and H. Nemoto, *J. Chem. Soc., Perkin 1*, 1981, 3077; T. Kametani, M. Tsubuki, and H. Nemoto, *Tetrahedron Lett.*, 1981, **22**, 2373.
[101] J. P. Schmit, M. Piraux, and J. F. Pilette, *J. Org. Chem.*, 1975, **40**, 1586.
[102] T. C. McMorris and S. R. Schow, *J. Org. Chem.*, 1976, **41**, 3759.
[103] S. R. Schow and T. C. McMorris, *J. Org. Chem.*, 1979, **44**, 3760.
[104] A. Fürst, L. Labler, and W. Meier, *Helv. Chim. Acta*, 1982, **65**, 1499.
[105] W. R. Nes, *J. Am. Chem. Soc.*, 1978, **100**, 999.
[106] G. R. Lenz and J. A. Schulz, *J. Org. Chem.*, 1978, **43**, 2334.
[107] G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, 1970, **35**, 1389.


SiMe3
Li
S
Ph
OH
SPh
SiMe3
57%
LiCH(MeOH)
O⁻
SPh
SiMe3
ICHMe2
KF
OH
H
SPh
85%
OH
SPh
SiMe3
45%
Cl
O
C
OOH
OH
H
O
SPh
57%
P(OMe)3
HO
H
OSPh
HO
H
OH
63%
H2-Pd CaCO3
HO
H
OH
HO
86%
(ref. 55)

Scheme 21

The reaction with the triethylphosphonoacetate was reported to proceed in high yield.[108] Some authors, however, reported problems in repeating this work.[106,109]



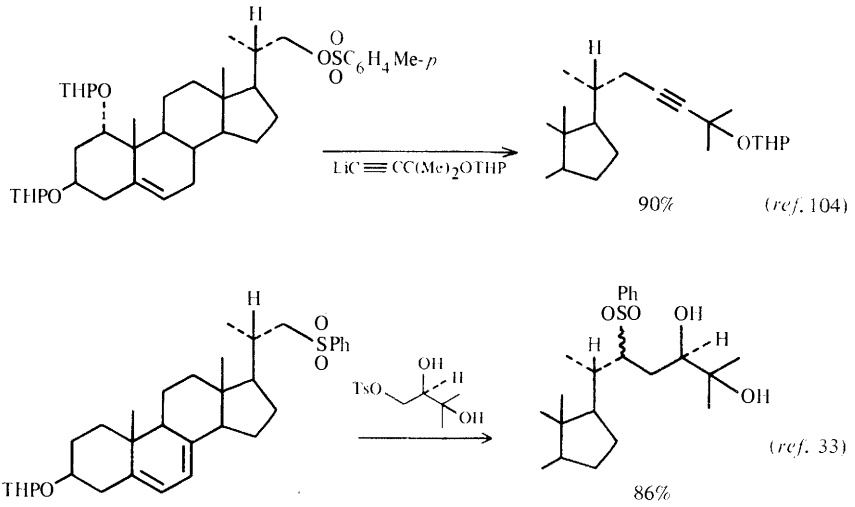
Scheme 22

An interesting example of an intramolecular Wittig cyclization was reported by Nickisch, Klose, and Bohlmann[110] (Scheme 22) using ketenylidentriphenylphosphoran. The reaction proceeds with a remarkable selectivity.

Reactions of 21-Toluene-*p*-sulphonates.—The sulphonyloxy-group can be displaced by the anion of diethylmalonate,[111] or of acetylides[104,112–114] or sulphones,[104] and by cuprate Grignard reagents.[114a,b] The 22-position can be activated by conversion of the toluene-*p*-sulphonate *via* bromide into sulphone. The anion can then be generated and used for coupling with electrophiles.[33] Similar approaches

[108] W. Fritsch, U. Stache, and H. Rushig, *Liebigs Ann. Chem.*, 1966, **699**, 195.
[109] E. Yoshii and K. Ozaki, *Chem. Pharm. Bull.*, 1972, **20**, 1585.
[110] K. Nickisch, W. Klose, and F. Bohlmann, *Chem. Ber.*, 1980, **113**, 2038.
[111] R. Hayatsu, *Chem. Pharm. Bull.*, 1957, **5**, 452.
[112] J. J. Partridge, S. Faber, and M. R. Uskoković, *Helv. Chim. Acta*, 1974, **57**, 764.
[113] Y. Fujimoto, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin 1*, 1975, 2302.
[114] E. Steiner and C. Djerassi, *Helv. Chim. Acta*, 1977, **60**, 475.
[114a] B. Lythgoe, D. A. Roberts, and I. Waterhouse, *J. Chem. Soc., Perkin 1*, 1977, 2608.
[114b] G. A. Leyes and W. H. Okamura, *J. Am. Chem. Soc.*, 1982, **104**, 6099.

have been described using the 24-toluene-*p*-sulphonates[115] and 24-sulphones.[116,117]



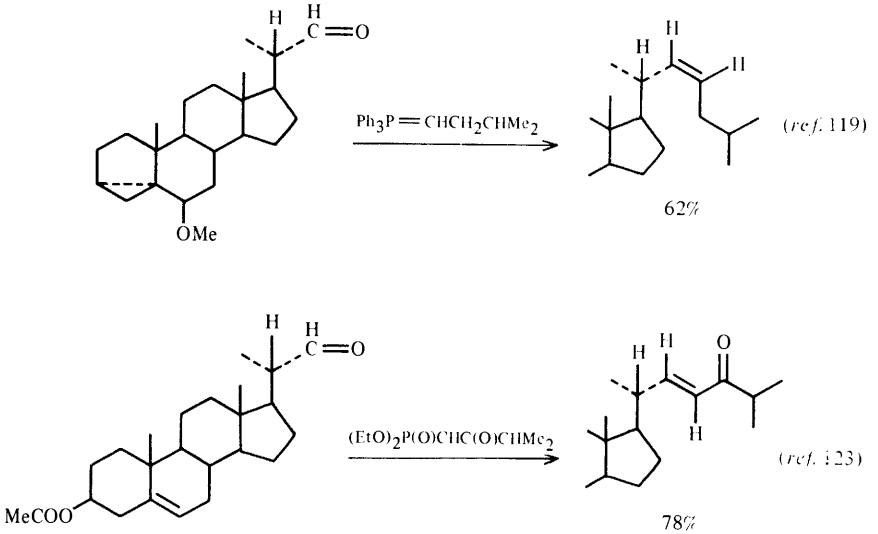
Scheme 23

Reactions of 20-Carboxaldehydes.—With 3β-hydroxypregn-5-ene-20-carboxaldehyde available by synthesis and by degradation of stigmasterol, it is often used as a starting material. It has the disadvantage that isomerization at the 20-position can occur.[100,118]

The Wittig reaction with non-stabilized ylides can be made to yield either predominantly the *E*-isomer or the *Z*-isomer at the 22(23) double bond, depending on the choice of reaction conditions.[85,119–121] This is a common feature of Wittig reactions of relatively unhindered aldehydes. The reaction with stabilized ylides yields, as expected, the *Z*-isomers[119,122,123] (Scheme 24). An alternative route to *Z*-alkenes proceeds *via* addition of alkylsulphones followed by reduction.[7a,32a,35,36,124]

The stereochemistry of addition reactions to these 22(23) double bonds is strongly dependent on substituents present in the side-chain. An example is the

[115] Y. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaka, and N. Ikekawa. *Tetrahedron Lett.*, 1979, 2023.
[116] Y. Kobayashi, T. Taguchi, N. Kanuma, N. Ikekawa, and J. Oshida, *J. Chem. Soc., Chem. Commun.*, 1980, 459.
[117] Y. Kobayashi, T. Taguchi, N. Kanuma, N. Ikekawa, and J. Oshida, *Tetrahedron Lett.*, 1981, **22**, 4309.
[118] D. H. R. Barton, T. Shiori, and D. A. Widdowson. *J. Chem. Soc., Chem. Commun.*, 1970, 939.
[119] R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, 1970, **15**, 113.
[120] R. W. Lang and C. Djerassi, *J. Org. Chem.*, 1982, **47**, 625.
[121] W. G. Salmond, M. A. Barts, and J. L. Havens, *J. Org. Chem.*, 1978, **43**, 790.
[122] G. D. Anderson, T. J. Powers, C. Djerassi, J. Fayos, and I. Clardy, *J. Am. Chem. Soc.*, 1975, **97**, 389.
[123] P. H. Le, M. W. Preus, and T. C. McMorris, *J. Org. Chem.*, 1982, **47**, 2163.
[124] P. J. Kocienski, B. Lythgoe, and D. A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1978, 834.

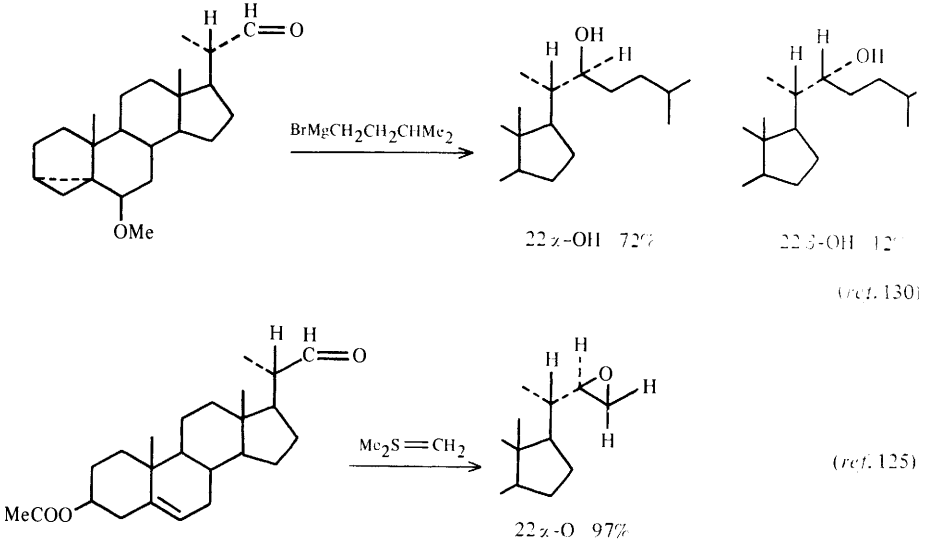


Scheme 24

OsO_4 hydroxylation of *E*-22(23) double bonds where the ratio between the $22\alpha_F,23\beta_F$- and $22\beta_F,23\alpha_F$-diols formed may vary between 70:30 and 15:85 depending on the substituents of the side-chain.[125-127] Reaction of *E*-cholest-22-en-24-ones with alkaline hydrogen peroxide[38,128,129] or with dimethyloxosulphonium methylide[122] gave almost exclusively the $22\beta_F,23\alpha_F$-oxide or $22\beta_F,23\alpha_F$-methylene derivatives.

Reactions of 20-carboxaldehydes with alkyl Grignard reagents, preferably in polar solvents,[130-132] or with dimethylsulphonium methylide[125] favour the formation of $22\alpha_F$ alcohols. Addition of vinylic,[133-136] and even more of the sterically less demanding acetylenic,[11,85,137,138] reagents tends to be less stereoselective.

[125] M. Ishiguro, H. Saito, A. Sakamoto, and N. Ikekawa, *Chem. Pharm. Bull.*, 1978, **26**, 3715.
[126] M. Hirayama, K. Gamoh, and N. Ikekawa, *J. Am. Chem. Soc.*, 1982, **104**, 3735.
[127] M. J. Thompson, W. J. Meudt, N. B. Mandava, S. R. Duthy, W. R. Lusby, and D. W. Spaulding, *Steroids*, 1982, **39**, 89.
[128] G. R. Weihe and T. C. McMorris, *J. Org. Chem.*, 1978, **43**, 3942.
[129] E. Glotter, M. Zviely, and I. Kirson, *J. Chem. Res.* (*S*), 1982, 32; (*M*), 1982, 373.
[130] J. P. Poyser and G. Ourisson, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2061.
[131] Y. Hirano and C. Djerassi, *J. Org. Chem.*, 1982, **47**, 2420.
[132] M. Ishiguro, A. Akaiwa, Y. Fujimoto, S. Sato, and N. Ikekawa, *Tetrahedron Lett.*, 1979, 763.
[133] T. A. Narwid, K. E. Cooney, and M. R. Uskoković, *Helv. Chim. Acta*, 1974, **57**, 771.
[134] R. D. Walkup, G. D. Anderson, and C. Djerassi, *Tetrahedron Lett.*, 1979, 767.
[135] S. Fung and J. B. Siddall, *J. Am. Chem. Soc.*, 1980, **102**, 6581.
[136] N. Ikekawa, Y. Hirano, M. Ishiguro, J. Oshida, T. Eguchi, and S. Miyasaka, *Chem. Pharm. Bull.*, 1980, **28**, 2852.
[137] M. Ishiguro, S. Takatsuto, M. Morisaka, and N. Ikekawa, *J. Chem. Soc., Chem. Commun.*, 1980, 962.
[138] T. B. Kline and G. D. Prestwich, *Tetrahedron Lett.*, 1982, **23**, 3043.



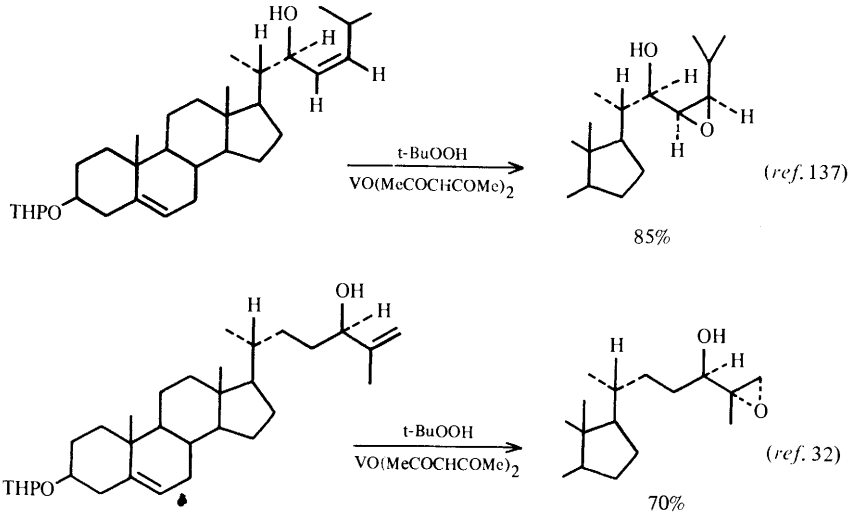
Scheme 25

Chirality Transfer.—In the flexible side-chains, diastereoselectivity is unimportant unless one uses reactions with a transition-state which freezes part of that chain. This is the concept of chirality transfer. We have already discussed Pd-catalysed 1,3-chirality-transfer used for the synthesis of 24-hydroxycholesterol.[85]

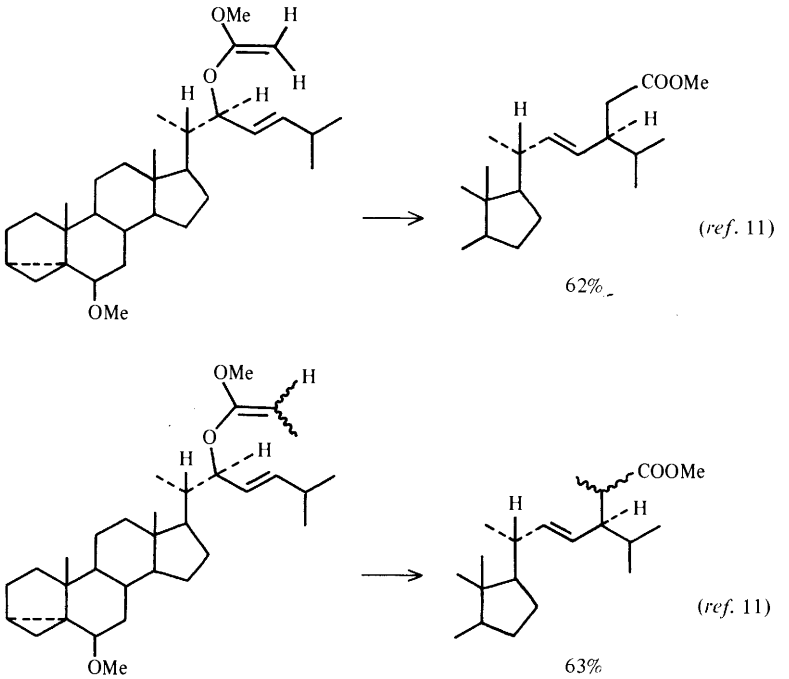
Epoxidation of allylic alcohols also proceeds *via* rigid transition-states resulting in high stereoselectivity for the formation of the *threo* isomer in the case of 1,3-dialkylsubstituted *cis*-allyl alcohols, or *erythro* isomers in the case of 1,2-dialkyl-substituted allyl alcohols.[139] This principle was used in two syntheses of brassinolide[135,137] and for the stereoselective syntheses of 25,26-dihydroxy-cholesterols[32] (Scheme 26).

The *Claisen* rearrangement proceeds *via* a chair-like 6-membered transition-state. For the 22-alcohols the stereochemistry at C-24 in the product is determined by the preference of the bulky steroid nucleus to occupy the equatorial position, by the configuration at C-22, and the stereochemistry of the double bond at C-23. Claisen rearrangement with trimethyl orthoacetate yields one product.[11,131] Rearrangement with orthopropionates yields products homogeneous at C-24 but epimeric at the 25-position[11,138,138a,140] (Scheme 27). This contrasts with the Claisen rearrangement using 1-methoxy-1-(dimethylamino)prop-1-ene, which was

[138a] A. Y. L. Shu and C. Djerassi. *Tetrahedron Lett.*, 1981. **22**, 4627.
[139] B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless. *Tetrahedron Lett.*, 1979, 4733.
[140] M. A. Gilhooly, D. S. Morris, and D. H. Williams. *J. Chem. Soc., Perkin Trans. 1*, 1982, 2111.



Scheme 26



Scheme 27

mentioned earlier and proceeds stereoselectively both for the 24- and 25-position.[37,38,141-144]

The Claisen rearrangement has also been used to transfer chirality from the 24-ols back to the 22-position for the stereoselective synthesis of both 22*R*- and 22*S*- 22-methylcholesterol.[29]

The nature of the Carroll rearrangement of a β-ketoacetate of 20*S*-6β-methoxy-20-ethenyl-3α,5-cyclo-5α-pregnan-20-ol remains unspecified but yielded a 1:2 mixture of *cis* and *trans* isomers.[133] It was, however, successfully applied with *E*-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-en-16α-ol.[145]

An oxy-Cope rearrangement was used for the stereoselective synthesis of 3β-(tetrahydropyran-2-yl)oxychola-5,23-dien-16-one.[146]

An interesting new development is the use of 1,3-dipolar addition reactions.[147]

[141] W. Sucrow, P. P. Caldeira, and M. Slopianka, *Chem. Ber.*, 1973, **106**, 2236.
[142] W. Sucrow, M. Slopianka, and P. P. Caldeira, *Chem. Ber.*, 1975, **108**, 1101.
[143] W. Sucrow and M. Slopianka, *Chem. Ber.*, 1975, **108**, 3721.
[144] H. W. Kircher and F. U. Rosenstein, *J. Org. Chem.*, 1982, **47**, 1722.
[145] M. Tanabe and K. Hayashi, *J. Am. Chem. Soc.*, 1980, **102**, 862.
[146] M. Koreeda, Y. Tanaka, and A. Schwartz, *J. Org. Chem.*, 1980, **45**, 1174.
[147] J. J. Partridge, N. K. Chadha, A. D. Batcho, and M. R. Uskokovic, Abstr. Papers, Am. Chem. Soc., 1981, 182 meeting, p. 35.