Various Approaches to the Construction of Aliphatic Side Chains of Steroids and Related Compounds

DAVID M. PIATAK* and JERZY WICHA*

Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115, and Institute of Organic Chemistry, Polish Academy of Sciences ul. Kasprzaka 44, 00-961 Warszawa, Poland

Received December 5, 1977

Contents

D. M. P., Northern Illinois University; J. W., Polish Academy of Sciences.

0009-2665/78/0778-0199$05.00/0

I. Introduction and Scope

During the early and middle years of steroid and related terpenoid chemistry, synthetic efforts focused primarily upon the ring system and some of the more simple functional side chains. These studies were directed primarily toward the development of synthetic methods for the construction and modification of the cyclic skeleton and were due, of course, to the demand for potent pharmaceutical agents. Comparatively little attention was paid to the side chain except for the two carbon unit present in the corticosteroids and other pregnane derivatives and interconversions between the side chains of cholesterol, plant sterols, and bile acids.

With the isolation and characterization of metabolites of cholesterol and other sterols from man, plants, and animals; the insect and crustacean moulting hormones; fungal sex hormones; brain sterols; new phytosterols; the various active metabolites of vitamin D; and marine sterols, the emphasis in steroid chemistry has been shifting to the chemical and biological potential of the side chain. In addition progress in synthetic methods and separation and identification techniques prompts more detailed studies of this conformationally flexible portion of steroid and terpene molecules.

Within the last decade intensive research on side-chain syntheses has yielded many imaginative syntheses of general interest and has contributed much to the development of stereospecific chiral carbon formation, in general. The aim of this review then is to survey the syntheses of steroid and related terpene side chains as well as some relevant chemistry involving transformations of the side chain for the preparation of compounds of biological importance and/or naturally occurring steroid molecules to provide not only steroid chemists but natural product chemists pursuing new syntheses of steroids or compounds with similar chain structures the literature base needed to ascertain how the syntheses of new isolates and analogs may be approached.

This review is limited to sequences commencing at carbons 20, 22, or subsequent ones since a rather complete review on the chemistry of pregnane side chains[1] is already available and to the completion of chains with the full amount (27 carbons) of and/or extra side-chain carbons but excluding steroid alkaloids and sapogenins since several reviews of these topics have appeared.[2-11] Stereochemical aspects of the approaches are especially featured so the problems encountered in forming chiral centers at different chain positions are brought together for the first time. This summarization has allowed for conformational and mechanistic correlation and analysis of the impact that reagents and structural relationships have on specific sites.

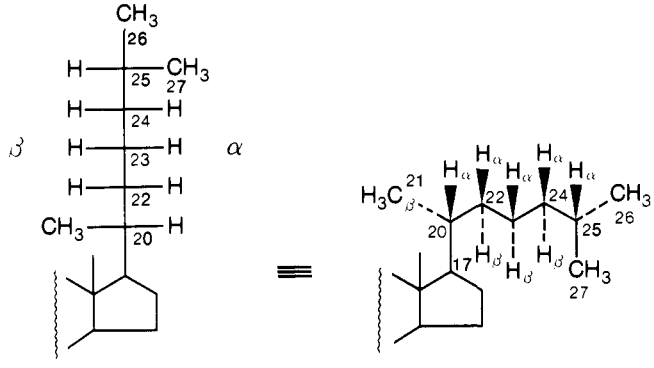
II. Stereochemical Notations for the Side Chain

During the initial investigations on steroids it became evident that the C-20 configuration of plant sterols, animal sterols, and

bile acids were identical; eventually this configuration was related to that of D(−)-citronellal.[12,13] It has been only recently[14] that one of the first natural sterols with the epimeric C-20 configuration was isolated from the brown alga *Sargassum ringgoldianum* and transformed into 20-isocholesterol (20*S* configuration).

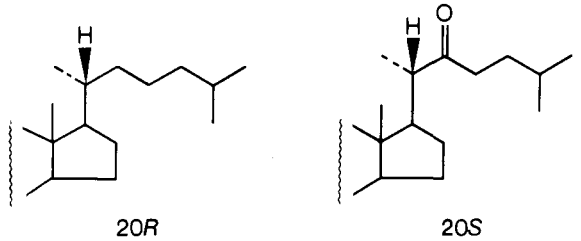
The need to systematically designate and name side-chain epimers first arose in connection with the synthesis of pregnan-20-ols.[15] Prior to this time notation of side-chain and ring stereochemical transformations in steroids consisted of using totally different names or a prefix, such as norm-, iso-, epi-, etc., and often side-chain epimers were not recognized as such.

The Fischer convention adapted by the Fiesers[15] for the pregnane chain and extended to the rest of the side chain by Plattner[16] was the first attempt to systemize the stereochemical nomenclature of the steroid side chain. According to this convention the C-17 chain **1** is placed so the longest chain extends



1

upward from ring D and basically under the plane of the drawing. The remaining functional groups then project above the plane (see **1**) in a manner similar to the alignment of sugars. Substituents appearing to the right of the chain are then denoted as being α, and those to the left, β, as illustrated (see **1**). This convention has been accepted for the C-20 position in the IUPAC-IUB 1971 Definite Rules for Steroid Nomenclature[17] mainly for historical reasons. However, the sequence rules of Cahn, Ingold, and Prelog[18] are recommended in the IUPAC-IUB rules for side chains. Although this latter convention eliminates much of the ambiguities and confusion, its use meets difficulties when transformations near, and or even sometimes remote, to the chiral center formally reverse the configuration; e.g.,



20*R* 20*S*

and comparison of the steric outcome of some reactions is easier when the Fieser–Plattner convention is used.

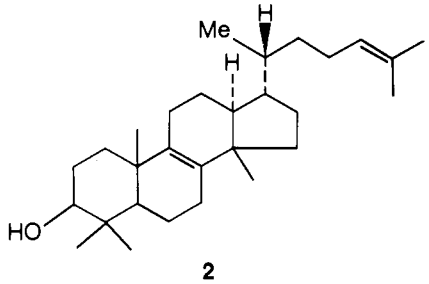
The sequence rules have also been applied to double-bond geometrical isomers.[19]

III. Spectroscopic and Physical Methods for Determining the Configuration of Chiral Carbons in the Side Chain

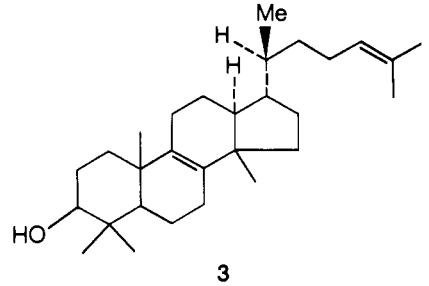
A great deal of information on spectral properties of side-chain epimers is now available permitting some generalizations; however, since spectra are influenced by many factors, generalizations may not be always directly applicable to new compounds.

Perhaps, the most informative method for stereochemical assignment has been NMR spectroscopy. For elucidating C-20 stereochemistry the C-21 protons give the best diagnostic signal. The 20β isomer generally has its signal more downfield than the 20α isomer. Representative values for C-21 protons of C-20 epimers are in Table I. ^{1}H NMR chemical shifts have also been used to distinguish the 20,22-diols of cholesterol,[20] and C-24 epimeric phytosterols at both 100[21,22] and 220 MHz.[23] More recently, the side-chain conformation of 22,23-substituted stigmast-3-ones has been examined.[24] ^{13}C NMR has been explored as a means for stereochemical determination of various cholesterol 22 epimers substituted by OH, NH_2, and N_3; it has been noted that *S* isomers give greater β effects than *R* isomers.[25] The four 20,22-epoxycholesterols have also been examined by ^{13}C NMR.[26]

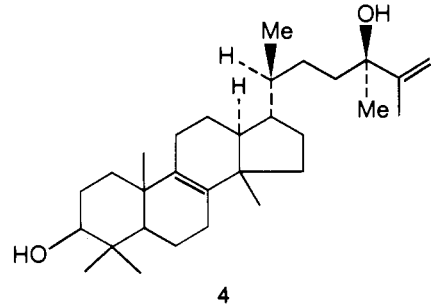
Application of ORD and CD for determination of C-20 configurations has limited scope; however, comparison[27] of plain positive and plain negative ORD curves of euphol **2** and tirucallol **3** derivatives with those of a new triterpene[28] corollatadiol **4** has



2



3



4

been employed to determine the configuration at this point. The empirical method of Dillon and Nakanishi[29] for elucidating the configuration of alcohols and diols by CD measurement of their complexes with rare-earth chelates promises to be of tremendous advantage once enough comparative data are accumulated. For some compounds, e.g., cholestenes, information has been gathered from optical rotations. In most cases, the 20β or 20*R* epimer shows higher positive or smaller negative rotation than the 20α (or *S*) epimer.[15,30,31]

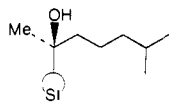
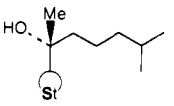
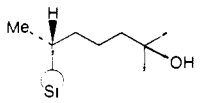
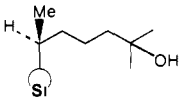
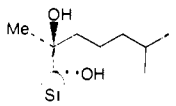
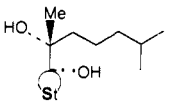
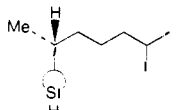
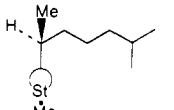
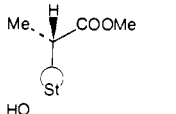
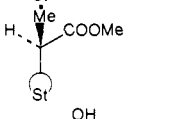
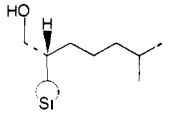
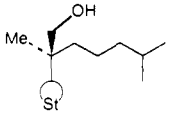
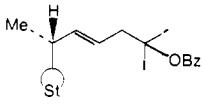
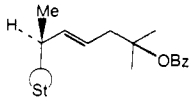
For several key compounds complete x-ray analysis of structure has been made.

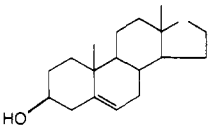
IV. Reactions Involving Position 20

A. Addition of Organometallic Reagents to C-20 Ketones

The reaction of Grignard and other organometallic reagents

TABLE I. Some Representative NMR Chemical Shifts for C-21 Protons of Steroid Compounds Epimeric at C-20

20β-Methyl isomer	δ[a]	20α-Methyl isomer	δ[a]	$\delta_{20\beta} - \delta_{20\alpha}$	Ref
	1.17 1.28		1.00 1.12	0.17 0.16	36b 41
	0.93		0.84	0.09	89
	1.30		1.22	0.08	41
	0.91 0.92		0.81 0.79	0.10 0.11	93 230
	1.21		1.11	0.10	68
	3.70		3.62	0.08	230
	0.98[b]		0.81[b]	0.17	236

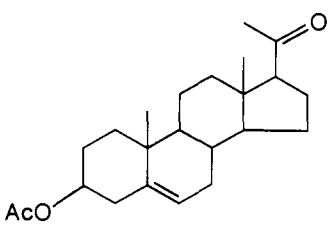
St = 

[a] Expressed in ppm. [b] An *i*-steroid system is present in rings A and B of this example.

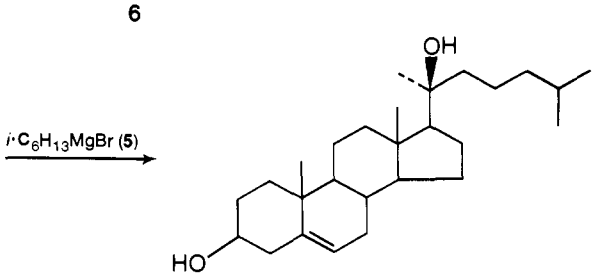
with 20-ketones has been utilized by a number of investigators to construct the side chain in one- and multistep sequences. In these reactions during which a chiral center at C-20 is created, mixtures of epimers usually ensue with the ratio depending greatly upon the structure of the steroids, particularly the nature of substituents near C-20 and the bulkiness of the reagent.

Essentially, two approaches have been followed. The first involves reaction of an appropriate 20-oxopregnane, e.g., **6** to give a complete side chain **7** (or partial side chain); and the second, by the addition of a single carbon atom to a norketone **9** initially prepared from an androstane derivative, such as **8** (see Tables II–IV).

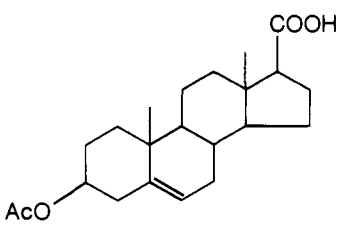
One of the first instances in which the former route was employed was in the total synthesis of cholesterol by Woodward[32,33]



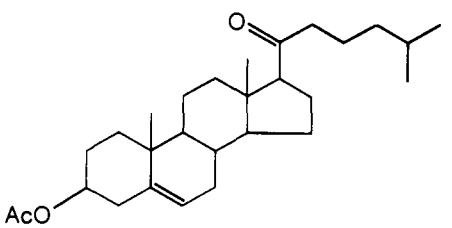
6



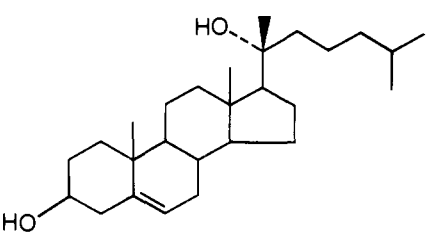
7



8



9



10 + 7

and Robinson.[34] However, they were not concerned with separation of the 20-hydroxy products and instead dehydrated them to unsaturated intermediates which were subsequently hydrogenated. Petrow and Stuart-Webb,[35] though, did prepare and

TABLE II. Reaction of Alkyl Organometallic Reagents and 20-Ketones

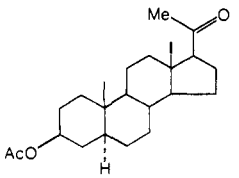
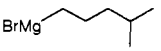
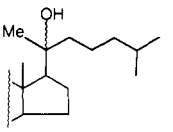
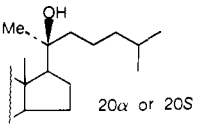
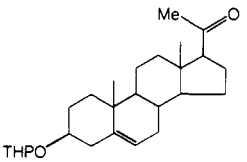
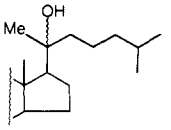
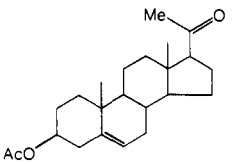
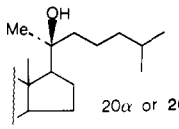
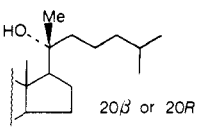
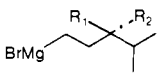
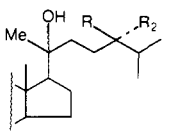
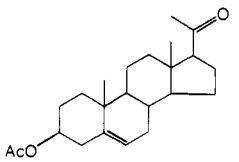
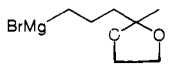
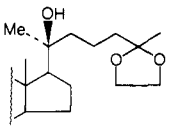
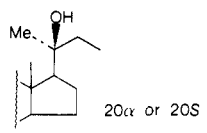
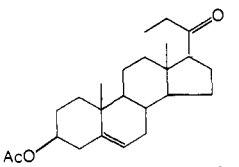
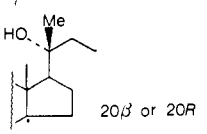
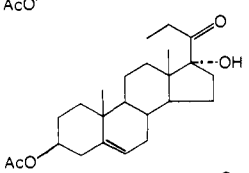
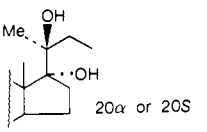
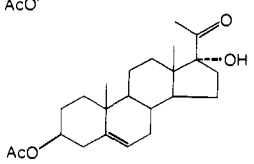
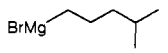
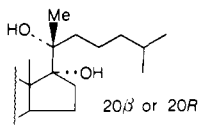
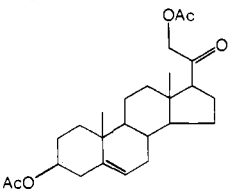
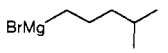
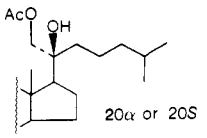
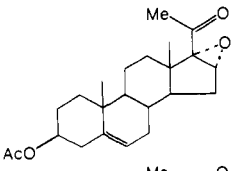
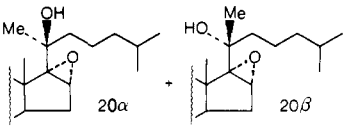
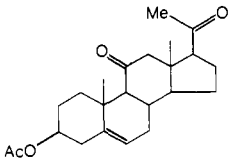
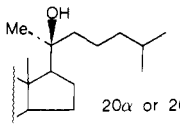
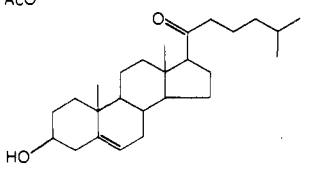
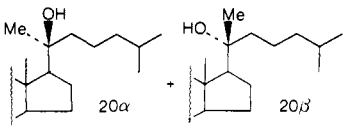
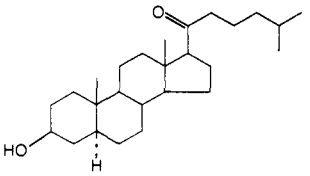
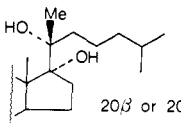
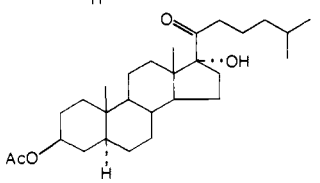
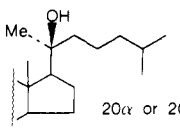
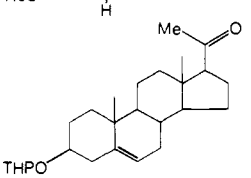
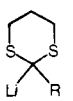
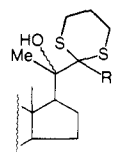
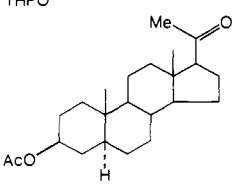
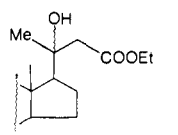
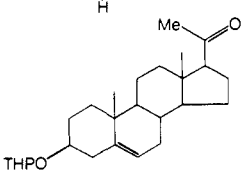
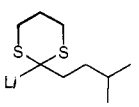
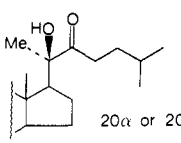
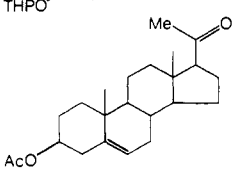
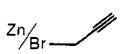
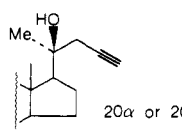
20-Ketone	Reagent	Product[a]	Comment	Ref
			*b–e*	32, 33
As above	As above	 20α or 20*S*	~90% yield	41
	As above		*b–e*	34
	As above	 20α or 20*S*	e; ~45% yield 48% yield	35 36
As above	As above	As above +  20β or 20*R*	Ratio 1.6:1 (by GLC)	219
As above			R_1 = Me; R_2 = H or R_1 = H; R_2 = Me *b–e* R_1 = Et; R_2 = H or R_1 = H; R_2 = Et *b–e*	81 82
			*c–e*	92
As above		 20α or 20*S*	*b*	40
	BrMgMe	 20β or 20*R*	*b*	40
	As above	 20α or 20*S*	*b*	40
		 20β or 20*R*	~50% yield	41
		 20α or 20*S*	~60% yield	41

TABLE II (*Continued*)

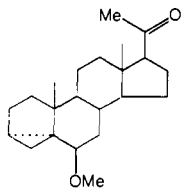
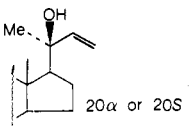
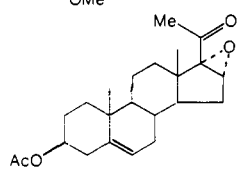
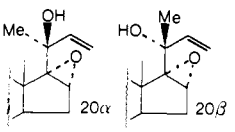
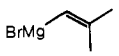
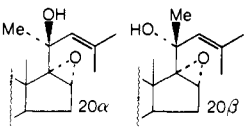
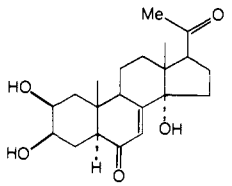
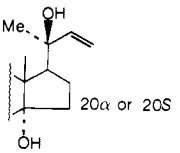
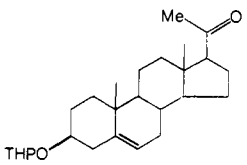
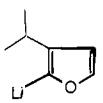
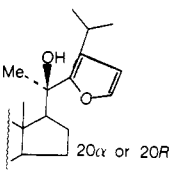
20-Ketone	Reagent	Product[a]	Comment	Ref
	As above		*c*; ratio 1:3	41
	As above		*d*; ~50% yield	31
	BrMgMe		Ratio 1:12	36, 219
	As above		~70% yield	41
	As above		~45% yield	41
			*c*, *e*; R = H, 77% yield; R = Me, 51% yield R = H, 80% yield; 20β (*R*) isomer	46 87
	$LiCH_2COOEt$		*b*, *d*, *e*; single isomer reported	83
			70% yield; product obtained after thioketal removal	47, 87
			*b*	50

[a] Isomer based on direction of hydroxyl moiety (α or β). [b] Yield not stated. [c] Stereoisomers not separated. [d] Alcohol group removed by dehydration. [e] Stereochemistry not determined.

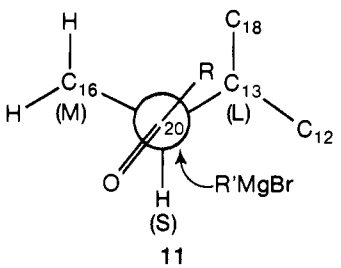
isolate a single epimer (45% yield) of 20-hydroxycholesterol **7** by reacting pregnenolone acetate with isohexylmagnesium bromide. The configuration was determined as being 20α(20*S*) by Lieberman and associates[36] when they repeated the reaction and compared the product with the 20β(20*R*) isomer **10**, resulting from the reaction of ketone **9** with MeMgBr. The steric course and yields of the reaction of Grignard and other reagents with 20-ketones are compiled in Tables II–IV.

In order to explain the difference in the Grignard results,[35,36] Fieser and Fieser[37] applied the Cram rule, which would involve a starting conformation of the 20-ketone as depicted by **11** and have the Grignard reagent approach from the side with the smallest substituent so product **12** will ensue. This analysis, however, cannot account for all the experimental data; in fact, it pays attention only to C-17 substituents and neglects shielding of the carbonyl group by ring C. More recently, conformations **13**, **14**, and **15** for the 20-ketone were analyzed by Rakhit and Engel[38] and Kier.[39] These conformations were later used by Gut and co-workers[40,41] to explain their experimental results with Grignard reagents and 20-ketones (see Table II). They concluded

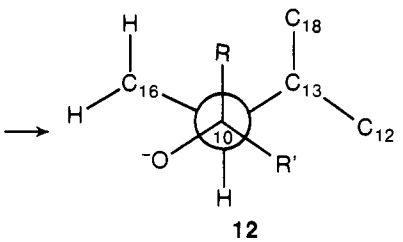
TABLE III. Reaction of 20-Ketones with Vinylic Organometallic Reagents

20-Ketone	Reagent	Product[a]	Comment	Ref
			86% yield	89
			Ratio 1:3	160
As above			Ratio 3:2	160
			*b*	110
			*c*; 38% yield	220

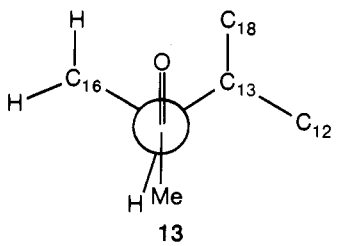
[a] Isomer (α or β) based on hydroxyl group direction. [b] Yield not stated. [c] Alcohol group removed by dehydration.



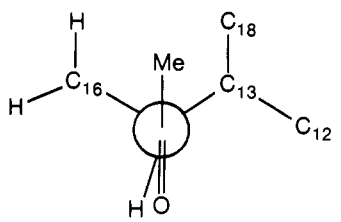
11



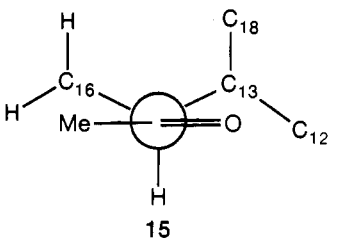
12



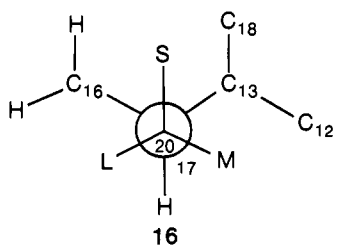
13



14



15

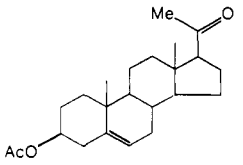
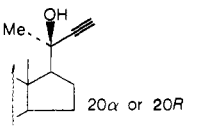
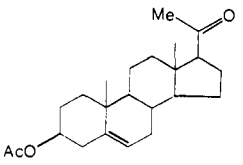
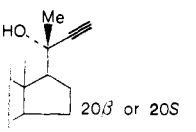
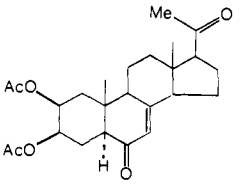
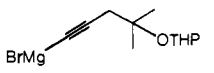
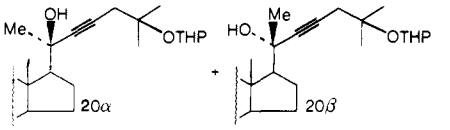
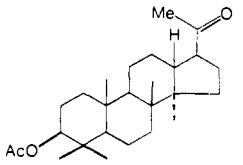
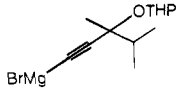
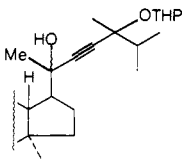


16

the conformation of the ketone must be either **13** or **14** since they are more conducive to attack from a less hindered side (C-16 side).

The results presented in Tables II–IV can be explained best by the following: (1) "steric approach" control favors attack of the carbonyl group from the C-16 or the "outside of the molecule" side; (2) "product development" control favors formation of the most stable epimer which has its substituents arranged on C-20 as in **16**; (3) the steric outcome can be most easily explained by assuming conformation **13** for 17-unsubstituted derivatives and **14** for 17α-hydroxy derivatives, the latter a result of strong hydrogen bonding;[42] (4) "steric approach" and "product

TABLE IV. Reaction of 20-Ketones with Acetylenic Organometallic Reagents

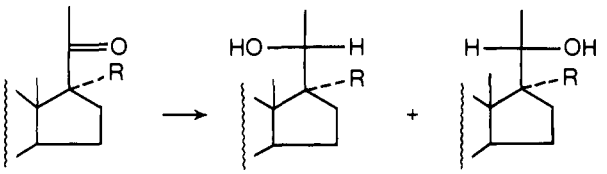
20-Ketone	Reagent	Product[a]	Comment	Ref
			70% yield	40, 221
				40
			Ratio 4:1	48
			*b–d*	49

[a] Isomer (α or β) based on direction of hydroxyl moiety. [b] Yield not stated. [c] Isomers not separated. [d] Stereochemistry not determined.

development" acting in the same direction gives higher specificity.

A rather complete study on the stereochemical aspects of the reaction of MeMgBr with 20-oxopregnanes was reported by Osawa et al.[231] after this manuscript was submitted. Their conclusions are in accord with the above analysis except they indicate 17α-hydroxy-20-pregnanones react in the same conformation **13** as other 20-ketones. Their suggestion for the Grignard reaction of 17α-hydroxy-20-pregnanones will undoubtedly prove valuable when the limited data now available are expanded to more bulky Grignard reagents.

The steric outcome of organometallic reagent addition to C-20 ketones parallels metal hydride reduction. For example, reduction of the 20-ketone **17a** in pregnane derivatives leads to a mixture of 20β(20*R*)-hydroxy **18a** and 20α(20*S*)-hydroxy **19a** derivatives with the β isomer **18a** predominating,[43-45] while reduction of 17α-hydroxy-20-ones **17b** gives rise[45] to mainly 20α(20*S*) alcohols **19b.**

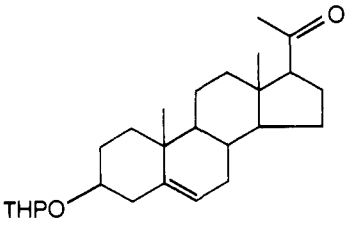


20β (20*R*) 20α (20*S*)

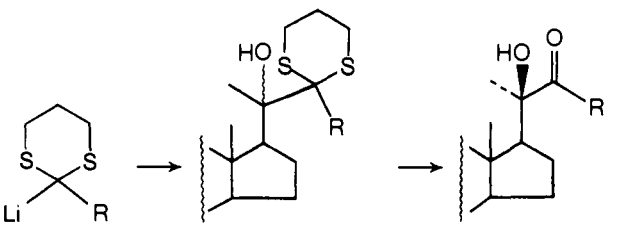
17 **18** **19**

a, R = H
b, R = OH

Although the main purpose of many of the Grignard and lithio reactions were for the preparation of a 20-hydroxysterol chain or, eventually, cholesterol or other sterol chain types, some of the nucleophilic additions to the carbonyl at C-20 have been a means to achieve other types of side chains, such as those in ecdysone and multihydroxy sterols. For example, addition of 1,3-dithianes **21** to the THP ether of pregnenolone **20** to acquire **22** has been studied by Lettré et al.,[46] to explore the formation of 20-hydroxyaldehyde **23a.** This route was successfully used by Koreeda et al.,[47] as a means of preparing dioxygenated cholesterol side chains **23b.**

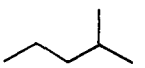


20

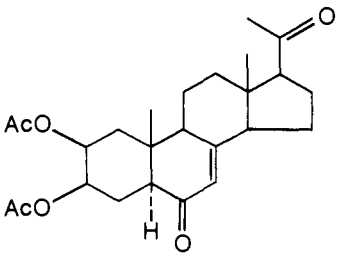


21 **22** **23**

21a, R = H

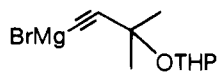
b, R = 

Kerb and workers,[48] after their addition of Grignard reagent **25** to **24,** continued to modify the resultant side-chain **26** during

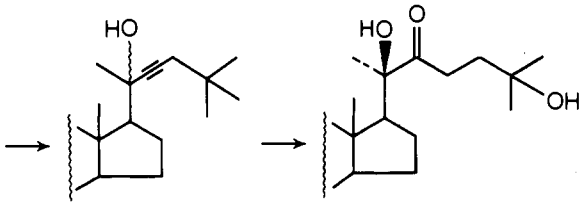


24

their crustecdysone (**29**) and 22-isocrustecdysone (**30**) synthesis by first cleavage of the THP moiety with acid, then hydration of the triple bond. The ketone **27** eventually had the 14α-hydroxy group introduced with SeO_2 and the C-5 position isomerized with

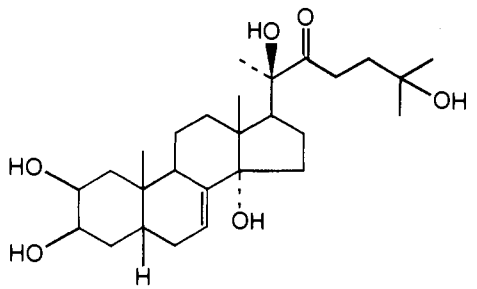


25

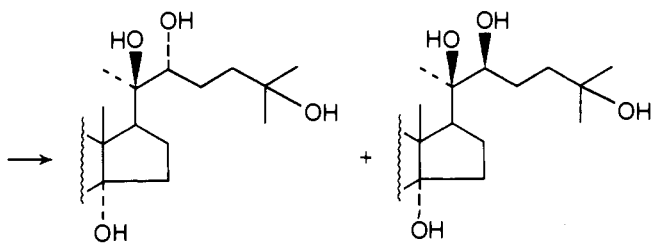


26 27

base to yield **28.** Reduction of the 22-ketone by $LiAlH(O\text{-}t\text{-}Bu)_3$ finally gave crustecdysone **29** and its 22-epimer **30.**

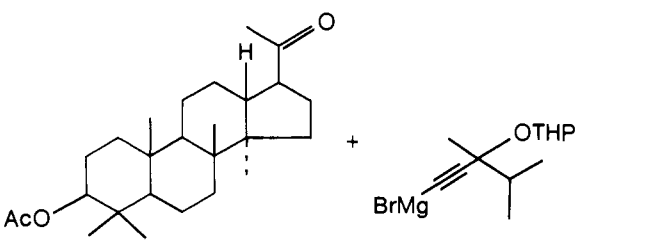


28

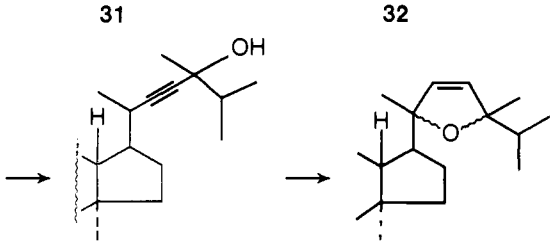


29 30

In the synthesis of alnincanone (**35**), Labriola and Ourisson[49] began with the addition of **32** to a degradation product **31** of dipterocarpol to secure **33.** Partial hydrogenation of the triple bond of **33** and cyclization of the product produced the dihydrofuran system of **34** which was reduced further. Oxidation at

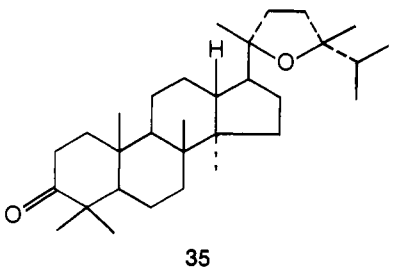


31 32

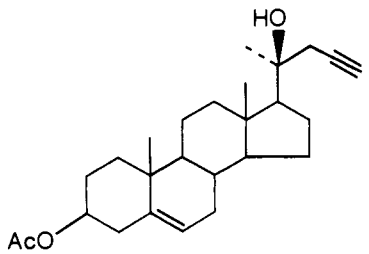


33 34

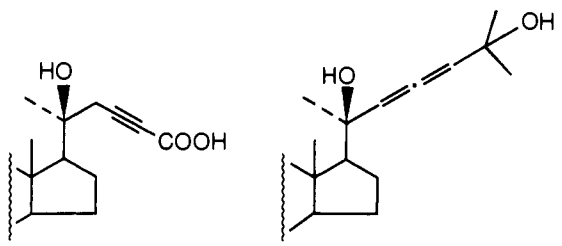
C-3 gave four diastereoisomers, one of which was identical with alnincanone (**35**). More recently, Sydykov and Segal[50] employed the acetylenic intermediate **36** to secure two side chains **37** and **38** by treating **36** with EtMgBr first, then adding CO_2 or acetone, respectively.



35



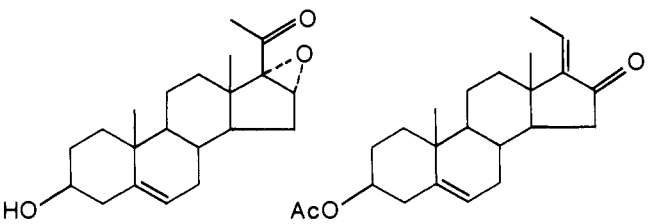
36



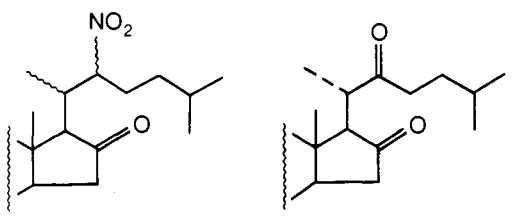
37 38

B. Side-Chain Completions Beginning with C-20 Deoxy Compounds

A stereospecific method of side-chain construction based upon Michael addition of nitroalkanes to 17(20)-en-16-ones has been devised by Kessar et al.,[51-54] mainly for sapogenin and steroidal alkaloid syntheses, but it has also been applied to the synthesis of cholesterol.[55] Addition of nitroalkane to unsaturated ketone **40,** obtained from a Huang-Minlon reduction[51] of

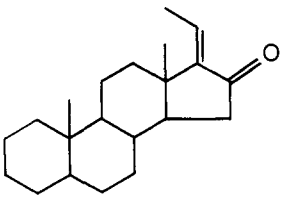


39 40

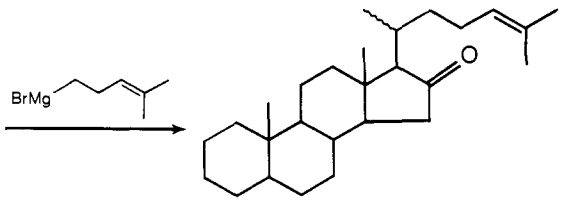


41 42

16α,17α-epoxypregnenolone (**39**), produces the 20-nitro ketone **41.** A Nef reaction on **41** then leads to dione **42** which is capable of equilibrating to the C-20 natural isomer because of the adjacent 22-ketone and the influence of the 16-oxygen moiety (for stereochemical explanation, see section IV.D). Clemmensen and Wolff-Kishner reduction of **42** completed the preparation of cholesterol. A similar approach involving a 1,4-Grignard addition was reported by Wyllie and Djerassi[56] for **43,** but it lacked the possibility of forming a preferred isomer at C-20 owing to the absence of a ketone moiety adjacent to C-20 in product **44.**

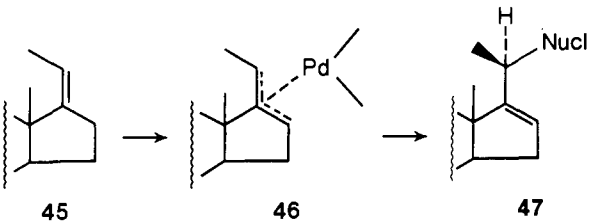


43

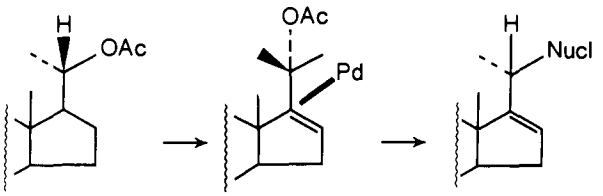


44

A very recent and quite interesting catalytic method for side-chain addition which might prove to have widespread application has been developed by Trost.[57] The method involves initial formation of an allylpalladium complex with either unsaturated compound **45** or a 20-acetoxy-16-ene **48.** In the non-acetate complex **46** the metal is on the α face, while in allylic acetate complex **49** the palladium sits on the β face owing to steric hindrance by the acetate moiety. The nucleophile can

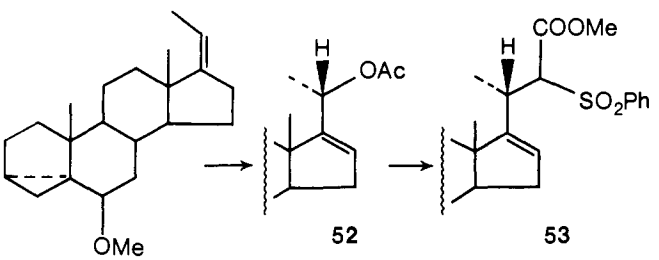


45 46 47

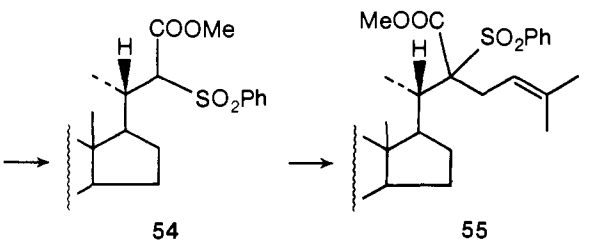


48 49 50

then add only from the β side of **46** yielding the "unnatural" configuration at C-20 because the palladium blocks the opposite face. Similarly, nucleophilic attack of **49** takes place from the acetate side yielding the "natural" configuration with simultaneous displacement of the acetate. The method has been applied for the synthesis of an ecdysone side chain in good overall yield[58] as follows. Allylic acetate **52** was prepared from **51** by stereo-

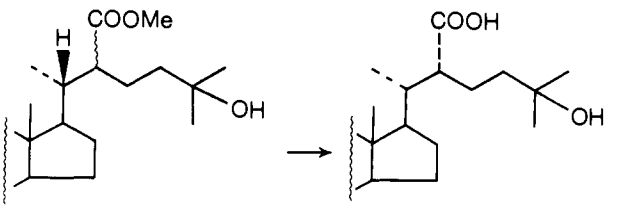


51 52 53

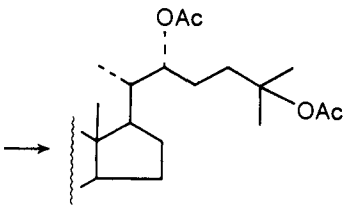


54 55

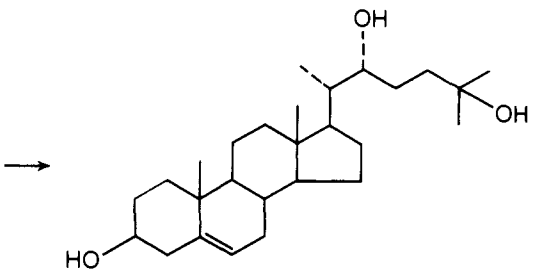
selective epoxidation on α face, epoxide opening with LDA, and acetylation. The acetate group in **52** was stereospecifically displaced via its palladium complex with $[PhSO_2CHCO_2Me]^-Li^+$ to give **53.** Reduction of the 16(17) double bond yielded **54,** which was then treated with NaH. Alkylation of the resultant sodio derivative with β,β-dimethylallyl bromide formed **55,** and removal of the sulfone moiety with Na(Hg) and hydration of the 24-double bond with $Hg(OAc)_2$ effected formation of **56.** Base hydrolysis



56 57



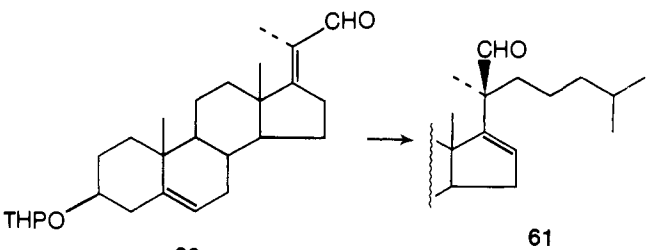
58



59

of ester **56** yielded acid **57** as a single isomer which could be converted by MeLi and Baeyer–Villiger oxidation with mCPBA to **58.** Finally, saponification of the acetate **58** and rearrangement of the *i*-steroid grouping gave the desired cholesterol derivative **59.**

Alkylation of the 17(20)-ene aldehyde **60** by isohexyl iodide began a novel approach by the Gut group[59] for the preparation of cholesterol. However, the alkylation product **61** was obtained in rather poor yield (15%). Reduction of the 16-double bond and aldehyde removal by $(Ph_3P)_3$ RhCl completed the side-chain sequence.

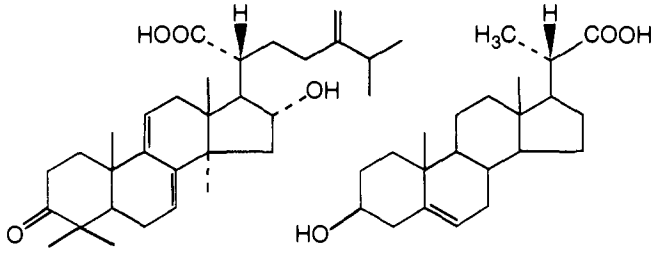


60 61

C. Stereochemical Consequences on C-20 of Adjacent Carbonyl-Containing Groups

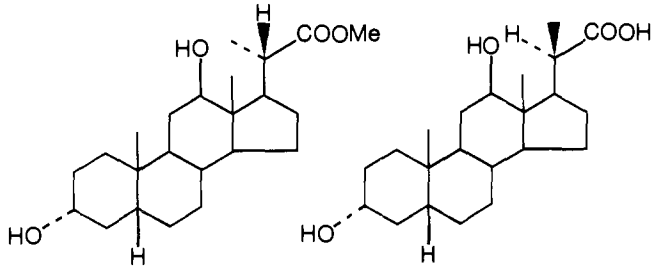
Compounds with a carbonyl group in positions 21 or 22 can be isomerized at C-20 through the appropriate enolate form. Such epimerization has been observed for acids, esters, aldehydes, and ketones. Complete analysis of the published data for information on the stability of C-20 epimers is complicated by the fact that often true equilibrium was not reached or it was not possible to quantitatively resolve or estimate the composition

of mixtures. In some instances authors have expressed the a priori statement that the "natural" configuration was the most stable. The stability of epimers has been analyzed, however, in connection with transformations of polyporenic acid C[61] (**62**) derivatives and bisnorcholenic acid[62] (**63**).

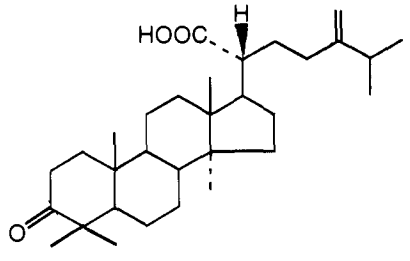


62 **63**

The first observation that bisnorcholanic acid could be isomerized was made in Wieland's laboratory.[62] Several years later, Sorkin and Reichstein[63] found ethyl 3α,12β-dihydroxybisnorcholanate (**64**) isomerizes extensively on refluxing with NaOEt in ethanol to give 20-isoacid **65** with an isolated yield of 50%.



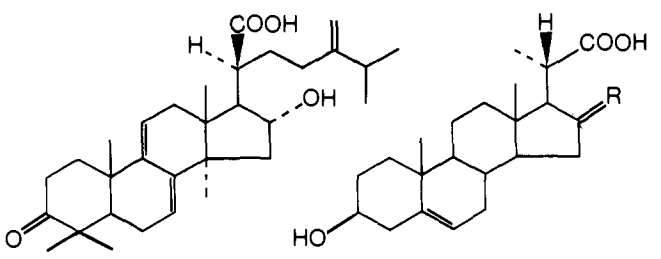
64 **65**



66

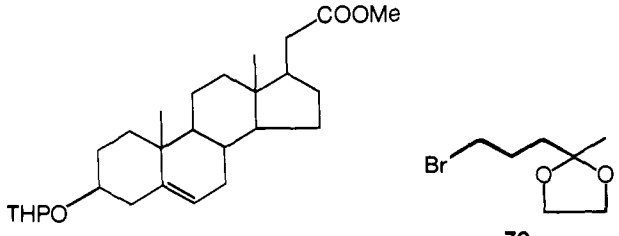
Similarly, methyl 3α,12α-dihydroxybisnorcholanate gave the corresponding 20-isoacid in 75% yield. Hayatsu[64] has also indicated that 3β-acetoxybisnorchol-5-en-22-oic acid isomerizes to the "unnatural" C-20 isomer in 65% yield on heating with KOH in ethylene glycol.

A substitution pattern at C-20 similar to the above iso acids is also present in the polyporenic acid family of triterpenes, e.g., eburicoric acid (**66**), but it is reverse to that in "natural" bisnorcholanic acids. Since the C-20 configuration of eburicoric acid (**66**) does not epimerize upon heating with KOH in ethylene glycol (Wolff–Kishner conditions)[60,65] and the bisnorcholanic acids do, as indicated above, it would seem the 20*R* configuration is preferred when a 21-carboxylic acid group is present. The configurational stability of this grouping, however, can be altered by a substituent at C-16 since polyporenic acid C (**62**) has been isomerized to its 20*S* epimer **67** with base[65] and bisnorcholenic acids containing 16-hydroxy and 16-oxo moieties **68** are more stable in their "natural" configuration.[61] This phenomenon was rationalized by stabilization of the 20*S* epimer through hydrogen bonding between the carboxylic acid group and the 16-oxygen moiety.[60,61]

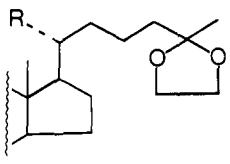


67 **68a**, R = H, ···OH
b, R = O

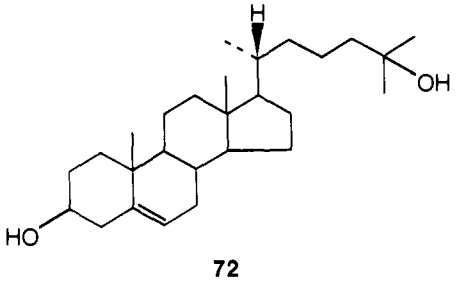
Since C-21 acids are capable, therefore, of greater stability in the 20*R* configuration, a side-chain synthesis for 25-hydroxycholesterol (**72**) incorporating this feature has been developed.[66] By alkylating the enolate of THP ester[67] **69**, formed with LDA, with bromoketal **70** the 20*R* ester **71a** in yields[68] as high as 80–90% was formed. Removal of the ester was effected by reduction with $LiAlH_4$ to alcohol **71b**, tosylation to **71c**, and hydrogenolysis of the tosylate with $LiAlH_4$ to **71d**. Hydrolysis of the ketal and THP protecting groups and MeMgI reaction with the 25-ketone gave 25-hydroxycholesterol (**72**) in 53% overall yield from **69**. This approach also gives easy access to C-21 functionalized cholesterols.



69 **70**

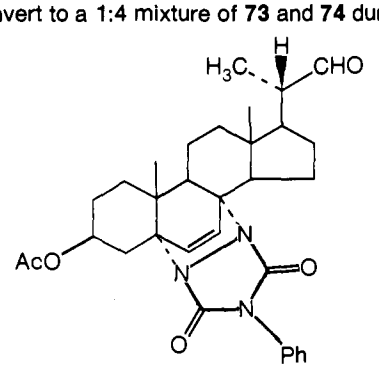


71a, R = COOMe
b, R = CH_2OH
c, R = $MePhSO_3CH_2$
d, R = Me

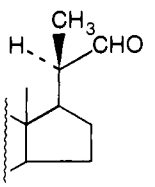


72

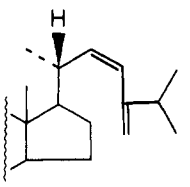
Aldehyde groups at C-22 were often used for the construction of the side chain; however, the first observation of epimerization at C-20 caused by this group has been made only recently.[69] Aldehyde **73** and its 20 epimer **74** were produced in a 7:1 ratio by ozonolysis of **75** and subsequent treatment of the ozonide with $(Et_2N)_3P$. The pure isomer **73** isolated by recrystallization was found to convert to a 1:4 mixture of **73** and **74** during chroma-



73

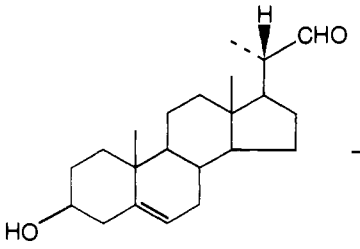


74

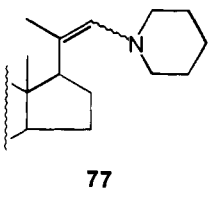


75

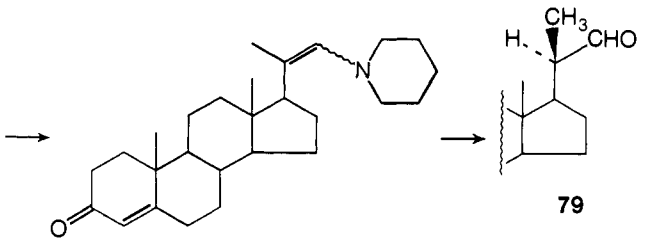
tography on alumina. Interestingly, when the ozonolysis was performed in a CH_2Cl_2 solution containing 1% pyridine, no isomerization took place. Also, no isomerization of aldehyde **73** resulted during a Wittig reaction. In several cases, though, variable amounts of 20-iso products have often appeared when 22-aldehyde **76** derived from stigmasterol was a component of Wittig reactions (see section V.E).



76



77

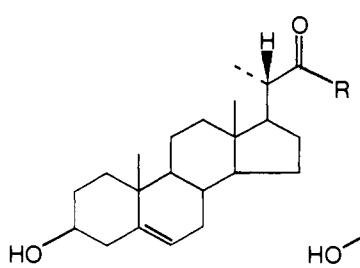


78

79

Enamine formation of the 22-aldehyde and its hydrolysis can profoundly effect a change at C-20 under comparatively mild conditions. In one such study[70] 20*S*-aldehyde **76** was converted to enamine **77** and then to 3-ketone **78.** Acid hydrolysis of enamine **78** gave only the isomeric 20β(20*R*) aldehyde **79.** Direct acid isomerization of **76,** on the other hand, leads only to a mixture containing 65% of the 20-isoaldehyde. In a similar enamine transformation[71] aldehyde **76** was completely isomerized; however, Wittig reaction of the 20-isoaldehyde proceeded with epimerization at C-20 and furnished a mixture of 22-enes although the corresponding 20-iso product predominated.

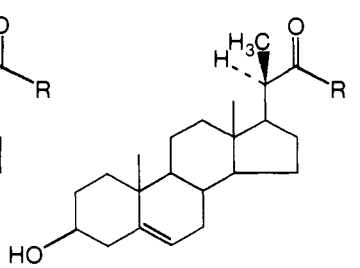
The first study on the isomerization of 22-ketones at C-20 was made by Cole and Julian[72] who found ketones with the "normal" configuration **80** are partially isomerized to "abnormal" ones **81** on heating with KOH in MeOH but not with Na_2CO_3. These observations were confirmed in a brief experiment by Caspi and co-workers.[73] Quantitative data on the isomerization of a 22-ketone are also available from the work of Hayatsu[64] since he obtained (20*R*)-22-ketocholesterol (**81b**) in 82% yield by heating **80b** with KOH in ethylene glycol.



80a, R = Me

b, R =

c, R = Ph

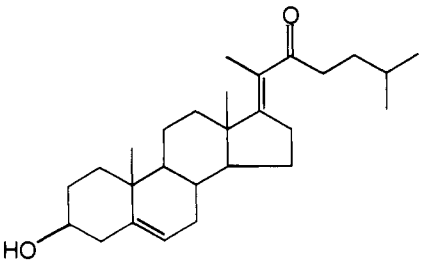


81a, R = Me

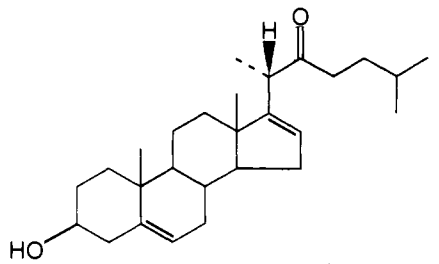
b, R =

c, R = Ph

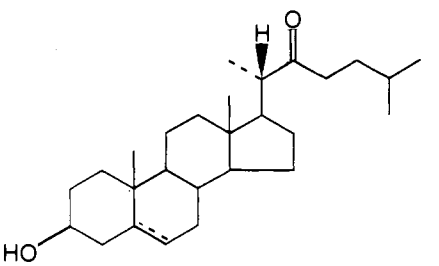
A contrary interpretation of the above isomerizations of C-20 by an adjacent C-22 ketone has been presented by Gut and workers.[74] However, analysis of their experimental data shows inconsistencies with their conclusions. When investigating the isomerization of α,β-unsaturated ketone **82** in alkaline medium, these workers found the equilibrium mixture contained 80% of β,γ isomers and 20% of starting ketone **82.** The major β,γ isomer **83** (reported C-21 NMR doublet at δ 1.15) was isolated readily and its structure deduced by subsequent steps. An NMR spectrum of the mother liquor revealed another isomer with a C-21 doublet at δ 1.22 remaining. Selective hydrogenation of the 16(17) double bond over 10% Pd-$CaCO_3$ and reduction of both double bonds with 10% Pd-C led to formation of 22-oxocholesterol **84a** and its saturated analog **84b,** respectively. After they reduced the ketone in **84a** to a methylene moiety, the resultant product was said to be cholesterol on the basis of its melting point. It was concluded, therefore, that the equilibration favored the 20*S* configuration and **83** was the major equilibration product. It is possible that the greater stability of their postulated 20*S* isomer **83** is promoted by the 16(17) double bond; however, the NMR chemical shifts they reported for the C-21 protons of the isolated isomer (δ 1.15) and the one remaining in the mother liquor (δ 1.22) are the reverse of those normally observed (see Table I).



82



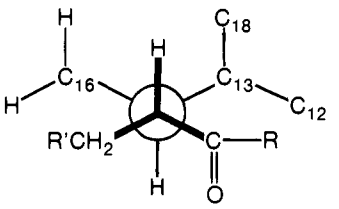
83



84a, 5-ene

b, 5α-H

If all of the above data on the stability of C-20 epimers of compounds containing C-21 or C-22 carbonyl groups is analyzed, several conclusions can be drawn. (1) The thermodynamically more stable epimer (20*R*) can be best placed as shown in **85,** where the hydrogen atom is located in the most crowded area, the medium-sized carbonyl moiety is placed toward ring C, and the alkyl group is "outside" the molecule. The assumption that the carbonyl is less bulky than a methyl or other alkyl group is

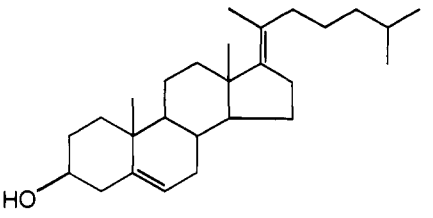


85

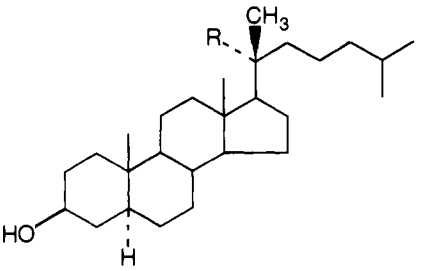
in accord with the measurement of conformational energy for substituents on a cyclohexane ring, the difference in standard free energy[75] between axial and equatorial substitution being CH_3, 1.70; COOH, 1.35; COOMe, 1.27; and COOEt, 1.20. (2) The difference in epimer stability is usually large. (3) The stability of C-20 epimers can be reversed by functional groups which interact with a carbonyl group, particularly those at C-16.

D. Reactions of 17(20) and 20(21) Double Bonds with Formation of a C-20 Chiral Center

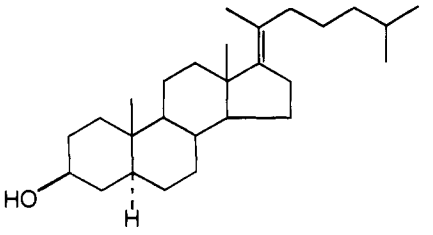
Several detailed reports concerning hydrogenation and other additions to double bonds formed between C-20 and one of the adjacent carbons at C-17 and C-20 have appeared. The Gut group,[41] for example, has reported that 17(20)-dehydrocholesterol (*E* isomer) (**86**) yields 20-isocholestanol (**87a**) on catalytic



86

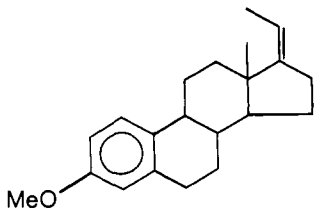


87a, R = H
b, R = OH

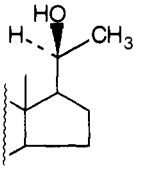


88

reduction (10% Pd-C), and hydroboration of 5α-cholest-17(20)-en-3β-ol (**88**) gives the 20β(20*R*)-diol **87b** in accord with the "rule of α-attack" for these reactions.[76] Similarly, hydroboration[77] of estratetraene **89** leads to the 20α(20*R*) alcohol **90.**

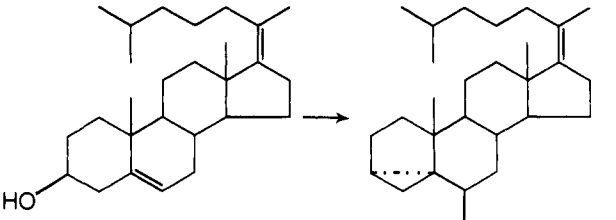


89

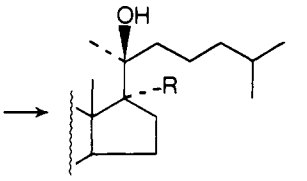


90

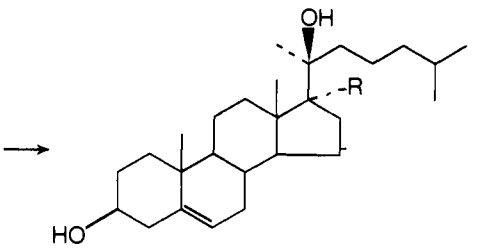
When (*Z*)-17(20)-dehydrocholesterol (**91**) was converted to **92** and hydroborated or treated with OsO_4, the same type of α attack was observed since after rearrangement 20α(20*R*)-hydroxycholesterol (**94a**) or 17α,20α(20*R*)-dihydroxycholesterol (**94b**) was produced, respectively.[78]



91 92

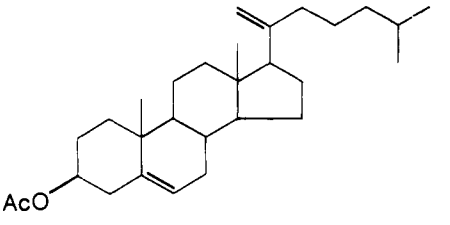


93a, R = H
b, R = OH

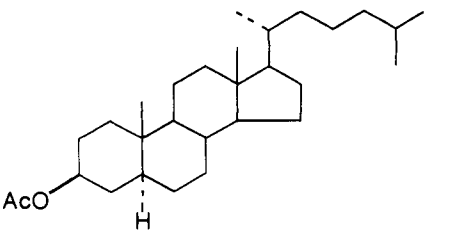


94

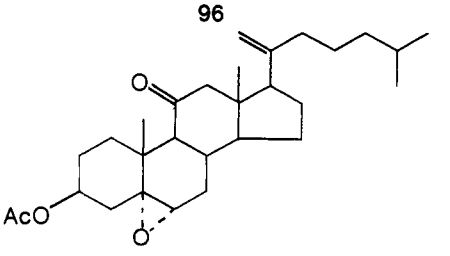
During hydrogenation of diene **95** Sondheimer and Mechoulam[79] obtained different products under various conditions. With PtO_2 in HOAc, saturation of both the 5(6) and 20(21) double bonds ensued and (20*R*)-cholestanol (**96**) crystallized in 25% yield from the crude reaction products. Hydrogenation of **95** over Pd-$CaCO_3$



95



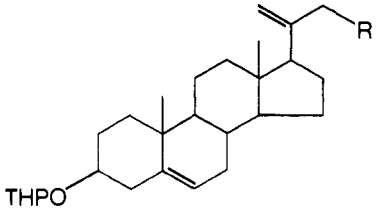
96



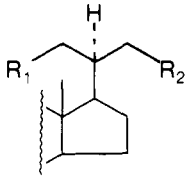
97

in ethanol did not affect the 5(6) double bond, and (20*S*)-cholesterol was isolated in 25% yield from the epimeric mixture. Nair and Mosettig,[80] however, reported that catalytic reduction of 5α-cholest-20(21)-ene leads to a mixture of cholestanes unseparable by column or gas chromatography; in contrast to the previous report they had not found differences in the behavior of mixtures obtained upon changing the catalysis and/or solvent. Similarly, Schneider,[31] during his study of the catalyic reduction of 20(21)-ene **97** found reduction with 5% Pd-C in EtOAc gave a 4:5 mixture of 20*R* and 20*S* products. When the reduction was performed in HOAc, no increase of the 20*R* isomer was noted.

Hydroboration of 20(21)-enes **98a** and **98b** with disiamylborane has been studied by Bottin and Fetizon.[229] The *S* isomer **99a** was formed in a 3:2 ratio over the *R* isomer **99b** from **98a**, while the *S* isomer **99c** resulted in a 95% yield from ene **98b**.



98a, R = H
b, R =



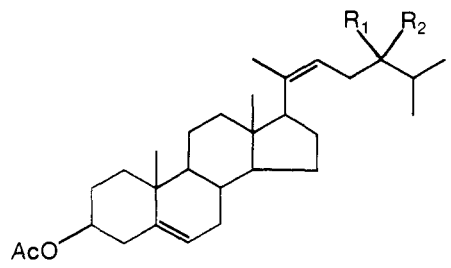
99a, R_1 = OH; R_2 = H
b, R_1 = H; R_2 = OH
c, R_1 = OH; R_2 =
d, R_1 = H; R_2 =
e, R_1 = ; R_2 = OH

The 21-alcohol **99c** was converted to isocholesterol **99d** by reduction of the corresponding tosylate. The same hydroboration of **98b** by the Gut group,[230] on the other hand, yielded a 1:2 ratio of the 20*S* alcohol **99c** to the 20*R* alcohol **99e** as did the use of B_2H_6 at 0 °C. Several methods for the synthesis of **98b** are also presented.

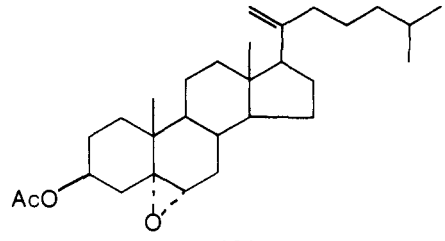
Hydrogenation of mixtures of various products unsaturated between C-20 and adjacent positions was, of course, also described in the first syntheses of cholesterol,[32-34] but detailed information about the character of the unsaturated products is unavailable.

E. Formation of 20(22) Double Bonds

Double bond formation at C-20(22) by dehydration of a C-20 alcohol is accompanied by 17(20)- and 20(21)-ene isomers. Thus, employing Grignard reaction of a 20-ketone and subsequent hydrogenation of the products is a somewhat impractical route for sterols because of the complexity of the product mixtures in each step. This sequence was used for the first total syntheses of cholesterol[32-34] and, undoubtedly, was partially responsible for the low yields in this portion of the syntheses. Similarly, low yields (15-30%) of the 20(22)-dehydro analogs of campesteryl acetate, its 24*S* epimer, β-sitosteryl acetate, and clionasteryl acetate (**100a-d**), respectively, were produced from

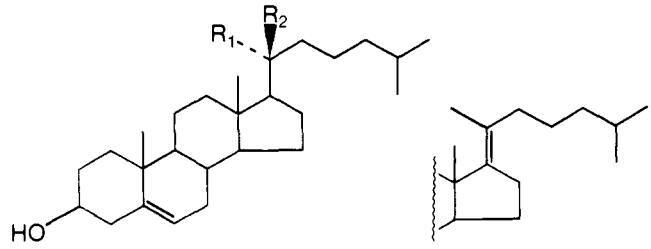


100a, R_1 = Me; R_2 = H
b, R_1 = H; R_2 = Me
c, R_1 = Et; R_2 = H
d, R_1 = H; R_2 = Et



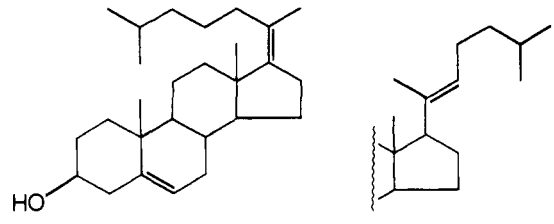
101

the reaction of pregnenolone acetate and the appropriate Grignard reagent, then dehydration of the resultant alcohol by acid.[81,82] On the other hand, the 20(21)-olefin **101** was formed[31] in fair yield (50%) by treating a 20-hydroxy Grignard product with $SOCl_2$-pyridine at 0 °C.



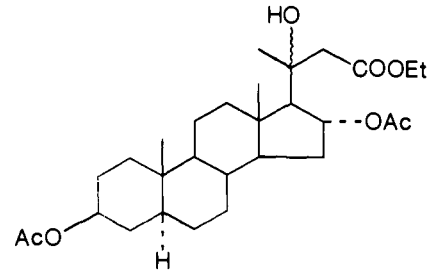
7, R_1 = Me; R_2 = OH
10, R_1 = OH; R_2 = Me

86

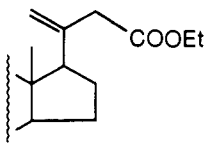


91 **102**

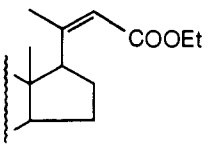
A detailed study by Nes et al.,[78] on the acid dehydration of both 20β(20*R*)- and 20α(20*S*)-hydroxycholesterol **10** and **7**, respectively, gave the (*Z*)-17(20)-**91**, the (*E*)-17(20)-**86**, and the (*E*)-20(22)-**102** double bond isomers in a ratio of 1:1:3. Also, Piancatelli and Scettri[83] found β-hydroxy ester **103**, which was an unspecified single isomer at C-20, dehydrated in $(CH_3)_2SO$ at 180 °C to a 1:6 ratio of the 20(21) double bond **104** and 20(22)



103

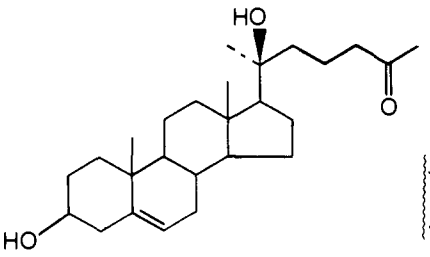


104

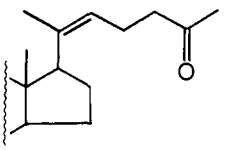


105

double bond **105** isomers. Recently,[92] acid dehydration of **106** was reported to give **107** in good yield.

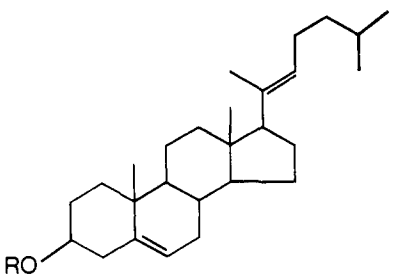


106

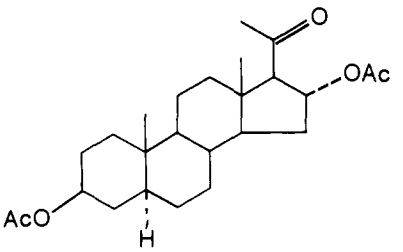


107

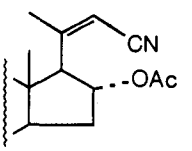
Wittig reaction of pregnenolone or its THP derivative with unstabilized ylides has been noted[84-87] to give exclusively the *E* isomer of 20(22)-dehydrocholesterol **108,** although 16-acetoxy ketone **109** with $(EtO)_2POCHLiCN$ is reported to yield nitrile **110** in 90% yield.[88]



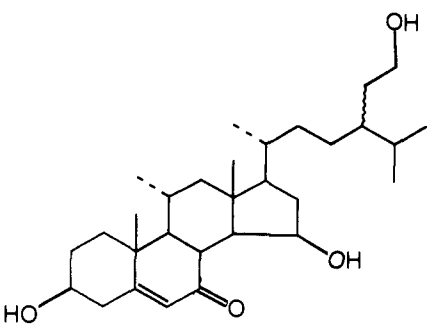
108 R = H, THP, or Bz



109

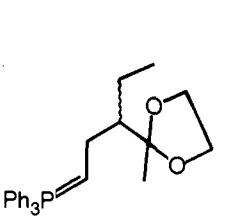


110

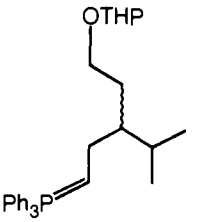


111

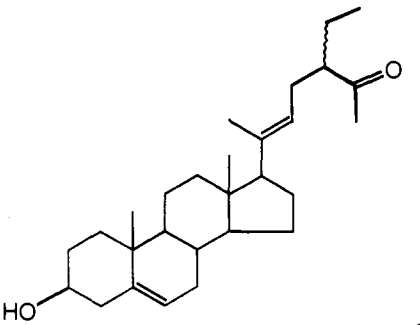
Model side-chain syntheses[238] of the system present in oogoniol (**111**) were also begun with a Wittig reaction of the THP of pregnenolone with ylides **112** and **113,** followed by acid hydrolysis, to form **114** and **115.** Yields of 80–85% were obtained for the *E* isomers with no detectable *Z* isomer. Wittig reaction[79,80,230] of 21-nor-20-ketone system **116** with $Ph_3P{=}CH_2$ has also been used to prepare 20(21)-enes **117.**



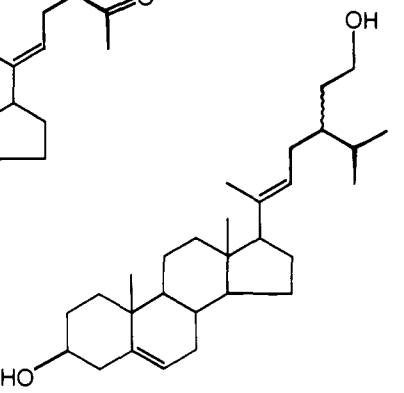
112



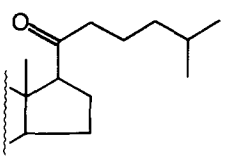
113



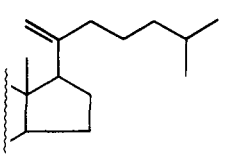
114



115

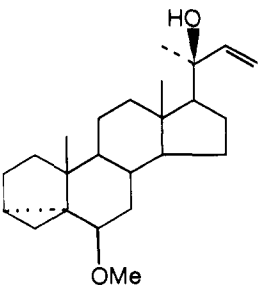


116

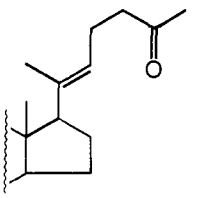


117

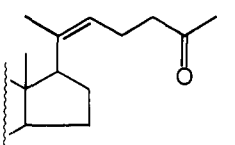
Diketene or ethyl acetoacetate addition to vinyl alcohol **118** forms a mixture of (*E*)-20(22)-**119** and (*Z*)-20(22)-**120** isomers in a 2:1 ratio.[89]



118



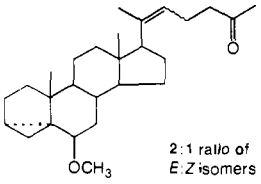
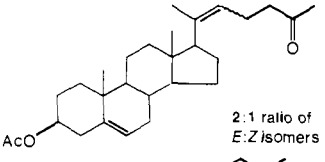
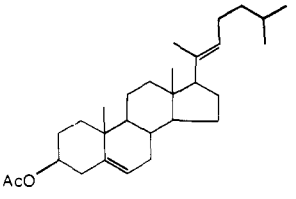
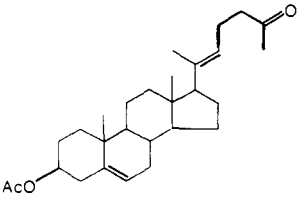
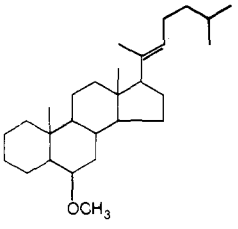
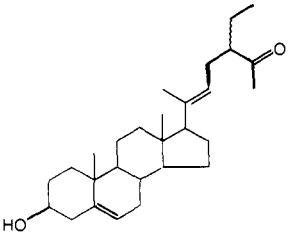
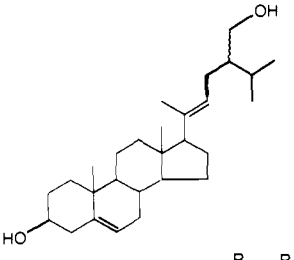
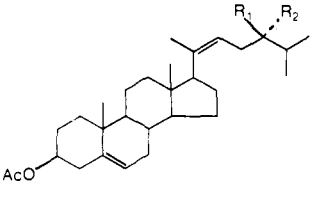
119



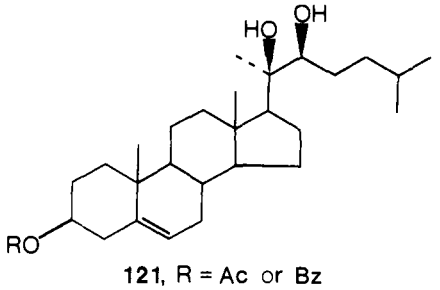
120

The pure *Z* isomer of 20(22)-dehydrocholesterol (**124**) has been most conveniently prepared by pyrolysis[90] of orthoformate **122** or by $(EtO)_3P$ reduction[47] of thiocarbonate **123,** both of which are formed from 20α,22α(20*R*,22*S*)-dihydroxycholesterol **121.** Alternatively, the *E* isomer **108** can be transformed[47] to the *Z* isomer **124** by epoxidation with *m*-chloroperbenzoic acid (mCPBA) to a 2:1 mixture of the (20*S*,22*S*)- and (20*R*,22*R*)-20,22-epoxides and treatment of the epoxides with the trimethylsilyl anion.[91]

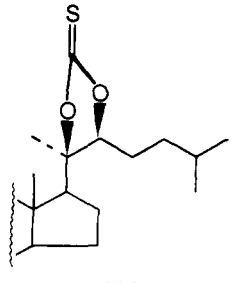
TABLE V. Hydrogenation of C-20(22) Double Bonds

Compound	Reaction conditions	Product	Ref
 2:1 ratio of *E*:*Z* isomers	*a*	1.5:1 ratio of 20*R*:20*S*	89
 2:1 ratio of *E*:*Z* isomers	*a*	20*R*; 50% yield	89
	*b*	20*R*; 80.5% yield reported; $[\alpha]_D$ −31.5°; *c*	84
As above	*b*	Mixture of C-20 epimers including 28% of 5,6-dihydro product	93
	*b*	20*R*; *d*; 90% yield	86
As above isomer not specified	*b*	20*R*; 78% yield	92
As above	*e*	20*R*-5α; 70% yield	92
	*b*	1:1 ratio of 20*R*: 20*S*; *f*	93
	*b*	2.8:1 ratio of 20*R*:20*S*	238
	*b*	2.8:1 ratio of 20*R*:20*S*	238
	*g*	20*R*; R_1 and/or R_2 = H, Me, Et	81, 82

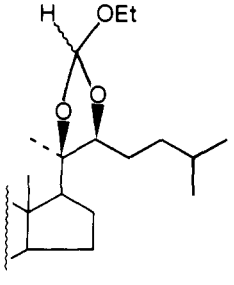
[a] PtO_2,EtOH. [b] PtO_2; dioxane–HOAc (50:1). [c] Handbook rotation for cholesteryl acetate $[\alpha]_D$ −47.4°. [d] Presence of 20 *S* epimer detected in mother liquors by GLC. [e] 10% Pd-C, dioxane-Ac_2O (50:1). [f] Isomer ratio determined by GLC. [g] 10% Pd-C, EtOAc.



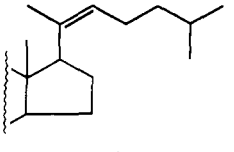
121, R = Ac or Bz



123



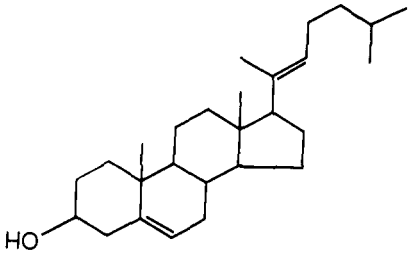
122



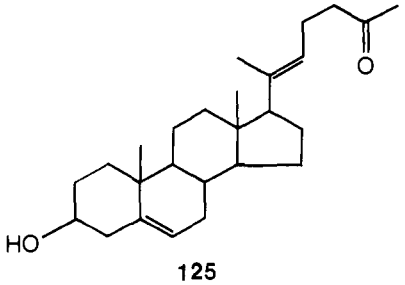
124

F. Hydrogenation of 20(22) Double Bonds

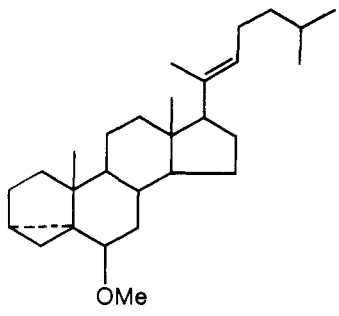
The hydrogenation of the 20(22) double bond has been studied recently by several groups, but the reported results differ considerably. In a detailed study Uskoković and co-workers[89] found a mixture of *Z* and *E* isomers (1:2 ratio) of **119** produced a 1.5:1 mixture of 20*R* and 20*S* products with Pt in EtOH indicating a nonstereospecific reduction of the *E* isomer, at least, occurred. Later, hydrogenation of 20(22)-dehydrocholesterol (**103**) over



108



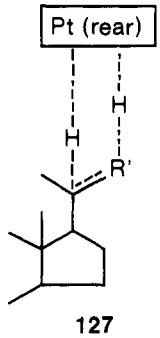
125



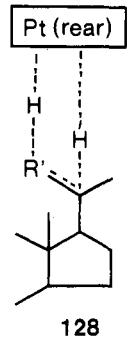
126

Pt in dioxane containing HOAc was reported to form cholesterol in 80.5% yield.[84] Similar high stereospecificity to a 20*R* product was noted when *E* isomer **125** was catalytically reduced under the same latter conditions.[86,92] Very recently, Nes et al.[93] again examined this reduction and indicated a 1:1 ratio of C-20 epimers results when the (*E*)-20(22) double bond of **126** is reduced under the same conditions. These results as well as other reductions of 20(22) double bonds are summarized in Table V. The marked differences between the results of very similar compounds are puzzling and, undoubtedly, further investigations will be needed to clarify the situation. In only two cases have the isomers formed been isolated and adequately identified. Also, it is surprising that a comparative analysis of the reduction of this double bond with the well-documented hydrogenations of 20(21) double bonds (see section IV.D) has not been made.

An attempt to interpret the steric course of the 20(22) double bond reduction has been made by Nes.[93] He postulates the reduction takes place by approach of the catalyst from the α side of the molecule and equal formation of two C-20 epimers results from two 17(20) conformers **127** and **128.** Trachtenberg et al.,[232] however, have pointed out the arguments on ground-state populations of the conformers are thermodynamically unsound, and the conformational implications made from NMR data are not convincing. Further conformational implications made from NMR data are not convincing. Further explanation in favor of his position by Nes[233] argues the reduction is analogous to the hydrogenation of 5(6) and 17(20) double bonds; however, the assumption of α attack by hydrogenation catalysts on the steroid ring system cannot be readily applied to side chains especially in view of results with the reduction of 4(5) double bonds and observations with homogeneous catalysts.



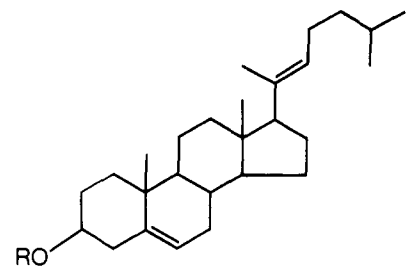
127



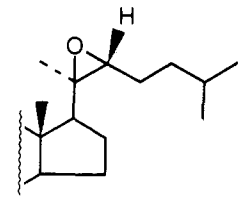
128

G. Preparations and Reactions of 20,22-Epoxides and 20,22-Diols

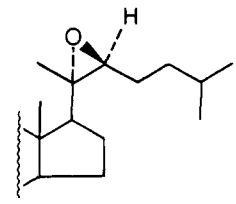
The interest in various 20,22-dihydroxycholesterols and 20,22-epoxycholesterols which have been implicated as biosynthetic intermediates in the cholesterol to pregnenolone conversion has prompted much of the studies on oxygenation of these two positions. Investigations on the epoxidation of diene **109** with mCPBA indicate the reaction proceeds regioselectively on the (*E*)-20(22) double bond in good yield (ca. 70%) to the 20*R*,22*R*-epoxide **129** and 20*S*,22*S*-epoxide **130** in about a 2:3 ratio.[85,87,90] A similar mixture of epoxides results when (*E*)-



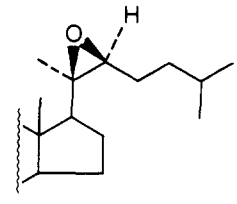
109



129



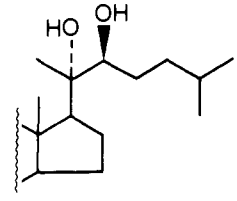
130



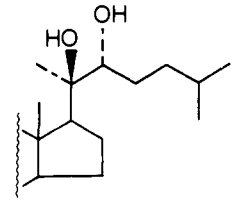
131

5α-cholest-20(22)-en-3β-ol was used.[85] The *Z* isomer **124,** on the other hand, yields[47,90] only the 20*R*,22*S*-epoxide **131** supposedly from approach of the reagent on the less sterically hindered side.[90]

OsO_4 hydroxylation of *E* isomer **129** and its corresponding 5α analog proceeds much more regioselectively yielding 20*S*,22*S*-diol **132** and 20*R*,22*R*-diol **133** in 10–17 to 1 ratios.[85,87,90] Diol **132** was also prepared from epoxide **131** by acid



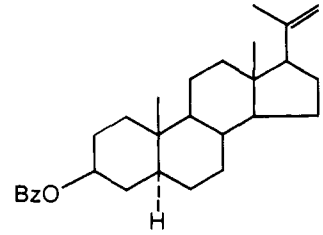
132



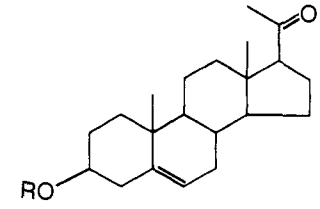
133

opening.[85] Epoxides not readily available by direct epodixation were prepared from 20,22-diols via selective mesylation at C-22 and nucleophilic displacement by the adjacent hydroxy group.[85,90]

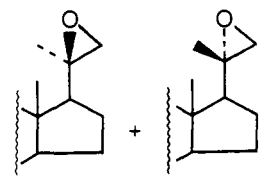
Epoxidation of 20(22)-ene **134** results in a 1:2 mixture of epoxides **135** and **136,** respectively,[94] comparable stereochemically to addition reactions of 20-ketones. Condensation[94,95] of 20-ketones **137a** and **137b** with $[Me_3SO]^+I^-$ or $Me_2S{=}CH_2$ gives rise to high yields (90%) of the 20*R* epoxides **138a** and **138b,** respectively, both of which have been transformed to 22-aldehyde **139** by $BF_3{\cdot}Et_2O$.



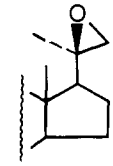
134



137a, R = THP
b, R = Ac

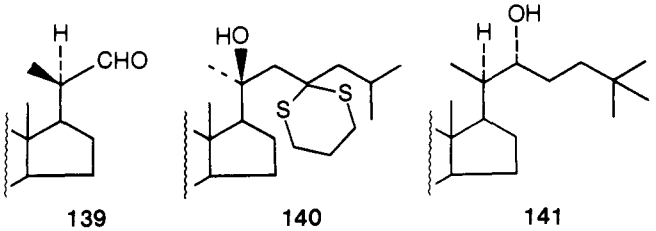


135 136

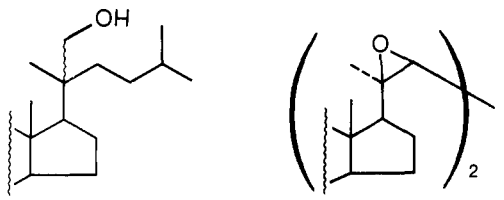


138

Interestingly, reaction of the lithio salt of 2-isobutyl-1,3-dithiane with epoxide **138a** forms (66% yield) the 20-hydroxy product **140,** while *i*-AmMgBr unexpectedly gives 22*R*-alcohol **141** in 80% yield,[94] most likely through intermediate formation of aldehyde **139.** Epoxide **138b** is, however, reported to produce 21-alcohol **142** and a dimer **143.**

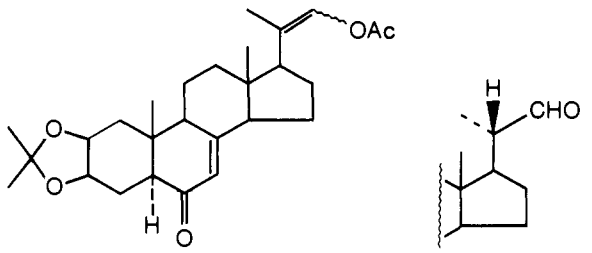


139 140 141

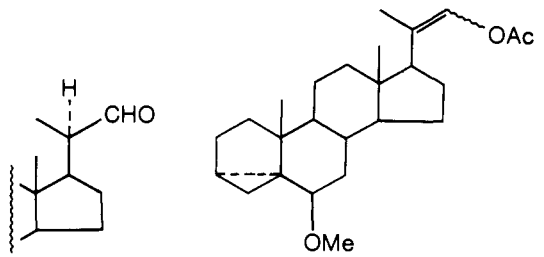


142 143

Enol acetate **144** has been epoxidized[97] with mCPBA and hydrolyzed to a 5:3 mixture of hydroxy aldehydes **145** and **146.** Similarly, epoxidation of *i*-steroid enol acetate **147** and corresponding rearrangement leads to a like isomeric mixture.[98]



144 145



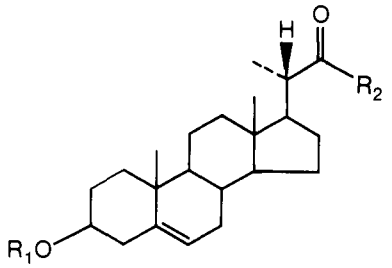
146 147

V. Reactions Involving Position 22

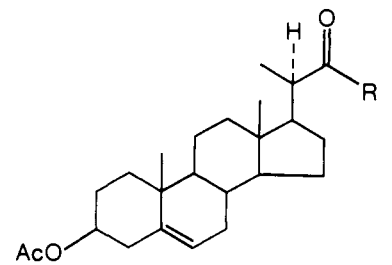
A. Organocadmium Reactions with C-22 Acid Chlorides

Acid **148a** conveniently obtained from a number of naturally occurring sterols, especially stigmasterol, by oxidation of the 22(23) double bond had been first used by Cole and Julian[72] to effect the synthesis of a variety of 22-ketosterols **148c.** They were made by addition of several cadmium reagents to acid chloride **148b.** They were not able, however, to remove the 22-oxo group because of difficulties encountered with the Wolff-Kishner reduction. Hayatsu[64] followed the same route with 20-isoacid chloride **149a** and obtained 20-isocholesterol (**149b**) albeit in low yield owing again to a poor Wolff-Kishner reduction.

The problems of removing the C-22 ketone was later circumvented by Romeo and Villotti.[99] By reducing the 22-ketone

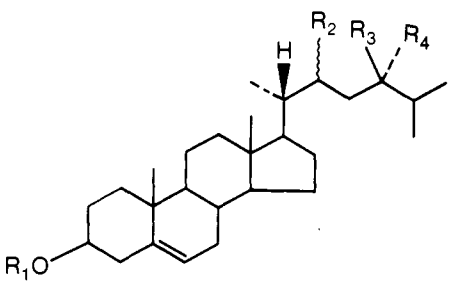


148a, R_1 = Ac; R_2 = OH
b, R_1 = Ac; R_2 = Cl
c, R_1 = Ac; R_2 = Me, Et, Ph, isoamyl, methyl
d, R_1 = Me; R_2 =

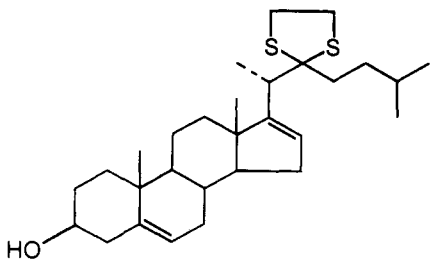


149a, R = Cl
b, R =

in **148d,** originally prepared by a cadmium reaction with the corresponding acid chloride, to alcohol **150a,** the latter could be removed as its tosylate **150b** to cholesterol methyl ether (**150c**). Later, this same group[100,101] synthesized 22,23-dihydrobrassicasterol (**150d**) and campesterol (**150e**) from the same starting acid and by the same route using cadmium reagents prepared from (2*R*)-2,3-dimethylbutyric acid and (2*S*)-2,3-dimethylbutyric acid, respectively. Yields in each step were quite good. Gut's group[74] also examined the Italians' method for removal of the 22-ketone in 22-oxo-16-dehydrocholesterol. In



150a, R_1 = Me; R_2 = OH; R_3 = R_4 = H
b, R_1 = Me; R_2 = OTs; R_3 = R_4 = H
c, R_1 = Me; R_2 = R_3 = R_4 = H
d, R_1 = R_2 = R_4 = H; R_3 = Me
e, R_1 = R_2 = R_3 = H; R_4 = Me

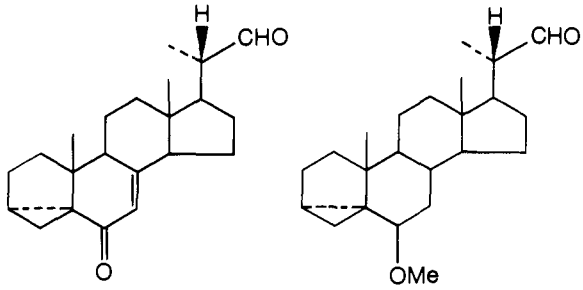


151

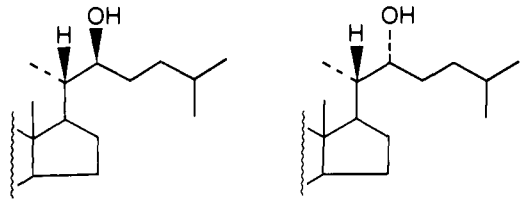
addition, they indicated the ketone removal to be more effective by Li–$EtNH_2$ reduction of thioketal **151.**

B. Reactions of C-22 Carbonyl Compounds and Nitriles with Organometallic Reagents

Addition of alkyl Grignard reagents to C-22 aldehydes to complete the side chain proceeds well in the absence of polar-directing groups and leads to a mixture of epimeric alcohols usually with preponderance of one epimer. For example, Barton et al.[102] obtained a 6:1 ratio of 22α(22*S*) isomer **154** to 22β(22*R*) isomer **155** upon addition of isoamylmagnesium bromide to aldehyde **152.** Similarly, Poyser and Ourisson[103]

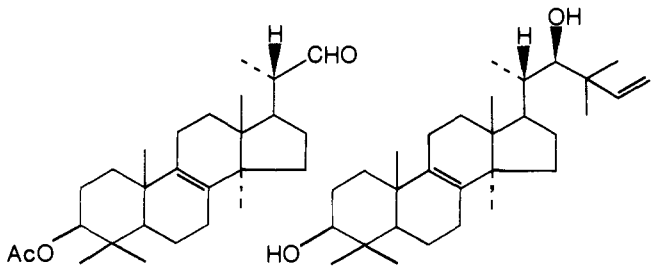


152 **153**



154 **155**

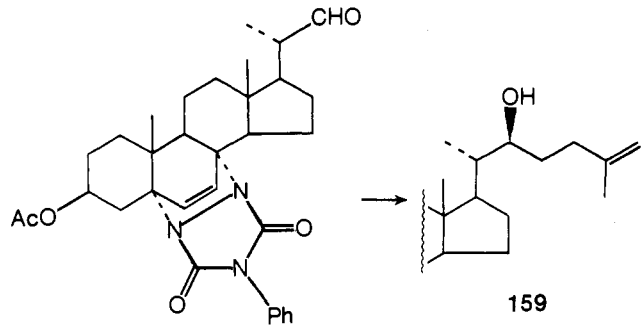
acquired the same 6:1 ratio of **154** to **155** with *i*-steroid aldehyde **153.** Ourisson's group[104] also found 22α(22*R*) alcohol **157** dominated the reaction product of lanostene-derived aldehyde **156** with the Grignard of 1-chloro-3-methyl-2-butene although



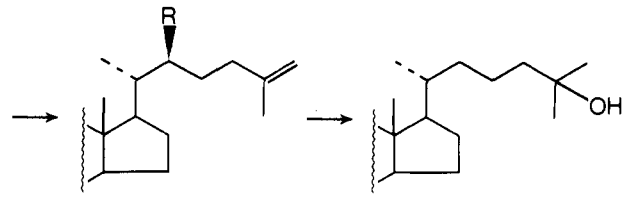
156 **157**

it did rearrange before addition occurred. In a synthesis[105] of 25-hydroxyprovitamin D_3 the reaction of the aldehyde moiety in adduct **158** with the Grignard of 4-chloro-2-methyl-1-butene favors the formation of mainly one hydroxy isomer **159** (82% yield) whose stereochemistry was not determined rigidly but was transformed to **160a** by formation of mesylate **160b** and reduction with $NaBH_4$. Introduction of a 25-hydroxyl group on **160a** by $Hg(OAc)_2$, then $NaBH_4$, and breaking of the triazolinedione adduct from **161** with $LiAlH_4$ completed the synthesis of the desired hydroxy analog of provitamin D_3 **162.**

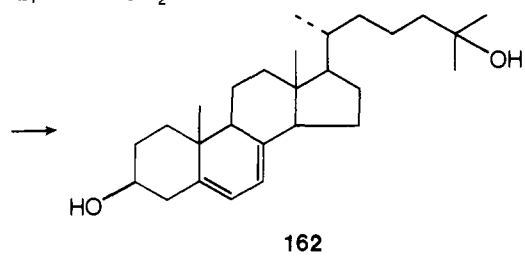
With 20-hydroxy-22-aldehydes[106] addition of *i*-AmMgBr takes place with a higher degree of stereospecificity and its steric course is greatly affected by the C-20 hydroxyl configuration as illustrated by the two epimers **163** and **166.** The 20α(20*R*) hydroxy aldehyde **163** yields a 9:1 mixture of 20α,22β(20*R*,22*R*)-diol **164** and 20α,22α(20*R*,22*S*)-diol **165,** while the 20β(20*S*)-hydroxyaldehyde **166** produces a 12:1



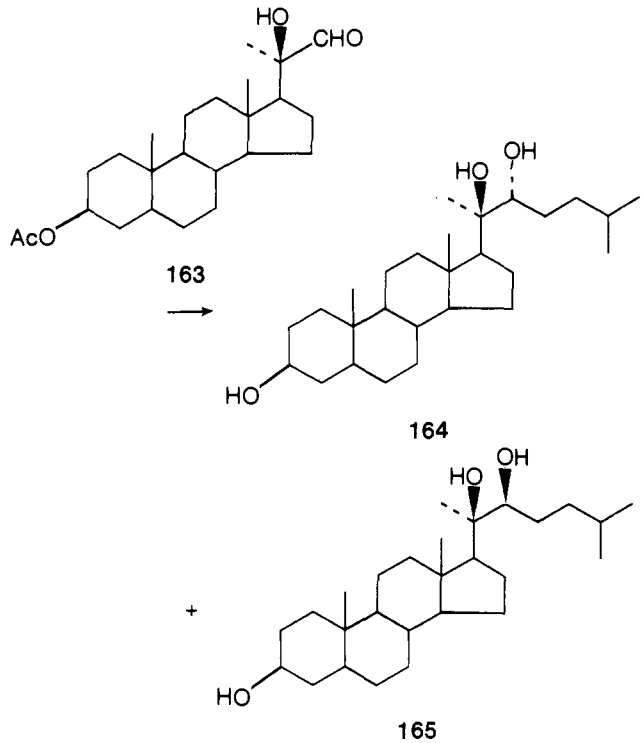
158 **159**



160a, R = H **161**
b, R = $MeSO_2O$–



162

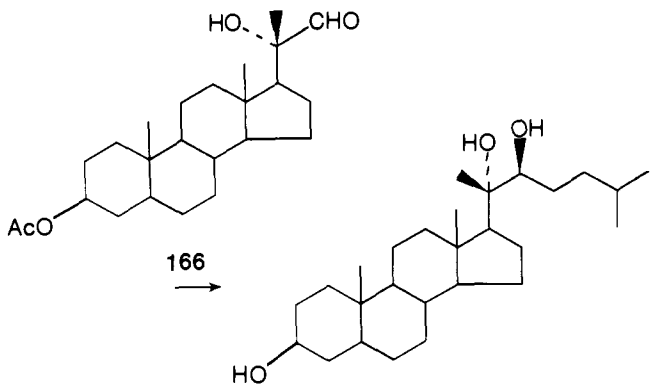


163 **164**

165

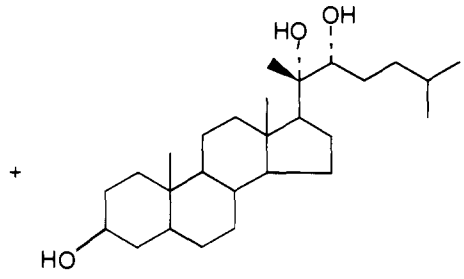
mixture of the 20β,22α(20*S*,22*S*)-diol **167** and the 20β,22β(20*S*,22*R*)-diol **168.**

An aldol condensation has also been utilized to complete the side chain.[107] Under the strong basic conditions (LDA) used to form the enolate of ketone **169,** the steroid aldehyde yields directly α,β-unsaturated ketone **170.** $NaBH_4$–pyridine reduction of the unsaturated ketone **170** yielded **171** as a mixture of epimers, and $LiAlH_4$ reductive removal of the ring B protecting group completed the formation of the hydroxy analogs of provitamin D **172.**

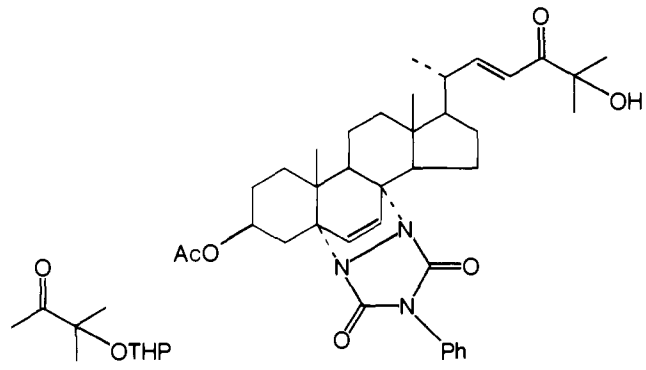


166

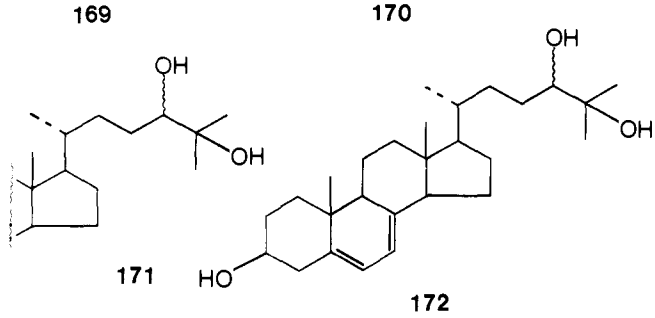
167



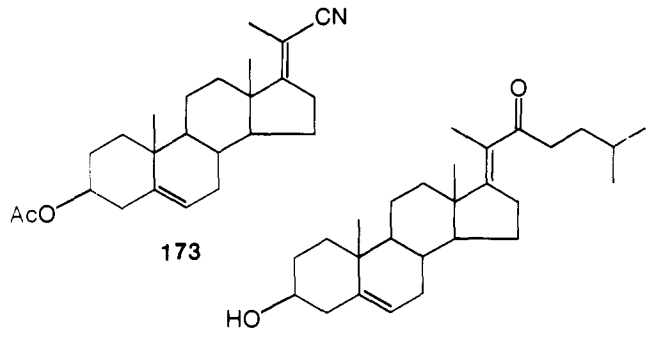
168



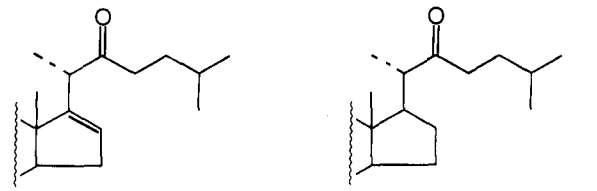
169 170



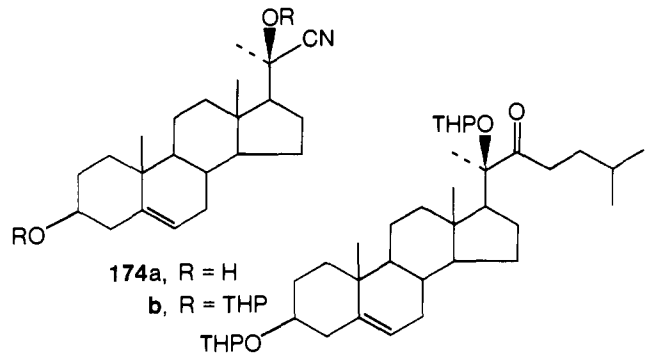
171 172



173 82

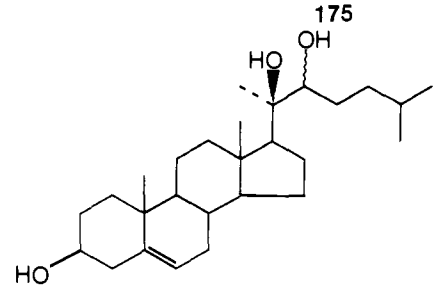


83 84



174a, R = H
b, R = THP

175



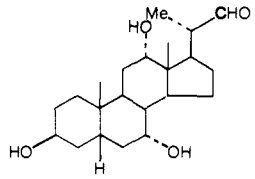
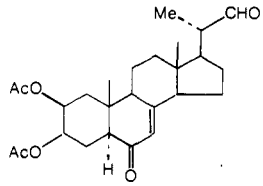
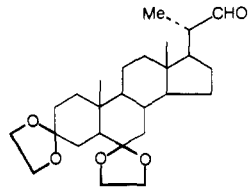
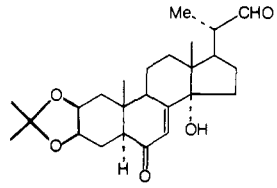
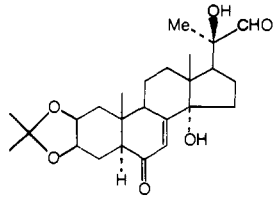
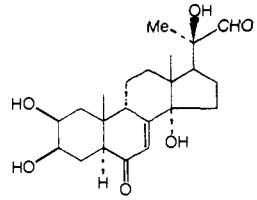
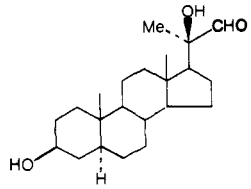
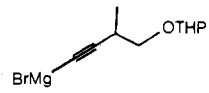
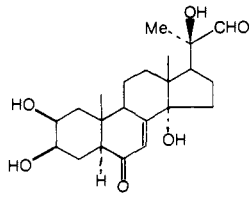
176

Addition of *i*-AmMgBr to 22-cyano moieties has also been a means of extending the side chain. This method had been first developed by Gut and his group[74] for the synthesis of cholesterol and 16-dehydrocholesterol. By starting with 22-cyano-17(20)-ene **173** they obtained 17(20)-en-22-one **82.** Deconjugation of the α,β-unsaturated ketone (see section III.C) to yield **83** followed by selective catalytic reduction of the 16-double bond gave 22-oxocholesterol **84.** Removal of the ketone group in both **83** and **84** by Li–$EtNH_2$ reduction of the corresponding thioketals completed the two syntheses. Later in their preparation of 20,22-dihydroxycholesterols[108] from pregnenolone, the intermediate 20α-hydroxy cyanide **174a,** obtained as the main product of cyanohydration of the ketone group, was reacted as its di-THP derivative **174b** with *i*-AmMgBr to form 22-ketone **175.** The sequence was completed when the ketone moiety was reduced and the protecting groups were removed to form **176** (see section IV.D for more on 22-ketone reduction).

Addition of the Grignard or lithio reagent of the THP derivative of 2-methyl-3-butyn-2-ol to a 22-aldehyde moiety **177,** then reduction of the triple bond in the resultant propargyl alcohols **178** and **180** to saturated chains **179** and **180,** respectively, has been the most popular method for introduction of the ecdysone **182** and crustecydsone **183** side chains (see Table VI). The reaction of acetylenic Grignards proceeds less stereospecifically than alkyl Grignard additions to 22-aldehydes. However, the predominating steric approach is the same; i.e., the 22α isomer **180** (R = H) is favored. Use of the lithium acetylenide reagent gives higher yields than the corresponding acetylenic Grignard reagent, but the reaction is far less stereospecific.[109] In the presence of a 20-hydroxy group, acetylenic Grignard reaction of **177** (R = OH) results in high stereoselectivity,[110] especially in the synthesis of inokosterone (**184**) (see last item in Table VI).[111]

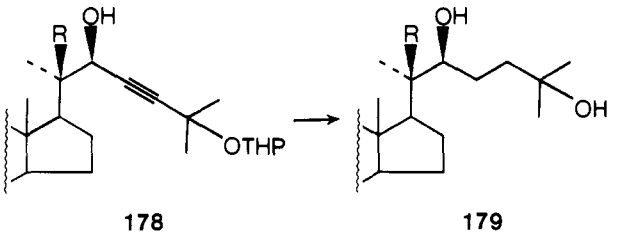
The various syntheses of ecdysones differed mainly in the choice of reaction sequence, e.g., introduction of the 14α-hydroxyl group before[97,110,112] or after[109,113-116] side-chain formation; in the use of acetonide[97,112] or acetate[109,113-116] protecting groups for the ring A hydroxyl moieties; or in the method utilized for formation of the 22-aldehyde group. In several instances rings A and B were manipulated while a 22-ester

TABLE VI. Reaction of C-22 Aldehydes with Alkyne Reagents (Ecdysone Side-Chain Syntheses)

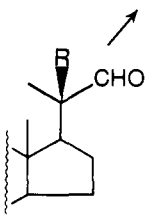
Starting Material	Reagent	Comments	Ref
	R = ≡—C(Me)—OTHP		
	RMgBr	*a*	120
	RMgBr or RLi	α isomer **179** predominates	113
As above	RMgBr	*a*	114
As above	As above	1:4.5 ratio of α:β isomers **179:181**	115
As above	As above	38% yield; β isomer **181** predominates	116
As above	EMgBr or RLi	*a*	109
	RMgBr	2:1 ratio of **179** to **181**	121
	RLi	1:1 ratio of α:β **179:181**	112
	RMgCl	3:5 ratio of α:β **179:181**	97
	RMgBr	β isomer **181** predominates	110
		β isomer only indicated	111
	As above	β isomer only indicated	111

[a] C-22 hydroxy isomer ratio not given.

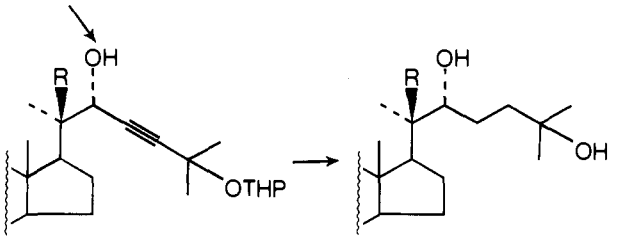
moiety **184** was present; later it was converted to the requisite aldehyde group by $LiAlH_4$ reduction to alcohol **186** and oxidation[97,112] of **186** by the Moffatt method,[117] or by hydride reduction of amide[114,115] **187** formed from the corresponding acid and carbonyldiimidazole.[118,119] Alternatively, the 22(23) double bond system **188** originally present in stigmasterol was left intact while



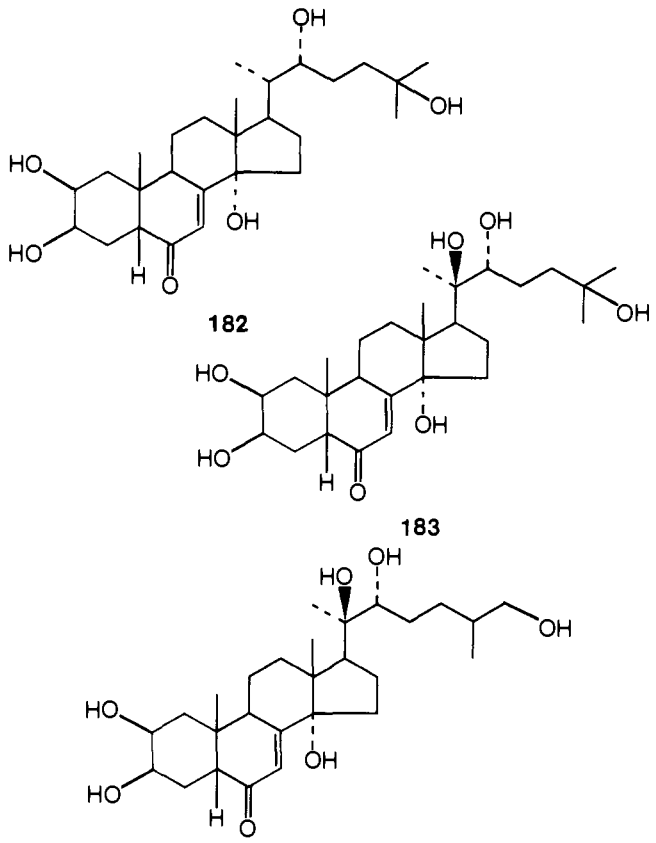
178 179



177



180 181

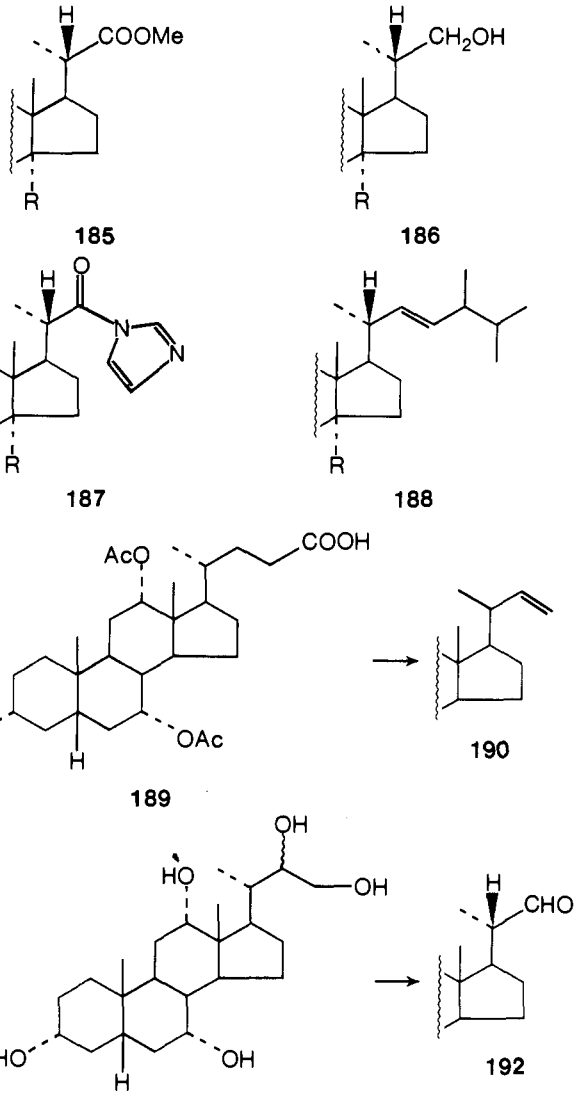


182 183 184

rings A and B were transformed; and when addition of the side chain was desired, the double bond was ozonized to yield the aldehyde.[113,116]

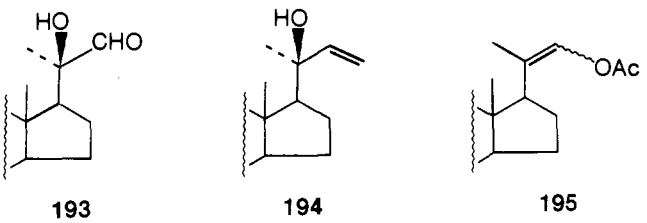
For some model studies[120] on the synthesis of the ecdysone side chain the cholic acid **189** side chain was converted to 22-aldehyde **192** by $Pb(OAc)_4$-$Cu(OAc)_2$ decarboxylation to **190,** glycol formation **191** with alkaline hydrogen peroxide, and $Pb(OAc)_4$ cleavage of glycol **191** to give **192.**

For crustecdysone (**183**) the needed 20-hydroxy-22-aldehyde system **193** was obtained either by ozonolysis[116] of the allylic



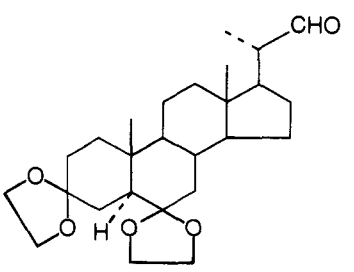
185 186 187 188 189 190 191 192

alcohol **194** (see section III.A) or epoxidation and hydrolysis[97] of enol acetate **195** (see section III.G).

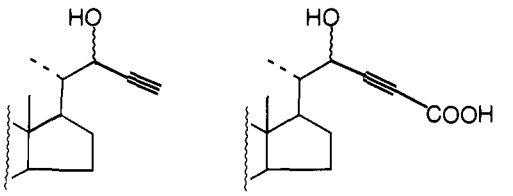


193 194 195

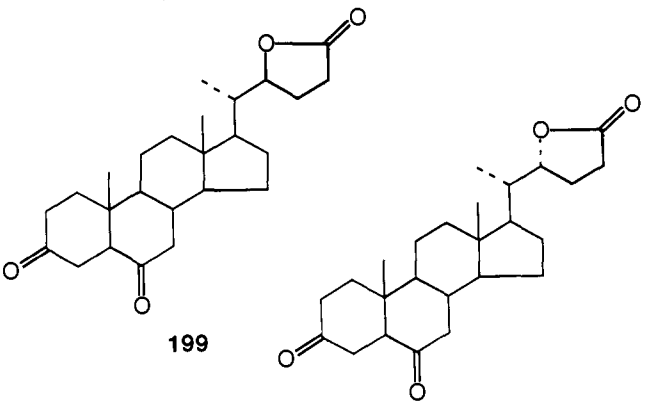
Instead of introducing the complete unit required for the ecdysone side chain in one step, Mori et al.[121,122] examined a stepwise procedure. By starting with aldehyde **196** obtained from stigmasterol, they added an acetylene moiety to secure propargyl alcohol **197.** Formation of an acetylene Grignard on **197** with MeMgBr and addition of CO_2 gave acid **198.** The triple bond was



196



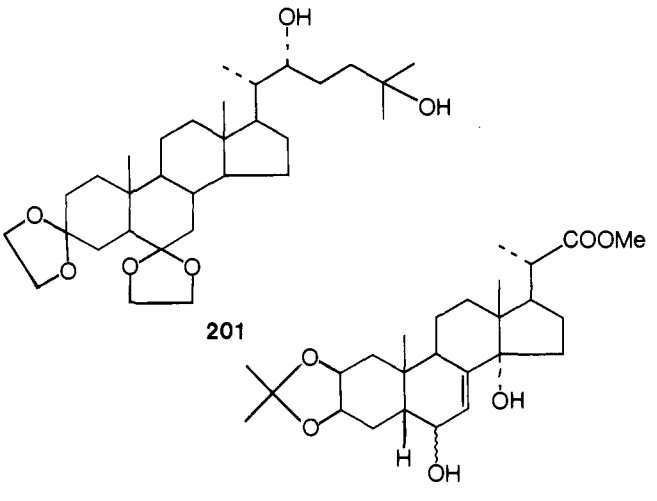
197 198



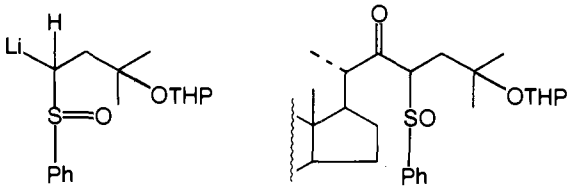
199 200

catalytically reduced, and the ketal groups were hydrolyzed to form a mixture of two isomeric lactones **199** and **200** in a 2:1 ratio indicating original formation of **197** was in favor of the *S* isomer. The ecdysone side chain **201** was then completed by reketalization of the 3- and 6-ketones and MeMgBr reaction of the lactone system.

An interesting variation[123] of the ecdysone side-chain attachment was done by adding lithio sulfone **203** to ester **202** to yield 22-ketone **204.** Subsequent removal of the sulfone group with Al(Hg), $LiAlH_4$ reduction of the 22-ketone, and oxidation of



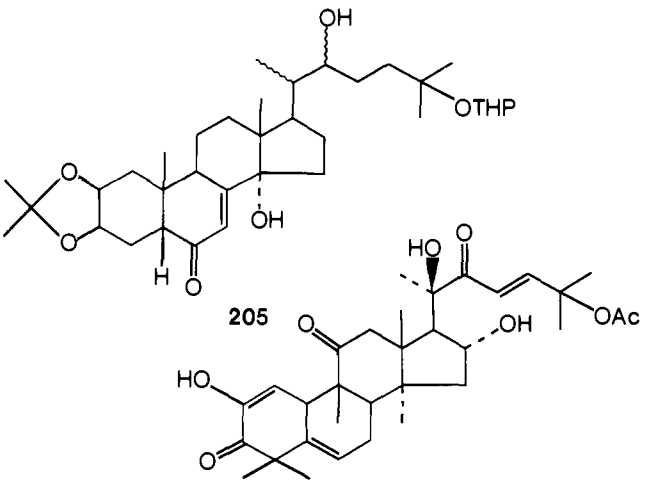
201 202



203 204

C-6 with MnO_2 gave **205** which was converted by acid hydrolysis of the protecting groups to a mixture from which ecdysone was isolated in 12% yield along with C-20 and/or C-22 epimers. Apparently, the basic conditions caused enolization of the ketone in **204** toward position 20 before its reduction took place.

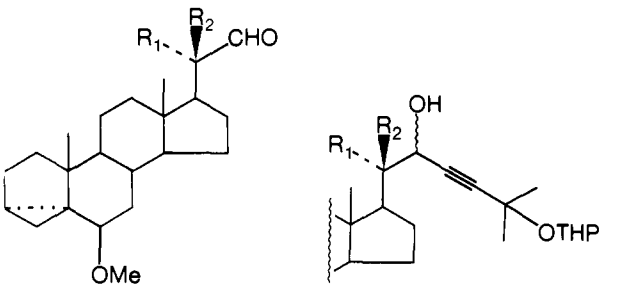
The Grignard of the THP ether of 2-methyl-3-butyn-2-ol has also been employed by Ourisson's group[98] for model studies of



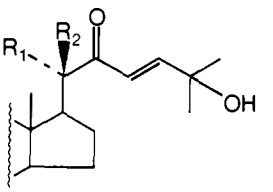
205

206

constructing the side chain of cucurbitacin I (**206**). Beginning with *i*-steroid **207a** and, later, with a mixture of **207b** and **207c** (see section III.G), the acetylene Grignard was added to the aldehyde moiety to produce the corresponding alcohols **208.** Acid cleavage of the THP ether, $LiAlH_4$ reduction of the triple bond, and oxidation of the 22-alcohol group with Fetizon's reagent yielded the planned side chains both without the hydroxy group **209a** and with the 20-hydroxyl group **209b** and **209c** as a mixture from which the appropriate C-20 isomer was isolated.



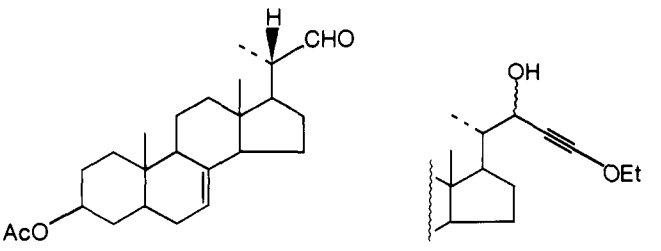
207 208



209

a, R_1 = Me; R_2 = H
b, R_1 = Me; R_2 = OH
c, R_1 = OH; R_2 = Me

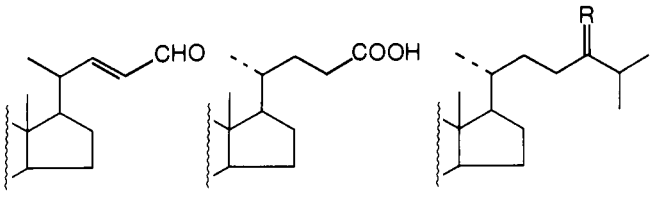
A 7,25(28)-stigmastadienol was prepared by Sucrow and Radüchel[124] by initially extending the chain through addition of the Grignard of ethoxyacetylene to aldehyde **210,** then converting the resultant adduct **211** to unsaturated aldehyde **212.** Catalytic



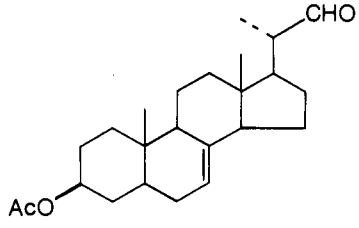
210 211

reduction of **212,** followed by oxidation gave cholenic acid (**213**), which could be reacted as its acid chloride with diisopropylcadmium to 24-ketone **214a.** A Wittig reaction of the 24-ketone then completed the synthesis of **214b.**

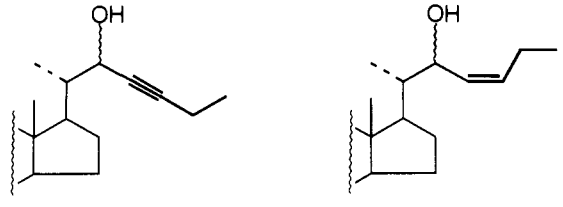
For the formation of some 22,25-stigmastadiene molecules, Sucrow and workers[125,126] started with an acetylene Grignard



212 213 214a, R = O
b, R = CHMe

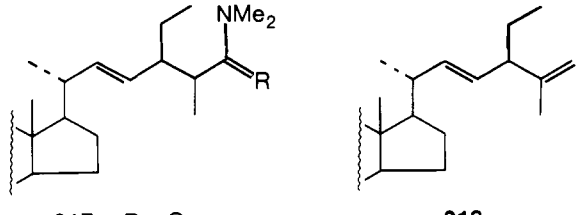


210



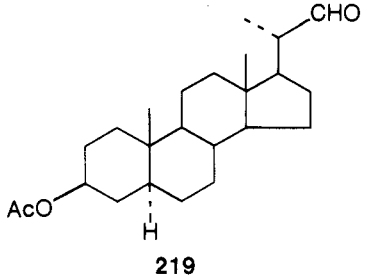
215 216

in the initial step of a new method for creating the side chain. In their first report,[125] they added the Grignard of ethylacetylene to the 7-dehydroaldehyde **210** and acquired alcohol **215** as a mixture of epimers. Reduction of the triple bond over Lindlar catalyst then gave rise to allylic alcohol **216.** Condensation of the enol ether of *N,N*-dimethylpropanamide with **216** and Claisen rearrangement formed **217a.** By reducing the amide moiety of **217a** to amine **217b** and subjecting the latter to a Cope elimination as its amine oxide resulted in the desired side chain **218.**



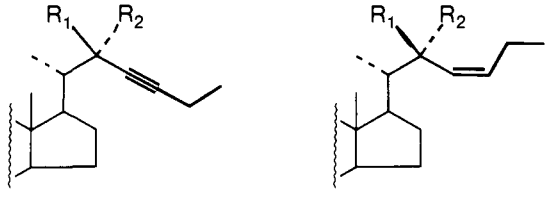
217a, R = O
b, R = H_2 218

Later,[126,127] utilizing separately the two C-22 epimers **220** formed from aldehyde **219,** the same reduction, condensation, and rearrangement sequence yielded four isomers. The 22*R*



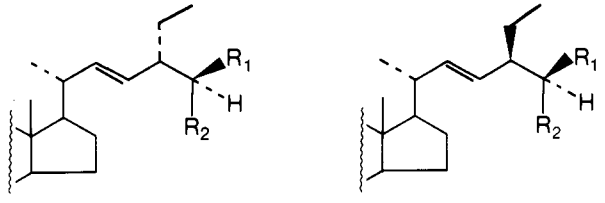
219

allylic alcohol **221a** gave two 24*S* diastereomers **222;** and the 22*S* alcohol **221b** gave two 24*R* diastereomers **223.** Reduction and Cope elimination as before eventually resulted in the side chain dienes **224** which could be selectively reduced to two C-24 epimeric poriferstenols (**225**) with $(Ph_3P)_3RhCl$ or completely saturated to the 5α-poriferstanols (**226**) by hydrogenation over platinum.



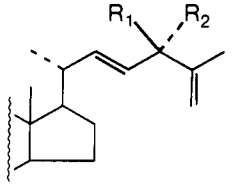
220 221

a, R_1 = OH; R_2 = H
b, R_1 = H; R_2 = OH

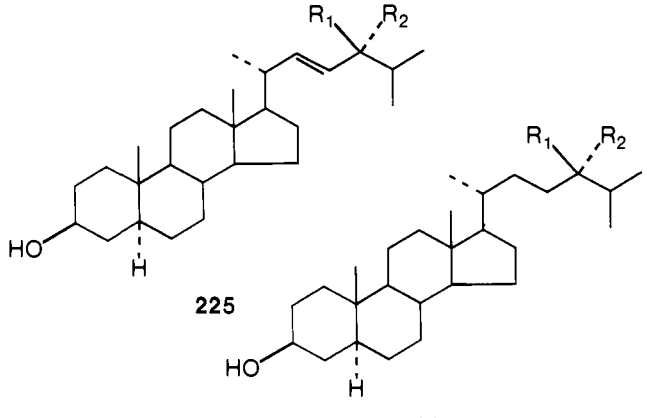


222 223

a, R_1 = Me; R_2 = $CONMe_2$
b, R_1 = $CONMe_2$; R_2 = H



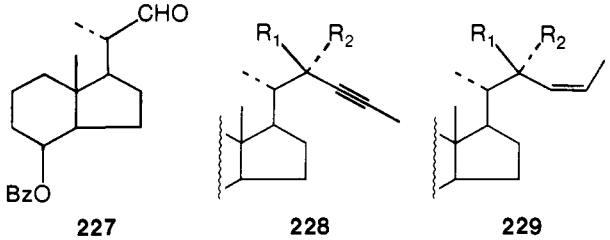
224a, R_1 = H; R_2 = Et
b, R_1 = Et; R_2 = H



225 226

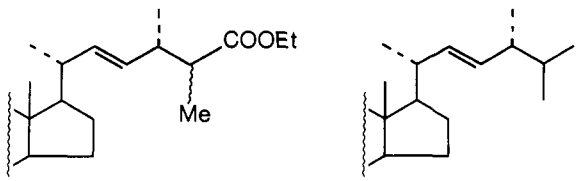
a, R_1 = H; R_2 = Et
b, R_1 = Et; R_2 = H

A related approach also produced the side chain in a total synthesis of ergocalciferol (vitamin D_2).[234] The sequence began with the addition of 1-propynemagnesium bromide to aldehyde **227,** forming a 1.3:1 ratio of 20*S* propargyl alcohol **228a** to the 20*R* isomer **228b.** Continuing the preparation by reduction of **228** over Lindlar catalyst yielded the cis allylic alcohols **229**



227 228 229

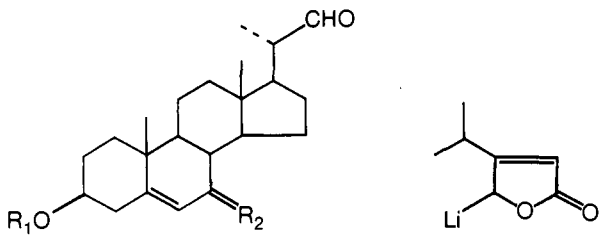
which were then subjected to Claisen rearrangements with ethyl orthopropionate to give **230.** The ester moiety at C-26 was then removed to achieve the requisite side chain **231.**



230 231

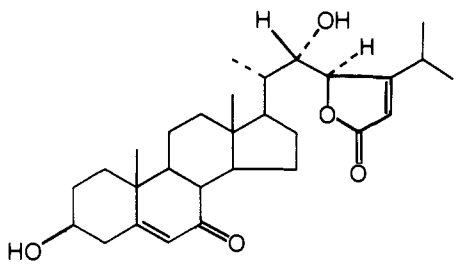
a, R_1 = H; R_2 = OH
b, R_1 = OH; R_2 = H

For the synthesis of antheridiol (**234**), the sex hormone of an aquatic fungus, addition to the 22-aldehyde moiety of **232a** and its 7-oxo derivative **232b** of lithiated lactone **233** was studied.[128] Yields were much better for the non-C-7 oxygenated aldehyde **232a** (>70%) than for its 7-oxo analog **232b** (40%). Later,[129]



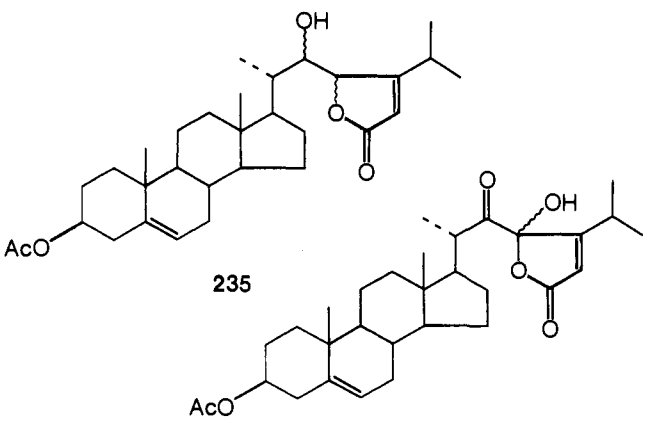
232a, R_1 = OAc; R_2 = H_2
b, R_1 = THP; R_2 = O
c, R_1 = THP; R_2 = H_2

233



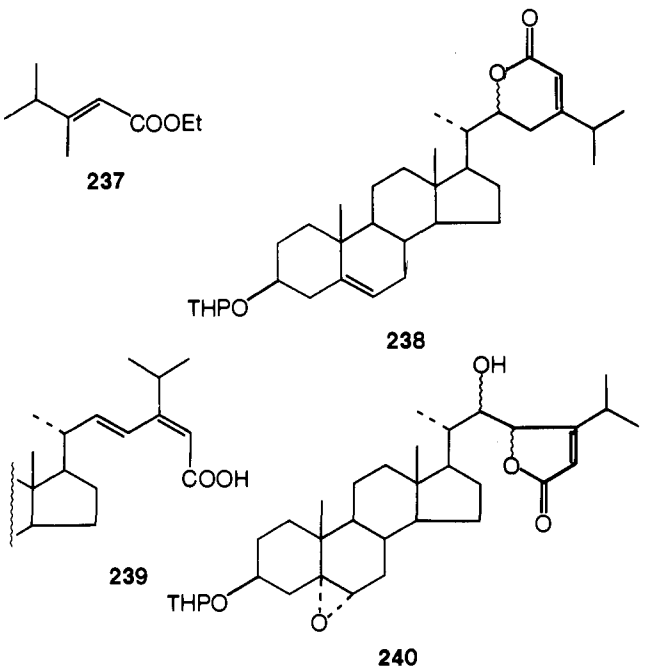
234

separation of four diastereomers (the 22*R*,22*S* isomer predominated) of the **235** produced thusly, and transformation of the 22*S*,22*R* (natural) isomer into antheridiol by photochemical oxygenation of C-5 and rearrangement of the resultant peroxide, were accomplished. The total yield of antheridiol could be raised[130] by oxidation of the unnatural isomers with Jones' reagent and oxygenation to lactol **236** which was then reduced by $NaBH_4$.



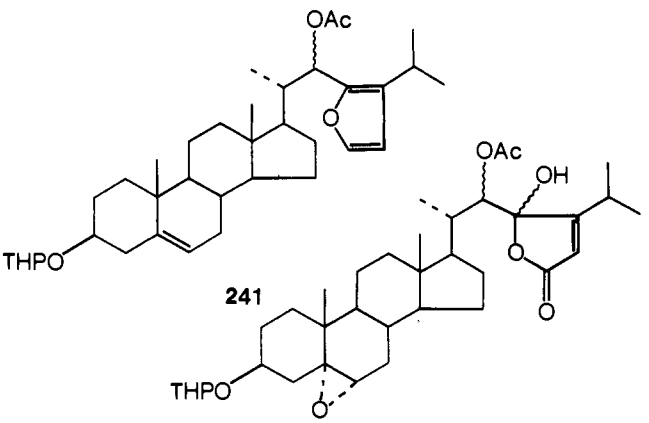
236

In an early synthesis by the Syntex group,[131] a slightly different approach was taken. The THP aldehyde **232c** was treated with the anion of **237** made by Ph_3CLi to yield the six-membered lactone **238** in 24% yield. Hydrolysis of the lactone ring and

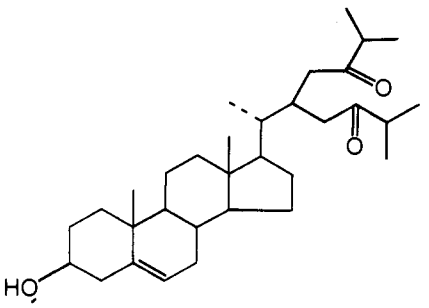


dehydration with acid gave conjugated acid **239** which, when treated with mCPBA, formed the five-membered lactone **240.** Osmylation of the 22(23) double bond in **239** was found to give better yields of the lactone.[132] Subsequent steps to secure antheridiol (**234**) included removal of the 5,6-epoxide by Zn–NaI–HOAc and formation of the 7-keto system as above.

A second synthesis[132] was begun by peroxide oxidation of the furan ring in **241,** which was introduced by addition of 2-lithio-3-isopropylfuran to **232c,** then acetylation. Reduction of the lactol system of **242** by $NaBH_4$ and removal of the 5,6-epoxide moiety formed the same isomeric mixture of intermediate **235,** which was converted to antheridiol as before.



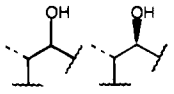
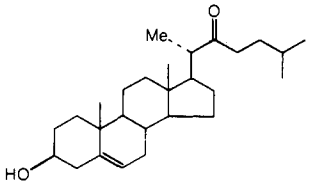
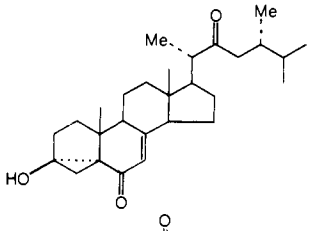
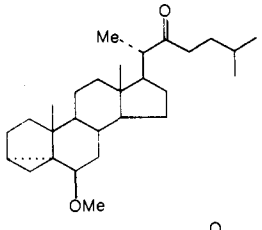
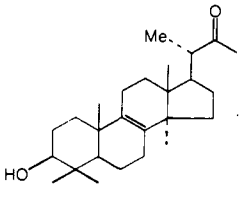
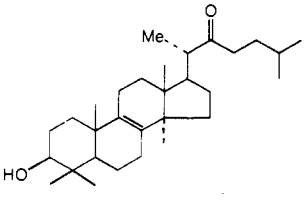
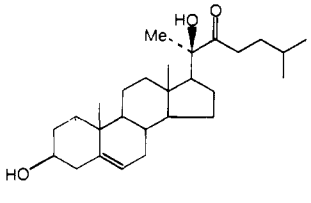
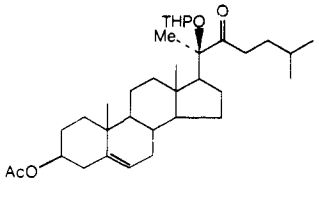
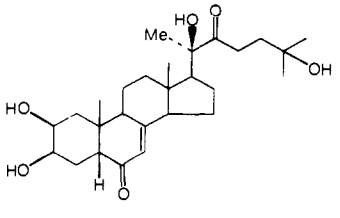
242



243

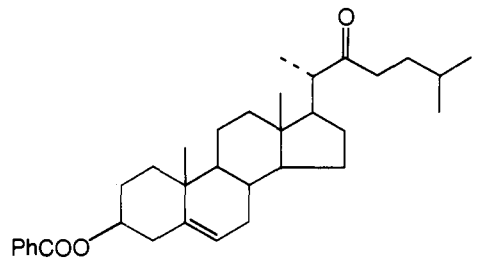
Attempts to condense an aldehyde **232a** with methyl isopropyl ketone in the presence of base gave only an unwanted product **243** in low yield.[133]

TABLE VII. Reduction of C-22 Ketones

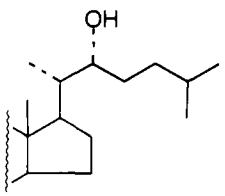
Starting material	Reducing agent	Alcohol isomer ratio 22β(*R*) to 22α(*S*)	Ref
			
	$NaBH_4$	1:3	73
	$LiAlH_4$	1:7; C-6 position reoxidized with MnO_2	102
	$LiAlH_4$	1:3; determined by TLC	102, 103
	$LiAlH_4$	1:4	136
	"Hydride"	1:2	222
	$NaBH_4$	1:6–7	87, 90, 108
As above	$Li–NH_3$	1:3 (~10%:30%); and equiv amts C-20 deoxy analogs by hydrogenolysis	108
As above	Na-*i*-PrOH	1:2.4	108
As above	$Li–EtNH_2$	1:1 and equiv amts of C-20 deoxy analogs	108
As above	$LiAlH(t\text{-}OBu)_3$	1:4	108
	Na–*i*-PrOH	1:3	108
	$LiAlH(t\text{-}OBu)_3$	Ratio not given	48

C. Reduction of C-22 Ketones

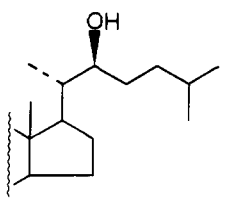
Earlier work[134] on hydride reduction of 22-oxocholesterol derivatives was reexamined by Caspi and workers.[73] They found instead that 22-oxocholesteryl benzoate (**244**) with $NaBH_4$ gives a high yield of the 22β(22*R*)-hydroxy-**245** and 22α(22*S*)-hydroxy-**246** cholesteryl benzoates in a 1:3 ratio. Similar preponderance of the α isomer was found during reduction of other C-22 ketosteroids. An extensive study of the reduction of (20*R*)-20-hydroxy-22-oxocholesterol by Gut's group[108] indicates that metal hydride reduction is more stereospecific than metal–amine or –alcohol reduction and that hydrogenolysis takes place to a large extent with the latter reagents (see Table VII).



244

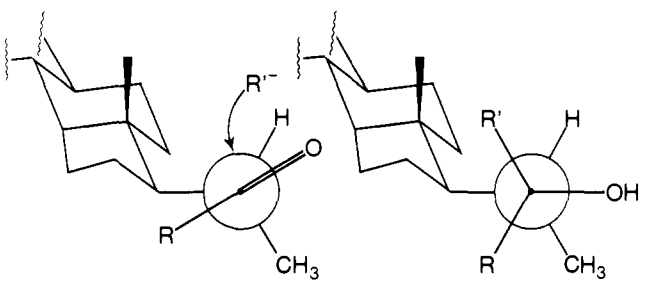


245



246

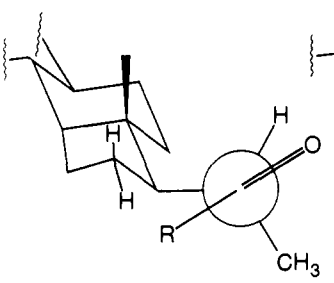
Surprisingly, reduction of C-22 ketones by hydrides and Grignard addition to a 22-aldehyde gives rise mainly to alcohols with the same configuration (22α or 22*S*). The preferred conformation for a C-22 ketone would be as shown by **247** and, according to the Cram rule,[135] addition of a nucleophile would take place from above yielding a product with the configuration indicated in **248.**



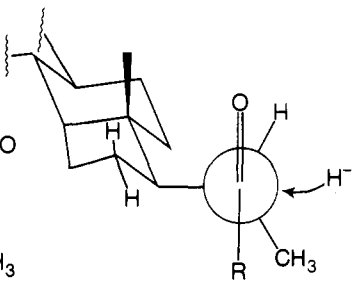
247 248

Grignard addition to an aldehyde, where R = H and R′ = alkyl, would proceed according to this scheme; on the other hand, hydride reduction where R = alkyl and R′ = H, does not obey the rule, but rather results in an "anti-Cram" situation. The abnormality, however, can be explained[136] if nonbonding interactions between the C-16 methylene and the C-23 methylene groups are considered (see **249**). Inspection of molecular models shows the more stable conformation for the 22-ketone to be **250,** so hydride attacks from the less bulky side would indeed give the observed products.[136]

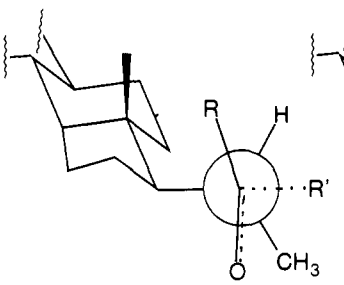
A similar conclusion[136] has been inferred from Felkin's analysis[137] of open-chain ketone reduction by $LiAlH_4$. In addition to carbonyl group torsional strain (Pitzer strain) involving partial bonds in the transition states, a substantial strain between fully formed bonds is also assumed, thus implying a staggered conformation for the transition state. Of the three most likely conformations **251–253** of the transition state for C-22 carbonyl



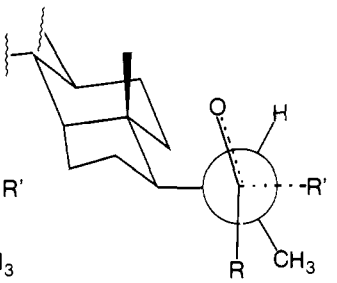
249



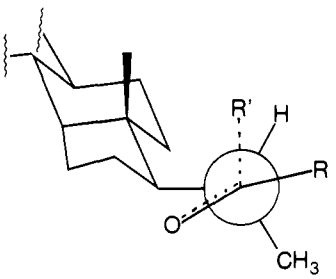
250



251



252

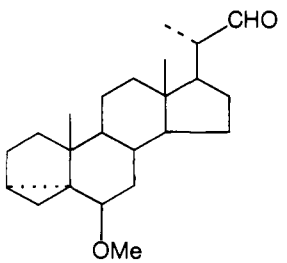


253

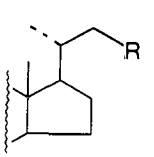
group reactions from the six possible, **251** would be the most favored while **253** would be the least. Grignard reaction with the 22-aldehyde (R ≪ R′) would then involve transition state **251** corresponding to the most favored state, whereas hydride reduction of a 22 ketone (R ≫ R′) involves the second most favored conformation **252.**

D. Chain Addition by Nucleophilic Displacement of Halogen at C-22

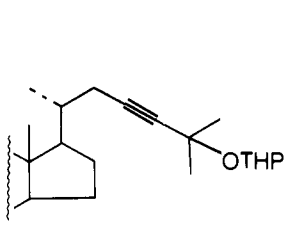
A few nucleophilic substitutions at C-22 have been employed to extend and/or complete the side chain of some sterols and hydroxysterols. In all instances, the halide or tosylate displaced has originated from an aldehyde or ester moiety at C-22. For example, the Hoffmann-La Roche group[138] started with aldehyde **151** obtained from stigmasterol and prepared tosylate **254a** by reduction with Red-Al and tosylation. Displacement by the lithio derivative of the THP ether of 2-methyl-3-butyn-2-ol (1 equiv, 65% yield, or 2 equiv, 90% yield) gave acetylene compound **255.** Use of the corresponding bromo Grignard or chloro Grignard reagents gave no reaction. Reduction of the triple bond in **255** and acid cleavage of the *i*-steroid system and THP ether yielded **256a** in 30% yield overall from stigmasterol. More recently,



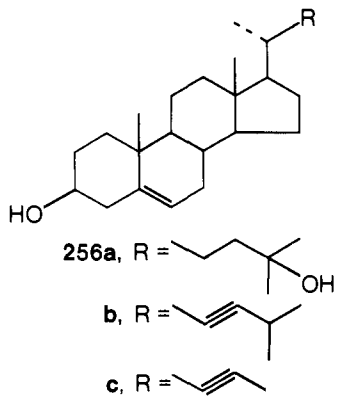
151



254a, R = OTs
b, R = I
c, R = Br



255



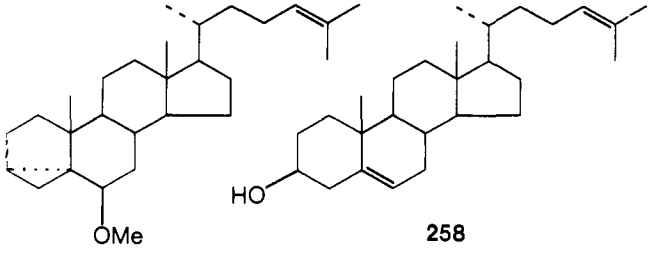
256a, R = OH

b, R =

c, R =

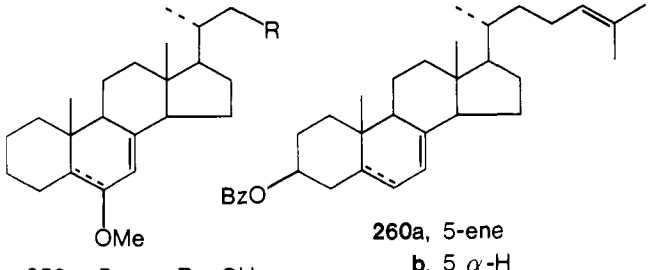
Steiner et al.[139] used tosylate **254a** to create two new marine sterols **256b** and **256c,** by nucleophilic substitution with 3-methylbutynyllithium and propynyllithium, then acid rearrangement of the *i*-steroid grouping.

Gut and workers[140] also employed tosylate **254a** as a starting point, but transformed it to iodide **254b** before coupling with π-(dimethylalkyl)nickel bromide[141] in 65% yield to obtain 24-ene **257,** which was converted to demosterol (**258**).



257 258

Caspi et al.[142] also prepared 24(25) double-bonded sterols. They began with diene alcohol **259a** and 7-dehydro alcohol **259b** and changed the hydroxyl groups to bromides (**259c** and **259d,** respectively) by tosylation, then displacement with LiBr, or better with Ph_3P and CBr_4. The desired sterols **260** were formed by



259a, 5-ene; R = OH

b, 5 α-H; R = OH

c, 5-ene; R = Br

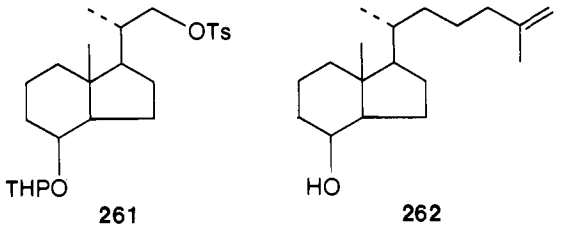
d, 5 α-H; R = Br

260a, 5-ene

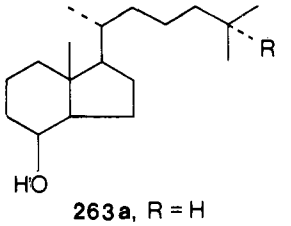
b, 5 α-H

coupling the bromides with γ,γ-dimethylallyl bromide in the presence of magnesium; however, yields were poor. Better yields for a Grignard coupling reaction were secured when tosylate **261** and the Grignard of 4-chloro-2-methyl-1-butene were reacted in the presence of dilithium tetrachlorocuprate[235] to **262.** Conversion of **262** to **263a** by catalytic reduction or to **263b** by acyloxymercuration-demercuration was accomplished afterwards.[234]

Another approach[143] to 25-hydroxycholesterol (**256a**) involved formation of an intermediate dithiane from iodide **254b** or bromide **254c** similar to a method by Lettré et al.[46] Lithiation of dithiane **264** and addition of isobutylene oxide resulted in completion of the chain **265.** Removal of the sulfur heterocycle with $TiCl_4$-$LiAlH_4$ and *i*-steroid rearrangement of **266** gave **256a.** In an alternate study[143] alkylation of **267** by **254b** or **254c** was unsuccessful.

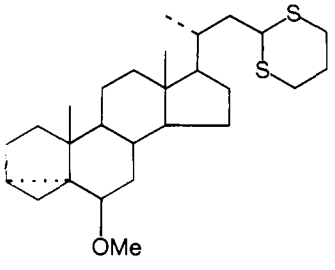


261 262

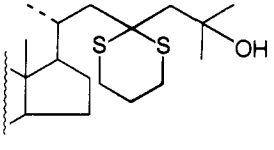


263a, R = H

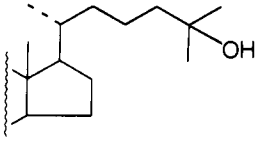
b, R = OH



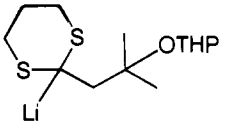
264



265

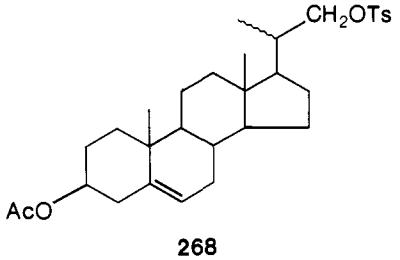


266

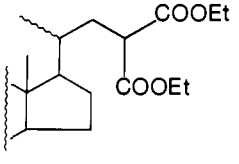


267

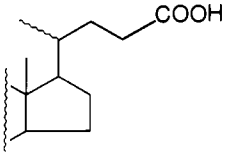
Alkylation of sodio diethyl malonate by a mixture of two C-20 epimers of tosylate **268** was another route used to extend the side chain.[64] Once diester **269** was hydrolyzed, it could be decarboxylated to cholic acid (**270**) which was eventually converted to fucosterol (**271**) and sargasterol (**272**) (see section VII.A).



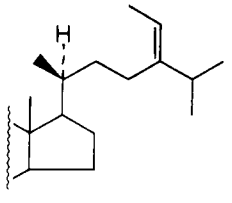
268



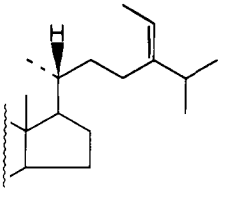
269



270



271



272

E. Preparation of 22(23) Double Bonds

Wittig reaction of a 22-aldehyde has been the most widely used method of essentially completing the major part of the chain

TABLE VIII. Wittig Reactions on C-22 Aldehydes

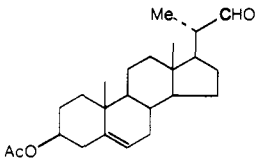
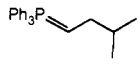
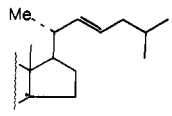
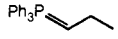
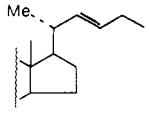
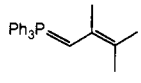
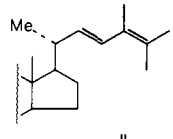
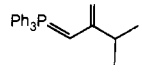
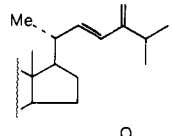
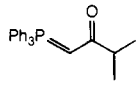
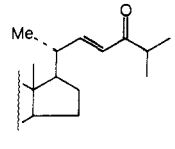
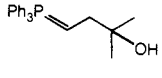
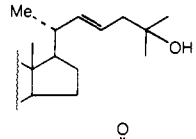
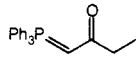
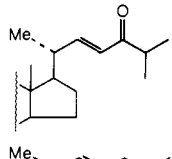
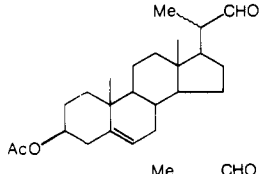
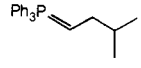
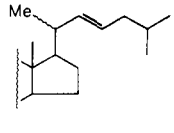
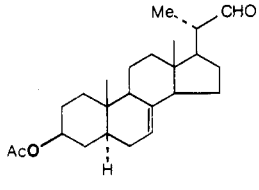
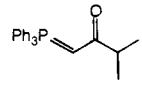
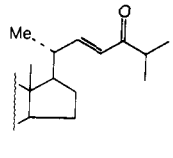
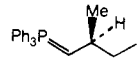
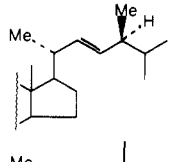
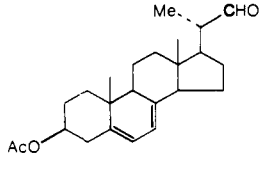
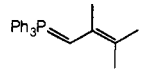
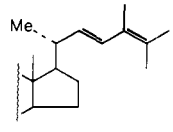
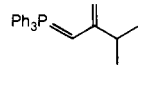
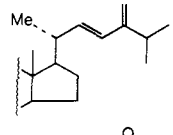
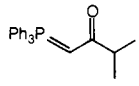
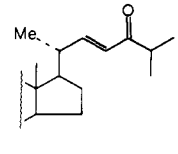
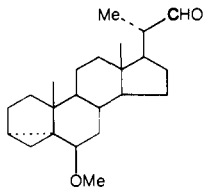
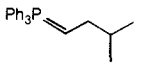
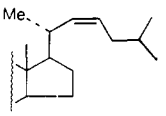
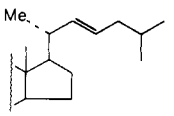
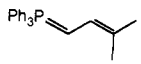
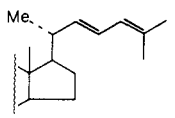
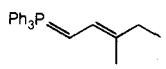
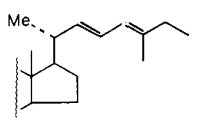
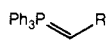
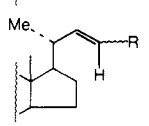
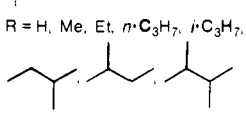
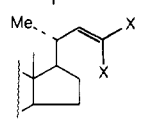
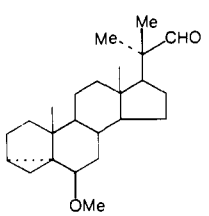
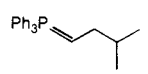
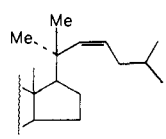
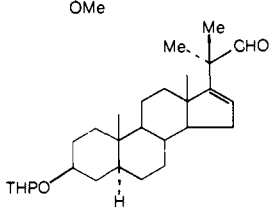
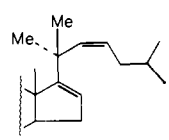
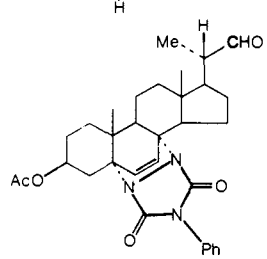
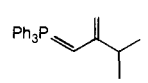
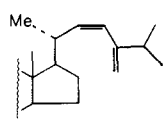
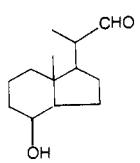
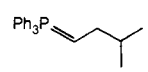
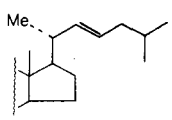
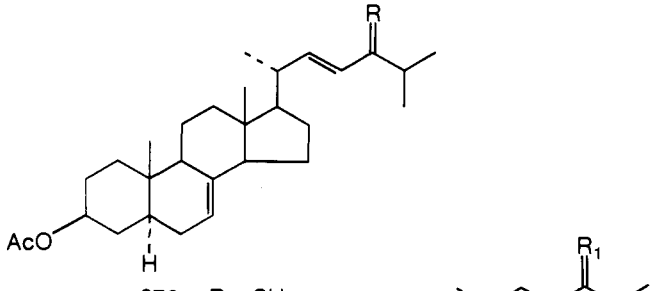
Starting aldehyde	Ylide	Product	Comments	Ref
				223
As above				223
As above			63% yield	146
As above			44% yield	146
As above			68% yield	146
As above			22(23) confign not specified	225
As above			82% yield	149
				71
				124, 148
As above				226
			73% yield	146
As above			54% yield	146
As above			Yield not given	146

TABLE VIII (*Continued*)

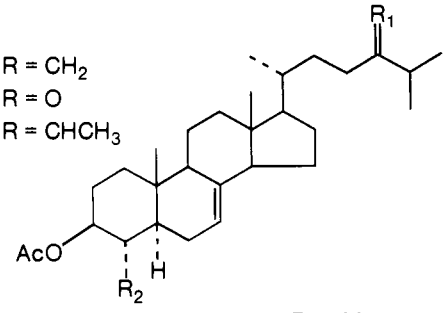
Starting aldehyde	Ylide	Product	Comments	Ref
			Corey modifn; *Z*, isomer almost exclusively	145
As above	As above	As above + 	2.5:1 ratio of *Z*:*E*	145
As above			Corey modifn; some *Z* isomer	145
As above			50% yield; Corey modifn	145
As above		 R = H, Me, Et, *n*-C_3H_7, *i*-C_3H_7, 	30–50% *Z* isomer; 50–70% *E* isomer	147
As above	$Ph_3P{=}CBr_2$ $Ph_3P{=}CCl_2$		X = Br, high yield X = Cl, 85% yield	162
				59
	As above		60% yield	59
				69
				224

while simultaneously forming a 22(23) double bond. The reaction with unstabilized ylides and in nonpolar solvents gives mainly (*E*)-22-olefins.[144] *Z* isomers can be made by the Corey modification, but not consistently.[59,145] There have been only a few comparative studies,[145-147] however, documenting exact isomer ratios (see Table VIII).

Although many of the Wittig reactions listed in Table VIII have been used for the preparation of essentially complete side chains, several cases have supplied the base unit for the further formation of 24-substituted sterols. For example, Fryberg et al.[146] prepared **273a** by Wittig reaction of ketone **273b** with $Ph_3P{=}CH_2$ as an alternate to a direct Wittig on the 22-aldehyde (see Table VIII). Similarly, they obtained the 24-ethyl analog **273c.** It should be noted that the structural assignment of the latter compound is based upon incorrect *Z* and *E* designations of a compound illustrated by these authors[146] to which it was compared.



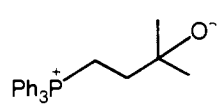
273a, R = CH_2
b, R = O
c, R = $CHCH_3$



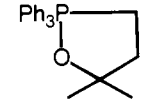
274a, R_1 = $CHCH_3$; R_2 = Me
b, R_1 = O; R_2 = H
c, R_1 = O; R_2 = Me
d, R_1 = H_2; R_2 = Me
e, R_1 = CH_2; R_2 = Me
f, R_1 = $CHCH_3$; R_2 = Me

Sucrow and his group have synthesized several natural sterols by similar procedures. One of their first syntheses[124] was formation of the 7,24(28)-diene sterol **274a** by reducing the 22(23) double bond of **274b,** then adding $Ph_3P{=}CHMe$ to the 24-ketone of **274b.** Similarly, 4α-methyl ketone **274c** was used later[148] to make lophenol acetate (**274d**) by a Wolff-Kishner reduction, 24-methylenelophenol acetate (**274e**) with $Ph_3P{=}CH_2$, and citrostadienol (**274f**) with $Ph_3P{=}CHMe$. A more complex preparation[149] of sterol **278b** started with reduction of ketone **275** to **276.** Addition of an isopropenyl moiety with the corresponding Grignard reagent yielded alcohol **277,** which was converted with PI_3 to iodide **278a.** The latter compound was not characterized, but directly reduced to the desired product **278b.**

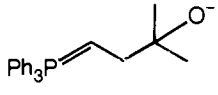
An interesting stereoselective Wittig reagent was recently devised by Salmond et al.[236] for the preparation of 25-hydroxy steroids. $Ph_3P{=}CH_2$ was reacted with isobutylene oxide to give adduct **279** which possesses either betaine structure **279a** or oxophospholane structure **279b.** Treatment of **279** with *n*-BuLi



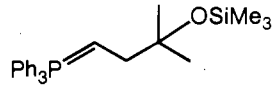
279a



279b

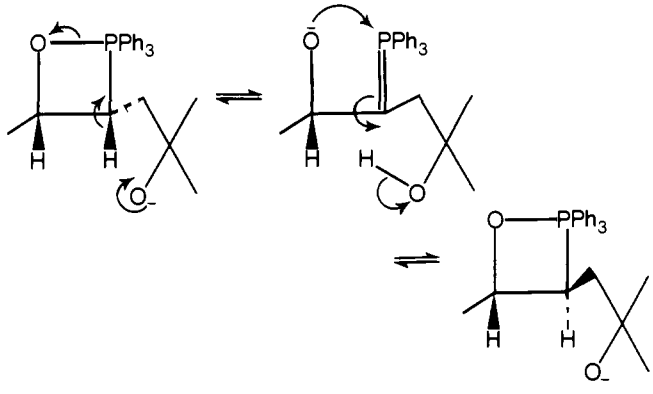


280

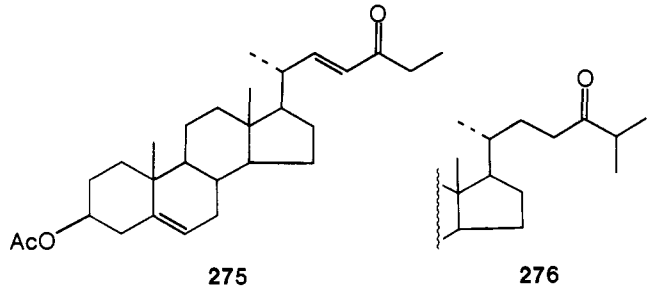


281

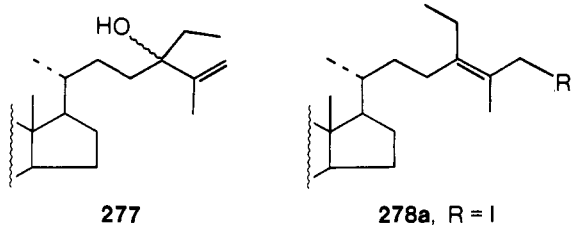
gives ylide **280** capable of reacting with aldehyde **153** without C-20 isomerization and with formation of *E*:*Z* 22(23) double bond isomers in a 85:15 ratio. Formation of the *E* double bond was explained by intramolecular betaine equilibration as shown below. The mechanism was supported by the fact that reaction of the silylated ylide **281** with aldehyde **153** gives a reverse *E*:*Z* ratio (15:85).



Double bonds at 22(23) have also been important intermediates for the completion of the side chain via nucleophilic displacement of their corresponding epoxides (see section V.G). Their formation includes addition of vinyl Grignards to 20-ketones (see Table III), Wittig reaction[103] of a 22-aldehyde with $Ph_3P{=}CH_2$ to form **282,** decarboxylation[104] of C-24 carboxylic acid **283** to the ene **284,** and, more recently, sodium amalgam reduction[58] of **285** to give **282.**

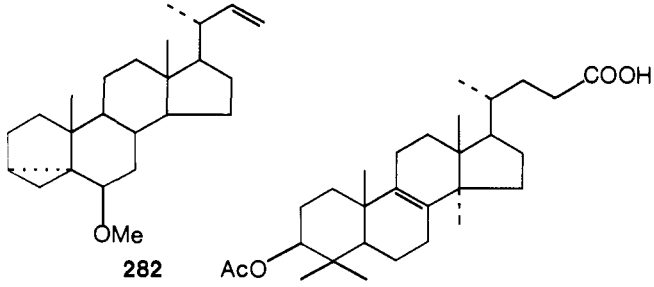


275 **276**



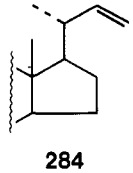
277

278a, R = I
b, R = H

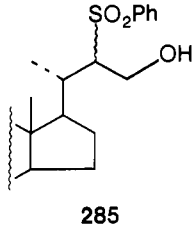


282

283



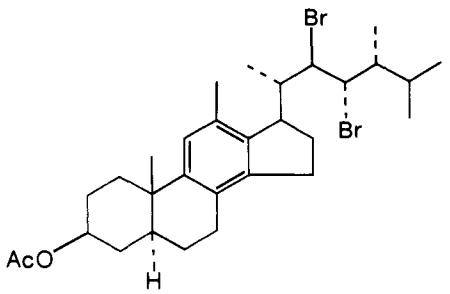
284



285

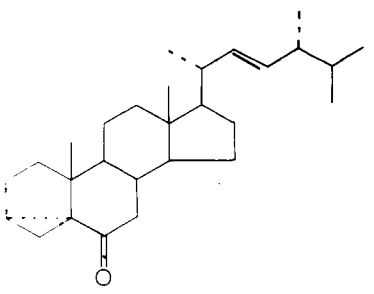
F. Electrophilic Reactions of Double Bonds at 22(23)

Addition of bromine or chlorine to a 22(23) double bond of several ergosterol derivatives gives one major dihalide product.[150-152] The structure of a dibromide **286** has been determined by x-ray crystallography.[153]

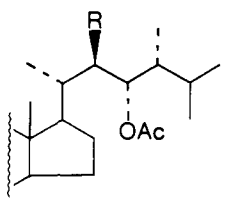


286

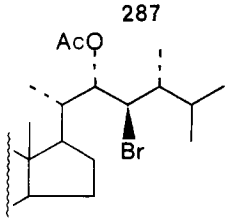
Ergostene derivative **287** with iodine and silver acetate[154] yields iodoacetate **289a** stereo- and regioselectively. Bromoacetoxylation under similar conditions is less selective and forms three (**288b, 289, 290**) of the four possible isomers in a 9:4:1 ratio.[107,155] Iodoacetoxylation of *i*-steroid olefin **282** leads to a mixture of iodoacetates **291a** and **292a** in a 2.5:1 ratio,[103] while the same reaction with stigmastene (**293**) forms iodoacetates **294** and **295** in a 3:1 ratio.[156]



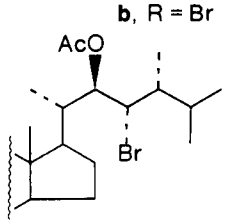
287



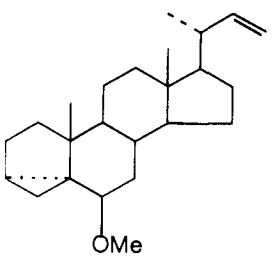
288a, R = I
b, R = Br



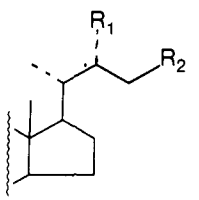
289



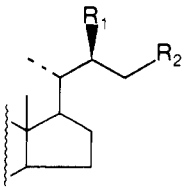
290



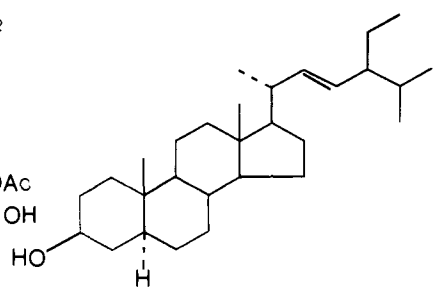
282



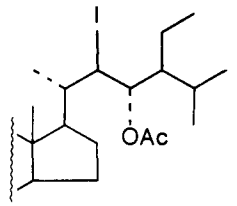
291a, R_1 = OAc; R_2 = I
b, R_1 = OH; R_2 = Br



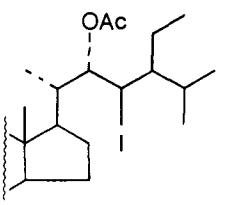
292a, R_1 = I; R_2 = OAc
b, R_1 = Br; R_2 = OH



293

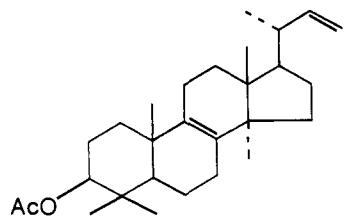


294

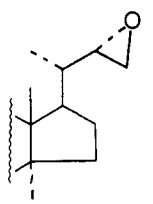


295

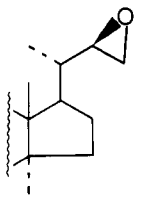
By combining 22(23)-ene **282** with *N*-bromosuccinimide in aqueous THF, bromohydrins **291** and **292** are prepared in almost equal amounts (39 and 24%, respectively).[155] Bromohydrin formation followed by base converted the norlanostene **296** into a mixture of epoxides **297** and **298** in a 5:1 ratio.[104] The 22*R* epoxide dominated the products (83% yield) when **282** was iodoacetoxylated, then treated with base.[58]



296

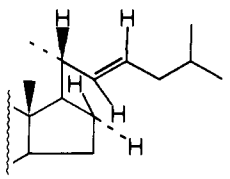


297

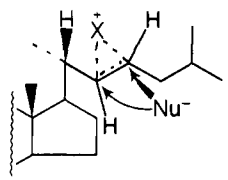


298

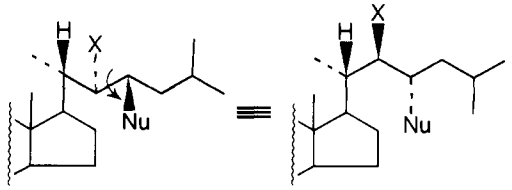
The steric course of previous reactions has been explained[104] by the following: (1) conformation of the 22(23)-ene side chain should be depicted in **299** as has been determined for ergocalciferol in the crystalline state,[155,157] since it is reasonable to assume this conformation predominates in solution as well. In this staggered conformation allylic interactions of the vinylic hydrogens (A-strain) are minimized,[158] (2) the double bond is then attacked by the positive ion from the less hindered side (opposite the polycyclic substituent) as depicted in **300;** (3) the intermediate halonium ion **300** is approached preferentially at C-23 by the nucleophile, e.g., OAc^-, since this position is markedly less hindered than C-22; (4) substitution occurs at C-23 opposite to the carbon–halonium bond to produce **301** as the main product; and (5) selectivity of the addition is dependent upon the size of



299



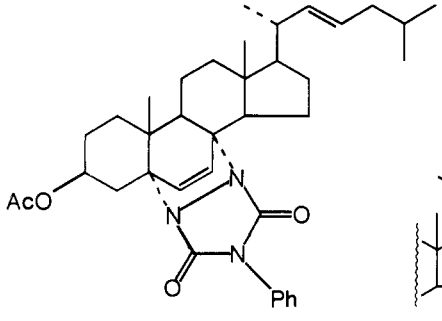
300



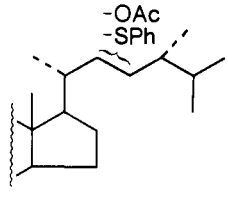
301

the halonium ion (iodonium being greater than bromonium). Alkyl substituents at C-24 seem to influence the course of the reaction very little.[156]

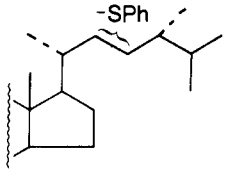
Two novel methods of removing a 22(23) double bond while protecting a 5,7-diene system have been reported by Barton et al.[159] In one PhSCl and $Hg(OAc)_2$ are added to the double bond of the triazolidenediene-protected compound **302** to yield a mixture of three epimeric 22,23-acetoxy sulfides **303** which are then reduced with $PhCH_2Me_2SiH$ to **304.** The sulfide moiety in **304** is finally removed with Ni(R). In the other, the 5,7-diene system was protected as the iron carbonyl complex **305,** and the side-chain double bond was reduced over PtO_2 in the presence of $PhCH_2Me_2SiH$ in 94% yield.



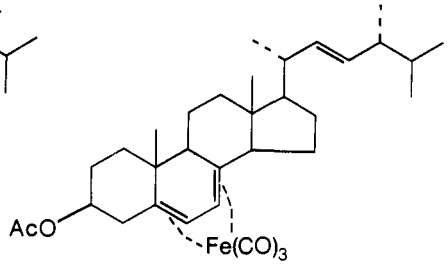
302



303



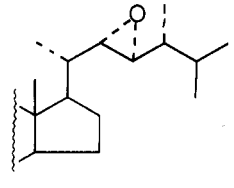
304



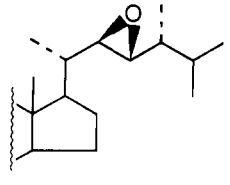
305

G. Formation of 22,23-Epoxides and Their Reactions

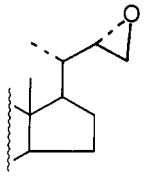
The oxidation of ergostene derivative **287** with monoperphthalic acid[102,155] leads to a 2:3 ratio of epoxides **306** and **307.** Similar steric results were observed when *i*-steroid olefin **282** was oxidized by p-$O_2NC_6H_4CO_3H$ to epoxides **308** and **309** in a 1:2 ratio.[103] Comparable stereoselectivity was found with



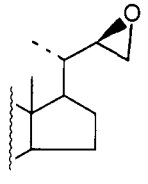
306



307



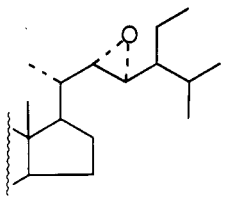
308



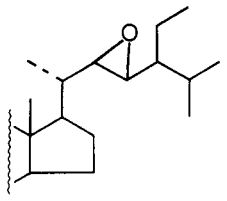
309

ergostene **293** which yielded epoxides **310** and **311** in a 3:5 ratio[156] and with dihydroxy compound **312** which forms epoxides **313** and **314** in a 2:3 ratio.[160] In one instance,[58] a somewhat better yield (79%) of single epoxide **309** was achieved from the action of mCPBA on ene **282.**

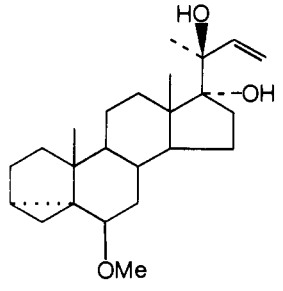
Epoxidation[127,159] of 22-en-24-one **315** with alkaline hydrogen peroxide proceeds stereospecifically to α,β-epoxide **316.**



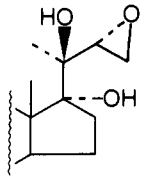
310



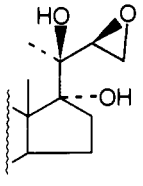
311



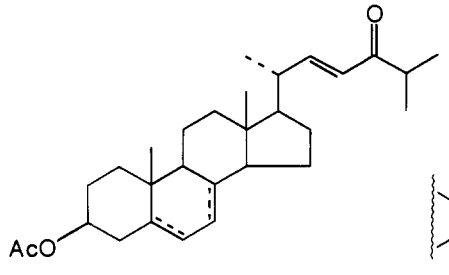
312



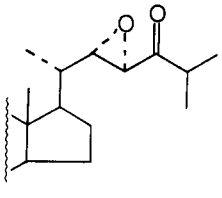
313



314

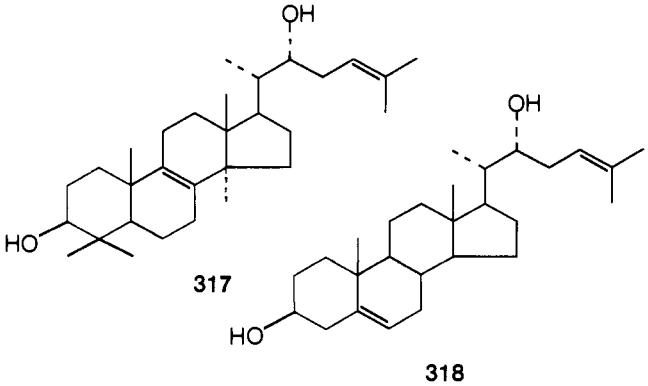


315a, 5α, 7-ene
b, 5-ene



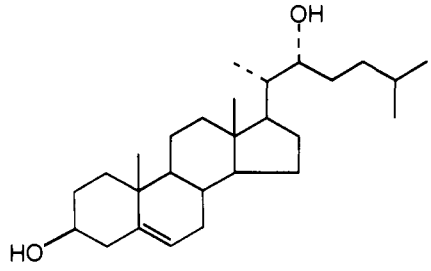
316

Nucleophilic substitution of several of the above-described epoxides at C-23 has been a means of completing the side chain and simultaneously generating a 22-hydroxyl group with specific stereochemistry. Addition of isobutenylmagnesium bromide to norlanostene epoxide (**297**) was such a method developed by Ourisson et al.[104] to synthesize inotodiol (**317**), a component of birch tree fungus *Inonotus obliquus* used in traditional Russian folk medicine for cancer treatment. Similarly prepared were (22*R*)-hydroxy-24-ene[103] **318,** and (22*R*)-22-hydroxycholesterol[103] (**319**) and two epimeric 22-acetoxy-25-dehydrocholesterols[58] (**320**) by reaction of epoxides **308** or **309** with the appropriate Grignard reagent, then rearrangement of the *i*-steroid



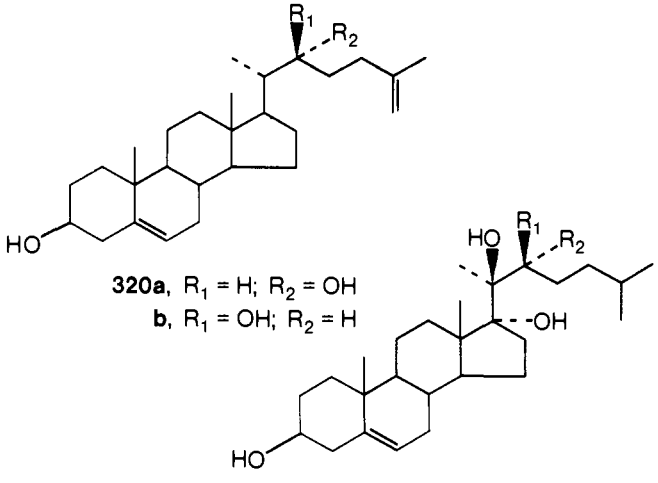
317

318



319

moiety. Nickolson and Gut[160] formed two epimeric trihydroxycholesterols **321a** and **321b** from epoxides **313** and **314** respectively, by first epoxide opening with *i*-BuLi, followed by rearrangement of the *i*-steroid system.



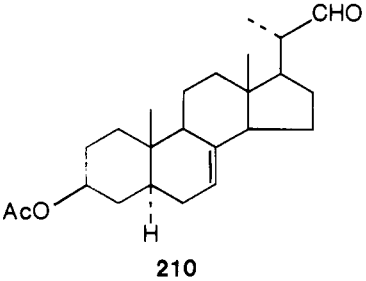
320a, R_1 = H; R_2 = OH
b, R_1 = OH; R_2 = H

321a, R_1 = H; R_2 = OH
b, R_1 = OH; R_2 = H

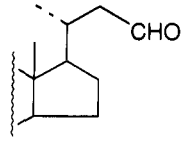
VI. Reactions Involving Position 23

A. Additions to C-23

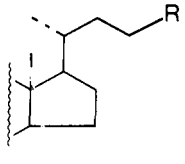
Not many major side syntheses using C-23 as a key point have been evolved owing probably to more readily available starting materials with appropriate functional groups at C-20, C-22, and C-24. Also there are not many naturally occurring compounds with important functional groups at C-23 except for antheridiol which has been considered already in section IV.B. Some syntheses, however, have utilized carbon 23 as an intermediate point. Sucrow and Girgensohn,[161] for instance, added the Wittig reagent $Ph_3P{=}CHOMe$ to 22-aldehyde **210**, then hydrolyzed it with acid to the 23-aldehyde **322**. Formation of iodide **323** by reduction, tosylation, and displacement ensued next. This C-23 moiety was then used to alkylate α-ethylacetoacetic ester to yield ketone **324a** after hydrolysis and decarboxylation. A Wittig reaction of the 25-ketone completed their preparation of the C-24 epimeric 7,25-stigmadiene (**324b**).



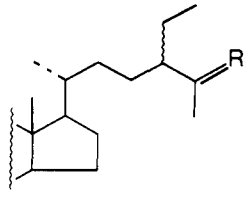
210



322

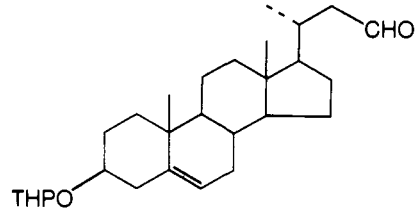


323a, R = OH
b, R = OTs
c, R = I



324a, R = O
b, R = CH_2

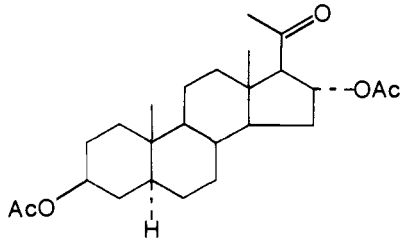
In a synthesis of demosterol, Gut et al.[140] used a similar aldehyde, **325**, to react with isobutenylmagnesium bromide forming alcohol **326a**. Alcohol **326a** was methylated by NaH–MeI



325

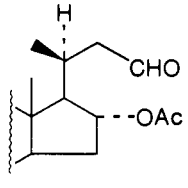
326a, R = OH
b, R = OMe
c, R = H

to ether **326b**, and the ether moiety was removed with Li–$EtNH_2$ to yield demosterol THP (**326c**). The side chain was also extended[88] with aldehyde **329** as an intermediate. By a Wittig reaction of **327** (see section III.E) to yield **328a**, then a series of reactions consisting of reduction, deamination, hydrolysis, oxidation, and hydrogenation, the aldehyde **329** was finally secured. Addition of the Grignard from 4-bromo-3-methyl-1-butene to **329** completed the chain of **330**.

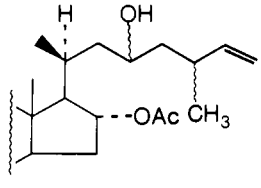


327

328a, R = CN
b, R = CH_2NH_2
c, R = CH_2OAc
d, R = CH_2OH
e, R = CHO

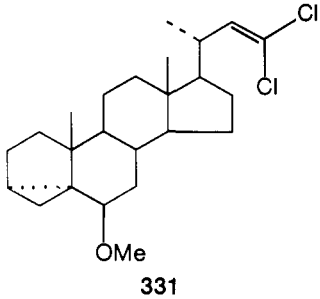


329

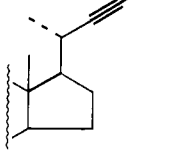


330

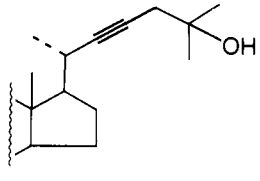
A recent new approach by Salmond and workers[162] for 24-hydroxycholesterol utilizes the lithio acetylide **332** formed from



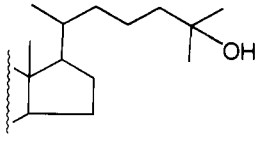
331



332



333

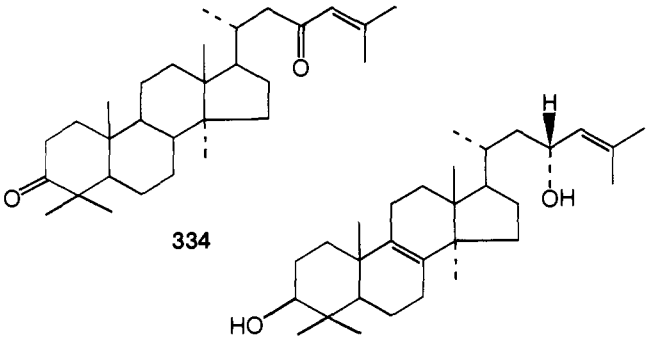


266

vinyl dihalide **331** (see Table VIII) by *n*-BuLi and adds isobutylene oxide to produce the remaining part of the chain. The alkyne **333** is then reduced catalytically to **266,** which is subsequently converted in rings A and B, to the desired product.

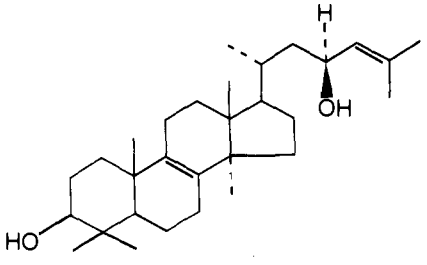
B. Reduction of 23-Ketones

$LiAlH_4$ reduction of the unsaturated side-chain ketone in lanosterol derivative **334** goes with little selectivity to the two epimeric alcohols **335** and **336** (9:11 ratio).[163] Ergostane de-



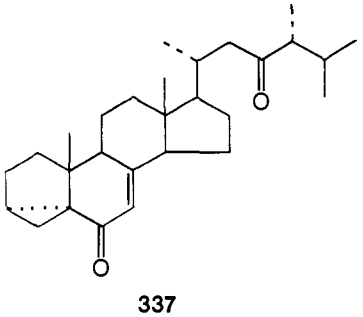
334

335

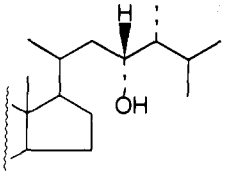


336

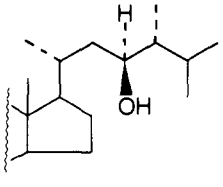
rivative **332** upon $LiAlH_4$ reduction at −20 °C and reoxidation at C-6 by MnO_2 yields a slightly higher amount of *S* isomer **339** over *R* isomer **338** (7:3 ratio).[102] In the latter case the steric



337

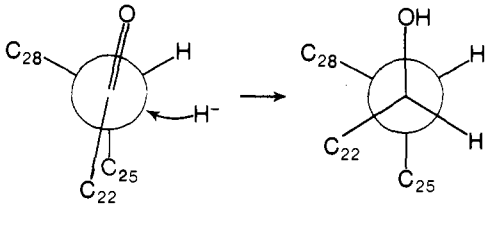


338



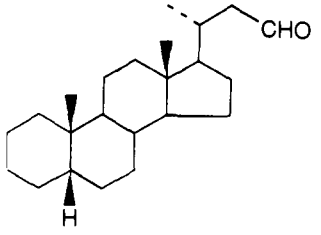
339

results of the reduction are in agreement with Cram's rule as illustrated by

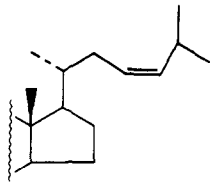


C. Formation of 23(24) Double Bonds

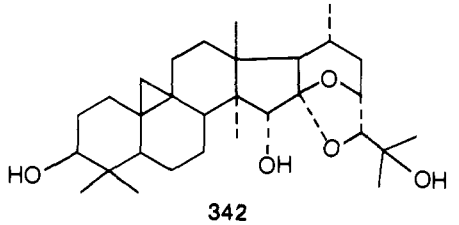
Wyllie and Djerassi[56] condensed $Ph_3P{=}CHCHMe_2$ with aldehyde **340** to obtain **341** (*Z* configuration). A similar reaction[164] was employed to obtain steroids isotopicaly labeled at C-25.



340

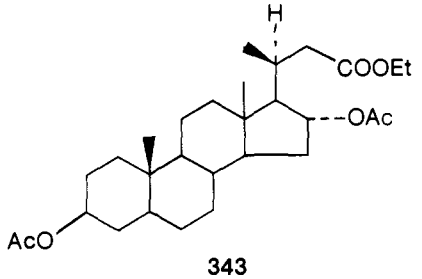


341

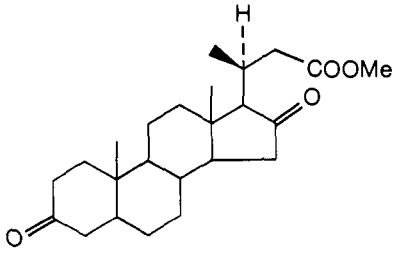


342

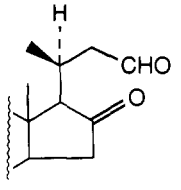
In a model study for the side-chain synthesis of natural genin (**342**), Piancatelli and Scettri[83] started with **343** (see section III.E). First, the ketone moieties depicted in **344** were introduced by base hydrolysis of **343,** oxidation at C-3 and C-16, and then methylation of the acid. The 23-ester group of **344** was transformed to an aldehyde **345** next by $LiAlH_4$ reduction and CrO_3–pyridine oxidation of the resultant alcohol while the ketone



343

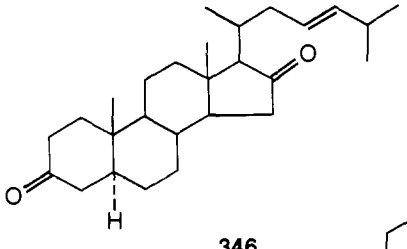


344

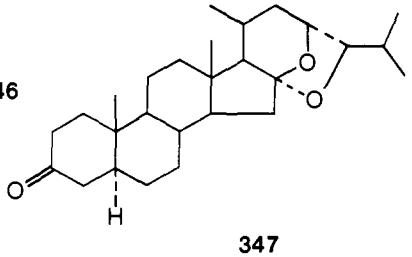


345

moieties were temporarily protected as ketals. Wittig reaction of **345** with $Ph_3P{=}CHCHMe_2$ gave 23-ene **346** determined by



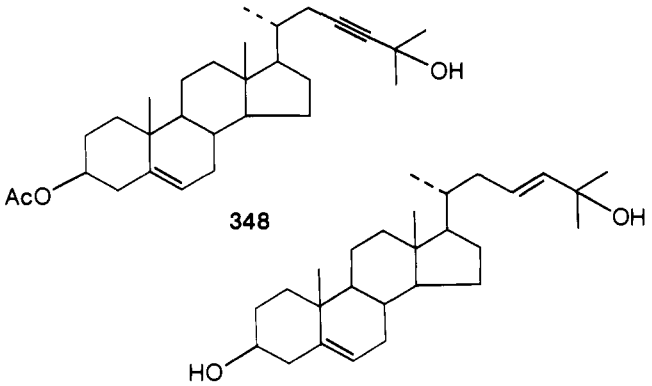
346



347

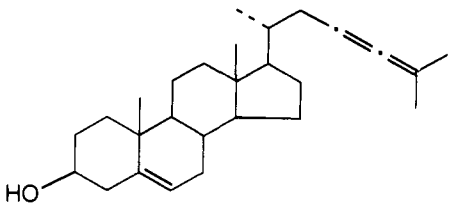
an infrared spectrum to be the *E* isomer. Glycol formation with OsO_4 gave two isomeric diols, one (23*R*,24*R*) of which cyclized to the natural and favored genin system **347.**

Propargyl alcohol **348** has been reduced to (*E*)-vinyl alcohol **349** and allene **350** in 80 and 13% yields[165] with $LiAlH_4$, while



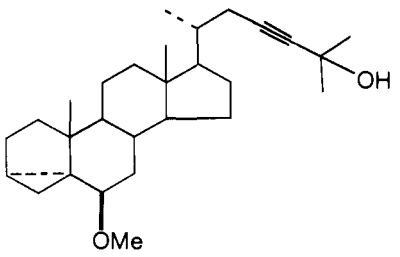
348

349

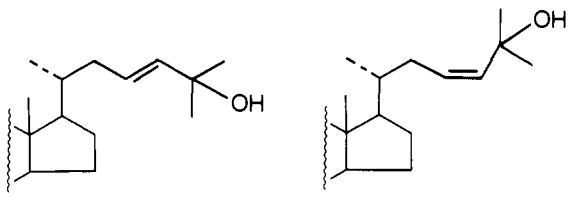


350

the corresponding *i*-steroid **351** forms (*E*)-vinyl alcohol **352** only.[166] The *Z* isomer of vinyl alcohol **353** results from catalytic reduction of the triple bond in **351** over Lindlar catalyst.[167]



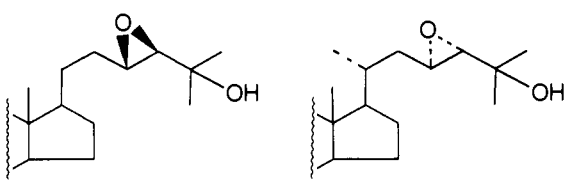
351



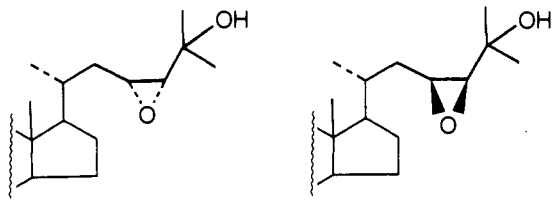
352 353

D. Preparation and Reactions of 23,24-Epoxides

Some chemistry of 23,24-epoxides has been done in connection with the synthesis of vitamin D metabolites.[167] Epoxidation of *E*-olefin **352** with mCPBA gives epoxides **354** and **355** in a 1:1 ratio; however, *t*-BuOOH in the presence of vanadyl acetoacetate[168] favors considerably **355** over **354** (85:15

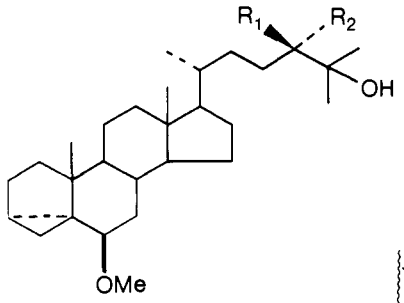


354 355

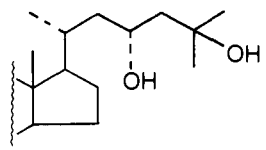


356 357

ratio).[167] Similarly, an 15:85 ratio of epoxides **356** and **357** was produced with the latter reagents from the *Z*-23(24)-ene **353.** Interestingly, when reduced by $LiAlH_4$, trans epoxide **355** gave 24*S*-alcohol **358a** and 23*R*-alcohol **359** in a 2:3 ratio, while cis epoxide yielded mainly 24*R* alcohol **358b** (95%) and a minor amount of **359** (5%). If both epoxides **355** and **356** are reduced by $(i\text{-Bu})_2AlH$, only **359** results. Eventually, the products were transformed to the corresponding cholesterol analogs by regeneration of the 5-en-3β-ol system.[167]



358a, R_1 = H; R_2 = OH
b, R_1 = OH; R_2 = H

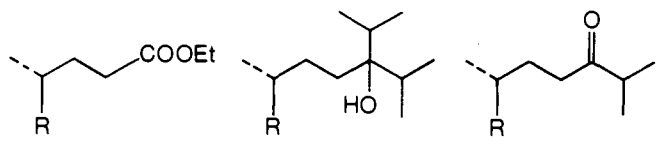


359

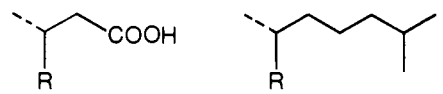
VII. Reactions Involving Position 24

A. Grignard and Organocadmium Reactions on C-24 Acids and Ketones

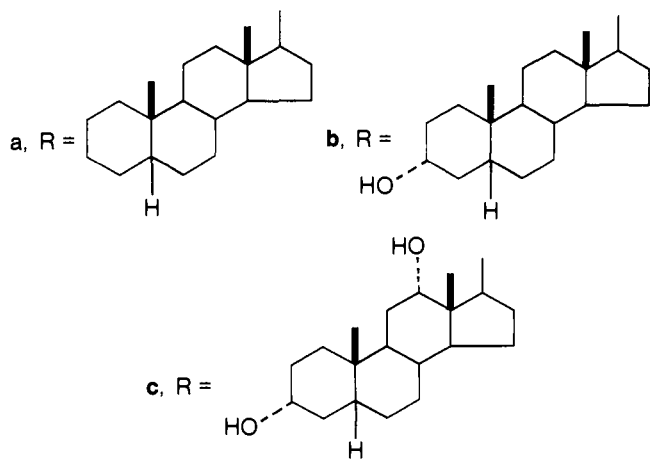
Addition of Grignard reagents to bile acid esters is the oldest known method of completing sterol side chains primarily because it was used to relate the two main naturally occurring steroids—cholesterol and cholic acid. One of the first reports[169] was the reaction of ethyl cholanate (**360a**) with *i*-PrMgBr to yield



360 361 362

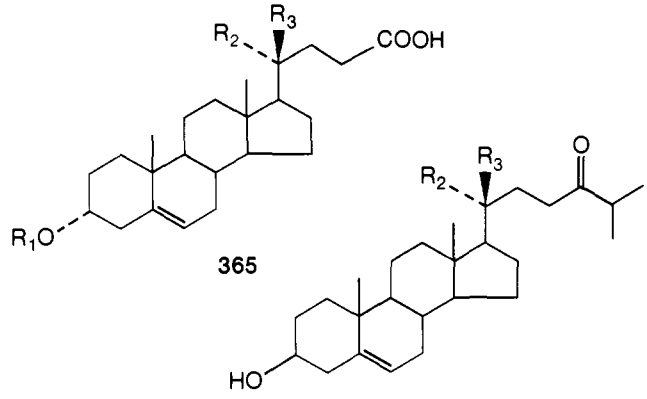


363 364



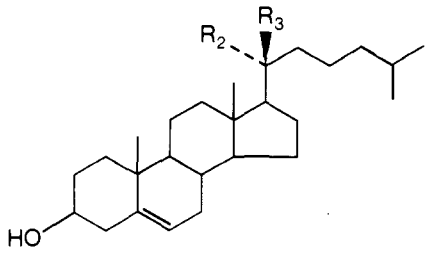
what was thought to be addition product **361a**. Furthermore, product **361** was oxidized to give ketone **362a** and acid **363a**. Their results, however, can be explained better if their product is either a mixture of ketone **362a** and starting ester **360a** or just the ketone **362** since the diaddition is unlikely and the oxidation products could arise from ketone **362a** just as well. Ten years later,[170] the ethyl lithiocholate (**360b**) was used in the same sequence to form ketone **362b** which supposedly gave a "pinacol" product during Wolff-Kishner reduction. One of us recently verified the ketone formation; however, the "pinacol" product claimed to result could not be secured—instead normal reduction to **364** results (25% yield).[171] The amide of deoxycholic acid also underwent addition by *i*-PrMgBr to yield ketone **362c** which was reduced to **364c** in low yield.[172]

Other means of completing the chain as 24-ketones **366a** and **366c** include the action of *i*-PrLi on acid[173] **365a** or $(i\text{-Pr})_2Cd$ on the "natural" acid[174] **365b** or 20-isoacid[64] **365c**. The ketones



365

366

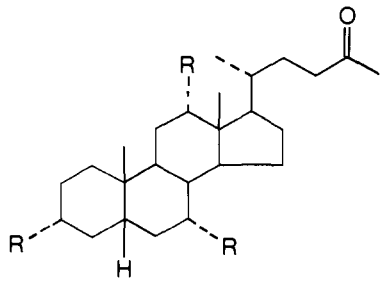


367

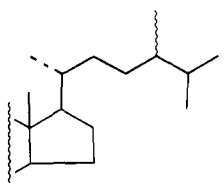
a, R_1 = H; R_2 = Me; R_3 = H
b, R_1 = Ac; R_2 = Me; R_3 = H
c, R_1 = Ac; R_2 = H; R_3 = Me

were then reduced[64,174] to cholesterol **367a** or isocholesterol **367c** in poor yield under the Wolff-Kishner conditions which seem to be characteristic for this ketone although lophenol (**274d**) has been reported to result in a 91% yield[148] from its corresponding 24-ketone **274c**.

Reaction of ketone **368a**, obtained from pyrolysis of the barium salt of cholanic acid and barium acetate, with *i*-PrMgBr gives an alcohol which can be dehydrated and hydrogenated to a mixture of ergostanes[175] **369** epimeric at C-24. Also ketone **368b** could be used in the same way.



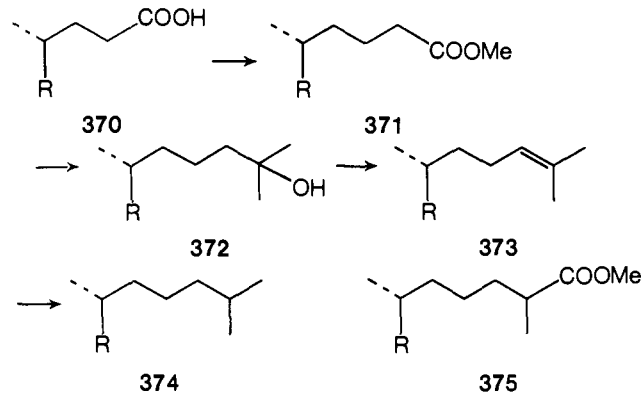
368a, R = H **b**, R = OH



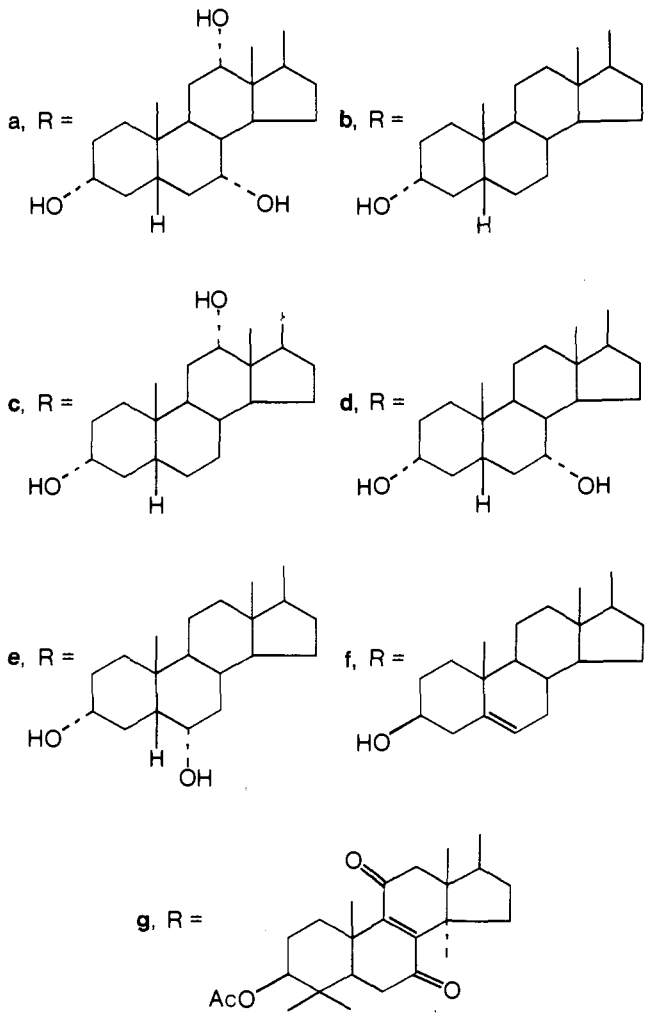
369

B. Syntheses Involving the Ardnt-Eistert Reaction on Bile Acids

Ardnt-Eistert extension of a cholic acid or cholenic acid (**370**) chains followed by MeMgX or MeLi reaction of the resultant ester **366** to yield a 25-hydroxycholestane (**372**) has been used by a number of groups after its introduction by Pearlman[177] in connection with cholic acid (**370a**). Lettré et al.[46,178] applied the sequence to several cholic acids **370b–c** obtaining in some cases 24-enes **373b–d** as had Mosbach and workers[179] for the formation of C-24 labeled triol **372d**.



370 **371** **372** **373** **374** **375**



a, R = **b**, R = **c**, R = **d**, R = **e**, R = **f**, R =

g, R =

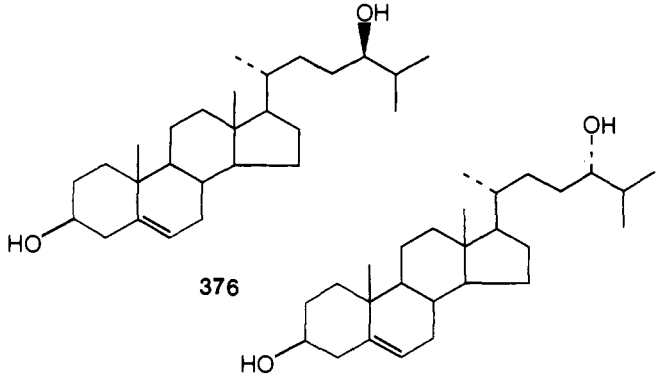
Of particular interest was the application of the sequence to cholenic acid (**370f**) to give alcohol **372f** which could be dehydrated and hydrogenated to cholesterol[180] (**374f**) and to lanostenoic acid (**365g**) as the means of finalizing the side chain of lanosterol (**373g**) in the Woodward-Barton total synthesis.[181]

C. Applications of the Kolbe Electrolysis Procedure

The Kolbe electrolysis procedure is a method which has been investigated very little for side-chain construction because bad yields of product are known to occur.[182] Although the method has been applied to the formation of cholestane side chains **374a–d** on various cholanic acids **370a–d** with isovaleric acid,[183-187] its chief utility lies in coupling cholanic acids **365a–d** with optically active half acid esters[188,189] to form steroids **375a–d** with known configurations at C-25.

D. Reduction of C-24 Ketones

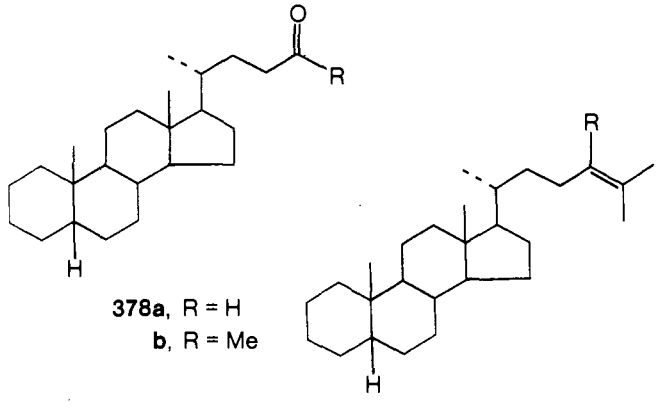
$NaBH_4$ reduction of 24-oxocholesterol (**366b**) yields (24*R*)-hydroxycholesterol (**376**) and cerebrosterol,[190] a brain sterol



(**377**), in a 5:4 ratio.[173,191] Configurations for the hydroxy groups at C-24 were assigned on the basis of CD measurement[192] of dibenzoates.

E. Formation of 24(25) Double Bonds

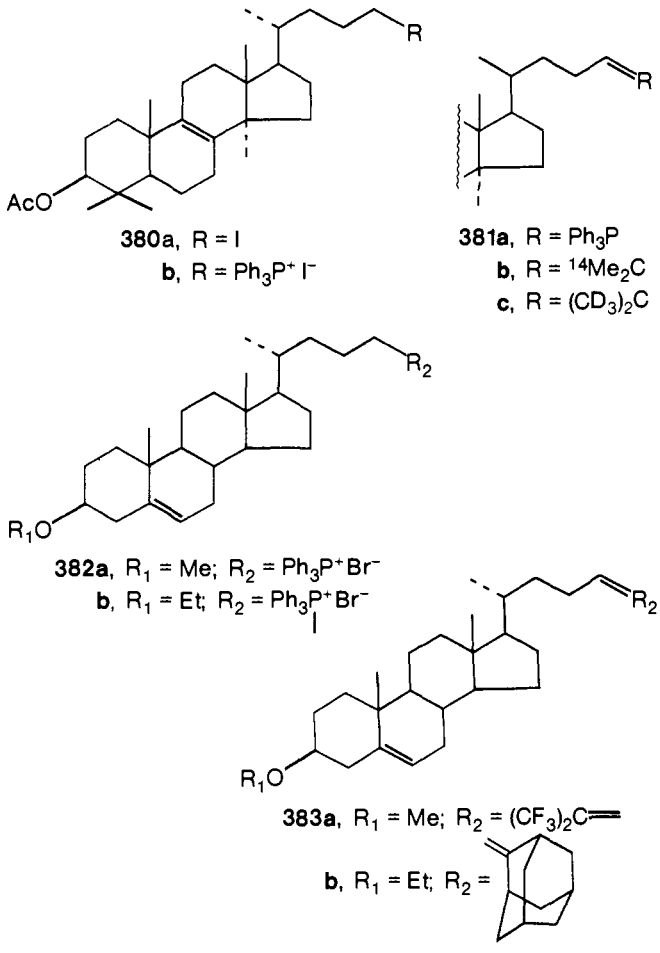
In addition to dehydration of 24-hydroxy and 25-hydroxy sterols[193-195] (also see section VI.B) the 24(25) double bond has been introduced along with the remainder of the side chain by Wittig reactions. For example, Wyllie and Djerassi[56] added $Ph_3P{=}CMe_2$ to both **378a** and **378b** to secure **379a** and **379b,** respectively. A different approach was taken by Ourisson et



378a, R = H
b, R = Me

379a, R = H
b, R = Me

al.[196] in that ylide **381a** was prepared on the side chain via iodide **380a** and phosphonium salt **380b,** affording thusly the opportunity to prepare both carbon-14 labeled **381b** and deuterated **381c** lanosterols. Similarly, Herz and Montalvo[197,198] prepared fluorinated **383a** and adamantyl **383b** steroids by addition of the appropriate ketone to ylides from **382a** and **382b,** respectively.



380a, R = I
b, R = $Ph_3P^+I^-$

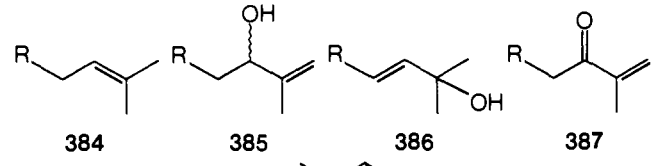
381a, R = Ph_3P
b, R = $^{14}Me_2C$
c, R = $(CD_3)_2C$

382a, R_1 = Me; R_2 = $Ph_3P^+Br^-$
b, R_1 = Et; R_2 = $Ph_3P^+Br^-$

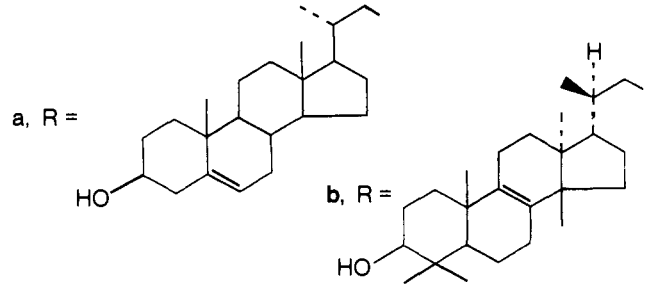
383a, R_1 = Me; R_2 = $(CF_3)_2C{=}$
b, R_1 = Et; R_2 =

F. Reactions of 24(25) Double Bonds

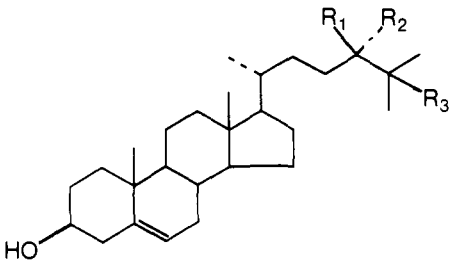
Photooxygenation of the 24(25) double bond in demosterol[199] (**384a**) and tirucallol[27] (**384b**) forms about equal amounts of allylic alcohols **385** and **386,** the former capable of being oxidized to unsaturated ketone **387.**



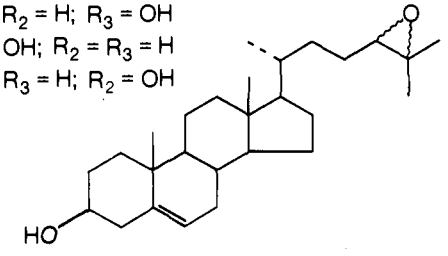
384 **385** **386** **387**



Oxidation of demosterol (**384a**) by OsO_4 or mCPBA leads to epimeric diols **388a** and **388b** or epoxides **389** in about a 1:1 ratio each, respectively.[195,199,200] The diols were resolved as their 3,24-dibenzoate-25-trimethylsilylate derivatives, and the configuration at C-24 was established[201,202] by the modified Horeau method.[203,204] A mixture of epoxides **389** was reduced by $LiAlH_4$ to 25-hydroxycholesterol (**388c**) or hydrolyzed to diol mixture **388a,b** by acid.[195,199,202] The individual epoxides (24*R* and 24*S*) were also reduced by $LiAlH_4$: $AlCl_3$ to 25-hydroxycholesterol (**388c**) along with the (24*R*)-**388d** or (24*S*)-**388e** hydroxycholesterol, respectively.[200] Acyloxymercuration–



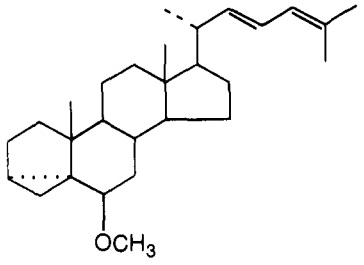
388a, $R_1 = R_3 = OH$; $R_2 = H$
b, $R_1 = H$; $R_2 = R_3 = OH$
c, $R_1 = R_2 = H$; $R_3 = OH$
d, $R_1 = OH$; $R_2 = R_3 = H$
e, $R_1 = R_3 = H$; $R_2 = OH$



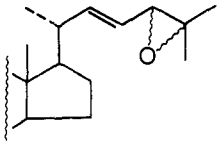
389

demercuration has also been employed to form 25-hydroxycholesterol (**388c**) from demosterol.[194,199]

The 24(25) double bond of **390** (see Table IX) has been selectively epoxidized over the 22(23) double bond by $MeCO_3H$–NaOAc in an efficient synthesis of 25-hydroxycholesterol from stigmasterol.[237] Catalytic reduction of both the double bond and epoxide in **391** to 25-hydroxy **388c**, followed by *i*-steroid moiety rearrangement, resulted in a 56% overall yield of 25-hydroxycholesterol from stigmasterol tosylate.

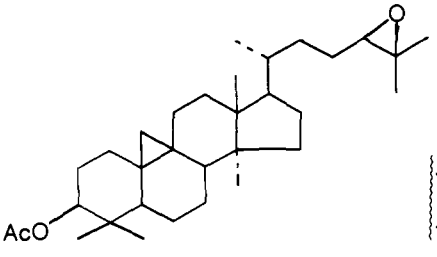


390

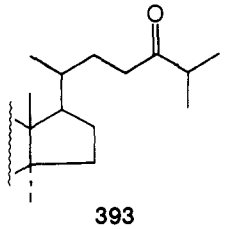


391

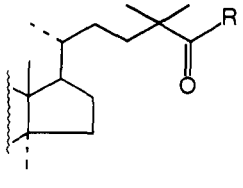
Cycloartenol epoxide (**392**) undergoes an interesting rearrangement with stannic chloride to 24-ketone **393** (35%) and aldehyde **394a** (30%). The latter compound was subsequently used to prepare cycloneolitsine (**395**) by oxidation and methylation to ester **394b**, followed by MeLi addition to the ester and dehydration of the resultant alcohol.[205,206]



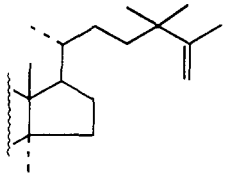
392



393



394a, R = H
b, R = OMe



395

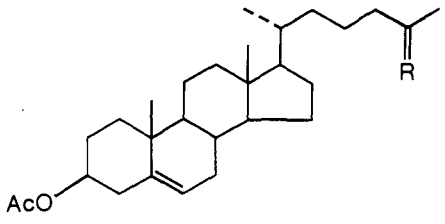
VIII. Reactions Involving Position 25

A. Grignard and Related Reactions of C-25 Oxygenated Derivatives

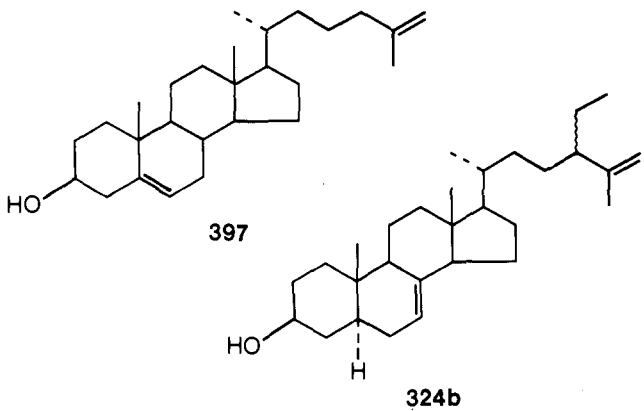
Completion of the side chain has been accomplished by MeMgX or MeLi addition to C-25 esters (see section VI.B and preceding paragraph) or MeMgI addition to 27-nor-25-oxocholesterol (**389a**) to form 25-hydroxycholesterol.[142,193,207,208]

B. Formation of 25(26) Double Bonds

Condensation of the appropriate 25-ketone[161,193] with $Ph_3P{=}CH_2$ or $Ph_3P{=}CHOMe$ has been used to prepare **397**,



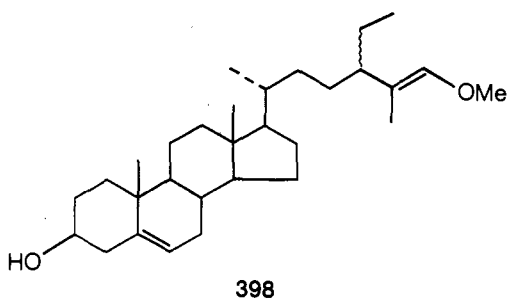
396a, R = O
b, R = CH_2



397

324b

324b, and **398**. 25-Hydroxycholesterol has been reported to give 25(26)-dehydrocholesterol (**396b**) by dehydration with $POCl_3$–pyridine[207] or PBr_3[208] and a 2:1 mixture of demosterol (**384a**) and **396b** with $POCl_3$.[195] The Cope elimination of C-26 amine oxides of ergostane derivatives also yields 25(26) double bonds.[125,126]



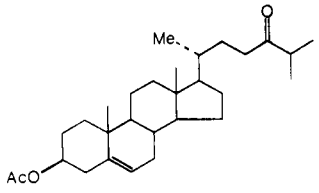
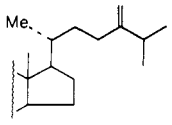
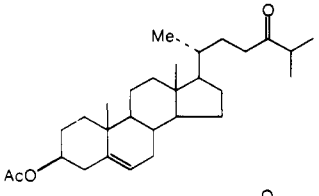
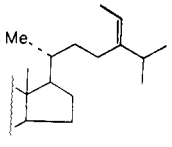
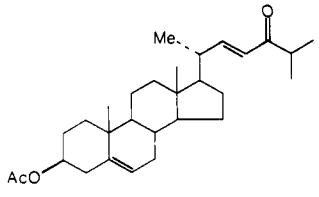
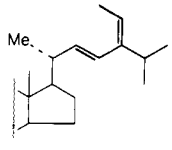
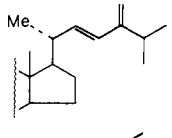
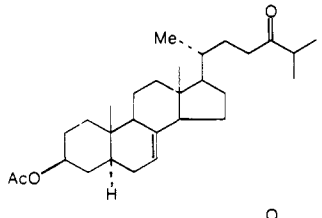
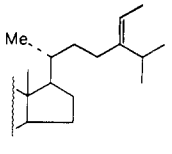
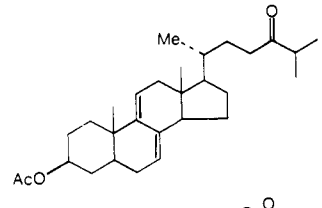
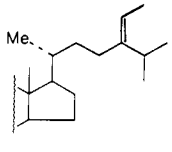
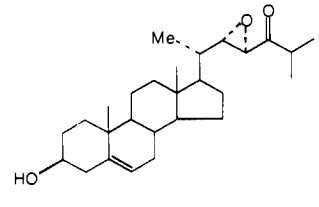
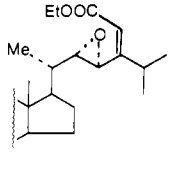
398

C. Reactions of 25(26) Double Bonds

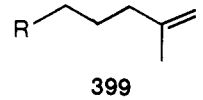
Epoxidation of **399a** at C-25(26) followed by $LiAlH_4$ reduction has been described[105] as yielding **400a** and **401a**, while acid cleavage of the epoxide gives only **400a**, and acyloxymercuration–demercuration, only **401a**. On the other hand, Trost and Matsumura[58] report a good yield of **403b** by epoxidation and then $LiAlH_4$ reduction of **402b**.

Sterols labeled with tritium have beem made[209] from **404b** with B_2T_6 to a 3:1 mixture of **405b** and **406b**. Hydroboration[210]

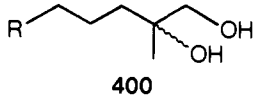
TABLE IX. Wittig Reaction on C-24 Ketones

C-24 Ketone	Ylid	Product	Yield, %	Ref
	$Ph_3P{=}CH_2$		85	227
As above	$Ph_3P{=}CHMe_2$	No reaction		227
	$Ph_3P{=}CHMe$		20	227
				146
As above	$Ph_3P{=}CH_2$		32	146
	$Ph_3P{=}CHMe$		41	124
	$Ph_3P{=}CHMe$		33	228
	$(EtO)_2P(=O)CHCOOEt$		30	214

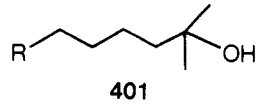
of **407** with disiamylborane leads to a 25% optically pure 25*S* isomer **408**, with (+)-diisopinocampheylborane to a C-25 racemic mixture of 26-hydroxycholesterol, and with (−)-diisopinocampheylborane to an 83% pure *S* isomer **408**.



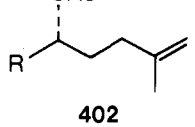
399



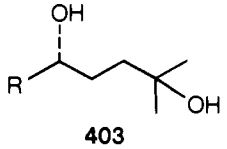
400



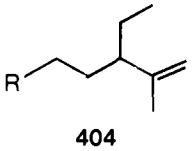
401



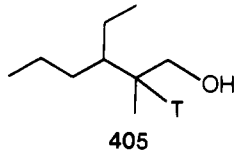
402



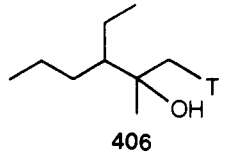
403



404

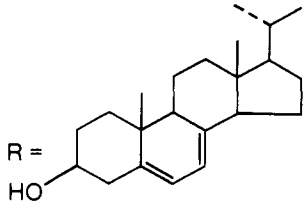


405

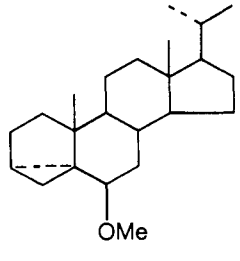


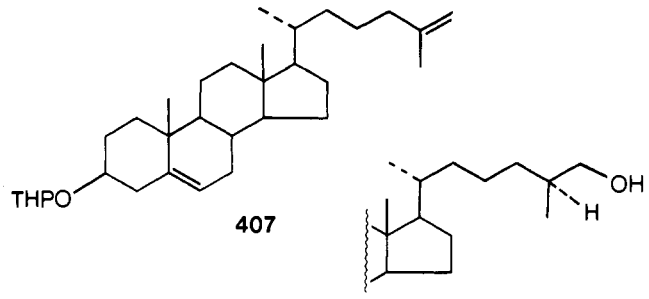
406

a, R =



b, R =





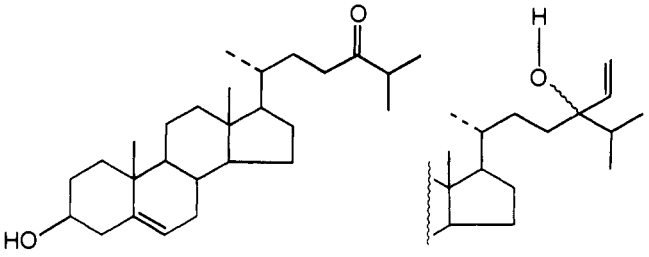
407 408

IX. Formation and Some Relevant Transformations of C-24(28) Bonds

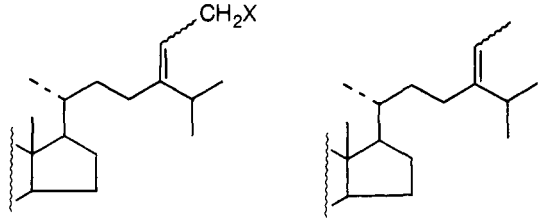
A. Addition of Moieties to C-24

The introduction of carbon atoms at C-24 on the steroid side chain has been done primarily to prepare naturally occurring sterols. Although frequently the carbons attached to C-24 have been part of a larger synthon, in some instances they have been added in the final stages of a synthetic sequence.

Saringosterol (**409**), a marine sterol, has been prepared, for example, by adding KC≡CH to 24-oxocholesterol (**366a**), then catalytically reducing the triple bond[211] and, alternatively, by adding vinylmagnesium bromide[212] to **366a**. Sterol **409** has also been rearranged by PBr_3 or PI_3 to allylic halides **410** in a 4:6 ratio of *Z*:*E* isomers, which could be separated and reduced to the corresponding 24(28)-ene sterols **411** by $LiAlH_4$.[212] A similar sequence was applied to 24-oxocholest-7-en-3β-ol.[212] The 24(28)-ene moiety in **411** has also been formed[64] by reaction of ketone **366a** with EtMgBr and dehydration of the resultant alcohol with $POCl_3$.



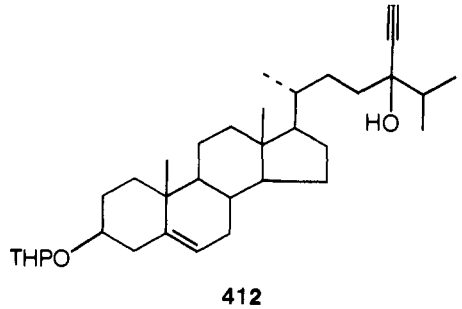
366a **409**



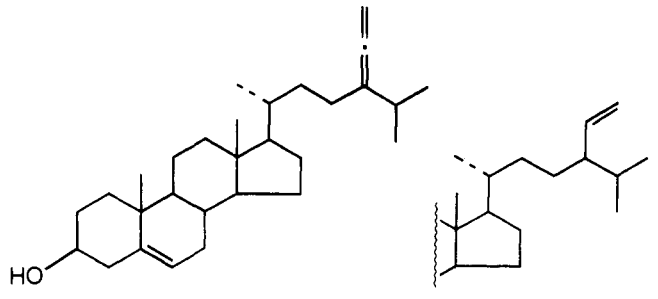
410 **411**

X = Br or I

By $LiAlH_4$–$AlCl_3$ reduction[165,166] of propargyl steroid **412**, saringosterol (**409**) and an allene sterol **413** have been prepared; $LiAlH_4$–$TiCl_4$ reduction[166] affords the 28(29)-ene **414**.

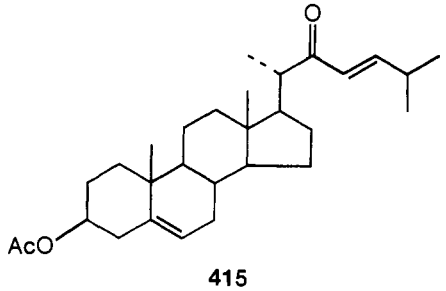


412

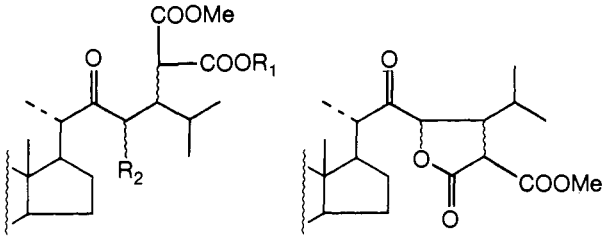


413 **414**

Michael condensation of dimethyl malonate at C-24 of the unsaturated ketone chain in **415** formed the basis for introducing the C-28 and -29 carbons in a synthesis of antheridiol. The lactone ring construction continued with hydrolysis of one ester moiety in **416a** to monoacid **416b**, bromination of **416b** at C-23 to yield **416c**, and closure of the ring **417**. Next, the ketone at C-22 was reduced to give the hydroxy compound **418**. Removal of the ester moiety and introduction of the ring double bond then



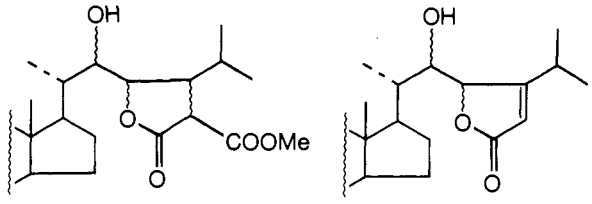
415



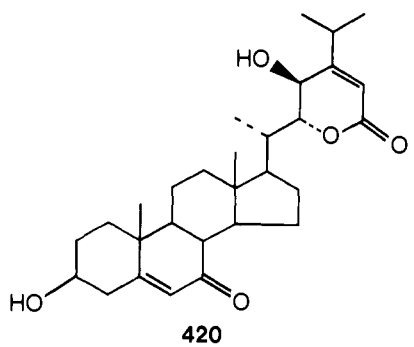
416a, R_1 = Me; R_2 = H
b, R_1 = R_2 = H
c, R_1 = H; R_2 = Br

417

followed, affording **419**. The 7-oxo group present in antheridiol was introduced as a last step.



418 **419**

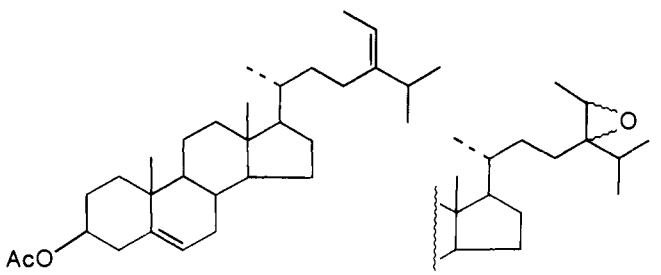


420

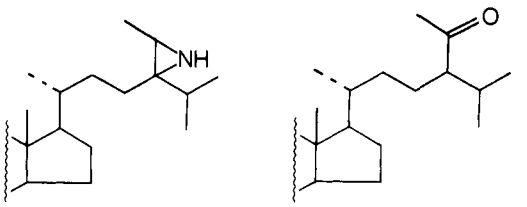
Wittig reactions of C-24 ketones have been, perhaps, the most explored means of adding carbon units at this position, and a number of different ketones and ylides have been used (see Table IX) although the yields are not the best. The last example[214] in Table IX is of interest because acid treatment of the Wittig product generated the lactone system of isoantheridiol (**420**).

B. Reactions of 24(28) Double Bonds

Selective epoxidation of fucosteryl acetate (**421**) with mCPBA gives a nonseparable mixture of epimeric epoxides **422** (1:1



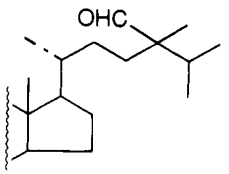
421 422



423 424

ratio), which were hydrolyzed to the corresponding diols.[215] The diols were separated as their α-methoxy-α-phenyltrifluoroacetyl derivatives[215] and identified by the Pr(dpm)$_3$ method.[216] 24,28-Iminofucosterol (**423**) has also been prepared from fucosterol (**421**) and found to inhibit the growth of silkworms.[217]

Treatment[218] of epoxide mixture **422** with boron trifluoride etherate in benzene curiously results in demosterol acetate (35% yield) and C-28 ketone **424** (45% yield) plus a minor amount (12%) of the aldehyde **425.**



425

X. References

(1) E. P. Oliveto in "Organic Reactions in Steroid Chemistry", Vol. 2, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, New York, N.Y., 1972.
(2) Y. Sato, in "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand-Reinhold, New York, N.Y., 1970, p 591.
(3) F. Khuong-Huu and R. Goutarel in Specialist Periodical Reports, "The Alkaloids", Vol. 2, J. E. Saxton, Ed., The Chemical Society, London, 1972.
(4) See portions of "M.T.P. International Review of Science, Organic Chemistry, Series One", Vol. 8, W. F. Johns, Ed., Butterworths, London, 1973.
(5) G. G. Habermehl in "M.T.P. International Review of Science, Organic Chemistry, Series One", Vol. 9, K. F. Wiesner, Ed., Butterworths, London, 1973.
(6) W. Turowska and V. Wrzeciono, *Wiad. Chem.*, **27**, 869 (1973).
(7) R. B. Herbert in Specialist Periodical Report, "The Alkaloids", Vol. 3, J. E. Saxton, Ed., The Chemical Society, London, 1973.
(8) Y. Kamano, *Yushi Kagaku Kyokaishi*, **31**, 202 (1973).
(9) J. Tomko and Z. Voticky, *Alkaloids (N.Y.)*, **14**, 1 (1973).
(10) K. Schreiber, *Biochem. Soc. Trans.*, **2**, 1 (1974).
(11) A summary of other reviews on a variety of topics in steroid chemistry may be found in Specialist Periodical Report, "Terpenoids and Steroids", Vol. 5, K. H. Overton, Ed., The Chemical Society, London, 1975, pp 361-366; see also P. E. Georghiou, *Chem. Soc. Rev.*, 6, 83 (1977).
(12) B. Riniker, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **37**, 546 (1954).
(13) J. W. Conforth, I. Youhotsky, and G. Popjak, *Nature (London)*, **173**, 536 (1954).
(14) K. Tsuda, R. Hayatsu, Y. Kishida, and S. Akagaki, *J. Am. Chem. Soc.*, **80**, 921 (1958).
(15) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).
(16) Pl. A. Plattner, *Helv. Chim. Acta*, **34**, 1693 (1951); *Bull. Soc. Chim. Fr.*, No. 3/4, viii-ix (1951).
(17) *Pure Appl. Chem.*, **31**, 283 (1972).
(18) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, **5**, 385 (1966).
(19) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Am. Chem. Soc.*, **90**, 509 (1968).
(20) T. A. Wittstruck, *J. Org. Chem.*, **38**, 1426 (1973).
(21) M. J. Thompson, S. R. Dutky, G. W. Patterson, and E. L. Gooden, *Phytochemistry*, **11**, 1781 (1972).
(22) T. A. Wittstruck, J. K. Sliwowski, and E. Caspi, *J. Chem. Soc., Perkin Trans. 1*, 1403 (1977).
(23) I. Rubenstein, L. J. Goad, A. D. H. Clague, and L. J. Mulheirn, *Phytochemistry*, **15**, 195 (1976).
(24) M. Nakane and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 1426 (1977).
(25) Y. Letourneux, Q. Khuong-Huu, M. Gut, and G. Lukacs, *J. Org. Chem.*, **40**, 1674 (1975).
(26) W. G. Anderson, C. Y. Byon, M. Gut, and F. H. Bissett, *Tetrahedron Lett.*, 2193 (1976).
(27) K. A. Reimann and D. M. Piatak, unpublished results.
(28) D. M. Piatak and K. A. Reimann, *Tetrahedron Lett.*, 4525 (1972).
(29) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 4055, 4057, 4059, (1974); **97**, 5409, 5417 (1975).
(30) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, p 337.
(31) J. J. Schneider, *Tetrahedron*, **28**, 2717 (1972).
(32) R. B. Woodward, F. Sondheimer, and D. Taub, *J. Am. Chem. Soc.*, **73**, 3548 (1951).
(33) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
(34) H. M. E. Cardwell, J. W. Conforth, S. R. Dufl, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).
(35) V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4675 (1956).
(36) (a) S. Lieberman, private communication, in ref 30, p 344; (b) A. Mijares, D. J. Cargill, J. A. Glasel, and S. Lieberman, *J. Org. Chem.*, **32**, 810 (1967).
(37) Reference 30, p 344.
(38) S. Rakhit and Ch. R. Engel, *Can. J. Chem.*, **40**, 2163 (1962).
(39) L. B. Kier, *J. Med. Chem.*, **11**, 915 (1968).
(40) N. K. Chaudhuri and M. Gut, *J. Org. Chem.*, **34**, 3754 (1969).
(41) N. K. Chaudhuri, J. G. Williams, R. Nickolson, and M. Gut, *J. Org. Chem.*, **34**, 3759 (1969).
(42) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2820 (1952).
(43) W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950).
(44) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).
(45) Reference 30, p 567.
(46) H. Lettré, J. Greiner, K. Rutz, L. Hofman, A. Egle, and W. Bieger, *Justus Liebigs Ann. Chem.*, **758**, 89 (1972).
(47) M. Koreeda, N. Koizumi, and B. A. Teicher, *J. Chem. Soc., Chem. Commun.*, 1035 (1976).
(48) V. Kerb, R. Wiechert, A. Furlenmeier, and A. Fürst, *Tetrahedron Lett.*, 4277 (1968).
(49) R. Labriola and G. Ourisson, *C. R. Acad. Sci., Ser. C*, **274**, 306 (1972).
(50) Zh. S. Sydykov and G. M. Segal, *Bioorg. Khim.*, **2**, 1531 (1976); *Chem. Abstr.*, 87, 23606 (1977).
(51) S. V. Kessar and A. L. Rampal, *Tetrahedron*, **24**, 887 (1968).
(52) S. V. Kessar, V. P. Gupta, R. K. Mahajan, and A. L. Rampal, *Tetrahedron*, **24**, 893 (1968).
(53) S. V. Kessar, V. P. Gupta, R. K. Mahajan, G. S. Joshi, and A. L. Rampal, *Tetrahedron*, **24**, 899 (1968).
(54) S. V. Kessar, A. L. Rampal, and V. P. Gupta, *Tetrahedron*, **24**, 905 (1968).
(55) S. V. Kessar, A. L. Rampal, S. Mangat, and V. P. Gupta, *Ind. J. Chem.*, **4**, 501 (1966).
(56) S. G. Wyllie and C. Djerassi, *J. Org. Chem.*, **33**, 305 (1968).
(57) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976).
(58) B. M. Trost and Y. Matsumura, *J. Org. Chem.*, **42**, 2036 (1977).
(59) Y. Letourneux, M. Bujüktür, M. T. Ryzlak, A. K. Banerjee, and M. Gut, *J. Org. Chem.*, **41**, 2288 (1976).
(60) A. Bowers, T. G. Halsall, and G. C. Sayer, *J. Chem. Soc.*, 3070 (1954).
(61) Y. Mazur and F. Sondheimer, *Experientia*, **16**, 181 (1960).
(62) H. Wieland, O. Schlichting, and R. Jacobi, *Z. Physiol. Chem.*, **161**, 80 (1927).
(63) H. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 875 (1945).
(64) R. Hayatsu, *Chem. Pharm. Bull.*, **5**, 452 (1957).
(65) D. Rosenthal, P. Grabowich, E. F. Sabo, and J. Fried, *J. Am. Chem. Soc.*, **85**, 3971 (1963).
(66) J. Wicha and K. Bal, *J. Chem. Soc., Chem. Commun.*, 968 (1975).
(67) J. Wicha and K. Bal, *J. Chem. Soc., Perkin Trans. 1*, in press.
(68) K. Bal, Ph.D. Thesis, Polish Academy of Science, Warsaw, 1977.
(69) D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *Chem. Commun.*, 939 (1970).
(70) M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **74**, 3627 (1952).
(71) K. Tsuda and K. Sakai, *Chem. Pharm. Bull.*, **9**, 529 (1961).
(72) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, **67**, 1369 (1945).
(73) E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, **34**, 103 (1969).

(74) N. K. Chaudhuri, R. Nickolson, J. G. Williams, and M. Gut, *J. Org. Chem.*, **34**, 3767 (1969).
(75) J. A. Hirsch in "Topics in Stereochemistry", Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Wiley, New York, N.Y., 1967.
(76) D. N. Kirk and M. P. Hartshorn, in "Reaction Mechanisms in Organic Chemistry", Vol. 7, C. Eaborn and N. B. Chapman, Ed., Elsevier, Amsterdam, 1968, p 82.
(77) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).
(78) W. R. Nes, T. E. Varkey, D. R. Crump, and M. Gut, *J. Org. Chem.*, **41**, 3429 (1976).
(79) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **80**, 3087 (1958).
(80) G. V. Nair and E. Mosettig, *J. Org. Chem.*, **27**, 4659 (1962).
(81) R. Ikan, A. Markus, and E. D. Bergmann, *Steroids*, **16**, 517 (1970).
(82) R. Ikan, A. Markus, and E. D. Bergmann, *J. Org. Chem.*, **36**, 3944 (1971).
(83) G. Piancatelli and A. Scettri, *Gazz. Chim. Ital.*, **105**, 473 (1975).
(84) J. P. Schmit, M. Piraux, and J. F. Pilette, *J. Org. Chem.*, **40**, 1586 (1975).
(85) K. Bannai, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 2116 (1976).
(86) T. C. McMorris and S. R. Schow, *J. Org. Chem.*, **41**, 3759 (1976).
(87) M. Koreeda, N. Koizumi, and B. A. Teicher, *Tetrahedron Lett.*, 4565 (1976).
(88) G. Piancatelli and A. Scettri, *Gazz. Chim. Ital.*, **104**, 343 (1974).
(89) T. A. Narwid, K. E. Cooney, and M. R. Uskoković, *Helv. Chim. Acta*, **57**, 771 (1974).
(90) C. Byon and M. Gut, *J. Org. Chem.*, **41**, 3716 (1976).
(91) P. B. Dervan and M. A. Shippey, *J. Am. Chem. Soc.*, **98**, 1265 (1976).
(92) R. Tschesche, B. Goossens, G. Piesterl, and A. Töpfer, *Tetrahedron*, **33**, 735 (1977).
(93) W. R. Nes, T. E. Varkey, and K. Krevitz, *J. Am. Chem. Soc.*, **99**, 260 (1977).
(94) M. Koreeda, private communication.
(95) Zh. S. Sydykov and G. M. Segal, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 258 (1976); *Chem. Abstr.*, 87, 23603 (1977).
(96) Zh. S. Sydykov and G. M. Segal, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1426 (1976); *Chem. Abstr.*, **86**, 16836 (1977).
(97) G. Hüppi and J. B. Siddall, *J. Am. Chem. Soc.*, **89**, 6790 (1967).
(98) F. Reinbach-Hirtzbach and G. Ourisson, *Tetrahedron Lett.*, 1363 (1973).
(99) A. Romeo and R. Villotti, *Ann. Chim. (Rome)*, **47**, 618 (1957); *Chem. Abstr.*, **51**, 16506 (1957).
(100) A. Martinez, A. Romeo, and V. Tortorella, *Gazz. Chim. Ital.*, **97**, 96 (1967).
(101) G. Tarzia, V. Tortorella, and A. Romeo, *Gazz. Chim. Ital.*, **97**, 102 (1967).
(102) D. H. R. Barton, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 53 (1972).
(103) J. P. Poyser and G. Ourisson, *J. Chem. Soc., Perkin Trans. 1*, 2061 (1974).
(104) J. P. Poyser, F. Reinach-Hirtzbach, and G. Ourisson, *Tetrahedron*, **30**, 977 (1974).
(105) E. C. Eyley and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 731 (1976).
(106) H. Hikino, T. Okuyama, S. Arihara, Y. Hikino, T. Takemoto, H. Mori, and K. Shibata, *Chem. Pharm. Bull.*, **23**, 1458 (1975).
(107) C. C. Eyley and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 727 (1976).
(108) N. K. Chaudhuri, R. Nickolson, H. Kimball, and M. Gut, *Steroids*, **15**, 525 (1970).
(109) D. H. R. Barton, P. G. Feakins, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc. C*, 1584 (1970).
(110) H. Mori and K. Shibata, *Chem. Pharm. Bull.*, **17**, 1970 (1969).
(111) H. Hikino, K. Mohri, Y. Hikino, S. Arihara, T. Takemoto, H. Mori, and K. Shibata, *Tetrahedron*, **32**, 3015 (1976).
(112) I. T. Harrison, J. B. Siddall, and J. H. Fried, *Tetrahedron Lett.*, 3457 (1966).
(113) A. Furlenmeier, A. Fürst, A. Langemann, G. Waldvogel, P. Hocks, U. Kerb, and R. Wiechert, *Experientia*, **22**, 573 (1966).
(114) U. Kerb, P. Hocks, and R. Wiechert, *Tetrahedron Lett.*, 1387 (1966).
(115) U. Kerb, G. Schulz, P. Hocks, R. Wiechert, A. Furlenmeier, A. Fürst, A. Langeman, and G. Waldvogel, *Helv. Chim. Acta*, **49**, 1601 (1966).
(116) A. Furlenmeier, A. Fürst, A. Langeman, G. Waldvogel, P. Hocks, U. Kerb, and R. Wiechert, *Helv. Chim. Acta*, **50**, 2387 (1967).
(117) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963); **87**, 5661, 5670 (1965).
(118) H. A. Staab, M. Lüking, and F. H. Dürr, *Chem. Ber.*, **95**, 1275 (1962).
(119) H. A. Staab and H. Braünling, *Justus Liebigs Ann. Chem.*, **654**, 119 (1962).
(120) K. Kihira, T. Kuramoto, and T. Hoshita, *Steroids*, **27**, 383 (1976).
(121) H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Chem. Pharm. Bull.*, **17**, 690 (1969).
(122) H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Tetrahedron*, **27**, 1157 (1971).
(123) J. B. Siddall, A. D. Cross, and J. H. Fried, *J. Am. Chem. Soc.*, **88**, 862 (1966).
(124) W. Sucrow and B. Radüchel, *Chem. Ber.*, **102**, 2629 (1969).
(125) W. Sucrow and B. Girgensohn, *Chem. Ber.*, **103**, 750 (1970).
(126) W. Sucrow, M. Slopianka, and P. P. Caldeira, *Chem. Ber.*, **108**, 1101 (1975).
(127) W. Sucrow, B. Schubert, W. Richter, and M. Slopianka, *Chem. Ber.*, **104**, 3689 (1971).
(128) T. C. McMorris and R. Seshadri, *Chem. Commun.*, 1646 (1971).
(129) T. C. McMorris, T. Arunachalan, and R. Seshadri, *Tetrahedron Lett.*, 2673 (1972).
(130) T. C. McMorris, R. Seshadri, and T. Arunachalan, *J. Org. Chem.*, **39**, 669 (1974).
(131) J. A. Edwards, J. S. Mills, J. Sundeen, and J. H. Fried, *J. Am. Chem. Soc.*, **91**, 1248 (1969).
(132) J. A. Edwards, J. Sundeen, W. Salmond, T. Iwadare, and J. H. Fried, *Tetrahedron Lett.*, 791 (1972).
(133) H. Ripperger and K. Schreiber, *Z. Chem.*, **14**, 273 (1974).
(134) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **81**, 5987 (1959).
(135) D. J. Cram and F. A. Abd-Elhafez, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
(136) J. P. Poyser, F. Reinbach-Hirtzbach, G. Ourisson, *J. Chem. Soc., Perkin Trans. 1*, 378 (1974).
(137) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).
(138) J. J. Partridge, S. Farber, and M. R. Uskoković, *Helv. Chim. Acta*, **57**, 764 (1974).
(139) E. Stelner, C. Djerassi, E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, and D. Sica, *Helv. Chim. Acta*, **60**, 475 (1977).
(140) S. K. Das Gupta, D. R. Crump, and M. Gut, *J. Org. Chem.*, **39**, 1658 (1974).
(141) M. F. Semmelhack, *Org. React.*, **19**, 115 (1972).
(142) J. P. Moreau, D. J. Aberhart, and E. Caspi, *J. Org. Chem.*, **39**, 2018 (1974).
(143) W. G. Salmond and K. D. Maisto, *Tetrahedron Lett.*, 987 (1977).
(144) For a general consideration of the Wittig reaction stereochemistry, see H. O. House, V. K. Jones, and G. A. Frank, *J. Org. Chem.*, **29**, 3327 (1964).
(145) R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, **15**, 113 (1970).
(146) M. Fryberg, A. C. Oehlschlager, and A. M. Unrau, *Tetrahedron*, **27**, 1261 (1971).
(147) Y. M. Sheikh and C. Djerassi, *Steroids*, **26**, 129 (1975).
(148) W. Sucrow, W. Littman, and B. Radüchel, *Chem. Ber.*, **110**, 1523 (1977).
(149) W. Sucrow, M. Slopianka, and P. Lamy, *Chem. Ber.*, **108**, 754 (1975).
(150) R. Budziarek, F. Johnson, and F. S. Spring, *J. Chem. Soc.*, 3410 (1952).
(151) R. C. Anderson, R. Stevenson, and F. S. Spring, *J. Chem. Soc.*, 2901 (1952).
(152) J. Elks, R. M. Evans, J. F. Oughton, and G. H. Thomas, *J. Chem. Soc.*, 463 (1954).
(153) T.N. Margulis, C. F.Hammer, and R. Stevenson, *J. Chem. Soc.*, 4396 (1964).
(154) P. S. Ellington, D. G. Hey, and D. G. Meakins, *J. Chem. Soc.*, 1327 (1966).
(155) D. H. R. Barton, J. P. Poyser, P. G. Sammes, M. B. Hursthouse, and S. Neidle, *Chem. Commun.*, 715 (1971).
(156) M. Nakane, M. Morisaki, and N. Ikekawa, *Tetrahedron*, **31**, 2755 (1975).
(157) D. C. Hodgkin, M. S. Webster, and J. D. Dunitz, *Chem. Ind. (London)*, 1148 (1957).
(158) F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492 (1965).
(159) D. H. R. Barton, A. A. L. Gunatilaka, T. Nakanishi, H. Patin, D. A. Widdowson, and B. R. Worth, *J. Chem. Perkin Trans. 1*, 821 (1976).
(160) R. C. Nickolson and M. Gut, *J. Org. Chem.*, **37**, 2119 (1972).
(161) W. Sucrow and B. Girgensohn, *Chem. Ber.*, **103**, 745 (1970).
(162) W. G. Salmond, M. C. Sobala, and K. D. Maisto, *Tetrahedron Lett.*, 1237 (1977).
(163) N. Entwistle and A. D. Pratt, *Tetrahedron*, **25**, 1449 (1969).
(164) A. O. Colonna and E. G. Gros, *J. Steroid Biochem.*, **4**, 171 (1973).
(165) M. Morisaki, N. Awata, Y. Fujimoto, and N. Ikekawa, *J. Chem. Soc., Chem. Commun.*, 362 (1975).
(166) Y. Fujimoto, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 2302 (1975).
(167) J. J. Partridge, V. Toome, and M. R. Uskoković, *J. Am. Chem. Soc.*, **98**, 3739 (1976).
(168) K. B. Sharpless, R. C. Michaelson, and J. D. Cuttings, *J. Am. Chem. Soc.*, **95**, 6136 (1973); S. Tanaka, H. Yamamoto, and H. Nozaki, *ibid.*, 96, 5254 (1974).
(169) H. Wieland and R. Jacobi, *Chem. Ber.*, **59**, 2064 (1926).
(170) F. Reindel and K. Niederländer, *Justus Liebigs Ann. Chem.*, **522**, 218 (1936).
(171) D. M. Piatak and J. Schwartzinger, unpublished results.
(172) T. Mochizuki, *Proc. Jpn. Acad.*, **32**, 206 (1956); *Chem. Abstr.*, **51**, 1221 (1957).
(173) Y. Y. Lin and L. L. Smith, *J. Labeled Compds.*, **10**, 541 (1974).
(174) B. Riegel and I. A. Kaye, *J. Am. Chem. Soc.*, **66**, 723 (1944).
(175) E. Fernholz, *Chem. Ber.*, **69**, 1792 (1936).
(176) H. Seno, *Proc. Jpn. Acad.*, **31**, 733 (1955).
(177) W. H. Pearlman, *J. Am. Chem. Soc.*, **69**, 1475 (1947).
(178) H. Lettré, A. Egle, J. von Jena, and K. Mathes, *Justus Liebigs Ann. Chem.*, **708**, 224 (1967).
(179) B. I. Cohen, G. S. Tint, T. Kuramoto, and E. H. Mosbach, *Steroids*, **25**, 365 (1975).
(180) W. G. Dauben and P. H. Payot, *J. Org. Chem.*, **21**, 129 (1956).
(181) R. B. Woodward, A. A. Patchett, D. H. R. Barton, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).
(182) For reviews, see B.C. L. Weedon, *Q. Rev. Chem. Soc.*, **6**, 380 (1952); *Adv. Org. Chem.*, **1**, 1 (1960).
(183) T. Kazuno, A. Mori, K. Sasahi, M. Kuroda, and M. Mizuguchi, *Proc. Jpn. Acad.*, **28**, 416 (1952).
(184) T. Kazuno and A. Mori, *Proc. Jpn. Acad.*, **30**, 486 (1954).
(185) S. Bergström, K. Pääbo, and J. A. Rumpf, *Acta Chem. Scand.*, **8**, 1109 (1954).
(186) S. Bergström and L. Karabisch, *Acta Chem. Scand.*, **11**, 1067 (1957).

(187) J. Bjorkhem, *Eur. J. Biochem.*, **51**, 137 (1975).
(188) R. J. Bridgwater, *Biochem. J.*, **64**, 593 (1956).
(189) T. Briggs, *J. Org. Chem.*, **35**, 1431 (1970).
(190) A. Ercoli and P. deRuggeri, *Gazz. Chim. Ital.*, **83**, 720 (1953).
(191) A. Ercoli and P. deRuggeri, *J. Am. Chem. Soc.*, **75**, 3284 (1953).
(192) N. Harada, M. Ohashi, and K. Nakanishi, *J. Am. Chem. Soc.*, **90**, 7349 (1968).
(193) W. Bergmann and J. P. Dusza, *J. Org. Chem.*, **23**, 459 (1958).
(194) M. Morisaki, J. Rubio-Lightbourn, N. Ikekawa, and T. Takeshita, *Chem. Pharm. Bull.*, **21**, 2568 (1973).
(195) M. Seki, J. Rubio-Lightbourn, M. Morisaki, and N. Ikekawa, *Chem. Pharm. Bull.*, **21**, 2783 (1973).
(196) U. Wrzeciono, C. F. Murphy, G. Ourisson, S. Corsano, J.-D. Ehrhardt, M.-F. Lhomme, and G. Teller, *Bull. Soc. Chim. Fr.*, 966 (1970).
(197) J. E. Herz and S. C. Montalvo, *J. Chem. Soc., Perkin Trans. 1*, 1233 (1973).
(198) J. E. Herz and S. C. Montalvo, *Org.Prep. Proced. Int.*, **7**, 16 (1975).
(199) M. Morisaki, J. Rubio-Lightbourn, and N. Ikekawa, *Chem. Pharm. Bull.*, **21**, 457 (1973).
(200) N. Koizumi, M. Morisaki, N. Ikelawa, A. Suzuki, and T. Takeshita, *Tetrahedron Lett.*, 2203 (1975).
(201) N. Ikekawa, M. Morisaki, N. Koizumi, Y. Kato, and T. Takeshita, *Chem. Pharm. Bull.*, **23**, 695 (1975).
(202) M. Seki, N. Koizumi, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 15 (1975).
(203) J. D. Gilbert and C. J. W. Brooks, *Anal. Lett.*, 639 (1973).
(204) C. J. W. Brooks and J. D.Gilbert, *J. Chem. Soc., Chem. Commun.*, 194 (1973).
(205) R. Labriola and G. Ourisson, *C. R. Acad. Sci.*, **270**, 1885 (1970).
(206) R. Labriola and G. Ourisson, *Tetrahedron*, **27**, 1901 (1971).
(207) A. I. Ryer, W. H. Gebert, and N. M. Murrill, *J. Am. Chem. Soc.*, **72**, 4247 (1950).
(208) W. G. Dauben and H. L. Bradlow, *J. Am. Chem. Soc.*, **72**, 4248 (1950).
(209) Y. Fujimoto, N. Awata, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 4335 (1974).
(210) R. K. Varma, M. Koreeda, B. Yagen, K. Nakanishi, and E. Caspi, *J. Org. Chem.*, **40**, 3680 (1975).
(211) N. Ikekawa, K. Tsuda, and N. Morisaki, *Chem. Ind. (London)*, 1179 (1966).
(212) W. Sucrow and B. Radüchel, *Chem. Ber.*, **103**, 2711 (1970).
(213) G. A. Smith and D. H. Williams, *J. Chem. Soc.,Perkin Trans. 1*, 2811 (1972).
(214) C. R. Popplestone and A. M. Unrau, *Can. J. Chem.*, **51**, 1223 (1973).
(215) S. M. L. Chen, K. Nakanishi, N. Awata, M. Morisaki, N. Ikekawa, and Y. Shimizu, *J. Am. Chem. Soc.*, **97**, 5297 (1975).
(216) K. Nakanishi, D. A. Schooley, M. Koreeda, and J. Dillon, *Chem. Commun.*, 1235 (1971).
(217) Y. Fujimoto, M. Morisaki, N. Ikekawa, Y. Horie, and S. Nakasone, *Steroids*, **24**, 367 (1974).
(218) N. Ikekawa, M. Morisaki, H. Ohtaka, and Y. Chiyoda, *Chem. Commun.*, 1498 (1971).
(219) W. R. Nes and T. E. Varkey, *J. Org. Chem.*, **41**, 1652 (1976).
(220) H. Ripperger and K. Schreiber, *Z. Chem.*, **14**, 274 (1974).
(221) F. Sondheimer, N. Danieli, and Y. Mazur, *J. Org. Chem.*, **24**, 1278 (1959).
(222) D. Arigoni, private communication in ref 104.
(223) W. Bergmann and J. P. Dusza, *J. Org. Chem.*, **23**, 1245 (1958).
(224) H. H. Inhoffen, *Angew. Chem.*, **70**, 576 (1958); H. H. Inhoffen and K. Irmscher, *Fortschr. Chem. Org. Naturst.*, **17**, 70 (1959).
(225) C. H. Schroeder, R. J. Lechnir, P. S. Cleveland, H. F. DeLuca, and P. H. Derse, U.S. Patent, 3,786,062 (Jan 15, 1974); *Chem. Abstr.*, **80**, 96229 (1974).
(226) M. Kobayashi and H. Mitsuhashi, *Tetrahedron*, **30**, 2147 (1974).
(227) H. Ohtaka, M. Morisaki, and N. Ikekawa, *J. Org. Chem.*, **38**, 1688 (1973).
(228) W. Littman and W. Sucrow, *Chem. Ber.*, **110**, 1607 (1977).
(229) J. Bottin and Fetizon, *Chem. Commun.*, 1087 (1971); *Bull. Soc. Chim. Fr.*, 2344 (1972).
(230) C.-Y. Byon, G. Büjüktür, P. Choay, and M. Gut, *J. Org. Chem.*, **42**, 3618 (1977).
(231) T. Makino, K. Shibata, D. C. Rohrer, and Y. Osawa, *J. Org. Chem.*, **43**, 276 (1978); Y. Osawa, T. Makino, K. Shibata, C. M. Weeks, and W. L. Duax, *J. Chem. Soc., Chem. Commun.*, 991 (1976).
(232) E. N. Trachtenberg, C. Byon, and M. Gut, *J. Am. Chem. Soc.*, **99**, 6145 (1977).
(233) W. R. Nes, *J. Am. Chem. Soc.*, **100**, 999 (1978).
(234) B. Lythgoe, D. A. Roberts, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 2608 (1977).
(235) M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, **13**, 701 (1974).
(236) W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 790 (1978).
(237) W. G. Salmond and M. Sobala, *Tetrahedron Lett.*, 1695 (1977).
(238) T. C. McMorris, S. R. Schow, and G. R. Weihe, *Tetrahedron Lett.*, 335 (1978).