

Synthesis of Vitamin D (Calciferol)

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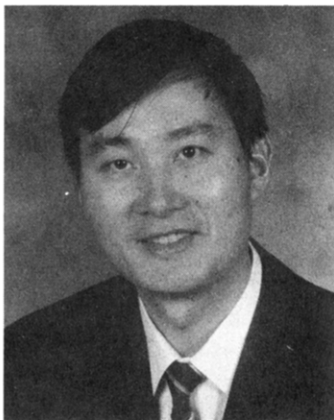
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I. Introduction

Vitamin D research from the viewpoint of its chemistry and pharmacology has expanded enormously in recent years with the discovery that 1 α ,25-dihydroxyvitamin D₃ (**1** (Figure 1), 1,25-D₃; also known as 1 α ,25-dihydroxycholecalciferol or calcitriol), the hormonally active metabolite of vitamin D, exhibits a much broader spectrum of biological activities than originally thought, well beyond its classical



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William H. Okamura was born in 1941 in Los Angeles, CA. He received his B.S. degree from UCLA in 1962 and his Ph.D. from Columbia University in 1966. As an undergraduate at UCLA Dr. Okamura carried out research with Professor Saul Winstein and then later with Professor Paul Haake. At Columbia he studied under the direction of Professor Thomas J. Katz in the area of nonbenzenoid aromaticity. After leaving Columbia, Dr. Okamura carried out one year of postdoctoral studies at Cambridge University with the late Professor Franz Sondheimer in the area of annulene chemistry. He joined the faculty at the University of California, Riverside, as Assistant Professor in 1967; he assumed his current position as Professor of Chemistry at the same institute in 1977. His major research interests are in synthetic and mechanistic organic chemistry and bioorganic chemistry. Specific areas of his research interests include the synthesis and structure–function studies of vitamin D and other bioactive molecules, studies of the mechanism and application to synthesis of pericyclic reactions, the development of allene chemistry, and studies of molecules of theoretical interest.

functions in regulating calcium and phosphorus metabolism. The diversity of activities in vitamin D research can be easily gleaned from several recent symposia-in-print including one appearing in the *Journal of Cellular Biochemistry* entitled "Vitamin D Research Frontiers" edited by A. W. Norman,¹ and another in *Bioorganic Chemistry and Medicinal Chemistry Letters* entitled "Recent Advances in Vitamin D Chemistry and Pharmacological Activity" edited by M. R. Uskokovic.² A description of the proceedings of a recent conference has appeared in the monograph, "Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications" edited by A. W. Nor-

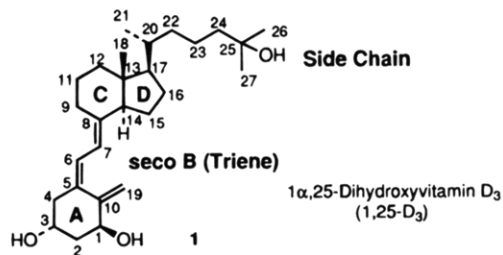


Figure 1.

man, M. Thomasset, and R. Bouillon.³ The steroid hormone 1,25-D₃ and its analogues have been used or have high potential for application as drugs in treating a diverse range of human diseases such as rickets,⁴ renal osteodystrophy,⁵ osteoporosis,⁶ psoriasis,^{7–9} leukemia,¹⁰ breast cancer,¹¹ prostate cancer,¹² AIDS,¹³ and Alzheimer's disease.^{14–16} These biomedically important applications continue to stimulate the growing interest in research on the chemistry, biology, and pharmacological applications of vitamin D.

Other detailed progress reports on various aspects of vitamin D research have been described in a series of review articles including those that relate to the endocrine system in general,^{17–23} clinical topics,^{24–27} 1,25-D₃ receptors and gene regulation,^{22,28–30} vitamin D metabolism,^{31–35} vitamin D and bone diseases,^{36,37} transcriptional control of vitamin D-regulated proteins,³⁸ immunology,^{39,40} vitamin D hydroxylases,⁴¹ cell differentiation,^{36,42} and structure–function relationships^{17,27,43–47} and chemistry (vitamin D analogues,^{45–48} synthesis of metabolites,^{49–54} and synthetic methods^{55–57}). It is the purpose of this article to provide background material including a comprehensive review of the known chemical strategies leading to the synthesis of the remarkable steroid hormone 1,25-D₃ and complimentary information which hopefully can be applied toward the synthesis of new vitamin D analogues with useful pharmacological properties of biomedical interest. The literature was surveyed through May 1995. During the preparation of this manuscript a review article on the construction of the triene unit of vitamin D and the synthesis of the vitamin D A-ring appeared.⁵⁷

A. Metabolism of Vitamin D₃

The seco-B-steroid 1,25-D₃, an essential hormonal regulator in higher animals, is produced by the metabolic pathway shown in Figure 2. The natural vitamin D₃ (**5**, D₃) is produced in skin upon ultraviolet irradiation of 7-dehydrocholesterol (**2**, 7-DHC; also called provitamin D₃) or is absorbed from the diet. The reaction in skin is believed to be a purely photochemical process, not requiring enzymes or proteins.⁵⁸ 7-DHC absorbs ultraviolet light, which effects an electrocyclic rupture of the 9,10 bond to produce previtamin D₃ (**3**, Pre-D₃). The latter is likely a biologically inert compound, which is thought to spontaneously isomerize to D₃, initially producing the 6-*s-cis* form **4** which rapidly rotates about its 6,7 single bond to its more commonly depicted (and more stable) 6-*s-trans* conformer **5**. At 37 °C in hexane, ~36 h are required for the formation of an equilibrium mixture of pre-D₃ and D₃ with the latter

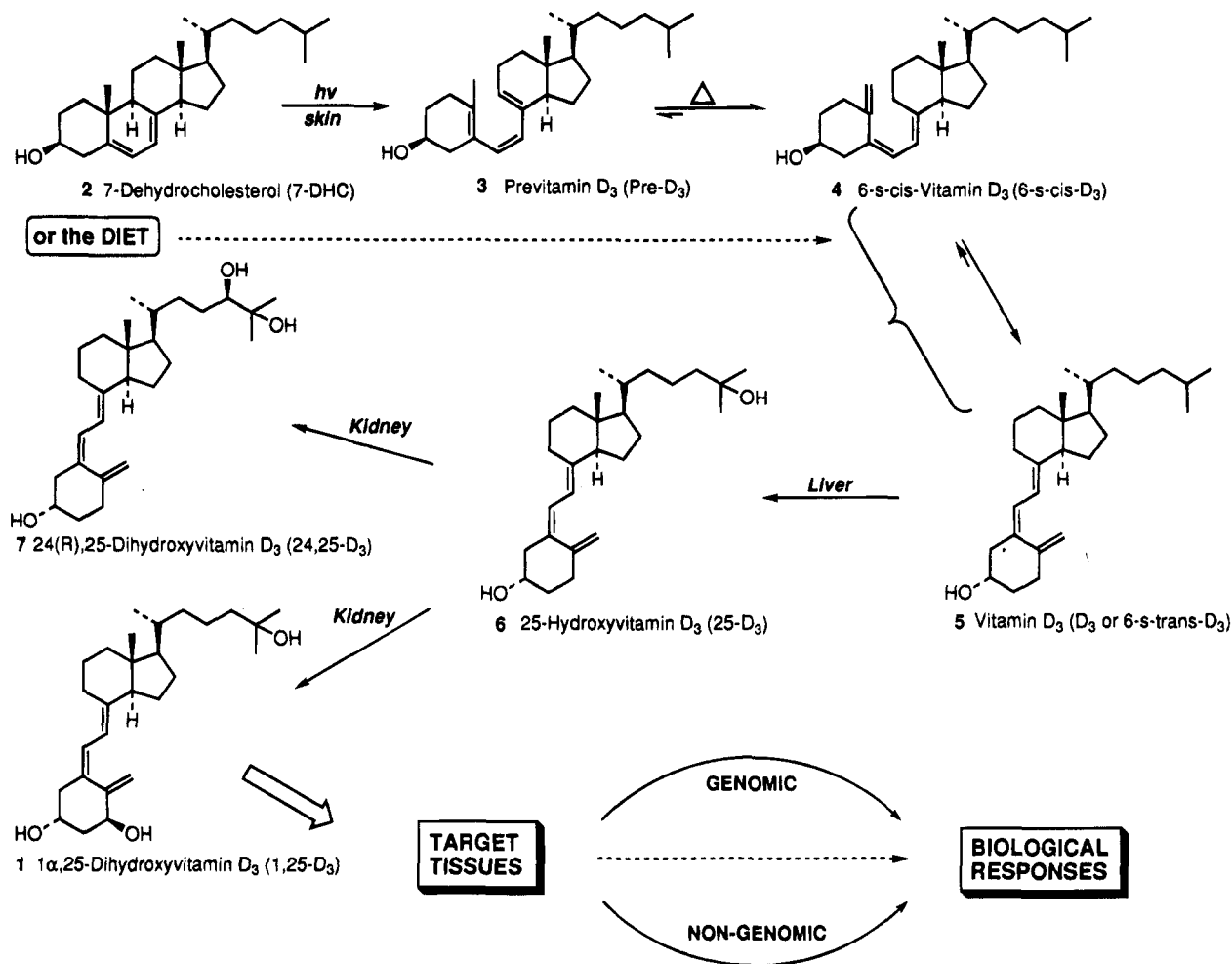


Figure 2.

predominating. This isomerization is markedly accelerated in other media such as the human skin,⁵⁹ the sea urchin *Psammechinus miliaris*,⁶⁰ phospholipid bilayers⁶¹ as well as in an aqueous solution of β -cyclodextrin.⁶² Entrapment of previtamin D₃ in its *s-cis,s-cis* conformation might be responsible for the enhanced conversion of previtamin D₃ to vitamin D₃.⁶³ A plasma protein, vitamin D binding protein (DBP), subsequently transports D₃ to the liver⁶⁴ where metabolic alteration required for hormonal function is initiated.⁶⁵ The conversion of D₃ to 25-hydroxyvitamin D₃ (**6**, 25-D₃) in liver is carried out by a microsomal system requiring NADPH, molecular oxygen, a flavoprotein, and a cytochrome P-450.⁶⁶ Additional 25-hydroxylation is carried out by a mitochondrial vitamin D₃ hydroxylase,⁶⁷ which has recently been cloned.⁶⁸ The metabolite 25-D₃, the major circulating form of the vitamin D in serum, is then further metabolized to 1,25-D₃ in the kidney. This 1 α -hydroxylation occurs exclusively in the renal mitochondrial fraction⁶⁹ except in the pregnant mammal in which the placenta can also perform the hydroxylation. 1 α -Hydroxylation involves NADPH, a flavoprotein, an iron sulfur protein, and a cytochrome P-450.⁷⁰ Other major metabolites of 25-D₃ includes 24(R),25-dihydroxyvitamin D₃ (**7**, 24,25-D₃), which is also produced in the kidney.^{31,32,41} The hormone 1,25-D₃ is transported via the plasma to target cells located for example in the intestine, kidney, and bone. In these target cells, 1,25-D₃

interacts with specific receptors of the hormone such as the vitamin D receptor (n-VDR).^{22,28–30} The interaction between the ligand and this receptor or other receptors then leads to genomic or nongenomic responses as described below.⁷¹

B. Mode of Action of the Steroid Hormone 1 α ,25-Dihydroxyvitamin D₃

It is currently believed⁷¹ that the steroid hormone 1,25-D₃ generates biological responses via genomic or nongenomic pathways. In the genomic pathway, the nuclear receptor for 1,25-D₃ (n-VDR) has been shown to belong to the same superfamily of transactivating regulators of gene transcription that includes the receptors for estradiol, progesterone, testosterone, dihydrotestosterone, cortisone, aldosterone, thyroid hormone, and retinoic acid.^{29,72} The functional form of steroid receptors, including that of 1,25-D₃, is a protein dimer, either homodimeric or heterodimeric, with a subset of the same or other steroid receptors.⁷³ The vitamin D receptor contains multiple dimerization interfaces that are functionally different.⁷⁴ This complex is the active factor in vitamin D-mediated transcription.⁷⁵ Binding of 1,25-D₃ to its receptors (n-VDRs) is believed to induce distinct conformational changes in the protein, considered to be central to the ligand-receptor complex activation,⁷⁶ rendering it able to activate gene, induce protein synthesis, and elicit a physiological response.

Rapid nongenomic activation by 1,25-D₃ has been observed both at the cellular and subcellular level. While an understanding of the mechanism of nongenomic actions of 1,25-D₃ is still at an early stage, such effects have been shown to occur in a number of target tissues. For example, the rapid nongenomic calcium transport effect in intestinal cell tissues is known as transcaltachia. These nongenomic actions of 1,25-D₃ including membrane voltage-gated calcium channel opening, prostaglandin production, phospholipase C, and protein kinase C (PKC) activation are believed to be mediated by a membrane 1,25-receptor (m-VDR).⁷⁷ Direct activation of PKC by 1,25-D₃ has also been observed.⁷⁸ It is postulated that the rapid nongenomic action generated by interaction with m-VDR modulate the effects of the hormone on gene transcription via an interaction with n-VDR.^{77a} m-VDR and n-VDR have different binding characteristics, the former recognizes 1,25-D₃ and its 1 β -epimer, 1 β ,25-dihydroxyvitamin D₃, as an antagonist.^{79,80} It has been suggested that the n-VDR and the m-VDR prefer strikingly different conformations of the agonist 1,25-D₃, m-VDR preferring the 6-*s-cis* conformation of 1,25-D₃ while n-VDR preferring its 6-*s-trans* conformation.⁸⁰

C. Structural Features of 1 α ,25-Dihydroxyvitamin D₃⁸¹

Structure Determines Biological Function. The structurally dynamic hormone 1,25-D₃ involves initial, highly stereoselective binding to a myriad of target proteins including receptors (n-VDR and m-VDR), serum transport protein (DBP) and various enzymes involved in its metabolic production or catabolism. A knowledge of the topology and dynamic behavior of the free steroidal guest molecule (or analogues) in its stereoselective binding to receptor or other protein hosts is most important to an assessment of intelligible structure–activity correlations. This information is essential in designing yet more effective analogues for therapeutic purposes.

Although the X-ray crystallographic structure of the hormone 1,25-D₃ has not yet been achieved, its solid-state structure can be deduced from well-documented X-ray results of other vitamin D metabolites, derivatives, and analogues.⁸² The solution structures of 1,25-D₃ was assessed primarily through ¹H NMR spectral studies.^{83–90} Together with studies on electronic absorption data and molecular mechanics computations,^{43,91–96} the structure of this vitamin D metabolite may be summarized as follows. The A-ring exists in dynamic equilibrium between nearly equimolar amounts of the two A-ring chair conformations **8** and **10** (Figure 3). In conformer **8**, the hydroxyl at C-1 is axially oriented, whereas that at C-3 is equatorial. In conformer **10**, the hydroxyl at C-1 is equatorial, whereas that at C-3 is axial. Because of the presence of two exocyclic double bonds, there is a >50° out of plane twist angle between the $\Delta^{5,6}$ - and the $\Delta^{10,19}$ -double bonds, which imparts a chairlike shape to the A ring. Moreover, the chairlike nature of the A ring was evident from X-ray crystallographic studies of other analogues. Because of the facile conformational isomerism about single bonds, the flattened twist boat form **9** may be present

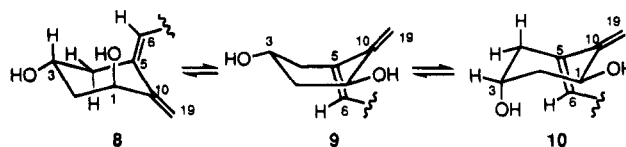


Figure 3.

in significant amounts. These twist boat forms of the A ring, although likely lower in concentration, are fully accessible and could equally as well be involved in receptor binding as the more stable chair conformers.

Regarding the triene structure (seco B-ring) of vitamin D, electronic spectra suggest that only two of the three double bonds of the triene system of the molecule are fully conjugated. The $\Delta^{5,6}$ - and the $\Delta^{7,8}$ -double bonds are nearly coplanar and *s-trans* (or *transoid*) as in **1** in Figure 4. The exocyclic $\Delta^{10,19}$

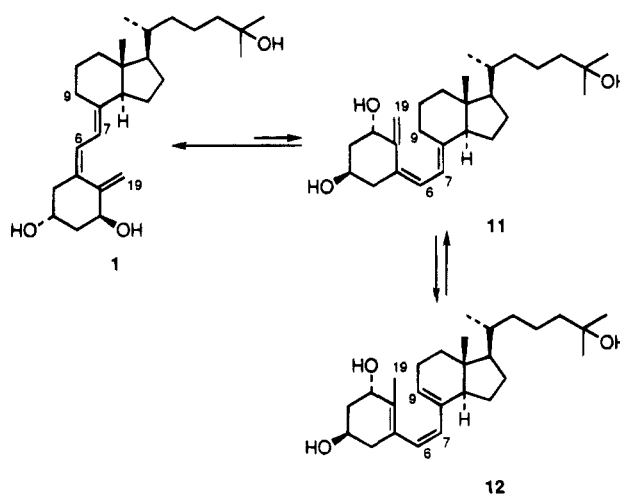


Figure 4.

double bond is oriented above or below the plane defined by the $\Delta^{5,7}$ -diene as implied in the structures shown in Figure 3. The ability of 1,25-D₃ to rotate about the $\Delta^{6,7}$ -single bond must be extremely facile, possessing barriers similar to that observed for 1,3-butadiene. DeLaroff⁸³ first showed that the $\Delta^{6,7}$ -single bond of D₃ in solution is *transoid* on the basis of ¹H NMR coupling constants. Although direct spectroscopic evidence for the presence of a 6-*s-cis* conformation is lacking, all of the D vitamins possessing the Z-hexatriene unit characteristic of 1,25-D₃ must possess kinetically competent concentrations of the 6-*s-cis* conformation **11** (Figure 4). It is this conformation which is required of the observation that 1,25-D₃ can equilibrate with the corresponding 1 α ,25-dihydroxyprevitamin D₃ (**12**, 1,25-pre-D₃) form via a [1,7]-sigmatropic shift (by hydrogen migration from C-9 to C-19). Likewise, the back rearrangement of a hydrogen from the C-19 to C-9 of 1,25-pre-D₃ to afford 1,25-D₃ is also known to occur.⁹⁷

The C-ring is chairlike, flattened in the vicinity of C-8 due to the presence of the exocyclic double bond, and possesses an unusually large torsion angle at C-13,C-14 due to the CD *trans*-ring junction. The conformation of the D-ring may be depicted as a dynamic mixture of envelope and half-chair forms (Figure 5). The CD hydrindan system is a relatively rigid portion of the 1,25-D₃ molecule with restricted

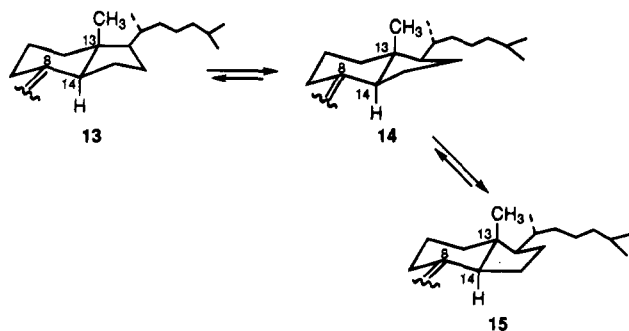


Figure 5.

dynamic behavior. To simplify matters, the CD ring of 1,25-D₃ can be depicted as a rigid anchor to which is attached at C-8 and C-17, the dynamic triene/A-ring and side chain, respectively.

The 25-hydroxycholesterol side chain is obviously the most flexible structural unit of 1,25-D₃. Six rotatable bonds (represented by the curved arrows in Figure 6) can lead to a large number of unique

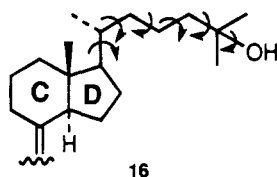


Figure 6.

staggered conformations ($3^6 = 729$). Molecular mechanics analyses have been carried out in order to usefully depict the large number of these energy-minimized side-chain conformers, to estimate the volume in space occupied by the side chain, and to locate possible occupation sites for the important 25-hydroxy group.^{43,96,98}

While these analyses provide a simple method for evaluating the orientation of the important side chain including analogues with conformationally restricted side chains, the application to an understanding of the conformation of ligand when bound to protein is limited. Molecular mechanics methods lead to conformational minima of free ligand, but less stable (higher energy) conformers may actually be involved in protein binding. In general, the conformational flexibility of the side chain, the seco-B triene system, the A-ring, and even the semirigid CD unit of 1,25-D₃ is such that there may be little resemblance between free ligand structure and the ligand structure when bound to protein. Moreover, with respect to the notion that steroid hormones function by inducing a conformational change in protein upon binding (from an inactive conformer to an active conformer induced by ligand binding), the situation for 1,25-D₃ and its metabolites is unique. Classical steroid hormones with the fully intact ABCD ring are relatively rigid. Because of the flexibility of the 1,25-D₃ molecule, there exists the possibility of a *mutually induced fit* between ligand and protein. An implication of the "mutually induced fit hypothesis" is that biologically effective analogues and metabolites will best initially fit into protein active sites in a loose, but not too loose, fashion.

The current strategy for gleaned useful structure-function information entails systematic studies of the

synthesis of conformationally biased analogues in terms of their ability to bind to various receptors and other proteins. This appears to be the only practical approach at this time, but future studies will undoubtedly provide more sophisticated approaches. Namely, as the molecular biology of 1,25-D₃ related proteins emerges, these proteins including site-directed mutated forms of binding proteins and hormone receptors will become available. This will make possible direct studies of the native ligand-protein complex. Nuclear magnetic resonance studies (e.g., using site specifically labeled protein and/or ligand, or even direct X-ray crystallographic applications) should be feasible in the not too distant future. *Collaborative efforts between chemists and biologists will be critical in this regard.*

II. General Synthetic Approaches to 1 α ,25-Dihydroxyvitamin D₃

A. Overview

Some of the major synthetic routes utilized in recent years to synthesize the hormone 1,25-D₃ and its various analogues are the eight methods A-H depicted in Figure 7. Method A, the classical approach, is patterned after the biosynthetic route leading to vitamin D₃ and also after the industrial synthesis of the latter.^{99,100} This entails the photochemical ring opening of a 1 α -hydroxylated side chain-modified derivative of 7-dehydrocholesterol **17**, initially producing a previtamin, which is easily thermolyzed to the vitamin D.

The phosphine oxide coupling approach B is probably the most useful method for producing side chain and other analogues. In this method first developed by Lythgoe,¹⁰¹⁻¹⁰⁶ the phosphine oxide **18** is coupled to a Grundmann's ketone derivative of type **19**, directly producing the 1,25-D₃ skeleton. The shortcoming of this route is that the synthesis of the A-ring fragment **18** is somewhat tedious, requiring close to 15 steps. Nevertheless, the Hoffmann-La Roche group,¹⁰⁷ as well as De Clercq in Belgium,¹⁰⁸ and Posner at Johns Hopkins¹⁰⁹ among others, have championed this method.

Method C, wherein dienynes of the type **20** are semihydrogenated to a previtamin structure which undergoes rearrangement to the corresponding vitamin D analogue, was also developed by Lythgoe.¹¹⁰ Approach C, including recent developments by Mouriño's laboratory in Spain^{111,112} as well as by the Okamura group,¹¹³ takes advantage of the fact that the A-ring synthon **21** is more easily available than **18**. The synthesis developed in the Okamura laboratory for **21** starting with (*S*)-carvone is probably the most efficient approach in this area.¹¹⁴

Method D, the vinylallene approach developed in the Okamura laboratory,¹¹⁵ involves the production of **22** from **21** and the subsequent rearrangement of the former using either heat or a combination of metal-catalyzed isomerization followed by sensitized photoisomerization.¹¹⁶

Method E, due to the recent findings of Trost¹¹⁷ and others,¹¹⁸ involves an acyclic A-ring precursor **23**, which is intramolecularly cross coupled to the vinylbromide **24** leading directly to the 1,25-D₃ skeleton.

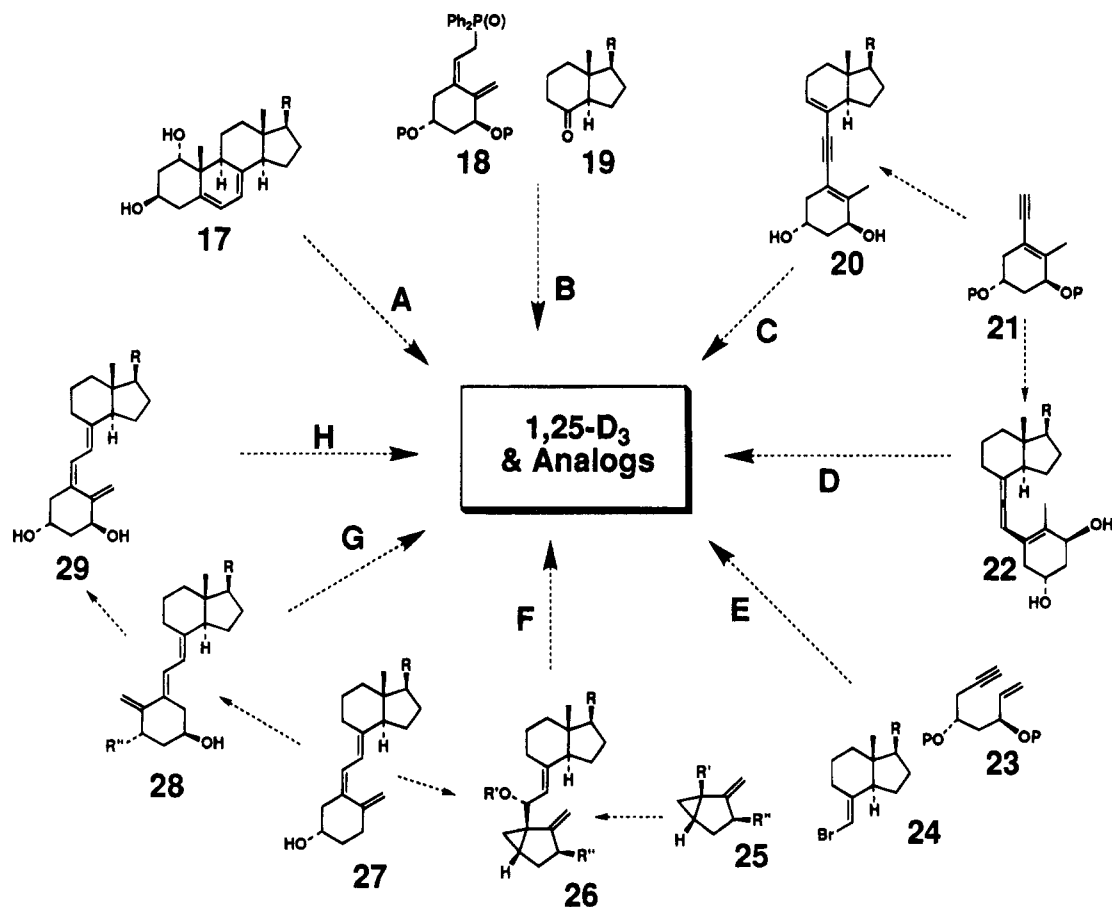


Figure 7.

This is a relatively new approach which will undoubtedly see further exploitation. Method F, based on initial studies of Mazur in Israel,¹¹⁹ has been nicely developed by several groups, particularly the Schnoes-DeLuca group in Wisconsin,¹²⁰ for the production of vitamin D metabolites and analogues. In the Mazur approach, the tosylate of **27** is isomerized to the *i*-steroid **26** which can be modified at carbon-1 and then subsequently back-isomerized under solvolytic conditions to afford $1\alpha,25\text{-D}_3$ or analogues. Recent studies, particularly by the Hoffmann-La Roche¹²¹ and Wilson¹²² groups, have led to the separate production of bicyclo[3.1.0] hexane derivatives **25** in a convergent total synthetic approach to **26**.

Method G, the direct modification of vitamin D derivatives of type **27** to 1-oxygenated 5,6-*trans* vitamin D derivatives **28**, is also a promising new approach. This approach, one of the best variants being attributable to Barton (Texas),¹²³ is an efficacious method because triplet photosensitizers are now known to efficiently geometrically isomerize **28** to $1,25\text{-D}_3$ and its analogues.^{116,124,125} Another very effective method is to use Diels-Alder cycloadducts of **27** or **28** which can be utilized as intermediates for modification of the side chain R.¹²⁶

Yet another method is to utilize Diels-Alder adducts of the previtamin D form of **27**, which after suitable modification, can then be cycloreverted to $1,25\text{-D}_3$ through the intermediacy of a previtamin form via thermal isomerization.¹²⁷ Method H entails the direct modification of $1,25\text{-D}_3$ or an analogue, generalized as structure **29**, through use of suitable protecting groups, such as transition metal deriva-

tives or by other chemical transformations directly on **29**. The latter method is now feasible because $1,25\text{-D}_3$ is relatively easy to access due to the development of methods A through G just cited. Finally, there are synthetic approaches not shown in Figure 7, which besides methods A-H, will be discussed in turn in sections II.B through II.I. Sections III and IV will cover a series of additional topics, which complement the core synthetic topics to be discussed in this section II.

B. Method A: Photochemical Ring Opening of Steroidal $\Delta^{5,7}$ -Dienes

The photochemical ring opening of 7-DHC **2** and derivatives **17** was the earliest method of semisynthesis of D_3 , 25-D_3 , and $1,25\text{-D}_3$ and still remains the main industrial procedure for conducting these syntheses. This approach, usually starting from an Δ^{5} -en- 3β -ol sterol, involves four main parts: photochemical conversion of 7-DHC derivatives to previtamin D and then vitamin D derivatives; introduction of the $\Delta^{7,8}$ -double bond; and modification of the A-ring including introduction of a 1α -hydroxy group; modification of the side chain to be discussed later in another section.

1. Photochemical Conversion of 1α -Hydroxy-7-dehydrocholesterol to 1α -Hydroxyvitamin D_3 ¹²⁸

The conversion of 7-DHC **2** to D_3 via Pre- D_3 **3** is the least efficient step in the classical commercial preparation of D_3 or in the application to the syn-

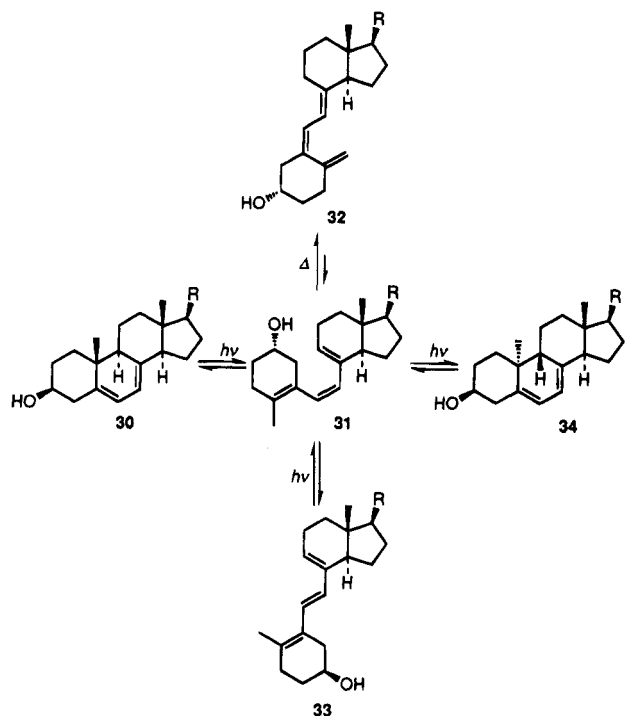


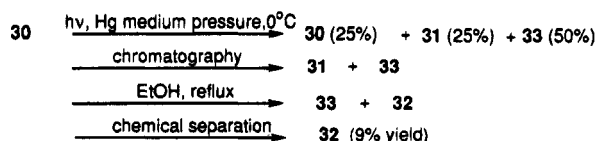
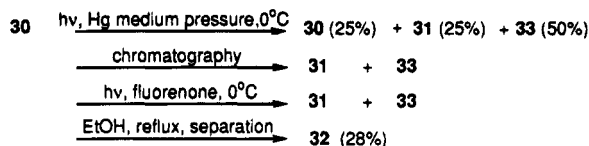
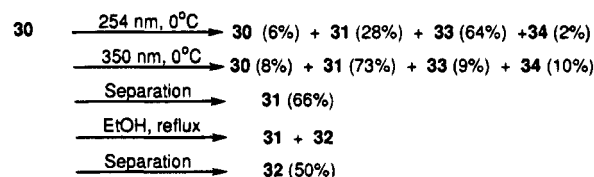
Figure 8.

thesis of biologically active metabolites and analogues. In general, the yield of provitamins **31**, and hence the vitamins **32**, obtained from the irradiation of the provitamins **30** is low, partly because of the photolytic conversion of the provitamins **31** into tachysterols **33**, lumisterols **34**, and other irradiation products (Figure 8).¹²⁹ The evolution of improved photochemical conditions for preparing vitamin D in terms of distribution of products, conversion and reaction conditions are summarized as approaches 1–3 in Table 1 using the simple provitamin **30** as substrate. Direct irradiation afforded only low yields of vitamin D (approach 1). It was later determined that reirradiation of the photolysis mixture in the presence of fluorenone as triplet photosensitizer afforded previtamin D as the major component (approach 2, Table 1).¹³⁰

The influence of wavelength on product distribution has been studied in detail.^{99,131–134} Initially, it was found that employment of light of 295 nm wavelength afforded the maximum yield of previtamin **31** (isolated yield, 31–33%), the calculated composition of which is 1% **30**, 70% **31**, 26% **33**, and 3% **34**. Later, Dauben showed that a two-step direct irradiation scheme, first using light of 254 or 300 nm followed by light of >330 nm, gave an 83% yield of **31** (HPLC) at 95% conversion of **30**.^{128,135,136} On a preparative scale the two-step irradiation of **30**, first at 254 nm and then at 350 nm light, gave a 66% isolated yield of **31**, which was converted to the vitamin D in an overall 50% yield (approach 3, Table 1).

Similar to the formation of vitamin D **32** by irradiating provitamin D **30**,¹³¹ an optimal yield of the 1 α -hydroxylated form of **32** was obtained on irradiation of 1 α -hydroxylated **30** with monochromatic UV light at 295 nm.¹³² Thermal conversion of **31** to **32** at 45 °C (24 h) gave the highest proportion of **32** relative to **31** (95/5). With regard to the industrial production of 1 α -hydroxyvitamin D₃ (**32**

Table 1

Approach 1: One Stage Broad Range Medium Pressure Hg Lamp Irradiation

Approach 2: Two Stage Irradiation

Approach 3: Wavelength Controlled Irradiation


with the cholesterol side chain), an economical UV light stable filter solution has been developed using a high-pressure mercury lamp to afford a 39% yield of the 1 α -hydroxylated form of **32**.¹³² Still improved yields of this same substance was obtained by using the two-step procedure given in approach 3 (Table 1).^{128,135} An overall 47% yield of vitamin was obtained on a gram scale via a two-step irradiation procedure with an economical medium-pressure mercury lamp, first by adding ethyl 4-(dimethylamino)benzoate and then second by inserting a uranium filter.¹³⁷

2. Introduction of the $\Delta^{7,8}$ Double Bond and 1 α -Hydroxy Group to Δ^5 -Steroids

There have been described at least five methods for introducing the 1 α -hydroxy group to cholesterol. In method i (Figure 9), the Δ^5 steroid was first transformed into **36** bearing a C-6 acetal^{138–140} or 6 β -alcohol^{141,142} in the form of ketone **36**. Bromination of **36** followed by dehydrohalogenation afforded the Δ^1 -enone **37**. Epoxy ketone **38** was then prepared by the treatment of **37** with alkaline hydrogen peroxide. The overall yield for the three-step sequence from **36**

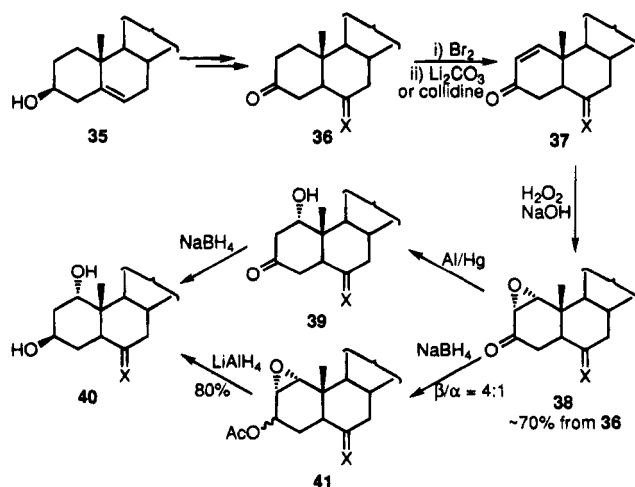


Figure 9.

is about 70%. Reduction of the epoxy ketone with LiAlH_4 gave a 1,3-diol, but with significant amounts of the 3 α -isomer¹⁴² or mainly the 3 α -isomer.¹³⁸ However, epoxide cleavage using aluminum amalgam to β -hydroxy ketone **39** followed by NaBH_4 reduction gave the desired 1 α ,3 β -diol **40**. Finally, the $\Delta^{5,6}$ -double bond was regenerated by elimination of the 6 β -alcohol or through suitable modification of the acetal. In an alternative route, selective reduction of the carbonyl group of **38** (X = H, OAc) with NaBH_4 followed by epoxide opening with LiAlH_4 afforded 80% of the desired 1 α -hydroxycholesterol.^{140,141}

Method ii involves oxymercuration–demercuration of 3 β -acetoxycholesta-1,5-diene (**42**, Figure 10) with mercuric trifluoroacetate followed by saponification, but the regioselectivity is poor.¹⁴³

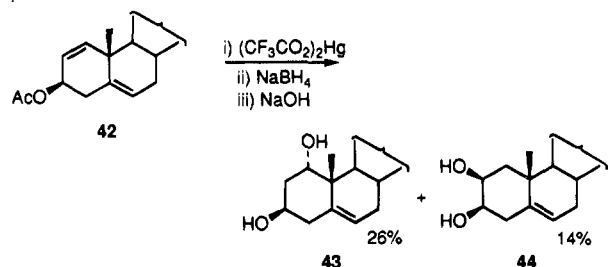


Figure 10.

The one-pot reduction of 1 α ,2 α -epoxycholesta-4,6-dien-3-one (**45**) to 1 α -hydroxycholesterol (**43**), perhaps via intermediates of the type **46**–**49**, developed by Barton et al.,^{99,100} makes method iii one of the shortest procedures for synthesis of 1,25- D_3 .^{144,145} (Figure 11).

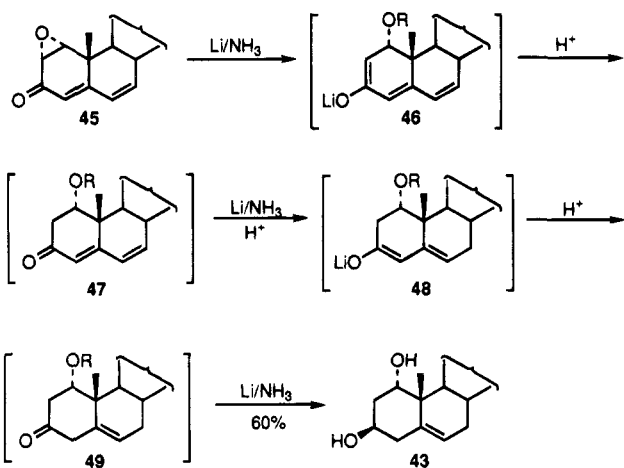


Figure 11.

In the Barton procedure, method iii, 25-hydroxycholesterol (**50**) was initially dehydrogenated with dichlorodicyanobenzoquinone (DDQ, 3.3 equiv, 50%). The resulting 25-hydroxycholesta-1,4,6-trien-3-one (**51**) was oxidized with alkaline hydrogen peroxide to give a 1 α ,2 α -epoxide (70%). Treatment of the latter with a large excess of lithium metal and NH_4Cl in ammonia–tetrahydrofuran (ca. 1:1) at reflux produced 1 α ,25-dihydroxycholesterol (**52**) in 40% yield^{100,146–148} (Figure 12).

In method iv, a modified version of the Barton reduction led to $\Delta^{6,7}$ -olefin **53** as the major component, which was converted in a straightforward

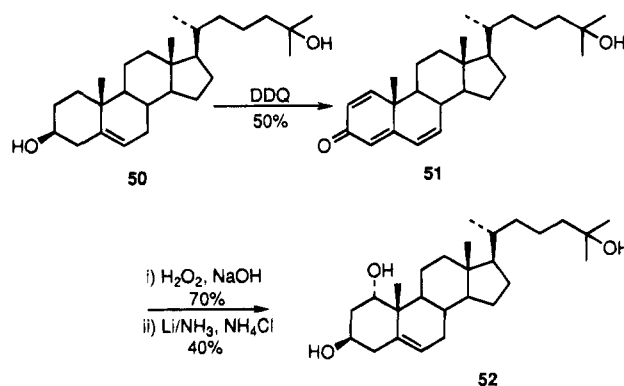


Figure 12.

manner to $\Delta^{5,7}$ -cholestadien-1 α ,3 β -diol diacetate (**55**), the photoprecursor of the physiologically active 1 α -hydroxyvitamin D_3 via bromination and double elimination (Figure 13).¹⁴⁹

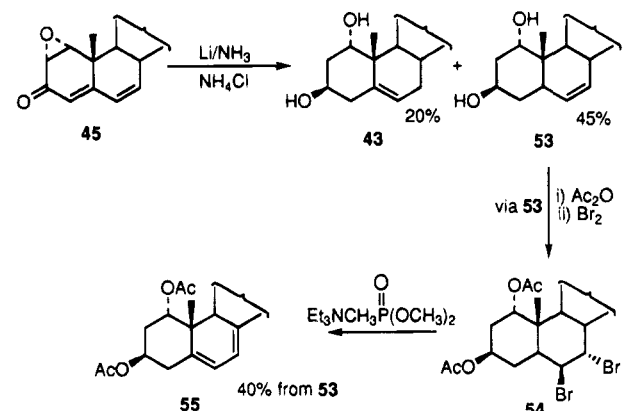


Figure 13.

Method v, perhaps a still earlier procedure for the preparation of 1 α -hydroxycholesterol,^{150,151} involved transannular cyclization of the 10-membered ring **57** to the oxetane derivative **58** as the key step. Acid-catalyzed opening of the four-membered ether ring in **58** afforded the desired 1 α -hydroxycholesterol derivative **59** (Figure 14).

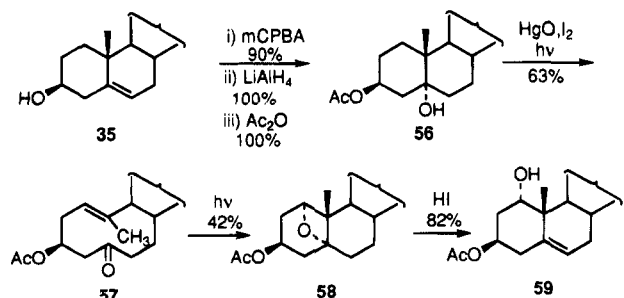


Figure 14.

The usual method for introduction of the $\Delta^{7,8}$ -double bond to 1 α -hydroxycholesterol is the classical bromination/dehydrobromination procedure shown in Figure 15 (X = Br). Wohl Ziegler bromination using 1,3-dibromo-5,5-dimethylhydantoin^{99,138,152} or *N*-bromosuccinimide (NBS)¹³⁹ has frequently been used. The resulting epimeric mixture of C-7 bromides is treated with trimethyl phosphite $(\text{MeO})_3\text{P}$ in xylene^{99,138,139} or collidine (in decalin or dioxane) typically affords about 40% of the desired 5,7-diene **62**

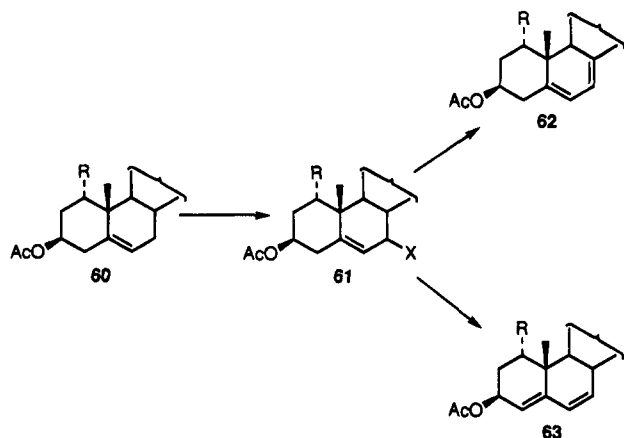


Figure 15.

along with a substantial quantity of the undesired 4,6-diene isomer **63** (25%).

The unwanted contaminant, $\Delta^{4,6}$ -diene **63**, has plagued this conversion despite many decades of exhaustive developmental studies.¹⁵³ However, an improved dehydrobromination of the 7α -bromide of the acetate of cholesterol with $\text{Bu}_4\text{NF}\cdot\text{H}_2\text{O}$ in either THF, DMF, or toluene was reported to give only the desired $\Delta^{5,7}$ -diene.¹⁵⁴ In this two-step procedure, provitamin D synthesis was achieved in 62% yield (>95% pure). The syn elimination of the corresponding 7-benzenesulfonic acid might also offer a viable alternative.¹⁵⁵ Equilibration of the epimeric bromide mixture **64** with excess lithium bromide afforded mainly 7α -bromide **65** (1:4 β/α). Treatment of the latter with benzenethiol yielded the 7β -phenyl sulfide **66**, which was oxidized to a readily separable mixture of sulfoxides **67** and **68** (1:2 ratio). Smooth syn elimination at 70 °C led to desired $\Delta^{5,7}$ -diene ester **69** in 53% overall yield (Figure 16).

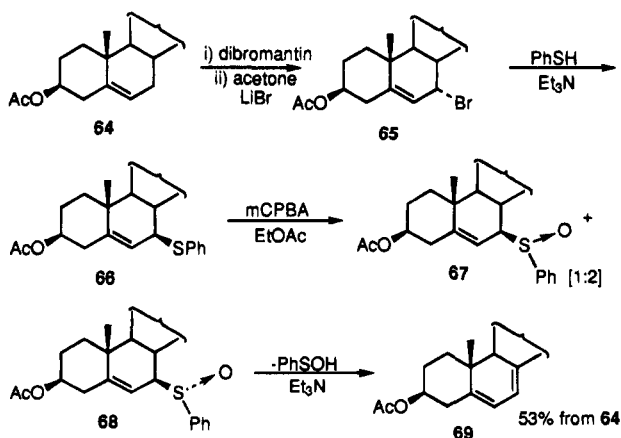


Figure 16.

Another possible alternative is the palladium-catalyzed elimination of allylic esters **61** ($\text{X} = \text{O}_2\text{-CCF}_3$) (Figure 15).¹⁵⁶ Refluxing of 7α -allylic trifluoroacetate with $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$, PBu_3 , and triethylamine in dioxane led only to the desired homoannular diene **62** in 90% yield. The less reactive 7β -epimer gave 66% of the same diene **62** accompanied by 23% starting material. None of the undesirable $\Delta^{4,6}$ -diene was detected in either reaction. It was noted that in the absence of triethylamine the reaction was either more complex (7α -isomer) or failed (7β -isomer).

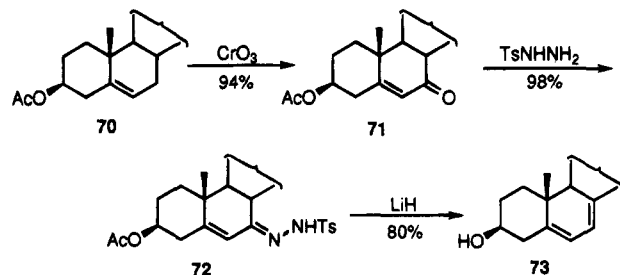


Figure 17.

The carbenoid route shown in Figure 17 features initial direct oxidation at C-7 of Δ^5 -ene- 3β -acetate **70**^{157–160} with CrO_3 and 3,5-dimethylpyrazole in pyridine.^{161,162} This is followed by Bamford–Stevens elimination¹⁶³ of the corresponding tosylhydrazone **72** to afford the $\Delta^{5,7}$ -diene **73** in 73% overall yield. Because introduction of the $\Delta^{7,8}$ -double bond is cumbersome, the Kaneko group generated the desired $\Delta^{5,7}$ -diene unit through base-catalyzed deconjugation of the easily available 1,4,6-trien-3-one **74**. This was followed by reduction and then diene protection as the Diels–Alder adduct **76**.^{164,165} Epoxidation of the adduct **76** with mCPBA afforded a mixture of $1\alpha,2\alpha$ -epoxide **79** and $1\beta,2\beta$ -epoxide **78** in 2:3 ratio. Reductive retro-Diels–Alder reaction of the α -isomer **79** led to the desired 1α -hydroxy-7-dehydrocholesterol. The β -isomer **78** under similar conditions led to a mixture of 2β -hydroxy and 3β -hydroxy compounds (Figure 18).

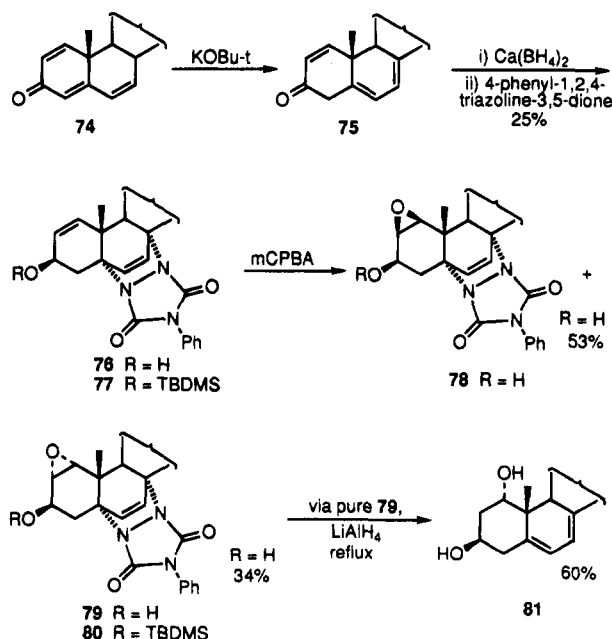


Figure 18.

Kaneko's procedure provided a simple route to 1α -hydroxy- $\Delta^{5,7}$ -dienes except for the low selectivity of the epoxidation step. This was however improved later by Whalley^{166,167} through epoxidation of the corresponding TBDMS-ether **77**, giving exclusively the α -isomer **80**. The tetraenol acetate deconjugation of 1,4,6-trien-3-one **74** as depicted in Figure 19 further improved the preparation of the key intermediate **83** of Kaneko's procedure.

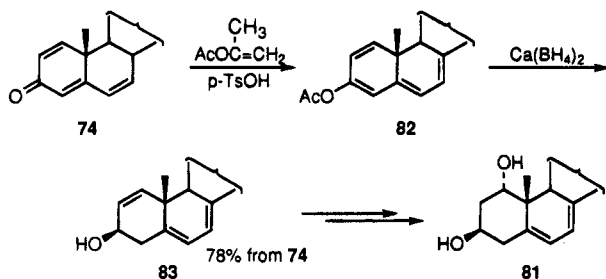


Figure 19.

3. Protection of the $\Delta^{5,7}$ -Diene for Direct Modification of the Side Chain

A highly attractive strategy for producing side-chain analogues and metabolites is to modify the side chain at a late stage in the synthesis, thus rendering all but the side chain as the basic building block. This involves proper protection of the fragile $\Delta^{5,7}$ -diene unit of the steroid. One of the most common procedures is Barton's strategy, which employs a Diels-Alder/retro-Diels-Alder reaction of 1,2,4-triazoline-3,5-dione (**84**)^{168,169} (Figure 20). In an improved

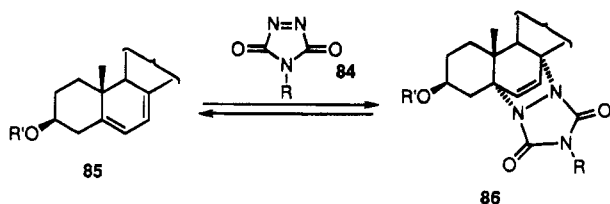


Figure 20.

version,¹⁷⁰ the ergosterol diene system **85** was reacted with 4-(*p*-nitrophenyl)-1,2,4-triazoline-3,5-dione (**84**, R = *p*-O₂NpH), generated by in situ oxidation of the appropriate hydrazide with benzeneselenic anhydride or benzeneselenic acid, to give an excellent yield of adduct **86** (97%). The diene unit can be smoothly regenerated by alkaline hydrolysis (98%).

C. Method B: The Horner-Wittig Olefination

In an early total synthesis study of vitamin D₃^{171,172} the conjugated triene system was not constructed directly (see section II.I). The first approach to the direct construction of the triene was reported by Lythgoe et al., employed a Horner-Wittig olefination.¹⁰¹⁻¹⁰⁶ The actual synthesis of 1,25-D₃ using this approach was effected later by others (see below) by the reaction between the (*Z*)-allylic phosphine oxide **88** and the appropriate bicyclic ketone **87** (Figure 21). The reaction proceeds completely stereoselectively, the $\Delta^{5,6}$ -double bond of the product retaining the natural *Z* geometry of the precursor and

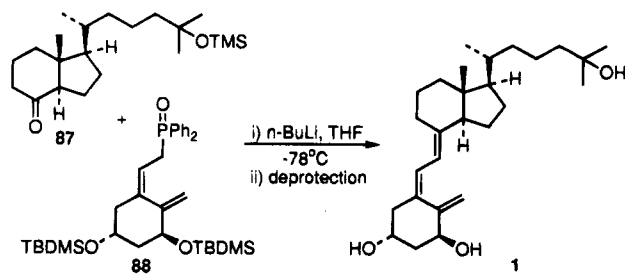


Figure 21.

the newly formed $\Delta^{7,8}$ -double bond assuming the natural *E* geometry.¹⁰⁷ The carbanion for the coupling is generated from **88** by *n*-butyllithium treatment at -78°C for 1 h. The coupling of the red carbanion with the CD-ring fragment is rapid, undergoing completion at -78°C within 1 h. The yield for the reaction is generally over 90%. An advantage of this coupling approach is its convergency. The synthesis of 1,25-D₃ or related analogues can therefore be divided into independent syntheses of the protected 25-hydroxy-Grundmann's ketone **87** and the A-ring phosphine oxide **88**.

1. Synthesis of 25-Hydroxy-Grundmann's Ketone

Some basic strategies for synthesis of 25-hydroxy-Grundmann's ketone (**89**) are outlined in Figure 22.

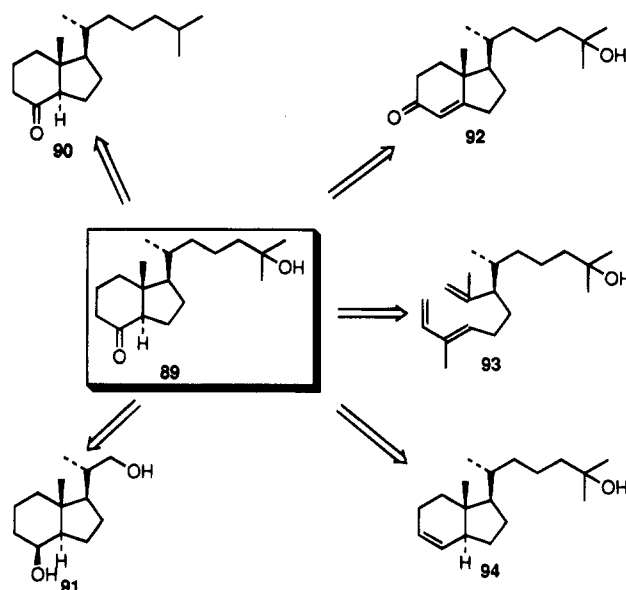


Figure 22.

The most practical approach to CD fragments is still the partial synthesis through D₃ degradation to **90** followed by direct 25-hydroxylation to **89**, or by side-chain modification of the Inhoffen-Lythgoe diol **91** (from vitamin D₂, possessing the ergosterol side chain). The direct transformation of **90** to **89** requires replacing the 25-tertiary hydrogen with a hydroxyl. The dioxirane method, recently developed by Bovicelli et al.¹⁷³⁻¹⁷⁵ appears impressive both in terms of conversion (80%) and selectivity (86% yield) (Figure 23). The reaction conditions of this mild

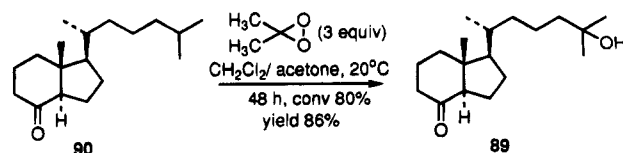


Figure 23.

oxidation procedure simply involves introducing ketone **90** into a solution of dimethyldioxirane in acetone or the more reactive methyl(trifluoromethyl)-dioxirane in 1,1,1-trifluoro-2-propanone. The dioxirane method could be a powerful method for late stage 25-hydroxyl introduction since the reported dioxirane procedure is limited to relatively small

scale reactions (<1 mmol). In our hands, together with limited input from other laboratories, the dioxirane route is less convenient than a ruthenium tetraoxide-based method. The latter method, developed by the Roche group¹⁷⁶ and reexamined by DeLuca et al.¹⁷⁷ involves treating Grundmann's alcohol **95a** with catalytic amounts of RuCl_3 and excess NaIO_4 (Figure 24). The alcohol is rapidly

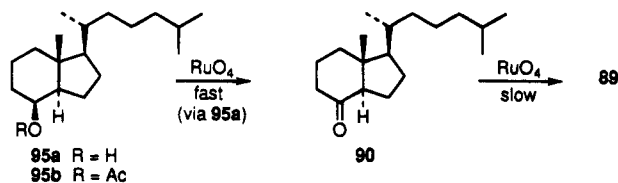


Figure 24.

oxidized to the corresponding ketone **90**, which is then more slowly hydroxylated in situ at C-25 to the desired compound. It has been indicated that the use of 0.1 molar equiv of RuCl_3 and 3.5 molar equiv of NaIO_4 generates 44% of the desired **89** accompanied by 13% of **90**, the latter being recyclable to produce an additional 5% of **89**. In our hands, this reaction could be scaled up to 2 g without obvious decrease in yield,¹⁷⁸ but the yields were initially erratic. However, recent studies in our laboratory have revealed that short reaction times (e.g., 1 day instead of 4 days) and the use of more RuCl_3 catalyst (up to 20%) leads to more reproducible results, comparable to those reported.

Dry ozonization of the acetate of Grundmann's alcohol **95b** on silica gel, a process developed in Mazur's laboratory,¹⁷⁹⁻¹⁸² gives, in addition to the starting material, a mixture of four isomers **96a-d**, the distribution of products being similar to that obtained by a peracetic acid oxidation procedure (Figure 25). In an optimized version of this process,

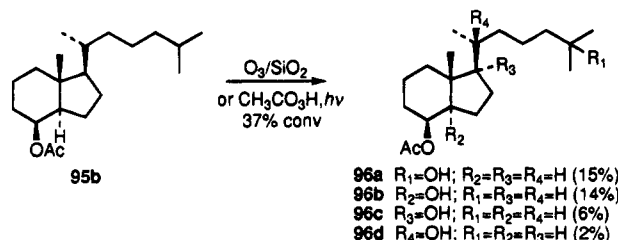


Figure 25.

ozonization of cholesterol derivative yielded 51% 25-hydroxylated steroid based on recovered starting material (11% conversion).^{176,181} In the laboratory of Vandewalle and De Clercq in Belgium, this method was further modified by conducting the ozonation at -15°C , the temperature at which evaporation of the solvent (Freon) occurs. Up to a 22% yield of 25-hydroxy-Grundmann's ketone **89** could be obtained in 20 g scale experiments. A 50% yield of C-25 hydroxylation product **98** was obtained by ozonation of 9,11-epoxy-Grundmann's ketone **97** (Figure 26) (De Clercq, Zhu; unpublished data).

The partial synthesis of 25-hydroxy-Grundmann's ketone **89** through degradation of vitamin D_2 takes more steps, but gives higher total yield (>40%), and can be easily extended to large-scale preparations. Ozonolysis of vitamin D_2 ¹⁸³ in methanol at -78°C

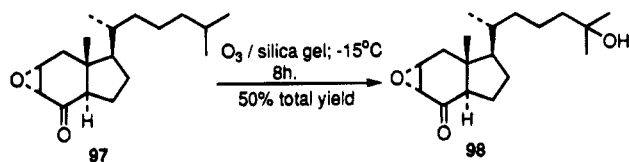


Figure 26.

affords Inhoffen-Lythgoe diol **91** in 85% yield. The side chain may be constructed easily through the two methods shown in Figure 27.

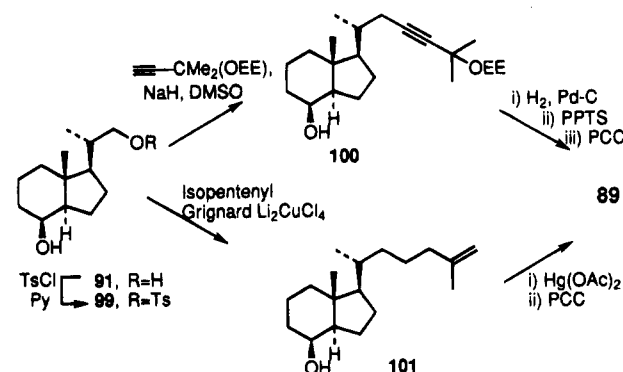


Figure 27.

The first total synthesis of Grundmann's ketone was reported by Inhoffen in 1958 in low yield (ca. <0.1%).^{171,184,185} Hagemann's ester **102** was elaborated to give the *trans*-perhydroindan-1-one **103**¹⁸⁵ in which the keto group allowed introduction of the isooctyl side chain (Figure 28). Since then, many

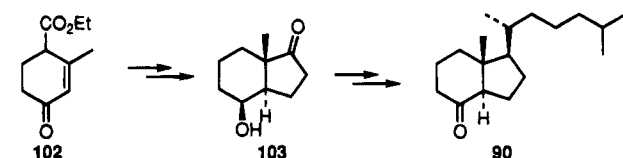


Figure 28.

efforts toward the total synthesis of appropriate vitamin D CD fragments, such as the Inhoffen-Lythgoe diol (**91**), have been reported, and this topic is described next.

Synthesis of Inhoffen-Lythgoe Diol Derivatives. Problems associated with the synthesis of CD fragments include some of the following. First, the *trans*-C/D ring is less stable than the *cis* form, a topic well recognized in steroid synthesis. Second, there is a need for the correct relative configuration at C-20, the C-17 stereochemistry being less of a problem for thermodynamic reasons. Finally, provision for suitable functionality at C-8 must be made.

Lythgoe^{186,187} was the first to report a total synthesis of the Inhoffen-Lythgoe diol and, in turn, vitamin D_2 (ergosterol side chain). Through a modified Claisen rearrangement scheme (Figure 29), the orthoester **105** and allylic alcohol **104** were reacted to give the homogeneous crystalline γ -lactone **106**. Methanolysis, without epimerization at the center adjacent to the lactonic carbonyl group, followed by Meerwein-Eschenmoser reaction of the resulting hydroxylactone, gave dimethylamide **107**. The latter was hydrolyzed and methylated (CH_2N_2) to the corresponding ester (40% yield from **104**). Subsequent cyclization with potassium *tert*-butoxide fol-

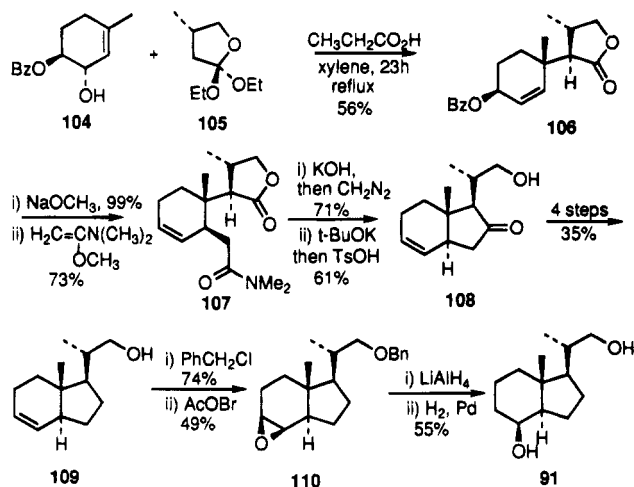


Figure 29.

lowed by removal of the methoxycarbonyl group afforded hydroxy ketone **108**. Reduction of the tetrahydropyranyl derivative with LiAlH_4 gave a secondary alcohol, which was deoxygenated by Barton's method to give, after removal of the protecting group, the alcohol **109**. The latter was transformed to the benzyl ether-protected β -epoxide **110**, which was reduced with LiAlH_4 and then hydrogenolyzed to give the desired Inhoffen-Lythgoe diol **91**.

Trost¹⁸⁸ also constructed the *trans* CD system by a 1,3-chirality transfer process, but before formation of the C-ring rather than before the D-ring as in Lythgoe's case (Figure 29). In addition, the correct configuration at C-20 was established by elaboration of a camphor derivative (Figure 30). The synthesis

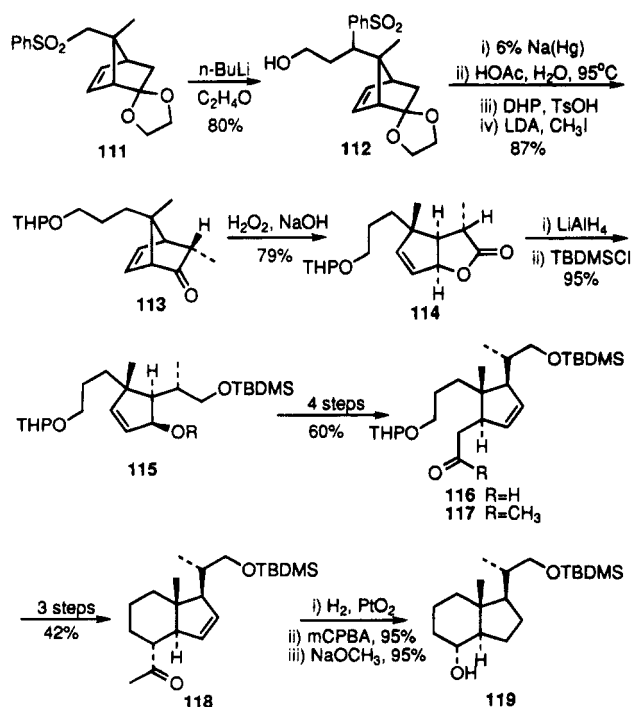


Figure 30.

started with sulfone **111**. Two alkylations and several additional steps gave **113**, which upon Baeyer-Villiger oxidation followed by allylic rearrangement gave lactone **114**. Reduction to a diol and selective protection of the primary alcohol as a

TBDMS ether gave **115**. The *trans*-ring junction was introduced by a Claisen rearrangement of the allylic alcohol, where the C-16 hydroxyl chirality was transferred to C-14 as indicated. This Claisen process (FVP, 500 °C) was reported in a later study (using a related substrate) to be achievable at 95 °C in aqueous base.¹⁸⁹ The resulting aldehyde **116** was converted into methyl ketone **117**. The THP group was then removed and hydriindene formation was accomplished by intramolecular alkylation of an intermediate keto tosylate to give **118**, with the acetyl group in an equatorial position. Subjection of **118** to hydrogenation, Baeyer-Villiger oxidation, and methanolysis yielded alcohol **119** (Figure 30).

Johnson¹⁹⁰ reported an asymmetric route to the Inhoffen-Lythgoe diol by acid-catalyzed polyene cyclization. In a key step, the cyclization of the chiral acetal **120** yielded **121**. The chiral auxiliary was removed and then acetylation of the resulting alcohol gave **122**. Semihydrogenation, wherein the addition of hydrogen occurred from the more exposed face of the terminal allene, gave exclusively the *Z*-isomer **123**, which was converted to the desired diol **91**, in 39% overall yield from **120** (Figure 31).

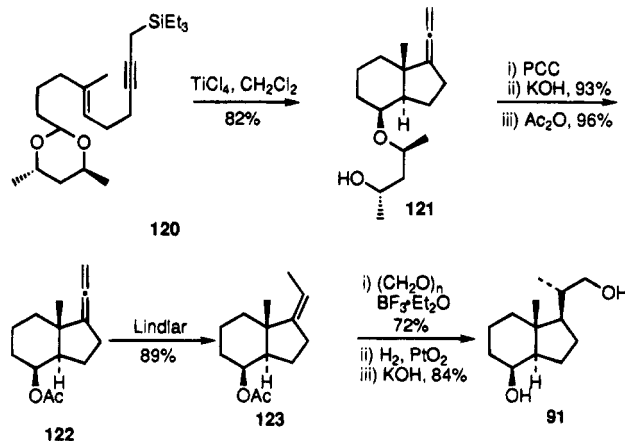


Figure 31.

A free radical cyclization-trapping approach, recently reported by Stork,¹⁹¹ started from optically active 3-methyl-2-cyclohexenol (**124**, Figure 32). The

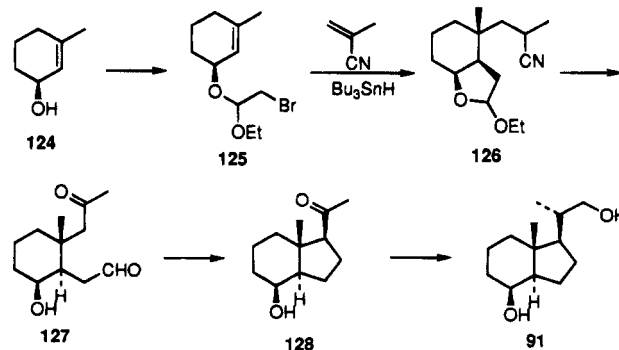


Figure 32.

absolute configuration at C-14 was introduced by intramolecular radical cyclization from the established stereogenic center. The *trans*-junction was controlled via stereospecific radical trapping. Later elaboration of the adduct **126**, hydrolysis, cyclocondensation, hydrogenation, Wittig olefination, and

hydroboration, afforded Inhoffen–Lythgoe diol **91**. The synthetic sequence, however, has not been reported in detail.

Another approach developed by Stork^{191,192} makes use of the so-called vicinal stereocontrol methodology (Figure 33). The reaction translates the stereochemistry of a simple *trans* epoxide into the stereocontrolled production of a substrate with three contiguous stereogenic centers, one of which is quaternary (illustrated in the transformation of **131** to **132**). The desired formation of a cyclohexane rather than a cyclopentane ring was achieved simply by making the distal end of the epoxide part of an allylic system. The carbanion orbital must remain perpendicular to the carbonyl plane in the transition state for the epoxide opening. A chairlike transition state with the enolate system in an equatorial arrangement is preferred, and this leads to diastereomerically pure lactone **132** in 60% yield.¹⁹² The latter could then be transformed to the Inhoffen–Lythgoe diol precursor **136** as shown.

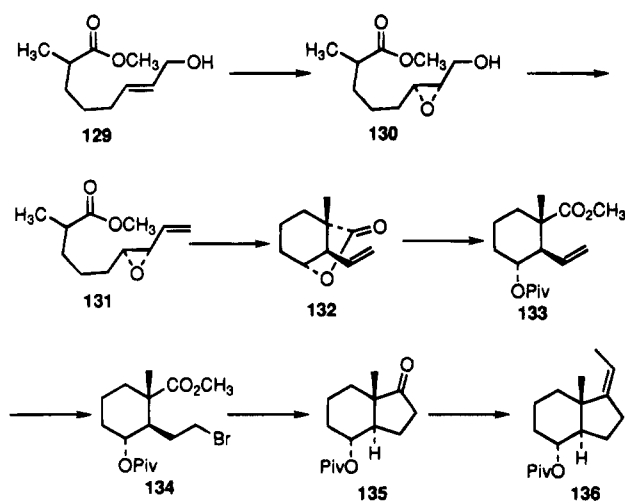


Figure 33.

Takano's route (Figure 34)¹⁹³ is based on Johnson's cationic polyene cyclization strategy.¹⁹⁰ The SnCl_2 -catalyzed reaction of the chiral epoxy alcohol **137**, derived from a Sharpless asymmetric epoxidation step, proceeds with a high degree of regio- and stereoselectivity, possibly via a transition state resembling **138**, to produce an allene diol which could be easily converted to Inhoffen–Lythgoe diol type derivative **119** by standard methods. The SnCl_4 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ mediated reaction of the corresponding acetate of **137** does not afford any hydrindan derivatives. This result suggests that tight complexation of the epoxy alcohol moiety to the metal center not only makes this type reaction feasible, but also restricts the stereochemical course of the cyclization.

Grieco's procedure (Figure 35)¹⁹⁴ features a novel aqueous intermolecular Diels–Alder strategy, wherein an intact C-20 stereocenter as part of the diene unit **144** is used to elaborate directly the stereocenters at C-13 and C-17 of the hydrindan ring system. Diels–Alder condensation¹⁹⁵ of methacrolein with the sodium salt of **144** (2.0 M in water) at 55 °C for 16 h afforded the desired carboxylic acid **146** and about 15% of the diastereoisomeric adduct **145**. The former (**146**) could be easily transformed to **147**. The use of

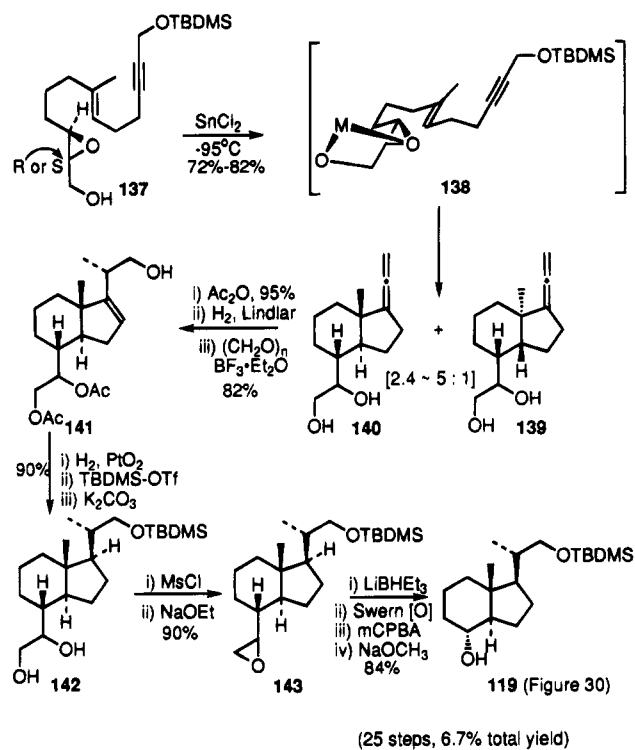


Figure 34.

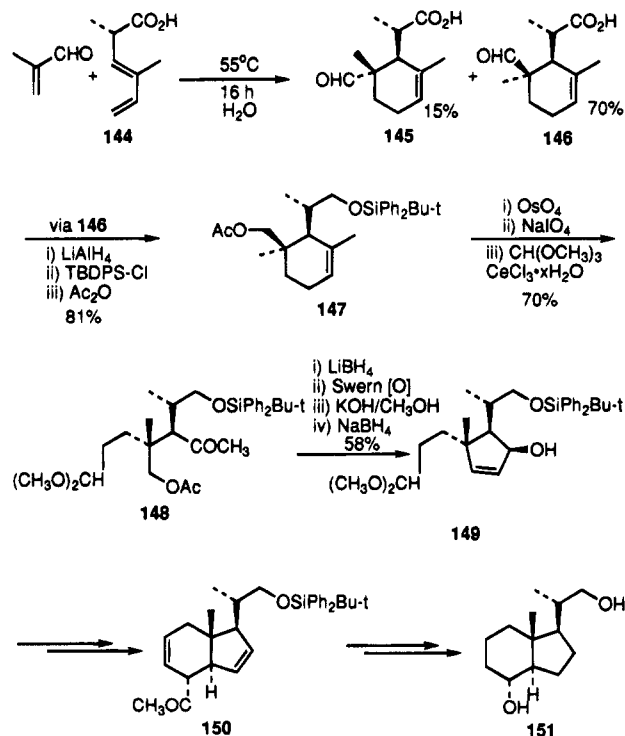


Figure 35.

the corresponding methyl ester of **144** in an excess of neat methacrolein at 55 °C required 63 h to realize only a 10% yield of a 1:1 mixture of Diels–Alder adducts. Oxidative cleavage of the olefinic bond in **147** was followed by transformation to keto acetal **148**. The desired alcohol **149** was obtained through reductive removal of the acetyl group, Swern oxidation, aldol condensation, and reduction of the resulting cyclopentenone. Elaboration of **149** similar to Trost's approach (Figure 30), afforded the intermediate **150**, which was transformed to the Inhoffen–Lythgoe diol derivative **151**.

Another approach leading to an Inhoffen–Lythgoe diol total synthesis is to construct the *trans*-hydrindan system from the commercially available, enantiomerically pure enedione **152**. Direct hydrogenation or hydroboration of **152** gives the thermodynamically favored *cis*-isomer as the major component.^{196–199} The main successful approaches for the construction of *trans*-CD systems using **152** as a starting point are summarized in Figure 36. Uskokovic

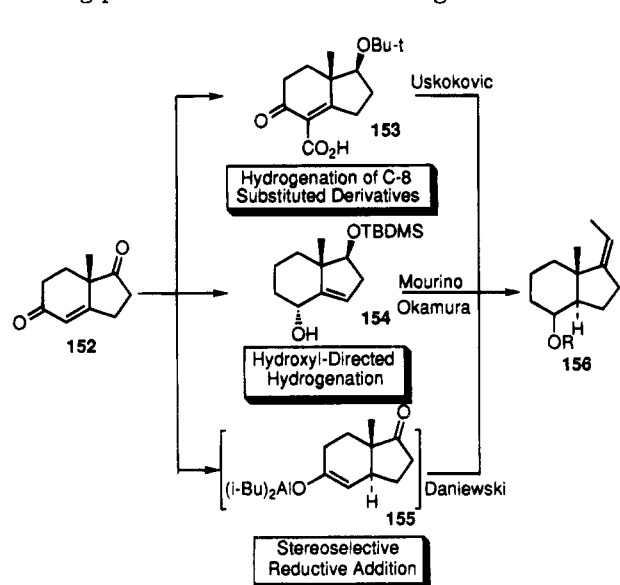


Figure 36.

ovic et al.^{200,201} reported a 13-stage approach (Figure 37) starting from keto acid **153**, which was originally

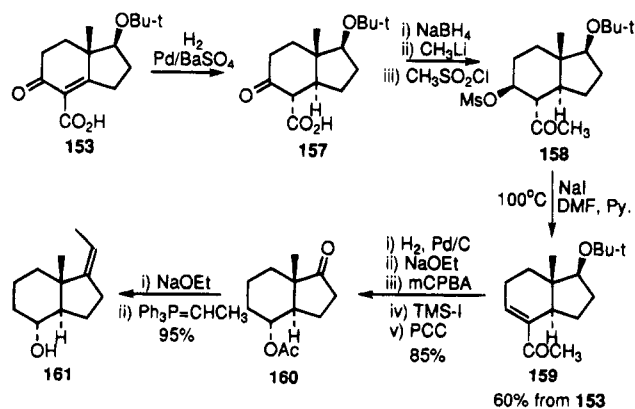


Figure 37.

synthesized from enedione **152**.^{202,203} The starting keto acid **153** was hydrogenated highly stereoselectively to the corresponding *trans*-hydrindan derivative **157** (H_2 , Pd/BaSO₄, EtOH). Formation of a pseudo B-ring via chelation is believed to be responsible for the high stereoselectivity.²⁰⁴ Reduction of **157** followed by methylation, mesylation and then elimination gave **159**. Catalytic hydrogenation of unsaturated ester **159** afforded a C-8 epimeric mixture, which on treatment with base afforded only the more stable equatorial acyl isomer. Baeyer–Villiger oxidation and selective removal of the *tert*-butyl group with trimethylsilyl iodide afforded an alcohol which was transformed to **160** by PCC oxidation. Saponification followed by Wittig reaction with ethylidene-triphenylphosphorane give a 96:4 ratio of the desired

17*Z*-olefin **161** and the corresponding 17*E*-isomer. The ene reaction of **161** with paraformaldehyde in the presence of BF₃·Et₂O followed by hydrogenation afforded the desired Inhoffen–Lythgoe diol derivative **151** (Figure 37).

In Mouriño's approach (Figure 38),²⁰⁵ the C-9 carbonyl group was first removed (Luche reduction, acetylation, and then lithium–ammonia reduction).

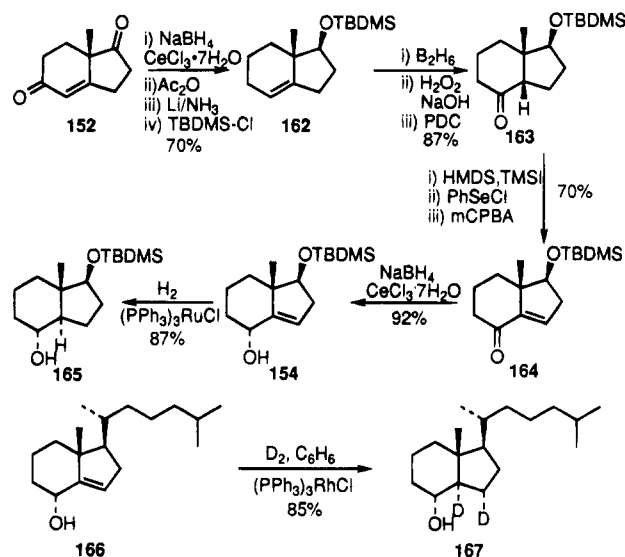


Figure 38.

The C-8 carbonyl group was introduced through hydroboration–oxidation, affording the *cis*-hydrindanone **163**. Introduction of the α,β -double bond was carried out via Okamura's procedure²⁰⁶ through thermodynamic enol silylation, phenylselenenyl chloride trapping, and mCPBA oxidation–elimination. Reduction of the resulting enone **164** under Luche's condition afforded **154** with high selectivity. Hydrogenation of hexahydrindanol **154** was studied under a variety of conditions, but only reduction using Wilkinson's catalyst in the presence of the free hydroxyl at C-8 afforded satisfactory results (3:1 *trans/cis*). The hydrogenation step leading to **165** was not nearly as α -face selective as the case reported by Okamura wherein the OTBDMS group is replaced by the isoctyl side chain of cholesterol (~37:1 *trans/cis* ratio in the transformation of **166** to **167**).²⁰⁶

In 1988, Daniewski et al.²⁰⁷ reported as shown in Figure 39 a yet simpler six-step synthesis of the diol **91** (via **173**, the epimer of **161**) starting from the same enedione **152** based on the stereoselective reductive addition of electrophiles to the latter.^{208–210} This reductive addition to **152** involves hydride transfer from the complex of *tert*-butylcopper with DIBAL,²¹¹ to generate the diisobutylaluminum enolate **155**, which is trapped by bromine. Further elaboration of the resulting **168** through the epoxide **170** smoothly afforded **173** in 22% overall yield as shown.

Synthesis of 25-Hydroxy-Grundmann's Ketone through Hydrindenones. This section differs from the previous section primarily in that the Inhoffen–Lythgoe diol (**91**) or its C-8 epimer or derivatives are not specific targets. Ficini's synthesis^{212–214} involves the initial construction of the C-17 and C-20 stereocenters followed by asymmetric induction at C-13 by

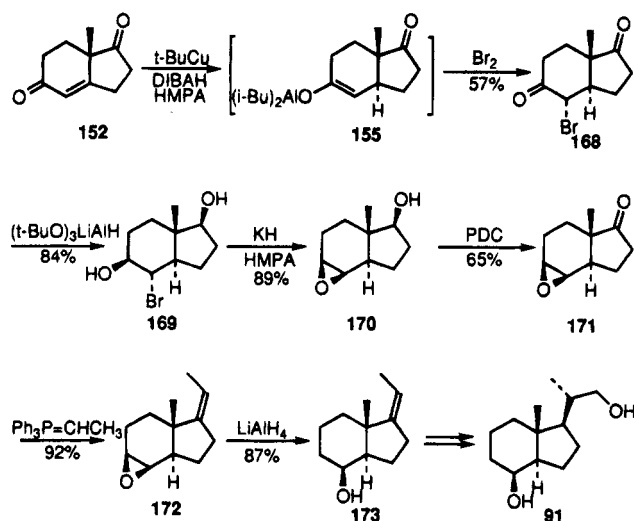


Figure 39.

influence of the already present C-17 center. The CD *trans*-junction is constructed through Uskokovic's hydrogenation approach discussed earlier in Figure 37 (Figure 40).

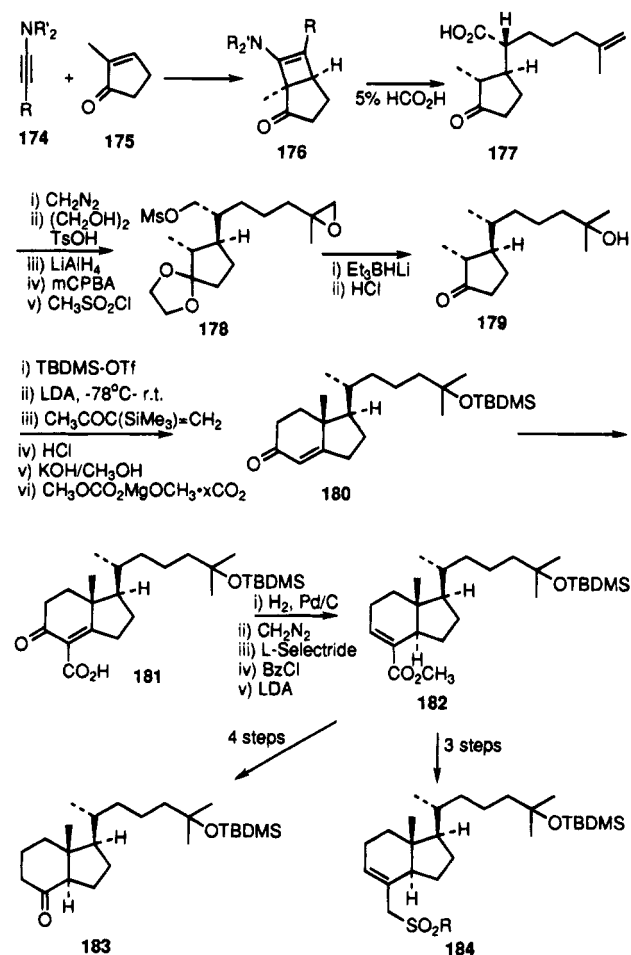


Figure 40.

Ficini's method to first establish the stereochemistry at C-17 and C-20 consisted of the hydrolysis of the adduct **176** formed by cycloaddition of the ynamine **174** with 2-methylcyclopentenone (**175**), ultimately the five-membered D ring. Resolution of the (\pm)-keto acid **177** was accomplished by fractional crystallization of its diastereomeric ammonium salts [from (-)-

ethylnaphthylamine]. The pure enantiomer **177**, obtained in 80% yield from this resolution, was easily converted to intermediate **179**. Successive reaction of the thermodynamic enolate of the latter with α -(trimethylsilyl)-2-butenone and intramolecular aldol condensation of the resulting dione afforded stereochemically pure **180**. Transformation of the latter to intermediate **182** was achieved in a manner similar to Uskokovic's procedure (Figure 37). The unsaturated ester **182** could be easily transferred to protected 25-hydroxy-Grundmann's ketone **183** via a Baeyer–Villiger procedure, or to sulfone **184** for Lythgoe's Julia elimination coupling approach (which will be discussed later in section II.I).

The conjugate addition–enolate trapping strategy developed by the Haynes group in Australia^{215,216} set up the correct stereochemistry at three centers in one chemical operation. Treatment of the lithiated phosphine oxide **185** to 2-methylcyclopentenone (**175**) generates a specific enolate **186**, which is proposed to exist in a 10-membered transition state referred to as *trans*-decalyl-like, or *trans*-fused chair–chair-like, shown in Figure 41. Trapping of this enolate

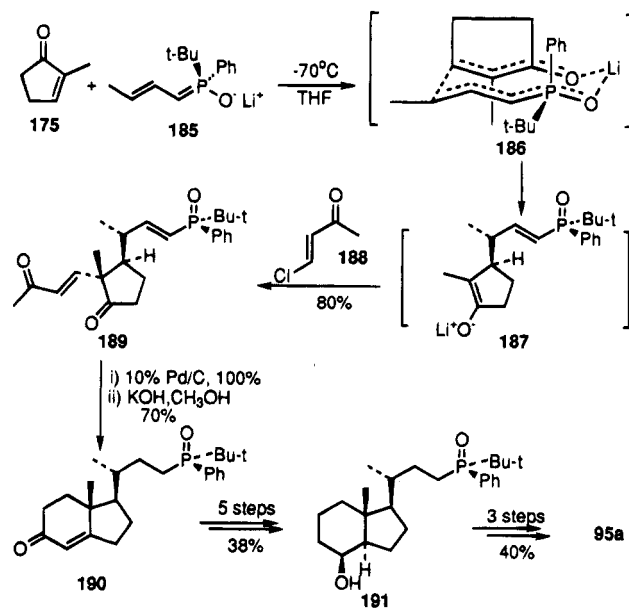


Figure 41.

with methyl vinyl ketone is rarely successful. However, treatment with chloroenone **188** afforded **189** with the stereochemistry shown (80% overall yield). Hydrogenation of the two double bonds followed by aldol cyclization afforded hydrindanone intermediate **190**, which was smoothly transformed to Grundmann's ketone **90** upon CD-ring elaboration (Daniewski's method in Figure 39) and side-chain extension.

Other lithiated reagents **193** can also be used for the reaction although for diastereomerically pure products lithiated phosphine oxide would appear to offer the best approach²¹⁷ (Figure 42). Hydrogenation of **195** at medium pressure (50–60 psi) is slow, giving a diastereomeric mixture of *trans*-hydrindan **196** and its *cis* counterpart **197** in a 80:20 ratio. The hydrogenation at 600–900 psi is much more rapid and increases the ratio of *trans*- to *cis*-hydrindans to 95:5. As with the lithiated phosphine oxide, the lithium

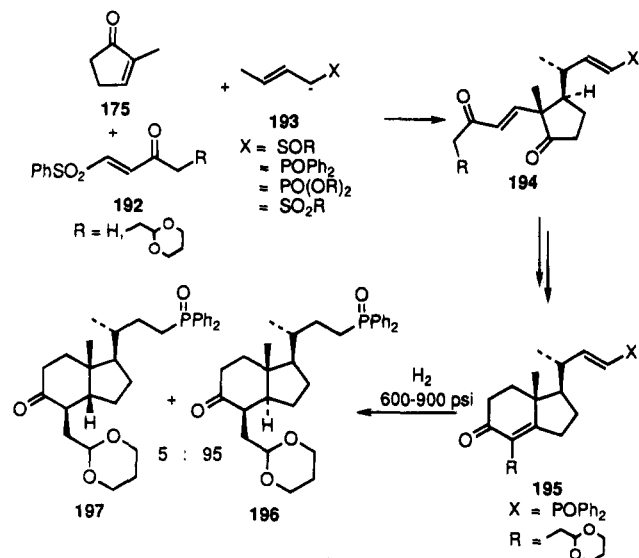


Figure 42.

anion of 2-[1(*E*)-propenyl]-1,3-dithiane (**198**)¹⁹⁸ (Figure 43) adds to 2-methylcyclopentenone (**175**) and

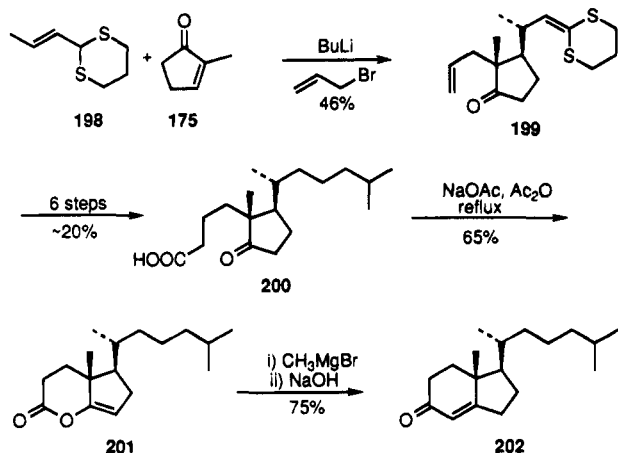


Figure 43.

produces, after alkylation, a racemic vitamin D intermediate **199** with the correct relative configuration. The ketenedithioacetal function of **199** was readily transformed to a cholesterol side chain through hydrolysis and Wittig olefination. Construction of the cyclohexenone ring was accomplished by the method of Fujimoto.²¹⁸ The lactone **201**, derived from the corresponding keto acid **200** (NaOAc, Ac₂O, reflux, 65%), was treated with methylmagnesium bromide and alkali to afford the de-*AB*-cholest-8-en-9-one (**202**, 75%).

In a synthesis related to that above, the stereoselectivity of the Michael conjugate addition decreases when ketene acetal **203** with a full steroidal side chain is employed in the strategy (Figure 44).²¹⁹ In the presence of trityl hexachloroantimonate, the reaction of enone **175** with **203** followed by direct alkylation gives a mixture of desired compound **204** (63%) and a diastereomer (7%). Reduction of the former oxoester with LiAlH₄ affords a diol which is directly selectively tosylated at the primary hydroxyl group to give **205** (89%) (2:1 epimers at C-14). Further C-21 elaboration and cyclization by Ziegler's method¹⁹⁸ completes the synthesis in 19% overall yield.

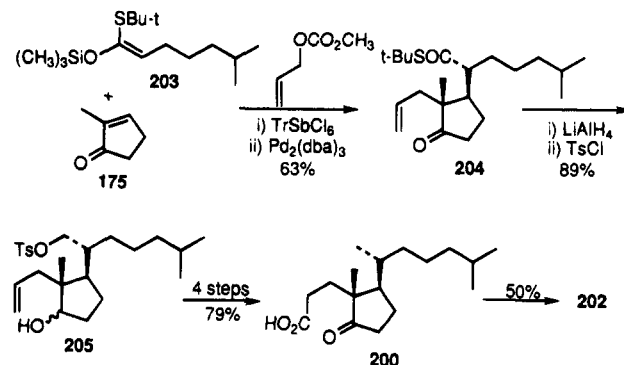


Figure 44.

Money's approach to hydrindenone **212**²²⁰ is based mainly on the efficient ring cleavage^{221,222} of (+)-9,10-dibromocamphor (**206**), readily derived from (+)-camphor (Figure 45). Swern oxidation of **207** fol-

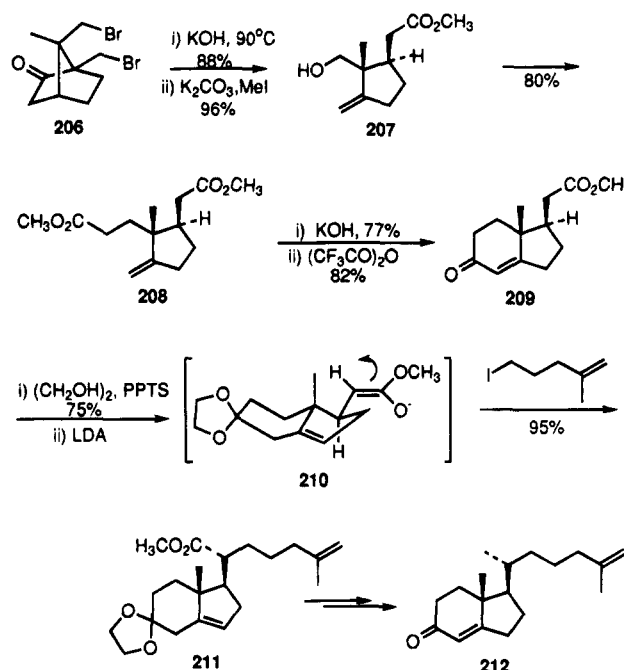


Figure 45.

lowed by Wittig reaction and reduction affords **208**. Cyclization of the corresponding diacid with trifluoroacetic anhydride followed by methanol workup produces hydrindenone ester **209**. Alkylation of keto ester enolate **210** with 5-iodo-2-methylpent-1-ene, in which the electrophile approaches from the less hindered face of the ester enolate ion,²²³ affords **211** in 85% yield together with 3–5% of its 20*S*-stereoisomer. Elaboration of C-21 and deprotection smoothly afforded **212**. Introduction of a wide variety of side chains at a later stage is made possible in this strategy by alkylation of **209** with different electrophiles.

A related approach from readily available 3,9-dibromocamphor (**213**) was reported by Stevens^{224,225} (Figure 46). The three contiguous stereocenters at C-20, C-17, and C-13 of the CD-ring fragment are derived from C-3, C-4, and C-7 of the camphor derivative. Reductive alkylation of **213** (75%) followed by homologation of the resulting monobromide through the corresponding C-9 iodide (66%) furnishes **214**. Reduction of the latter keto ester with lithium aluminum hydride in THF affords an *exo*-alcohol

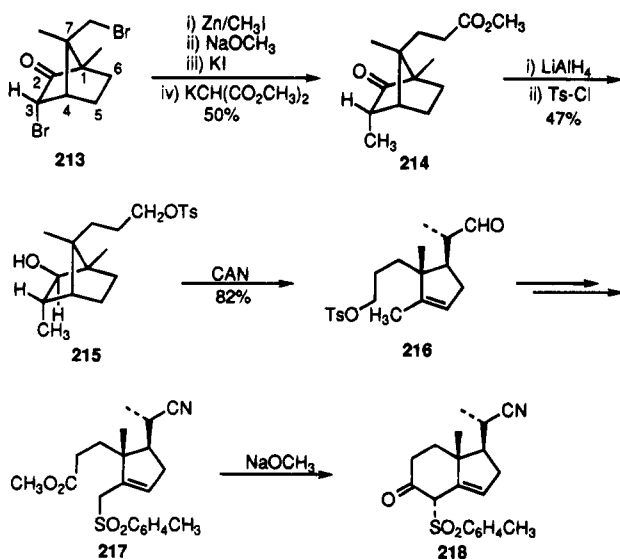


Figure 46.

as a single isomer, which is selectively tosylated to **215**. The fragmentation of the latter with ceric ammonium nitrate²²⁶ in aqueous acetonitrile at 0 °C yields aldehyde **216** in 82% yield. Oxidation of the corresponding nitrile ester with selenium dioxide afforded an unstable aldehyde which is immediately reduced to an allylic alcohol. Chlorination of the allylic alcohol with oxalyl chloride (96%), followed by treatment with sodium *p*-toluenesulfonate leads to sulfone **217** which is cyclized (CH₃ONa) to the potential vitamin D intermediate **218**.

Highly stereoselective double-Michael addition of *cis*-vinylcopper phosphine complex **219** (derived from the corresponding iodide and synthesized in 6 steps from D-leucine) to enone **175** and 2-(trimethylsilyl)-1-butene-3-one (**220**) followed by aldol condensation affords hydrindenone **221**. A variety of substituents at C-21 could be introduced at this stage through Cope-Claisen rearrangement (Figure 47).^{227,228} By

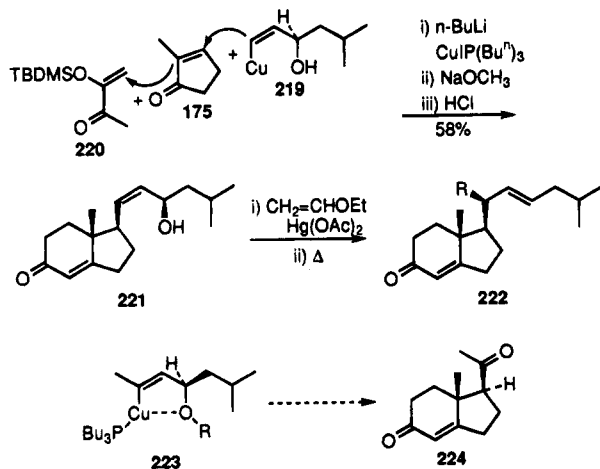


Figure 47.

employing an analogous alkenylcopper phosphine complex **223** in the double-Michael addition, after site-selective ozonolysis of the $\Delta^{20(22)}$ -olefin, there was obtained a seemingly versatile intermediate **224**, which also has potential as a vitamin D synthesis intermediate.²²⁹

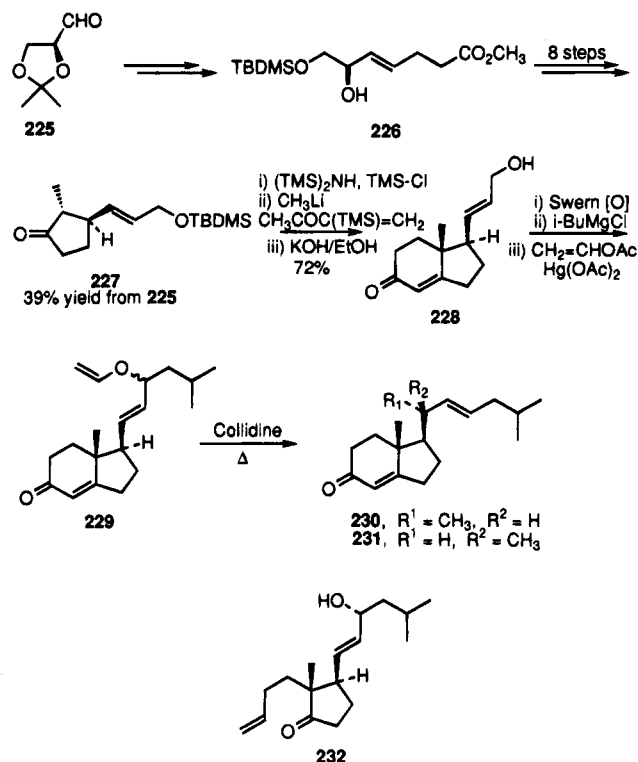


Figure 48.

Suzuki's synthesis^{230,231} (Figure 48) makes convenient side-chain modification, especially at C-20, possible at a late synthetic stage. The key intermediate **227**, possessing both the requisite stereochemistry and functionality for further elaboration of the side chain at C-17, can be accessed from **225** through a tandem orthoester Claisen rearrangement followed by Dieckmann condensation via the 6(*R*)-monoprotected allylic alcohol **226**. Michael addition of **227** via its thermodynamic enolate to methyl vinyl ketone followed by aldolization affords **228**, which is further transformed to **229**. Claisen rearrangement of the latter provides a separable mixture of two aldehydes (17% and 22% yields), which could be decarbonylated with tris(triphenylphosphine)rhodium chloride in refluxing benzene to **230** (50%) and **231** (89% yield). Two related strategies through prior synthesis of **232** employing palladium-catalyzed cyclization of a 1,3-diene monoepoxide²³² or two Claisen rearrangements were reported in earlier studies.²³³

The synthesis of the 25-hydroxy-CD-enone **92** (Figure 22) based on elaboration of optically active indenone **233** (the enantiomer of **152**, Figure 36) was also investigated.²³⁴ Conversion of **233** (Figure 49) in several steps via C-8 methylenation and following 1,4-addition of the side-chain isoamyl unit furnishes keto enol acetate **234**. Ozonolysis of the latter followed by hydrolysis and protection affords keto acid **235**, which could be easily elaborated to **236**. Hydrolysis and then Wittig olefination furnishes **237**, which is oxidized to lactone **201**, whose conversion to **202** was described earlier in Figure 43.²³⁵

Another synthesis of the key intermediate **179** (Figure 40) for vitamin D has also been studied. One of the important contributions is Shimizu's norbornane reductive cleavage method²³⁶ (Figure 50). Elaboration of the readily available Diels-Alder adduct **238** (both in racemic or optically pure form), in

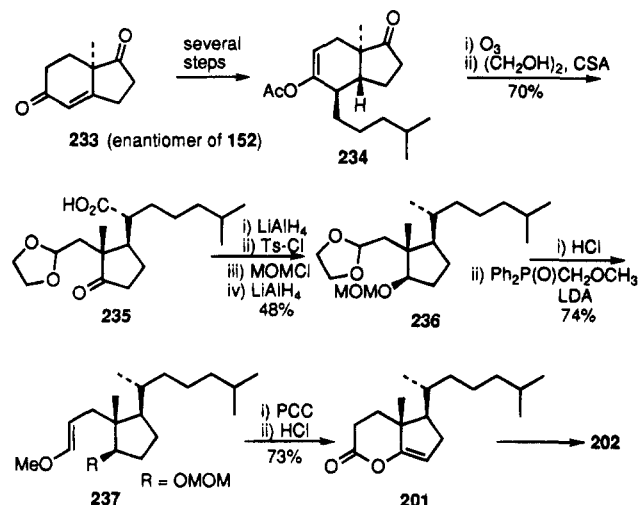


Figure 49.

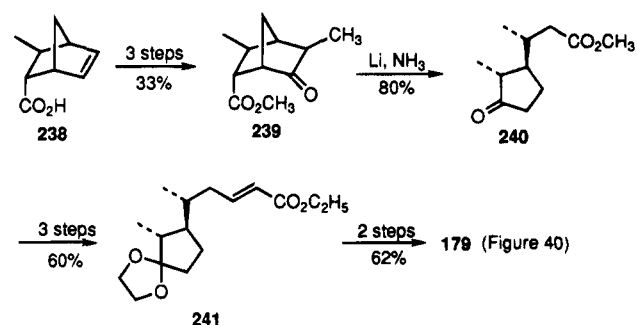


Figure 50.

several steps via iodolactonization, esterification, and α -methylation, furnishes **239**. Reductive cleavage of **239** with lithium in liquid ammonia gives disubstituted cyclopentanone ester **240**, which was smoothly elaborated to **179** by chain extension and methylmagnesium chloride addition. A synthesis from the Takano laboratory²³⁷ centers on the use of lactone **242** bearing a bulky γ -(trityloxy)methyl group. Transformation of the *S*-isomer of the latter to **243** with the desired stereochemistry, and then further conversion of **243** through **244**, **245**, and **246** in a straightforward manner leads to the key CD precursor **179** (Figure 51).

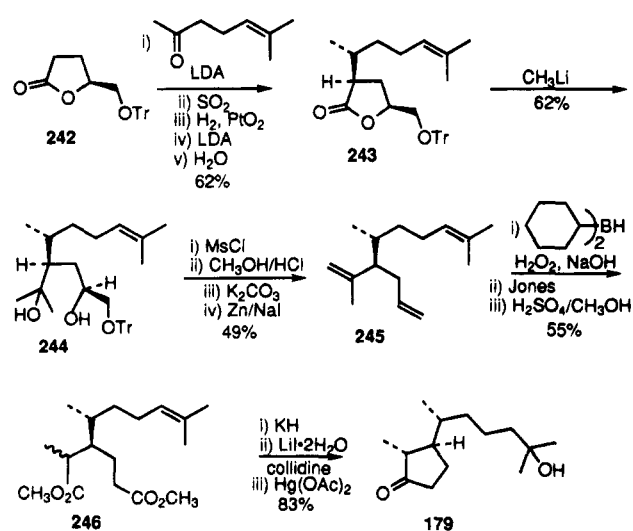


Figure 51.

The 24(*S*)-Hydroxylated synthon **256** was synthesized by Warchol's group in Poland.²³⁸ Natural (-)-menthone **247** was oxidized to a lactone which was alkylated with allylic bromide to a single product **248**. The latter was converted to the important intermediate **256** by several different routes as outlined in Figure 52, but most notably through highly reactive

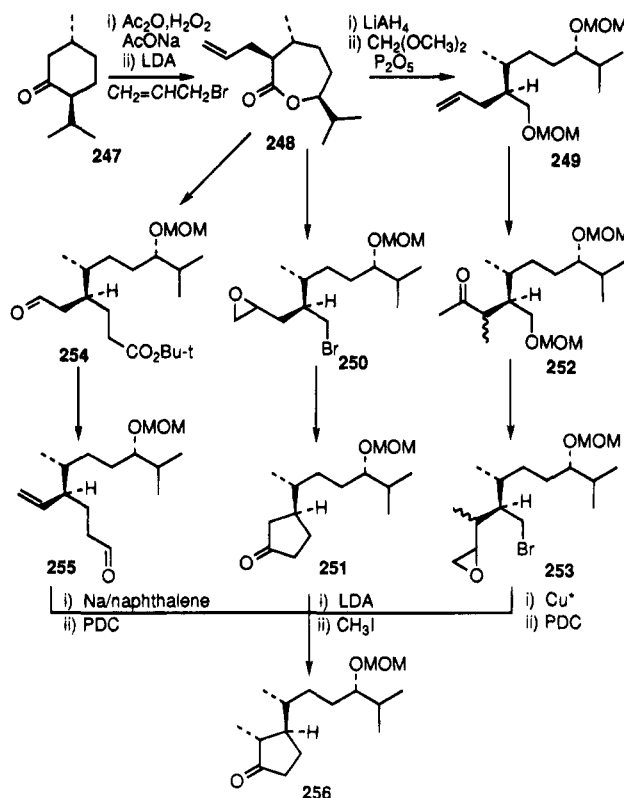


Figure 52.

copper (Cu^*)-catalyzed cyclization of **253** or free radical cyclization of enaldehyde **255**.

The synthesis of 22-oxa CD-ring synthon **260** was recently developed by Tanimori and co-workers²³⁹ based on homoconjugate 1,5-addition of alcohol **258** to doubly activated cyclopropane **257** in the presence of Lewis acid (Figure 53). The treatment of cyclo-

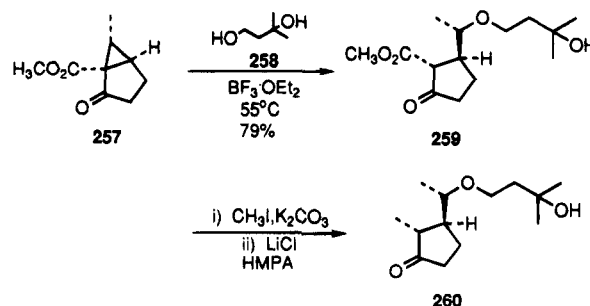


Figure 53.

propane **257** with 3-methyl-1,3-butanediol **258** in the presence of $\text{BF}_3\text{-Et}_2\text{O}$ affords good yield of 1,5-adduct **259** and 3% of a stereoisomer. The main adduct **259** with the correct stereochemistry was easily converted to **260** through methylation and decarboxylation. However, Robinson annulation, the general method for appending the C-ring, unlike that of earlier examples (Figures 40–52), was not very successful here (11% overall yield for Robinson annulation).

Ketone **261** and enone **262** may serve as crucial intermediates for steroid synthesis in general as well as for vitamin D. Their syntheses and transformations have been studied by several groups^{240–243} and include transformations to C-8 substituted derivatives **265** and **266**, which are directly useful for vitamin D applications (Figure 54).

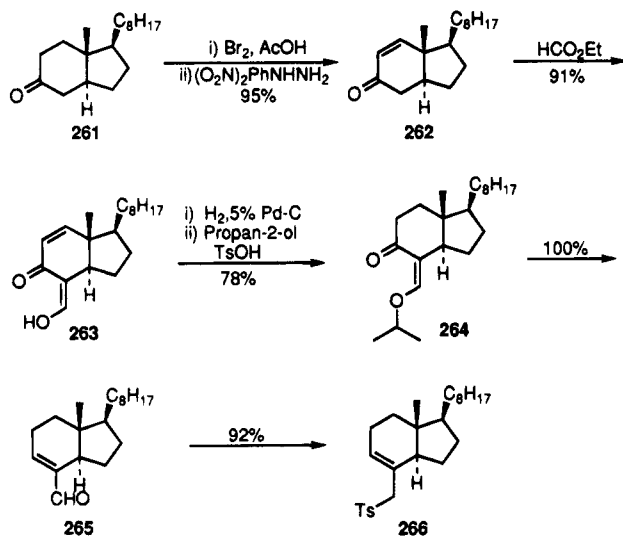


Figure 54.

One of the examples pertinent to the preceding scheme is the synthesis from a readily available bicyclo[2.2.1]heptane derivative by Grieco.²⁴⁴ Grieco's synthesis centers around the key bicyclic lactone **269**, in which the carbonyl unit of the lactone serves to introduce the remaining carbon atoms of the side chain. The oxygen function at C-16 (the lactone ring oxygen) provides a handle for establishing the stereochemistry at C-14 via a C–O to C–C chirality transfer (Figure 55).

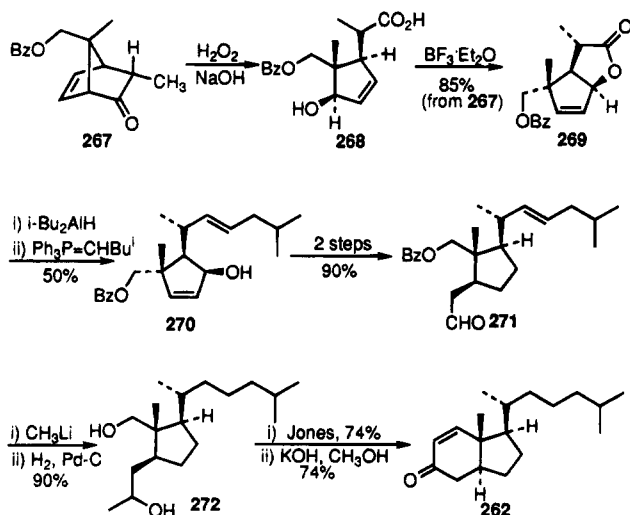


Figure 55.

As previously discussed, a key problem for the synthesis of 25-hydroxy-Grundmann's ketone (**89**, Figure 22) is to establish the *trans*-hydrinan CD-ring system. Many solutions have been suggested from different laboratories. Stork's intramolecular Michael addition^{245,246} provides a unique approach to the construction of *trans*-hydrindans. As shown in Figure 56, intramolecular Michael addition takes pre-

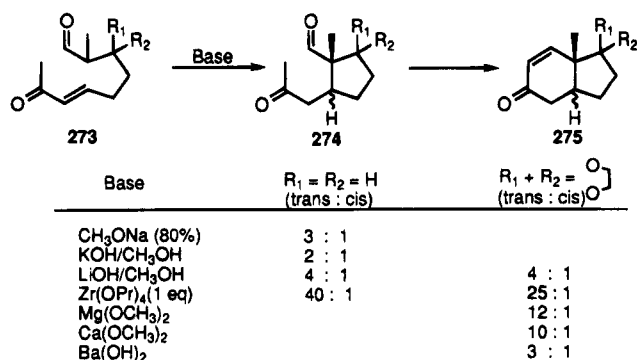


Figure 56.

cedence over the vinylogous aldol condensation and the stereochemical result can be controlled to give the desirable *trans* arrangement about the cyclopentane ring of the two carbonyl chains, thus leading to a simple route to the *trans*-hydrindones. The data shown in Figure 56 reveals that the nature of the base markedly affects the stereochemical outcome of the reaction, and the ratio of *trans*- to *cis*-hydrindones eventually formed follows the order that the metals forming the tighter bond to oxygen leads to more *trans* product. This methodology has been successfully applied to a short synthesis of adrenosterone.²⁴⁷

A three-step asymmetric approach to the synthesis of indenedione **278** (24% overall yield, 62% e.e) was developed in Tsuji's laboratory in 1984.²⁴⁸ A metalated acetone imine of (*R*)-*tert*-butylleucinol methyl ether was added in a 1,4-fashion to methylcyclopentenone **175** followed by enolate trapping. Multiple aldol condensation of the resulting **277** led to **278** together with 2% of the *cis* isomer. Tin(IV) chloride was reported to be the only choice for introducing the formyl group equivalent to the enol silyl ether **277** (Figure 57).

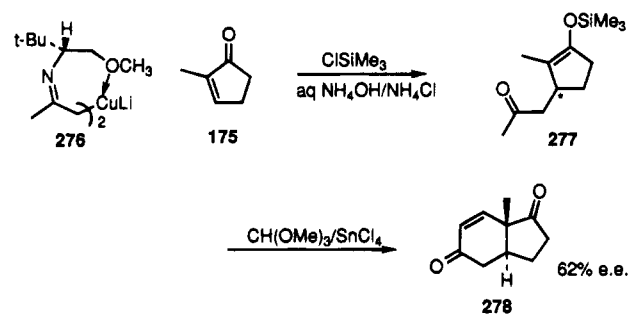


Figure 57.

MeAlCl₂-initiated ene cyclization of dienone **279** (Figure 58) provides the functionalized *trans*-fused hydrindone **281**, which could be transformed via **284** or **286** to the intermediate **278** or more usefully to the Inhoffen–Lythgoe diol (**91**, Figure 22).^{249,250} The cyclization of **279** to **281** proved to be very sensitive to the reaction conditions, requiring an excess of the optimal Lewis acid MeAlCl₂. The proposed zwitterionic intermediate **280** can be envisaged to undergo hydrogen and methyl shifts to give **281**. If uncomplexed ketone is present, the zwitterionic intermediate can react by intermolecular proton transfer to the basic carbonyl group of the uncomplexed ketone in competition with the desired 1,2-

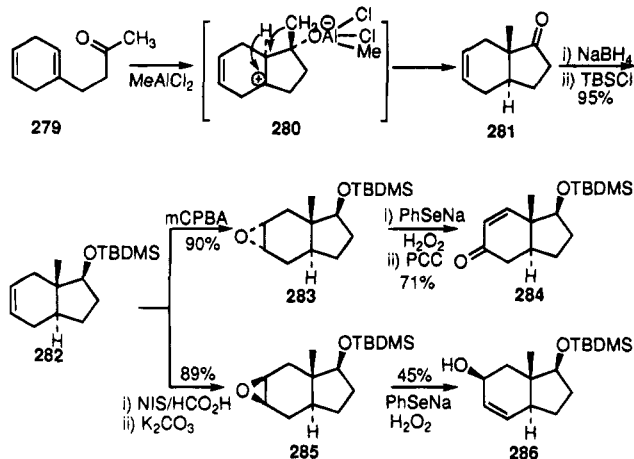


Figure 58.

hydrogen shift.²⁵¹ The preference for forming a *trans*-fused bicyclic system could not be easily rationalized. The effect of ring size on the cyclization reaction was also studied.²⁵¹ Seven-membered enone proved to give a higher yield of the cyclized product (85%, 9:1 *trans/cis*) and five-membered enone, under the same conditions, failed to cyclize. Substitution α to the double bond seemed to decrease the yield of the cyclization.

Another approach, relying again on the well-documented preference for a *trans* orientation of substituents derived from a conjugate addition/trapping sequence with 2-methyl-2-cyclopentenone (**175**), was reported by Denmark.²⁵² A synthetic equivalent of vinyl- α,β -dianion, α -(trimethylsilyl)vinyl cuprate, was utilized with methyl α -bromoacetate as an acceptor. After C-ring annulation, the target compound **290** was obtained in 34% overall yield (based on **175**) (Figure 59). This synthesis was originally developed for a conceptually different approach to 11-oxosteroids but the product **290** could be envisaged as a precursor to vitamin D.

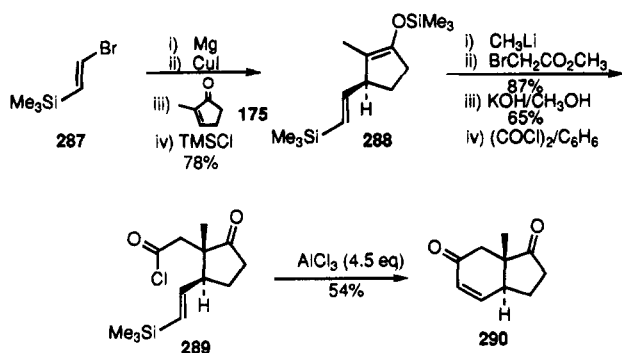


Figure 59.

The highly stereoselective Claisen rearrangement of the vinyl ether of 1-(1-hydroxyethyl)-2-methyl-3-alkylcyclopentene **291** introduces the *trans* stereochemistry to **294**, which, after intramolecular alkylation, leads to a synthetic precursor of various steroids, as well as a potential vitamin D CD-ring synthon (Figure 60).²⁵³ The thermal reaction of intermediate **292** (160 °C, 1 h) gives only the *trans* isomer, suggesting that the transition state **292** is favored over transition state **293** due to the 1,3-diaxial interaction of the two methyl groups in the latter.

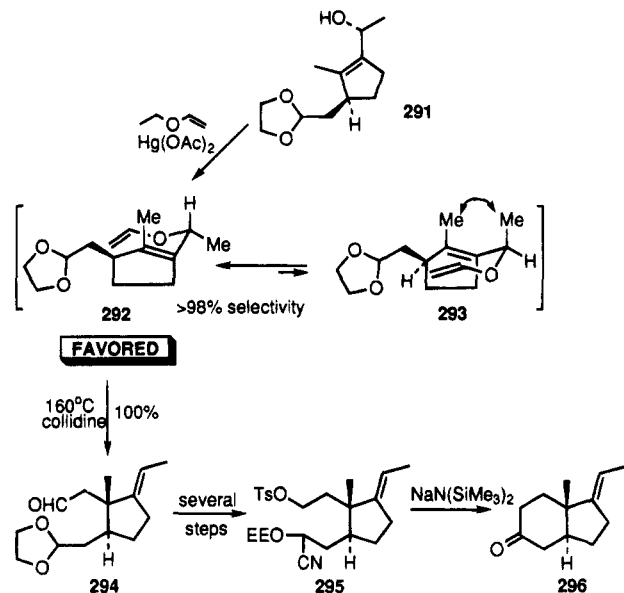


Figure 60.

The tandem Cope–Claisen rearrangement of triene **297** affords aldehyde **299** as the major component (Figure 61).²⁵⁴ The ratio of aldehyde **299** to **298**

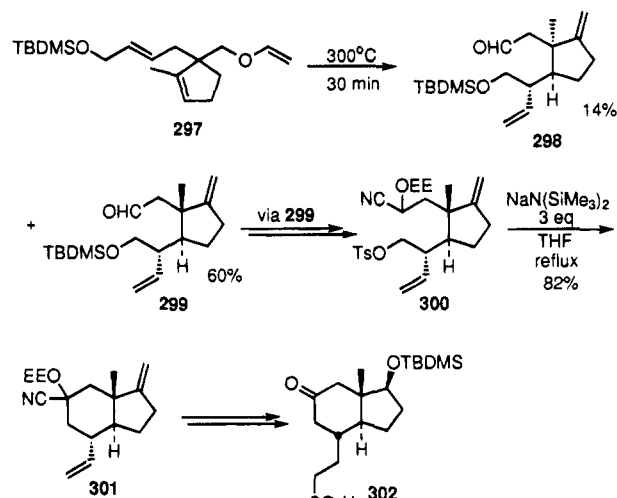


Figure 61.

proved to be temperature dependent. Lower temperatures give higher proportions of **299**, but affords lower yields of product. By employing sodium hexamethyldisilazane as base, the intramolecular alkylation of **300** proceeds without obvious β -elimination of its tosylate group. The *trans* intermediate **301** was smoothly converted to Stork's keto acid **302**, which also has potential as a precursor for the synthesis of a vitamin D CD fragment.^{255,256}

Intramolecular Diels–Alder Strategy. Vicinal stereochemistry can often be controlled very effectively via cycloaddition processes and the intramolecular Diels–Alder reaction clearly comes to mind. The stereochemistry of the cyclization is established by the spatial orientation of the dienophile as it approaches suprafacially to the diene while the ring fusion is determined by a complex interplay of conformational, steric, and electronic effects as well as reaction conditions. Table 2^{257–266} outlines the outcome of the Diels–Alder reactions of some nona-

Table 2

R ₁	R ₂	R ₃	R ₄	R ₅	conditions	yield	% 304	% 305	references
R ₁ + R ₂ = O		H	H	CH ₃	190°C/13h 170°C/24h	100%	30%	70%	257
R ₁ + R ₂ = O		CH ₃	H	CH ₃	190°C/18h	31%	31%	69%	258
OCH ₃	OCH ₃	H	H	CH ₃	170°C/24h	98%	72%	28%	257
OEt	OEt	H	H	CH ₃	170°C/24h	98%	70%	30%	257
-OCH ₂ CH ₂ CH ₂ O-		H	H	CH ₃	200°C/15h	85%	75%	25%	259
OR	H	H	H	CH ₃	220°C/30h	42%	50%	50%	259,260
	H	CH ₃	OH	CH ₃	160°C/20h	78%	75%	25%	261
	H	-CH ₂ C ₆ H ₄ - (-m-OCH ₃)	OH	CH ₃	160°C/20h	96%	80%	20%	261
	H	-CH ₂ CH ₂ OH	OH	CH ₃	160°C/20h	80%	80%	20%	262
	H	H	H	CH ₃	200°C/18h	23%	50%	50%	263
	H	H	H	CH ₃	200°C/6h	100%	50%	50%	263
C ₈ H ₁₇	H	CH ₃	H	CH ₃	200°C/18h	62%	75%	25%	264
C ₈ H ₁₇	H	Br	H	CH ₃	200°C/60h	71%	58%	42%	264
C ₈ H ₁₇	H	SC ₆ H ₅	H	CH ₃	210°C/18h	50%	50%	50%	264
-SCH ₂ CH ₂ CH ₂ S-		H	H	CH ₃	170°C/24h	96%	53%	47%	265
		CH ₃	H	CF ₃	170°C/18h	90%	83%	17%	266

trienes. Substitution at C-3 and/or C-7 of the 1,3,8-nonatrienes was the most effective way to increase the proportion of *trans*-fused adducts. If C-12 substituted analogues are desired corresponding to C-9 in **303**, maximum selectivity is achieved with terminally activated dienophiles.^{264,267,268} Selected vitamin D cases are described in more detail below.

The Diels–Alder precursor **308** of Wilson²⁶¹ with established stereochemistry at C-17 and C-20 was synthesized via condensation of aldehyde **307** and pentadienyl lithium or a methyl derivative (Figure 62). The diene **307** was obtained through an Ire-

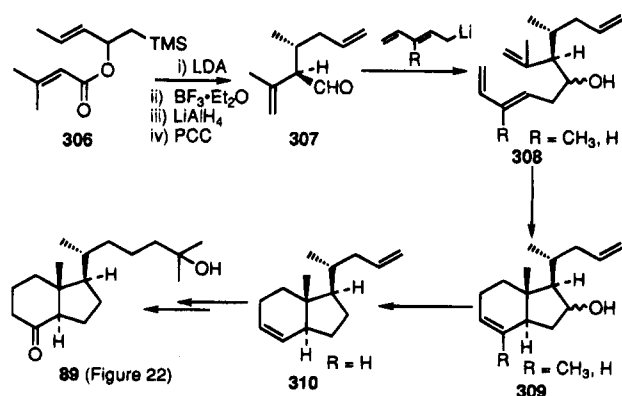


Figure 62.

land–Claisen rearrangement of **306**. The cyclization of the two diastereoisomers of **308** gave **309** with the desired β -stereochemistry of the side chain. Removal of the C-16 hydroxyl, extension of the side chain, and C-8 functionalization (Lythgoe's epoxidation strategy)¹⁸⁷ furnished 25-hydroxy-Grundmann's ketone **89**. This method was also extended to the synthesis of aldehyde **312** for application of Mazur's cyclopropane solvolysis strategy^{262,269} (Figure 63). By em-

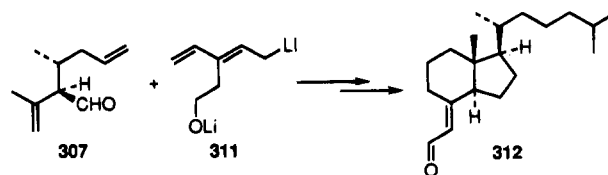


Figure 63.

ploying [3-[(triethylsilyl)oxy]-1,3-pentadienyl]lithium (**313**) instead of **311**, Wilson also reported a total synthesis of the 25-hydroxyvitamin D₂ CD precursor **317** through a similar intramolecular Diels–Alder reaction²⁷⁰ (Figure 64). However, the stereochemistry of the Diels–Alder adduct at C-14 appeared not to be fully detailed.

In another approach, Parker²⁶³ used the ester enolate Claisen rearrangement of **318** to generate the proper stereochemistry at C-17 and C-20. The con-

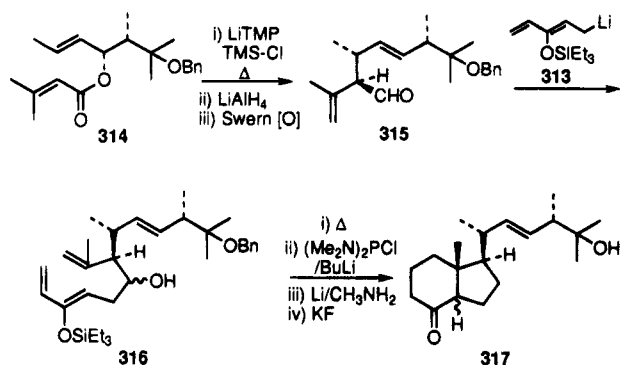


Figure 64.

figuration at C-17 in **319** in turn, upon intramolecular Diels–Alder reaction, induces the desired stereochemistry at C-13 and C-14 in products **320** and **321**, the former being a known intermediate in the total synthesis of vitamin D (Figure 65). As is evident, the undesired *cis* isomer is formed in equivalent amounts to the desired *trans* compound.

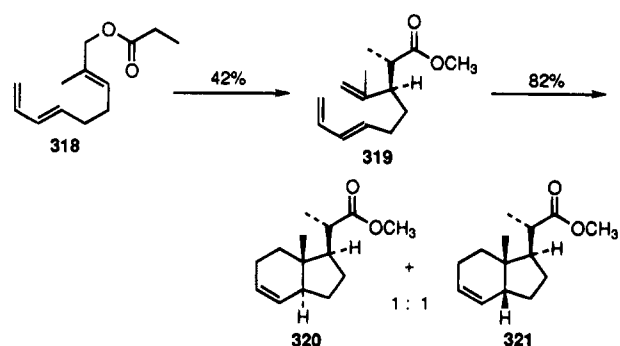


Figure 65.

Other Strategies including the Degradation of Natural Products. A novel *o*-quinodimethane strategy was recently reported by Fukumoto et al. (Figure 66).²⁷¹ The highly diastereoselective synthesis of 25-hydroxy CD fragment **333** was achieved via an intramolecular [4 + 2] cycloaddition reaction of the transient *o*-quinodimethane (**325** to **326**) and a regiocontrolled C–C bond formation by an intramolecular epoxide ring opening reaction of a bis-sulfonyl epoxide **331** as key steps. The important intermediate **327** has all of the required stereogenic centers of the 25-hydroxy CD fragment and was prepared from **322** (via D-mannitol). The double bond in adduct **327** was epoxidized and was subsequently cleaved by hydrazine treatment. The straightforward elaboration of **329** afforded **331**, poised for C-ring cyclization. Base treatment (LDA) led to the required exo opening of the epoxide and then the two phenylsulfonyl groups were removed reductively to afford **332**. Elaboration of the side chain and then deprotection afforded the 25-hydroxy-Grundmann's ketone precursor **333**.

Synthesis of side chain derivatives of Grundmann's ketone from the degradation of steroids has also been studied. One of the recent contributions to this approach is the report by Dauben.²⁷² Norrish type II photochemical degradation of the seco-steroid **335** derived from Δ^5 -unsaturated steroids provides the useful intermediate **336**. Hydrolysis of **336** followed by Barton decarboxylation–hydroxylation affords the aldehyde **337** which could serve as a CD-ring frag-

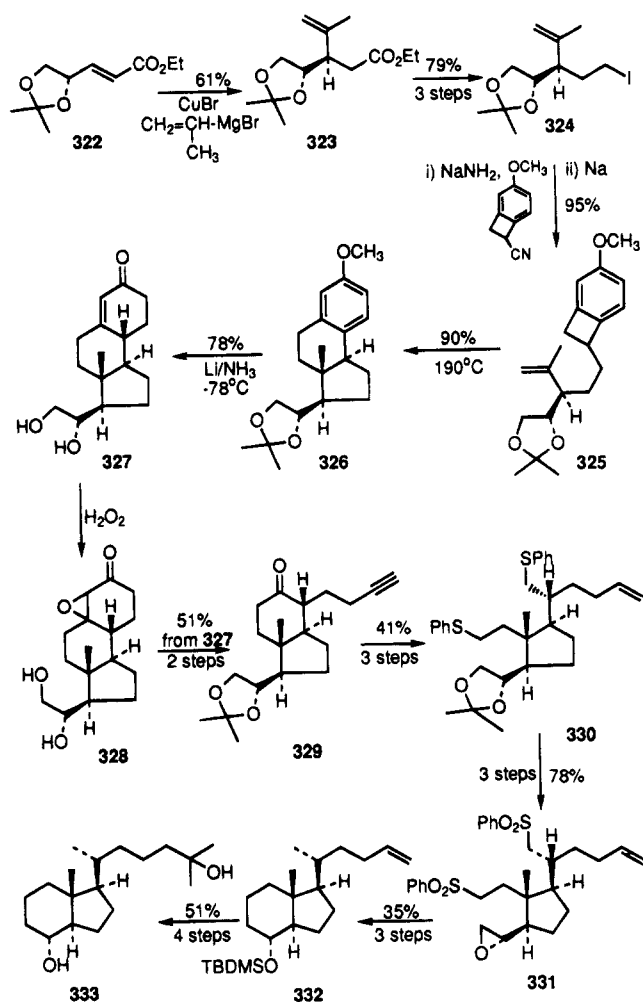


Figure 66.

ment for the Julia elimination coupling to vitamin D (see the later section II.I) or could be converted further to ketones of type **19** (e.g., R = C₈H₁₇ as in Grundmann's ketone, **90**) (Figure 67).

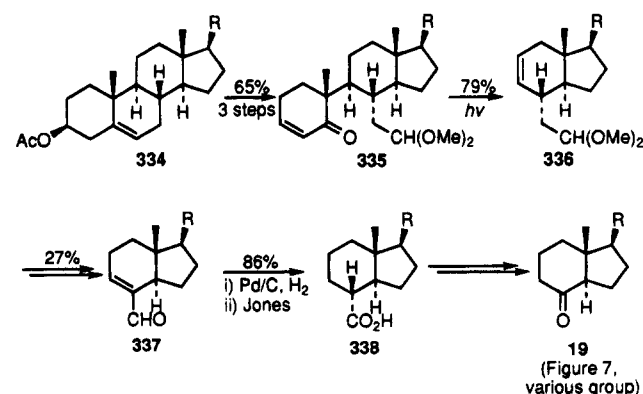


Figure 67.

Another reported steroid-based approach for the synthesis of useful vitamin D CD fragments, reported by Morzycki et al.,^{273,274} entails degradation of ketone **339** (Figure 68). Fragmentation of the monooxime of triketone **341**, the crucial step of the synthesis, affords the desired enone **342** as the major component (50%). The latter was converted to the alcohol **344** by Wharton's two-step procedure.²⁷⁵ The Wharton sequence involves epoxidation of **343** with hy-

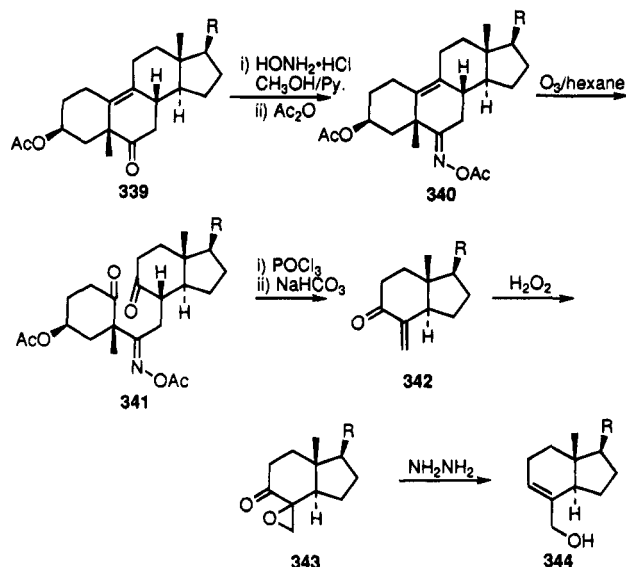


Figure 68.

drogen peroxide followed by treating the epoxy ketone mixture with hydrazine to give the alcohol **344**.

In summary, despite the emergence of considerable new chemistry resulting from efforts in the CD construction area,²⁷⁶ the shortest synthesis (and perhaps the most practical synthesis) of 25-hydroxy-Grundmann's ketone (**89**) remains the degradation of vitamin D₃ followed by 25-hydroxylation (Figures 23 and 24) or the degradation of vitamin D₂ followed by side-chain construction (e.g., Figure 27). While microbiological approaches (not covered in this review) or other chemical approaches might eventually prove superior, these remain for future evaluation. One can imagine however that for synthesizing certain side chain or CD analogues, or isotopically labeled derivatives, total synthesis approaches may prove practical.

2. Synthesis of A-Ring Phosphine Oxides

The A-ring phosphine oxide **348** is most easily obtained through degradation of vitamin D₃ (or vitamin D₂ with the ergosterol side chain) as shown in Figure 69.¹⁰⁶ From an economical point of view, Okamura's adaptation²⁷⁷ of a previously described

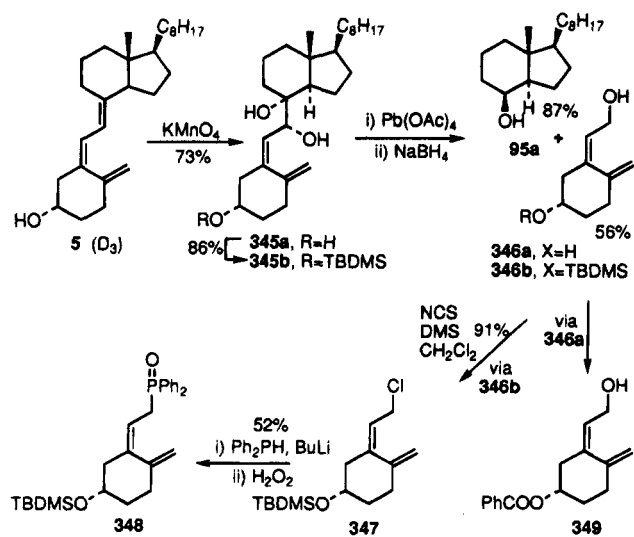


Figure 69.

procedure²⁷⁸ using KMnO₄ as the initial oxidant is probably the most efficient one for selective Δ^{7α,8α}-bis-hydroxylation of D₃ (**5**) (Figure 69). The C–C bond of 7α,8α-glycol **345** is easily cleaved via a lead tetraacetate oxidation–NaBH₄ reduction sequence. The phosphine oxide **348** is obtained from **346** by reaction of the corresponding TBDMS chloride **347** with lithium diphenyl phosphide, followed by hydrogen peroxide treatment.^{103,106} Lythgoe's procedure via the intermediate **349** was reported still earlier.¹⁰⁶

The total synthesis of the intermediate diol **346a** or a related C-3 derivative presents two stereochemical problems. In Lythgoe's synthesis (Figure 70),^{102,105}

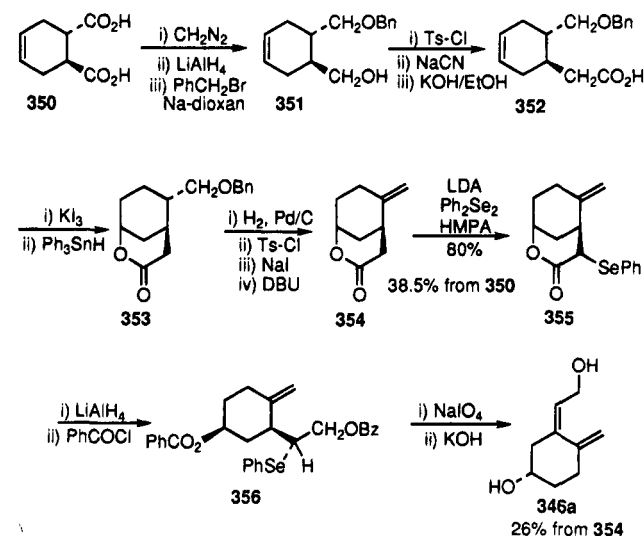


Figure 70.

the first problem of securing the proper stereogenicity at the secondary hydroxyl center was solved by using the readily available (*S*)-cyclohex-4-ene-1,*trans*-2-dicarboxylic acid (**350**) as starting material. When this acid was converted into the lactone **353**, chirality was transferred to provide the required one at the secondary hydroxyl center in the end product. The second problem, the stereospecific formation of the *Z* geometry of the trisubstituted double bond, was solved by selective thermal syn elimination of the selenoxide of **356**.

The Roche investigation of the chemical conversion of vitamin D₃ to its 1α,25-dihydroxy metabolite¹⁷⁶ makes it possible to convert the vitamin D₃ (or D₂) degradation product **346b** directly to the 1α-hydroxylated phosphine oxide **88** (Figure 71). In this approach, the more reactive Δ^{5,6}-double bond of **346b** was protected as the corresponding epoxide through *t*-BuOOH/VO(acac)₂ oxidation, affording a 6.3:1 ratio of β and α epoxides **357a** and **358a**, respectively, while mCPBA produced only the α-epoxide **358a**. Oxidation with SeO₂/pyridine *N*-oxide in dioxane was found to be highly selective for C-1 hydroxylation. Starting from **357b**, a single 1α-hydroxy isomer **359a** was obtained while under the same condition, acetate **358b** leads to a 78:22 mixture of 1α- and 1β-hydroxy isomers **360a** and **360b**, respectively. Only the method of Ganem²⁷⁹ was reported to be productive for the regeneration of the Δ^{5,6}-double bond when the bis-TBDMS protected form of **359a**, namely **359b**, was subjected to deoxygenation, affording **361a**. However, the overall yield of this transformation is only 22%.

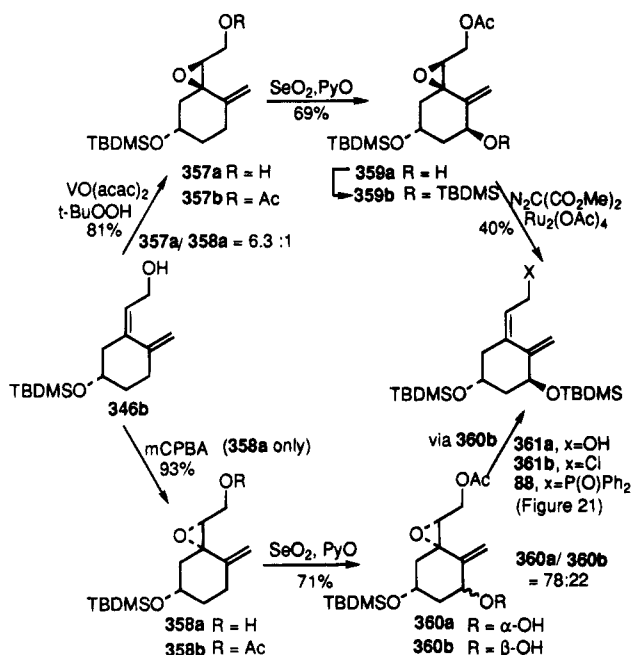


Figure 71.

Carvone Approach. The 14-step procedure of the Hoffmann-La Roche group (Figure 72)^{107,200} remains one of the most efficient total syntheses of the 1 α -hydroxy A-ring phosphine oxide **88** (Figure 72).

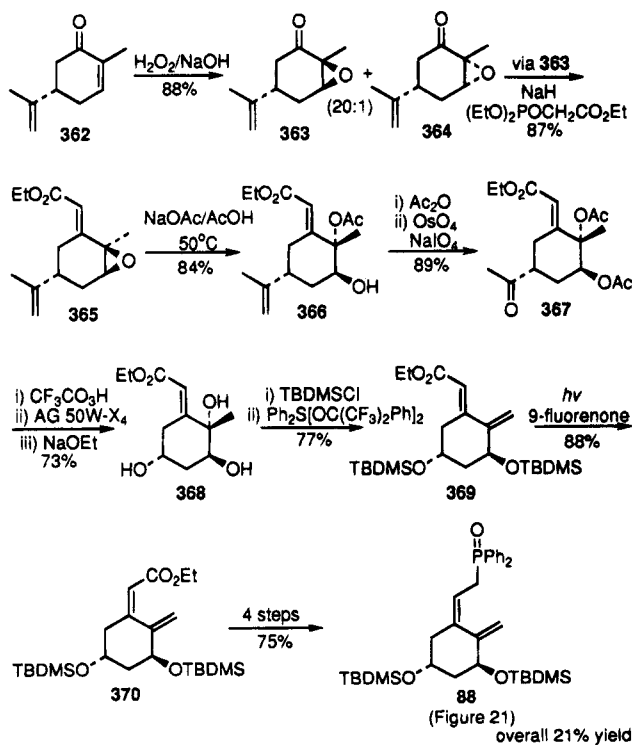


Figure 72.

Horner–Emmons reaction of (*S*)-carvone epoxide **363** gave ester epoxide **365**, which was cleaved with sodium acetate in acetic acid and esterified to produce a diacetate. The latter on ozonolysis gave methyl ketone **367**. Baeyer–Villiger oxidation and hydrolysis gave triol ester **368**. The two secondary alcohols were protected and the exomethylene group was introduced by treatment with a dialkoxydiarylsul-

furane reagent to induce β -elimination. The resulting *E*-ester **369** was isomerized to the *Z*-ester **370** via triplet sensitized photoisomerization. Conversion of the latter to the phosphine oxide **88** required several more steps as in Figure 69.

Diels–Alder Approach. De Clercq's method¹⁰⁸ highlights the stereoselective cycloaddition between a 1,3-disubstituted allene **371** and the furan **372** to give appropriately functionalized A-ring skeleton **373**, possessing in particular the *Z* configuration of the $\Delta^{5,6}$ -double bond (Figure 73). The subsequent reduc-

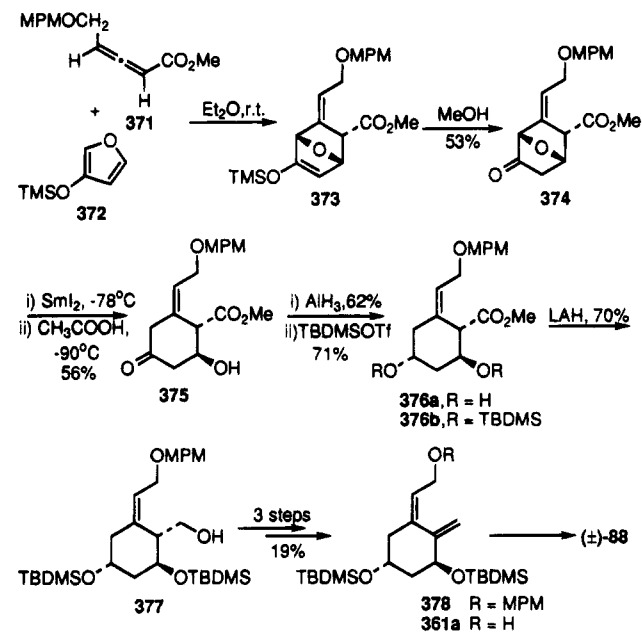


Figure 73.

tive opening of the oxygen bridge in **374** with samarium(II) iodide, followed by careful low-temperature acid quenching, afforded **375**. The latter was then reduced with aluminum hydride stereoselectively to the *trans*-diol **376a**, presumably via prior complexation with the axially oriented 1 α -hydroxy group. The remaining steps leading to racemic **88** were relatively straightforward, but there remains the problem of extending this approach to the enantiomerically pure series, such as starting with an optically active allene **371**.

Utilizing a Lewis acid-catalyzed [4 + 2] cycloaddition process, Posner¹⁰⁹ reported a 14-step synthesis of **88** in 34.6% overall yield (Figure 74). The reaction of 3-pyrone sulfone **379** with enantiomerically pure vinyl ether **380** in the presence of Yamamoto's "MAD" Lewis acid **381** gave bicyclic lactone **383** with 98:2 endo to exo diastereoselectivity. The rationale assumes transition state structure **382**. The lactone ring of **383** was opened with methanol and then elimination induced to afford the conjugated enoate **384**. Sacrifice of the chiral auxiliary via trifluoroacetolysis involved exclusive cleavage of the secondary benzylic carbon–oxygen bond and survival of the secondary allylic-oxygen bond. The novel sulfonyl orthoacetate **386** was utilized to convert allylic alcohols directly into the corresponding 2-carbon extended dienolate esters. This tandem Claisen rearrangement–sulfoxide thermolysis of **385** produced

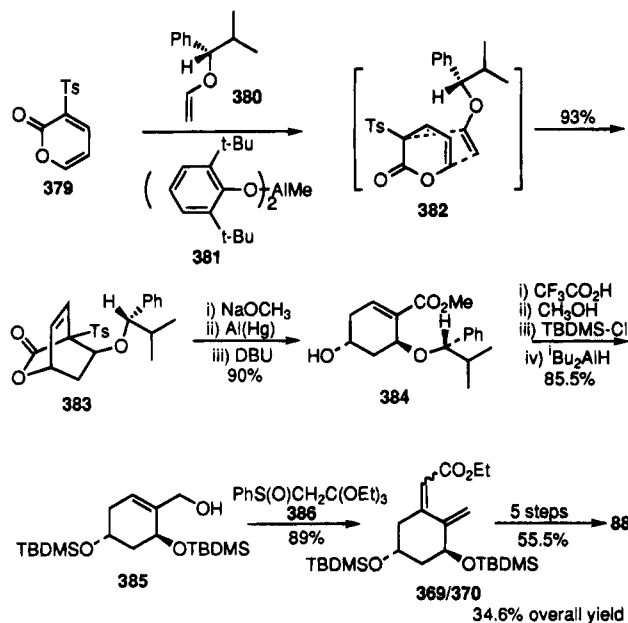


Figure 74.

the known dienoate ester **369/370** as a 4:1 mixture of *E/Z* geometrical isomers in 89% yield. The mixture was transformed to the A-ring phosphine oxide **88** by the Roche procedure shown in Figure 72. This high-yielding sequence may be limited by the accessibility and loss of the chiral auxiliary on the dienophile **380** and the availability of the starting pyrone sulfone **379**, which requires some five steps from commercial material.²⁸⁰

A complement to the approach in Figure 74, reported later by Posner,²⁸¹ features a highly stereocontrolled Diels–Alder cycloaddition of **389** with easily prepared, enantiomerically pure 2-pyrone (*S*)-lactate **388** using the appropriately matched enantiomeric form of the NMR shift reagent **387** (Figure 75). This catalyzed [4 + 2] cycloaddition proceeded

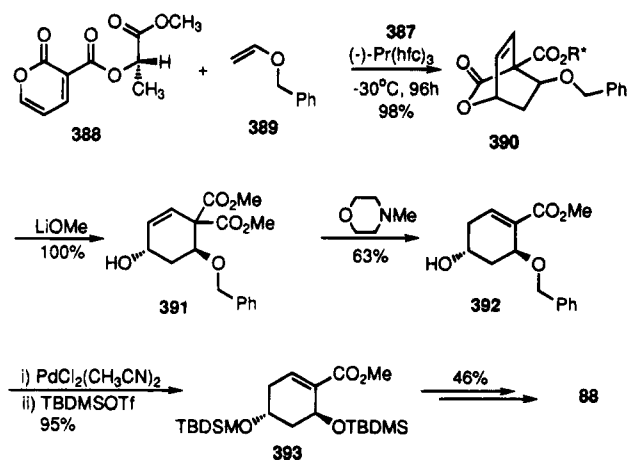


Figure 75.

with double stereodifferentiation in which the absolute stereochemistry of the chiral diene and the absolute stereochemistry of the chiral Lewis acid were mutually compatible, leading quantitatively to bicyclic lactone **390** as a 98:2 ratio of endo to exo diastereomers. Methanolysis of the endo diastereomer followed by decarboxylation and shift of the

double bond into conjugation afforded cyclohexenol ether **392**. Palladium-promoted debenzoylation followed by silylation produced the intermediate **393**. The latter could then be converted to A-ring phosphine oxide **88** in 46% overall yield as in Figure 74.

Further investigations by the Posner laboratory on the Lewis acid-promoted inverse-electron-demand [4 + 2] cycloaddition scheme^{282,283} revealed that the reaction of the commercially available vinyl ethers **394** or **395** with methyl 2-pyrone-3-carboxylate (**396**), in the presence of the chiral Lewis acidic titanium species, also produces adducts of the type **397**, exhibiting high enantiomeric purity (Figure 76). The

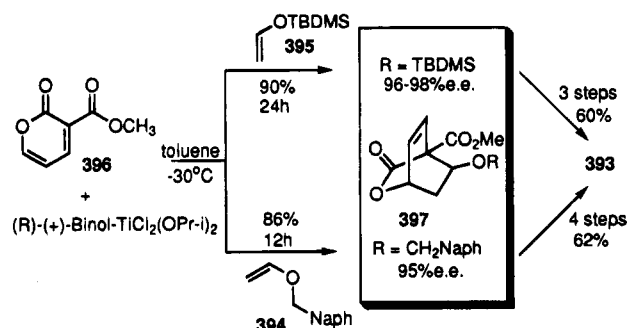


Figure 76.

adducts are easily transformed in 3–4 steps to the same intermediate **393** as in Figure 75. The easy availability of the starting material and the high overall yield of highly enantiomerically enriched A-ring components render the Posner approach as highly attractive for the synthesis of certain phosphine oxides related to **88**.

Cr(III)-Mediated Reaction. In the approach shown in Figure 77, the intermediate **406** for synthesis of A-ring phosphine oxide **88** was synthesized starting from (*R*)-(-)-carvone (**398**), using a diastereoselective chromium(III)-mediated addition of an allylic halide to aldehyde as a key step.²⁸⁴ The epoxide **399** obtained from **398** was stereoselectively reduced with lithium tri-*sec*-butylborohydride to give a 13:1 mixture of **400** and its epimer. Oxidative degradation of the isopropenyl group, TBDMS protection, and then epoxide rearrangement with diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) led to regioselective formation of allyl alcohol **402**. The latter was then converted to iodide **403**, which was utilized in the crucial chromium(III)-mediated reaction with aldehyde **404** to afford alcohol **406** with excellent diastereoselectivity (~100% yield of a single diastereomer), possibly through the chairlike transition state **405**. Dehydration of the alcohol (Mitsunobu reagent) afforded, after oxidative deprotection, the desired alcohol **378**, which could be converted to the A-ring phosphine oxide **88** by a procedure outlined earlier. This 15-step procedure from (*R*)-(-)-carvone, in 25% overall yield, is comparable to that of the Hoffmann-La Roche group (Figure 72), and is of additional use since other A-ring precursors **407** and **408** are also available from the common intermediate **406**.

Kobayashi's procedure²⁸⁵ involves the modification of an enzymatically resolved chiral monoester **409**

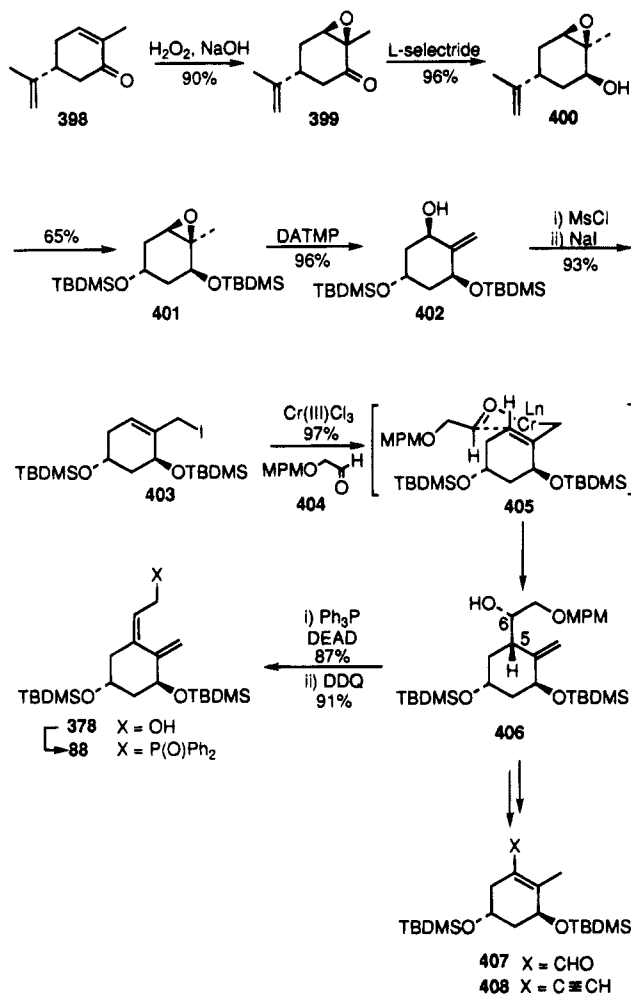


Figure 77.

(Figure 78). Stereogenicity at C-3 was induced via iodolactonization to **410**, which upon epoxidation afforded a single isomer, β -epoxide **411**. After transformation to ketenedithioacetal **412**, and then to the key C-1 α oxygenated synthon **413**, functional group modification including a selenoxide elimination step afforded the previously described **378** (from Figure 77).

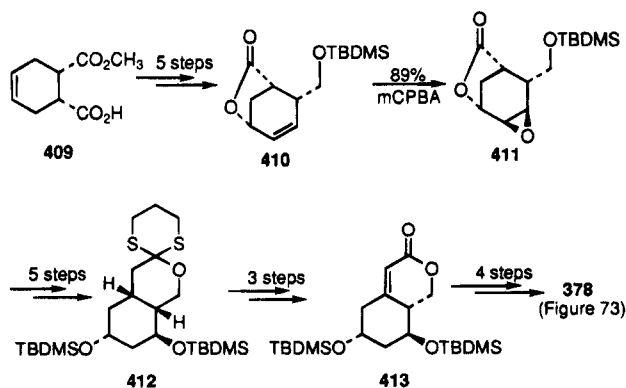


Figure 78.

Ene Reaction. In both procedures of Stork (Figures 79 and 80),¹⁹¹ an intramolecular chirality transfer step was used for two-carbon homologation at C-5 and the 1 α -hydroxyl was introduced through epoxidation–ring opening of the resulting double bond

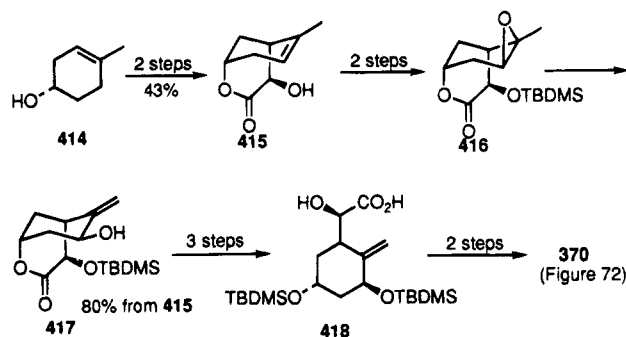


Figure 79.

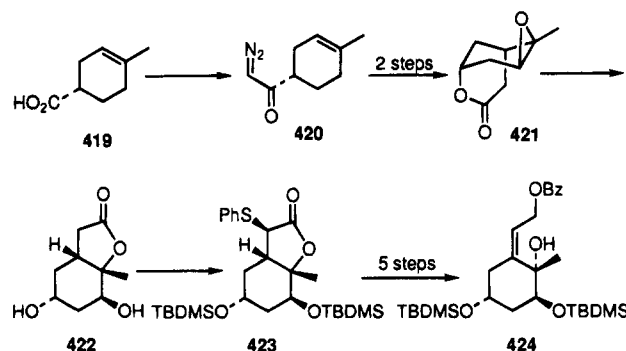


Figure 80.

introduced in the first step. The two routes are conceptually related but the first one (Figure 79) requires starting with the difficultly accessible 4-methyl-3-cyclohexenol (**414**) having high optical purity. The advantage of the second is that the starting material is the readily available, optically pure 4-methyl-3-cyclohexenecarboxylic acid (**419**, Figure 80). The two routes lead to the attractive intermediates **370** and **424**, respectively.

Another procedure recently developed²⁸⁶ features a highly stereoselective intramolecular ene reaction to set the proper configuration of the C-1 hydroxyl and the $\Delta^{5,6}$ -Z-double bond (Figure 81). Two catalytic asymmetric routes to the ene reaction precursor **428**

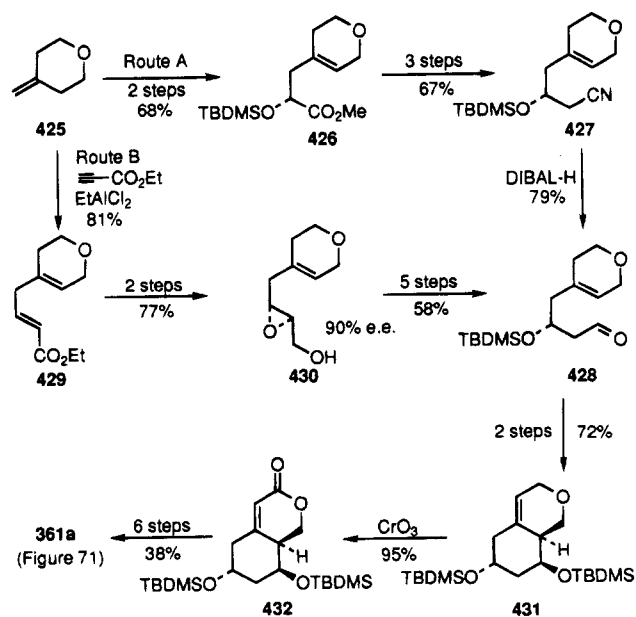


Figure 81.

were described. In the first procedure (route A), Mikami's catalytic system,^{287,288} the Lewis acid system from $\text{TiBr}_2(\text{OiPr})_2$, and (*R*)-(+)-1,1'-bi-2-naphthol were used for the ene reaction. Route B to aldehyde **428** was based on the Sharpless catalytic asymmetric epoxidation of the allylic alcohol generated from the ene intermediate **429**. Regioselective reduction of the resulting epoxide **430** (90% ee) with sodium bis(2-methoxyethoxy)aluminum hydride yielded exclusively a 1,3-diol which was smoothly converted to the aldehyde **428**. For the next stage of the synthesis, ene reaction of aldehyde **428** upon treatment with methoxyaluminum chloride gave a 10:1 mixture of the desired alcohol and its epimer, the former was converted in a series of steps to the known alcohol **361a** (Figure 71).

Pd-Catalyzed Cyclization. A short and versatile approach for regio- and stereoselective synthesis of bis-exocyclic conjugated dienes was developed in Mouriño's laboratory in Spain (Figure 82).^{289,290} The

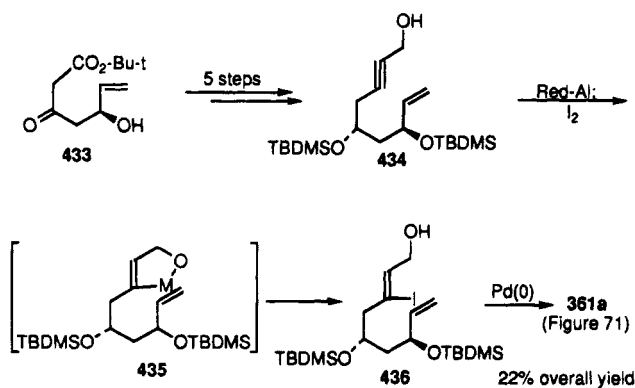


Figure 82.

requisite (*Z*)-vinyl iodide **436** for cyclization was prepared by Corey's reductive iodination method or Denmark's modification. Reflux of the vinyl iodide **436** with 5 mol % $\text{Pd}(\text{PPh}_3)_4$ and Et_3N gave exclusively desired cyclization product **361a** (22% overall yield).

Shimizu's synthesis¹¹⁸ appears to be the first reported palladium-catalyzed cyclization strategy of acyclic compounds for vitamin D synthesis (Figure 83). The advantage of this strategy is the easy

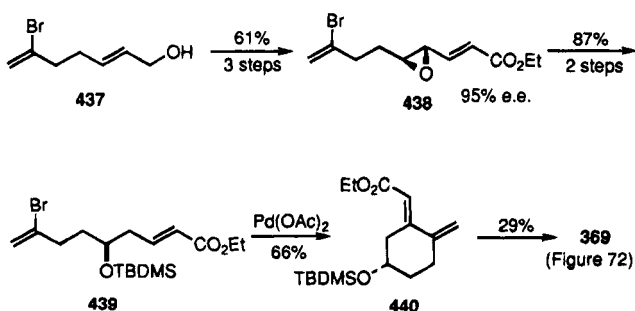


Figure 83.

accessibility of acyclic components. The earlier described intermediate **369** (Figure 72) was synthesized by several methods. One of the routes was based on a direct late hydroxylation of **440** wherein the acyclic substrate **439** ready for cyclization was prepared from alcohol **437** via Sharpless asymmetric epoxida-

tion (95% ee), Swern oxidation, Horner-Emmons reaction, palladium-catalyzed epoxide hydrogenolysis, and silylation. The cyclization of **439** to **440** was induced with 5 mol % $\text{Pd}(\text{OAc})_2\text{-PPh}_3$ (1:2) and K_2CO_3 (2 equiv) in CH_3CN . An obvious drawback of this route is the inefficiency of the oxidative conversion **440** to **369** (29% yield). An improved route involved the stereoselective synthesis of the protected 1,3-anti alcohol **443**, synthesized by reduction of β -hydroxy ketone **442** [$\text{Me}_4\text{NBH}(\text{OAc})_3$]²⁹¹ followed by protection. The ketone **442** was in turn derived from the reaction of α -bromoacrolein with the dianion of methyl acetoacetate (Figure 84). The transformation

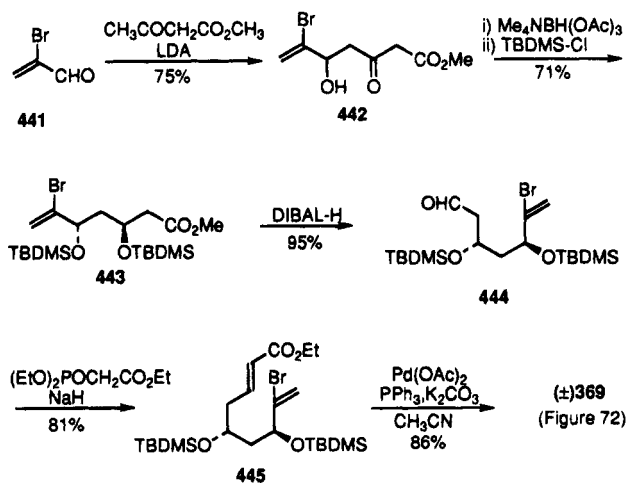


Figure 84.

443 to racemic **369** was carried out conventionally and in parallel to that in Figure 83. The optically pure version of this synthesis²⁹² is outlined in Figure 85. Asymmetric aldol reaction of α -bromoacrolein

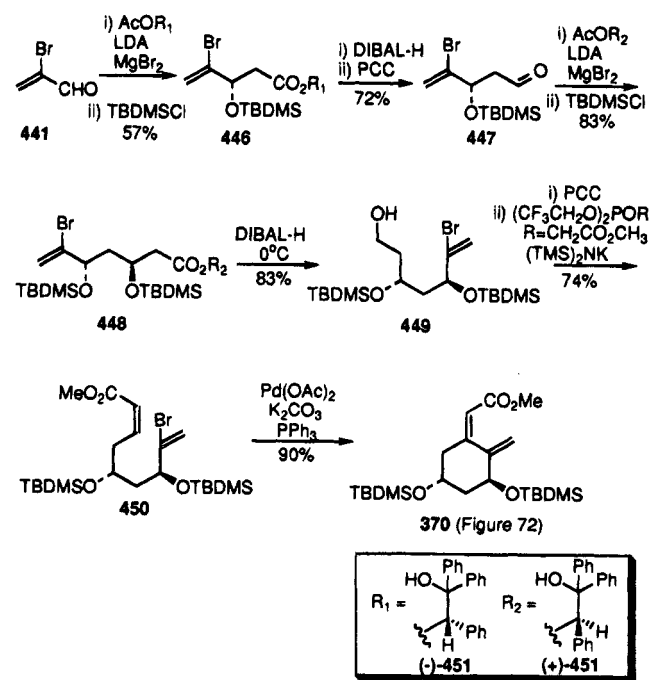


Figure 85.

(**441**) with the lithium enolate of acetic acid ester (*-*)-**451** in the presence of MgBr_2 at -100°C gave after protection **446** in 71% de. Recrystallization of **446**

from MeOH/CH₂Cl₂ provided stereoisomerically pure material in 57% yield. After transforming **446** to aldehyde **447**, similar asymmetric aldol reaction (followed by protection) with the lithium enolate of acetic acid ester (+)-**451** occurred with the same 71% de, affording **448**. After transforming the latter to *Z*-ester **450**, cyclization led to the desired *Z* isomer **370** (Figure 72). Thus, the known intermediate **370** was synthesized asymmetrically from α -bromoacrolein in 10 steps (19% overall yield).

A recent procedure developed in the laboratory of Ogasawara in Japan (Figure 86)²⁹³ could be used for

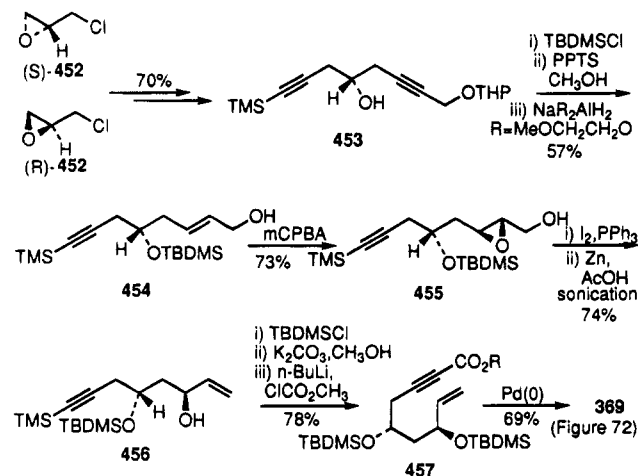


Figure 86.

synthesis of the A-ring phosphine oxide precursor or the acyclic A-ring precursor of the Trost type (**23**, Figure 7).¹¹⁷ The stereogenic center at C-3 of the A-ring synthon was generated from the modification of both (*S*)-epichlorohydrin [(*S*)-**452**] and (*R*)-epichlorohydrin [(*R*)-**452**]. The 1α -hydroxy group was introduced via ring opening of the epoxide **455**, which was derived from asymmetric epoxidation. The cyclization of **457** was best carried out in the presence of tris(dibenzylideneacetone)dipalladium chloroform [Pd₂(dba)₃CHCl₃] to give exclusively known *E* diene **369**, while **456** serves as linear A-ring precursor for Trost coupling. Shortly after publication of Ogasawara's work, a similar approach was reported by Hatakeyama's laboratory.²⁹⁴

Radical Cyclization. Radical cyclization of acyclic vinyl selenide or an acyl radical cyclization leading to the synthesis of A-ring synthons have been also studied.^{295,296} The improved version of this strategy (nine steps to **369**, 26% overall yield) is outlined in Figure 87 starting from α -bromoacrolein (**441**).^{297,298}

Evans-type syn-selective asymmetric aldol reaction of bromoacrolein **441** with the boronenolate of 3-(chloroacetyl)-4(*S*)-isopropylloxazolidinone (**458**) gave a single diastereoisomer **459**. Reductive removal of the unwanted chlorine atom followed by saponification with LiO₂H afforded **460**. The two-carbon homologated β -hydroxy ketone **461** was reduced by the Evans protocol (tetramethylammonium triacetoxy borohydride), affording the diol **462** as a 13:1 anti/syn mixture (87%). After further transformation, radical cyclization of the resulting **464** (Bu₃SnH, AIBN) generated **465** (94%). The latter was dehydrogenated to give a mixture of **369** and **370**. However, the bromide **464** could be efficiently converted

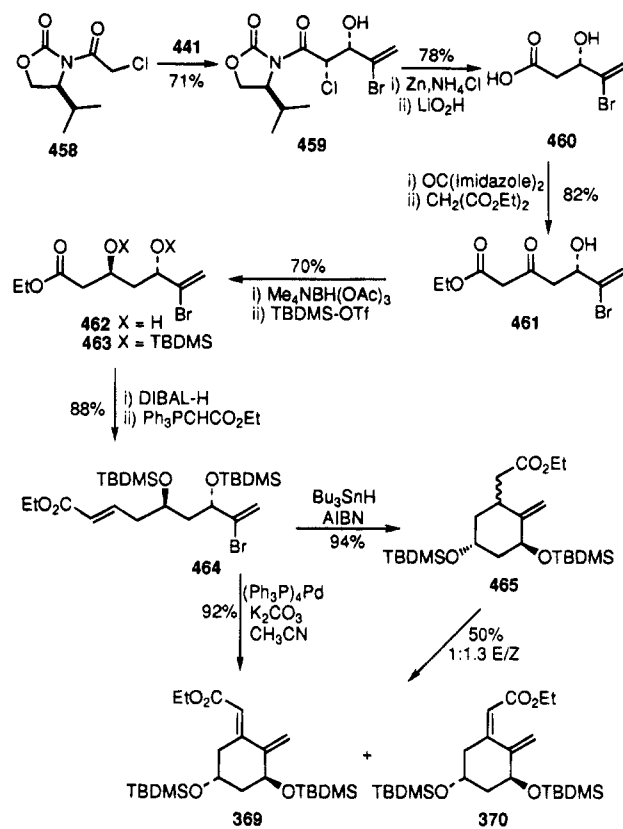


Figure 87.

to the single *E*-isomer **369** by palladium-catalyzed cyclization [(Ph₃P)₄Pd, K₂CO₃, CH₃CN, 92%].

D. Method C: A Plus CD Cross-Coupling Approaches

The cross-coupling approach (method C), developed by Lythgoe (Figure 88)²⁹⁹⁻³⁰¹ involves reacting 8α -

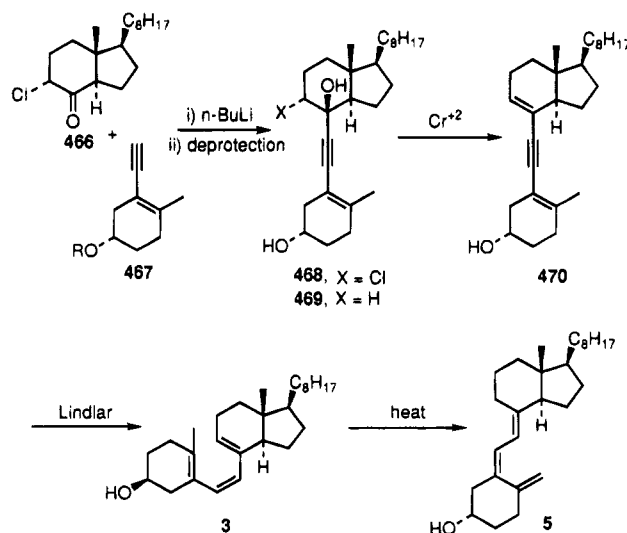


Figure 88.

chloro ketone **466** with the lithium derivative of enyne **467** to give, after deprotection, the vicinal chlorohydrin **468**. Elimination (Cr²⁺) generated the $\Delta^{8,9}$ -ene **470**, which was semihydrogenated over Lindlar's catalyst to give pre-D₃ (**3**, Figure 2). The latter undergoes thermal rearrangement to vitamin D₃ (**5**). The overall yield was about 20%. Dehydra-

tion of the more readily available **469** also yields the enynene **470**, but elimination also affords the $\Delta^{8,14}$ -isomer. The difficulty with this approach includes the fact that many steps are needed for the preparation of the enynene precursor chloro ketone **466** (about 7% from Grundmann's ketone).

Recent developments from the Mouriño-Castedo laboratory have very much improved the efficiency of this approach (Figure 89). Using Stille's coupling

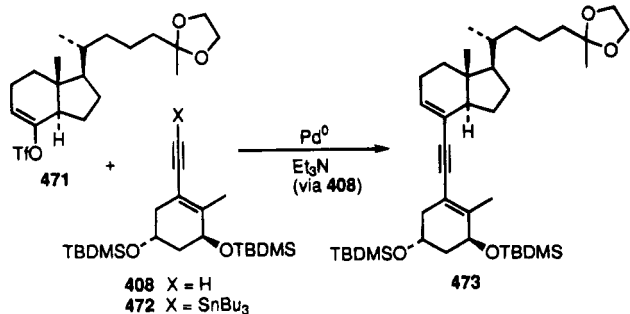


Figure 89.

protocol, dienyne **473** was prepared by palladium-catalyzed coupling of Grundmann's type enol triflate **471** with the A-ring enyne **408** or a suitable derivative **472**.^{111,112,302} The coupling of **408** involves use of a catalytic amount of Pd(PPh₃)₂Cl₂ (2–3 mol %) in DMF (75 °C) in the presence of triethylamine (3–4 equiv) affording **473** in 85–95% yield. This coupling reaction is quite mild and may be conducted in the presence of a carbonyl group,¹¹² but the presence of a free alcohol group significantly decreased the yield of the coupled product.^{111,302} In general, in successfully utilizing the Mouriño-Castedo approach, the kinetic enolate of Grundmann's ketone or its derivatives such as the precursor of **471** may be generated through addition of a THF solution of the ketone to a solution of LDA (1.1 equiv) at –78 °C. The solution is maintained at –78 °C for 30 min and then allowed to warm to room temperature (2 h). The enolate is then quenched with *N*-phenyltrifluoromethanesulfonimide (PhNTf₂, 1.06 equiv) at –78 °C, generally affording high yields of enol triflates such as **471** (80–90%). Thus, no unusual conditions are necessary to obtain these useful CD fragments.

Synthesis of A-Ring Enynes 408 and 467. In the pioneering work of Lythgoe, A-ring enyne **467** was prepared from optically pure 1-methylcyclohex-4-ene-1,2-dicarboxylic acid (**474**) or from 5-methoxy-2-methylbenzoic acid (**475**)^{303,304} via the intermediates **476** and **477** (Figure 90). The route proceeding

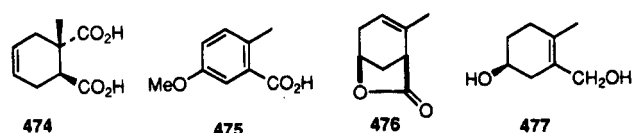


Figure 90.

through **477** was preferred, affording higher overall yield of **467** (4.2%). Since then the synthesis of **467** was not intensively investigated because of the lack of the 1 α -hydroxyl group, which characterizes the more active metabolites and analogues of vitamin D. For studies of thermal [1,7]-sigmatropic shifts of previtamin D₃ to vitamin D₃, a 12-step synthesis of

the unlabeled (**486a**) or trideuterated A-ring **486b** from *p*-methoxyphenol was developed in the Okamura laboratory, wherein label was introduced using (methyl-*d*₃)magnesium iodide to either the ketothiomethylene intermediate **481** or the ketoketal **485**³⁰⁵ (Figure 91). The racemic A-ring enyne **486a** was

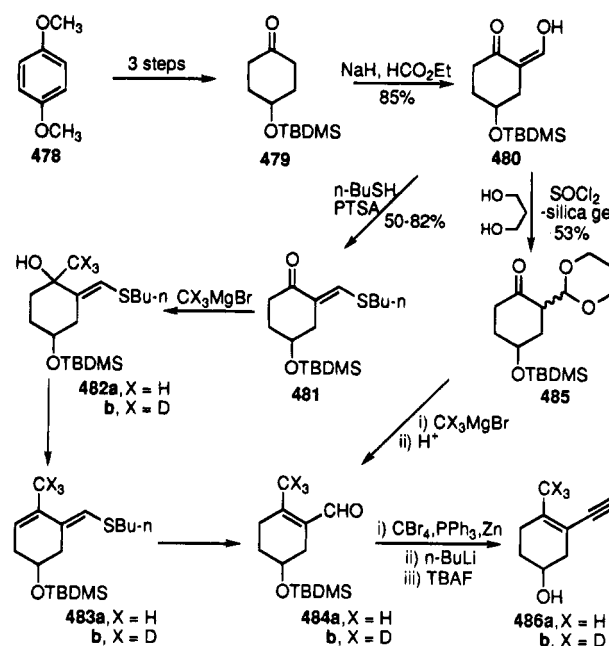


Figure 91.

efficiently resolved by *Chromobacterium viscosum* lipase (CVL)-catalyzed acylation (Figure 92, unpub-

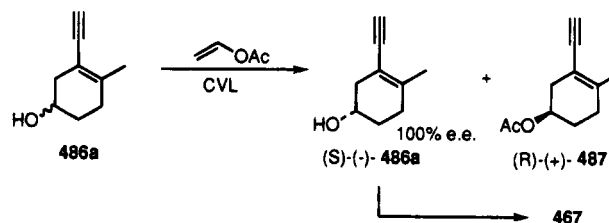


Figure 92.

lished observations).

The A-ring enyne **408** (see also the earlier Figure 77) was first synthesized by Lythgoe through modification of the lactone **476** (7 steps, 17% overall yield from **476**).^{110,301} This route has been further improved by the Lythgoe group (Figure 93).²⁴⁰

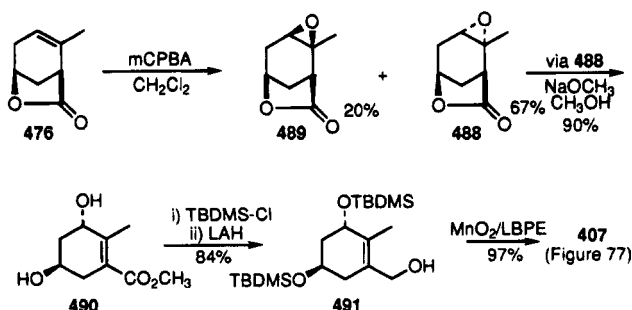


Figure 93.

A different synthetic sequence affording the same aldehyde **407** was developed by Desmaele et al. in France based on modification of quinic acid (**492**,

Figure 94).³⁰⁶ The starting material was first trans-

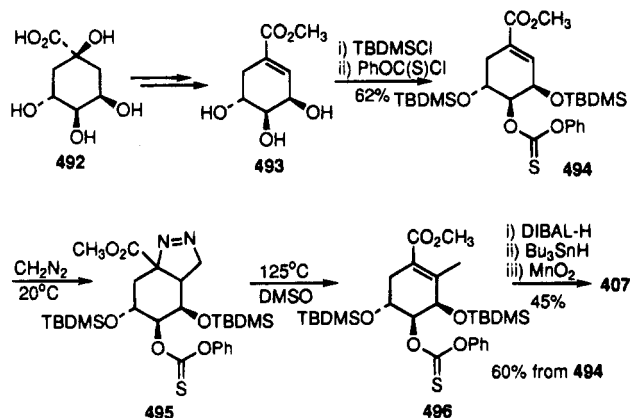


Figure 94.

formed to methyl shikimate (**493**) and then converted to **494**. Addition of diazomethane to **494** (3:1 *cis/trans*) and then pyrolysis (125 °C) was found to be effective for introducing the 19-methyl group.

The Hoffmann-La Roche synthesis started from (*S*)-(+)-carvone (**362**)³⁰⁷ (Figure 95). The strategy

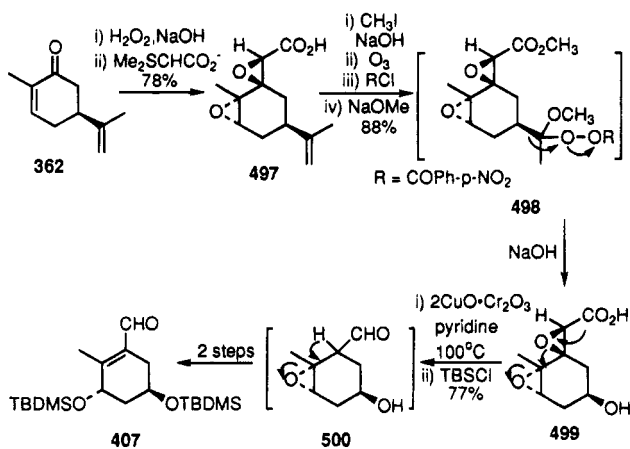


Figure 95.

involved the oxidative degradation of the isopropenyl side chain of the known carvone epoxide **363** to the reduced β -hydroxyl group and also by establishment of the suitable configuration of the 1α -allylic alcohol in **407** via an epoxide moiety. Criegee's procedure,³⁰⁸ wherein ozonization in methanol was followed by direct acylation with *p*-nitrobenzoyl chloride to induce a Baeyer–Villiger-type rearrangement via **498** to **499** provided an excellent solution to the isopropenyl to acetoxy conversion, especially in view of the presence of the sensitive bis-epoxide group. In the copper chromite-assisted decarboxylation of **499**, the transformation probably involves the epoxy aldehyde **500**, which suffers base-catalyzed isomerization to **407**, or through a concerted process in which the decarboxylation takes place with simultaneous opening of both epoxides.

A conceptually similar methodology (Figure 96) was reported by Castedo and Mouriño.^{302,309} Again the isopropenyl side chain of (*S*)-carvone (**362**) was ultimately transformed into the β -hydroxy group by the Criegee-type procedure. The homologous alcohol

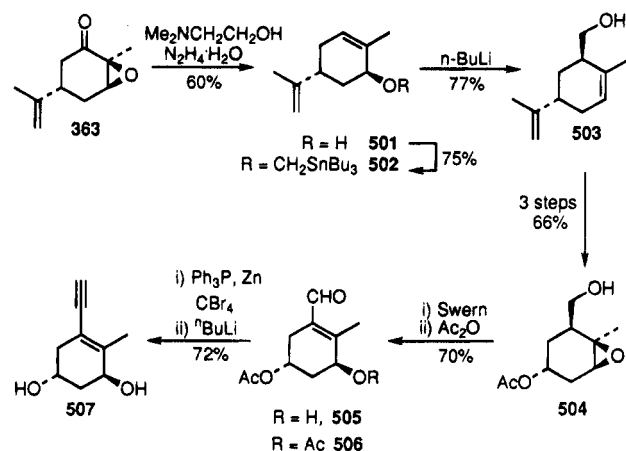


Figure 96.

or aldehyde was introduced via a combination of the Wharton protocol (**363** to **501**) and a [2,3]-sigmatropic rearrangement (**502** to **503**).³¹⁰ Swern oxidation of epoxy alcohol **504** afforded the desired oxidized and epoxide-opened product **505**, which was acetylated, one-carbon homologated (Corey–Fuchs procedure) to enyne **507** (11 steps, 10% overall yield).

The most practical synthesis leading to the same A-ring enyne synthon (**507**) is the five-pot procedure (37% overall yield)^{114,115} developed in the Okamura laboratory (Figure 97). A single experienced co-

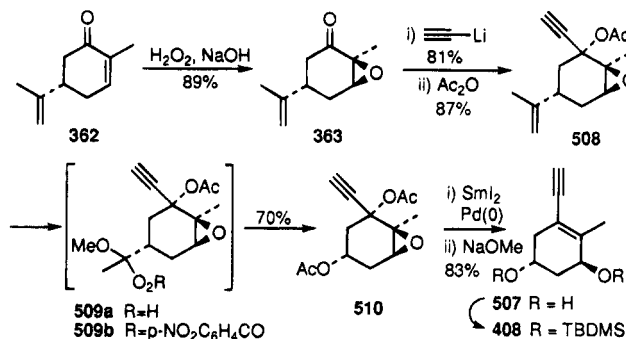


Figure 97.

worker has produced up to 15 grams of the A-ring enyne **408** from commercial (*S*)-(+)-carvone **362** in only 3 weeks.³¹¹ Addition of lithium acetylide to the known carvone epoxide **363** (89% from **362**) proceeded highly stereoselectively. After acetylation of the hydroxyl group (87%), ozonolysis of the isopropenyl side chain in methanol followed by direct acetylation (*p*-nitrobenzoyl chloride) and in situ Criegee rearrangement³⁰⁸ of the resulting methoxy peroxyester afforded diacetate **510**, an easily purified, highly crystalline material. A novel SmI₂-promoted reductive elimination of the epoxy propargyl acetate **510** with concomitant ring opening of the epoxide moiety afforded the known optically pure enynol **507** and then the silylated material **408**.

In summary, the cross-coupling approach has been widely recognized as one of the most important coupling methods for synthesis of vitamin D or its analogues. It is a completely general chemical synthetic route highlighting the following: (i) providing a common convergent route to side chain analogues of vitamin D; (ii) allowing for modifications

in A-ring, triene, and CD portions of these molecules; (iii) providing a means for synthesizing the previtamin D's; (iv) allowing for the direct modification of the chromophoric unit in previtamin D and vitamin D such as radioisotope incorporation via Lindlar semihydrogenation near the end of the synthesis.³¹¹

E. Method D: The Vinylallene Approach^{312,313}

Two diastereomeric vinylallenes of **511** and **512** were first isolated by the Havinga group³¹⁴ as minor (11%) photoproducts of vitamin D₃ (Figure 98).

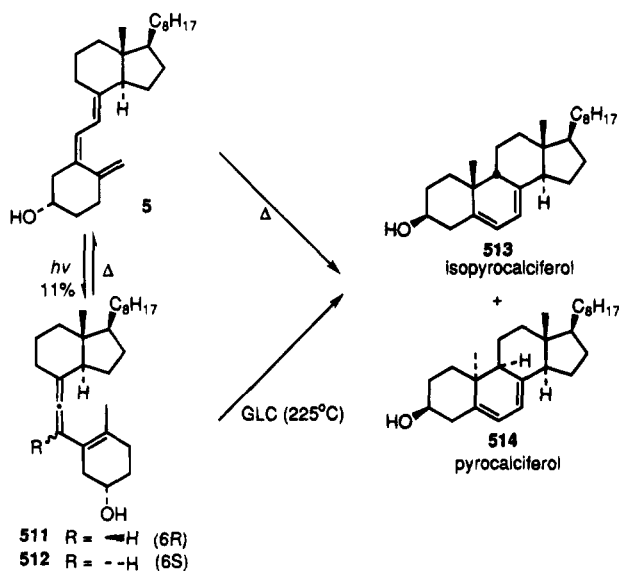


Figure 98.

Under gas chromatographic conditions (225 °C) the two vinylallenes were found to exhibit a chromatographic profile characteristic of vitamin D₃. Later Havinga's primary hypothesis that the vinylallenes undergo initial [1,5]-sigmatropic hydrogen shift to vitamin D₃, which then undergoes its characteristic thermal rearrangement to pyro- (**514**) and isopyrociferol (**513**), was investigated in detail in the Okamura laboratory,^{312,313} leading to a novel synthetic approach to vitamin D and its analogues.

1. Synthesis of Vitamin D Vinylallenes

Several approaches leading to the synthesis of vitamin D type vinylallenes have been developed in the Okamura laboratory. The CD-ring fragments used for the syntheses were of three types: Grundmann's type ketone **19**, its acetylene analogue **515**, and its allene derivatives **516**, the latter pair being derived from or related to ketone **19**³¹³ (Figure 99).

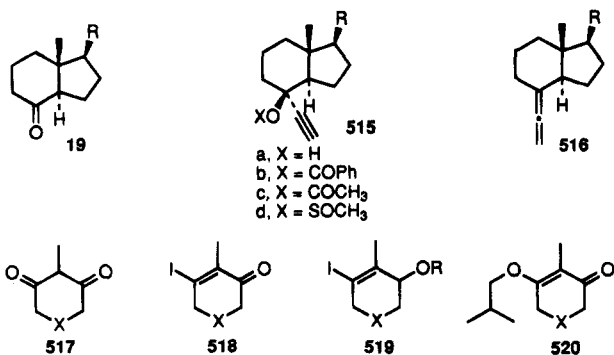
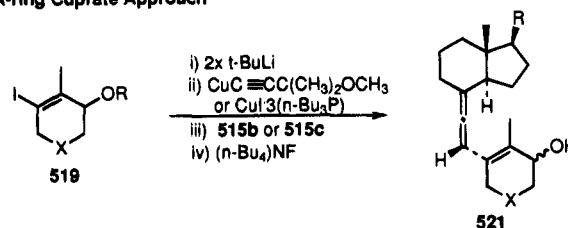


Figure 99.

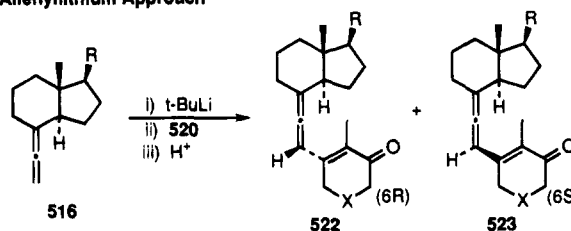
In earlier studies, A-ring fragments (**518–520**) were synthesized from the readily available 2-methylcycloalkane-1,3-diones **517**.

Four general routes have proven useful for effecting coupling of the A and CD fragments (Figure 100).

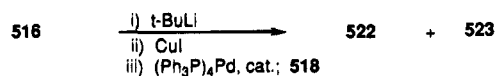
A. A-ring Cuprate Approach



B. Allenyllithium Approach



C. Pd⁰ Catalyzed Allenyl Cuprate Approach



D. Stannylcuprate S_N2' Reaction and Destannylation

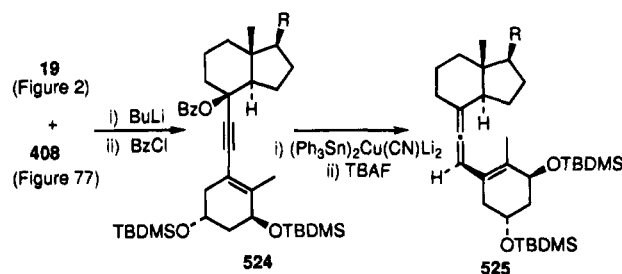


Figure 100.

The A-ring vinylcuprate route A^{315–318} produced essentially exclusively the (6R)-allene **521**. The allenyllithium method B is less capricious than method A, but both (6R)-**522** and (6S)-**523** were produced.^{316,319–322} However, exceptional large 6R/6S selectivity was observed (e.g., 13.5/1.0 in the case of **520**). The allenylcuprate method C was found to be necessary when using the A-ring iodide **518**, but only a 2.2/1 ratio of 6R/6S allenes was observed. Method D, the three step sequence with the key step being a triphenylstannyl cyanocuprate S_N2' displacement reaction of propargyl benzoate **524**, was anticipated to be an attractive method for preparation of predominant (6S)-vinylallene.^{115,323} The S_N2' reaction of **524** with a "CuH" species or equivalent, as well as an indirect method using a higher order triphenylstannyl cyanocuprate reagent followed by destannylation failed. However, the two-step scheme utilizing a Δ^{9,11}-dehydro derivative of **19** was successful (see below).

2. Thermal Studies of Vitamin D Vinylallenes

Thermal studies (typically, in refluxing isooctane, 10–12 h or longer, 100 °C) of the vinylallenes revealed that the rearrangement proceeds via two competing [1,5]-sigmatropic hydrogen shift pathways (Figure 101), the *E* pathway affording the desired

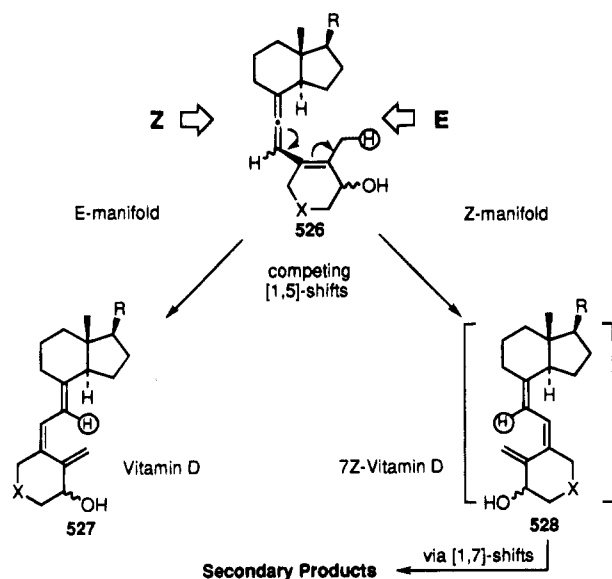


Figure 101.

vitamin D system possessing a 7*E* geometry (527) and the *Z* pathway leading to a triad of secondary and tertiary products related by [1,7]-sigmatropic shifts of the 7*Z* geometric isomer (528) of the vitamin D system.

The configuration at C-1 bearing the hydroxyl group markedly influences the 7*E*/7*Z* pathways (i.e., the ratio of *E* to *Z* manifold of products in Figure 101), but the ratios are reversed for the 6(*R*)- and 6(*S*)-allenes.³²¹ In the 6*R* case 529 ($R_2 = R_2' = H$), the 1 α -epimer 529b afforded a 1:4.1 7*E*/7*Z* ratio, but this ratio was reversed (2.7:1) for the 1 β -epimer 529c. In the 6*S* case, 533b and 533c afforded 7*E*/7*Z* ratio of products of 3.7:1 and 1:6.6, respectively (Figure 102). In other words, the favored trajectory of the

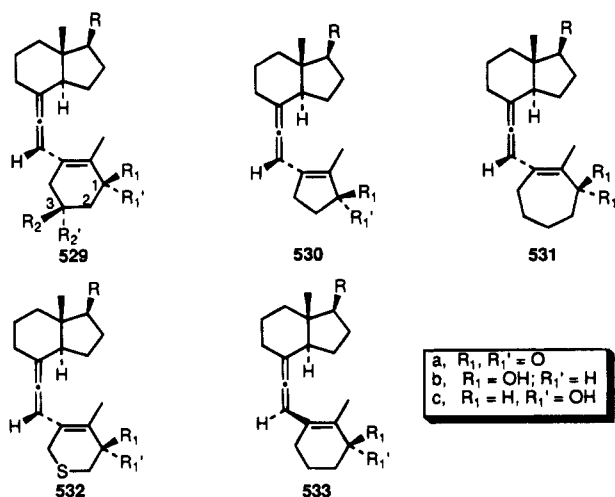


Figure 102.

migrating hydrogen is always opposite or anti to the A-ring face bearing the hydroxyl. Thermolysis of the

parent ketones 529a ($R_2 = R_2' = H$) and 533a, wherein the two A-ring faces are now equivalent, resulted in an attenuated 7*E*/7*Z* ratio of 1:1 for the former and 1:2 for the latter.

The size of the A-ring has a marked effect on the relative ease of the [1,5]-sigmatropic shift, the ring size reactivity order being 7 (531) > 6 (529, 533) > 5 (530), the six-membered ring sulfur analogue 532 being a unique case since its reactivity resembles that of the seven-membered ring case 531. The latter may be due to the longer carbon–sulfur bonds, rendering its A-ring to assume seven-membered ring-like character. Overall, the ring size effect can be attributed to an effect of distance between the migrating hydrogen termini, C₁₉ and C₇, for the [1,5]-shift. When bond angle corrected dreiding models were used, this distance for the five-, six-, and seven-membered A-ring cases are 2.9, 2.6, and 2.4 Å, respectively.³¹³ The situation is likely more complex, but the distance postulate may play a dominant role in the ring size reactivity effect.^{324,325}

3. Application to Vitamin D Syntheses

The vitamin D vinylallene approach has proven useful for preparing a family of C-3 modified vitamin analogues, the primary goal of the development of the vinylallene method. A typical example of such an application is represented by the preparation of 1 α ,25-dihydroxy-9,11-dehydrovitamin D₃ (540)¹¹⁵ (Figure 103). Coupling of known A-ring enyne 408 with 9,11-dehydro ketone 534, followed by benzoylation, afforded propargyl ester 535. Stannyl cuprate S_N2' displacement of the propargyl benzoate^{326,327} pro-

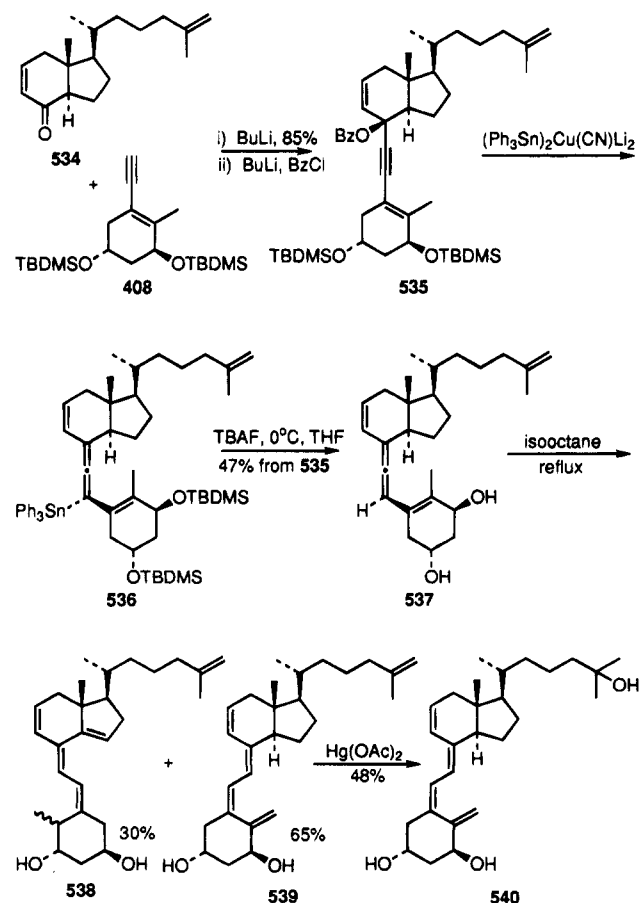


Figure 103.

ceeded stereoselectively to afford the 6 β -stannylallene **536**. Simultaneous fluoride-induced destannylation and desilylation led to a 10:1 mixture of the desired 6 β -vinylallene **537** and its 6 α -epimer. Thermolysis of **537** gave a mixture of vitamin **539** (65%) and the epimeric tetraenes **538** (30%). Oxymercuration–demercuration of **539** produced the desired **540**.

The heat-induced suprafacial [1,5]-sigmatropic shift of a vinylallene as a way to prepare the natural vitamin D triene unit is novel, but unfortunately, the concomitant formation of a triad of interequilibrating triene isomers (via the *Z* manifold in Figure 101), as well as minor amounts of previtamin makes the thermal vinylallene route of limited generality for use as a synthetic approach. These drawbacks, however, have been overcome in part by Okamura's recent discovery¹¹⁶ of a metal-mediated approach to inducing vinylallene rearrangements in a stereoselective fashion (described next).

4. Metal-Mediated Isomerization of Vinylallenes

On the basis of Shibasaki's investigation of catalytic [1,5]-hydrogen migration processes of (3*Z*)-1,3-pentadienes using (naphthalene)tricarbonylchromium [(np)(CO)₃Cr],^{328–330} the Okamura laboratory has examined this same chromium(0)-mediated isomerization on the four diastereomeric vinylallenes **529bc** (R₂ = R₂' = H) and **533bc** shown in Figure 102.¹¹⁶ All four diastereomers could be induced to undergo highly selective (50:1) production of hindered 7,8-*cis* geometric isomers [with 1.1 equiv of (np)(CO)₃Cr in acetone, 38 °C, 4 h]. The results, summarized collectively for the four diastereomeric vinylallenes in Figure 104 and Table 3 provide new mechanistic

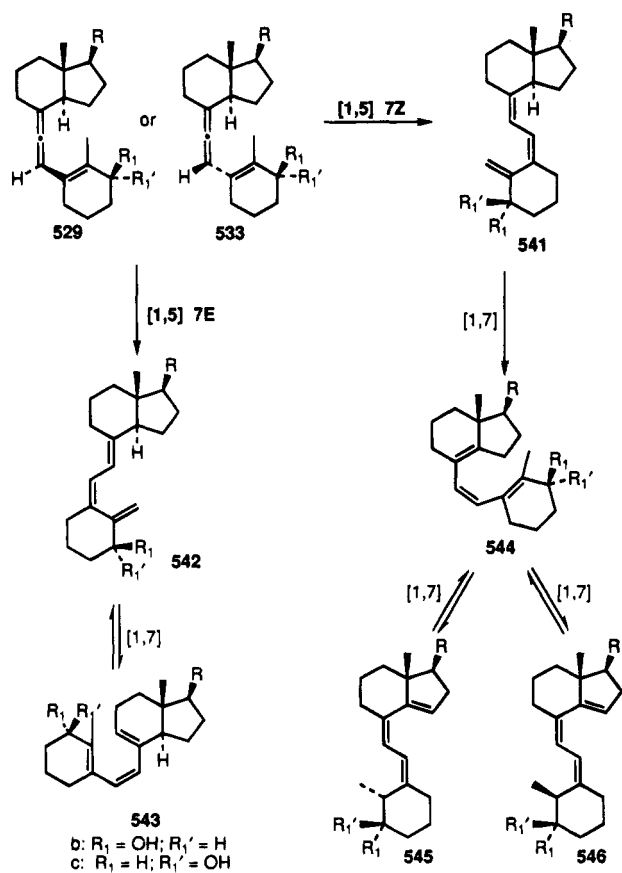


Figure 104.

Table 3. Chromium-Mediated Isomerization of Vinylallenes

substrate ^a	product (yield, %) ^b			
533b	544b (2)	542b (2)	541b (75)	
533c	544c (5)		541c (81)	
529b	544b (2)	542b (1)	541b (89)	529b (4)
529c	544c (7)	542c (1)	541c (75)	

^a R = C₈H₁₇ in all cases and, for **531**, R₂ = R₂' = H (see Figure 104). ^b Actual isolated yields, including recovered starting material, are given in parentheses. In several cases, small quantities of minor components could be detected by ¹H NMR analyses, but were not isolated.

insight into the Shibasaki [1,5]-hydrogen shift because of the stereochemical features present in the four vinylallenes studied. The significant features of the metal-mediated isomerization may be discussed in terms of the 7*E* and 7*Z* pathways for isomerization shown in Figure 104. Neither the allene nor carbinol configuration affects the stereochemical course of the isomerization in the same manner as in the complex thermal process previously described in Figure 101. Very simply, 7,8-*cis*-vitamin **541** is formed in preference to the 7,8-*trans*-isomer **542** with 50:1 geometric selectivity. Thermolysis of either **529** or **533** results in **542–546** (but no **541**). A simple rationale is presented in the mechanistic scheme given in Figure 105. In the first step, it is

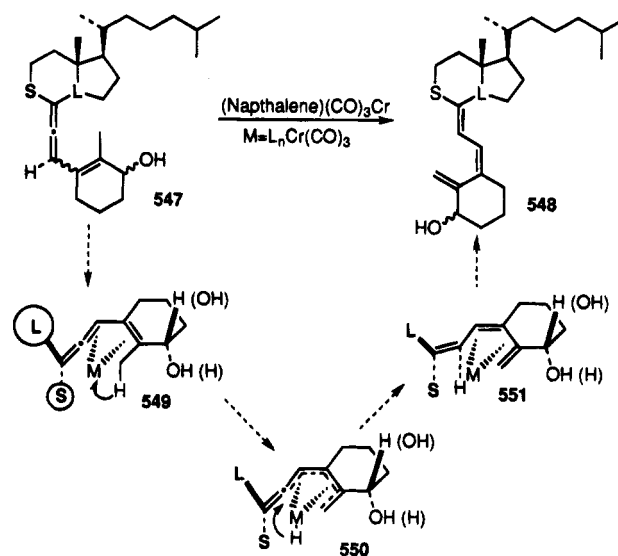


Figure 105.

envisaged that a chromium(0) species M metalates the vinylallene from its less hindered face to form the η^4 -species **549**. Despite the presence of the C₁-hydroxyl, which could in principle direct metal coordination as has been previously observed,³³¹ the overriding effect is attributed here to a steric effect imparted by the substituents on the allene terminus, C-9 being small (*S*) and C-14 being large (*L*). The species **549** can then be considered to isomerize to the η^2 -intermediate **550** and then to **551**. Subsequent loss of the chromium(0) species then completes the catalytic cycle, affording **548**.

5. Synthesis of 1,25-Vinylallene, Its Rearrangement, and the Preparation of 1,25-D₃ and Its Geometric Isomers

The best previous application of the vinylallene synthesis approach was based on stannyl cuprate

S_N2' displacement of a propargyl benzoate¹¹⁵ and fluoride-induced destannylation (Figure 103). The coupling procedure has been improved by the finding that Pd(0)–Sm^{II}–iPrOH reduction of the propargyl benzoate **552** (see **524** of Figure 100). This Inanaga propargyl ester to allene transformation is stereoselective (10:1), involving a formal anti- S_N2' displacement of a benzoate by hydrogen (Figure 106). Simple

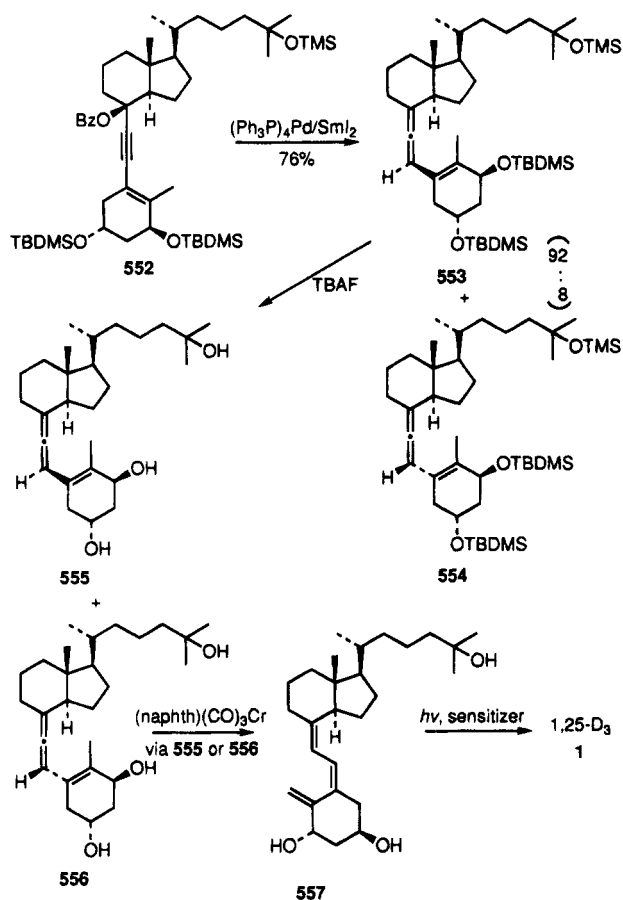


Figure 106.

TBAF deprotection affords the vinylallene **555**, which, as a mixture with the minor allene **556**, was isomerized according to the above metal-mediated protocol (Figures 104 and 105 and Table 3) to afford 7,8-*cis*-1,25- D_3 **557** (80% yield, > 50:1 geometric selectivity, **557**/1; 7% starting allene **555** was recovered).

Photoisomerization (Hanovia medium-pressure Hg lamp, pyrex) of 7,8-*cis*-1,25 **557** in the presence of a 5-fold molar excess of triplet photosensitizer, 9-acetyl-anthracene, resulted in its almost complete isomerization to the hormone 1,25 (92% by ¹H NMR analysis). The formation of practical amounts of hormone completes a new synthetic scheme to this natural metabolite. Taken collectively, the new variant of the vinylallene approach (Figure 107) leading to the synthesis of the hormone 1,25-(OH)₂ D_3 has overcome major drawbacks of the thermal procedure, such as modest yields and selectivity. The most useful feature of this approach is that it provides access to all four geometric isomers of 1,25- D_3 (**1**, **557**, **558**, and **559**) from a single starting material **555**. As also noted in Figure 107, selective isomerization of the central double bond ($\Delta^{5,6}$) is achieved using cheletropic addition–extrusion of

sulfur dioxide, a known procedure, which will be discussed later in section II.H.2.

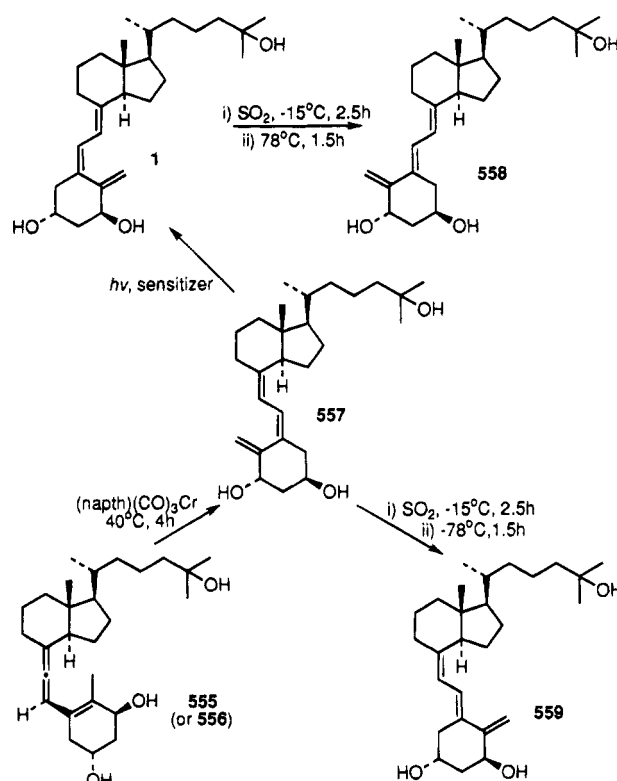


Figure 107.

F. Method E: Seco-A-Ring Tandem Palladium-Catalyzed Cyclization Approach

1. Palladium-Catalyzed Intramolecular Carbometalation: A Tandem Coupling Methodology

In order to develop a novel approach to 1,2-dialkylidenecycloalkanes, Trost has explored in detail the palladium-catalyzed cycloisomerization of enynes as outlined in Figure 108.³³² In the presence of acetic

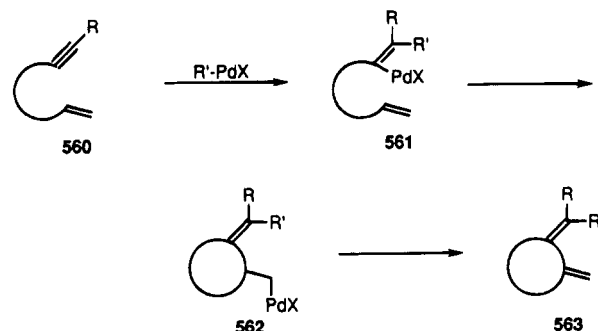


Figure 108.

acid the Pd(0)-catalyzed reaction generates the dienes of the type **563**. An alkylative cycloaddition provides an entry to substituted bis(alkylidene)cycloalkanes possessing the R' introduced stereospecifically *Z* as depicted in **563**.³³³

A direct application of this discovery led to a conceptually novel synthetic approach to vitamin D in which ring A is created from an acyclic unit in which the $\Delta^{5(6),10(19)}$ -diene is created from the enyne cyclization, and the $\Delta^{7,8}$ -double bond with CD-ring moiety in the alkylative cyclization (R'–PdX) (Figure

109).^{117,334,335} This concept offers a quite distinct

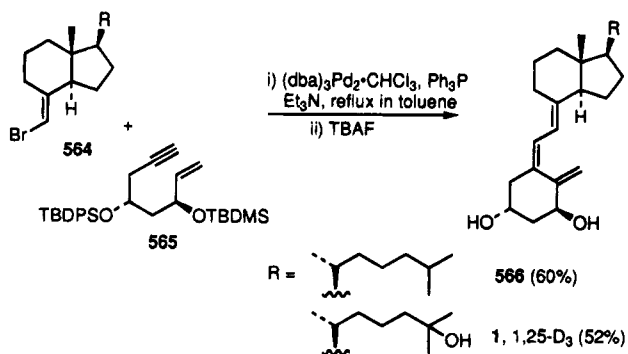


Figure 109.

modular approach to the vitamin D system whereby creation of the requisite triene, formation of the A-ring, and attachment of this entire unit to the CD fragment occurs in a single reaction! Intramolecular carbometalation effects both formation of the key C₁₀-C₅ bond (and the A-ring) and affords complete control over the C₅-C₆ olefin geometry. As depicted in Figure 110 the reaction proceeds through the same

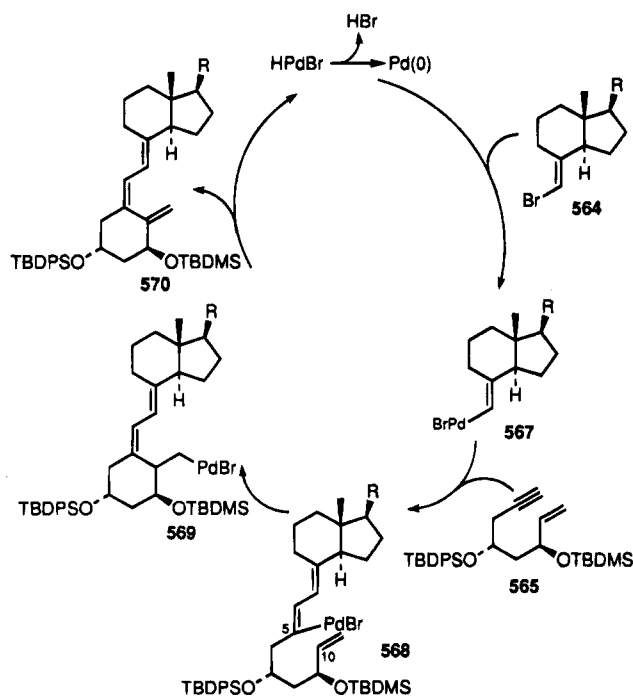


Figure 110.

mechanism as the general entry shown in Figure 108. Initial oxidative insertion of palladium(0) to the labile C₇-Br bond of **564** forms intermediate **567** which is followed by *cis*-addition to the alkyne **565** to give second intermediate **568**. Bond formation between C₁₀ and C₅ closes the A-ring. Reductive elimination of HPdBr liberates the product **570** and regenerates the catalyst Pd(0).

The best method so far to synthesize (*E*)-vinyl bromide **564** is Trost's Wittig procedure (Figure 111). The high *E* geometrical selectivity of the olefination is remarkable in light of the known propensity of (bromomethylene)triphenylphosphorane to undergo *Z*-selective additions to aldehydes.³³⁶ The mechanism is proposed to involve transition state **571** that

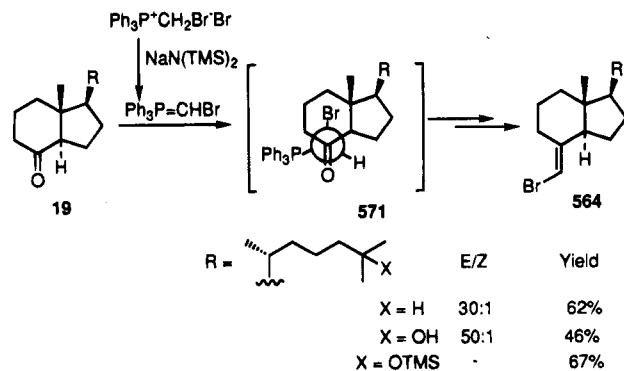


Figure 111.

minimizes both dipole-dipole and steric interaction (Figure 111). The presence of free hydroxyl group somewhat decreases the yield of the reaction. The use of freshly prepared sodium hexamethyldisilazide is very important for the success of this Wittig bromomethylation.

Figure 112 outlines an asymmetric synthesis of the enyne unit **565** from the monoacetal of malonaldehyde **572**. Addition of vinyl bromide to the corresponding aldehyde of **573** favors *syn* addition. The resulting adduct was converted to the desired anti-isomer **574** under Mitsunobu conditions. Kinetic resolution of the racemic allylic alcohol **574** gives virtually quantitative recovery of the desired alcohol **575** (98% ee), which was protected to give **565**. Another synthesis of a related derivative of the latter enyne served as an intermediate for synthesis of an A-ring phosphine oxide through modification of (*R*)- or (*S*)-epichlorohydrin as discussed earlier (Figures 85-87; see also Figures 83 and 84).²⁹³

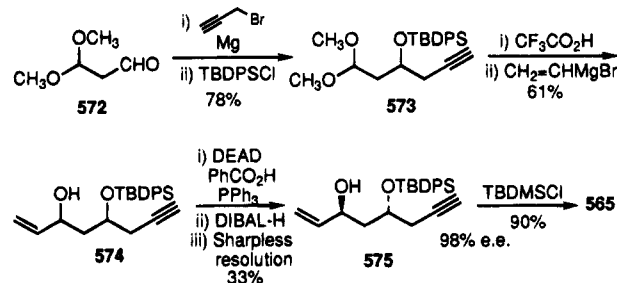


Figure 112.

The route shown in Figure 112,¹¹⁷ although short, suffers from a nonselective vinyl-Grignard addition (~1.0:1.5 anti/*syn*) favoring the undesired isomer. Sharpless kinetic resolution of the racemic allylic alcohol **574** is very effective (98% ee) but the unwanted enantiomer is nevertheless lost (46% yield). In Trost's improved version (Figure 113),³³⁷ the desired stereoisomer was generated by a Noyori asymmetric hydrogenation of inexpensive ethyl 4-chloroacetate, a reaction known to afford high enantiomeric selectivity (96% ee). The anti stereochemistry of the diol **580** was introduced via Evans reduction. TMS-acetylide opening of epoxide **581**, furnished, after TBDMS protection, the desired A-ring enyne **583** in eight steps (20% overall yield). The instability of enone **579**, which is prone to polymerization on storage, was noted to be the only significant problem in this sequence.

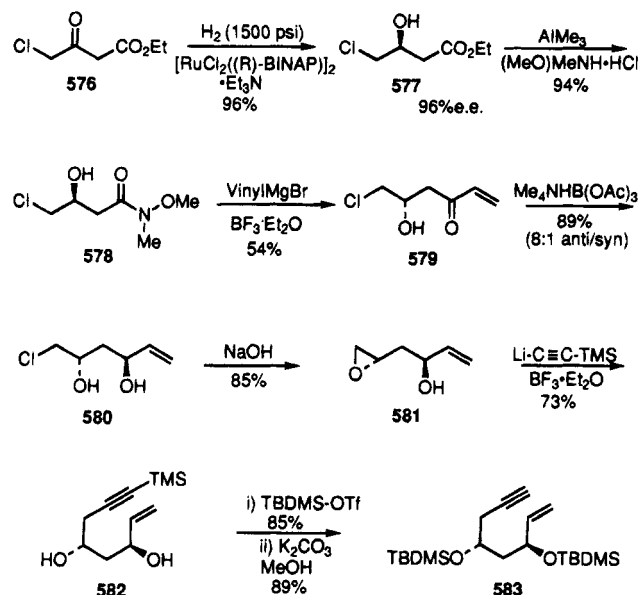


Figure 113.

Moriarty's recent synthesis relies on modification of D-xylose (**584**) as shown in Figure 114.^{338,339}

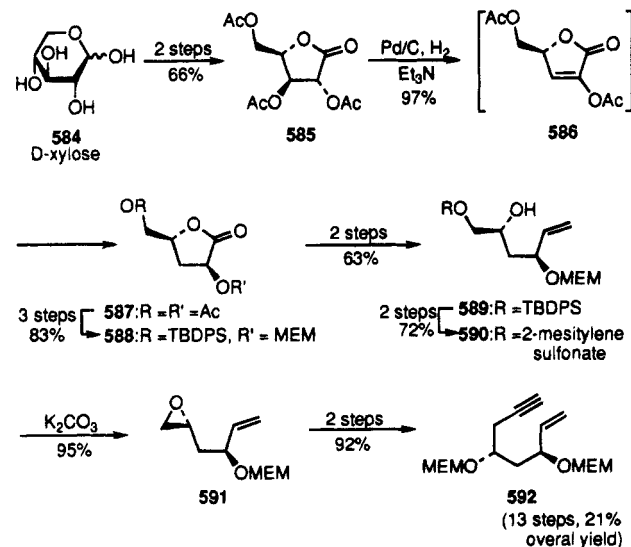


Figure 114.

Catalytic reduction of **585** (derived from **584** via bromine oxidation followed by acetylation) in the presence of triethylamine afforded **587** having the proper C-1 configuration (latent steroidal numbering). The role of the triethylamine is to effect a β -elimination to yield the enol acetate **586**, which undergoes catalytic hydrogenation from the less hindered face of the five-membered ring. Elaboration of **587** in a straightforward manner produced the A-ring enyne **592** (related to **583**) in 21% overall yield (13 steps). It was suggested that by starting with other pentoses or derivatives, one may access other A-ring hydroxylated vitamin D analogues.³³⁹

Returning to the Trost procedure, the palladium-catalyzed alkylative cyclization could be initiated by either palladium acetate, which is reduced in situ to generate the active Pd(0), or tris(dibenzylideneacetone)dipalladium-chloroform solvate [Pd(0)]. Because of the relatively high temperature (reflux in a mixture of toluene and triethylamine) used to conduct

this reaction, the products obtained consists of a mixture of vitamin D and previtamin (10:1). The latter of course can be thermally converted back to the desired vitamin. Under the same conditions, cyclization of the vinyl bromide with a free 25-hydroxy group **564** gives 52% of the desired vitamin D product instead of 76% for vinyl bromide 25-OTMS-protected derivative of **564** (Figure 109).

The regioselectivity of the intramolecular carbopalladation (**568** to **569** to **570** in Figure 110) depends upon both tether and substituents. As depicted in Figure 115 the reaction could proceed in an exo

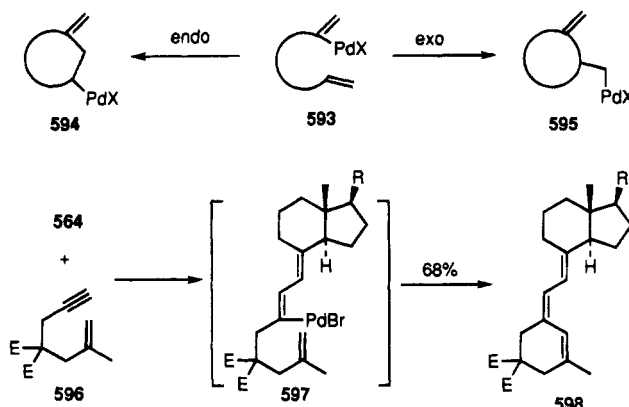
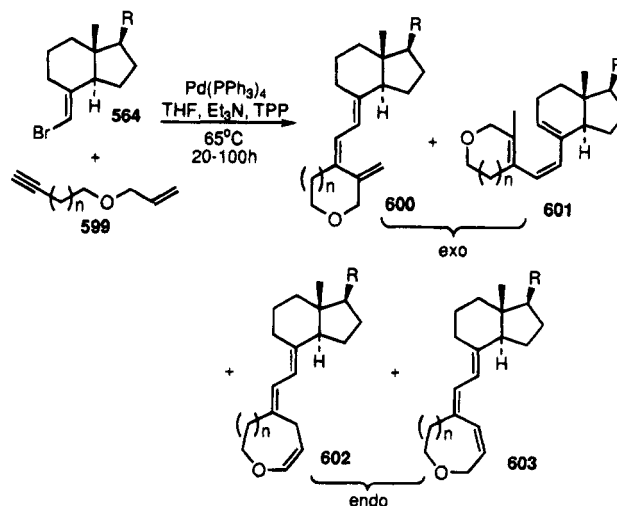


Figure 115.

fashion to give **595** or in an endo direction leading to **594**.³⁴⁰ For example, alkylative cyclization of enyne **596** with vinyl bromide **564** produces only triene **598** which arises by a formal intramolecular carbometallation of **597** in the reverse sense (endo). Although other mechanisms may be operative, the direct endo addition of **597** is the most appealing. Okamura and co-workers observed in synthesis of potential inhibitors of 25-hydroxyvitamin D₃ 1 α -hydroxylase that the tandem palladium coupling of several simple enynes actually gives mixtures of exo (desired) and endo adducts, the proportion of endo products increasing with the smaller rings (Figure 116).¹⁷⁸ A parallel



	endo/exo	600	601	602	603
n = 0	1.4	0	23%	22%	10%
n = 1	0.56	—	41%	0	23%
n = 2	0	36%	0	0	0

Figure 116.

series of studies were carried out starting with the $\Delta^{9,11}$ -dehydro derivatives of **564**¹⁷⁸ in which similar results were obtained.

2. Other Related Transition Metal-Catalyzed Coupling Approaches

Nuss' approach³⁴¹ is conceptually similar to Trost's version (Figure 110), but operates uniquely in the opposite sense for construction of the triene and A-ring from an acyclic unit. The A-ring was closed first by carbometalation of the acyclic precursor, vinyl bromide **604** (Figure 117). Complete control over the

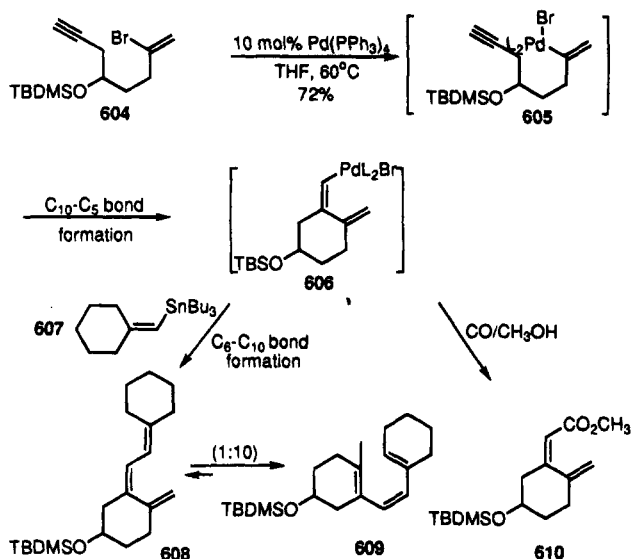


Figure 117.

C₅-C₆ olefin geometry is afforded by the required syn facial carbometalation. A Stille-type coupling of the diene-Pd intermediate **606** with vinyltin **607** completes the construction of triene **608**, which equilibrates with **609** via a [1,7]-sigmatropic hydrogen shift. Trapping of the dienylmetal intermediate **606** with carbon monoxide in the presence of methanol produces the A-ring precursor **610**. This approach should also prove useful for analogue synthesis due to the simplicity of the precursors.

Mouriño's synthesis (Figure 118)^{342,343} is based on the zirconium-promoted cyclization of 1,7-enynes.

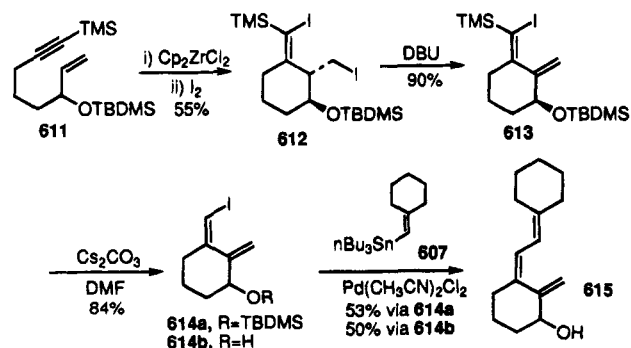


Figure 118.

The exocyclic double bond was efficiently introduced by dehalodation with DBU (90%). Most interestingly, compound **612** can be transformed in a one pot reaction to **614b** by treatment with 3 equiv of TBAF (83%). The cross coupling of **614** with the stannane

607 under Stille conditions furnishes the desired triene system **615**. The coupling of iodide **614a** with the tributyltin derivative of **607** (Figure 110) failed to give the coupled product. However, using the trimethyltin derivative as the organometallic partner³⁴³ 32% of vitamin was obtained.

G. Method F: Mazur's Cyclovitamin D Solvolysis Approach

1. The Vitamin D-3,5-Cyclovitamin D Rearrangement

In an attempt to functionalize vitamin D while protecting its reactive triene system, Mazur¹¹⁹ uncovered the interesting interconversion between vitamin D and its *i*-steroid form, 3,5-cyclovitamin D. Treatment of vitamin D₃ tosylate **616** with NaOAc in methanol/acetone (4:1) gave 6(*R*)-cyclovitamin D (**617**) as the major product together with **618** and **619**. Treatment of **617** with a catalytic amount of *p*-toluenesulfonic acid in aqueous dioxane restored the conjugated triene system, yielding a 13:1 ratio of vitamin D₃ (**5**) and 5,6-*trans*-vitamin D₃ (**621**) in 80% yield (Figure 119). Analogous treatment of the

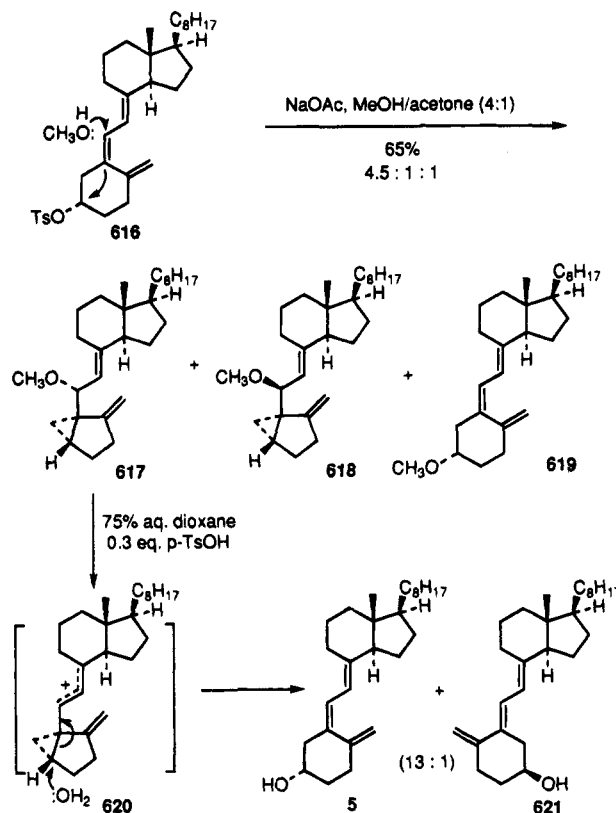


Figure 119.

6*S*-isomer **618** also gave 80% of **5** and **621** but in a 2:1 ratio. This type of homoallylic displacement reaction is directly analogous to the well-known *i*-steroid rearrangement of cholesterol tosylate, which has been used extensively as a means of protecting the 5,6-olefin during certain chemical transformations.

In aqueous acetone buffered with KHCO₃, solvolysis of the tosylate **616** afforded the corresponding (6*R*)-alcohol **622** as the major product (60%) together with 20% of the 3-*epi*-vitamin D₃ [Okamura, Zhu; unpublished data]. The major alcohol **622** upon acid solvolysis rearranged back to vitamin D₃ (**5**) and 5,6-

trans-vitamin D₃ (**621**) in a 2.5:1 ratio (Figure 120).³⁴⁴

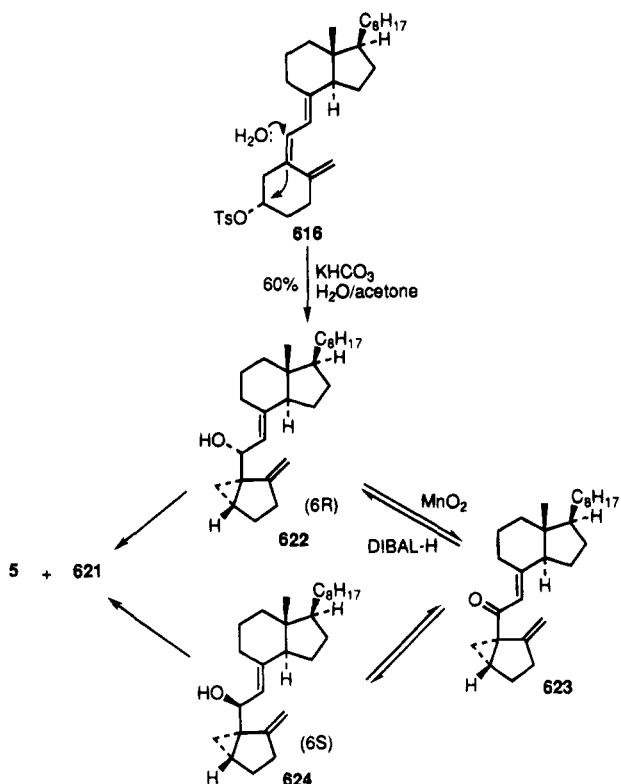


Figure 120.

Under the same conditions the acid-catalyzed solvolysis of (*S*)-alcohol **624**, prepared from oxidation (freshly prepared MnO_2) and then reduction (DIBALH, 1:3 *6R*/*6S*) of (*6R*)-alcohol **624**, yielded a 1:1 mixture of vitamin **5** and its 5,6-*trans* isomer **621**. In 1988, Wilson³⁴⁵ elegantly established that the vinylogous model system **625** (Figure 121) behaved similarly to Mazur's system (Figures 119 and 120).

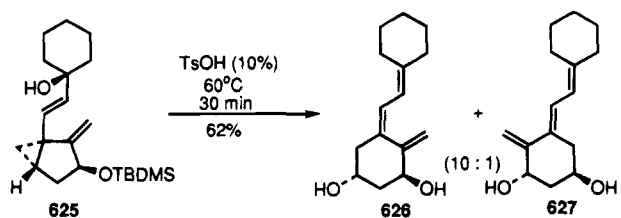


Figure 121.

Regarding the mechanism of the cyclovitamin–vitamin rearrangement (Figure 122), the acid cata-

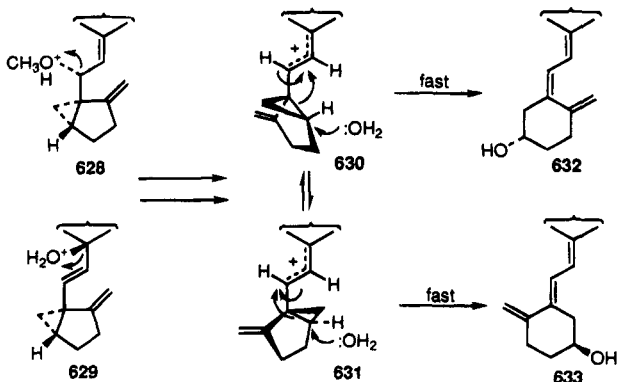
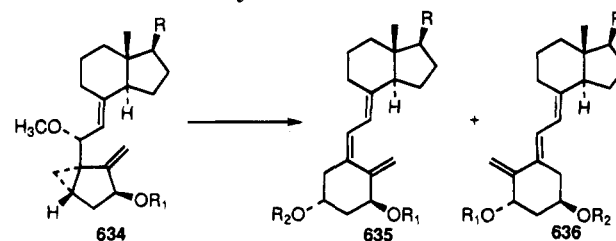


Figure 122.

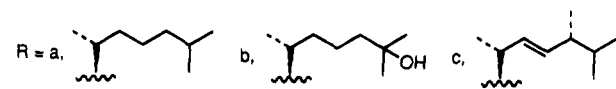
lyzed reaction starting from **628** or **629** proceeds via a homoallylic cation intermediate **630** and **631** in equilibrium with one another. This rotation about the 5,6-bond of the homoallylic cation intermediate after H_2O interception leads to a mixture of natural 5,6-*cis*-vitamin D **632** and its 5,6-*trans*-isomer **633**. The marked stereoselectivity in the solvolysis of tosylate **616** (4.5:1 **617**/**618**) and the back solvolysis of **617** (13:1 **5**/**621**) suggests that the formation of cyclopropylcarbanyl cation with conformation **630** is preferred over **631**, starting from either of the two compounds.

In an investigation utilizing C-1 oxygenated derivatives, the variation of the *cis/trans*-isomer ratio in the cycloreversion reaction seems to correlate with the nucleophilic strength of the medium (Table 4).¹²⁰

Table 4. Conditions for the Cycloreversion of α -Functionalized Cyclovitamins



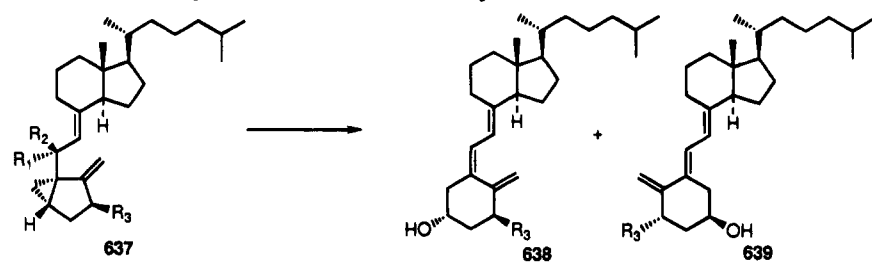
R ₁	catalyst/nucleophile	R ₂	% cis	% trans
COCH ₃	p-TsOH/H ₂ O	H	40	10
COCH ₃	HOAc	COCH ₃	52	18
COCH ₃	i) HCO ₂ H, ii) NaHCO ₃	H	46	22
COCH ₃	p-TsOH/Me ₂ SO	H	42	8
H	HOAc	COCH ₃	55	20



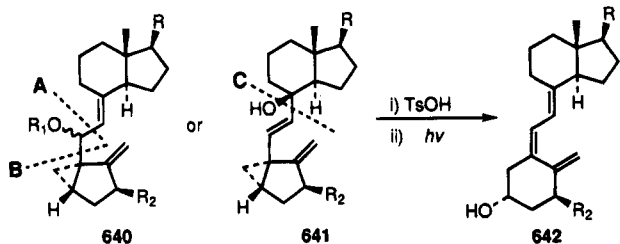
The higher *cis/trans* ratio (4:1) was obtained with water as the attacking nucleophile while lower ratios, 3:1 and 2:1, were produced with the weaker nucleophiles, acetic acid and formic acid. The structural influence of cyclovitamin D on the *cis/trans* ratios in the acid-catalyzed solvolysis has not yet been systematically studied. A spectrum of results using varied substrates have been reported and Table 5^{119,120,344,346,347} summarizes some of the other studies reported during the past two decades. In general, substituents at C-1 of the cyclovitamin D's are beneficial both in terms of reaction yields and the desired ratio of the 5,6-*cis*-vitamins; β orientation of the 6-hydroxy group consistently increases the proportion of the undesirable 5,6-*trans*-isomer.

2. Application of the Cyclovitamin Approach to Synthesis

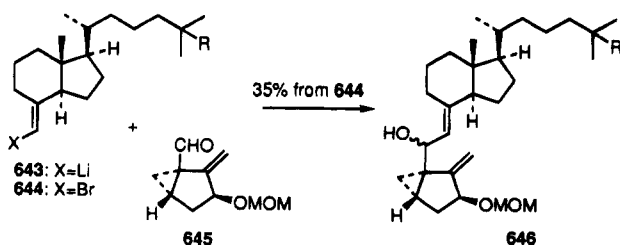
On the basis of Mazur's (and later, Wilson's) observation on the vitamin–cyclovitamin conversion, novel and convergent approaches toward the total synthesis of vitamin D have been developed. The reported syntheses may be divided into three approaches as outlined in Figure 123: A, the Fukumoto–Kametani method; B, Wilson's initial strategy; and C, Wilson's new approach.

Table 5. Additional Results for the Cycloversion of Some Cyclovitamins


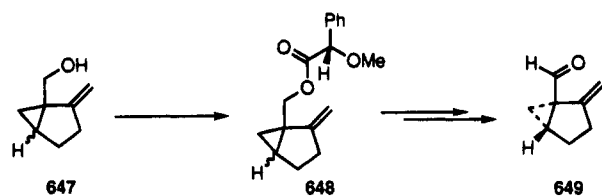
R ₁	R ₂	R ₃	Conditions	% cis	% trans	yield	References
MeO	H	H	TsOH (0.3 eq), 1:3 H ₂ O/dioxane, 55°C, 2h	93	7	80%	119
H	MeO	H	TsOH (0.3 eq), 1:3 H ₂ O/dioxane, 55°C, 2h	66	34	80%	119
OH	H	H	TsOH, 55°C, 10 min	100	0	54.8%	346
H	OH	H	TsOH, 55°C, 10 min	55	45	43%	346
OH	H	H	TsOH, H ₂ O / dioxane	71	29	-	344
~OH	~H	OMOM	TsOH, H ₂ O/dioxane, 55°C, 5 min	100	0	77%	347
MeO	H	OAc	TsOH (0.2eq), 1:3 H ₂ O/dioxane, 65°C, 15 min	80	20	50%	120
H	OH	H	TsOH, H ₂ O / dioxane	50	50	-	344

**Figure 123.**

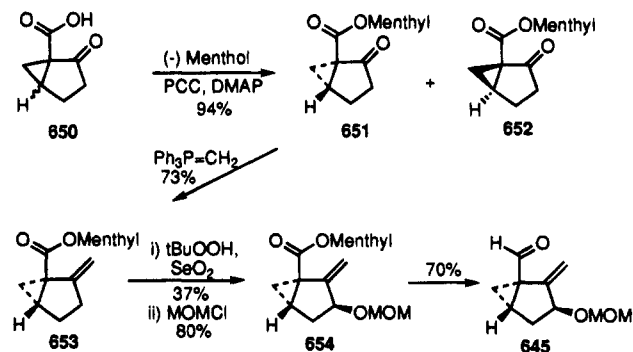
Fukumoto-Kametani Method (A). In the Fukumoto-Kametani approach the cyclovitamin **646** was constructed as a mixture of stereoisomers in 34% yield by addition of lithio anion **643** to the chiral A-ring aldehyde **645** (Figure 124).³⁴⁶⁻³⁵⁰ The vinyl-lithium was generated by *tert*-butyllithium treatment of corresponding vinyl bromide **644**, which was synthesized from Grundmann's ketone by sequential treatment with dibromomethane in the presence of LDCA (43%) followed by reduction with zinc and acetic acid (89%).³⁴⁶ An improved one-step synthesis of the vinyl bromide was reported later by Trost (67%, Figure 111).

**Figure 124.**

The optically pure A-ring aldehyde **649** was prepared via resolution of bicyclo[3.1.0]hexane **647** as its (*S*)-(+)-*O*-methylmandelic ester **648** (Figure 125).³⁴⁶

**Figure 125.**

The A-ring aldehyde with the 1 α -hydroxyl group **645** was synthesized in five steps in 10% overall yield via resolution of the racemic acid **650** using (-)-menthol followed by standard functional group transformations as shown in Figure 126.^{350,351}

**Figure 126.**

Wilson's Initial Approach (B). The initial method that Wilson adopted was the umpolung version of the Fukumoto-Kametani sequence.²⁶² The 1-deoxycyclovitamin D molecule **622/624** was assembled along line B (Figure 123) through addition of a lithiated A-ring **655** to a CD-ring aldehyde **312** as shown in Figure 127. The aldehyde may be easily synthesized from Grundmann's ketone or can be obtained via total synthesis as described earlier involving an

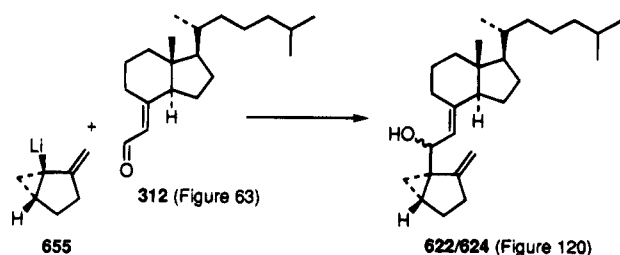


Figure 127.

intramolecular Diels–Alder reaction as the key step (Figure 63).^{261,262} The A-ring moiety **661**,²⁶⁹ the precursor of lithium reagent **655**, was synthesized in conventional fashion from 2-bromocyclopentenone (**656**)³⁵² through reduction, cyclopropanation, oxidation, and methylenation as shown in Figure 128.

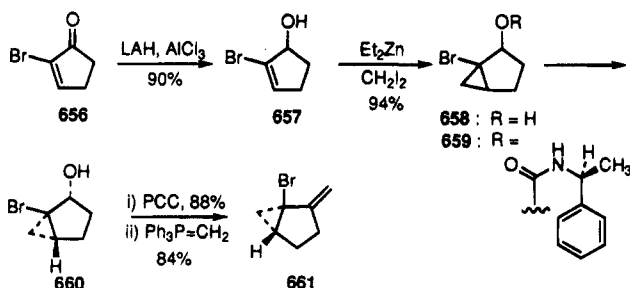


Figure 128.

Resolution of **658** was accomplished by the formation of Pirkle carbamate derivatives **659** followed by chromatography. Compound **661** readily forms the lithium reagent (*t*-BuLi) **655**, which is reacted with **312** to produce the desired cyclovitamin (Figure 127), ready for solvolysis.

Wilson's New Approach (C). Wilson's observation on the acid solvolytic behavior of the vinylogous cyclovitamin **664**^{122,345} established an excellent approach to vitamin D (see the earlier Figure 121). The solvolysis of **664** likely involves an intermediate similar to the allyl cation **620** (see also Figure 122). Construction of the cyclovitamin **664** involves as a key step, the addition of the lithium acetylide **662** to the readily accessible 25-oxygenated Grundmann's ketone **87** (Figure 129). The *trans*-allylic alcohol **664**

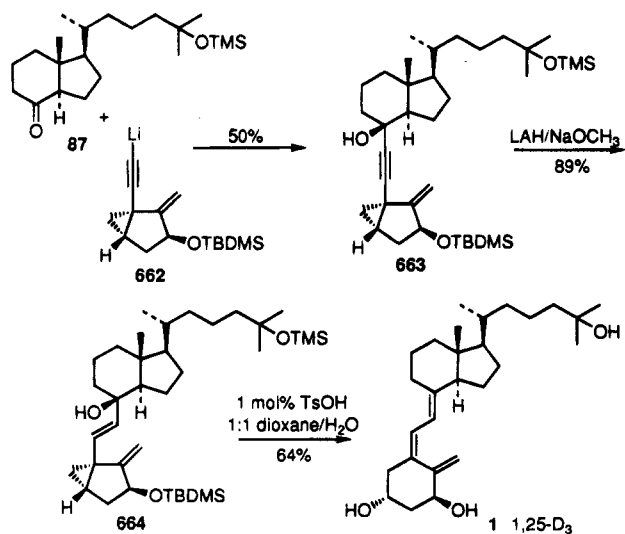


Figure 129.

was obtained by reduction of the propargyl alcohol using LAH modified with NaOCH₃. Solvolysis and hydrolysis of the silyl ether protecting group was accomplished in one pot using a catalytic amount of *p*-TsOH in 50% aqueous dioxane, affording 1,25-D₃ as the sole product (64% yield).

Wilson's synthesis of A-ring **662** via **672** shown in Figure 130¹²² involves the following key steps: (i)

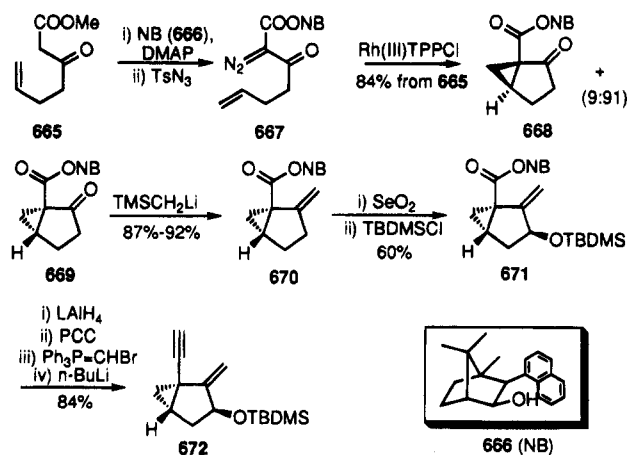


Figure 130.

rhodium-catalyzed diastereoselective intramolecular cyclization of diazoester **667**; (ii) facial selective allylic oxidation to afford **671**; and (iii) chain elongation by one carbon unit to furnish the key acetylenic intermediate **672**. It should be noted that the new chiral auxiliary, 1(*S*),3(*S*)-*exo*-hydroxy-2(*S*)-*exo*-naphthylborane (NB, **666**), used for the intramolecular cyclization of **667**, is more effective than for example, menthol, both in terms of the level of diastereoselectivity (91/9 in favor of the desired isomer **668**; menthol affords a 1:1 ratio) and ease of separation of the two diastereoisomers, **668** and **669** ($\Delta R_f = 0.11$ for NB). An alternative procedure for the intramolecular cyclopropanation was recently reported by Moriarty³⁵³ using iodonium ylides (Figure 131). In

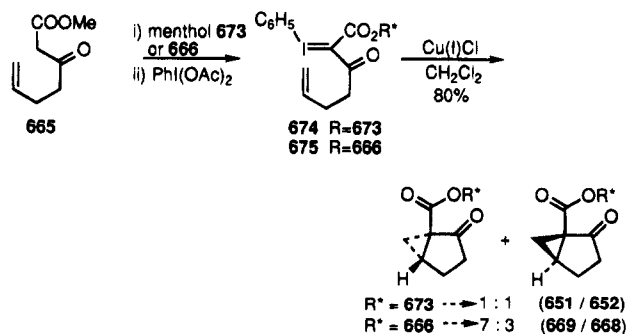


Figure 131.

Wilson's procedure the allylic oxidation of **670** with SeO₂ is reasonably effective, producing the desired 1 α -hydroxy compound in over 60% yield. The cyclopropanation of the diazo keto ester with an established 1 α -hydroxyl group (latent steroidal numbering), however, was reported to succeed leading to an efficient enantioselective synthesis of the A-ring precursor.³⁵⁴ The introduction of the triple bond (**671** to **672**) in Wilson's synthesis could be improved by Gilbert's method.³⁵⁵

In the first synthetic approach to A-ring enyne **681** by the Roche group (Figure 132),¹²¹ the desired

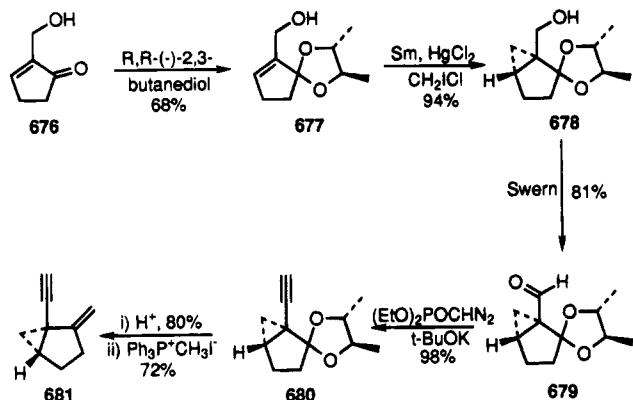


Figure 132.

chirality of the cyclopropane ring was generated under the influence of the two stereogenic centers of the (*R,R*)-2,3-butanediol ketal using Molander's cyclopropanation conditions.^{356–358} The diastereoselectivity of the reaction was estimated to be 95:5 in favor of the desired stereoisomer **678**. The major drawback of this approach is the high cost of chiral ketalizing reagent (*R,R*)-(-)-2,3-butanediol. The starting enone **676** is also not very easily available.

In the second approach by the same group (Figure 133), the chirality was introduced by borane reduc-

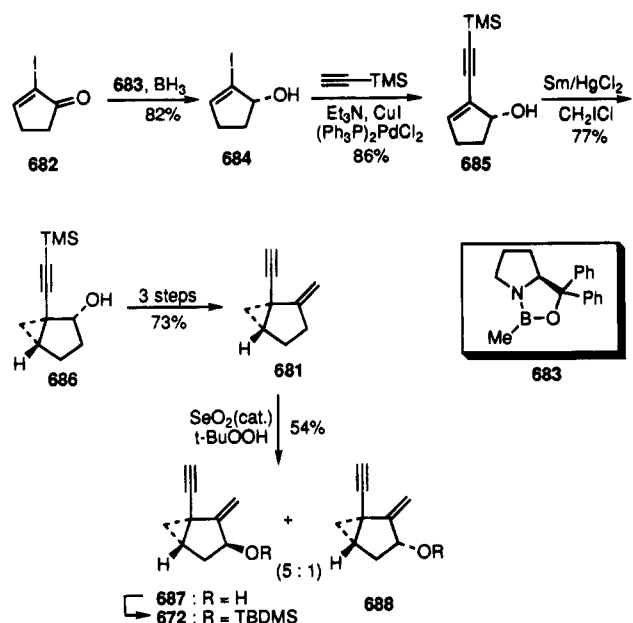


Figure 133.

tion of **682** to **684** (96% ee after recrystallization) using CBS catalyst **683**. The acetylene side chain in **685** was introduced by palladium-catalyzed coupling of iodoalkene **684** with TMS-acetylene. Samarium amalgam-mediated cyclopropanation, in this case, was entirely directed by the allylic hydroxyl group to generate the cyclopropyl alcohol **686**. The allylic hydroxylation of **681** with $\text{SeO}_2/\text{t-BuOOH}$ produced a 5:1 easily separable mixture of desired **687** and its epimer **688** in 54% yield. It was further

demonstrated that after transforming **687** to **689** via **672**, Mazur solvolysis afforded a 63/37 mixture of the desired **1** and its 5,6-*trans* counterpart **558** (Figure 134). The undesired 5,6-*trans* isomer **558** in the

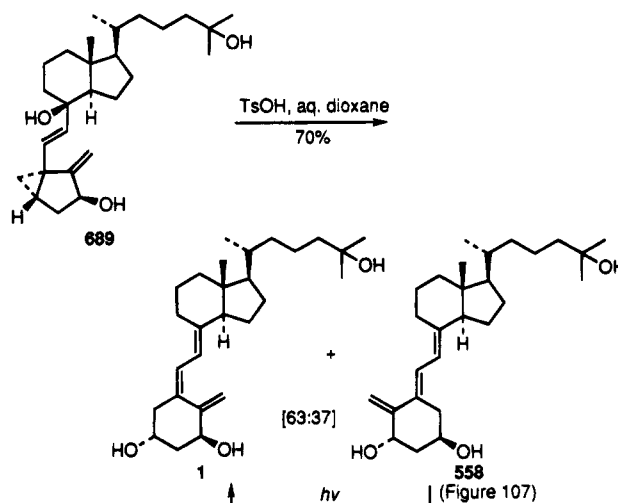


Figure 134.

solvolysis step can be photoisomerized to the desired hormone. Thus the 63:37 mixture of 1,25- D_3 (**1**) and its geometric isomer **558** generated from Mazur solvolysis of cyclovitamin D, without separation, was converted to pure **1** in an overall yield of 70%.

Lipase PS-mediated kinetic acetylation of racemic ethyl 5-hydroxy-1-cyclopentencarboxylate (**690**),³⁵⁹ derived from treatment of aqueous glutaraldehyde and triethylphosphonoacetate in aqueous KHCO_3 , afforded optically pure (*R*)-acetate **691** and (*S*)-alcohol **692**, each in nearly quantitative yield after flash chromatography (Figure 135). The acetate **691**

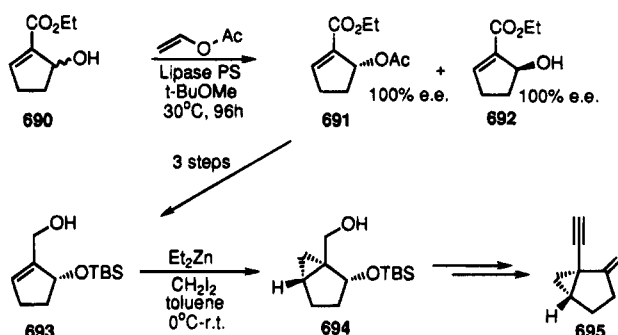


Figure 135.

possessing the desired stereochemistry was transformed using conventional methods into **695**, a known intermediate leading A-ring enyne **681** (8 steps, 30% overall yield). It is noteworthy that the Simmons–Smith cyclopropanation of **693**, as well as its corresponding deprotected, or differentially protected derivatives, did not proceed with complete diastereoselectivity, affording a mixture of syn **694** and the corresponding anti product (6:1, 80% yield).

Similarly, treatment of racemic 2-[(trimethylsilyl)ethynyl]-2-cyclopentanol ((±)-**685**)³⁶⁰ with vinyl acetate in the presence of lipase PS in toluene yielded a 1:1 mixture of acetate (*R*)-**696** and the unreacted

alcohol (*S*)-**685** (Figure 136). The latter alcohol (*S*)-

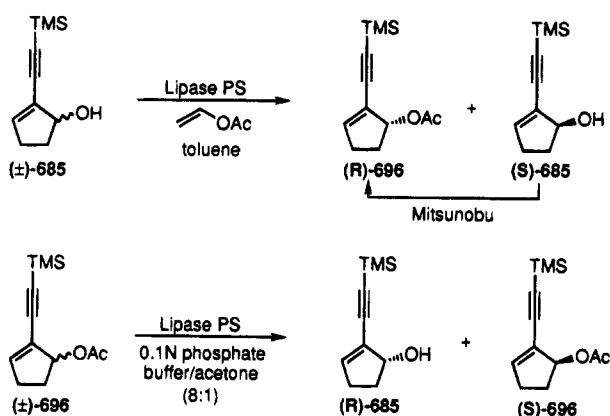


Figure 136.

685 could be converted to the desired (*R*)-acetate by Mitsunobu reaction in the same reaction medium without isolation. In addition, hydrolysis of the racemic acetate (\pm)-**696** in a phosphate buffer with the same lipase gave a 1:1 mixture of the alcohol (*R*)-**685** and the unreacted acetate (*S*)-**696**. All four compounds from the enzyme-catalyzed reaction were essentially completely enantiomeric pure (>99% ee) and could be easily transformed to the A-ring precursor **672** via a combination of cyclopropanation and Mitsunobu reactions.

3. Selective Degradation and Modification of Vitamin D

A direct application of Mazur's solvolytic interconversion of vitamin D₃ and 3,5-cyclovitamin D₃ was to develop a means for selective functionalization of vitamin D, one of Mazur's goals.¹¹⁹ In other words, this solvolytic process could serve as a protecting group for the sensitive triene unit.

C-1 Hydroxylation of Vitamin D Compounds. Direct allylic oxidation of vitamin D is feasible, but because of difficulty in controlling the site, extent, and stereochemistry of the hydroxylation, it has not yet emerged as an efficient process.^{361,362} On the basis of Mazur's reversible vitamin D solvolytic rearrangement protocol, DeLuca^{120,362} first reported an experimentally simple procedure of broad scope which affords the corresponding 1 α -hydroxylated analogues in 20–25% overall yield (Figure 137).

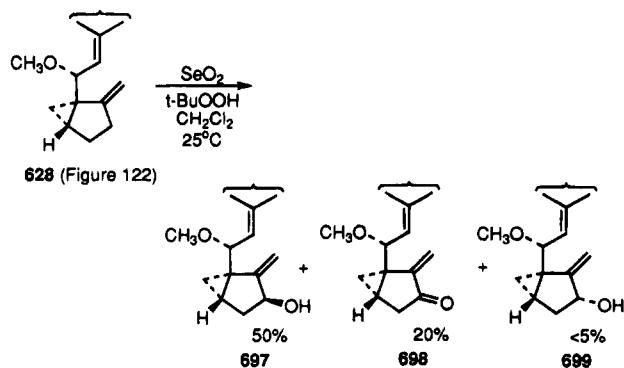


Figure 137.

Oxidation of cyclovitamin D₃ **628** with SeO₂/t-BuOOH afforded the desired 1 α -hydroxycyclovitamin D₃ (**697**,

50%), oxidized ketone **698** (20%; which, upon hydride reduction gave the 1 α -alcohol **697** in 80% yield), and the epimeric alcohol **699** (<5%). Different results for the hydride reduction of **698** were later reported by Tachibana,³⁶³ who reported that the hydride reduction of the ketone **698** (NaBH₄, LAH, or DIBALH) actually afforded the 1 β -alcohol **699**, both in ether and THF (1.7–5:1 ratio). The allylic oxidation reaction of cyclovitamin is extremely rapid in comparison to the same reaction of vitamin D₃ (20 times faster at 25 °C). The 1 β -hydroxycyclovitamin D₃ was detected in some reactions, particularly at lower reaction temperatures (5–10 °C), in less than 5% yield.¹²⁰ The selenium dioxide oxidation is considered to proceed initially through an "ene"-type mechanism in which the allylic proton is abstracted, the double bond isomerized, and a selenium–carbon bond formed (Figure 138).¹²⁰ The resulting organoselenium in-

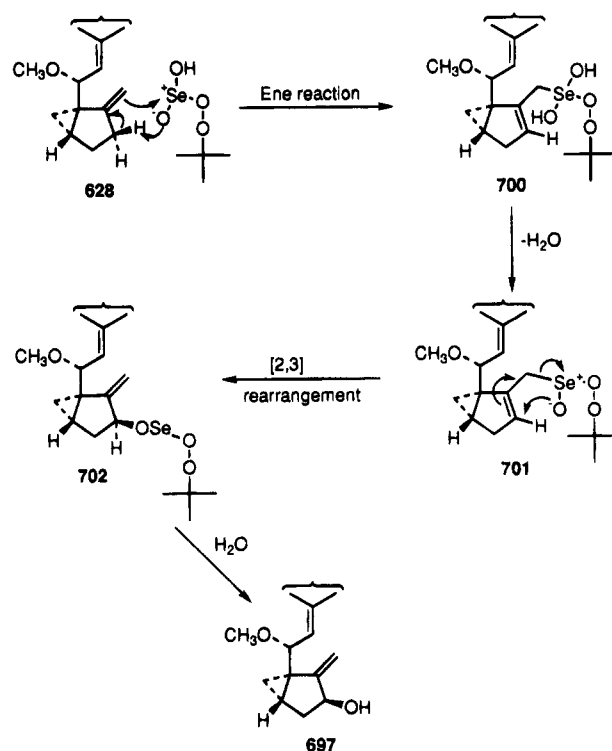


Figure 138.

intermediate **701** then undergoes a concerted [2,3] shift, yielding after hydrolysis the allylic alcohol of the original olefinic system. The remarkable rate increase for the oxidation of cyclovitamin is believed to be due to the conformationally rigid pseudoaxial orientation of the 1 α -hydrogen.¹²⁰ This situation results in maximum orbital overlap for the developing π -system during the initial "ene" step of the reaction. The angular orientation of the cyclopropyl ring effectively prevents oxidant approach from the β -face of the A-ring during the following [2,3]-rearrangement leading to stereoselective oxidation of the intermediate.

The allylic oxidation process via cyclovitamin intermediates is generally applicable to the preparation of a broad spectrum of 1 α -hydroxyvitamin D analogues. As shown in the general conversion in Figure 139, application of this scheme to vitamin D₃, 25-

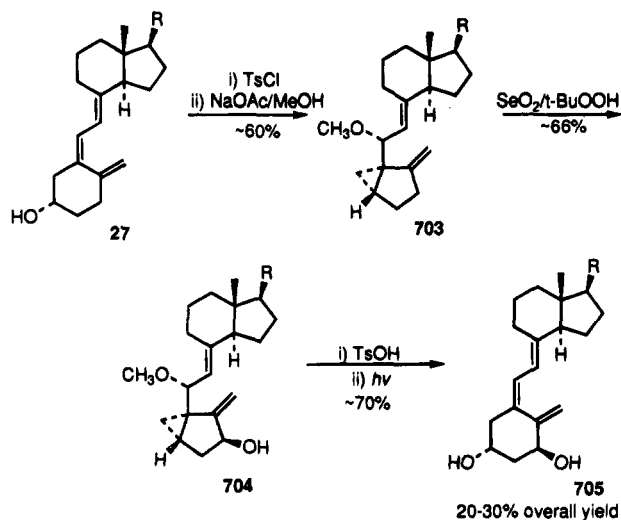


Figure 139.

hydroxyvitamin D₃, etc. has been shown to afford the 1 α -hydroxy products in about 20% overall yield.¹²⁰ This approach has also been used in the recent years for synthesis of 1 α ,25-dihydroxy-10,19-dihydrovitamin D₃ isomers,³⁶⁴ preparation of 25-hydroxy-1 α -³H-vitamin D₃,³⁶⁵ 1 β -hydroxyvitamin D₂ and D₃,^{363,366,367} and 1 α ,25-dihydroxy-28-norvitamin D₂³⁶⁸ and synthesis of ring A-stereoisomers of 1-hydroxyvitamin D₃,³⁶⁹ the Δ^{22} -unsaturated C-1-hydroxylated derivatives.³⁷⁰

Selective Degradation of Vitamin D: Synthesis of 19,13C-Labeled Vitamin D Analogues. Treatment of the C-3 acetate of 25-D₃ (6) in pyridine with OsO₄ (1.2 equiv) afforded a 75% yield of 7,8-dihydroxylated compound 706. The unique regioselectivity of this reaction on the normal vitamin D skeleton changes dramatically when the 3,5-cyclovitamin 707a is utilized as a substrate (Figure 140). The latter

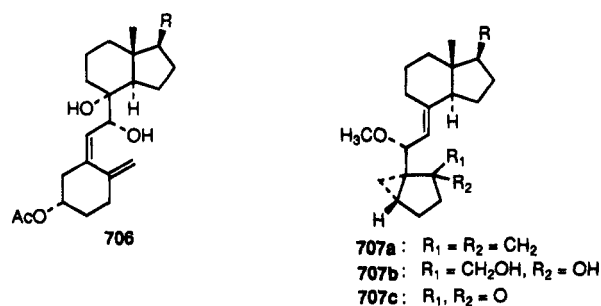


Figure 140.

reaction very rapidly afforded 10,19-dihydroxylated compound 707b, which upon treatment with NaIO₄, led to the 19-oxo compound 707c.³⁷¹ The pronounced change in the olefinic reactivity toward osmium tetroxide was rationalized on the basis of the known preference for osmic acid addition to strained, but sterically accessible double bond. The inductive effect of the C-6 methoxyl could also deactivate the $\Delta^{7,8}$ -double bond. A direct application of this 10,19-selective degradation led directly to the synthesis of [19-¹³C]1 α -hydroxyvitamin D₃ 709 through Wittig olefination⁸⁹ (Figure 141). Isotopically labeled vitamin D molecules will be discussed later in section IV.B.

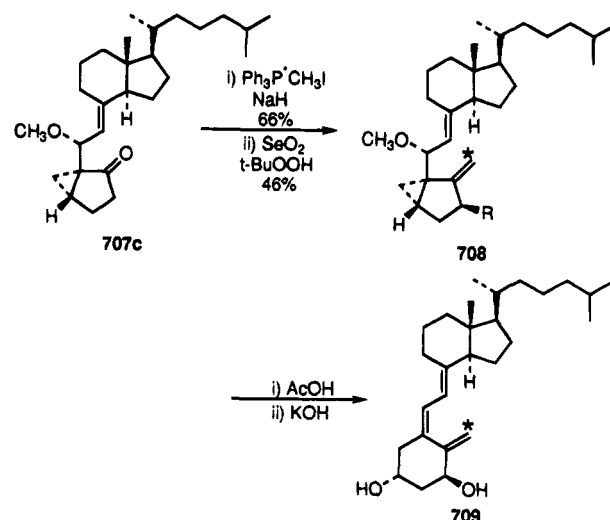


Figure 141.

H. Methods G and H: Direct Modification of Vitamin D

1. Method G: Direct Hydroxylation of Vitamin D

Direct modification of D₃ (5), vitamin D₂, and 25-D₃ (6) is becoming more attractive for the synthesis of 1 α ,25-dihydroxyvitamin D or its analogues because of the increasing availability of these materials by methods A–F (Figure 7) just discussed. Method G entails regio- and stereoselective C-1 hydroxylation and, if necessary, C-25 hydroxylation. For introduction of the C-1 hydroxyl group, the simple allylic hydroxylation of the triene of D₃ has thus far not been practical because of the difficulty in controlling the site, extent, and stereochemistry of the hydroxylation.³⁶² However, direct 1 α -hydroxylation of a TB-DMS protected 5,6-*trans* geometric isomer of vitamin D, which is available in high yield from vitamin D through cheletropic addition of SO₂, thermal elimination of SO₂, and then silylation was reported to be very successful.^{123,124} The details shown in Figure 142 for the specific case of vitamin D₃ (5) includes its initial reaction with SO₂ in benzene/water. The

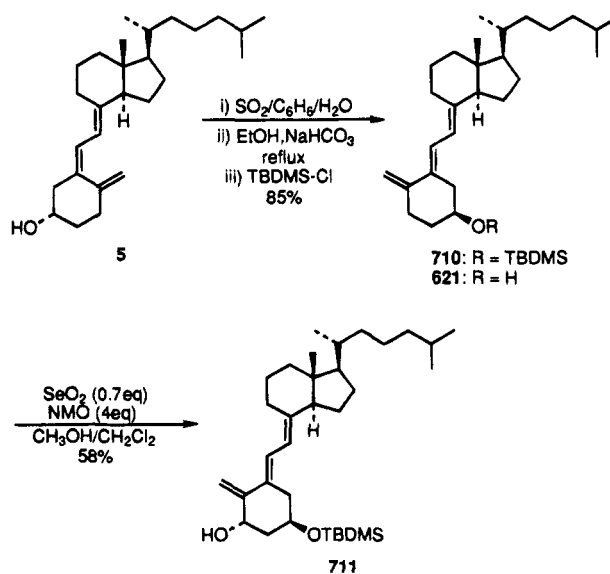


Figure 142.

resulting diastereomeric mixture of the adduct is heated in ethanolic NaHCO₃ to afford 5,6-*trans*-D₃ (**621**), which is then protected as the TBDMS ether **710** (85% yield for the three steps). The later oxidation [SeO₂(0.7 equiv), NMO (4 equiv) in methanol-CH₂Cl₂] affords the 1 α -hydroxy derivative **711** (58%), which upon illumination in the presence of acridine isomerized cleanly to the monoprotected natural 5,6-*cis* isomer (82%). Removal of the silyl group (TBAF) then affords crystalline 1 α -hydroxyvitamin D₃ in 35% overall yield.

Oxidation of unprotected 5,6-*trans*-vitamin D₃ **621** under the same conditions is less selective, leading to a mixture of two isomers (1 α /1 β = 3:1). The silyl ether **710** was originally reported to lead to higher selectivity (1 α /1 β = 20:1).¹²³ The origin of this selectivity is suggested to be due to enforcement of conformation **712** rather than **713** (Figure 143) for

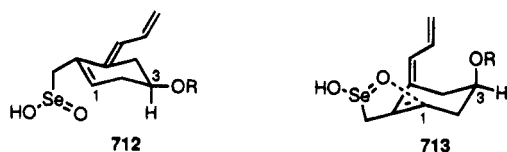


Figure 143.

the putative selenoxide intermediate during its C-1 oxygen transfer step, the product-determining process. In our hands, as well as others,^{372,373} the ratio of 1 α - to 1 β -hydroxylated products was found to be ca. 6:1 (not 20:1 as indicated above) by HPLC analysis of the reaction mixture.

An alternative route to the direct oxidation of 5,6-*trans*-vitamin D₃ was later reported by Reischl³⁷⁴ (Figure 144). Treatment of vitamin D₃ with Hg-

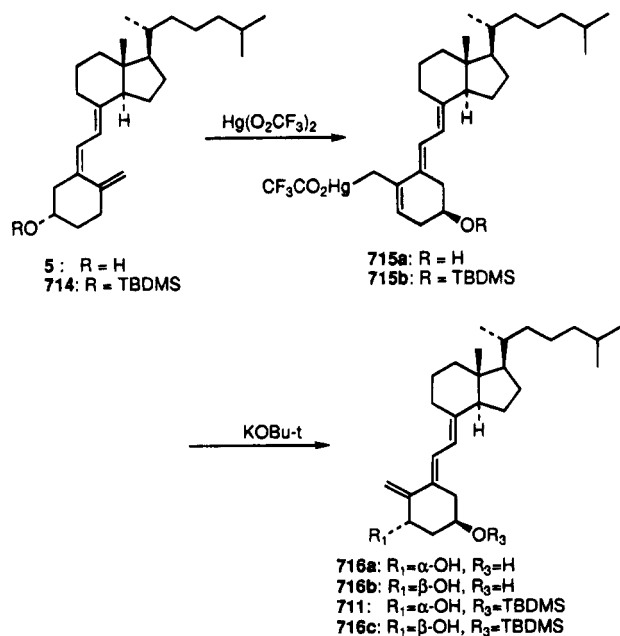


Figure 144.

(OCOCF₃)₂ in dry THF yields quantitatively, a single organomercurial compound **715a**, which upon treatment with potassium *tert*-butoxide gave a mixture of **716a** and **716b** (48% yield, 1 α /1 β = 1:1). When TBDMS-protected vitamin D₃ (**714**), suggested as being a factor in forcing the flexible A-ring toward a

conformer having the C-3 substituent equatorial (similar to that suggested in Figure 143) was used, there was observed an increased preference in favor of the 1 α -stereochemistry (1 α /1 β = 5:1). The mechanism of this transformation is not yet clear, but an intermolecular S_N2' process was proposed in which trifluoroacetate is the attacking nucleophile. The trifluoroacetates formed are hydrolyzed immediately under the reaction conditions. In this sequence, the trifluoroacetate anion acts as the base in generating the organomercurial derivative (**715a** or **715b**) as well as the nucleophile in the subsequent hydroxylation step. Whatever the mechanism, this is a short, more direct sequence for conversion of vitamin D to its 1 α -hydroxyl derivatives with a competitive overall yield (30% from **714**).

Direct 25-hydroxylation of vitamin D₃ on a practical scale, to the best of our knowledge, has not yet been achieved. However, methyl(trifluoromethyl)dioxirane-mediated stepwise oxidation of vitamin D₃ was recently reported by Curci's laboratory (Figure 145).¹⁷⁵

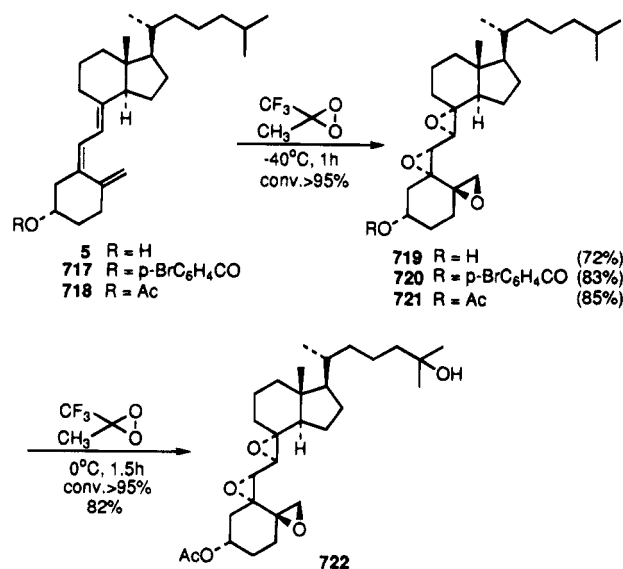


Figure 145.

Oxidation of vitamin D₃ and derivatives (**5**, **717**, and **718**) with methyl(trifluoromethyl)dioxirane at low temperature (-40 °C) affords a single diastereomeric *all-R* triepoxide **719**, **720**, and **721**. It is interesting that no oxidation of the secondary 3-OH functionality in the case of vitamin D₃ was observed. At higher temperature (0 °C), the reaction of **721** with the fluorinated dioxirane reagent was found to be highly chemoselective and site selective, producing the desired C-25 hydroxy derivative **722** in high yield (82%). However, selective deoxygenation of all three epoxide functionalities was not reported and this might be a problem in such a complex molecule.¹⁷⁶

2. Method H: Direct Modification of Vitamin D via Triene Protection

For direct modification of vitamin D, the first objective is the preparation of a derivative in which the heat-, light-, and air-sensitive triene unit is protected in such a way that oxidative reaction, or other transformations, can be performed in ring A as well as the side chain. The second objective of

course is that the vitamin D triene system can be easily recoverable after such transformations. The commonly used protecting groups are shown in Figure 146.

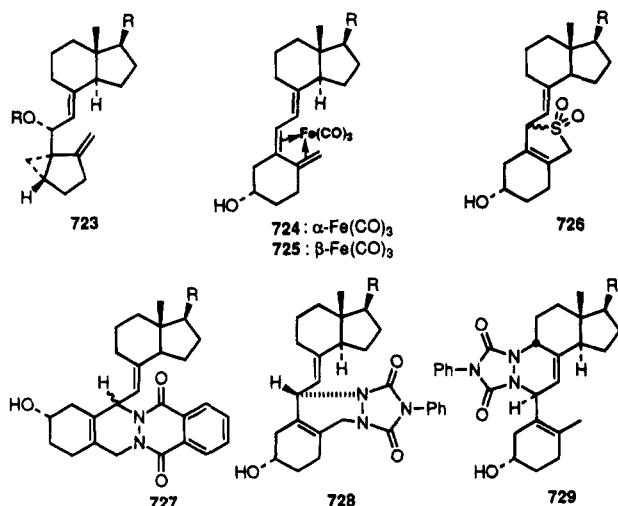


Figure 146.

Triene protection through Mazur's cyclovitamin D **723** was discussed earlier in section II.G. This method serves very usefully for C-1 hydroxylation of vitamin D compounds, and is an experimentally simple procedure of broad scope which affords the corresponding 1 α -hydroxylated analogues in 20–25% overall yield.

Treatment of vitamin D with nonacarbonyldiiron leads in high yields to the diastereomeric tricarbonyl complexes **724** and **725** (2:1). Both of the isomers can be efficiently deprotected under very mild conditions using ferric chloride (FeCl_3).³⁷⁵ These complexes are stable to oxidation (dimethylsulfonium salts) and reduction (LiAlH_4) conditions. For this reason, the tricarbonyliron group has been used to a limited extent as a protecting group of the labile triene part of vitamin D.³⁷⁵ However, this protecting system is not compatible with harsher oxidants such as those required for oxidative cleavage of the side-chain double bond of vitamin D₂.¹²⁴

The Yamada³⁷⁶ and Zbiral³⁷⁷ groups independently established that vitamin D reacts spontaneously and quantitatively with liquid sulfur dioxide at its $\Delta^{5,10(19)}$ -diene unit to give the α - and the β -face adducts **726** in about a 1:1 ratio. Both adducts extruded sulfur dioxide upon thermolysis to give 5,6-*trans*-vitamin (see Figure 142) in about 80% overall yield. The extrusion of SO_2 can also be brought about by means of $\text{KOH}/\text{CH}_3\text{OH}$ or on an alumina surface affording 5,6-*trans*-vitamin D. Through deuterium labeling experiment, it was proposed that the mechanism of SO_2 extrusion under basic conditions was an ionic stepwise process (Figure 147). However, since **726** itself undergoes exchange, and since the transformation **731** to **732** seems not well precedented, the proposed mechanism needs further study. Nevertheless, this is a very efficient method for the vitamin D to 5,6-*trans*-vitamin D conversion^{378,379} as discussed earlier (Figure 142). Because it is now well documented that 5,6-*trans*-vitamin D (**733**) may be easily and cleanly converted back to the corresponding

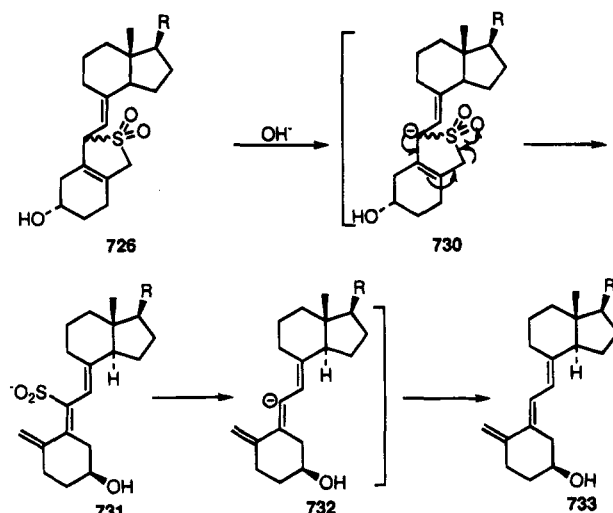


Figure 147.

vitamin D with high selectivity (ca. 95%) by photo-sensitized isomerization, the sulfur dioxide procedure has considerable potential. This protecting group is stable under various chemical transformation conditions such as radical conditions ($n\text{-Bu}_3\text{SnH}$, $h\nu$),³⁸⁰ ozone oxidative conditions,^{372,379,381} and acidic condition.³⁸¹ In **734** (Figure 148), sulfur dioxide not only

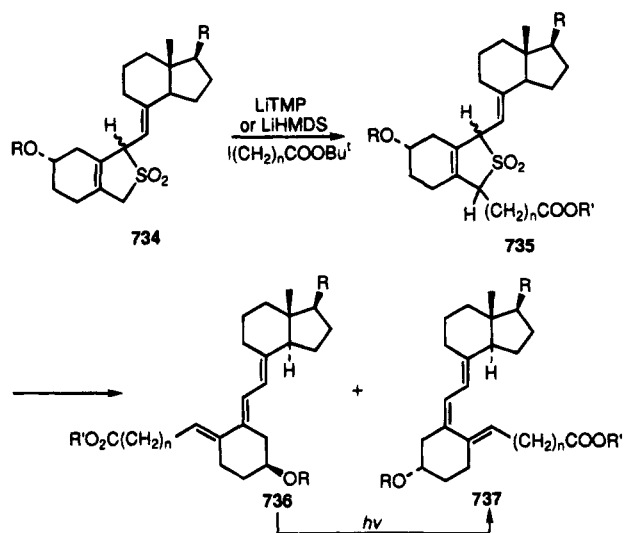


Figure 148.

protects the diene of vitamin D but it also activates allylic C-19 position of the latent diene group for electrophilic substitution.^{382,383} Of the three active hydrogens adjacent to the sulfonyl group, bulky bases such as lithium tetramethylpiperidide (LiTMP) or lithium bis(trimethylsilyl)amide (LiHMDS) were observed to selectively abstract only the least hindered proton at C-19 leading to a transient carbanion, which in the presence of an alkylating agent, undergoes C-19 alkylation. Thermolysis of the single alkylation product obtained (**735**, 50–70% yield) afforded the C-19 substituted 5,6-*trans*-vitamin D **736** as the major product together with smaller amounts of the 5,6-*cis*-isomer **737** (85–95% yield). Lower temperature and addition of NaHCO_3 favors the formation of 5,6-*trans*-vitamin D. Photochemical irradiation then transforms **736** to **737**.

Vitamin D₃ reacts rapidly with 4-phenyl-1,2,4-triazoline-3,5-dione (**738**) at the $\Delta^{5,10(19)}$ -diene position

to give mainly the α -face adduct **739** (95%) accompanied by small amounts of the β -face adduct **740** (5%) (Figure 149).^{384–386} With KOH in ethylene

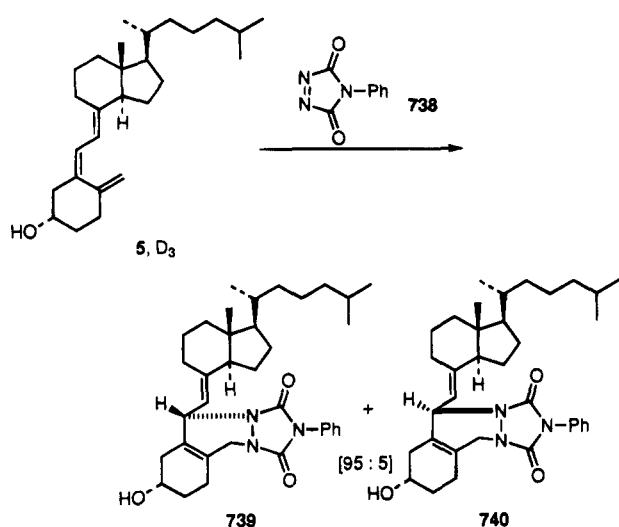


Figure 149.

glycol–water (100 °C), **739** or **740** affords 5,6-*trans*-vitamin D₃ (**621**). The high selectivity toward formation of the α -face adduct has been suggested to be due to the influence of the β -oriented 18-methyl group and steroidal side chain, which significantly interfere with the approach of **738** to the β -face of **5**. This hypothesis was supported by the finding that treatment of 5,6-*trans*-vitamin D₃ (**621**), in which the 18-methyl group and side chain are somewhat more remote to the $\Delta^{5,10(19)}$ -diene, with **738** gave approximately equal amounts of **739** and **740**.

The adduct **739** is highly stable toward oxidation conditions (e.g., the Jones' reagent).³⁸⁴ On treatment with strong acid (HCl) in various solvents, even under vigorous conditions, no deterioration of the adduct occurs. The adduct is also reasonably resistant to reduction with LiAlH₄ (in THF) or sodium bis(2-methoxyethoxy)aluminum hydride (in benzene) after 3 days refluxing.

Andrews et al.¹²⁴ reported in early studies that deprotection of the adduct from vitamin D₂ (**741**) and **738** under the reported conditions (KOH in refluxing ethylene glycol or in refluxing butanol) gave the corresponding 5,6-*trans*-vitamin D₂ (**746**) in very poor yield (15%) together with substantial quantities of the semihydrolyzed product **742** (Figure 150). Subsequent reports,³⁸⁷ however, described the successful regeneration of dienes from PTAD (**738**) adducts by basic hydrolysis followed by an oxidation step. In one case, the oxidation of a semihydrolyzed adduct led to diene formation.

An alternative protecting group to **738**, phthalazine-1,4-dione (**744**), which was prepared in situ from phthalhydrazide **743** and lead tetraacetate, has the advantage of being easily deprotected through oxidation with dianisyl telluroxide (Figure 150). The phthalazine protecting group is stable under Wittig reaction conditions and ozone oxidative conditions. The 5(10) and 7(8) double bonds of the adduct **745** were completely unreactive toward hydrogenation (5% Pd on charcoal) in the process of side chain double bond reduction.

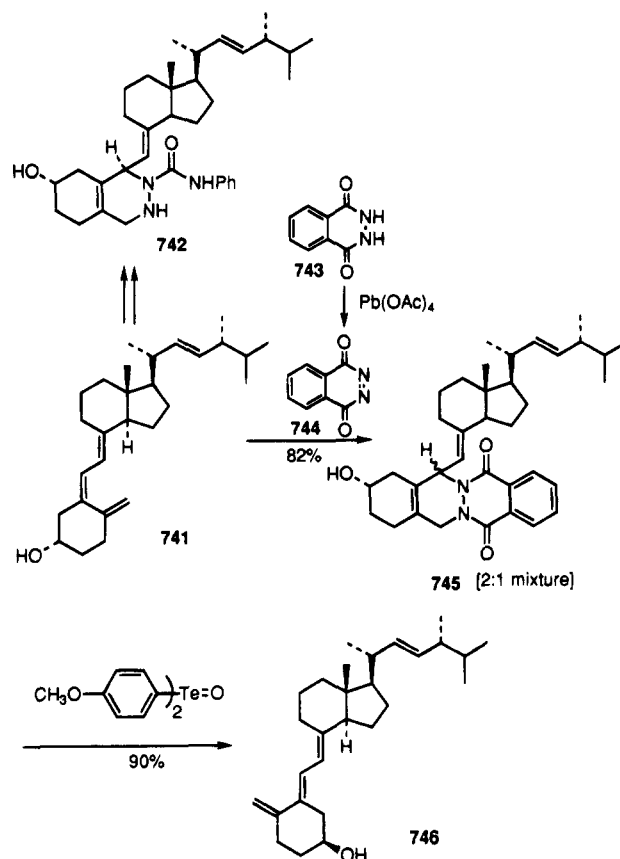


Figure 150.

Selective Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (**738**) with the $\Delta^{6,8}$ -diene of pre-vitamin D₃ generates a single adduct **747**, suitable for the stereoselective introduction of **748** bearing the 1 α -hydroxyl group (Figure 151).^{127,388–390} Cyclorever-

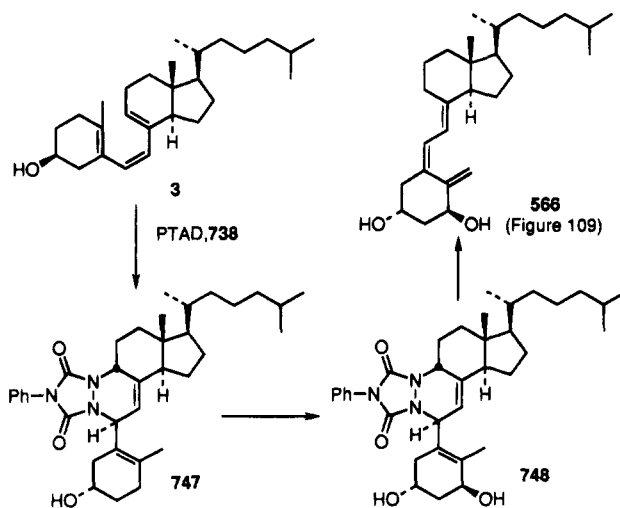


Figure 151.

sion of the modified adduct under basic conditions (KOH–MeOH, 80 °C, 24 h) leads to the desired pre-vitamin D₃ and then to 1 α -hydroxyvitamin D₃ (**566**) (Figure 109). The same sequence starting from 25-hydroxyprevitamin D₃ leads the hormone 1,25-D₃ (**1**).

I. Other Synthetic Approaches

In addition to the commonly used synthetic approaches A–H (Figure 7), other coupling approaches

are also employed in the synthesis of 1,25-D₃ (**1**) or its analogues. First, the Julia³⁹¹ olefination approach,^{392,393} which was first reported by Lythgoe is a conceptually similar approach to the Horner–Wittig olefination approach. The lithium anion of CD-ring sulfone **749**, which was prepared either from Grundmann's ketone³⁹² or through total synthesis,^{393–396} was coupled with the A-ring aldehyde **750**. The resulting oxyanion adduct was silylated or acetylated in situ, leading to a mixture of all four diastereoisomers of **751**. Reductive elimination of the mixture with lithium–amalgam afforded exclusively 7,8-*trans*-olefin **27**³⁹⁷ (45% overall yield) (Figure 152).

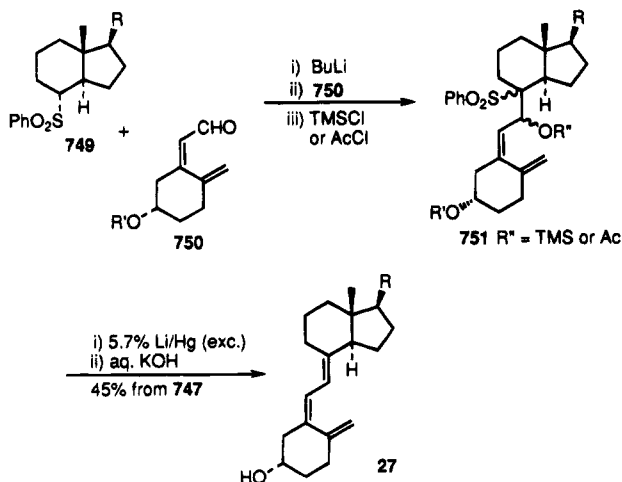


Figure 152.

The reaction of the corresponding benzoates (**751**, R = Bz) with sodium amalgam gave a mixture of **27** (36%) and its 5,6-*trans*-isomer (20%).³⁹²

The same strategy was also employed for C₆–C₇ bond formation through coupling of CD-ring methylene sulfone **752** with A-ring α,β -unsaturated aldehyde **753**.²⁴⁰ Julia elimination of the mixture of diastereoisomers **754** led to a triene compound with the *trans*- $\Delta^{6,7}$ -double bond, which was photo- and then thermo-isomerized to the natural vitamin D (Figure 153). Julia reductive elimination of keto

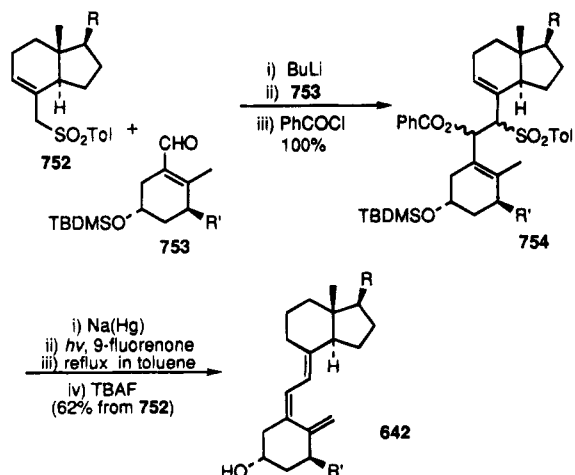


Figure 153.

sulfone **756**,³⁹⁸ derived from the coupling between **752** and **755**, via the corresponding enol phosphate **757**, provides the dienyne **758**, an intermediate related to

that observed in the earlier cross coupling approach discussed in section II.D (Figure 154).

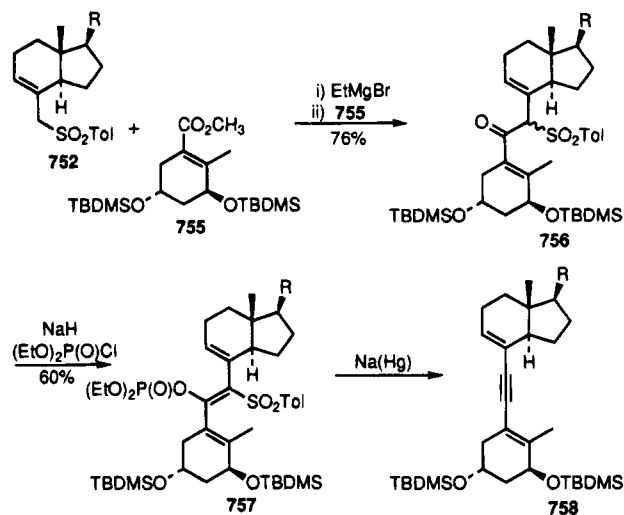


Figure 154.

A conceptually novel chromium(II)-mediated coupling of A-ring allyl iodide **760** and a known type of CD-ring, α,β -unsaturated aldehyde **759** (cf. Figure 63) was developed in Takano's laboratory in Japan.^{284,399} The highly diastereoselective Cr(II)-mediated addition of the allylic halide **760** to the aldehyde **759** was proposed to proceed through transition state **761**, leading to **762** as the sole product in high yield (83%). However, formation of a substantial amount of 1,4-elimination product **763** in the following dehydration step strongly limits the broad applicability of this strategy for constructing the triene unit of vitamin D (Figure 155).

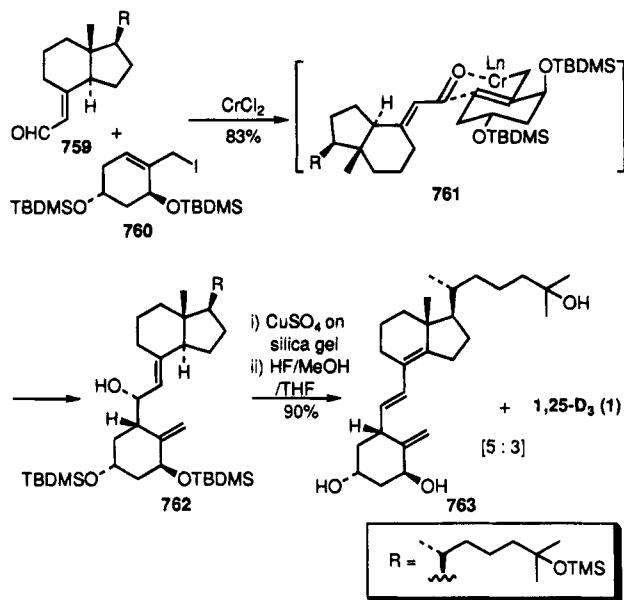


Figure 155.

We conclude the main methodological portion of this review to remind the reader of the pioneering studies of Inhoffen and Lythgoe in the area of vitamin D synthesis. Inhoffen's contributions were mentioned only briefly in this review (Figure 28) although Lythgoe's contributions to important vitamin D construction in methodologies (e.g., sections II.C and

II.D) have been mentioned on numerous occasions. We conclude this section with the original aldol condensation–Wittig approach used in the earliest studies by both Inhoffen and Lythgoe. For example, in 1958, Lythgoe⁴⁰⁰ reported the first partial synthesis of vitamin D₂ (**741**) by an aldol condensation of the A-ring enolate of **765** with the known, enantiomerically pure CD-ring aldehyde **764** to give a 5,6-*trans*-dienone **766**. Photoisomerization of the latter followed by Wittig reaction afforded a mixture of natural vitamin D₂ (**741**) and its 3 α -epimer **768** in which the *epi* isomer predominated (Figure 156).

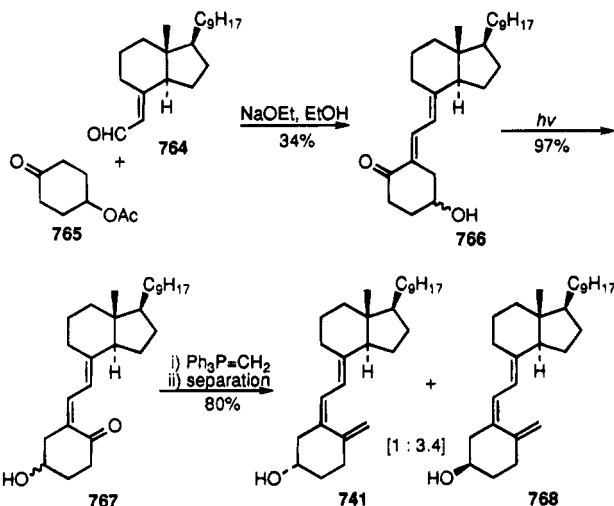


Figure 156.

III. Selected Topics for Modification of Vitamin D

A. Selected Methods for Side-Chain Construction

Among the 820 structural modifications of 278 vitamin D analogues summarized in the review article of Bouillon et al.,¹⁷ 82% involve the side chain. It is perhaps not surprising therefore that most of the potentially applicable vitamin D drugs as well as continuing interest appear to focus on side-chain analogues of 1,25-D₃. It is not clear whether even more chemotherapeutically interesting analogues may be lurking among the still unknown A-ring, triene, or CD analogues, which of course involve more complex synthetic procedures. One cannot of course argue with the success realized with side-chain analogues. General strategies for side-chain construction of steroids have been reviewed in detail in a series of review articles over the years.^{49,401,402} Here we limit discussion to common strategies of side-chain construction, many developed after appearance of the earlier review articles.

1. Nucleophilic Displacement at C-22

As briefly introduced in previous sections, nucleophilic substitution at C-22 has been one of the most popular methods for construction of the 25-hydroxycholesterol side chain or its side chain-modified analogues (Figure 157). Treatment of either tosylate **769a** or iodide **769b** with sodium acetylide **770** (M = Na) in DMSO resulted in the alkylation product **771** in 60–70% yield. The reaction of the lithiated compound **770** (M = Li) produced 55–66% yield of

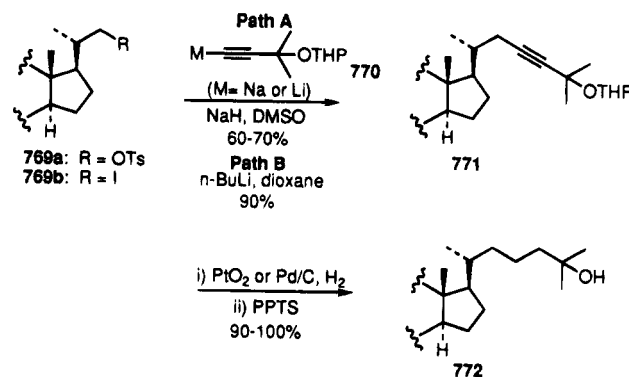


Figure 157.

771 together with substantial amounts of the chloro derivative of **769**, probably resulting from the presence of halide ions in commercial butyllithium. To remove the competing halide ions, the lithium acetylide **770** (M = Li) was prepared in dioxane solution, the lithium chloride present being precipitated as the insoluble lithium chloride–dioxane complex. Reproducible 90% yields of the desired alkylation product **771** were then achieved.⁴⁰³ Hydrogenation of the acetylenic bond of **771** to the saturated side chain (~100% yield) was carried out using either platinum oxide or 10% Pd–C catalyst in dioxane, buffered ethanol, or ethyl acetate. Subsequent removal of the protecting group afforded the desired **772**.

The Grignard coupling procedure shown in Figure 158 was originally developed by Lythgoe^{187,404} and

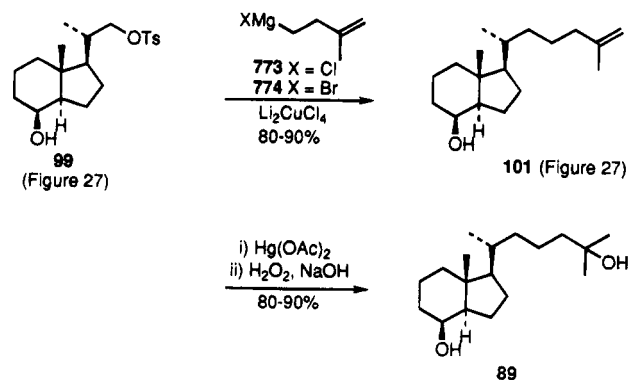


Figure 158.

later modified by Okamura.³¹⁸ The Grignard reagent **773** was coupled with tosylate **99** in either 8 β -OH protected or unprotected forms¹¹³ in the presence of dilithium tetrachlorocuprate to give (after deprotection in the first case) the alkylation product **101** in excellent yield. However, the corresponding Grignard reagent of 4-bromo-2-methyl-1-butene, under the same conditions, does not couple to tosylate **99**. The complexation of Li₂CuCl₄ only to the Grignard reagent with chloride (**773**) and not bromide (**774**) seems to be responsible for this difference. Oxymercuration–demercuration of **101** completes the construction of the 25-hydroxy side chain of vitamin D.

As shown in Figure 159, coupling of iodide **769b** with π -(dimethylallyl)nickel bromide **776** produced **778** in 65% yield.⁴⁰⁵ The corresponding bromide **775** did couple to the Grignard reagent **777**, but only in very poor yield.⁴⁰⁶

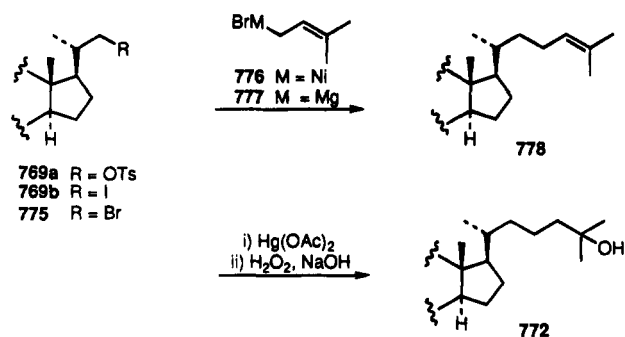


Figure 159.

The shortest pathway for construction of the 25-hydroxyvitamin D side chain (Figure 160) might be

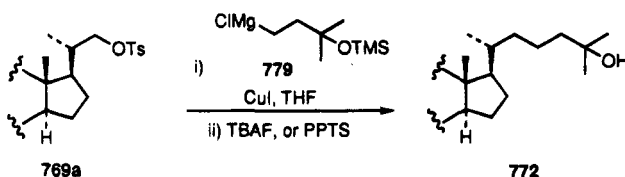


Figure 160.

the direct coupling of the tosylate **769a** with the Grignard reagent **779**, which in the presence of copper(I) iodide, leads to the side chain with the 25-hydroxy group **772** in good yield.^{407,408}

Coupling of iodide **769b** with nickelacycle **780** as a propionic acid equivalent^{407,409} gave, after esterification, a high yield of the C-25 methyl carboxylate **781** (Figure 161). Treatment of **781** with suitable

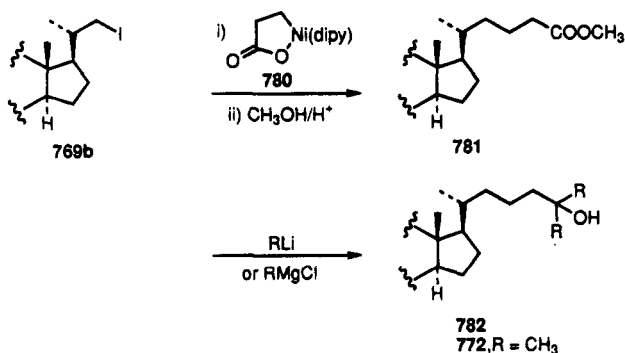


Figure 161.

metalated reagents leads to the desired side chain, as well as its 26,27-homologues or isotopically labeled derivatives **782**.

An improved procedure developed in Mouriño's laboratory in Spain employed a zinc-copper-mediated conjugate addition of the iodides **783**–**785** with methyl acrylate under sonochemical conditions^{410–412} (Figure 162). In a typical procedure, the reaction of **783** with methyl acrylate afforded hydroxy ester **786** (X = OH, Z = CO₂CH₃) in 75% yield.⁴¹³ This method is general. A wide range of iodides, including substrates with the full vitamin D skeleton,⁴¹⁴ were successively coupled with a wide range of electron-deficient olefins⁴¹⁵ in reasonable or good yields. A clear advantage of this method over organometallic approaches⁴⁰⁹ is its easy operation, including the use of aqueous reaction conditions. In general, polar substrates afford higher yields of product.

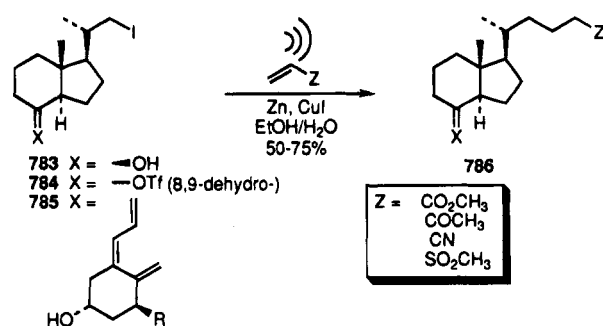


Figure 162.

2. $\Delta^{22,23}$ -Double-Bond Formation

Wittig Reaction. Wittig reaction of a steroidal C-22 aldehyde is one of the most widely used methods of introducing the side chain, particularly in connection with the $\Delta^{22,23}$ -double bond⁴⁰¹ together with the 24-methyl group characteristic of ergosterol and vitamin D₂ as in **789** (Figure 163).^{416,417} The reaction with

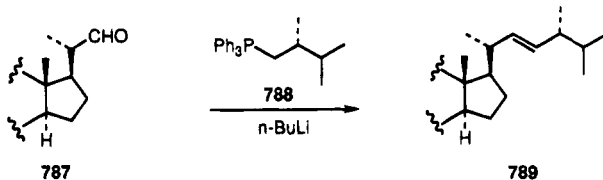


Figure 163.

unstabilized ylides in nonpolar solvents gives mainly (*E*)-22-olefins. (For a general consideration of the Wittig reaction stereochemistry, see House et al.⁴¹⁸). The *Z*-isomers can be obtained by a modification introduced by Corey.^{419,420} A useful Wittig reagent is **790** (Figure 164), originally devised by Salmond

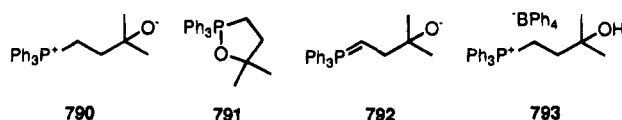


Figure 164.

et al.^{421,422} for the preparation of 25-hydroxy steroids. Methylene triphenylphosphorane was treated with isobutylene oxide to give **790** which may possess either the classical betaine structure **790** or oxophospholane structure **791**. The reaction of **790** (or **791**) with a second mole of *n*-butyllithium gives ylide **792** capable of reacting with aldehyde **787** without C-20 epimerization to give an 85:15 of *E/Z* mixture of the $\Delta^{22(23)}$ -double-bond isomers (75–86% yield). The stoichiometry of the Wittig reagent **790** employed is critical. A simple modification of the method was later developed by Andrew et al.¹²⁴ using phenyllithium as base instead of *n*-butyllithium. Phosphonium tetraphenyl borates **793** as a pure, stable salt can be used and it generates the ylide **792** by treatment with 2 equiv of phenyllithium.

By using the same strategy, the 25-hydroxyvitamin D₂ side chain was constructed (45%) via addition of aldehyde **787** to a ylide **798** (Figure 165). The latter was synthesized as shown in five steps from commercially available (*S*)-(+)-methyl-2-methyl-3-hydroxypropanoate (**794**).⁴²³

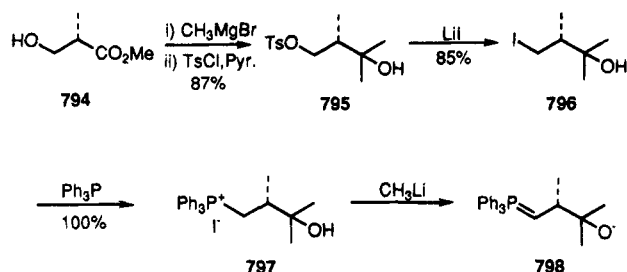


Figure 165.

Julia Olefination. The Julia olefination³⁹¹ approach (Figure 166), which was first utilized for

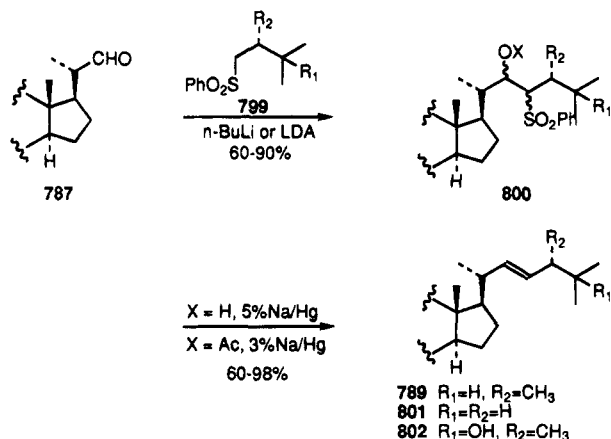


Figure 166.

vitamin D applications by Lythgoe,⁴²⁴ is an alternative to the Wittig approach. The Julia scheme has the advantage with regard to stereoselective $\Delta^{22,23}$ -*E* double-bond formation if the vitamin D₂ type side chain is desired. Condensation of aldehyde **787** with deprotonated sulfone **799** (*n*-BuLi or LDA) produced a mixture of four C-22/C-23 diastereoisomers of **800**. Reductive desulfonation of **800** furnishes the coupled products with exclusive *E* geometry of the side-chain olefin. Elimination of **800** with free alcohol (X = H) requires the use of 5% sodium amalgam while 3% sodium amalgam is sufficient for elimination of the corresponding acetate (**800**, X = Ac).

In general, the overall yield of the Julia olefination approach is lower than that of the Wittig scheme,⁴²⁵⁻⁴²⁷ although in some cases, very high yields may be achieved.^{428,429} In recent years though, the Julia olefination approach has been widely employed for side chain construction in the synthesis of various vitamin D analogues. Several recent applications of the Julia olefination approach have been reported.^{370,373,430-432}

3. Stereoselective Introduction of the Steroid Side Chain at C-17 and C-20

Ene Reaction. A simple and efficient method for the highly stereoselective (at C-17 and C-20) introduction of steroid side chains, suitably functionalized for further elaboration, using the ene reaction was developed by the Roche laboratory^{433,434} and by Dauben (Figure 167).⁴³⁵ Wittig reaction of 17-keto steroid **803** with ethylenetriphenylphosphorane (THF, 25 °C) gave the desired 17*Z*-olefin **804** (96:4,

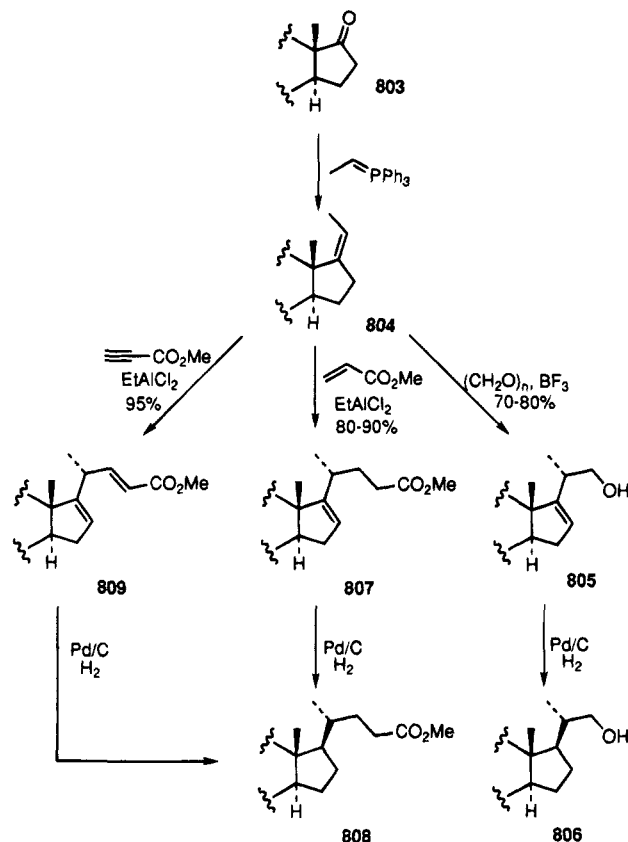


Figure 167.

17(20)*Z*/17(20)*E* ratio).¹⁹⁹ The reaction with other stabilized ylides leads to the more stable *E*-isomer.^{436,437}

Treatment of the 17(*Z*)-ethylenide steroid **804** and paraformaldehyde in the presence of 10 mol % of boron trifluoride etherate in methylene chloride (15 min, room temperature) afforded alcohol **805** in 84% yield.⁴³⁴ Longer reaction times led to a decrease in yield. The main side reaction to be avoided was formation of formaldehyde acetals of the resulting alcohol product. A variety of acids (both Lewis and protic) were found to be more or less effective as catalysts in hydrocarbon or chlorocarbon solvents as well as in aqueous media. The ene reaction of the olefin **804** with free alcohol in the A-ring seems to give lower yield of the desired product.

The ene reaction is highly stereospecific. The reaction of **804** generates the ene product with exclusive natural configuration at C-20 (Figure 168).

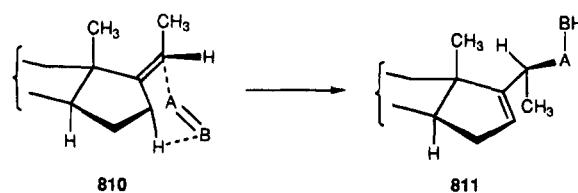


Figure 168.

The stereochemical control is attributed to the virtually exclusive attack of the enophile at C-20 from the less hindered α -face of the molecule. The ene reaction of **804** was also reported to occur faster than that of 17(*E*)-ethylenide steroid.²⁰⁰

The ene reaction of **804** with methyl acrylate in the presence of stoichiometric amounts of ethylaluminum

dichloride also gives high yields (80–90%) of product **807** (Figure 167) although the reaction proceeds slowly (24–48 h). To overcome the basicity of functional groups present elsewhere in the molecule, 1 equiv of ethylaluminum dichloride is required for each basic functional group present in the ene component as well as in the enophile. Aluminum chloride (or bromide) can also be effective in catalyzing the reaction when used in conjunction with a proton scavenger such as pyridine. This system (in toluene) leads to shorter reaction times (1.5–2 h), but to avoid product decomposition, the reaction time must be as short as possible and the workup must be carried out under stringently controlled conditions.

The ene reaction of **804** with methyl propynoate and diethylaluminum chloride in benzene afforded the ene product **809** with exclusive natural configuration at C-20 and *E* double bond at the $\Delta^{22,23}$ position in excellent yield (95%), presumably through the transition state **812** shown in Figure 169. The

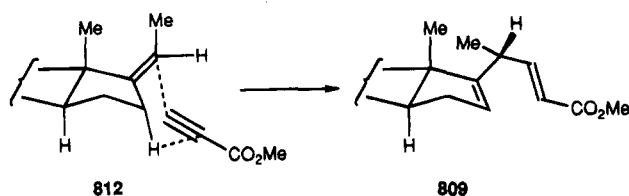


Figure 169.

substrates with free alcohol in the A-ring gave the same results.⁴³⁵ Catalytic hydrogenation of the ene products (**805**, **807**, and **809**) on Pd–C (EtOH, 25 °C) proceeded selectively to afford the products (Figure 167) with the natural C-17 configuration in almost quantitative yields.

The reactions of **804** (more specifically, **813** and **816**) with other saturated aldehydes under similar conditions resulted in formation of steroid side chains with 22-hydroxy groups (Figure 170). The ene reac-

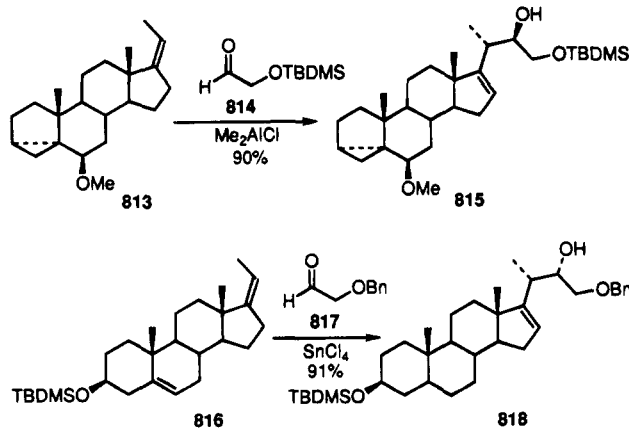


Figure 170.

tion of the steroidal olefin **813** with α -silyloxy aldehyde **814** and Me_2AlCl (1 equiv) in CH_2Cl_2 at -78°C was reported to afford the 22(*R*)-hydroxy product **815** as a single stereoisomer in 90% isolated yield.⁴³⁸ In sharp contrast, the reaction of **816** with α -benzyloxy aldehyde **817** and SnCl_4 (1 equiv of each) in CH_2Cl_2 at -78°C exhibited complete reversal of diastereoselectivity at C-22, affording the 22(*S*)-hydroxy product **818** in 91% isolated yield with >99% diastereo-

selectivity. This difference might be attributed to chelation versus nonchelation control in the ene reaction (Figure 171). In the first case, the ene

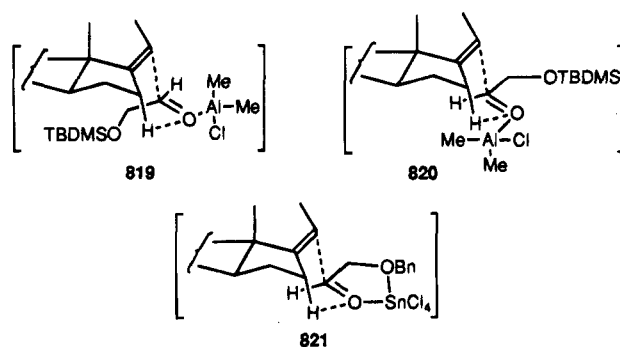


Figure 171.

reaction of the nonchelated α -silyloxy aldehyde proceeds preferentially via the endo transition state **819**, since the exo conformer **820** suffers steric repulsion between the steroid D ring and the Lewis acid complexed to the aldehyde in an anti (nonchelation) fashion. By contrast, the ene reaction of α -benzyloxy aldehyde well reflects the chelation situation in that the cyclic chelate would possess the sterically favorable exo oriented **821**. Others have reported similar results.⁴³⁹

Palladium-Catalyzed Reaction. Trost's palladium-catalyzed approach (Figure 172)^{440–442} involves initial

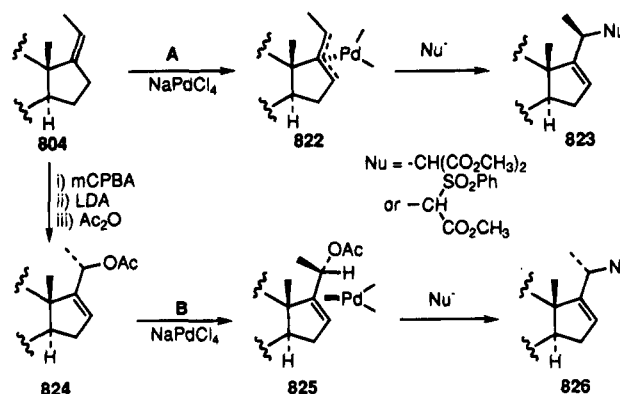


Figure 172.

formation of an allyl–palladium complex with either 17(*Z*)-ethylidene steroid **804** or a 20-acetoxy-16-ene **824**. The latter (**824**) was prepared by stereoselective epoxidation on the α -face of **804** followed by epoxide opening with LDA and acetylation. In the nonacetylated complex **822**, the metal resides on the α -face, while in the allylic acetate complex **825**, the palladium reacts on the β -face owing to steric hindrance by the acetate moiety. The nucleophile adds only to the β -face of **822**, yielding the unnatural configuration at C-20 (**823**). On the other hand, for **824**, initial elimination of acetate in **825** to produce the β -face diastereomer of **822**, followed by nucleophilic displacement, affords the product with the natural C-20 configuration (**826**). Decarboxylation of dimethyl malonate or reductive desulfonylation of (methylphenyl)sulfonyl acetate then leads to the side chain with functional groups available for further elaboration. Thus, either stereochemistry at the C-20 posi-

tion of a steroid can be obtained via π -allyl palladium complex chemistry.

Alkylation of the allylic acetate **827** (Figure 173), which can be derived from oxidation of **804** with

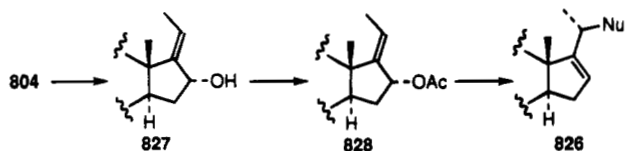


Figure 173.

selenium dioxide (65%), proved substantially more difficult than that of **824** (Figure 172), but at higher temperature (120 °C), afforded the identical products, in both regio- and stereospecific fashion. Allylic oxidation of **804** to alcohol **827** using Sharpless' procedure⁴⁴³ was reported to be superior to the classical selenium dioxide/ethanol procedure (74%).⁴⁴⁴

Claisen and Cope Rearrangements. The natural C-20 configuration including the complete vitamin D side chain may also be introduced by Claisen rearrangement of the *E*-isomer **829** (Figure 174), which

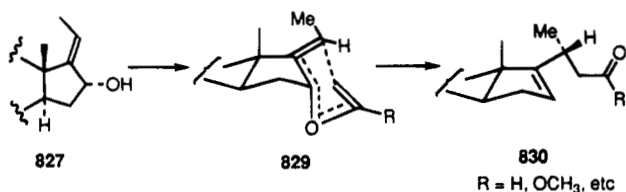


Figure 174.

is easily accessible from 17(*Z*)-ethylidene steroids.⁴⁴⁵ The Claisen rearrangement of *E* isomer **829** can be considered to proceed through a chairlike transition state to give the well-functionalized side-chain compounds **830** with the natural configuration at C-20.

Similarly, potassium-assisted oxy-Cope rearrangement of **833** (Figure 175), derived from **804** generates

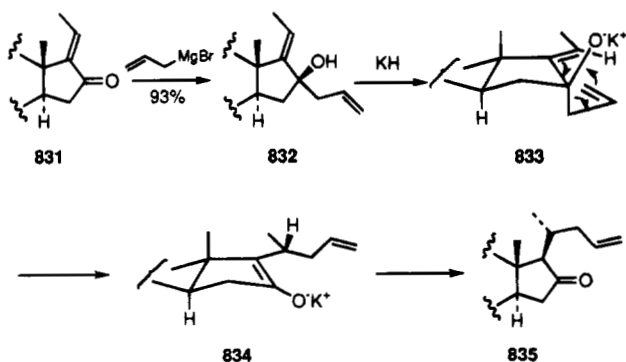


Figure 175.

stereospecifically, presumably via a chairlike transition state, the natural side chain stereochemistry of the steroid.⁴⁴⁶ Quenching of the reaction with water leads to keto olefin **835** with the quasiequatorial 17 β -stereochemistry of the side chain. However, the necessity of removal of the extra 19-keto group of the Cope product is cumbersome.

Hydroboration. Hydroboration of ethylidene steroids with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds in a stereoselective manner from the α -face

(Figure 176). Coupling of the borane derivative **836**

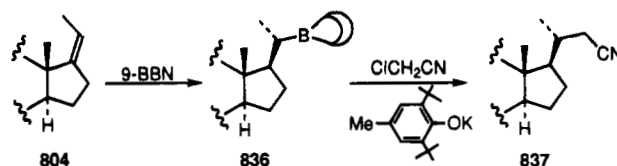


Figure 176.

with chloroacetonitrile (in a manner similar to hydrogen peroxide oxidation) gave cyano steroids which can be easily converted to the 25-hydroxyvitamin D side chain.^{447,448} This process has recently been applied to the total synthesis of ent-cholesterol.⁴⁴⁹

S_N2' Substitution. The reaction of epimeric pivalate esters **838** and **839** with lithium isohexyl cyanocuprate **840** (Figure 177) proceeds through a

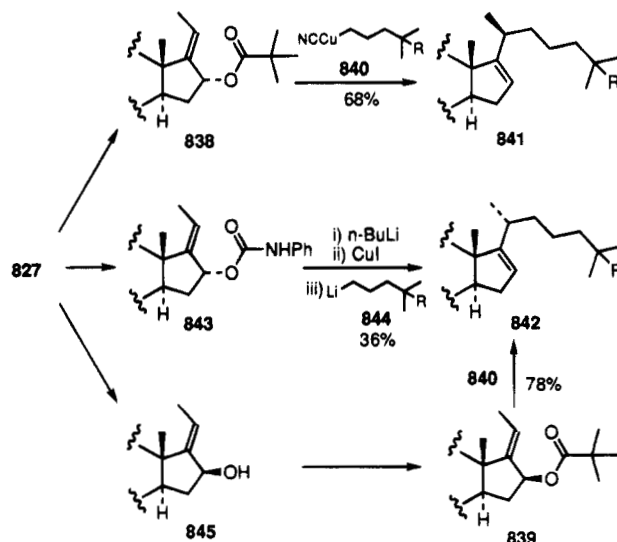


Figure 177.

regio- and stereospecific S_N2' process to give **841** and **842**, respectively, products of the expected anti facial mode of reaction.⁴⁴⁴ In each case, a trace ($\sim 5\%$) of the corresponding regioisomer could be discerned in the crude ^1H NMR spectrum. Neither **841** nor **842** was contaminated with the other C-20 epimer to any detectable extent. Reaction of **843**, which was also prepared from **827**, first with 1 equiv of *n*-butyllithium followed by sequential treatment with cuprous iodide and **844**, afforded a 36% isolated yield of **842**, a result of the expected syn facial mode of reaction. Thus, the reaction of the 16 α -carbamate **843** is seen to give complementary stereochemical results to that from the 16 α -pivalate **838**. From a synthetic viewpoint, this approach involves relatively few steps, each of which can be expediently conducted on a large or small scale. The flexibility of this sequence lies in its potential convergence with a wide assortment of available cuprate side-chain components. However, the yield of each step in this procedure is not particularly high.

[2,3]-Wittig Sigmatropic Rearrangement. The [2,3]-Wittig rearrangement of *n*-butyllithium generated dianion of propargyl ether **847** produces a mixture of the two C-22 stereoisomers of **849** with the natural C-20 chirality and the 25-hydroxy group (Figure 178).⁴⁵⁰ The reaction of the corresponding MOM-

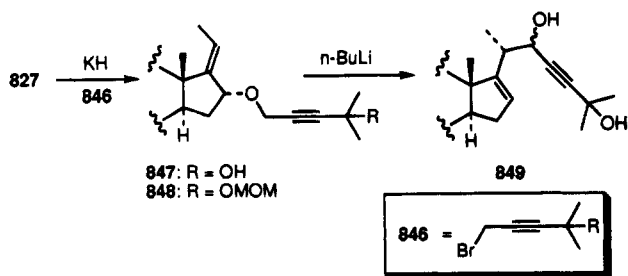


Figure 178.

protected derivative **848** failed to give the expected [2,3]-Wittig product. Instead, an unstable compound resulting from the elimination of the protected hydroxy group was obtained. The side chain of **849** could be readily converted to that of either the vitamin D₂ or vitamin D₃ types.

4. Construction of the Vitamin D₂ Side Chain

Claisen Rearrangement. One of the most useful routes to construct the vitamin D₂ side chain is the Claisen rearrangement of appropriate allylic alcohols **852** or **854**, which permits control of the configuration at C-24, and also provides the desired *trans* geometry of the 22-double bond (Figure 179).^{187,451} This method

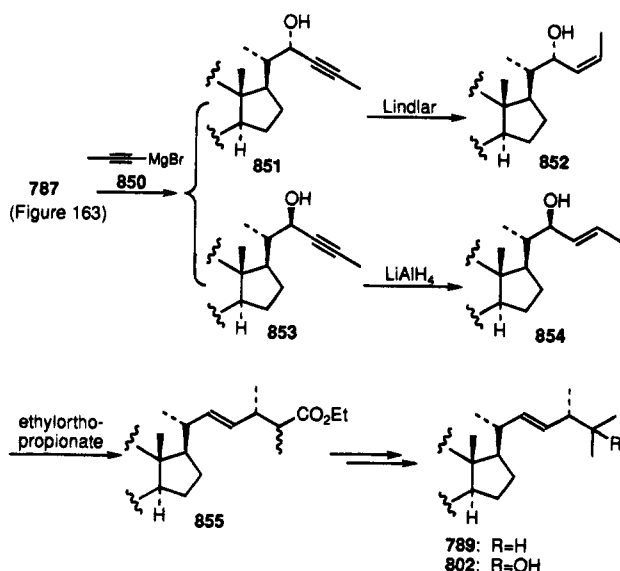


Figure 179.

was first developed by Sucrow.⁴⁵²⁻⁴⁵⁴ The aldehyde **787** reacted with propynylmagnesium bromide (**850**) to give a mixture of easily separable acetylenic alcohols **851** and **853** (1:1). Semihydrogenation of **851** with Lindlar catalyst gave the *cis*-allylic alcohol **852** which reacted with ethyl orthopropionate in a stereospecific Claisen rearrangement through a chair-like transition state to give in good yield a mixture of the two esters **855**. The reaction of the *trans*-ethylenic alcohol **854**, obtained by lithium aluminum hydride reduction of **853**, with ethyl orthopropionate gave the same diester, which could be easily converted to a substance with the vitamin D₂ side chain. Thus, through Claisen rearrangement of *cis*- or *trans*-ethylenic alcohol, it is possible to control the stereochemistry at C-24.

S_N2' Substitution. Mouriño's approach (Figure 180)^{183,455,456} involves a stereospecific S_N2' type dis-

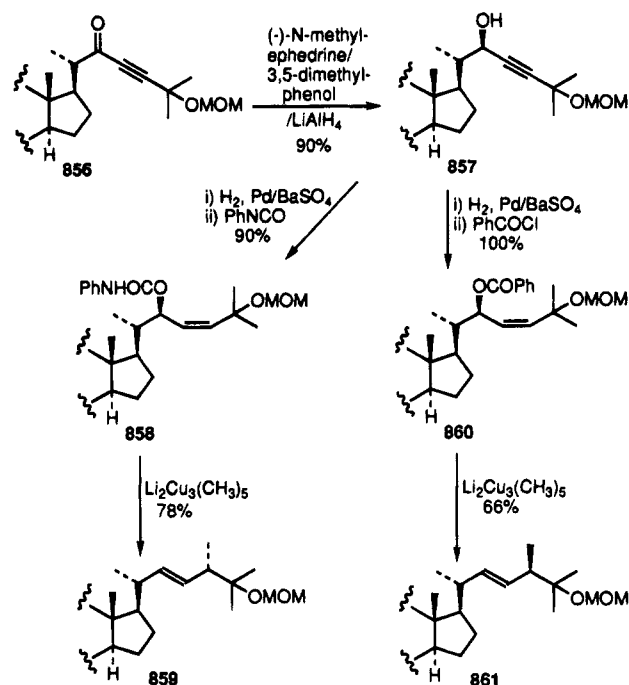


Figure 180.

placement of an allylic carbamate by cuprates [Li₂-Cu₃(CH₃)₅], a process which is known to take place in a *syn* fashion with carbamates and in an *anti* one with benzoates and other esters.⁴⁵⁷⁻⁴⁵⁹ Reduction of easily accessible ketone **856** with the LiAlH₄/(-)-*N*-methylephedrine/3,5-dimethylphenol system afforded the major propargyl alcohol **857** (in a C-22 epimeric ratio of 13:1 in 90% yield). When using the *d*-(+) enantiomer, the selectivity is much lower (1:2.5, 70% conversion). Semihydrogenation of **857** followed by direct treatment with PhNCO or PhCOCl afforded **858** or **860**, which upon treatment with Li₂Cu₃(CH₃)₅ furnished the natural (24*S*) vitamin D₂ side chain **859** or the unnatural (24*R*) isomer **861**. The *syn* S_N2' substitution of carbamate **858** is very clean and proceeds with complete stereoselectivity. In the case of benzoate **858**, however, 10% of the C-24 epimer **859** accompanied the desired isomer **861**.

Solvolysis of a Cyclopropane Intermediate. Solvolysis of cyclopropyl carbinols **863** with catalytic amounts of *p*-toluenesulfonic acid in aqueous dioxane (Figure 181) directly produces the 1α,25-dihydroxy-

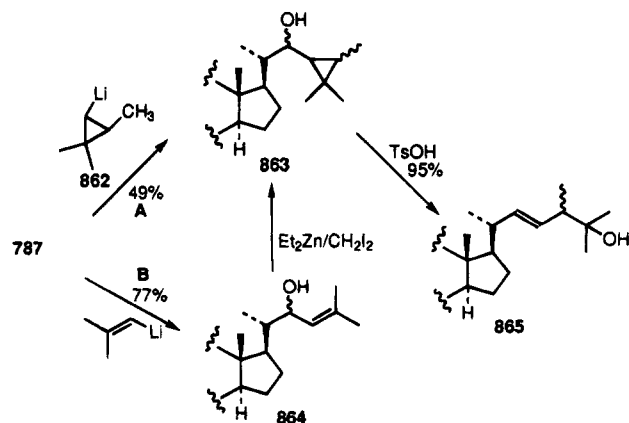


Figure 181.

vitamin D₂ side chain.⁴⁶⁰ The reaction of all four C-22

and C-23 diastereomers (**863**) leads to stereoselective production of the same *trans*-olefin, probably as a consequence of the stability of the cation, whose lifetime is long enough to allow isomerization to the more stable *trans* geometry. The cyclopropyl carbinols could be prepared through two pathways. In route A, aldehyde **787** was treated with cyclopropyllithium **862** (derived from cyclopropanation of isobutene) in presence of TMEDA to give the mixture of two diastereoisomers **863**. In the alternative route B leading to **863**, the same aldehyde **787** was reacted with dimethylvinylolithium to give an epimeric mixture of **864** (77%). Cyclopropanation of the mixture with diethylzinc/methylene iodide afforded **863**, which was converted to **865** without prior purification.

B. Approaches to CD-Ring-Modified Vitamin D Analogues

1. C-11 Analogues

The hypothesis that the C-11 position is a biologically important position⁴⁶¹ derives from the presence of C-11 substituents in other steroid hormones and analogues (e.g., cortisol and RU-486), thus leading to C-11-modified vitamin D as an attractive target. There are three common strategies for introduction of a C-11 hydroxyl group. The first is selective hydroxylation followed by photochemical irradiation of the appropriate 7-dehydrosteroids.⁴⁶²⁻⁴⁶⁵ The prototypical sequence **866** to **870** is shown in Figure 182

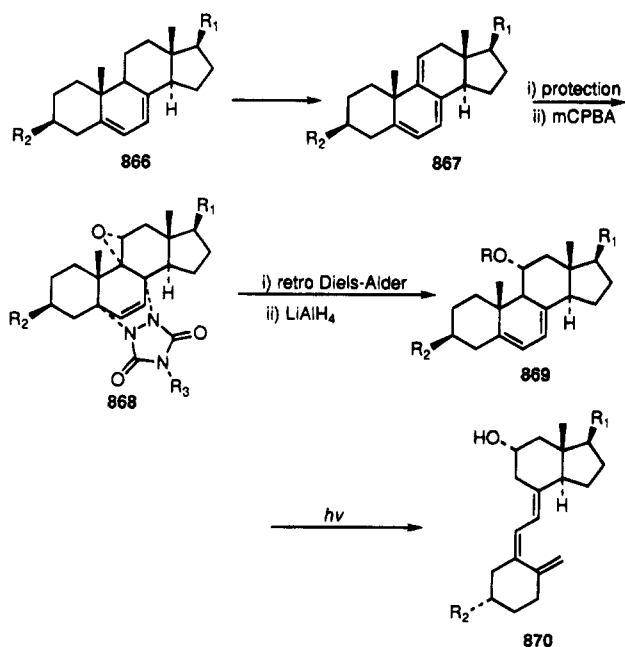


Figure 182.

and the details of such a sequence have been discussed in a previous section (section II.B).

Okamura's convergent approach⁴⁶⁶ shown in Figure 183 relies mainly on a samarium-promoted epoxide opening of an epoxy propargyl alcohol. The epoxy ketone **97** was synthesized via diastereoselective epoxidation of Grundmann's enone **871** with alkaline hydrogen peroxide (H_2O_2). The coupling of **97** with an appropriate A-ring enyne **872** and then esterification gave the epoxypropargyl- β -alcohol benzoate

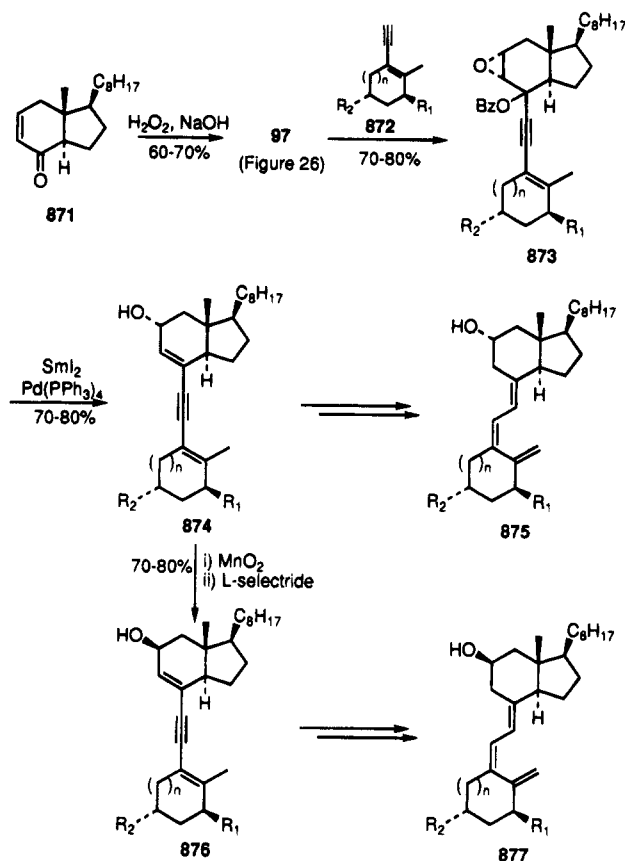


Figure 183.

873. The reaction of the latter with SmI_2 in the presence of $\text{Pd}(0)$ smoothly produced the 11α -dienynol **874**, which by known steps was converted to the 11α -hydroxyvitamin D analogues **875**. The 11β isomer **877** could be easily synthesized through oxidation of **874** followed by reduction with the sterically hindered L-selectride.

In a synthesis of 11β -fluoro- 1α -hydroxyvitamin D_3 (**880**) (Figure 184), part of a quest for experimental

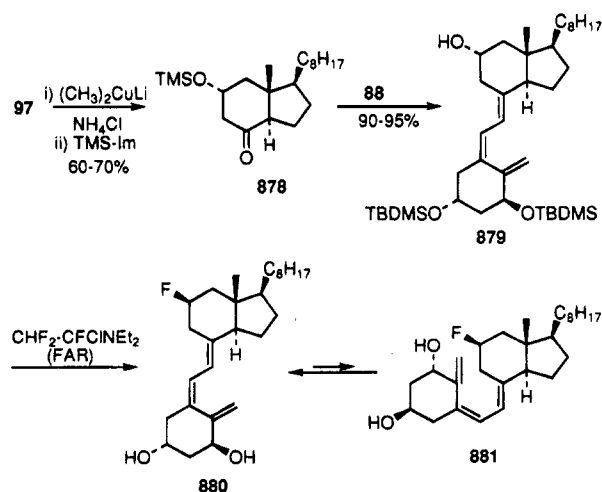


Figure 184.

evidence for the folded 6-*s-cis*-vitamin D conformation, the De Clercq laboratory in Belgium⁹⁵ synthesized 11α -hydroxyvitamin D analogues through coupling of protected 11α -hydroxy Grundmann's ketone **878** with A-ring phosphine oxide **88**. C-11 alkyl-substituted vitamin D analogues have been synthe-

sized via a similar strategy in the Mouriño laboratory in Spain⁴⁶⁷ and the De Clercq–Vandewalle laboratory in Belgium.^{468,469} Mouriño's procedure (Figure 185)

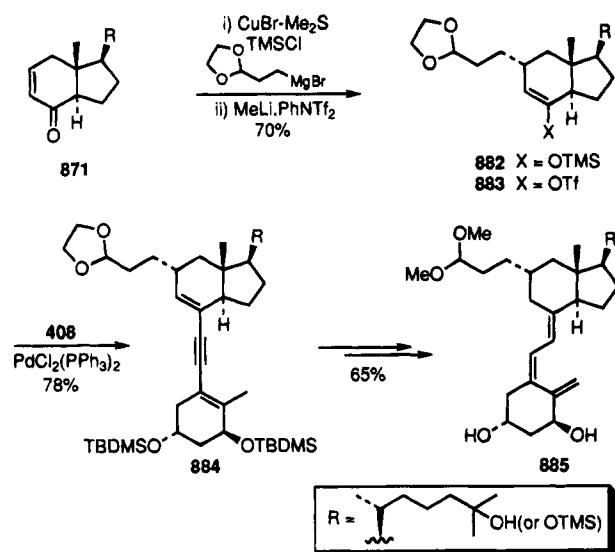


Figure 185.

relies on the conjugate addition of an organocopper reagent to 25-substituted Grundmann's enone **871** in the presence of trimethylchlorosilane. The resulting silyl enol ether **882** was converted, by metalation with CH_3Li and triflation with *N*-phenyl triflimide, to the vinyl triflate **883**, which was coupled with A-ring enyne **408** via the cross coupling approach. Attempts to trap the enolate from the 1,4-conjugate addition directly with PhNTf_2 were not successful. Using Saegusa's method,⁴⁷⁰ the preparation of Grundmann's enone **871**, through Pd(II)-promoted reaction of the kinetic enol silyl ether, was reported to be more efficient than the alternative two-step, selenoxide elimination procedure (Figure 186).

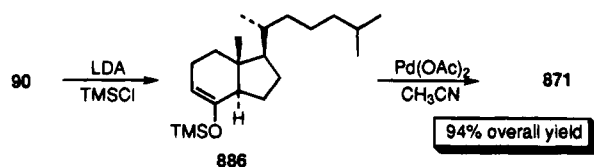


Figure 186.

The De Clercq–Vandewalle synthesis involves initial preparation of 11-substituted Grundmann's ketone for Wittig coupling and also allows preparation of 11 β -alkylvitamin D analogues (Figure 187). The C-11 stereochemistry of the vitamin D analogues was established through ^1H NMR and NOE experiments, the latter indicating the proximity of H-11 β and CH_3 -18 in 11 α -series (for **887** and **889**). The yields of the coupling to phosphine oxide **88**, in the 11 α -series varied from 70% to 90%. However, in the β -series, under the same conditions, only 15–30% of the desired products were obtained together with recovered starting material. The decrease of reactivity in the β -series may be due to a steric affect resulting from a conformational change of the C-ring from chair to twist boat upon 1,3-interaction of 11 β -substituents with the 18-methyl group.

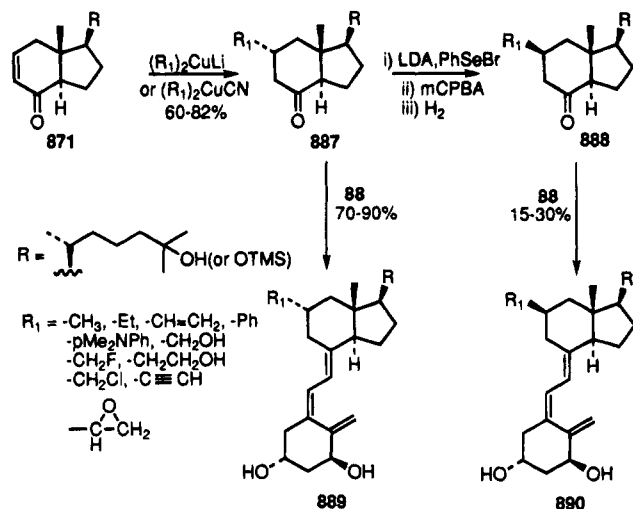


Figure 187.

2. C-14 Modification

Attempts to synthesize 14 α -fluoro- and 9 α -fluoro-vitamin D analogues have not succeeded (Figure 188).⁴⁷¹ Fluorination of the thermodynamic silyl enol

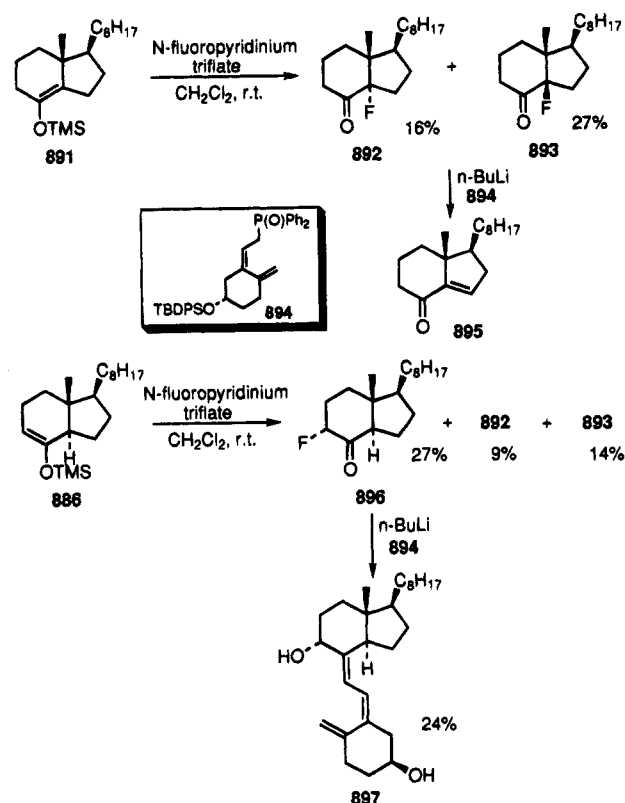


Figure 188.

ether **891** with *N*-fluoropyridinium triflate in refluxing methylene chloride gave 16% 14 α -fluoro Grundmann's ketone **892** and 27% of its 14 β -isomer **893**. Attempted coupling of either of these fluorinated ketones with the conjugate base of phosphine oxide **894** resulted in elimination of HF to give the α,β -unsaturated ketone **895**. The reaction of the kinetic enol silyl ether **886** with *N*-fluoropyridinium triflate gave 9 α -fluoro Grundmann's ketone **896** in 27% yield together with 9% 14 α -fluoro **892** and 14% 14 β -fluoro compound **893**. Horner–Wittig coupling of the 9 α -

fluoro ketone **896** with phosphine oxide **894** under standard conditions did not give the desired product. After hydrolysis, compound **897** with the novel $\Delta^{7,8}$ -*Z* geometry was isolated in 24% yield. In an independent investigation, Mouriño's laboratory reported this same compound in a completely different manner.⁴⁷²

An effort directed toward the synthesis⁴⁷³ of 14 α -methylvitamin D₃ started from *trans*-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (**898**), an intermediate in a terpene synthesis (Figure 189). Addition of

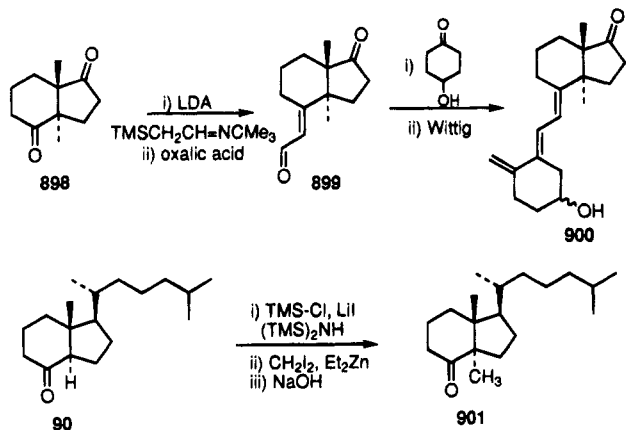


Figure 189.

trimethylsilyl aldimine to the latter diketone followed by acid hydrolysis was reported to be the best method for converting **898** to **899**. Aldol condensation of the latter with 4-hydroxycyclohexanone followed by Wittig reaction with triphenylphosphonium methylide affords triene **900**, but its possible conversion to 14 α -methylvitamin D₃ remains incomplete. However, a recent report by Corey⁴⁷⁴ on the synthesis of 14 α -methyl-Grundmann's ketone **901** from **90** may provide a straightforward solution to preparing this 14-substituted vitamin D analogue.

Okamura's approach (unpublished) to the synthesis of 14 α ,15 α -methylene vitamin D analogues (Figure 190) relies on a hydroxyl directed Simmons–Smith

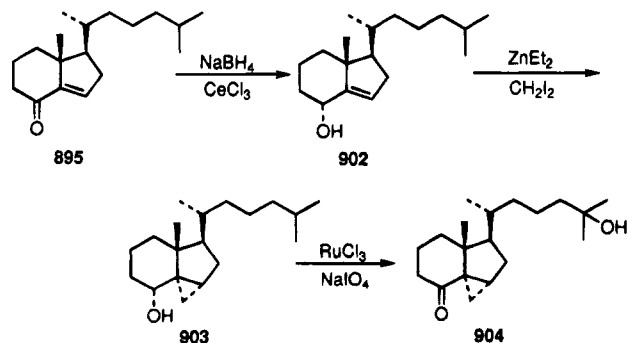


Figure 190.

cyclopropanation of 8 α -alcohol **902**. Treatment of **902**, derived from reduction of **895**,²⁰⁶ with diethyl zinc and methylene iodide, afforded **903** as the only stereoisomer. The study remains incomplete however.

3. C-18 Analogues

The Okamura laboratory⁴⁷⁵ in Riverside and the Mouriño laboratory^{476,477} in Spain have independently

reported the synthesis of C-18 modified analogues for further structure–function analyses (Figure 191).

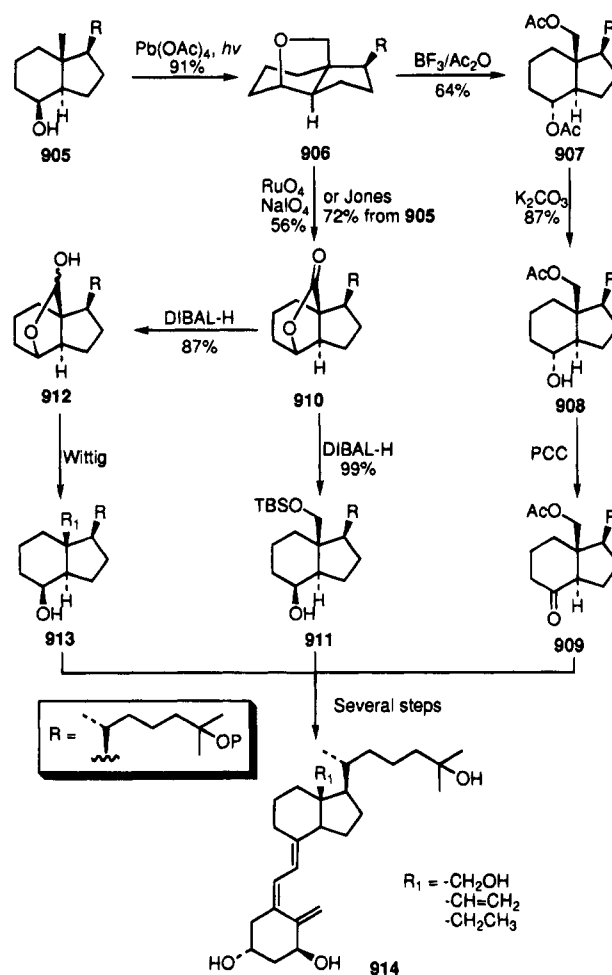


Figure 191.

The key feature of both syntheses involves the 8 β -hydroxyl directed radical oxidation of the 18-methyl group to form the tetrahydrofuranlyl bridged ether **906**. The results of the intramolecular functionalization is not dependent on the nature of the side chain. Okamura's photoinduced lead tetraacetate oxidation condition (Mihailovic's procedure,⁴⁷⁸ 91% yield) affords somewhat higher yield than Mouriño's conditions (57–60%). In the Okamura laboratory, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ mediated ring opening of the bridged ether **906** in acetic anhydride led to the diacetate **907**, a process which occurs with inversion of configuration at C-8. Saponification of **907** with K_2CO_3 in methanol surprisingly gave the monoacetate **908** (87%) despite the presence of the primary acetoxy at C-18, an observation accountable assuming the exceptional, sterically congested nature of the primary alcohol ester. Further transformations afforded **914** ($\text{R} = \text{CH}_2\text{OH}$). In the Mouriño laboratory, the bridged ether **906** was oxidized with $\text{RuO}_4/\text{NaIO}_4$ or Jones' reagent to afford lactone **910**, which upon complete or semireduction with DIBAL-H led to **911** or hemiacetal **912**. Further elaboration of **912** or **911** afforded various C-18 derivatives of Grundmann's ketone, which were coupled with appropriate A-ring fragments to afford various 18-substituted analogues of **914**.

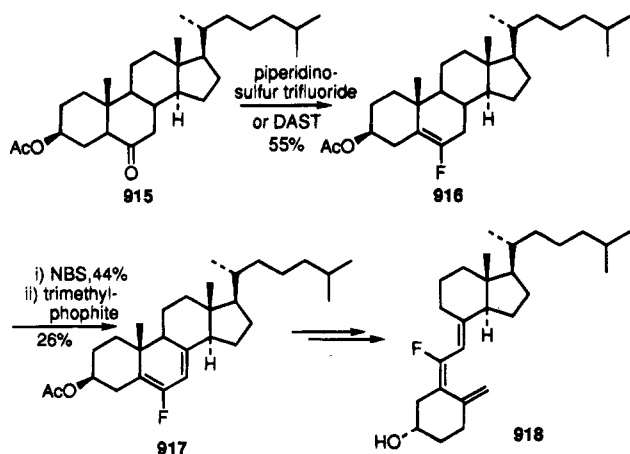


Figure 192.

C. Selected Synthesis of Vitamin D Analogues with Seco-B-Ring Modifications

1. C-6 Analogues

6-Fluorovitamin D₃^{471,479} (Figure 192) is the first vitamin D₃ analogue lacking the C-1 and C-25 hydroxyls observed to bind significantly to the 1,25-D₃ receptor (n-VDR) *in vitro*. It however does not display any biological activity in terms of either intestinal calcium absorption (ICA) or bone calcium mobilization (BCM). Its synthesis is relatively straightforward, employing the classical irradiation approach starting from the known 6-fluorocholesteryl acetate (916).

To investigate the influence of C-6 substituents on the equilibrium between the 6-*s-trans* conformer and 6-*s-cis* conformer of vitamin D as well as the equilibrium between the latter and previtamin D, 6-methylvitamin D₃ (920) was synthesized using the Mazur solvolysis approach (Figure 193).⁴⁸⁰ Addition of

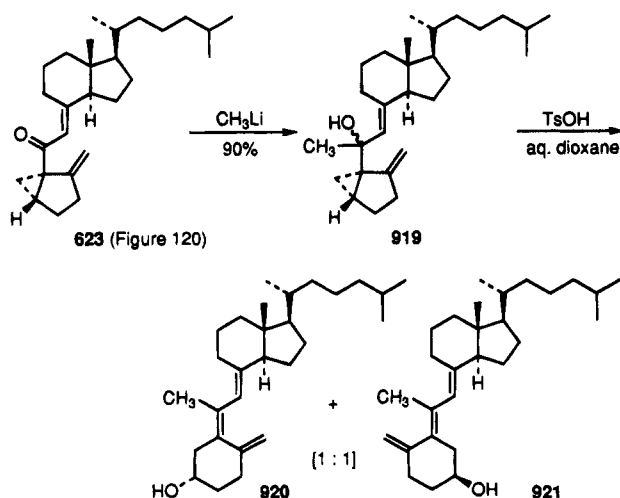


Figure 193.

methyl lithium to 6-oxo-3,5-cyclovitamin D₃ 623, obtained in three steps from vitamin D₃, afforded a 3:1 mixture of separable epimeric 6-methyl alcohols 919. Solvolysis of either isomer with *p*-toluenesulfonic acid in aqueous dioxane resulted in a 1:1 mixture of 6-methylvitamin D₃ (920) and its 5,6-*trans* isomer 921.

The diastereomeric vitamin D₃-sulfur dioxide adducts 734 undergo regioselective methylation at C-6

with sodium hydride as the base to afford 922 and at C-19 with lithium tetramethyl piperidide to afford 923 (Figure 194).³⁸³ Reductive desulfonylation of the

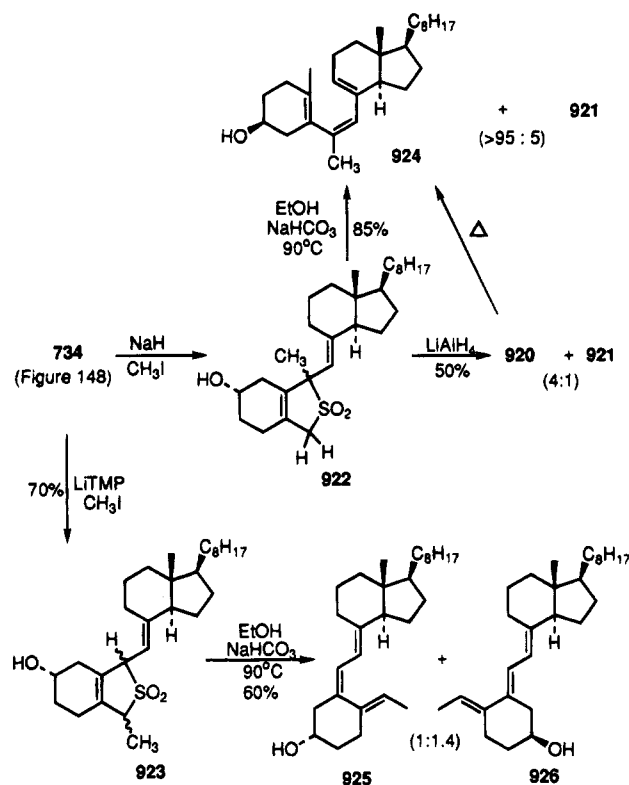


Figure 194.

mixture of 6-methyl adducts 922 (LiAlH₄, Et₂O, reflux) gave 40% 6-methylvitamin D₃ 920 together with 10% of its *trans*-isomer 921. However, thermolysis of 922 (EtOH, NaHCO₃, 90 °C) yielded 6-methylprevitamin D₃ (924) as the major product (>95%) together with minor amounts of 6-methyl-5,6-*trans*-vitamin D₃ (921, <5%; 85% combined yield). Under thermolysis conditions, the predominantly formed primary product, 6-methylvitamin D₃ 920, is isomerized completely to the thermodynamically more stable 6-methylprevitamin D₃ (924).

As indicated above, the methyl iodide–lithium tetramethylpiperidide (LiTMP) route via 734 afforded an unresolvable mixture of four diastereomers of 923 (70%), which upon thermolysis, gave 19-methylvitamin D₃ (925) and its 5,6-*trans*-isomer 926. All of the C-6 and C-19 protons of 734 are relatively acidic, and could be exchanged with deuterium by equilibration with deuterium oxide in DMF in the presence of potassium *tert*-butoxide at room temperature, a subject which will also be discussed later (section IV.B).³⁸³

2. C-19 Analogues

A biologically significant triene analogue of 1,25-D₃ is its 19-nor derivative 929 (Figure 195), a locked vitamin D analogue incapable of equilibration with the corresponding previtamin. Another analogue of 1,25-D₃ also incapable of isomerizing to its previtamin form is 540, discussed earlier in Figure 103. The analogue 929 exhibits similar cell differentiation activity to, but with much less calcemic activity, than the natural hormone 1,25-D₃.¹⁷ The 19-nor analogue 929 was first synthesized by DeLuca⁴⁸¹ via oxidative

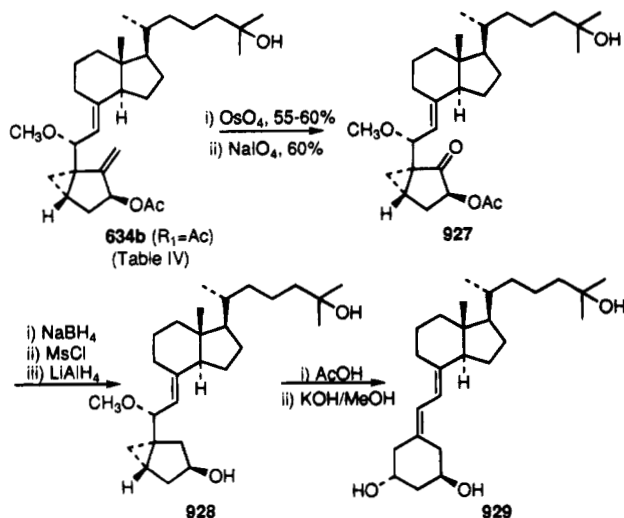


Figure 195.

degradation of a 1 α -hydroxycyclovitamin D **634b** ($R_1 = \text{Ac}$) (Mazur's solvolysis approach). Hydroxylation of the latter cyclovitamin D followed by diol cleavage (NaIO_4) afforded 10-oxo analogue **927**, which was deoxygenated in 3 steps to **928**. Because of the locally symmetric nature of the A-ring in the product, cycloreversion with acetic acid (55 °C, 30 min) followed by saponification furnished **929** as the only product (2% overall yield from **634b**). An improved synthesis (Figure 196) later reported by DeLuca⁴⁸²

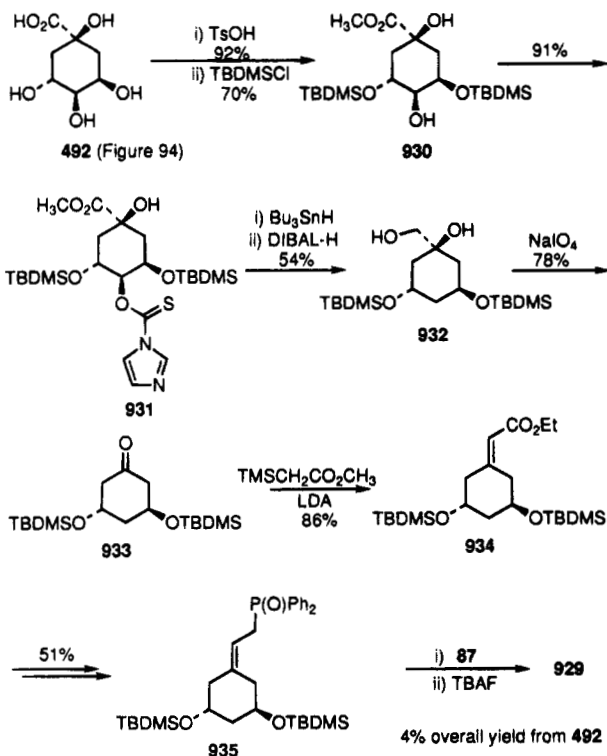


Figure 196.

relied on the synthesis of 19-nor-A-ring phosphine oxide **935** via elaboration of (-)-quinic acid (**492**). Esterification of the latter followed by silylation gave ester **930** in which the secondary alcohol was removed via Barton's procedure and then the ester was reduced to the alcohol **932** with DIBAL-H. Oxidation with NaIO_4 followed by ethyl (trimethylsilyl)acetate/

LDA treatment gave the cyclohexylidene ester **934**. The latter was converted to the 19-nor-A-ring phosphine oxide **935** and then Horner-Wittig condensation with CD-ring fragment **87** yielded after deprotection the 19-nor analogue **929** (4% overall yield from **492**). Through coupling of **87** with the hydrazone of **933** a 6,7-diaza analogue of the 19-norvitamin D has also been synthesized and shows essentially no biological activity in comparison to 1,25- D_3 .⁴⁸³

1 α ,25-Dihydroxy-19-nor previtamin D_3 **941** (Figure 197), an analogue of 1,25- D_3 locked into its pre- D_3

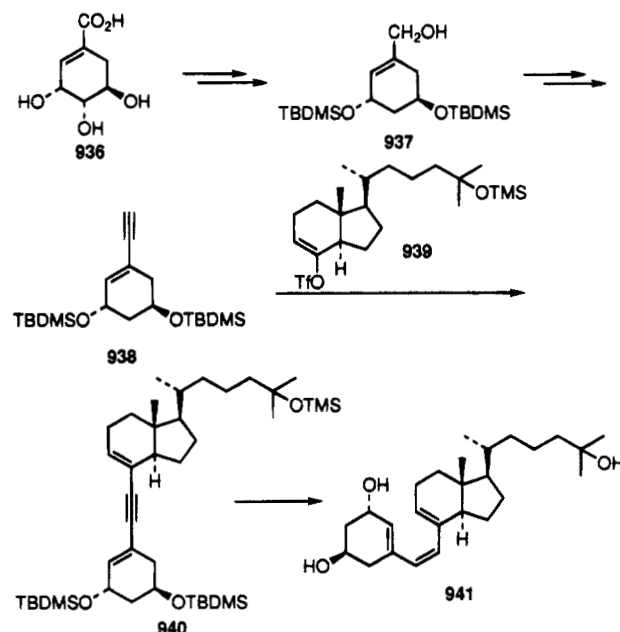


Figure 197.

min form, was synthesized in Mouriño's laboratory⁴⁸⁴ in Spain to explore the biological significance of the previtamin form of 1,25- D_3 . Through a strategy similar to DeLuca's in Figure 196, 19-nor-A-ring enyne **938** was synthesized in eight steps (25% overall yield) from shikimic acid **936**. The enyne **938** was then coupled to CD-ring triflate **939** and then further transformed to give the pre-D locked analogue **941**.

D. Selected Strategies for Modification of the A-Ring

A-ring modification of 1,25- D_3 is the second most extensive area of analogue studies next to side chain modifications. A large variety of strategies have been employed in the synthesis of A-ring analogues, but most deal with general coupling strategies A-H (Figure 7) with only slight modifications of the A-ring related to the natural metabolites, such as C-1 and C-3 hydroxyl modifications. For example, the synthesis of the A-ring diastereomer of 1,25- D_3 (**942**) (Figure 198) entailed an independent preparation of an enantiomeric A-ring enyne *ent*-**408** together with cross coupling with CD-ring fragment **939**.⁴⁸⁵ Selected analogues with more extensive A-ring changes are discussed below although A-ring heterocyclic analogues were discussed earlier (Figure 116).

1. C-1 Analogues

The 1 β -epimer of 1,25- D_3 was easily prepared through oxidation of the 1 α -hydroxyl followed by

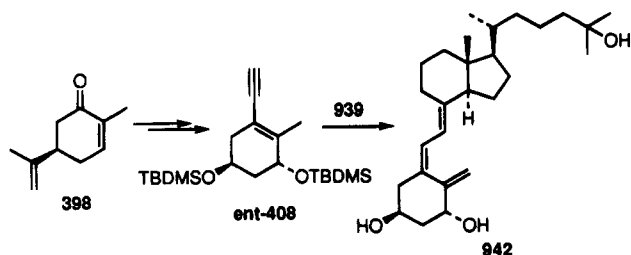


Figure 198.

hydride reduction.^{366,367} Displacement of the mesylate or tosylate of the 1α -hydroxyl with other nucleophiles (e.g. KSAc) led to other 1β -substituted analogues (e.g. 1β -SH-25-D₃).⁴⁸⁶ The 1α -fluoro derivative of 25-hydroxyvitamin D₃ (**946**, Figure 199) was

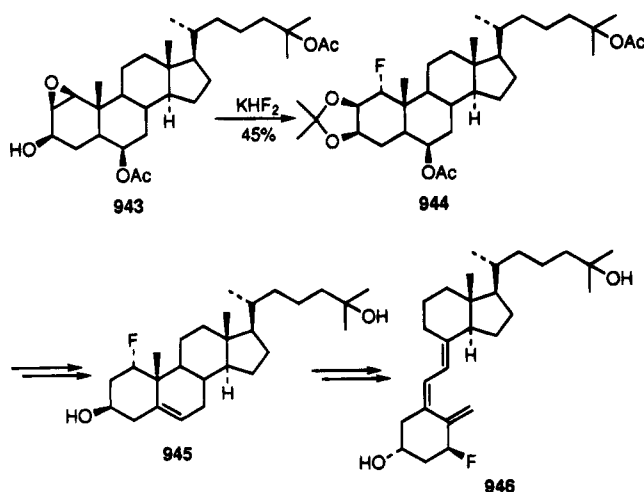


Figure 199.

synthesized via *trans*-diaxial opening of epoxide **943** with potassium hydrogen difluoride, radical deoxygenation of the 2β -hydroxy group, and a series of standard transformations.⁴⁸⁷ The 1α -fluoro analogue **946** was also obtained by modification of Roche's procedure for synthesizing the A-ring phosphine oxide **88** (Figure 72).¹⁰⁷ The key steps in the synthesis (Figure 200) are (diethylamido)sulfur trifluo-

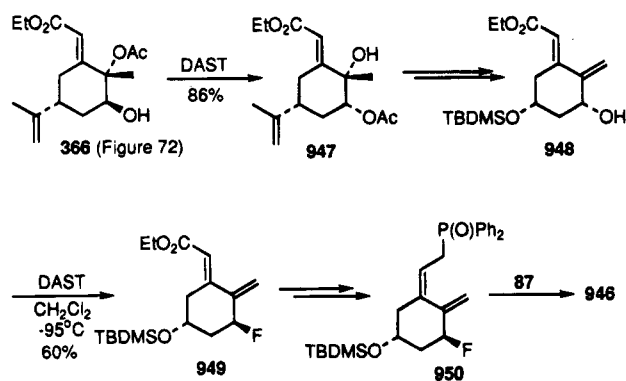


Figure 200.

ride (DAST)-induced epimerization of the *trans*-acetoxy alcohol **366** to *cis* regioisomer **947** and the stereospecific fluorination of alcohol **948** with complete configurational inversion.⁴⁸⁸ Horner–Wittig coupling of the lithium anion of **950** with CD-ring fragment **87**, followed by deprotection, provided the 1α -fluorovitamin **946**.

Posner's approach to A-ring phosphine oxide **88**, which has been discussed in detail previously (Figures 74–76), represents a general method for synthesis of corresponding C-1 and C-2 analogues as outlined in Figure 201. For example, thermal [4 +

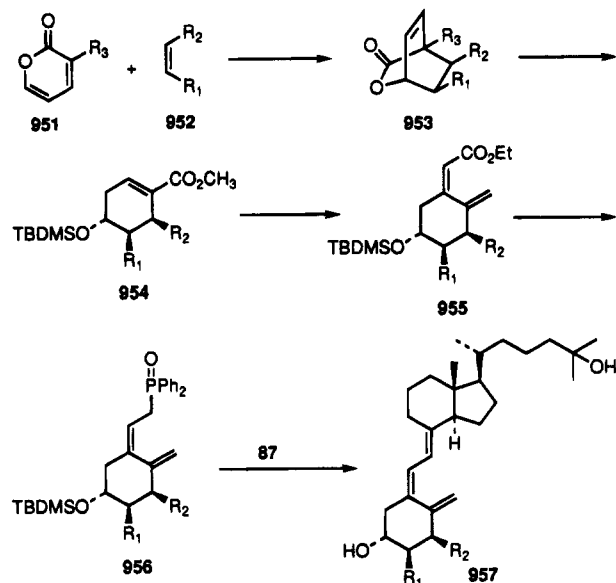


Figure 201.

2] cycloaddition of 3-bromo-2-pyrone (**951**, R₃ = Br) and acrolein (**952**, R₁ = H, R₂ = CHO) afforded adduct **953**, which was converted to 1α -analogues of 1,25-D₃ **957**.^{82f,489–493} By starting with electron-rich dienophiles **952** (R₁ = alkoxy or alkyl; R₂ = alkoxy or silyloxy), the Diels–Alder reaction yielded adducts which were transformed to 2β -analogues of 1,25-D₃.^{494,495} In principle, by replacing the ring oxygen of α -pyrone **951** with other heteroatoms (e.g., NSO₂-Tol), 3β -heteroatom-substituted 3β -deoxy analogues of 1,25-D₃ could be synthesized using the same strategy.⁴⁹⁶

2. C-2 Analogues

Most of the C-2 substituted analogues of vitamin D, such as 2β -fluoro-,⁴⁹⁷ 2α -fluoro,⁴⁹⁸ 2β -hydroxy,⁴⁹⁹ and 2β -hydroxyalkoxy⁵⁰⁰ analogues, were synthesized through C-2 modification of steroid intermediates using the classical synthetic approach (method A, section II.B). Takahashi's synthesis⁵⁰¹ of $1\alpha,2\beta$ -25-trihydroxyvitamin D₃ (**968**, Figure 202) employed a Pd-catalyzed cyclization of (*Z*)-vinyl iodide **965** as the key reaction. Elaboration of *d*-mannitol (**958**) via protection and selective deprotection gave epoxide **962**. The BF₃-mediated epoxide opening of the latter with lithiated derivative **963** afforded **964**, which, upon hydroalumination/iodine quenching and Pd-catalyzed cyclization, was smoothly converted to the intermediate **966** for preparation of 2β -hydroxy A-ring phosphine oxide **967** and then 2β -hydroxy analogue **968**.

In an alternative procedure,⁵⁰² the intermediate **962** was transformed to **966** (Figure 203) by using (3 + 2) cycloaddition of the nitrile oxide **970**, Peterson olefination of **972** and syn elimination of the *o*-nitrophenyl selenoxide **974** as key steps. Both the (3 + 2) cycloaddition and the Peterson reaction are

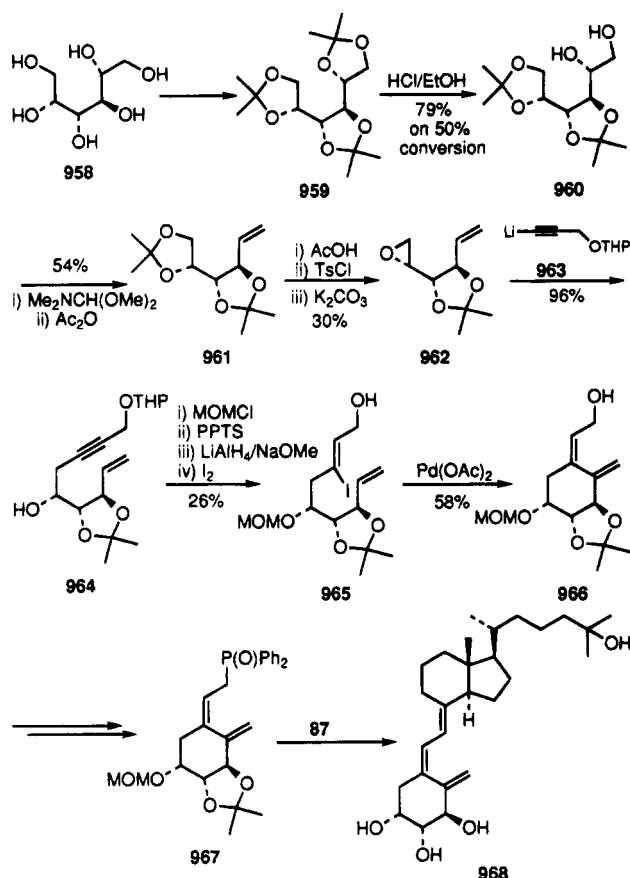


Figure 202.

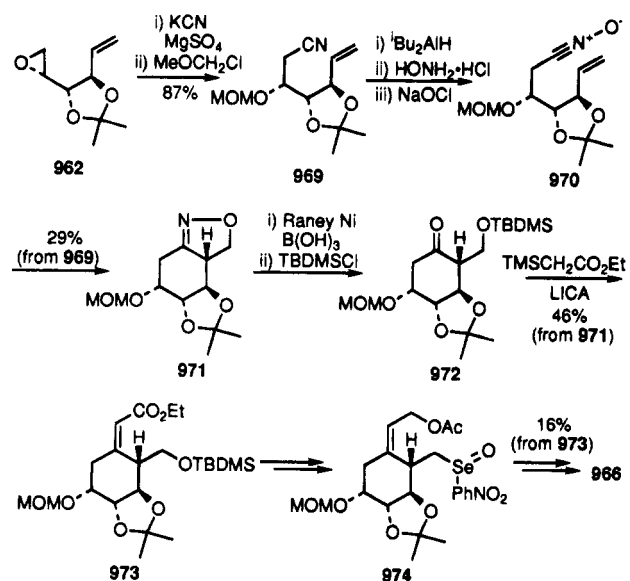


Figure 203.

stereospecific, no other stereoisomers being detectable. In a manner similar to Moriarty's method for the synthesis of the seco-A-ring synthon **592** (Figure 114) for Trost-type palladium coupling, D-arabinose (**975**) was converted to **976** (Figure 204), which upon

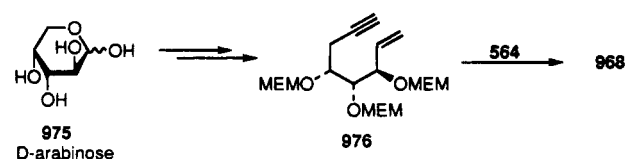


Figure 204.

Pd coupling to vinyl bromide **564** results in another alternative synthesis of 2 β -analogue **968**.⁵⁰³

3. C-3 Analogues

Mitsunobu configurational inversion might be the most direct method for the synthesis of 3-epivitamin D analogues⁵⁰⁴ while 3 β -thiovitamin can be obtained through substitution of the tosylate of vitamin D with thiourea⁵⁰⁵ or thiocyanate⁵⁰⁶ followed by hydrolysis or reduction. Solvolysis⁵⁰⁷ of 6(R)-hydroxy-3,5-cyclo-vitamin D₃ (**624**, Figure 205) with HF, HCl and HBr

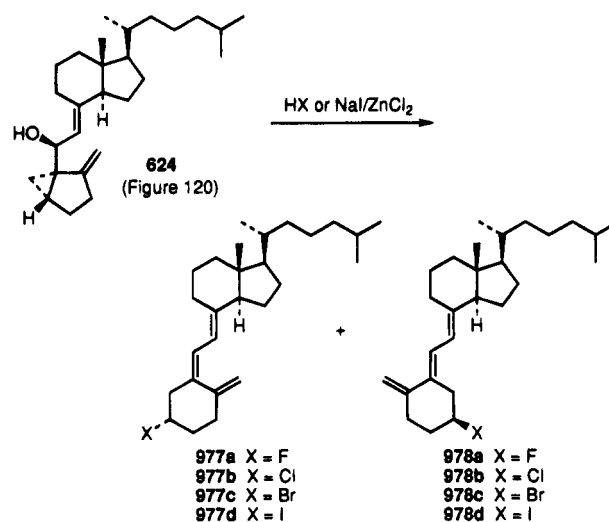


Figure 205.

in nonprotic solvents resulted in 3 β -fluoro, 3 β -chloro, and 3 β -bromo analogues of D₃ together with 10% of 5,6-*trans*-isomers. The solvolysis with HI under the same conditions mainly led to elimination while rearrangement with ZnCl₂ and NaI afforded a 2:3 mixture of iodo derivatives **977d** and **978d**. The classic nucleophilic substitution of sulfonyloxy group of vitamin D with halides or halogenating reagents resulted in mainly elimination products. Fluorination of a derivative of **86** (Figure 20) with (diethyl-amido)sulfur trifluoride (DAST) gave 35% 3 β -fluoro compound **979** with configurational retention (Figure 206).

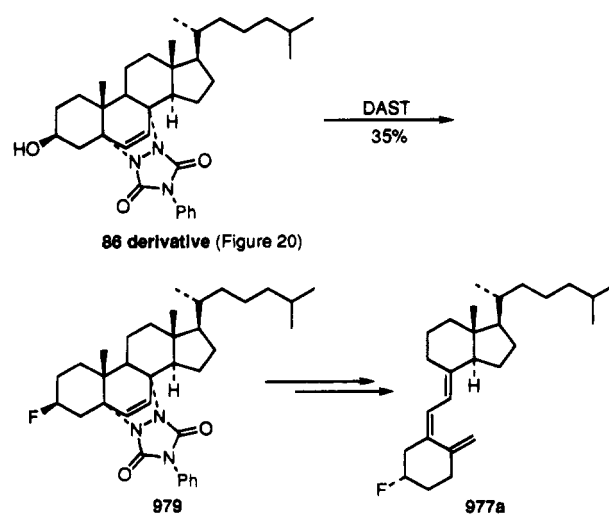


Figure 206.

IV. Other Interesting Syntheses of Vitamin D Analogues and Derivatives

A. Synthesis of Potential Chemotherapeutic Vitamin D Drugs

Because of the broad biological profile of 1,25-D₃ and the promising clinical application of some analogues, the synthesis of potential chemotherapeutic vitamin D drugs has been and will continue to be one of the most interesting goals of vitamin D research. Figure 207 lists some representative examples of

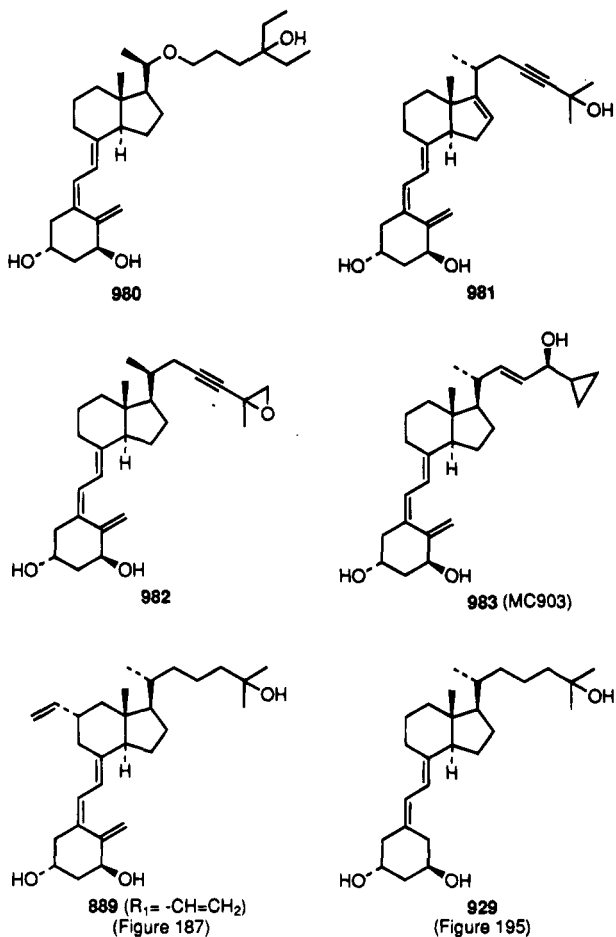


Figure 207.

some interesting structurally modified vitamin D analogues which exhibit an exceptionally high ratio of high cell differentiation activity to low calcemic action, arguably the primary aim of the synthesis of most vitamin D analogues today.¹⁷ 22-Oxa modification (either alone or in combination with other side chain modifications), homologation of the side chain (either 24 or 26,27) and C-20 epimerization are among those structural modifications of 1,25-D₃ which have thus far resulted in a high intrinsic activity of cell differentiation. The first two modifications lead to decreased calcemic activity while 20-epi analogues retain relatively significant calcemic action. Combination of the three modifications has created the vitamin D analogue, the 20-epi-22-oxatrihomovitamin D₃ analogue **980**, which possesses exceptionally high cell differentiation activity (20 000-fold higher than 1,25-D₃). This result has been questioned however.¹⁷ (In a preliminary *in vitro* study 20(*R*)-1α,25-dihydroxy-26,27-dimethyl-22-thia-

vitamin D₃ was reported about 100 000 times as active as 1,25-D₃ to HL-60 cells).⁵⁰⁸ Combination of 23-yne with either a 16-ene as in 1,25-(OH)₂-16-ene-23-yne-D₃ (**981**) or a 25,26-epoxide as in 1α-(OH)-25,26-epoxy-23-yne-20-epi-D₃ (**982**), results in a marked separation of calcemic and cell differentiating activities. The analogue 1α,24*S*-(OH)₂-22-ene-25,27-cyclopropyl-D₃ (**983**, also known as MC-903) is already approved for clinical use in both Europe and the United States as an antipsoriatic drug. The 11α-vinyl-1,25-D₃ (**889**) and the 1,25-(OH)₂-19-nor-D₃ (**929**) analogues are also remarkable in terms of high cell differentiating activity and low calcemic activity. As cited in the Introduction, there continues to be considerable interest in developing new vitamin D drugs for the many new physiological functions which seem to be associated with the action of the hormone 1,25-D₃ and its metabolites. The reader is referred to some of the earlier references cited (section I) for a more comprehensive review of recent progress in these areas.

B. Synthesis of Isotopically Labeled Vitamin D Molecules for Mechanistic Studies

Although there have been considerable advances in the development of structure-function relationships for vitamin D through design, synthesis, and biological studies of a large number of analogues, including the impressive array of structural modifications via the methodologies just cited, our understanding of the mode of action at the molecular level remains limited. The metabolic picture of vitamin D as it transverse the endocrine maze, particularly the precise details of how vitamin D metabolites interact with proteins, is not known. Isotopically labeled vitamin D compounds are therefore of great importance in this regard. Tritium-labeled vitamin D analogues provide an effective tool for studies of metabolic pathways and provide specific information as to the action of enzymes.⁵⁰⁹ A variety of stable deuterium-labeled analogues have been synthesized to study the stereochemistry of the enzymatic hydroxylation and the vitamin/previtamin equilibrium via a [1,7]-sigmatropic shift. In terms of acquisition of a detailed understanding of the three-dimensional organization of the vitamin D-receptor complex, the synthesis of mono- or multi-¹³C-labeled vitamin D compounds will be most useful for studying the topology of vitamin D in the receptor ligand complex (e.g., by direct solid or solution NMR studies). This section briefly outlines recent, but relatively limited studies which have been carried out in this area.

1. Synthesis of Radiolabeled Vitamin D

A number of methodologies have been developed for the synthesis of tritium-labeled vitamin D compounds. The 25-hydroxy-[26,27-³H]vitamin D analogues **985** (Figure 208) have been synthesized

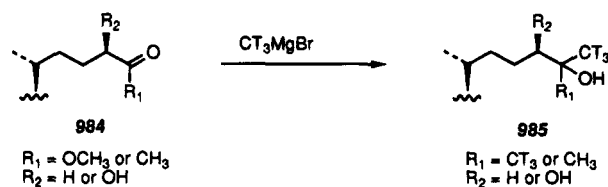


Figure 208.

through addition of tritium-labeled methyl magnesium bromide to the C-25 carbonyl group.^{510–513} Reduction of the 23-yne- and 22-ene-unsaturated side chains of either steroids or vitamin D (Figure 209)

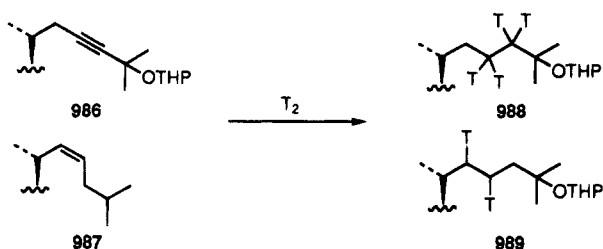


Figure 209.

with tritium gas has resulted in 23,24-T₄-**988** and 22,23-T₂-**989** vitamin D derivatives.^{514,515} Labeled NaBH₄ reduction of a carbonyl group or removal of hydroxyl groups through reduction of tosylates or mesylates with labeled LiAlH₄ or super hydride are common procedures for introduction of tritium at various positions (24-T;⁵¹⁶ 1,2-T;⁵¹⁷ 1β-T;^{518,519} 6-T;⁵²⁰ 1α-T and 1β-T).³⁶⁵ Although ¹⁴C-labeled derivatives are known, only ¹³C-labeled derivatives will be discussed in this review (see section B.3 below).

2. Synthesis of Deuterium-Labeled Vitamin D

Deuterium-labeled reagents are easily available. Because deuterium is a stable isotope, it is much easier to carry out the synthesis of deuterium-labeled compounds. Many deuterium-labeled vitamin D compounds should be easily synthesized via the known approaches A–H (Figure 7) with only slight modifications employing appropriate deuterium-containing reagents.

The penta-deuterated derivative of 1,25-D₃ **1000** (Figures 210–212) has been prepared via the cross-coupling approach (section II.D, method C), which involved independent syntheses of 9,14-dideuterio-CD-ring fragment **993** (Figure 210) and 19,19,19-

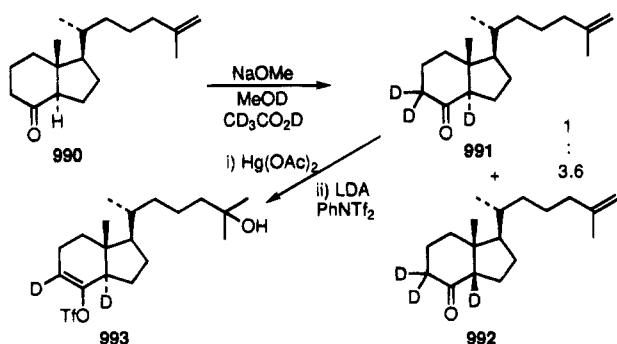


Figure 210.

trideuterio-A-ring enyne **998** (Figure 211), to study the thermal [1,7]-sigmatropic shift of previtamin D to vitamin D.^{72,97,305} Deuteriation of the ketone **990** (derived by oxidation of **101** in Figure 27) with sodium methoxide/methanol-*O*-d₁ exchange followed by acetic acid-*d*₄ quench (three cycles)⁵²¹ gave the desired **991** (98% D₃) along with the C-14 epimerized product **992**. Trapping of the kinetic enolate of **991** with *N*-phenyltrifluoromethane sulfonamide, followed by oxymercuration–demercuration, furnished the labeled CD-ring fragment **993**. The trideuterio-

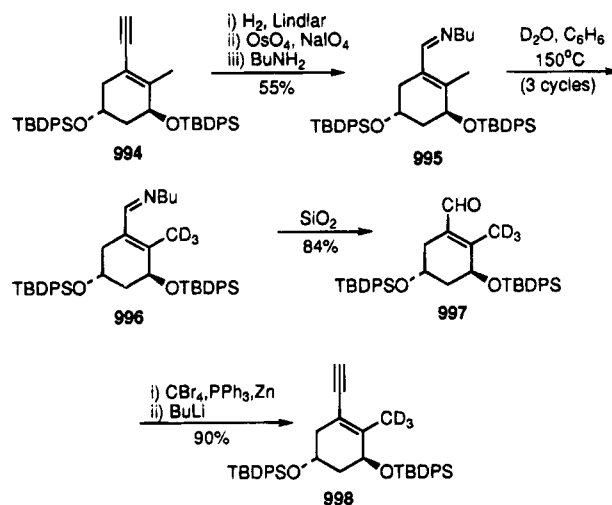


Figure 211.

A-ring enyne **998** was obtained via conversion of the easily accessible A-ring enyne **994** (related to **408**). Successive semihydrogenation (Lindlar), oxidative cleavage (OsO₄/NaIO₄) and *n*-butylamine treatment of **994** provided imine **995**, which underwent clean deuterium exchange (D₂O, benzene, 150 °C, three cycles), wherein no deuterium incorporation was found at the ring allylic position. Flash chromatography of the crude imine **996** resulted in formation of aldehyde **997** (>97% deuterium incorporation), which was converted to the trideuterio A-ring **998** via the Corey–Fuchs procedure. Cross coupling of the deuteriated A-ring **998** with CD-ring **993** (Figure 212) afforded previtamin **999** which undergoes a

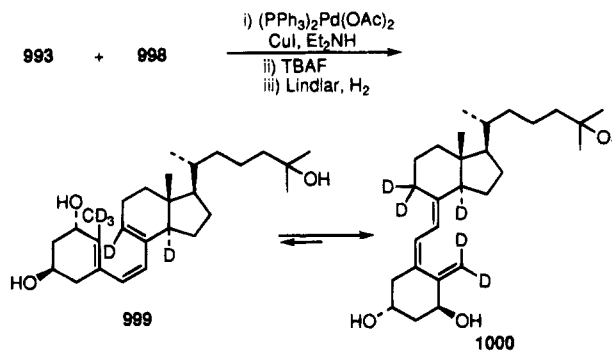


Figure 212.

[1,7]-sigmatropic deuterium shift at 25 °C to penta-deuteriated 1,25-D₃ **1000** (a normal primary kinetic isotope effect (k_H/k_D) of 5.5 was determined). Base-catalyzed (*t*BuOK) exchange of vitamin D–sulfur dioxide adducts of the type **1001** in anhydrous DMF–D₂O (Figure 213), followed by thermal extrusion of SO₂ and photosensitized isomerization, provided 6,19,19-trideuteriovitamin D compounds of the type **1003** with >95% deuterium incorporation. The presence of a 1α-hydroxy group (R₃ = OH) dramatically decreased the efficiency of this sequence.^{522,523}

Other deuterium-labeled compounds such as 24-(*R*)-deuterio-,⁵²⁴ 26-deuterio-,^{525,526} and other vitamin D's⁵²⁷ have also been synthesized via known strategies of side chain construction.

3. Synthesis of ¹³C-Labeled Vitamin D Analogues

¹³C-Enriched reagents are much more expensive than deuteriated reagents. Synthesis of vitamin D

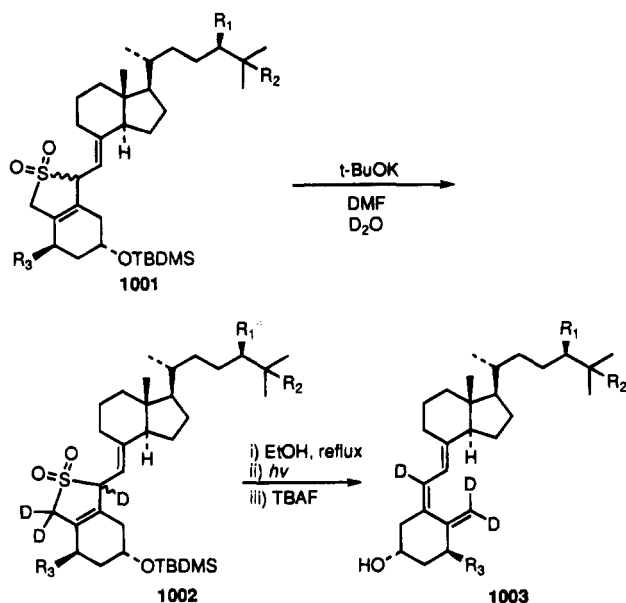


Figure 213.

compounds with ^{13}C label at various positions then is a great challenge for chemists, but these could be especially useful for direct conformational studies of ligands bound to proteins. Measuring the distances between ^{13}C atoms by rotational resonance NMR spectroscopy⁵²⁸ or detecting the NOE effect of the protons attached at ^{13}C -labeled positions via heteronuclear-resolved half-filter experiments⁵²⁹ could provide information on the binding conformation of vitamin D. To date, however, only the synthesis of $1\alpha\text{-}[^{19}\text{-}^{13}\text{C}]\text{hydroxyvitamin D}_3$ has been reported through Wittig olefination of ketone **710** followed by 1α -hydroxylation⁸⁹ (Figure 141). This compound was used only for A-ring conformational analysis by ^{13}C NMR. Recently, the synthesis of 7,9,19-triply ^{13}C -labeled D_3 and 25- D_3 was completed (Zhu and Okamura, unpublished observations).

C. Synthesis of Affinity-Labeled Analogues of Vitamin D⁵³⁰

Affinity labeling is an important biochemical technique to study the amino acid topography of specific binding sites in proteins. It is not surprising therefore that with the increasing accessibility of proteins (e.g., see section I, which discusses DBP, enzymes, and various receptors) which bind vitamin D attention has turned toward developing affinity-labeled analogues of vitamin D. Synthesis of affinity-labeled vitamin D, from the point view of chemistry, has thus far been quite simple. $1\alpha,25\text{-Dihydroxyvitamin D}_3$ 3β -bromoacetate **1005**, an affinity-labeled analogue for studies of $1,25\text{-D}_3$ receptor (n-VDR), was prepared through condensation of appropriately protected vitamin D **1004** and bromoacetic acid (Figure 214).⁵³¹ Binding and competition studies of the labeled analogue **1005** have shown that it is able to block the entry of $1,25\text{-D}_3$ into the active site of n-VDR and is possibly covalently linked to the receptor protein. The photoaffinity-labeled $1,25$ analogue **1006** was also prepared, by condensation of **1004** with N -(4-azido-2-nitrophenyl)glycine followed by deprotection.^{532,533} Similar coupling of radioactive fragments (T-labeled) resulted in radioactive analogues.⁵³⁴⁻⁵³⁶ It was re-

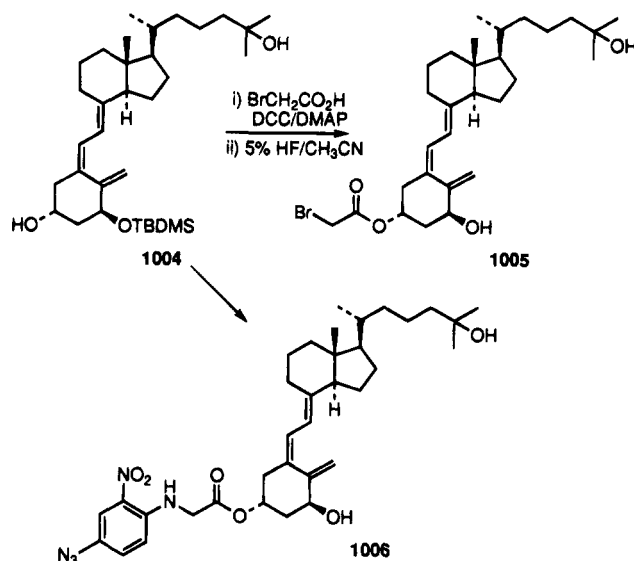


Figure 214.

ported that this label containing the C-3 azido substituent (**1006**) showed a high affinity for receptor.^{537,538}

In the vitamin D research field, the indirect affinity-labeling approach just discussed might still be the only practical method to determine the topography of the binding sites of the hormone-specific proteins (DBP or VDR) as long as a reasonable quantity of ligand bound complex is difficult to obtain.⁵³⁹ It remains for future studies as to whether affinity labeling will provide substantive insight into this dynamic system of ligand and protein. Nevertheless, a combination of affinity-labeling and radioisotope labeling has already allowed the determination, identification, and isolation of certain protein fragments, for example the 11.5 kDa DBP fragment containing the binding pocket for 25-D_3 .⁵⁴⁰ This result may lead to a real advance in learning precisely how the vitamin D ligand binds to protein, perhaps through NMR or crystallographic studies.

V. Concluding Remarks

Figure 215 delineates some of the current frontiers of vitamin D research efforts. At least 11 research areas can be identified as among the frontiers of international efforts in the vitamin D field. Major efforts are under way to develop these areas, both at the basic and applied levels including the development of new drugs for clinical applications. This review has focused principally on only one of these research areas, namely on the synthesis of $1,25\text{-D}_3$ and its analogues. More specifically, this article has sought to provide the chemical audience with a detailed review of the chemical synthesis advances in the area of $1,25\text{-D}_3$, its metabolites, and analogues. One of the major goals at the chemistry-biology interface concerns the development of an understanding of the topology or three-dimensional shape of the hormone $1,25\text{-D}_3$ and ultimately the hormone-receptor complex as discussed in the Introduction. This entails a need for exhaustive structural studies of $1,25$ and its analogues and, of course, the coupling of this information with biological data for developing structure-function analyses. Achieving these goals

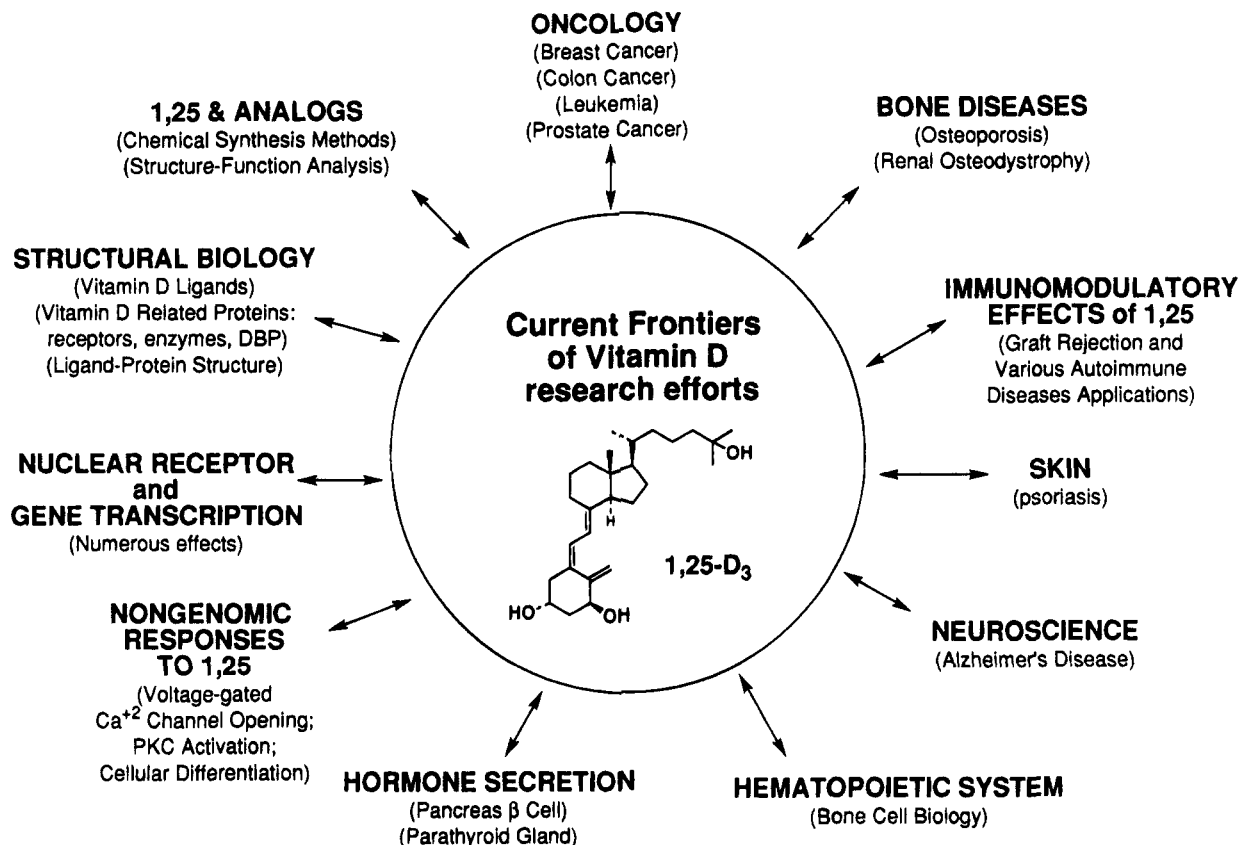


Figure 215.

demands an interdisciplinary approach which is expected to lead to a basic molecular understanding of the mechanism of action of vitamin D and the more intelligent design of analogues with selective physiological action. Many laboratories have been especially heavily engaged in developing analogues that elicit high cellular differentiation and low cellular proliferation while exerting minimal toxic hypercalcemia. The linchpin to achieving these goals requires chemical synthesis developments. Despite the many advances in vitamin D synthetic developments in total and partial syntheses in recent years, target-directed efforts to solve specific biological problems are gaining increasing importance. It is hoped that the reader will in fact develop an appreciation of some of the specific biological problems posed in Figure 215 by following up on some of the leading references provided in the Introduction. The recent review by Bouillon et al.,¹⁷ co-authored by one of the authors of the present article, is suggested as a possible starting point. The present article should provide leading references to the synthetic chemist who is interested in solving some of the contemporary biological problems via chemical approaches. Perhaps, the chemistry described in this article may be useful in other areas of chemistry or biology as well. At least we hope so!

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VII. References for Text

Please note that article titles are given immediately following the journal citations.

- (1) Norman, A. W. *J. Cell. Biochem.* **1992**, *49*, 1–3 and accompanying articles (pp 1–58). Vitamin D Research Frontiers.
- (2) Uskokovic, M. R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1783 and accompanying articles (pp 1783–1896). Recent Advances in Vitamin D Chemistry and Pharmacological Activity.
- (3) Norman, A. W., Bouillon, R., Thomasset, M., Eds. *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Walter de Gruyter: Berlin, 1994.
- (4) (a) Shah, B. R.; Finberg, L. *J. Pediatr.* **1994**, *125*, 487–490. Single-day Therapy for Nutritional Vitamin D-deficiency Rickets: A Preferred Method. (b) Glorieux, F. H. *Metab., Clin. Exp.* **1990**, *39*, 10–12. Calcitriol Treatment in Vitamin D-Dependent and Vitamin D-Resistant Rickets. (c) Wilton, P. *Can. Med. Assoc. J.* **1995**, *152*, 1516–1517. Cod-Liver Oil, Vitamin D and the Fight Against Rickets.
- (5) Fournier, A.; Morinière, Ph.; Yverneau-Hardy, P.; Westeel, P. F.; Mazouz, H.; El Esper, N.; Ghazali, A.; Boudailliez, B. *Néphrologie* **1995**, *16*, 165–190. Traitement Vitaminique D et Ostéodystrophies Rénales: Indications et Modalités (Optimal Use of 1- α Hydroxy Vitamin-D₃ Derivatives in Renal Osteodystrophy).
- (6) Nordin, B. E. C.; Morris, H. A. *J. Cell. Biochem.* **1992**, *49*, 19–25. Osteoporosis and Vitamin D.
- (7) (a) Morimoto, S.; Yoshikawa, K.; Kozuka, T.; Kitano, Y.; Imanaka, S.; Fukuo, K.; Koh, E.; Onishi, T.; Kumahara, Y. *Calcif. Tissue Int.* **1986**, *39*, 209–212. Treatment of Psoriasis Vulgaris by Oral Administration of 1 α -Hydroxyvitamin D₃—Open-Design Study. (b) Morimoto, S.; Onishi, T.; Imanaka, S.; Yukawa, H.; Kuzuka, T.; Kitano, Y.; Yoshikawa, K.; Kumahara, Y. *Calcif. Tissue Int.* **1986**, *38*, 119–122. Topical Administration of 1,25-Dihydroxyvitamin D₃ for Psoriasis: Report of Five Cases.
- (8) Kragballe, K. *J. Cell. Biochem.* **1992**, *49*, 46–52. Vitamin D Analogues in the Treatment of Psoriasis.
- (9) A leading reference on the influence of vitamin D analogues to the pathomechanisms of psoriasis: van de Kerkhof, P. C. M. *Br. J. Dermatol.* **1995**, *132*, 675–682. Biological Activity of Vitamin D Analogues in the Skin, with Special Reference to Antipsoriatic Mechanisms.
- (10) (a) Petrini, M.; Caracciolo, F.; Carulli, G.; Conte, A.; Sabbatini, A.; Mattii, L.; Grassi, B. *Acta Haematol.* **1993**, *89*, 184–188.

- Vitamin D₃ Administration and Multidrug Resistance in Acute Nonlymphoblastic Leukemia. (b) Inaba, M.; Koyama, H.; Hino, M.; Okuno, S.; Terada, M.; Nishizawa, Y.; Nishino, T.; Morii, H. *Blood* **1993**, *82*, 53–59. Regulation of Release of Hepatocyte Growth Factor From Human Promyelocytic Leukemia Cells, HL-60, by 1,25-Dihydroxyvitamin D₃, 12-*O*-Tetradecanoylphorbol 13-Acetate, and Dibutylryl Cyclic Adenosine Monophosphate.
- (11) (a) A review on vitamin D and cancer: Eisman, J. A. *Vitamin D and Cancer: New Insight into Vitamin D Physiology and Potential for Cancer Therapy*. In *Bone and Mineral Research*; Heersche, J. N. M., Kanis, J. A., Eds.; Elsevier: Amsterdam, 1994; Vol. 8, pp 45–76. (b) Gross, M.; Kost, S. B.; Ennis, B.; Stumpf, W.; Kumar, R. *J. Bone Miner. Res.* **1986**, *1*, 457–467. Effect of 1,25-Dihydroxyvitamin D₃ on Mouse Mammary Tumor (GR) Cells: Evidence for Receptors, Cellular Uptake, Inhibition of Growth and Alteration in Morphology at Physiological Concentrations of Hormone. (c) Wijngaarden, T. V.; Pols, H. A. P.; Buurman, C. J.; van den Bemd, G. J. C. M.; Dorssers, L. C. J.; Birkenhäger, J. C.; van Leeuwen, J. P. T. M. *Cancer Res.* **1994**, *54*, 5711–5717. Inhibition of Breast Cancer Cell Growth by Combined Treatment with Vitamin D₃ Analogues and Tamoxifen.
 - (12) Skowronski, R. J.; Peehl, D. M.; Feldman, D. *Endocrinology* **1995**, *136*, 20–26. Actions of Vitamin D₃ Analogs on Human Prostate Cancer Cell Lines: Comparison with 1,25-Dihydroxyvitamin D₃.
 - (13) Connor, R. I.; Rigby, W. F. C. *Biochem. Biophys. Res. Commun.* **1991**, *176*, 852–859. 1 α ,25-Dihydroxyvitamin D₃ Inhibits Productive Infection of Human Monocytes by HIV-1.
 - (14) Saporito, M. S.; Brown, E. R.; Hartpence, K. C.; Wilcox, H. M.; Vaught, J. L.; Carswell, S. *Brain Res.* **1994**, *633*, 189–196. Chronic 1,25-Dihydroxyvitamin D₃-Mediated Induction of Nerve Growth Factor mRNA and Protein in L929 Fibroblasts and in Adult Rat Brain.
 - (15) Saporito, M. S.; Wilcox, H. M.; Hartpence, K. C.; Lewis, M. E.; Vaught, J. L.; Carswell, S. *Exp. Neurol.* **1993**, *123*, 295–302. Pharmacological Induction of Nerve Growth Factor mRNA in Adult Rat Brain.
 - (16) Carswell, S. *Exp. Neurol.* **1993**, *124*, 36–42. The Potential for Treating Neurodegenerative Disorders with NGF-Inducing Compounds.
 - (17) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200–257. Structure-Function Relationships in the Vitamin D Endocrine System.
 - (18) Walters, M. R. *Endocr. Rev.* **1992**, *13*, 719–764. Newly Identified Actions of the Vitamin D Endocrine System.
 - (19) Brommage, R.; DeLuca, H. F. *Endocr. Rev.* **1985**, *6*, 491–511. Evidence that 1,25-Dihydroxyvitamin D₃ is the Physiologically Active Metabolite of Vitamin D₃.
 - (20) DeLuca, H. F. *FASEB J.* **1988**, *2*, 224–236. The Vitamin D Story: A Collaborative Effort of Basic Science and Clinical Medicine.
 - (21) Ross, T. K.; Darwish, H. M.; DeLuca, H. F. *Vitam. Horm.* **1994**, *49*, 281–326. Molecular Biology of Vitamin D Action.
 - (22) A leading review on the classical actions of 1,25-(OH)₂D₃: DeLuca, H. F.; Burmester, J.; Darwish, H.; Krisinger, J. *Molecular Mechanism of the Action of 1,25-Dihydroxyvitamin D₃*. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1129–1143.
 - (23) (a) Weishaar, R. E.; Simpson, R. U. *Endocr. Rev.* **1989**, *10*, 351–365. The Involvement of the Endocrine System in Regulating Cardiovascular Function: Emphasis on Vitamin D₃. (b) Bikle, D. D.; Pillai, S. *Endocr. Rev.* **1993**, *14*, 3–19. Vitamin D, Calcium, and Epidermal Differentiation. (c) DeLuca, H. F. The Evolution of Vitamin D from a Nutritional Factor to a Multifunctional Hormone, Vitamin D: Past, Present, and Future. In *The Second International Forum on Calcified Tissue and Bone Metabolism*; Suda, T., Ed.; Chugai Pharmaceutical Co., Ltd.: Tokyo, 1993; pp 6–11. (d) Fraser, D. R. *The Lancet* **1995**, *345*, 104–107. Vitamin D.
 - (24) Reichel, H.; Koeffler, H. P.; Norman, A. W. *New Engl. J. Med.* **1989**, *320*, 980–991. The Role of Vitamin D Endocrine System in Health and Disease.
 - (25) Reichel, H.; Norman, A. W. *Annu. Rev. Med.* **1989**, *40*, 71–78. Systemic Effects of Vitamin D.
 - (26) Audran, M.; Kumar, R. *Mayo Clin. Proc.* **1985**, *60*, 851–866. The Physiology and Pathophysiology of Vitamin D.
 - (27) Bikle, D. D. *Endocr. Rev.* **1992**, *13*, 765–784. Clinical Counterpoint: Vitamin D: New Actions, New Analogs, New Therapeutic Potential.
 - (28) Haussler, M. R. *Annu. Rev. Nutri.* **1986**, *6*, 527–562. Vitamin D Receptors: Nature and Function.
 - (29) Lowe, K. E.; Maiyar, A. C.; Norman, A. W. *Crit. Rev. Eukar. Gene Exp.* **1992**, *2*, 65–109. Vitamin D Mediated Gene Expression.
 - (30) Haussler, R.; Mangelsdorf, D. J.; Komm, B. S.; Terpening, C. M.; Yamaoka, K.; Allegretto, E. A.; Baker, A. R.; Shine, J.; McDonnell, D. P.; Hughes, M.; et al. *Recent Prog. Horm. Res.* **1988**, *44*, 263–305. Molecular Biology of the Vitamin D Hormone.
 - (31) Henry, H. L.; Norman, A. W. *Metabolism of Vitamin D*. In *Disorders of Bone and Mineral Metabolism*; Coe, F. L., Favus, M. J., Eds.; Raven Press: New York, 1991; pp 149–162.
 - (32) Holick, M. F. *Kidney Int.* **1987**, *32*, 912–929. Vitamin D and the Kidney.
 - (33) Smith, E. L.; Holick, M. F. *Steroids* **1987**, *49*, 103–131. The Skin: The Site of Vitamin D₃ Synthesis and a Target Tissue for Its Metabolite 1,25-Dihydroxy-Vitamin D₃.
 - (34) Holick, M. F.; MacLaughlin, J. A.; Parrish, J. A.; Anderson, R. R. The Photochemistry and Photobiology of Vitamin D₃. In *The Science of Photomedicine*; Regan, J. D., Parrish, J. A., Eds.; Plenum Press: New York, 1982; pp 195–218.
 - (35) Holick, M. F. The Photobiology of Vitamin D₃ in Man. In *Vitamin D: Basic and Clinical Aspects*; Kumar, R., Ed.; Martinus Nijhoff Publishing: Boston, 1984; pp 197–216.
 - (36) Suda, T.; Shinki, T.; Takahashi, N. *Annu. Rev. Nutri.* **1990**, *10*, 195–211. The Role of Vitamin D in Bone and Intestinal Cell Differentiation.
 - (37) Suda, T.; Takahashi, N.; Abe, E. *J. Cell. Biochem.* **1992**, *49*, 53–58. Role of Vitamin D in Bone Resorption.
 - (38) Lian, J. B.; Stein, G. S. *J. Cell. Biochem.* **1992**, *49*, 37–45. Transcriptional Control of Vitamin D-Regulated Proteins.
 - (39) (a) Lemire, J. M. *J. Cell. Biochem.* **1992**, *49*, 26–31. Immunomodulatory Role of 1,25-Dihydroxyvitamin D₃. (b) Bouillon, R.; Garmyn, M.; Verstuyl, A.; Segaeert, S.; Casteels, K.; Mathieu, C. *Eur. J. Endocrinol.* **1995**, *133*, 7–16. Paracrine Role for Calcitriol in the Immune System and Skin Creates New Therapeutic Possibilities for Vitamin D Analogs.
 - (40) Amento, E. P. *Steroids* **1987**, *49*, 55–72. Vitamin D and the Immune System.
 - (41) Henry, H. L. *J. Cell. Biochem.* **1992**, *49*, 4–9. Vitamin D Hydroxylases.
 - (42) Ostrem, V. K.; DeLuca, H. F. *Steroids* **1987**, *49*, 73–102. The Vitamin D-Induced Differentiation of HL-60 Cells: Structural Requirements.
 - (43) Okamura, W. H.; Palenzuela, J. A.; Plumet, J.; Midland, M. M. *J. Cell. Biochem.* **1992**, *49*, 10–18. Vitamin D: Structure-Function Analyses and the Design of Analogs.
 - (44) Proscal, D. A.; Okamura, W. H.; Norman, A. W. *Am. J. Clin. Nutri.* **1976**, *29*, 1271–1282. Vitamin D, Its Metabolites and Analogs: A Review of the Structural Requirements for Biological Activity.
 - (45) Ikekawa, N. *Med. Res. Rev.* **1987**, *7*, 333–366. Structures and Biological Activities of Vitamin D Metabolites and their Analogs.
 - (46) Ikekawa, N.; Ishizuka, S. Molecular Structure and Biological Activity of Vitamin D Metabolites and their Analogs. In *Molecular Structure and Biological Activity of Steroids*; Bohl, M., Duax, W. L., Eds.; CRC Press: Boca Raton, 1992; pp 293–316.
 - (47) Calverley, M. J.; Jones, G. Vitamin D. In *"Vitamin D" in Antitumor Steroids*; Blickenstaff, R. T., Ed.; Academic Press: San Diego, 1992; pp 193–270.
 - (48) Tachibana, Y.; Tsuji, M. Synthetic Studies on Active Forms of Vitamin D and Their Analogs. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 11, pp 379–408.
 - (49) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98–114. Synthèse des Métabolites de la Vitamine D (Synthesis of Vitamin D Metabolites. Review).
 - (50) Lythgoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449–475. Synthetic Approaches to Vitamin D and its Relatives.
 - (51) Quinkert, G. *Synform* **1985**, *3*, 41–122. Vitamin D Active Compounds.
 - (52) Quinkert, G. *Synform* **1986**, *4*, 131–258. Vitamin D Active Compounds Part II.
 - (53) Quinkert, G. *Synform* **1987**, *5*, 1–86. Vitamin D Active Compounds Part III.
 - (54) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83–107. The Chemistry of Vitamin D: The Hormonal Calciferols.
 - (55) Kametani, T.; Furuyama, H. *Med. Res. Rev.* **1987**, *7*, 147–171. Synthesis of Vitamin D₃ and Related Compounds.
 - (56) Wilson, S. R.; Yasmin, A. Stereoselective Synthesis of Vitamin D. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman., Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 43–75.
 - (57) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398. Synthetic Approaches to Vitamin D.
 - (58) A leading reference on the photochemistry of 7-DHC in skin: Holick, M. F. *Am. J. Clin. Nutr.* **1994**, *60*, 619–630. McCollum Award Lecture, 1994: Vitamin D—New Horizons for the 21st Century.
 - (59) Tian, X. Q.; Chen, T. C.; Matsuoka, L. Y.; Wortsman, J.; Holick, M. F. *J. Biol. Chem.* **1993**, *268*, 14888–14892. Kinetic and Thermodynamic Studies of the Conversion of Previtamin D₃ to Vitamin D₃ in Human Skin.
 - (60) Hobbs, R. N.; Hazel, C. M.; Smith, S. C.; Carney, D. A.; Howells, A. C.; Littlewood, A. J.; Pennock, J. F. *Chem. Scr.* **1987**, *27*, 199–205. Metabolism of Vitamin D₃ by a Marine Echinoderm, *Psammechinus miliaris*.
 - (61) Yamamoto, J. K.; Borch, R. F. *Biochemistry* **1985**, *24*, 3338–3344. Photoconversion of 7-Dehydrocholesterol to Vitamin D₃ in Synthetic Phospholipid Biolayers.

- (62) Tian, X. Q.; Holick, M. F. *J. Biol. Chem.* **1995**, *270*, 8706–8711. Catalyzed Thermal Isomerization between Previtamin D₃ and Vitamin D₃ via β -Cyclodextrin Complexation.
- (63) Holick, M. F.; Tian, X. Q.; Allen, M. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3124–3126. Evolutionary Importance for the Membrane Enhancement of the Production of Vitamin D₃ in the Skin of Poikilothermic Animals.
- (64) Tian, X. Q.; Chen, T. C.; Lu, Z.; Shao, Q.; Holick, M. F. *Endocrinology* **1994**, *135*, 655–661. Characterization of the Translocation Process of Vitamin D₃ from the Skin into the Circulation.
- (65) Ponchon, G.; DeLuca, H. F. *J. Clin. Invest.* **1969**, *48*, 1273–1279. The Role of the Liver in the Metabolism of Vitamin D.
- (66) (a) Madhok, T. C.; DeLuca, H. F. *Biochem. J.* **1979**, *184*, 491–499. Characteristics of the Rat Liver Microsomal Enzyme System Converting Cholecalciferol into 25-Hydroxycholecalciferol. (b) Axén, E.; Bergman, T.; Wikvall, K. *J. Steroid Biochem. Mol. Biol.* **1994**, *51*, 97–106. Microsomal 25-Hydroxylation of Vitamin D₂ and Vitamin D₃ in Pig Liver.
- (67) Björkhem, I.; Holmberg, I.; Oftebro, H.; Pedersen, J. I. *J. Biol. Chem.* **1980**, *255*, 5244–5249. Properties of a Reconstituted Vitamin D₃ 25-Hydroxylase from Rat Liver Mitochondria.
- (68) (a) Usui, E.; Noshiro, M.; Okuda, K. *FEBS Lett.* **1990**, *262*, 135–138. Molecular Cloning of cDNA for Vitamin D₃ 25-Hydroxylase from Rat Liver Mitochondria. (b) Andersson, S.; Davis, D. L.; Dahlbäck, H.; Jörnvall, H.; Russell, D. W. *J. Biol. Chem.* **1989**, *264*, 8222–8229. Cloning, Structure, and Expression of the Mitochondrial Cytochrome P-450 Sterol 26-Hydroxylase, a Bile Acid Biosynthetic Enzyme.
- (69) Fraser, D. R.; Kodicek, E. *Nature*, **1970**, *228*, 764–766. Unique Biosynthesis by Kidney of a Biologically Active Vitamin D Metabolite.
- (70) Ghazarian, J. G.; Jefcoate, C. R.; Knutson, J. C.; Orme-Johnson, W. H.; DeLuca, H. F. *J. Biol. Chem.* **1974**, *249*, 3026–3033. Mitochondrial Cytochrome P₄₅₀.
- (71) Norman, A. W.; Nemere, I.; Zhou, L.; Bishop, J. E.; Lowe, K. E.; Maiyar, A. C.; Collins, E. D.; Taoka, T.; Sergeev, I.; Farach-Carson, M. C. *J. Steroid Biochem. Mol. Biol.* **1992**, *41*, 231–240. 1,25(OH)₂-Vitamin D₃, A Steroid Hormone that Produces Biologic Effects via Both Genomic and Nongenomic Pathways.
- (72) (a) Baker, A. R.; McDonnell, D. P.; Hughes, M.; Crisp, T. M.; Mangelsdorf, D. J.; Haussler, M. R.; Pike, J. W.; Shine, J.; O'Malley, B. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3294–3298. Cloning and Expression of Full-Length cDNA Encoding Human Vitamin D Receptor. (b) McDonnell, D. P.; Mangelsdorf, D. J.; Pike, J. W.; Haussler, M. R.; O'Malley, B. W. *Science* **1987**, *235*, 1214–1217. Molecular Cloning of Complementary DNA Encoding the Avian Receptor for Vitamin D. (c) Although the X-ray structure of vitamin D receptor is unknown, the crystal structure of a member of the same superfamily, the human retinoid-x receptor RXR- α ligand-binding domain has been recently reported. Bourguet, W.; Ruff, M.; Chambon, P.; Gronemeyer, H.; Moras, D. *Nature* **1995**, *375*, 377–382. Crystal Structure of the Ligand-Binding Domain of the Human Nuclear Receptor RXR- α .
- (73) Rosen, E. D.; Beninghof, E. G.; Koenig, R. J. *J. Biol. Chem.* **1993**, *268*, 11534–11541. Dimerization Interfaces of Thyroid Hormone, Retinoic Acid, Vitamin D, and Retinoid X Receptors.
- (74) Nishikawa, J.; Kitaura, M.; Imagawa, M.; Nishihara, T. *Nucleic Acids Res.* **1995**, *23*, 606–611. Vitamin D Receptor Contains Multiple Dimerization Interfaces That are Functionally Different.
- (75) MacDonald, P. N.; Sherman, D. R.; Dowd, D. R.; Jefcoate, S. C., Jr.; DeLisle, R. K. *J. Biol. Chem.* **1995**, *270*, 4748–4752. The Vitamin D Receptor Interacts with General Transcription Factor IIB.
- (76) (a) Allan, G. F.; Leng, X.; Tsai, S. Y.; Weigel, N. L.; Edwards, D. P.; Tsai, M.-J.; O'Malley, B. W. *J. Biol. Chem.* **1992**, *267*, 19513–19520. Hormone and Antihormone Induce Distinct Conformational Changes Which Are Central to Steroid Receptor Activation. (b) Peleg, S.; Sastry, M.; Collins, E. D.; Bishop, J. E.; Norman, A. W. *J. Biol. Chem.* **1995**, *270*, 10551–10558. Distinct Conformational Changes Induced by 20-epi Analogues of 1 α ,25-Dihydroxyvitamin D₃ are Associated with Enhanced Activation of the Vitamin D Receptor.
- (77) (a) Baran, D. T. *J. Cell. Biochem.* **1994**, *56*, 303–306. Nongenomic Actions of the Steroid Hormone 1 α ,25-Dihydroxyvitamin D₃. (b) Boyan, B. D.; Dean, D. D.; Sylvia, V. L.; Schwartz, Z. *J. Cell. Biochem.* **1994**, *56*, 331–339. Nongenomic Regulation of Extracellular Matrix Events by Vitamin D Metabolites. (c) Beno, D. W. A.; Brady, L. M.; Bissonnette, M.; Davis, B. H. *J. Biol. Chem.* **1995**, *270*, 3542–3647. Protein Kinase C and Mitogen-activated Protein Kinase Are Required for 1,25-Dihydroxyvitamin D₃-stimulated Egr Induction.
- (78) (a) Slater, S. J.; Kelly, M. B.; Taddeo, F. J.; Larkin, J. D.; Yeager, M. D.; McLane, J. A.; Ho, C.; Stubbs, C. D. *J. Biol. Chem.* **1995**, *270*, 6639–6643. Direct Activation of Protein Kinase C by 1 α ,25-Dihydroxyvitamin D₃. (b) Bissonnette, M.; Wali, R. K.; Hartmann, S. C.; Niedziela, S. M.; Roy, H. K.; Tien, X.-Y.; Sitrin, M. D.; Brasitus, T. A. *J. Clin. Invest.* **1995**, *95*, 2215–2221. 1,25-Dihydroxyvitamin D₃ and 12-O-Tetradecanoyl Phorbol 13-Acetate Cause Differential Activation of Ca²⁺-dependent and Ca²⁺-independent Isoforms of Protein Kinase C in Rat Colonocytes.
- (79) (a) Baran, D. T.; Ray, R.; Sorensen, A. M.; Honeyman, T.; Holick, M. F. *J. Cell. Biochem.* **1994**, *56*, 510–517. Binding Characteristics of a Membrane Receptor That Recognizes 1 α ,25-Dihydroxyvitamin D₃ and Its Epimer, 1 β ,25-Dihydroxyvitamin D₃. (b) Nemere, I.; Dormanen, M. C.; Hammond, M. W.; Okamura, W. H.; Norman, A. W. *J. Biol. Chem.* **1994**, *269*, 23750–23756. Identification of a Specific Binding Protein for 1 α ,25-Dihydroxyvitamin D₃ in Basal-Lateral Membranes of Chick Intestinal Epithelium and Relationship to Transcaltachia. (c) Zhou, L.; Nemere, I.; Norman, A. W. *J. Bone Miner. Res.* **1992**, *7*, 457–463. 1,25-Dihydroxyvitamin D₃ Analog Structure-Function Assessment of the Rapid Stimulation of Intestinal Calcium Absorption (Transcaltachia).
- (80) (a) Norman, A. W.; Okamura, W. H.; Farach-Carson, M. C.; Allewaert, K.; Branisteanu, D.; Nemere, I.; Muralidharan, K. R.; Bouillon, R. *J. Biol. Chem.* **1993**, *268*, 13811–13819. Structure-Function Studies of 1,25-Dihydroxyvitamin D₃ and the Vitamin D Endocrine System: 1,25-Dihydroxy-Pentadeuterio-Previtamin D₃ (As a 6-s-Cis Analog) Stimulates Nongenomic But Not Genomic Biological Responses. (b) Bhatia, M.; Kirkland, J. B.; Meckling-Gill, K. A. *J. Biol. Chem.* **1995**, *270*, 15962–15965. Monocytic Differentiation of Acute Promyelocytic Leukemia Cells in Response to 1,25-Dihydroxyvitamin D₃ Is Independent of Nuclear Receptor Binding. (c) Elstner, E.; Lee, Y. Y.; Hashiya, M.; Pakkala, S.; Binderup, L.; Norman, A. W.; Okamura, W. H.; Koefler, H. P. *Blood* **1994**, *84*, 1960–1967. 1 α ,25-Dihydroxy-20-Epi-Vitamin D₃: An Extraordinarily Potent Inhibitor of Leukemic Cell Growth In Vitro.
- (81) (a) A leading reference on conformation of vitamin D: Okamura, W. H.; Midland, M. M.; Hammond, M. W.; Abd-Rahman, N.; Dormanen, M. C.; Nemere, I.; Norman, A. W. *J. Steroid Biochem. Mol. Biol.* **1995**, *53*, 603–613. Chemistry and Conformation of Vitamin D Molecules. (b) Okamura, W. H.; Wing, R. M. Conformational Analysis of Vitamin D and Related Compounds. In *Vitamin D: Molecular Biology and Clinical Nutrition*; Norman, A. W., Ed.; Marcel Dekker: New York, 1980; pp 59–92 and pp 685–691.
- (82) (a) Hodgkin, D. C.; Rimmer, B. M.; Dunitz, J. D.; Trueblood, K. N. *J. Chem. Soc.* **1963**, 4945–4955. The Crystal Structure of a Calciferol Derivative. (b) Knobler, C.; Romers, C.; Braun, P. B.; Hornstra, J. *Acta Crystallogr.* **1972**, *B28*, 2097–2103. The Conformation of Non-Aromatic Ring Compounds. LXXV. The Crystal and Molecular Structure of the 3,20-Bis(ethylenedioxy) Analogue of Vitamin D. (c) Hull, S. E.; Leban, I.; Main, P.; White, P. S.; Woolfson, M. M. *Acta Crystallogr.* **1976**, *B32*, 2374–2381. The Crystal and Molecular Structure of Ergocalciferol (Vitamin D₂). (d) Trinh-Toan; Ryan, R. C.; Simon, G. L.; Calabrese, J. C.; Dahl, L. F.; DeLuca, H. F. *J. Chem. Soc., Perkin Trans. 2* **1977**, 393–401. Crystal Structure of 25-Hydroxy-vitamin D₃ Monohydrate: A Stereochemical Analysis of Vitamin D Molecules. (e) Trinh-Toan; DeLuca, H. F.; Dahl, L. F. *J. Org. Chem.* **1976**, *41*, 3476–3478. Solid-State Conformations of Vitamin D₃. (f) Posner, G. H.; Dai, H.; Afarinkia, K.; Murthy, N. N.; Guyton, K. Z.; Kensler, T. W. *J. Org. Chem.* **1993**, *58*, 7209–7215. Asymmetric Total Synthesis, X-ray Crystallography, and Preliminary Biological Evaluation of 1-(1'-Hydroxyethyl)-25-hydroxyvitamin D₃ Analogs of Natural Calcitriol.
- (83) Delaroff, V.; Rathle, P.; Legrand, M. *Bull. Soc. Chim. Fr.* **1963**, 1739–1741. N° 280.—Étude de la Résonance Magnétique Nucléaire du Précalciférol, du Tachystérol et du Calciférol. (NMR Study of Precalciferol, Tachysterol, and Calciferol).
- (84) (a) Wing, R. M.; Okamura, W. H.; Pirio, M. R.; Sine, S. M.; Norman, A. W. *Science* **1974**, *186*, 939–941. Vitamin D in Solution: Conformations of Vitamin D₃, 1 α ,25-Dihydroxyvitamin D₃, and Dihydrotachysterol₃. (b) Wing, R. M.; Okamura, W. H.; Rego, A.; Pirio, M. R.; Norman, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 4980–4985. Studies on Vitamin D and Its Analogs. VII. Solution Conformations of Vitamin D₃ and 1 α ,25-Dihydroxyvitamin D₃ by High-Resolution Proton Magnetic Resonance Spectroscopy.
- (85) (a) La Mar, G. N.; Budd, D. L. *J. Am. Chem. Soc.* **1974**, *96*, 7317–7324. Elucidation of the Solution Conformation of the A Ring in Vitamin D Using Proton Coupling Constants and a Shift Reagent. (b) Berman, E.; Friedman, N.; Mazur, Y.; Sheves, M. *J. Am. Chem. Soc.* **1978**, *100*, 5626–5634. Conformational Equilibria in Vitamin D. Synthesis and ¹H and ¹³C Dynamic Nuclear Magnetic Resonance Study of 4,4-Dimethylvitamin D₃, 4,4-Dimethyl-1 α -hydroxyvitamin D₃, and 4,4-Dimethyl-1 α -hydroxyepivitamin D₃. (c) Tsukida, K.; Akutsu, K.; Saiki, K. *J. Nutr. Sci. Vitaminol.* **1975**, *21*, 411–420. Carbon-13 Nuclear Magnetic Resonance Spectra of Vitamins D and Related Compounds. (d) Kotovych, G.; Aarts, G. H. M.; Bock, K. *Can. J. Chem.* **1980**, *58*, 1206–1210. A Proton Magnetic Resonance Nuclear Overhauser Enhancement Study. Application to Vitamin D Derivatives D₂ and D₃.

- (86) Kotowycz, G.; Nakashima, T. T.; Green, M. K.; Aarts, G. H. M. *Can. J. Chem.* **1980**, *58*, 45–50. A Proton Magnetic Resonance Relaxation Time Study of Several Vitamin D Derivatives.
- (87) Helmer, B.; Schnoes, H. K.; DeLuca, H. F. *Arch. Biochem. Biophys.* **1985**, *241*, 608–615. ¹H Nuclear Magnetic Resonance Studies of the Conformations of Vitamin D Compounds in Various Solvents.
- (88) Eguchi, T.; Ikekawa, N. *Bioorg. Chem.* **1990**, *18*, 19–29. Conformational Analysis of 1 α ,25-Dihydroxyvitamin D₃ by Nuclear Magnetic Resonance.
- (89) Eguchi, T.; Kakinuma, K.; Ikekawa, N. *Bioorg. Chem.* **1991**, *19*, 327–332. Synthesis of 1 α -[19-¹³C]Hydroxyvitamin D₃ and ¹³C NMR Analysis of the Conformational Equilibrium of the A-Ring.
- (90) Berman, E.; Luz, Z.; Mazur, Y.; Sheves, M. *J. Org. Chem.* **1977**, *42*, 3325–3330. Conformational Analysis of Vitamin D and Analogues. ¹³C and ¹H Nuclear Magnetic Resonance Study.
- (91) Wilson, S. R.; Unwala, R.; Cui, W. Computer Calculations of the Active Conformation of 1,25-Dihydroxyvitamin D₃. In *Vitamin D, Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schefer, K., Grigoletti, H.-G., Herrath, D., Eds.; Walter de Gruyter: Berlin, 1988; pp 78–79.
- (92) Mosquera, R. A.; Rios, M. A.; Tovar, C. A. *J. Mol. Struct.* **1989**, *213*, 297–307. Conformational Analysis of Vitamin D₃ Derivatives by Molecular Mechanics.
- (93) Kutner, A.; Choliński, J.; Chodyński, M.; Halkes, S. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1795–1798. Conformational Analysis of Disubstituted Side-Chain of Vitamin D₃ Analogs: Molecular Modeling and Semiempirical Calculations.
- (94) Hofer, O.; Kählig, H.; Reischl, W. *Monatsh. Chem.* **1993**, *124*, 185–198. On the Conformational Flexibility of Vitamin D.
- (95) Zhu, G.-D.; Van Haver, D.; Jurriaans, H.; De Clercq, P. J. *Tetrahedron* **1994**, *50*, 7049–7060. 11-Fluoro-1 α -hydroxyvitamin D₃: The Quest for Experimental Evidence of the Folded Vitamin D Conformation.
- (96) (a) Midland, M. M.; Plumet, J.; Okamura, W. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1799–1804. Effect of C20 Stereochemistry on the Conformational Profile of the Side Chains of Vitamin D Analogs. (b) Wilson, S. R.; Guarnieri, F. Calculation of the Side Chain Flexibility for Vitamin D Analogs. In *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 186–187. (c) Yamamoto, K.; Ohta, M.; DeLuca, H. F.; Yamada, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 979–984. On the Side Chain Conformation of 1 α ,25-Dihydroxyvitamin D₃ Responsible for Binding to the Receptor.
- (97) Curtin, M. L.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 6958–6966. 1 α ,25-Dihydroxyprevitamin D₃: Synthesis of the 9,14,19,19,19-Pentadeuterio Derivative and a Kinetic Study of Its [1,7]-Sigmatropic Shift to 1 α ,25-Dihydroxyvitamin D₃.
- (98) Okamura, W. H.; Midland, M. M.; Hammond, M. W.; Rahman, N. A.; Dormanen, M. C.; Nemere, I.; Norman, A. W. Conformation and Related Topological Features of Vitamin D: Structure-Function Relationships. In *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 12–20.
- (99) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Rizzardo, E. *J. Am. Chem. Soc.* **1973**, *95*, 2748–2749. A Convenient Synthesis of 1 α -Hydroxy-Vitamin D₃.
- (100) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Rizzardo, E. *J. Chem. Soc., Chem. Commun.* **1974**, 203–204. Convenient Synthesis of Crystalline 1 α ,25-Dihydroxyvitamin D₃.
- (101) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, 3863–3866. Allylic Phosphine Oxides as Precursors of Dienes of Defined Geometry: Synthesis of 3-Deoxyvitamin D₂.
- (102) Lythgoe, B.; Nambudiry, M. E. N.; Tideswell, J. *Tetrahedron Lett.* **1977**, 3685–3688. Direct Total Synthesis of Vitamins D₂ and D₃.
- (103) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 590–595. Calciferol and Its Relatives. Part 22. A Direct Total Synthesis of Vitamin D₂ and Vitamin D₃.
- (104) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2386–2390. Allylic Phosphine Oxides as Precursors of Conjugated Dienes of Defined Geometry.
- (105) Lythgoe, B.; Manwaring, R.; Milner, J. R.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 387–395. Calciferol and Its Relatives: Part 21. A Synthesis of (S)-(Z)-2-(5-Hydroxy-2-methylenecyclohexylidene)-ethanol.
- (106) Frosch, J. V.; Harrison, I. T.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2005–2009. Calciferol and Its Relatives: Part XVII. Ring-A Components for Synthetic Work on Vitamin D₃ and on Model Compounds.
- (107) Baggolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098–3108. Stereocontrolled Total Synthesis of 1 α ,25-Dihydroxycholecalciferol and 1 α ,25-Dihydroxyergocalciferol.
- (108) De Schrijver, J.; De Clercq, P. J. *Tetrahedron Lett.* **1993**, *34*, 4369–4372. A Novel Synthesis of an A-Ring Precursor to 1 α -Hydroxyvitamin D.
- (109) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967–3969. Asymmetric Total Synthesis of an A-Ring Precursor to Hormonally Active 1 α ,25-Dihydroxyvitamin D₃.
- (110) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2654–2657. Calciferol and Its Relatives. Part XVIII. Total Synthesis of 1 α -Hydroxyvitamin D₃.
- (111) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203–1206. Palladium-Catalyzed Synthesis of Dienes Related to 1 α ,25-Dihydroxyvitamin D₃.
- (112) Castedo, L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1986**, *27*, 1523–1526. Palladium-Catalyzed Synthesis of Dienes Related to Vitamin D from Enol Triflates.
- (113) Barrack, S. A.; Gibbs, R. A.; Okamura, W. H. *J. Org. Chem.* **1988**, *53*, 1790–1796. Potential Inhibitors of Vitamin D Metabolism: An Oxa Analogue of Vitamin D.
- (114) Aurrecoechea, J. M.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 4947–4950. A Short, Enantiospecific Synthesis of the 1 α -Hydroxyvitamin D Enyne A-Ring Synthon.
- (115) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072–4083. Synthesis and Biological Activity of 9,11-Dehydrovitamin D₃ Analogues: Stereoselective Preparation of 6 β -Vitamin D Vinylallenes and a Concise Enynol Synthesis for Preparing the A-Ring.
- (116) VanAlstyne, E. M.; Norman, A. W.; Okamura, W. H. *J. Am. Chem. Soc.* **1994**, *116*, 6207–6216. 7,8-Cis Geometric Isomers of the Steroid Hormone 1 α ,25-Dihydroxyvitamin D₃.
- (117) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845. New Strategies for the Synthesis of Vitamin D Metabolites via Pd-Catalyzed Reactions.
- (118) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937–4940. Stereoselective Synthesis of 1 α -Hydroxyvitamin D₃ A-Ring Synthons by Palladium-Catalyzed Cyclization.
- (119) Sheves, M.; Mazur, Y. *J. Am. Chem. Soc.* **1975**, *97*, 6249–6250. The Vitamin D-3,5-Cyclovitamin D Rearrangement.
- (120) Paaren, H. E.; DeLuca, H. F.; Schnoes, H. K. *J. Org. Chem.* **1980**, *45*, 3253–3258. Direct C(1) Hydroxylation of Vitamin D₃ and Related Compounds.
- (121) Kabat, M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1991**, *32*, 2343–2346. Control of Stereoselectivity in Samarium Metal Induced Cyclopropanations. Synthesis of 1,25-Dihydroxycholecalciferol.
- (122) Wilson, S. R.; Venkatesan, A. M.; Augelli-Szafran, C. E.; Yasmin, A. *Tetrahedron Lett.* **1991**, *32*, 2339–2342. A New Synthetic Route to 1,25-Dihydroxy-vitamin D₃.
- (123) Andrews, D. R.; Barton, D. H. R.; Cheng, K. P.; Finet, J.-P.; Hesse, R. H.; Johnson, G.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 1635–1637. A Direct, Regio- and Stereoselective 1 α -Hydroxylation of (5E)-Calciferol Derivatives.
- (124) Inhoffen, H. H.; Quinkert, G.; Schütz, S. *Chem. Ber.* **1957**, *90*, 1283–1286. Studien in der Vitamin D-Reihe, XXIII. Aufbau des trans-Hydrindan-Ketons aus Vitamin D₃ zum Vinyloger Aldehyd. (Studies on the Vitamin D Series, XXIII. Conversion of the trans-Hydrindan-Ketone from Vitamin D₃ to Vinylogous Aldehydes).
- (125) Inhoffen, H. H.; Quinkert, G.; Hess, H.-J.; Hirschfeld, H. *Chem. Ber.* **1957**, *90*, 2544–2553. Studien in der Vitamin D-Reihe, XXIV. Photo-Isomerisierung der trans-Vitamine D₂ und D₃ zu den Vitaminen D₂ und D₃. (Studies on the Vitamin D Series, XXIV. Photo-isomerization of trans-Vitamins D₂ and D₃ to Vitamins D₂ and D₃).
- (126) Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819–4828. Synthesis of 25-Hydroxy- and 1 α ,25-Dihydroxyvitamin D₃ from Vitamin D₂ (Calciferol).
- (127) Vanmaele, L.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1985**, *41*, 141–144. An Efficient Synthesis of 1 α ,25-Dihydroxy Vitamin D₃.
- (128) Malatesta, V.; Willis, C.; Hackett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 6781–6783. Laser Photochemical Production of Vitamin D.
- (129) (a) Rappoldt, M. P.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 369–381. Studies on Vitamin D and Related Compounds XI. Investigations on Sterols XIII. The Photoisomerisation of Ergosterol. (b) Jacobs, H. J. C. *Pure Appl. Chem.* **1995**, *67*, 63–70. Photochemistry of Conjugated Trienes: Vitamin D Revisited.
- (130) Eyley, S. C.; Williams, D. H. *J. Chem. Soc., Chem. Commun.* **1975**, 858. Photolytic Production of Vitamin D. The Preparative Value of a Photo-sensitizer.
- (131) Kobayashi, T.; Yasumura, M. *J. Nutr. Sci. Vitaminol.* **1973**, *19*, 123–128. Studies on the Ultraviolet Irradiation of Provitamin D and Its Related Compounds III. Effect of Wavelength on the Formation of Potential Vitamin D₂ in the Irradiation of Ergosterol by Monochromatic Ultraviolet Rays.
- (132) Sato, T.; Yamauchi, H.; Ogata, Y.; Kuni, T.; Kagei, K.; Katsui, G.; Toyoshima, S.; Yasumura, M.; Kobayashi, T. *J. Nutr. Sci. Vitaminol.* **1980**, *26*, 545–556. Effect of Wavelength on the Formation of 1 α -Hydroxyprevitamin D₃ in the Ultraviolet Ir-

- radiation of a Cholesta-5,7-Diene-1 α ,3 β -Diol and Use of a Filter Solution in the Photochemical Reaction in the Synthesis of 1 α -Hydroxy-Vitamin D₃.
- (133) Pfoertner, K.; Weber, J. P. *Helv. Chim. Acta* **1972**, *55*, 921–937. 96. Photochemie in der Vitamin D-Reihe. I. Kinetik und Quantenausbeuten der Ergosterinbestrahlung bei $\lambda = 253,7$ nm (Photochemistry in the Vitamin D Series. I. Kinetics and Quantum Yields of Ergosterol Irradiation at 253.7 nm).
- (134) Pfoertner, K. *Helv. Chim. Acta* **1972**, *55*, 937–947. 97. Photochemie in der Vitamin D-Reihe. II. Die Wellenlängenabhängigkeit der Photoisomerisation des Präcalciferols (Photochemistry in the Vitamin D Series. II. Influence of the Wavelength on the Photoisomerization of Precalciferols).
- (135) Dauben, W. G.; Phillips, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 355–356. Wavelength-Controlled Production of Previtamin D₃.
- (136) Dauben, W. G.; Phillips, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 5780–5781. Effects of Wavelength on the Photochemistry of Provitamin D₃.
- (137) Okabe, M.; Sun, R.-C.; Scalone, M.; Jibilian, C. H.; Hutchings, S. D. *J. Org. Chem.* **1995**, *60*, 767–771. Synthesis of 25-Hydroxycholecalciferol-16-en-23-ynol: A Potential Antipsoriatic Agent.
- (138) Semmler, E. J.; Holick, M. F.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1972**, 4147–4150. The Synthesis of 1 α ,25-Dihydroxycholecalciferol—A Metabolically Active Form of Vitamin D₃.
- (139) Morisaki, M.; Saika, A.; Bannai, K.; Sawamura, M.; Rubio-Lightbourn, J.; Ikekawa, N. *Chem. Pharm. Bull.* **1975**, *23*, 3272–3278. Synthesis of Active Forms of Vitamin D. X. Synthesis of 1 α -Hydroxyvitamin D₃.
- (140) Rubio-Lightbourn, J.; Morisaki, M.; Ikekawa, N. *Chem. Pharm. Bull.* **1973**, *21*, 1854–1856. Synthesis of Active Forms of Vitamin D. III. Synthesis of 1 α ,25-Dihydroxycholesterol.
- (141) Morisaki, M.; Bannai, K.; Ikekawa, N. *Chem. Pharm. Bull.* **1973**, *21*, 1853–1854. Synthesis of Active Forms of Vitamin D. II. Synthesis of 1 α -Hydroxycholesterol.
- (142) Narwid, T. A.; Blount, J. F.; Iacobelli, J. A.; Uskokovic, M. R. *Helv. Chim. Acta* **1974**, *57*, 781–789. 87. Vitamin D₃ Metabolites III. Synthesis and X-ray Analysis of 1 α ,25-Dihydroxycholesterol.
- (143) Morisaki, M.; Bannai, K.; Ikekawa, N. *Chem. Pharm. Bull.* **1976**, *24*, 1948–1949. Studies on Steroids. XXXVIII. A New Preparation of 1 α -Hydroxycholesterol.
- (144) Mitra, M. N.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1974**, *39*, 2931–2933. Studies on Vitamin D and Its Analogs. I. Synthesis of 1 α -Hydroxycholesterol-5-ene.
- (145) Fürst, A.; Labler, L.; Meier, W. *Helv. Chim. Acta* **1981**, *64*, 1870–1892. 180. Eine ergiebige Herstellung von 1 α ,3 β -Dihydroxy- Δ^5 -steroiden durch Reduktion von 1 α ,2 α -Epoxy-4,6-dien-3-onen mit Lithium in Ammoniak (Productive Synthesis of 1 α ,3 β -Dihydroxy- Δ^5 -steroids by Reduction of 1 α ,2 α -Epoxy-4,6-dien-3-ones with Lithium in Ammonia).
- (146) Morisaki, M.; Rubio-Lightbourn, J.; Ikekawa, N.; Takeshita, T. *Chem. Pharm. Bull.* **1973**, *21*, 2568–2569. Synthesis of Active Forms of Vitamin D. V. A Practical Route to 1 α ,25-Dihydroxycholesterol.
- (147) Morisaki, M.; Koizumi, N.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1421–1424. Synthesis of Active Forms of Vitamin D. Part IX. Synthesis of 1 α ,24-Dihydroxycholecalciferol.
- (148) Sato, T.; Yamauchi, H.; Ogata, Y.; Tsujii, M.; Kunii, T.; Kagei, K.; Toyoshima, S.; Kobayashi, T. *Chem. Pharm. Bull.* **1978**, *26*, 2933–2940. Studies on 1 α -Hydroxyl Derivatives of Vitamin D₃. I. Syntheses of 1 α -Hydroxyvitamin D₃ and 1 α ,25-Dihydroxyvitamin D₃.
- (149) Freeman, D.; Acher, A.; Mazur, Y. *Tetrahedron Lett.* **1975**, 261–264. Synthesis of 1 α -Hydroxy-Provitamin D₃.
- (150) Mihailovic, M. Lj.; Lorenc, Lj.; Pavlovic, V. *Tetrahedron* **1977**, *33*, 441–444. A Convenient Synthesis of 1 α - and 1 β -Hydroxycholesterol.
- (151) Mihailovic, M. Lj.; Lorenc, Lj.; Popov, N.; Kalvoda, J. *Helv. Chim. Acta* **1971**, *54*, 2281–2287. 222. Synthese, Struktur und Reaktionen von Secosteroiden mit einem mittleren Ring V. (Photochemische Cyclisation von *cis*- and *trans*-3 β -Acetoxy-5-oxo- $\Delta^{1(10)}$ -5,10-secocholesten) (Steroids. 222. Synthesis, Structure, and Reactions of Secosteroids with a Medium Ring. V. (Photochemical Cyclization of *cis*- and *trans*-3 β -Acetoxy-5-oxo- $\Delta^{1(10)}$ -5,10-secocholestenes)).
- (152) Kaneko, C.; Yamada, S.; Sugimoto, A.; Ishikawa, M.; Suda, T.; Suzuki, M.; Sasaki, S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1104–1107. Synthesis and Biological Activity of 2 α -Hydroxyvitamin D₃.
- (153) Tachibana, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3085–3086. (Hydroxyalkyl)pyridines as Bifunctional Catalysts. Dehydrobromination of 7-Bromocholesterol.
- (154) Rappoldt, M. P.; Hoogendoorn, J.; Pauli, L. F. An Improved Synthesis of 7-Dehydrocholesterols. In *Vitamin D, Chemical, Biochemical and Clinical Endocrinology of Calcium Metabolism*; Norman, A. W., Schaefer, K., v. Herrath, D., Grigoleit, H.-G., Eds.; Walter de Gruyter: Berlin, 1982; pp 1133–1135.
- (155) Confalone, P. N.; Kulesha, I. D.; Uskokovic, M. R. *J. Org. Chem.* **1981**, *46*, 1030–1032. A New Synthesis of 7-Dehydrocholesterols.
- (156) Takahashi, T.; Nakagawa, N.; Minoshima, T.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 4333–4336. Palladium Catalyzed Selective Formation of Homoannular Conjugated Dienes from Allylic Esters in Decalin Derivatives, and Its Application to the Synthesis of 1- α -Hydroxy-Provitamin D₃.
- (157) Dauben, W. G.; Fullerton, D. S. *J. Org. Chem.* **1971**, *36*, 3277–3282. Steroids with Abnormal Internal Configuration. A Stereospecific Synthesis of 8 α -Methyl Steroids.
- (158) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587–3592. Allylic Oxidation of Olefins with Chromium Trioxide-Pyridine Complex.
- (159) Barner, R.; Hübscher, J.; Daly, J. J.; Schönholzer, P. *Helv. Chim. Acta* **1981**, *64*, 915–938. 87. Zur Konfiguration des Vitamin-D₃-Metaboliten 25,26-Dihydroxycholecalciferol: Synthese von (25S,26)- und (25R,26)-Dihydroxycholecalciferol (Configuration of the Vitamin-D₃-Metabolite 25,26-Dihydroxycholecalciferol: Synthesis of (25S,26)- and (25R,26)-Dihydroxycholecalciferol).
- (160) Jones, G.; Rosenthal, A. *Tetrahedron Lett.* **1979**, 177–180. 24-(R), 25-Dihydroxyvitamin D₂ Synthesis, Determination of Absolute Configuration by X-ray Analysis and Identification as A Kidney Metabolite of Vitamin D₂.
- (161) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057–2059. Allylic Oxidation with 3,5-Dimethylpyrazole. Chromium Trioxide Complex. Steroidal Δ^5 -7-Ketones.
- (162) Corey, E. J.; Fleet, G. W. *J. Tetrahedron Lett.* **1973**, 4499–4501. Chromium Trioxide-3,5-Dimethylpyrazole Complex as a Reagent for Oxidation of Alcohols to Carbonyl Compounds.
- (163) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735–4740. The Decomposition of Toluene-p-sulphonylhydrazones by Alkali.
- (164) Kaneko, C.; Sugimoto, A.; Eguchi, Y.; Yamada, S.; Ishikawa, M.; Sasaki, S.; Suda, T. *Tetrahedron* **1974**, *30*, 2701–2705. A New Synthetic Method of 1 α -Hydroxy-7-Dehydrocholesterol.
- (165) Ochi, K.; Matsunaga, I.; Nagano, H.; Fukushima, M.; Shindo, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 165–169. Synthetic Studies of Vitamin D₃ Analogues from Bile Acids. Part 3. Syntheses of 1 α ,25-, 1 α ,24R-, and 1 α ,24S-Dihydroxycholecalciferols from Lithocholic Acid and their Biological Activities.
- (166) Emke, A.; Hands, D.; Midgley, J. M.; Whalley, W. B.; Ahmad, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 820–822. Unsaturated Steroids. Part 6. A Route to Cholesta-5,7-diene-1 α ,3 β -diol; Preparation of Steroidal 4,6,8(14)-Trienes.
- (167) Guest, D. W.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1695–1697. A Modified Synthesis of 1 α -Hydroxyvitamin D₃.
- (168) Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. (C)* **1971**, 1968–1974. Biosynthesis of Terpenes and Steroids. Part V. The Synthesis of Ergosta-5,7,22,24(28)-tetraen-3 β -ol, a Biosynthetic Precursor of Ergosterol.
- (169) Katsumi, K.; Okano, T.; Ono, Y.; Maegaki, E.; Nishimura, K.; Baba, M.; Kobayashi, T.; Miyata, O.; Naito, T.; Ninomiya, I. *Chem. Pharm. Bull.* **1987**, *35*, 970–979. Synthesis of 24,25-Dihydroxyvitamin D₂, 24,25-Dihydroxy-22-dehydrovitamin D₃, 25-Hydroxy-24-oxo-22-dehydrovitamin D₃ and 22,24,25-Trihydroxyvitamin D₃.
- (170) Barton, D. H. R.; Lusinch, X.; Ramirez, J. S. *Tetrahedron Lett.* **1983**, *24*, 2995–2998. Improved Synthesis of 1,2,4-Triazolone-3,5-Dione Derivatives of Ergosterol and a New Method for Their Reconversion to Ergosterol.
- (171) Inhoffen, H. H.; Burkhardt, H.; Quinkert, G. *Chem. Ber.* **1959**, *92*, 1564–1572. Studien in der Vitamin D-Reihe, XXIX. Aufbau der Seitenkette des Vitamins D₃ zugleich Beendigung der Totalsynthese des Vitamins D₃. (Studies on the Vitamin D Series, XXIX. Synthesis of the Vitamin D₃ Side Chain and the Completion of the Total Synthesis of Vitamin D₃).
- (172) Inhoffen, H. H.; Irmischer, K. In *Fortschr. Chem. Org. Natur.; Zechmeister, L., Ed.; Springer-Verlag: West Berlin, 1959; Vol. 17, pp 70–123; Chem. Abstr. 1959, 53, 22752a. Fortschritte der Chemie der Vitamine D und ihrer Abkömmlinge. (Progress on the Chemistry of Vitamin D and Its Derivatives.)*
- (173) Bovicelli, P.; Lupattelli, P.; Mincione, E. *J. Org. Chem.* **1992**, *57*, 5052–5054. Oxidation of Natural Targets by Dioxiranes. 2. Direct Hydroxylation at the Side-Chain C-25 of Cholestane Derivatives and of Vitamin D₃ Windaus-Grundmann Ketone.
- (174) Bovicelli, P.; Lupattelli, P.; Fracassi, D. *Tetrahedron Lett.* **1994**, *35*, 935–938. Sapogenins and Demethyldioxirane: A New Entry to Cholestanes Functionalized at the Side Chain.
- (175) Curci, R.; Detomaso, A.; Prencipe, T.; Carpenter, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 8112–8115. Oxidation of Natural Targets by Dioxiranes. 3. Stereoselective Synthesis of (all-R)-Vitamin D₃ Triepoxide and of Its 25-Hydroxy Derivative.
- (176) Kiegiel, J.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057–6060. Chemical Conversion of Vitamin D₃ to Its 1,25-Dihydroxy Metabolite.
- (177) Sicinski, R. R.; DeLuca, H. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 159–162. Ruthenium Tetroxide Oxidation of Grundmann's Ketone Derived from Vitamin D₃.
- (178) Daniel, D.; Okamura, W. H. Synthesis of Potential Inhibitors of 25-Hydroxyvitamin D₃-1 α -Hydroxylase: A-Ring Analogs. In *Vitamin D, A Pluripotent Steroid Hormone. Structural Studies Molecular Endocrinology and Clinical Applications*; Norman, W.

- W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 35–36.
- (179) Cohen, Z.; Berman, E.; Mazur, Y. *J. Org. Chem.* **1979**, *44*, 3077–3080. Convenient Method for the Synthesis of 25-Hydroxyvitamin D₃ Analogue. Structure Determination of Tertiary Alcohols by Carbon-13 Nuclear Magnetic Resonance Spectroscopy.
- (180) Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T. H. *J. Org. Chem.* **1975**, *40*, 2141–2142. Dry Ozonation. A Method for Stereoselective Hydroxylation of Saturated Compounds on Silica Gel.
- (181) Cohen, Z.; Keinan, E.; Mazur, Y.; Ulman, A. *J. Org. Chem.* **1976**, *41*, 2651–2652. Hydroxylation with Ozone on Silica Gel. The Synthesis of 1 α ,25-Dihydroxyvitamin D₃.
- (182) Cohen, Z.; Varkony, T.; Keinan, E.; Mazur, Y. Tertiary Alcohols from Hydrocarbons by Ozonation on Silica Gel: 1-Adamantanol. In *Organic Synthesis*; Holand, W. E., Ed.; John Wiley & Sons: New York, 1988; Collect. Vol. 6, pp 43–50.
- (183) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264–1269. Studies on the Synthesis of Side-Chain Hydroxylated Metabolites of Vitamin D. 2. Stereocontrolled Synthesis of 25-Hydroxyvitamin D₃.
- (184) Inhoffen, H. H.; Schütz, S.; Rossberg, P.; Berges, O.; Nordsiek, K.-H.; Plenio, H.; Höroldt, E. *Chem. Ber.* **1958**, *91*, 2626–2629. Studien in der Vitamin D-Reihe, XXVII. (+)- und (-)-8-Methyl-trans-hydrindanol-(4)-ons-(1). (Studies in the Vitamin D Series, XXVII. (+)- and (-)-8-Methyl-trans-hydrindanol-4-ol-1-one).
- (185) Inhoffen, H. H.; Prinz, E. *Chem. Ber.* **1954**, *87*, 684–689. Studien in der Vitamin D-Reihe IV: Synthese der 3-Methyl-3-carboxycyclohexanon-(1)-propionsäure-(2 β) sowie ihre Überführung in das 8-Methyl-hydrindan-dion-(1.4). (Studies in the Vitamin D Series, IV: Synthesis of 3-Methyl-3-carboxycyclohexane-1-one-2 β -propionic acid As Well as Its Conversion into 8-Methyl-hydrindane-1,4-dione).
- (186) Chapleo, C. B.; Hallett, P.; Lythgoe, B.; Waterhouse, I.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1211–1218. Calciferol and Its Relatives. Part 19. Synthetic Applications of Cyclic Orthoesters: Stereospecific Synthesis of a Bicyclic Alcohol Related to the Vitamins D.
- (187) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608–2612. Calciferol and Its Relatives. Part 20. A Synthesis of Windaus and Grundmann's C₁₉ Ketone.
- (188) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378–4380. A Stereocontrolled Approach Toward Vitamin D Metabolites. A Synthesis of the Inhoffen-Lythgoe Diol.
- (189) Grieco, P. A.; Brandes, E. B.; Mc Cann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849–5851. Water as a Solvent for the Claisen Rearrangement: Practical Implications for Synthetic Organic Chemistry.
- (190) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. Asymmetric Synthesis via Acetal Templates. 6. A Stereoselective Approach to a Key Intermediate for the Preparation of Vitamin D Metabolites.
- (191) Stork, G.; Hutchinson, D.; Okabe, M.; Parker, D.; Ra, C.; Ribéreau, F.; Suzuki, T.; Zebovitz, T. *Pure Appl. Chem.* **1992**, *64*, 1809–1812. A Total Synthesis of Calcitriol.
- (192) Stork, G.; Kobayashi, Y.; Suzuki, T.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 1661–1663. The Allylic Epoxide Cyclization. A Method for the Control of Regiochemistry and Stereochemistry in Cyclohexane Systems.
- (193) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1893–1895. Enantioselective Synthesis of a C/D-Ring Synthon for the Preparation of Vitamin D₃ Metabolites.
- (194) Brandes, E.; Grieco, P. A.; Garner, P. *J. Chem. Soc., Chem. Commun.* **1988**, 500–502. Diastereoselection in an Aqueous Diels-Alder Reaction: a Formal Total Synthesis of the Inhoffen-Lythgoe Diol.
- (195) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137–3139. Aqueous Intermolecular Diels-Alder Chemistry: Reactions of Diene Carboxylates with Dienophiles in Water at Ambient Temperature.
- (196) Baggaley, K. H.; Brooks, S. G.; Green, J.; Redman, B. T. *J. Chem. Soc. (C)* **1971**, 2671–2680. Bicyclo[4.3.0]nonanes (Hydrindanes). Part I.
- (197) Baggaley, K. H.; Brooks, S. G.; Green, J.; Redman, B. T. *J. Chem. Soc. (C)* **1971**, 2678–2680. Bicyclo[4.3.0]nonanes (Hydrindanes). Part II. Stability Relationships.
- (198) Ziegler, F. E.; Mencil, J. *J. Tetrahedron Lett.* **1983**, *24*, 1859–1862. Application of Dithianylidene Anions to the Synthesis of DE-AB-8-Carbomethoxycholestan-9-One: A Steroid and Vitamin D Synthon.
- (199) Rao, H. S. P.; Reddy, K. S. *Tetrahedron Lett.* **1994**, *35*, 171–174. Palladium Assisted Transfer Hydrogenation of Cyclic α,β -Unsaturated Ketones by Ammonium Formate.
- (200) Baggolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945–2948. Stereoselective Total Synthesis of 1 α ,25-Dihydroxycholecalciferol.
- (201) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggolini, E. G.; Hennessy, B. M.; Uskokovic, M. R. *Tetrahedron* **1984**, *40*, 2283–2296. Stereoselective Total Synthesis of 1 α ,25S,26-Trihydroxycholecalciferol.
- (202) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612–1615. Synthesis and Conversion of 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione to the Isomeric Racemic Ketols of the [3.2.1]-Bicyclooctane and of the Perhyrindan Series.
- (203) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry.
- (204) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239–3243. The Stereocontrolled Synthesis of *trans*-Hydrindan Steroidal Intermediates.
- (205) Fernández, B.; Pérez, J. A. M.; Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 3173–3178. Synthesis of Hydrindan Derivatives Related to Vitamin D.
- (206) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268–270. On the Antarafacial Stereochemistry of the Thermal [1,7]-Sigmatropic Hydrogen Shift.
- (207) Daniewski, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, *53*, 5534–5535. A Simple Way to (3 α R,4S,7 α S)-(Z)-1-Ethylideneoctahydro-7 α -methyl-1H-4-indenol, a Synthon for Total Synthesis of Vitamins D.
- (208) Daniewski, A. R.; Kiegiel, J.; Piotrowska, E.; Warchol, T.; Wojciechowska, W. *Liebigs Ann. Chem.* **1988**, 593–594. Copper(I) Iodide-Promoted Reaction of Some Electrophiles with the Aluminum Enolate Generated by the Stereoselective Conjugate Reduction of (7 α S)-(+)-5,6,7,7a-Tetrahydro-7a-methylindan-1,5-dione.
- (209) Daniewski, A. R.; Kiegiel, J. *Synth. Commun.* **1988**, *18*, 115–118. Stereoselective Conjugate Reduction of (+)-(7 α S)-5,6,7,7a-Tetrahydro-7a-methyl-1,5-indandione.
- (210) Tsuda, T.; Kawamoto, T.; Kumamoto, Y.; Saegusa, T. *Synth. Commun.* **1986**, *16*, 639–643. Stereoselective Synthesis of Angularly Methylated *Trans* Fused Hydrindanone by Conjugate Reduction.
- (211) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540. Methylcopper(I)-Catalyzed Selective Conjugate Reduction of α,β -Unsaturated Carbonyl Compounds by Diisobutylaluminum Hydride in the Presence of Hexamethylphosphoric Triamide.
- (212) Ficini, J. *Pure Appl. Chem.* **1989**, *61*, 381–384. Stereocontrolled Synthesis of Dihydroxycholecalciferol Precursors.
- (213) Desmaële, D.; Ficini, J.; Guingant, A.; Touzin, A. M. *Tetrahedron Lett.* **1983**, *24*, 3083–3086. Synthèse Totale et Stereoselective du P. Tollysulfonylemethyl-8 des-AB-Cholestene-8 (Total Stereoselective Synthesis of 8-*p*-Tollysulfonylemethyl-des-AB-cholest-8-ene).
- (214) Desmaële, D.; Ficini, J.; Guingant, A.; Kahn, Ph. *Tetrahedron Lett.* **1983**, *24*, 3079–3083. Influence de la Substitution en 1 sur la Stereoselectivité de l'Hydrolyse de N,N Diethylamino-7 Dialkyl-1,6 Bicyclo (3,2,0) Heptene-6 Ones-2; une Nouvelle Voie d'Accès au Contrôle des Centres C₁₇ et C₂₀ de Stéroïdes (Effect of Substitution at the 1 Position on the Stereoselectivity of the Hydrolysis of N,N-Diethyl-7-amino-1,6-dialkylbicyclo[3.2.0]hept-6-en-2-ones; A New Path for Access to the Control of Steroidal C₁₇ and C₂₀ Centers).
- (215) Freeman, R.; Haynes, R. K.; Loughlin, W. A.; Mitchell, C.; Stokes, J. V. *Pure Appl. Chem.* **1993**, *65*, 647–654. Synthetic Utilization of Highly Stereoselective Conjugate Addition Reactions of Phosphorus and Sulfur Stabilized Allylic Carbanions.
- (216) (a) Haynes, R. K.; Stokes, J. P.; Hambley, T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58–60. The Preparation of (*R*)- and (*S*)-(*E*)-But-2-enyl-*t*-butylphenylphosphine Oxides and their Enantiospecific Conversion into Enantiomeric Hydrindanones Related to Vitamin D. (b) Loughlin, W. A.; Haynes, R. K. *J. Org. Chem.* **1995**, *60*, 807–812. An Efficient Stereoselective Synthesis of a Racemic CD-Intermediate of Vitamin D. (c) Loughlin, W. A.; Haynes, R. K. *Aust. J. Chem.* **1995**, *48*, 663–668. Model Studies on the Construction of Side Chains for CD Intermediates of Vitamin D. (d) Loughlin, W. A.; Haynes, R. K.; Sitpaseuth, S. *Australia J. Chem.* **1995**, *48*, 491–503. Studies Towards CD Intermediates of Vitamin D₃: Enolate Trapping of Ketone Enolates with Novel Sulfonyl Electrophiles.
- (217) (a) Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *J. Org. Chem.* **1989**, *54*, 5162–5170. Use of β -Sulfonyl Vinyl Ketones as Equivalents to Vinyl Ketones in Robinson Annulation. Convergent, Highly Stereoselective Preparation of a Hydrindanol Related to Vitamin D from 2-Methylcyclopent-2-enone and Lithiated (*E*)-But-2-enyldiphenylphosphine Oxide. (b) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1987**, 92–94. Preparation of Hydrindanones from 2-Methylcyclopent-2-enone and the Carbanion of (*E*)-But-2-enyldiphenylphosphine Oxide: Efficient Enolate Trapping with β -Sulphonylvinyl Ketones.
- (218) Fujimoto, G. I. *J. Am. Chem. Soc.* **1951**, *73*, 1856. Labeling of Steroids in the 4-Position.
- (219) (a) Marczak, S.; Wicha, J. *Tetrahedron Lett.* **1993**, *34*, 6627–6630. A Total Synthesis of the C/D Rings - Side Chain Fragment of Vitamin D and Sterols, Using Mukaiyama - Michael Conjugate Addition. (b) Marczak, S.; Michalak, K.; Wicha, J. *Tetrahedron Lett.* **1995**, *36*, 5425–5428. Short Total Synthesis of the CD Rings-Side Chain Fragment of 25-Hydroxyvitamin D₃ and De-

- AB-Cholestane Derivatives, Involving Two Tandem Mukaiyama-Michael Conjugate Additions.
- (220) Clase, J. A.; Money, T. *Can. J. Chem.* **1992**, *70*, 1537–1544. An Enantiospecific Route to C,D Ring Synthons for Steroid Synthesis.
- (221) Hutchinson, J. H.; Money, T.; Piper, S. E. *Can. J. Chem.* **1986**, *64*, 854–860. Ring Cleavage of Camphor Derivatives: Formation of Chiral Synthons for Natural Product Synthesis.
- (222) Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, *26*, 1819–1822. An Enantiospecific Synthesis of Estrone.
- (223) Hutchinson, J. H.; Money, T. *J. Chem. Soc., Chem. Commun.* **1986**, 288–289. Enantiospecific Synthetic Approach to C,D-Ring System of Steroids with Functionalized Side-chains.
- (224) Stevens, R. V.; Lawrence, D. S. *Tetrahedron* **1985**, *41*, 93–100. Camphorae: Chiral Intermediates for the Total Synthesis of Steroids. Part 2. An Enantiospecific Approach Toward Vitamin D Metabolites.
- (225) Stevens, R. V.; Gaeta, F. C. A.; Lawrence, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 7713–7719. Camphorae: Chiral Intermediates for the Enantiospecific Total Synthesis of Steroids. 1.
- (226) Trahanovsky, W. S.; Flash, P. J.; Smith, L. M. *J. Am. Chem. Soc.* **1969**, *91*, 5068–5072. Oxidation of Organic Compounds with Cerium(IV). VIII. Oxidation of Bicyclo[2.2.1]-2-heptanols and Bicyclo[2.2.2]-2-octanol.
- (227) Takahashi, T.; Okumoto, H.; Tsuji, J. *J. Org. Chem.* **1984**, *49*, 948–950. Synthesis of a Chiral Steroid CD-Ring Synthon from D-Leucine by means of Diastereotopic Face-Selection.
- (228) Takahashi, T.; Naito, Y.; Tsuji, J. *J. Am. Chem. Soc.* **1981**, *103*, 5261–5263. A Simple Synthesis of De-AB-cholesta-8(14),22-dien-9-one by Highly Stereoselective Double Michael Addition Involving Alkenylcopper-Phosphine Complex, Vinyl Ketone, and 2-Methyl-2-cyclopentenone Followed by Claisen Rearrangement and Rhodium-Promoted Decarbonylation.
- (229) Takahashi, T.; Okumoto, H.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 1925–1928. New Synthesis of a Chiral Steroid CD-Ring Synthon by means of Enantioselective Double Michael Addition.
- (230) Suzuki, T.; Sato, E.; Unno, K. *Chem. Pharm. Bull.* **1993**, *41*, 244–247. Potential Intermediates to Vitamin D₃ and Steroids: Enantioselective Syntheses of (20R)- and (20S)-De-AB-cholesta-8(14),22-dien-9-one from (S)- and (R)-2,3-O-Isopropylidene-glyceraldehyde.
- (231) Suzuki, T.; Sato, E.; Unno, K.; Kamentani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 724–726. New Route to (+)-(20R)-De-AB-cholesta-8(14),22-dien-9-one and (+)-(20S)-De-AB-cholesta-8(14),22-dien-9-one from (S)- and (R)-2,3-O-Isopropylidene-glyceraldehyde.
- (232) Takahashi, T.; Miyazawa, M.; Ueno, H.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 3881–3884. Palladium-Catalyzed Stereoccontrolled Cyclization of 1,3-Diene Monoepoxide: A Route to a New Synthetic Intermediate for De-AB-Cholestane Derivative.
- (233) Takahashi, T.; Ueno, H.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 4463–4466. Stereoselective Synthesis of Steroid Side Chain and CD-Rings. A Route to (±)-De-AB-Cholesta-8(14),22-dien-9-one.
- (234) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1984**, *25*, 4669–4672. A Novel Stereoccontrolled Approach to Steroid Side Chain Construction: Asymmetric Synthesis of Potential Synthon of the Vitamin D Series.
- (235) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311–5320. A Novel Approach to the Stereoccontrolled Synthesis of Steroid Side Chains Including the CD-Ring System: The First Total Synthesis of (+)-8α-(Phenylsulfonyl)-des-AB-cholestane and Its Efficient Conversion into Grundmann's Ketone and Vitamin D₃.
- (236) Shimizu, I.; Matsuda, N.; Noguchi, Y.; Zako, Y.; Nagasawa, K. *Tetrahedron Lett.* **1990**, *31*, 4899–4902. Synthesis of Vitamin D₃ D Ring Synthons by Reductive Cleavage of Norbornan-6-one-2-carboxylates.
- (237) Hatakeyama, S.; Numata, H.; Takano, S. *Tetrahedron Lett.* **1984**, *25*, 3617–3620. A Novel Stereoselective Synthesis of a Chiral Key Intermediate for the Preparation of Vitamin D₃.
- (238) Daniewski, A. R.; Warchol, T. *Liebigs Ann. Chem.* **1992**, 965–973. Synthesis of the Ring D-Building Block of (24S)-24-Hydroxy Vitamin D₃ from Menthol, I.
- (239) Tanimori, S.; He, M.; Nakayama, M. *Synth. Commun.* **1993**, *23*, 2861–2868. Stereoselective Syntheses of 22-Oxavitamin D₃ D and CD Ring Synthones by Using Cleavage of Activated Cyclopropane.
- (240) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1400–1404. Calciferol and its Relatives. Part 27. A Synthesis of 1α-Hydroxyvitamin D₃ by way of 1α-Hydroxytachysterol.
- (241) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1979**, 4419–4422. New Routes to 1α-Hydroxyvitamin D₃.
- (242) Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. (C)* **1971**, 2955–2959. Calciferol and its Relatives. Part XV. The Preparation of Des-AB-cholest-8-ene-8-carbaldehyde {1β-[(1R)-1,5-Dimethylhexyl]-3α,6,7,7aβ-tetrahydro-7aβ-methylindane-4-carbaldehyde} and 9α-Chloro-des-AB-cholestan-8-one {5α-Chloro-1β-[(1R)-1,5-dimethylhexyl]-7aβ-methyl-trans-perhydroindan-4-one}.
- (243) Kocienski, P. J.; Lythgoe, B.; Roberts, D. A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 897–901. Calciferol and its Relatives. Part 26. A Conversion of Cholesterol into 8-Hydroxymethyl-des-AB-cholest-8-ene.
- (244) Grieco, P. A.; Takigawa, T.; Moore, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 4380–4381. Bicyclo[2.2.1]heptanes in Organic Synthesis. Stereoccontrolled Approach to Sterol Side-Chain Construction: Synthesis of De-AB-cholest-11-en-9-one.
- (245) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310–312. Stereochemical Control of the Internal Michael Reaction. A New Construction of trans-Hydrindane Systems.
- (246) Stork, G.; Atwal, K. S. *Tetrahedron Lett.* **1982**, *23*, 2073–2076. An Isomerization-Claisen Rearrangement Route to Olefinic Dicarbonyl Starting Materials for Conjugate Cyclization.
- (247) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767–3768. Stereochemical Control of Intramolecular Conjugate Addition. A Short, Highly Stereoselective Synthesis of Adrenosterone.
- (248) Yamamoto, K.; Iijima, M.; Ogimura, Y.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 2813–2816. An Asymmetric Approach to the Synthesis of Trans-Dihydrindandione.
- (249) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364–2368. A New Route to Functionalized trans-Hydrindenones.
- (250) Karras, M.; Snider, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951–7953. Alkylaluminum Chloride Induced Cyclization of Unsaturated Carbonyl Compounds.
- (251) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153–157. A New Method for Cyclopentanone Annelation.
- (252) Denmark, S. E.; Germanas, J. P. *Tetrahedron Lett.* **1984**, *25*, 1231–1234. A Vinylsilane Route to Trans-7a-methylhydrind-4-en-1,6-dione.
- (253) Takahashi, T.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 233–234. Highly Stereoselective Claisen Rearrangement of Vinyl Ether of 1-(1-Hydroxyethyl)-2-methyl-3-alkylcyclopentene. A Route to Cis- and Trans (1E)-Ethylidene-8-methylhydrindan-5-one.
- (254) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1984**, *49*, 3278–3281. Tandem Cope-Claisen Rearrangement in the Synthesis of Steroids: Stork's Keto Acid.
- (255) Stork, G.; Mah, R. *Tetrahedron Lett.* **1989**, *30*, 3609–3612. Introduction of Angular Methyl Groups Via Radical Cyclization.
- (256) Shimada, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1988**, *29*, 6961–6964. Efficient Stereocontrol of a Quaternary Chiral Center in the Cyclohexene Systems. Potential Chiral Synthons for Vitamin D and Related Compounds by Enzymatic Approach.
- (257) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929–3932. Simple Regioselective Synthesis of Trans-7a-methylhydrind-4-en-1-one, A Key Intermediate for Steroid Total Synthesis.
- (258) Taber, D. F.; Campbell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141–5144. The Intramolecular Diels-Alder Reaction: Stereocontrol Through Nonsynchronous Bond Formation?
- (259) Bal, S. A.; Helquist, P. *Tetrahedron Lett.* **1981**, *22*, 3933–3936. Synthesis of Steroid Precursors. Intramolecular Diels-Alder Approach to the Trans-Hydrindenone System.
- (260) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269–2283. Stereochemical Aspects of the Intramolecular Diels-Alder Reactions of Deca-2,7,9-trienoate Esters. 3. Thermal, Lewis Acid Catalyzed, and Asymmetric Cyclizations.
- (261) Wilson, S. R.; Haque, M. S. *J. Org. Chem.* **1982**, *47*, 5411–5413. A Stereoselective Approach to Steroid Trans C/D Ring Synthons.
- (262) Wilson, S. R.; Haque, M. S. *Tetrahedron Lett.* **1984**, *25*, 3147–3150. An Asymmetric Total Synthesis of Vitamin D₃ (Cholecalciferol).
- (263) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1982**, *47*, 337–342. New Approaches to the Synthesis of Vitamin D Metabolites. 1. Stereocontrol in the Intramolecular Diels-Alder Reaction.
- (264) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1987**, *52*, 4369–4377. New Approaches to the Synthesis of Vitamin D Metabolites. 2. The Effect of Some Substituents on Stereochemistry in the Intramolecular Cycloadditions of Nonatrienes.
- (265) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, *25*, 2121–2124. Stereoselectivity in Intramolecular Diels-Alder Reactions; A Short Total Synthesis of (±)-Estrone.
- (266) Zhu, G.-D.; Van Lancker, B.; Van Haver, D.; De Clercq, P. *J. Bull. Soc. Chim. Belg.* **1994**, *103*, 263–271. Intramolecular Diels-Alder Reaction of 8-Trifluoromethyl-1,3,8-nonatrienes: An Access to Angular Trifluoromethylated Hydrindenones.
- (267) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696–6704. Intramolecular Diels-Alder Reactions: The Angularly Methylated trans-Perhyrindand Ring System.
- (268) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183–234. The Intramolecular Diels-Alder Reaction: Recent Advances and Synthetic Applications.
- (269) Wilson, S. R.; Haque, M. S. *Tetrahedron Lett.* **1984**, *25*, 3151–3154. Chiral Ring A Synthons for Vitamin D Synthesis.
- (270) Wilson, S. R.; Jacob, L. *J. Org. Chem.* **1992**, *57*, 4380–4385. An Intramolecular Diels-Alder Approach to the Cis Ring Fused Isomer of the 25-Hydroxy Vitamin D₂ Grundmann Ketone.

- (271) Nemoto, H.; Ando, M.; Fukumoto, K. *Tetrahedron Lett.* **1990**, *31*, 6205–6208. A Novel *o*-Quinodimethane Strategy for an Active Metabolite of Vitamin D₃. A Total Synthesis of 25-Hydroxy Windaus-Grundmann Ketone.
- (272) Dauben, W. G.; Ollmann, R. R., Jr.; Wu, S. C. *Tetrahedron Lett.* **1994**, *35*, 2149–2152. Photochemical Synthesis of C/D-Ring Synthons of Vitamin D.
- (273) Morzycki, J. W.; Jurek, J.; Rodewald, W. J. *Tetrahedron Lett.* **1985**, *26*, 4243–4244. The Convenient Route to CD Fragment for the Synthesis of Vitamin D₃ Relatives.
- (274) Morzycki, J. W.; Jurek, J.; Rodewald, W. J. *Can. J. Chem.* **1986**, *64*, 1540–1543. Synthesis of 8-Methylene-des-AB-cholestan-9-one by Cholesterol Degradation.
- (275) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615–3616. Hydrazine Reduction of α,β -Epoxy Ketones to Allylic Alcohols. (b) Benn, W. R.; Dodson, R. M. *J. Org. Chem.* **1964**, *29*, 1142–1148. The Synthesis and Stereochemistry of Isomeric 16-Hydroxy-17(20)-pregnenes.
- (276) Additional references include: (a) Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847–5849. A New Candidate for a Properly Substituted CD Ring Component of Vitamin D₃ via Intramolecular Asymmetric Olefination of a 1,3-Cyclopentanedione Derivative. (b) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962–2963. Transition Metal-Catalyzed Intramolecular [4+2] Cycloadditions: Initial Studies on Stereochemistry and on Steroid and Vitamin D Analog Syntheses. (c) Takahashi, T.; Katouda, W.; Sakamoto, Y.; Tomida, S.; Yamada, H. *Tetrahedron Lett.* **1995**, *36*, 2273–2276. Stereochemical Prediction for Tandem Radical Cyclization Based on MM2 Transition State Model. New Approach to Steroid CD-Ring.
- (277) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414–1417. Studies on a Convergent Route to Side-Chain Analogues of Vitamin D: 25-Hydroxy-23-oxavitamin D₃.
- (278) Wang, Y.; Ting, H.-S.; Huang, J.-J.; Chow, Y.-C.; Huang, Y.-T. *Acta Chim. Sin.* **1958**, *24*, 126–133. Studies on Vitamin D. I. 7,8-Dihydroxy-7,8-Dihydrovitamin D₂.
- (279) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251–254. Epoxides as Alkene Protecting Groups. A Mild and Efficient Deoxygenation.
- (280) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041–5044. 3-Cuprio-2-pyrone: A Extraordinary Organocopper Reagent.
- (281) Posner, G. H.; Carry, J.-C.; Anjeh, T. E. N.; French, A. N. *J. Org. Chem.* **1992**, *57*, 7012–7014. A New and Efficient Asymmetric Synthesis of an A-Ring Precursor to Physiologically Active 1 α -Hydroxyvitamin D₃ Steroids.
- (282) Posner, G. H.; Eydoux, F.; Lee, J. K.; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541–7544. Binaphthol-titanium-promoted, Highly Enantiocontrolled, Diels-Alder Cycloadditions of Electronically Matched 2-Pyrones and Vinyl Ethers: Streamlined Asymmetric Synthesis of an A-Ring Precursor to Physiologically Active 1 α -Hydroxyvitamin D₃ Steroids.
- (283) Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, *35*, 7545–7548. Lewis Acid-Catalyzed, High Pressure, Stereospecific, Regiospecific, Diels-Alder Cycloaddition of Unsubstituted 2-Pyrone: Short Synthesis of a Racemic A-Ring Precursor to Physiologically Active 1-Hydroxyvitamin D₃ Steroids.
- (284) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515–3517. Efficient Enantiospecific Synthesis of Key A-Ring Synthons for the Preparation of 1 α ,25-Dihydroxyvitamin D₃ Using a Chromium(II)-Mediated Reaction.
- (285) Kobayashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577–1580. An Enantioselective Synthesis of the A-Ring Synthon for Vitamin D₃ Metabolites by Chemicoenzymatic Approach.
- (286) Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701–7704. Asymmetric Synthesis of a Key 1 α ,25-Dihydroxy-Vitamin D₃ Ring A Synthon.
- (287) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954. Catalytic Asymmetric Glyoxylate-Ene Reaction: A Practical Access to α -Hydroxy Esters in High Enantiomeric Purities.
- (288) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940–1941. Asymmetric Glyoxylate-Ene Reaction Catalyzed by Chiral Titanium Complexes: A Practical Access to α -Hydroxy Esters in High Enantiomeric Purities.
- (289) Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 4365–4368. A Short, Efficient Route to 1-Hydroxylated Vitamin D Ring A Fragments.
- (290) Torneiro, M.; Vrielynck, S.; García, A. M.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. A New Route to the Lythgoe-Roche's A Ring Precursor of 1 α ,25-Dihydroxyvitamin D₃. In *Vitamin D. A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 39–40.
- (291) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939–5942. The Directed Reduction of β -Hydroxy Ketones Employing Me₄NHB(OAc)₃.
- (292) Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523–2529. An Efficient Asymmetric Synthesis of 1 α ,25-(OH)₂ Vitamin D₃ A-Ring Synthon.
- (293) Tazumi, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1903–1904. Enantioconvergent Preparation of the A-Ring Precursors of Calcitriol from Either (R)- or (S)-Epichlorohydrin.
- (294) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369–13376. An Efficient Route to a Key A-Ring Synthon for 1 α ,25-Dihydroxyvitamin D₃ and its Analogs.
- (295) Batty, D.; Crich, D. *J. Chem. Soc. Perkin Trans. I* **1991**, 2894–2895. A Radical Cyclization Approach to 1 α ,25-Dihydroxyvitamin D₃.
- (296) Batty, D.; Crich, D.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1366–1368. Synthesis of a 1 α ,25-Dihydroxyvitamin D₃ A Ring Model by an Acyl Radical Cyclization.
- (297) Chen, C.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 1945–1948. An Asymmetric Synthesis of a 1 α ,25-Dihydroxyvitamin D₃ A-Ring Synthon.
- (298) Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943–7954. The Cyclization Route to the Calcitriol A-ring: A Formal Synthesis of (+)-1 α ,25-Dihydroxyvitamin D₃.
- (299) Dawson, T. M.; Dixon, J.; Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. (C)* **1971**, 2960–2966. Calciferol and its Relatives. Part XVI. Total Synthesis of Precalciferol.
- (300) Dixon, J.; Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc., Chem. Commun.* **1970**, 993–994. Total Synthesis of Precalciferols.
- (301) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *Tetrahedron Lett.* **1973**, 3649–3652. Total Synthesis of 1 α -Hydroxyvitamin D₃.
- (302) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485–3498. Palladium-catalysed Coupling of Vinyl Triflates with Enynes and its Application to the Synthesis of 1 α ,25-Dihydroxyvitamin D₃.
- (303) Dawson, T. M.; Dixon, J.; Lythgoe, B.; Siddiqui, I. A. *J. Chem. Soc., Chem. Commun.* **1970**, 992. (S)-3-Ethynyl-4-methylcyclohex-3-en-1-ol.
- (304) Dawson, T. M.; Dixon, J.; Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. (C)* **1971**, 2960–2966. Calciferol and its Relatives. Part XVI. Total Synthesis of Precalciferol₂.
- (305) Okamura, W. H.; Elnagar, H. Y.; Ruther, M.; Dobreff, S. *J. Org. Chem.* **1993**, *58*, 600–610. Thermal [1,7]-Sigmatropic Shift of Previtamin D₃ to Vitamin D₃: Synthesis and Study of Penta-deuterio Derivatives.
- (306) Desmaele, D.; Tanier, S. *Tetrahedron Lett.* **1985**, *26*, 4941–4944. Nouvelle Synthèse du Cycle a du 1S-Hydroxycholecalciferol a Partir de l'Acide Quinique (Novel Synthesis of Ring A of 1S-Hydroxycholecalciferol from Quinic Acid).
- (307) Baggolini, E. G.; Hennessy, B. M.; Iacobelli, J. A.; Uskokovic, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095–2098. Stereospecific Synthesis of the Lythgoe's Ring A Aldehyde for the Preparation of 1 α -Hydroxylated Tachysterols and Calciferols.
- (308) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363–2366. Criegee Rearrangement of α -Alkoxy Hydroperoxides a Synthesis of Esters and Lactones that Complements the Baeyer-Villiger Oxidation of Ketones.
- (309) Castedo, L.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 2099–2102. An Improved Synthesis of 1 α ,25-Dihydroxyvitamin D₃ A Synthons.
- (310) Still, W. C.; Mitri, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927–1928. A Highly Stereoselective Synthesis of Z-Trisubstituted Olefins via [2,3]-Sigmatropic Rearrangement. Preference for a Pseudo-axially Substituted Transition State.
- (311) Okamura, W. H.; Craig, A. S.; Curtin, M. L.; De Lera, A. R.; Figadère, B.; Muralidharan, K. R.; Palenzuela, J. A. Side-Chain and Deuterium Labeled Analogs of 1 α ,25-Dihydroxyvitamin D₃. In *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 169–177.
- (312) Okamura, W. H.; Condra, P., Jr.; Hammond, M. L.; Mouriño, A.; Messing, A. W. The Vinylallene Approach to 1 α -Hydroxyvitamin D Analogs. In *Vitamin D. Basic Research and Its Clinical Application*; Norman, A. W., Schaefer, K., v. Herrath, D., Grigoleit, H.-G., DeLuca, H. F., Mawer, E. B., Suda, T., Eds.; Walter de Gruyter: Berlin, 1979; pp 5–12.
- (313) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81–88. Pericyclic Reactions of Vinylallenes: From Calciferols to Retinoids and Drimanens.
- (314) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459–1464. Studies on Vitamin D and Related Compounds XXII. New Reactions and Products in Vitamin D₃ Photochemistry.
- (315) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907–4908. Sigmatropic Rearrangement of Vinylallenes: A Novel Route to the 1-Hydroxyvitamin D System.
- (316) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6259–6267. Studies on Vitamin D (Calciferol) and Its Analogues. 18. The Vinylallene Approach to the 1-Hydroxyvitamin D System. New Sigmatropic Reactions in the Vitamin D Series.

- (317) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4015–4020. Studies on Vitamin D (Calciferol) and Its Analogues. 20. Synthesis of 3-Deoxy-3,3-dimethyl-1-hydroxyvitamin D₃ from Vinylallene Intermediates and Related Thermal and Configurational Studies.
- (318) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099–6105. Effect of 3-Methyl Substituents on the Thermal [1,5]- and [1,7]-Sigmatropic Hydrogen Shifts of Vinylallenes and Other Seco Steroids Related to Vitamin D: Synthesis of 3-Methyl- and 3,3-Dimethyl-Substituted Analogues of 3-Deoxy-1 α ,25-dihydroxyvitamin D₃.
- (319) Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1980**, *45*, 4011–4015. Studies on Vitamin D (Calciferol) and Its Analogues. 19. Rearrangement of Vinylallenes to 1-Hydroxylated Vitamin D Model Systems Lacking the D Ring and Side Chain.
- (320) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 5197–5200. Synthesis and Thermolysis of A-Norvinylallenes Related to Vitamin D.
- (321) Haces, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6105–6109. Heterocalciferols: Novel 3-Thia and 3-Sulfinyl Analogues of 1 α -Hydroxyvitamin D₃.
- (322) Jeganathan, S.; Johnston, A. D.; Kuenzel, E. A.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1984**, *49*, 2152–2158. Thermal Rearrangement of Vinylallenes: Synthesis of 3-Deoxy-1 α -hydroxy-14-epiprevitamin D₃.
- (323) Gibbs, R. A.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 6021–6024. Synthesis of 3-Deoxy-1 α ,25-dihydroxy-9,11-dehydrovitamin D₃: Selective Formation of 6 β -Vitamin D Vinylallenes and Their Thermal [1,5]-Sigmatropic Hydrogen Shift.
- (324) Gerdes, J. M.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 4030–4035. Effect of Seven-Membered Ring Fusion on Thermal Pericyclic Processes of Vinylallenes and Other Seco Steroids Related to A-Homovitamin D.
- (325) Wu, K.-M.; Midland, M. M.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 4381–4392. Structural Effects on [1,5]-Sigmatropic Hydrogen Shifts of Vinylallenes.
- (326) Silveira, M. H.; Okamura, W. H. *J. Org. Chem.* **1985**, *50*, 2390–2392. An Improved Synthesis of Seven-Membered Ring-Fused 12-s-Cis Conformationally Locked 11-cis-Retinoids.
- (327) Shen, G.-Y.; de Lera, A. R.; Norman, T. C.; Haces, A.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 2917–2920. Thermal Rearrangement of Tert-Butyl Substituted 9,10- and 11,12-Allenic Retinoids: 11-Cis-Isomers of 19,19,19- and 20,20,20-Trimethylretinoids.
- (328) Sodeoka, M.; Satoh, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823–4824. Highly Efficient Synthesis of Carbacyclin Analogue. Stereospecific Synthesis of Aryl-Substituted Exocyclic Olefin.
- (329) Sodeoka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906–4911. A New Method for the Stereocontrolled Synthesis of Silyl Dienol Ethers Using (Naphthalene)chromium Tricarbonyl Catalyzed Isomerization.
- (330) Yamada, H.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4569–4574. A New Method for the Stereocontrolled Synthesis of Dienamine Derivatives Using (Naphthalene)chromium Tricarbonyl Catalyzed Isomerization.
- (331) Davies, S. G.; Goodfellow, C. L. *J. Organomet. Chem.* **1988**, *340*, 195–201. Stereoselective Synthesis of Arenechromium Tricarbonyl Complexes: Origins of the Benzylic Oxygen Directing Effects for 1-Tetralol Derivatives.
- (332) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42. Palladium-Catalyzed Cycloisomerizations of Enynes and Related Reactions.
- (333) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923–1924. Palladium-Catalyzed Alkylative Cyclization of 1,6- and 1,7-Enynes.
- (334) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924–1925. New Strategy for the Total Synthesis of 1 α -Hydroxyvitamin D Derivatives.
- (335) (a) Trost, B. M.; Dumas, J. *PCT Int.* **1993**, *16*, 022, 1993; US, 831, 687, 1992; *Chem. Abstr.* **1994**, *120*, 107474f. Palladium-catalyzed Alkylative Cyclization Useful in Synthesis of Vitamin D and Analogs. (b) Okamoto, M.; Fujii, T.; Tanaka, T. *Tetrahedron* **1995**, *51*, 5543–5556. The First Convergent Synthesis of 1 α ,24-(R)-Dihydroxyvitamin D₃ via Diastereoselective Isopropylation and Alkylative Enyne Cyclization.
- (336) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905–3909. Mechanism of Wittig Reaction: Evidence against Betaine Intermediate.
- (337) Trost, B. M.; Hanson, P. R. *Tetrahedron Lett.* **1994**, *35*, 8119–8122. A Practical Asymmetric Synthesis of a 1,7-Enyne A-Ring Synthon En Route Toward the Total Synthesis of Vitamin D Analogues.
- (338) Moriarty, R. M.; Kim, J.; Brumer, H., III. *Tetrahedron Lett.* **1995**, *36*, 51–54. A General Synthetic Route to A-Ring Hydroxylated Vitamin D Analogs from Pentoses.
- (339) Moriarty, R. M.; Kim, J.; Brumer, H., III. A General Synthetic Route to A-Ring Hydroxylated Vitamin D Analogs from D-Pentoses. In *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 27–28.
- (340) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19–22. On the Regioselectivity of Pd Catalyzed Intramolecular Carbometalations.
- (341) Nuss, J. M.; Murphy, M. M.; Rennels, R. A.; Heravi, M. H.; Mohr, B. J. *Tetrahedron Lett.* **1993**, *34*, 3079–3082. Convergent Approaches to the Vitamin D Skeleton Using a Transition Metal Catalyzed Carbometalation/Capture Strategy.
- (342) Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 7589–7592. A Novel Entry to the Vitamin D Triene System.
- (343) Mascareñas, J. L.; García, A. M.; Varela, C.; Castedo, L.; Mouriño, A. A New Route to the Vitamin D Triene System. In *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 49–50. See also: García, A. M.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1995**, *36*, 5413–5416. A Mild Palladium-Catalyzed Convergent Approach to the Vitamin D Skeleton.
- (344) Sheves, M.; Mazur, Y. *Tetrahedron Lett.* **1976**, 2987–2990. Cyclovitamins D₃: The Preparation of C₆-Ketocyclovitamin and Its Conversion to A Ring B/C Spirosteroid.
- (345) Wilson, S. R.; Venkatesan, A. M.; Augelli-Szafran, C. E. A Practical Synthesis of 1-Alpha-OH Vitamin D₃ Analogs. In *Vitamin D: Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schaefer, K., Grigoleit, H.-G., v. Herrath, D., Eds.; Walter de Gruyter: Berlin, 1988; pp 43–50.
- (346) Nemoto, H.; Wu, X.-M.; Kurobe, H.; Ihara, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1984**, *25*, 3095–3098. Convergent and Stereoselective Synthesis of Vitamin D₃ Via 3,5-Cyclovitamins D₃.
- (347) Nemoto, H.; Kimura, T.; Kurobe, H.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1985**, 1131–1132. A Stereoselective Synthesis of 1 α -Hydroxy-vitamin D₃.
- (348) Nemoto, H.; Wu, X.-M.; Kurobe, H.; Ihara, M.; Fukumoto, K. *Tetrahedron Lett.* **1983**, *24*, 4257–4260. Synthetic Studies Toward to 1 α -Hydroxyvitamin D₃—Stereoselective Synthesis of (\pm)-(Z)-2-(3 β ,5 α -Dihydroxy-2-methylenecyclohexylidene)ethylidenecyclohexane.
- (349) Nemoto, H.; Wu, X.-M.; Kurobe, H.; Minemura, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. I* **1985**, 1185–1190. A General Method for the Synthesis of 3,5-Cyclovitamin D₃ and Derivatives. A Stereoselective Synthesis of Vitamin D₃.
- (350) Nemoto, H.; Kimura, T.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Perkin Trans. I* **1986**, 1777–1780. A Stereoselective Synthesis of 1 α -Hydroxyvitamin D₃.
- (351) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699–4702. Preparation of Cyclohexanones and Cyclopentanones of High Optical Purity.
- (352) Branca, S. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1978**, *100*, 7767–7768. A Stereospecific Total Synthesis of (\pm)-Pentenomycin I, (\pm)-Pentenomycin II, and Dehydropentenomycin I Exploiting a Versatile Latent α -Ketovinyl Anion Equivalent.
- (353) (a) Moriarty, R. M.; Kim, J.; Guo, L. *Tetrahedron Lett.* **1993**, *34*, 4129–4132. Intramolecular Cyclopropanation Using Iodonium Ylides. The 3,5-Cyclovitamin D Ring A Synthon. (b) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc.* **1989**, *111*, 6443–6444. A Novel Intramolecular Cyclopropanation Using Iodonium Ylides.
- (354) Dauben, W. G.; Hendricks, R. T.; Pandey, B.; Wu, S. C.; Zhang, X.; Luzzio, M. J. *Tetrahedron Lett.* **1995**, *36*, 2385–2388. Stereoselective Intramolecular Cyclopropanations: Enantioselective Syntheses of 1 α ,25-Dihydroxyvitamin D₃ A-Ring Precursors.
- (355) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997–4998. Elaboration of Aldehydes and Ketones to Alkynes: Improved Methodology.
- (356) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942–3944. Samarium-Promoted, Stereocontrolled Cyclopropanation Reactions.
- (357) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525–3532. Samarium-Promoted Cyclopropanation of Allylic Alcohols.
- (358) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679–692. Homochiral Ketals in Organic Synthesis. Diastereoselective Cyclopropanation of α,β -Unsaturated Ketals Derived from 1,4-Di-O-benzyl-L-threitol.
- (359) Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Synlett* **1992**, 410–412. Efficient Chiral Route to a Key Building Block of 1,25-Dihydroxyvitamin D₃ via Lipase-Mediated Resolution.
- (360) Takano, S.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1043–1046. Enantiocomplementary Preparation of Optically Pure 2-Trimethylsilylethynyl-2-cyclopentenol by Homochiralization of Racemic Precursors: A New Route to the Key Intermediate of 1,25-Dihydroxycholecalciferol and Vincamine.
- (361) Pelc, B. *Steroids* **1977**, *30*, 193–201. The Selenium Dioxide Oxidation of Cholecalciferol.
- (362) Parren, H. E.; Hamer, D. E.; Schnoes, H. K.; DeLuca, H. F. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 2080–2081. Direct C-1 Hy-

- droxylation of Vitamin D Compounds: Convenient Preparation of 1 α -Hydroxyvitamin D₃, 1 α ,25-Dihydroxyvitamin D₃, and 1 α -hydroxyvitamin D₂.
- (363) Tachibana, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2090–2092. Syntheses of 1 β -Hydroxyvitamin D₂ and D₃.
- (364) Sicinski, R. R.; DeLuca, H. F. *Bioorg. Chem.* **1994**, *22*, 150–171. Synthesis, Conformational Analysis, and Biological Activity of the 1 α ,25-Dihydroxy-10,19-Dihydroxyvitamin D₃ Isomers.
- (365) Brown, A. J.; Perlman, K.; Schnoes, H. K.; DeLuca, H. F. *Anal. Biochem.* **1987**, *164*, 424–429. A New Tritium-Release Assay for 25-Hydroxyvitamin D-1 α -Hydroxylase.
- (366) Paaren, H. E.; Schones, H. K.; DeLuca, H. F. *J. Chem. Soc., Chem. Commun.* **1977**, 890–892. Synthesis of 1 β -Hydroxyvitamin D₃ and 1 β ,25-Dihydroxyvitamin D₃.
- (367) Sheves, M.; Friedman, N.; Mazur, Y. *J. Org. Chem.* **1977**, *42*, 3597–3599. Conformational Equilibria in Vitamin D. Synthesis of 1 β -Hydroxyvitamin D₃.
- (368) Moriarty, R. M.; Kim, J.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 3741–3744. A Convenient Synthesis of 1 α ,25-Dihydroxy-28-norvitamin D₂.
- (369) Paaren, H. E.; Mellon, W. S.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1985**, *13*, 62–75. Ring A-Stereoisomers of 1-Hydroxyvitamin D₃ and Their Relative Binding Affinities for the Intestinal 1 α ,25-Dihydroxyvitamin D₃ Receptor Protein.
- (370) Sicinski, R. R.; DeLuca, H. F.; Schnoes, H. K.; Tanaka, Y.; Smith, C. M. *Bioorg. Chem.* **1987**, *15*, 152–166. Δ^{22} -Unsaturated Analogs of Vitamin D₃ and Their C(1)-Hydroxylated Derivatives.
- (371) Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *J. Org. Chem.* **1983**, *48*, 3819–3820. Electrophilic Addition of OsO₄ to 25-Hydroxycholecalciferol and Its 3,5-Cyclo Derivative.
- (372) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609–4619. Synthesis of MC 903, A Biologically Active Vitamin D Metabolite Analogue.
- (373) Choudhry, S. C.; Belica, P. S.; Coffen, D. L.; Focella, A.; Maehr, H.; Manchand, P. S.; Serico, L.; Yang, R. T. *J. Org. Chem.* **1993**, *58*, 1496–1500. Synthesis of a Biologically Active Vitamin-D₂ Metabolite.
- (374) Reischl, W.; Kalchhauser, H. *Tetrahedron Lett.* **1992**, *33*, 2451–2454. Allylic Hydroxylation of Vitamin D with Mercury(II)-trifluoroacetate.
- (375) Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 829–831. Chemistry of the Tricarbonyliron Complexes of Calciferol and Ergosterol.
- (376) Yamada, S.; Takayama, H. *Chem. Lett.* **1979**, 583–586. Studies on the Adducts of Sulfur Dioxide with Vitamin D.
- (377) Reischl, W.; Zbiral, E. *Helv. Chim. Acta* **1979**, *62*, 1763–1769. Strukturelle Abwandlungen am Vitamin D₃. Synthese und Eigenschaften von SO₂-Addukten des (5Z)- und (5E)-Vitamins D₃ (Structural Modifications of Vitamin D₃. Part 3. Synthesis and Properties of the Sulfur Dioxide Adducts of (5Z)- and (5E)-Vitamin D₃).
- (378) Neef, G.; Steinmeyer, A. *Tetrahedron Lett.* **1991**, *32*, 5073–5076. Synthesis of 23-Oxa-calcitriol Derivatives.
- (379) Ando, K.; Kondo, F.; Koike, F.; Takayama, H. *Chem. Pharm. Bull.* **1992**, *40*, 1662–1664. An Improved Synthesis of 24,24-Difluoro-1 α ,25-Dihydroxyvitamin D₃ from Vitamin D₂.
- (380) Calverley, M. J.; Strugnell, S.; Jones, G. *Tetrahedron* **1993**, *49*, 739–746. The Seleno-acetal Route to 1 α -Hydroxy-vitamin D Analogues: Synthesis of 24-Oxa-1 α -hydroxy-vitamin D₃, A Useful Vitamin D Metabolism Probe.
- (381) (a) Calverley, M. J. *Tetrahedron Lett.* **1987**, *28*, 1337–1340. Reductive Alkylation of a Selenoacetal in the Elaboration of Steroid Side Chains: Stereochemistry and Application in a Synthesis of 1 α -Hydroxyvitamin D₃. (b) Ando, K.; Koike, F.; Kondo, F.; Takayama, H. *Chem. Pharm. Bull.* **1995**, *43*, 189–192. An Improved Synthesis of 24,24-Difluoro-1 α ,25-dihydroxyvitamin D₃ from Readily Available Vitamin D₂.
- (382) Yamada, S.; Suzuki, T.; Takayama, H.; Miyamoto, K.; Matsunga, I.; Nawata, Y. *J. Org. Chem.* **1983**, *48*, 3483–3488. Stereoselective Synthesis of (5E)- and (5Z)-Vitamin D₃ 19-Alkanoic Acids via Vitamin D₃-Sulfur Dioxide Adducts.
- (383) Yamada, S.; Suzuki, T.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 3085–3088. Novel Regioselective C-6 and C-19 Alkylation of Vitamin D₃ via Its Sulfur-Dioxide Adducts.
- (384) (a) Aberhart, D. J.; Hsu, A. C.-T. *J. Org. Chem.* **1976**, *41*, 2098–2102. Studies on the Adduct of 4-Phenyl-1,2,4-triazoline-3,5-dione with Vitamin D₃. (b) Aberhart, D. J.; Chu, J. Y.-R.; Hsu, A. C.-T. *J. Org. Chem.* **1976**, *41*, 1067–1069. Synthesis of 3-epi-Cholecalciferol and 5,6-trans-3-epi-Cholecalciferol.
- (385) Reischl, W.; Zbiral, E. *Liebigs Ann. Chem.* **1978**, 745–756. Strukturelle Abwandlung am Vitamin D₃ via 4-Phenyl-1,2,4-triazolin-3,5-dion-Addukte (Structural Modifications on Vitamin D₃ via 4-Phenyl-1,2,4-triazolin-3,5-dione Adducts).
- (386) Shimizu, M.; Yamazaki, T.; Yamada, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1809–1814. Fluorescence-Labeling Reaction of Vitamin D Metabolites and Analogs with Fluorescent 1,2,4-Triazolin-3,5-dione (DMEQ-TAD).
- (387) Sato, T.; Itô, S. *Tetrahedron Lett.* **1979**, 1051–1054. Vinyllogous Di- π -Methane Rearrangement. Thermal Transposition of Bicyclo-[4.4.1]undeca-2,4,7,9-tetraen-11-ol.
- (388) Vanmaele, L. J.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Lett.* **1982**, *23*, 995–998. A Stereocontrolled Partial Synthesis of 1 α -Hydroxy Vitamin D₃.
- (389) Vanmaele, L. J.; De Clercq, P. J.; Vandewalle, M.; Halkes, S. J.; Overbeek, W. R. M. *Tetrahedron* **1984**, *40*, 1179–1182. 1 α -Hydroxy Previtamin D₃ and Its Selective Formation from 1-Keto Previtamin D₃.
- (390) Nerinckx, W.; De Clercq, P. J.; Couwenhoven, C.; Overbeek, W. R. M.; Halkes, S. J. *Tetrahedron* **1991**, *47*, 9419–9430. An Improved Synthesis of 1 α -Hydroxy Vitamin D₃.
- (391) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836. Synthesis à l'Aide de Sulfones V⁽⁺⁾-Methode de Synthèse Generale de Doubles Liaisons (Syntheses with the Help of Sulfones. V. General Method of Synthesis of Double Bonds).
- (392) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1290–1293. Calciferol and Its Relatives. Part 24. A Synthesis of Vitamin D₃.
- (393) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1985**, 259–262. A General Method for the Stereoselective Construction of Des-AB-cholestanes. A First Total Synthesis of (+)-8 α -Phenylsulfonyl-des-AB-cholestane.
- (394) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *Heterocycles* **1985**, *23*, 567–569. A Modified Synthesis of the (+)-8 α -Phenylsulfonyl-des-AB-Cholestane via an Intramolecular Nucleophilic Attack to Epoxide—A Total Synthesis of Vitamin D₃.
- (395) Clasby, M. C.; Craig, D.; Marsh, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1444–1446. Vitamin D₃ Synthetic Studies: Enantioselective Synthesis of the CD Ring Fragment.
- (396) Haynes, R. K.; Loughlin, W. A.; Hambley, T. W. *J. Org. Chem.* **1991**, *56*, 5785–5790. Novel Formation of Isomeric Bicyclo[3.2.0]heptan-1-ols from Phenyl Vinyl Sulfoxide and the Cyclopentanone Lithium Enolate Generated by Conjugate Addition of Lithiated (*E*)-But-2-enyldiphenylphosphine Oxide to 2-Methylcyclopent-2-enone.
- (397) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829–834. Scope and Stereochemistry of an Olefin Synthesis from β -Hydroxy-sulphones.
- (398) Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1960**, 1405–1406. Calciferol and Its Relatives. Part 28. A Stereoselective Synthesis of 1 α -Hydroxyprecalciferol₃ from 8-Hydroxy-methyl-des-AB-cholest-8-ene.
- (399) Hatakeyama, S.; Sugawara, K.; Numata, H.; Takano, S. *J. Org. Chem.* **1991**, *56*, 461–463. A Novel Convergent Synthesis of (+)-1 α ,25-Dihydroxyvitamin D₃ Using a Chromium(II)-Mediated Coupling Reaction.
- (400) Harrison, I. T.; Lythgoe, B. *J. Chem. Soc.* **1958**, 837–843. Calciferol and Its Relatives. Part III. Partial Synthesis of Calciferol and of epiCalciferol.
- (401) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199–241. Various Approaches to the Construction of Aliphatic Side Chains of Steroids and Related Compounds.
- (402) Redpath, J.; Zeelen, F. *J. Chem. Soc. Rev.* **1983**, *12*, 75–98. Stereoselective Synthesis of Steroid Side-chains.
- (403) Partridge, J. J.; Faber, S.; Uskokovic, M. R. *Helv. Chim. Acta* **1974**, *57*, 764–771. Vitamin D₃ Metabolites I. Synthesis of 25-Hydroxycholesterol.
- (404) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701–706. Prescriptions and Ingredients for Controlled CC Bond Formation with Organometallic Reagents.
- (405) Dasgupta, S. K.; Crump, D. R.; Gut, M. *J. Org. Chem.* **1974**, *39*, 1658–1662. New Preparation of Desmosterol.
- (406) Moreau, J. P.; Aberhart, D. J.; Caspi, E. *J. Org. Chem.* **1974**, *39*, 2018–2023. Synthesis of 5 α -Cholesta-7,24-dien-3 β -ol and Cholesta-5,7,24-trien-3 β -ol.
- (407) Schönecker, B.; Prousa, R.; Schrötter, E.; Schick, H.; Droscher, P.; Fischer, R.; Walther, D.; Reichenbacher, M.; Gliesing, S. Efficient Synthesis of 25-Hydroxy-vitamin D₃ and its 26,27-Homologues. In *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 212–213.
- (408) Chorvat, R. J.; Desai, B. N.; Radak, S. E.; McLaughlin, K. T.; Miller, J. E.; Jett, C.; Rohrbacher, E. *J. Med. Chem.* **1985**, *28*, 194–200. 22-Hydroxycholesterol Derivatives as HMG CoA Reductase Suppressors and Serum Cholesterol Lowering Agents.
- (409) Schönecker, B.; Walther, D.; Fischer, R.; Nestler, B.; Bräunlich, G.; Eibische, H.; Droscher, P. *Tetrahedron Lett.* **1990**, *31*, 1257–1260. A Nickelacycle as Propionic Acid Equivalent for Carbon-Carbon Coupling Reactions; Application to the Synthesis of C₂₅ Steroid Carboxylic Acids.
- (410) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149–3152. Conjugate Additions to α,β -Unsaturated Carbonyl Compounds in Aqueous Media.
- (411) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369–5372. Ultrasound in Organic Synthesis 16. Optimisation of the Conjugate Additions to α,β -Unsaturated Carbonyl Compounds in Aqueous Media.
- (412) Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373–5374. Ultrasound in Organic Synthesis 17

- Mechanistic Aspects of the Conjugate Additions to α -Enones in Aqueous Media.
- (413) Mascareñas, J. L.; Pérez-Sestelo, J.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1991**, *32*, 2813–2816. A Short, Flexible Route to Vitamin D Metabolites and their Side Chain Analogues.
- (414) Pérez-Sestelo, J.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1994**, *35*, 275–278. A Short, Flexible Approach to Vitamin D₃ Analogues with Modified Side Chains.
- (415) Pérez-Sestelo, J.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1993**, *58*, 118–123. Ultrasonically Induced Conjugate Addition of Iodides to Electron-Deficient Olefins and Its Application to the Synthesis of Side-Chain Analogs of the Hormone 1 α ,25-Dihydroxyvitamin D₃.
- (416) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1993**, *34*, 6533–6536. An Efficient Synthesis of (22E,25R)-1 α ,25,26-Trihydroxy- Δ^2 -Vitamin D₃.
- (417) Calverley, M. J. *Synlett* **1990**, 157–159. The Seleno-Acetal Route to Side-Chain-Modified 1 α -Hydroxy-Vitamin D Analogues: Stereoselective Synthesis of the New 22Z Isomer of MC 903 (Calcipotriol).
- (418) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327–3333. The Chemistry of Carbanions. VI. Stereochemistry of the Wittig Reaction with Stabilized Ylides.
- (419) Letourneux, Y.; Büjüktür, G.; Ryzlak, M. T.; Banerjee, A. K.; Gut, M. *J. Org. Chem.* **1976**, *41*, 2288–2292. 20-Methylcholesterol.
- (420) Hutchins, R. F. N.; Thompson, M. J.; Svoboda, J. A. *Steroids* **1970**, 113–121. The Synthesis and the Mass and Nuclear Magnetic Resonance Spectra of Side Chain Isomers of Cholesta-5,22-dien-3 β -ol and Cholesta-5,22,24-trien-3 β -ol.
- (421) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 790–792. A Stereoselective Wittig Reagent and Its Application to the Synthesis of 25-Hydroxylated Vitamin D Metabolites.
- (422) Salmond, W. G.; Sobala, M. C. *Tetrahedron Lett.* **1977**, 1695–1698. An Efficient Synthesis of 25-Hydroxycholesterol from Stigmaterol.
- (423) Hanekamp, J. C.; Rookhuizen, R. B.; v. d. Heuvel, H. L. A.; Bos, H. J. T.; Brandsma, L. *Tetrahedron Lett.* **1991**, *32*, 5397–5400. A Short and Efficient Synthesis of DE-A,B(22E,24S)-8 β -(benzoyloxy)-25-hydroxyergost-22-ene a Valuable Intermediate in the Total Synthesis of 25-Hydroxylated Vitamin D₂-Metabolites.
- (424) Kocienski, P. J.; Lythgoe, B.; Roberts, D. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 834–837. Calciferol and its Relatives. Part 23. An Alternative Synthesis of Windaus and Grundmann's C₁₉ Ketone.
- (425) Yamada, S.; Shiraishi, M.; Ohmori, M.; Takayama, H. *Tetrahedron Lett.* **1984**, *25*, 3347–3350. Facile and Stereoselective Synthesis of 25-Hydroxyvitamin D₂.
- (426) Perlman, K. L.; Schnoes, H. K.; DeLuca, H. F. *J. Chem. Soc., Chem. Commun.* **1989**, 1113–1115. A Convenient Synthesis of (24S)-1 α -Hydroxyvitamin D₂.
- (427) Kutner, A.; Perlman, K. L.; Sicinski, R. R.; Phelps, M. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1987**, *28*, 6129–6132. Vitamin D C-22 Aldehydes. New Key Intermediates for the Synthesis of Side Chain Modified Vitamin D Analogues.
- (428) Yamamoto, K.; Shimizu, M.; Yamada, S.; Iwata, S.; Hoshino, O. *J. Org. Chem.* **1992**, *57*, 33–39. Facile Stereoselective Synthesis of (23S,25R)-1 α ,25-Dihydroxyvitamin D₃ 26,23-Lactone, a Major Metabolite of 1 α ,25-Dihydroxyvitamin D₃.
- (429) Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 2591–2594. Stereoselective Synthesis of (25S)-25-Hydroxyvitamin D₃ 26,23-Lactone.
- (430) Kutner, A.; Perlman, K. L.; Lago, A.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *J. Org. Chem.* **1988**, *53*, 3450–3457. Novel Convergent Synthesis of Side-Chain-Modified Analogues of 1 α ,25-Dihydroxycholecalciferol and 1 α ,25-Dihydroxyergocalciferol.
- (431) Kutner, A.; Chodynski, M.; Halkes, S. J.; Brugman, J. *Bioorg. Chem.* **1993**, *21*, 13–23. Novel Concurrent Synthesis of Side-Chain Analogues of Vitamins D₂ and D₃: 24,24-Dihomo-25-hydroxycholecalciferol and (22E)-22-Dehydro-24,24-dihomo-25-hydroxycholecalciferol.
- (432) Perlman, K. L.; DeLuca, H. F. *Tetrahedron Lett.* **1992**, *33*, 2937–2940. 1 α -Hydroxy-19-Nor-Vitamin D C-22 Aldehyde. A Valuable Intermediate in the Synthesis of Side Chain Modified 1 α ,25-Dihydroxy-19-Nor-Vitamin D.
- (433) Batcho, A. D.; Berger, D. E.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1293–1295. C-20 Stereospecific Introduction of a Steroid Side Chain.
- (434) Batcho, A. D.; Berger, D. E.; Davoust, S. G.; Wovkulich, P. M.; Uskokovic, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682–1687. Stereoselective Introduction of Steroid Side Chains at C(17) and C(20).
- (435) Dauben, W. G.; Brookhart, T. *J. Am. Chem. Soc.* **1981**, *103*, 237–238. Stereoccontrolled Synthesis of Steroidal Side Chains.
- (436) Krubiner, A. M.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 24–26. The Conversion of 17-Keto Steroids to 20-Oxygenated Steroids. A Facile Synthesis of 19-Norprogesterone.
- (437) Wicha, J.; Bal, K.; Piekut, S. *Synth. Commun.* **1977**, *7*, 215–222. Synthesis of Pregn-17/20-en-21-oic Acid Derivatives. The Wittig-Horner Reaction on Steroidal 17-Ketones.
- (438) Mikami, K.; Kishino, H.; Loh, T.-P. *J. Chem. Soc., Chem. Commun.* **1994**, 495–496. A Unified Approach to (22S)- or (22R)-Hydroxy Steroid Side Chain: Lewis Acid-promoted Carbonyl-ene Reaction with α -Alkoxyaldehydes.
- (439) Houston, T. A.; Tanaka, Y.; Koreeda, M. *J. Org. Chem.* **1993**, *58*, 4287–4292. Stereoselective Construction of 22-Oxygenated Steroid Side Chains by Dimethylaluminum Chloride-Mediated Ene Reactions of Aldehydes.
- (440) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630–632. New Synthetic Reactions. Catalytic vs. Stoichiometric Allylic Alkylation. Stereoccontrolled Approach to Steroid Side Chain.
- (441) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435–3443. Stereoccontrolled Approach to Steroid Side Chain via Organopalladium Chemistry. Partial Synthesis of 5 α -Cholestanone.
- (442) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036–2038. Stereoccontrolled Synthesis of the Ecdysone Side Chain via Organopalladium Chemistry.
- (443) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528. Allylic Oxidation of Olefins by Catalytic and Stoichiometric Selenium Dioxide with *tert*-Butyl Hydroperoxide.
- (444) Schmuft, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404–1412. Organocuprate-Mediated Methods for the Stereospecific Introduction of Steroid Side Chains at C-20.
- (445) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862–863. Stereoccontrolled Synthesis of Sterol Side Chains.
- (446) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172–1174. Stereochemically Controlled Synthesis of Steroid Side Chains: Synthesis of Desmosterol.
- (447) Midland, M. M.; Kwon, Y. C. *J. Org. Chem.* **1981**, *46*, 229–230. Stereoccontrolled Synthesis of a Steroid Side Chain.
- (448) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1982**, *23*, 2077–2080. Stereoccontrolled Synthesis of Steroid Side Chains via Organoboranes. Stereospecific Synthesis of 20R- and 20S-25-Hydroxycholesterol.
- (449) Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732–2736. Synthesis of *ent*-cholesterol, the Unnatural Enantiomer.
- (450) Granja, J. R. *Synth. Commun.* **1991**, *21*, 2033–2038. [2,3]-Wittig Sigmatropic Rearrangement of Steroidal 16 β -Propargyl Ethers for the Synthesis of 25-hydroxyvitamin D Side Chain Analogues.
- (451) Gilhooly, M. A.; Morris, D. S.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2111–2116. Synthesis of 25 ξ ,26-Dihydroxyvitamin D₂.
- (452) Sucrow, W.; Girgensohn, B.; *Chem. Ber.* **1970**, *103*, 750–756. Die Synthese von 5 α -Stigmastatrien-(7.22.25)-ol-(3 β) (Synthesis of 5 α -Stigmasta-7,22,25-trien-3 β -ol).
- (453) Sucrow, W.; Schubert, B.; Richter, W.; Slopianka, M. *Chem. Ber.* **1971**, *104*, 3689–3703. Stereochemie einer Claisen-Umlagerung in der Sterin-Seitenkette (Stereochemistry of a Claisen Rearrangement in the Sterol Side Chain).
- (454) Sucrow, W.; Caldeira, P. P.; Slopianka, M. *Chem. Ber.* **1973**, *106*, 2236–2245. Die Synthese von (24S)- und (24R)-24-Äthylcholesta-5,22,25-trien-3 β -ol sowie von Poriferasterin und Stigmaterin (Synthesis of (24S)- and (24R)-24-Ethylcholesta-5,22,25-trien-3 β -ol and of Poriferasterol and Stigmaterol).
- (455) Sardina, F. J.; Mouriño, A.; Castedo, L. *Tetrahedron Lett.* **1983**, *24*, 4477–4480. Studies on the Synthesis of Side Chain Hydroxylated Metabolites of Vitamin D. Stereospecific Syntheses of 25-Hydroxy-7,8-Dihydro-Ergosterol and its C-24 Epimer.
- (456) Castedo, L.; Granja, J.; Maestro, M. A.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 4589–4590. Stereoselective Synthesis of 25-Hydroxyvitamin D₂ Side Chain via the Acetal Template Route.
- (457) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093–3096. Regio and Stereospecific Synthesis of *Cis* and *Trans* 3-Methyl-6-methyl-ethyl Cyclohexenes and 3-Methyl-4-methylethylcyclohexenes. Reactions of Allylic Acetates and Carbamates with Li₂Cu₃Me₅ and LiCuMe₂.
- (458) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035–1036. Conversion of Allylic Carbamates into Olefins with Lithium Dimethylcuprate. A New Formal S_N2' Reaction.
- (459) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715–721. Alkylation of Allylic Derivatives. 4. On the Mechanism of Alkylation of Allylic *N*-Phenylcarbamates with Lithium Dialkylcuprates.
- (460) Wilson, S. R.; Davey, A. E.; Guazzaroni, M. E. *J. Org. Chem.* **1992**, *57*, 2007–2012. Two New Approaches to the 25-Hydroxyvitamin D₂ Side Chain.
- (461) Bouillon, R.; Allewaert, K.; van Leeuwen, J. P. T. M.; Tan, B.-K.; Xiang, D. Z.; De Clercq, P.; Vandewalle, M.; Pols, H. A. P.; Bos, M. P.; Van Baelen, H.; Birkenhäger, J. C. *J. Biol. Chem.* **1992**, *267*, 3044–3051. Structure Function Analysis of Vitamin D Analogues with C-ring Modifications.
- (462) Revelle, L.; Solan, V.; Londowski, J.; Bollman, S.; Kumar, R. *Biochemistry* **1984**, *23*, 1983–1987. Synthesis and Biologic Activity of a C-Ring Analogue of Vitamin D₃: Biologic and Protein Binding Properties of 11 α -Hydroxyvitamin D₃.

- (463) Kobayashi, N.; Kitahori, J.; Mano, H.; Shimada, K. *Chem. Pharm. Bull.* **1993**, *41*, 1321–1323. Production of Highly Specific Antibodies to 1 α ,25-Dihydroxyvitamin D₃ Utilizing a Novel Haptenic Derivative Having a Chemical Bridge at 11 α -Position.
- (464) Kobayashi, N.; Higashi, T.; Shimada, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 269–275. Synthesis of (24R)-11 α -(4-Carboxybutyryloxy)-24,25-dihydroxyvitamin D₃: A Novel Haptenic Derivative Producing Antibodies of High Affinity for (24R)-24,25-Dihydroxyvitamin D₃.
- (465) Kobayashi, N.; Hisada, A.; Shimada, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 31–37. Syntheses of Novel 25-Hydroxyvitamin D₃ Haptens having Chemical Bridges at the C-11 α Position.
- (466) Enas, J. D.; Palenzuela, J. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 1355–1363. A-Homo-11-hydroxy-3-deoxyvitamin D: Ring Size and π -Facial Selectivity Effects on the [1,7]-Sigmatropic Hydrogen Shift of Previtamin D to Vitamin D.
- (467) Torneiro, M.; Fall, Y.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 105–108. An Efficient Route to 1 α ,25-Dihydroxyvitamin D₃ Functionalized at C-11.
- (468) D'Halleweyn, C.; Van Haver, D.; Van der Eycken, J.; De Clercq, P.; Vandewalle, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 477–480. Synthesis of (C-11)-Substituted Analogues of 1 α ,25-Dihydroxyvitamin D₃.
- (469) De Clercq, P. J.; De Wilde, H.; D'Halleweyn, C.; Zucker, P.; Van Hijfte, L.; Mijngheer, R.; Van Haver, D.; Vandewalle, M. Total Synthesis of (C-11)-Substituted Analogues of 1 α ,25-Dihydroxyvitamin D₃. In *Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 210–211.
- (470) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013. Synthesis of α,β -Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers.
- (471) Dauben, W. G.; Greenfield, L. J. *J. Org. Chem.* **1992**, *57*, 1597–1600. Fluorinated Chirons for Vitamin D₃ Syntheses. A Serendipitous Synthesis of a 9 α -Hydroxy Derivative of (7Z)-Vitamin D₃.
- (472) Maestro, M. A.; Sardina, F. J.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1991**, *56*, 3582–3587. Stereoselective Synthesis and Thermal Rearrangement of the First Analogue of (7Z)-Vitamin D.
- (473) Shau, J.-H.; Reusch, W. J. *Org. Chem.* **1980**, *45*, 2013–2015. Synthesis of a 14 α -Methyl Vitamin D Precursor.
- (474) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149–9152. First Demonstration of a Carbocation-Olefin Cyclization Route to the Lanosterol Series.
- (475) Maynard, D. F.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1992**, *57*, 3214–3217. 18-Substituted Derivatives of Vitamin D: 18-Acetoxy-1 α ,25-dihydroxyvitamin D₃ and Related Analogues.
- (476) Vallés, M. J.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 1503–1506. Functionalization of Vitamin D Metabolites at C-18 and Application to the Synthesis of 1 α ,18,25-Trihydroxyvitamin D₃ and 18,25-Dihydroxyvitamin D₃.
- (477) Nilsson, K.; Vallés, M. J.; Castedo, L.; Mouriño, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1855–1858. Synthesis and Biological Evaluation of 18-Substituted Analogues of 1 α ,25-Dihydroxyvitamin D₃.
- (478) Mihailovic, M. L.J.; Jakovljevic, M.; Cekovic, Z. *Tetrahedron* **1969**, *25*, 2269–2273. Thermal and Photolytic Decomposition of Alkoxylead(IV)-acetates Derived from Saturated Aliphatic Alcohols.
- (479) Dauben, W. G.; Kohler, B.; Roesle, A. *J. Org. Chem.* **1985**, *50*, 2007–2010. Synthesis of 6-Fluorovitamin D₃.
- (480) Sheves, M.; Mazur, Y. *J. Chem. Soc., Chem. Commun.* **1977**, 21–22. Equilibria in Vitamin D₃. Preparation and Properties of 6-Methylvitamin D₃ and its Isomers.
- (481) Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823–1824. 1 α ,25-Dihydroxy-19-norvitamin D₃, A Novel Vitamin D-Related Compound with Potential Therapeutic Activity.
- (482) Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1991**, *32*, 7663–7666. Novel Synthesis of 19-nor-Vitamin D Compounds.
- (483) Sicinski, R. R.; DeLuca, H. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 899–904. Synthesis of 6,7-Diaza-19-norvitamin D Compounds.
- (484) Sarandeses, L. A.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 5445–5448. Synthesis of 1 α ,25-Dihydroxy-19-norprevitamin D₃.
- (485) (a) Muralidharan, K. R.; de Lera, A. R.; Isaëff, S. D.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1993**, *58*, 1895–1899. Studies on the A-Ring Diastereomers of 1 α ,25-Dihydroxyvitamin D₃. (b) Ishida, H.; Shimizu, M.; Yamamoto, K.; Iwasaki, Y.; Yamada, S. *J. Org. Chem.* **1995**, *60*, 1828–1833. Synthesis of 1-Alkyl-1,25-dihydroxyvitamin D₃. (c) Yamada, S.; Ishizaka, H.; Ishida, H.; Yamamoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 423–424. New Photoisomerization of Provitamin D Caused by Hydroxylation at C(1).
- (486) de Costa, B. R.; Holick, S. A.; Holick, M. F. *J. Chem. Soc., Chem. Commun.* **1989**, 325–326. Synthesis of 19-Acetylthio-3- β -acetoxy-9,10-secochola-1(10),5Z,7E-triene, and 1- β -Acetylthio-3- β -acetoxy-9,10-secochola-5Z,7E,10(19)-triene. An Approach to 1 β - and 19-Thiolation of the Vitamin D Skeleton.
- (487) (a) Ohshima, E.; Sai, H.; Takatsuto, S.; Ikekawa, N.; Kobayashi, Y.; Tanaka, Y.; DeLuca, H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3525–3531. Synthesis and Biological Activity of 1 α -Fluoro-25-hydroxyvitamin D₃. (b) Ohshima, E.; Takatsuto, S.; Ikekawa, N.; DeLuca, H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3518–3524. Synthesis of 1 α -Fluorovitamin D₃.
- (488) Shiuey, S.-J.; Kulesha, I.; Baggolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1990**, *55*, 243–247. Total Synthesis of 1 α -Fluoro-25-hydroxycholecalciferol and -ergocalciferol.
- (489) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.* **1992**, *35*, 3280–3287. New Vitamin D₃ Derivatives with Unexpected Antiproliferative Activity: 1-(Hydroxymethyl)-25-hydroxyvitamin D₃ Homologs.
- (490) Posner, G. H.; Dai, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1829–1834. 1-(Hydroxyalkyl)-25-hydroxyvitamin D₃ Analogs of Calcitriol. 1. Synthesis.
- (491) Posner, G. H. Design, Synthesis, and Sar of some 1-Substituted A-Ring Analogs of Calcitriol. In *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 25–26.
- (492) Posner, G. H.; White, M. C.; Dolan, P.; Kensler, T. W.; Yukihiro, S.; Guggino, S. E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2919–2924. 1 α ,25-Dihydroxyvitamin D₃ Hybrid Analogs with Structural Changes at Both the A-Ring and the C,D-Ring Side-chain.
- (493) Yukihiro, S.; Posner, G. H.; Guggino, S. E. *J. Biol. Chem.* **1994**, *269*, 23889–23893. Vitamin D₃ Analogs Stimulate Calcium Currents in Rat Osteosarcoma Cells.
- (494) Posner, G. H.; Nelson, T. D. *J. Org. Chem.* **1991**, *56*, 4339–4341. Stereocontrolled Synthesis of a Trihydroxylated A Ring as an Immediate Precursor to 1 α ,2 α ,25-Trihydroxyvitamin D₃.
- (495) (a) Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994**, *59*, 7855–7861. Stereocontrolled Total Synthesis of Calcitriol Derivatives: 1,25-Dihydroxy-2-(4'-hydroxybutyl)vitamin D₃ Analogs of an Osteoporosis Drug. For a 2 α -analogue see: (b) Posner, G. H.; Cho, C.-G.; Anjeh, T. E. N.; Johnson, N.; Horst, R. L.; Kobayashi, T.; Okano, T.; Tsugawa, N. *J. Org. Chem.* **1995**, *60*, 4617–4628. 2-Fluoroalkyl A-Ring Analogs of 1,25-Dihydroxyvitamin D₃. Stereocontrolled Total Synthesis via Intramolecular and Intermolecular Diels-Alder Cycloadditions. Preliminary Biological Testing.
- (496) Posner, G. H.; Vinader, V.; Afarinkia, K. *J. Org. Chem.* **1992**, *57*, 4088–4097. Diels-Alder Cycloadditions Using Nucleophilic 2-Pyridones. Regiocontrolled and Stereocontrolled Synthesis of Unsaturated, Bridged, Bicyclic Lactams.
- (497) Oshida, J.-I.; Morisaki, M.; Ikekawa, N. *Tetrahedron Lett.* **1980**, *21*, 1755–1756. Synthesis of 2 β -Fluoro-1 α -hydroxyvitamin D₃.
- (498) Kobayashi, Y.; Nakazawa, M.; Kumadaki, I.; Taguchi, T.; Ohshima, E.; Ikekawa, N.; Tanaka, Y.; DeLuca, H. F. *Chem. Pharm. Bull.* **1986**, *34*, 1568–1572. Studies on Organic Fluorine Compounds. L. Synthesis and Biological Activity of 2 α -Fluorovitamin D₃.
- (499) Kaneko, C.; Yamada, S.; Sugimoto, A.; Ishikawa, M. *Chem. Pharm. Bull.* **1975**, *23*, 1616–1619. Synthesis of 2 β -Hydroxycholecalciferol [2 β -OH-D₃].
- (500) (a) Miyamoto, K.; Murayama, E.; Ochi, K.; Watanabe, H.; Kubodera, N. *Chem. Pharm. Bull.* **1993**, *41*, 1111–1113. Synthetic Studies of Vitamin D Analogues. XIV. Synthesis and Calcium Regulating Activity of Vitamin D₃ Analogues Bearing a Hydroxyalkoxy Group at the 2 β -Position. (b) Ono, Y.; Watanabe, H.; Kawase, A.; Kubodera, N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1523–1526. Synthesis and Biological Character of 1 β -Hydroxylated Vitamin D₃ Analogues.
- (501) Takahashi, T.; Nakazawa, M. *Synlett* **1993**, 37–39. Pd-Catalyzed Cyclization Approach to Chiral A-Ring Synthon for 1 α ,2 β ,25-Trihydroxyvitamin D₃.
- (502) Takahashi, T.; Nakazawa, M.; Sakamoto, Y.; Houk, K. N. *Tetrahedron Lett.* **1993**, *34*, 4075–4078. A (3+2)-Cycloaddition Approach to 1 α ,2 β ,25-Trihydroxyvitamin D₃ A Ring Synthon.
- (503) Moriarty, R. M.; Kim, J.; Brumer, H., III. A General Synthetic Route to A-Ring Hydroxylated Vitamin D Analogs from D-Pentoses. In *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 27–28.
- (504) Okamura, W. H.; Pirio, M. R. *Tetrahedron Lett.* **1975**, 4317–4320. Studies on Vitamin D (Calciferol) and Its Analogs. IX. 1 α -Hydroxy-3-epivitamin D₃: Its Synthesis and Conformational Analysis.
- (505) Londowski, J. M.; Revelle, L. K.; Kost, S. B.; Corradino, R. A.; Kumar, R. *J. Steroid Biochem.* **1985**, *23*, 81–85. Synthesis and Biologic Activity of 3 β -Thiovitamin D₃.
- (506) Strating, J.; Backer, H. J. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 909–920. Compounds Related to Provitamin D₃ (II). The Sulphur Analogue of Provitamin D₃.
- (507) Sheves, M.; Sialom, B.; Mazur, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 554–555. Stereoselective Conversion of Vitamin D₃ into

- its β -Halogenated Derivatives. The Synthesis of a 1α -Hydroxy- 3β -fluorovitamin D₃ Analogue.
- (508) Kawase, A.; Hirata, M.; Endo, K.; Kubodera, N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 279–282. Synthesis of $1\alpha,25$ -Dihydroxy-22-thiavitamin D₃ and Related Analogs.
- (509) Halloran, B. P.; Bikle, D. D.; Castro, M. E.; Gee, E. *Biochemistry* **1989**, *28*, 1278–1281. Isotopic Labeling Affects 1,25-Dihydroxyvitamin D Metabolism.
- (510) (a) Napoli, J. L.; Fivizzani, M. A.; Hamstra, A. J.; Schnoes, H. K.; DeLuca, H. F. *Anal. Biochem.* **1979**, *96*, 481–488. Synthesis of 25-Hydroxy[26,27-³H]vitamin D₃ with High Specific Activity. (b) Perlman, K.; Schnoes, H. K.; Tanaka, Y.; DeLuca, H. F.; Kobayashi, Y.; Taguchi, T. *Biochemistry* **1984**, *23*, 5041–5048. Chemical Synthesis of (24R)-24,25-Dihydroxy[26,27-³H]vitamin D₃ of High Specific Activity.
- (511) Napoli, J. L.; Mellon, W. S.; Fivizzani, M. A.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1980**, *19*, 2515–2521. Direct Chemical Synthesis of $1\alpha,25$ -Dihydroxy[26,27-³H]vitamin D₃ with High Specific Activity: Its Use in Receptor Studies.
- (512) Sicinski, R. R.; Tanaka, Y.; Phelps, M.; Schnoes, H. K.; DeLuca, H. F. *Anal. Biochem.* **1987**, *161*, 96–102. Synthesis of 25-Hydroxy[26,27-³H]vitamin D₂, 1,25-Dihydroxy-[26,27-³H]vitamin D₂ and Their (24R)-Epimers.
- (513) Suda, T.; DeLuca, H. F.; Hallick, R. B. *Anal. Biochem.* **1971**, *43*, 139–146. Synthesis of [26,27-³H]-25-Hydroxycholecalciferol.
- (514) Yamada, S.; Schnoes, H. K.; DeLuca, H. F. *Anal. Biochem.* **1978**, *85*, 34–41. Synthesis of 25-Hydroxy[23,24-³H]vitamin D₃.
- (515) DeLuca, H. F.; Weller, M.; Blunt, J. W.; Neville, P. F. *Arch. Biochem. Biophys.* **1968**, *124*, 122–128. Synthesis, Biological Activity, and Metabolism of 22,23-³H-Vitamin D₄.
- (516) Bannai, K.; Ishizuka, S.; Naruchi, T.; Hashimoto, Y. *J. Steroid Biochem.* **1979**, *10*, 411–418. Synthesis of (24S)- and (24R)- 1α -Hydroxy-[24-³H]-cholecalciferol.
- (517) Neville, P. F.; DeLuca, H. F. *Biochemistry* **1966**, *5*, 2201–2207. The Synthesis of [1,2-³H]Vitamin D₃ and the Tissue Localization of a 0.25- μ g (10 IU) Dose per Rat.
- (518) Holick, S. A.; Holick, M. F.; MacLaughlin, J. A. *Biochem. Biophys. Res. Commun.* **1980**, *97*, 1031–1037. Chemical Synthesis of [1 β -³H] $1\alpha,25$ -Dihydroxyvitamin D₃ and [1 α -³H] $1\beta,25$ -Dihydroxyvitamin D₃: Biological Activity of $1\beta,25$ -Dihydroxyvitamin D₃.
- (519) Holick, S. A.; Holick, M. F.; Frommer, J. E.; Henley, J. W.; Lenz, J. A. *Biochemistry* **1980**, *19*, 3933–3937. Synthesis of [3 β -³H]-3-Epivitamin D₃ and Its Metabolism in the Rat.
- (520) Holick, M. F.; Tavela, T. E.; Holick, S. A.; Schnoes, H. K.; DeLuca, H. F.; Gallagher, B. M. *J. Biol. Chem.* **1976**, *251*, 1020–1024. Synthesis of 1α -Hydroxy[6-³H]-vitamin D₃ and Its Metabolism to $1\alpha,25$ -Dihydroxy[6-³H]vitamin D₃ in the Rat.
- (521) Okamura, W. H.; Hoeger, C. A.; Miller, K. J.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 973–974. A Study of the [1,7]-Sigmatropic Shift of a 1-Hydroxylated 3-Desoxy Previtamin D to Vitamin D: Observation of a Modest Primary Deuterium Kinetic Isotope Effect.
- (522) Ray, R.; Vicchio, D.; Yergey, A.; Holick, M. F. *Steroids* **1992**, *57*, 142–146. Synthesis of 25-Hydroxy-[6,19,19'-²H₃]vitamin D₃ and $1\alpha,25$ -Dihydroxy-[6,19,19'-²H₃]vitamin D₃.
- (523) Yamada, S.; Shimizu, M.; Fukushima, K.; Niimura, K.; Maeda, Y. *Steroids* **1989**, *54*, 145–157. Synthesis of 24R,25-Dihydroxy-[6,19,19-³H]vitamin D₃ and 24R,25-Dihydroxy-[6,19,19-²H]vitamin D₃.
- (524) Meadows, J. D.; Williams, D. H. *Tetrahedron Lett.* **1980**, *21*, 4373–4376. Substrates to Study the Mechanism of Vitamin D Hydroxylation: Synthesis of [24R-²H]-25-Hydroxyprovitamin D₃.
- (525) Lindley, M. R.; Williams, D. H. *Tetrahedron Lett.* **1980**, *21*, 4377–4378. Substrates to Study the Mechanism of Vitamin D Hydroxylation: Synthesis of 25-R-[26-²H₃]-Cholecalciferol.
- (526) Coldwell, R. D.; Trafford, D. J. H.; Varley, M. J.; Kirk, D. N.; Makin, H. L. *J. Steroids* **1990**, *55*, 418–432. Stable Isotope-Labeled Vitamin D, Metabolites and Chemical Analogs: Synthesis and Use in Mass Spectrometric Studies.
- (527) Uskokovic, M. R.; Baggolini, E.; Batcho, A.; Shiuey, S.-J.; Wovkulich, P.; Horst, R. L. Synthesis of 26,27-Hexadeutero and Epimeric 26-Trideutero 1,25-Dihydroxycholecalciferols. In *Vitamin D, Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schaefer, K., Grigoleit, H.-G., v. Herrath, D., Eds.; Walter de Gruyter: Berlin, 1988; pp 22–24.
- (528) (a) Creuzet, F.; McDermott, A.; Gebhard, R.; Van der Hoef, K.; Spijker-Assink, M. B.; Herzfeld, J.; Lugtenburg, J.; Levitt, M. H.; Griffin, R. G. *Science* **1991**, *251*, 783–786. Determination of Membrane Protein Structure by Rotational Resonance NMR: Bacteriorhodopsin. (b) Griffiths, J. M.; Lakshmi, K. V.; Bennett, A. E.; Raap, J.; van der Wielen, C. M.; Lugtenburg, J.; Herzfeld, J.; Griffin, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 10178–10181. Dipolar Correlation NMR Spectroscopy of a Membrane Protein.
- (529) Wider, G.; Weber, C.; Wüthrich, K. *J. Am. Chem. Soc.* **1991**, *113*, 4676–4678. Proton-Proton Overhauser Effects of Receptor-Bound Cyclosporin A Observed with the Use of a Heteronuclear-Resolved Half-Filter Experiment.
- (530) Sweet, F.; Murdock, G. L. *Endocr. Rev.* **1987**, *8*, 154–184. Affinity Labeling of Hormone-Specific Proteins.
- (531) Ray, R.; Ray, S.; Holick, M. F. *Bioorg. Chem.* **1994**, *22*, 276–283. $1\alpha,25$ -Dihydroxyvitamin D₃- 3β -Bromoacetate, an Affinity-Labeling Analog of $1\alpha,25$ -Dihydroxyvitamin D₃ Receptor.
- (532) Ray, R.; Holick, S. A.; Holick, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 702–703. Synthesis of a Photoaffinity-labelled Analogue of 1,25-Dihydroxyvitamin D₃.
- (533) Ray, R.; Rose, S.; Holick, S. A.; Holick, M. F. *Biochem. Biophys. Res. Commun.* **1985**, *132*, 198–203. Evaluation of a Photolabile Derivative of 1,25-Dihydroxyvitamin D₃ as a Photoaffinity Probe for 1,25-Dihydroxyvitamin-D₃ Receptor in Chick Intestinal Cytosol.
- (534) Ray, R.; Holick, M. F. *Steroids* **1988**, *51*, 623–630. The Synthesis of a Radiolabeled Photoaffinity Analog of 1,25-Dihydroxyvitamin D₃.
- (535) Ray, R.; Holick, S. A.; Hanafin, N.; Holick, M. F. *Biochemistry* **1986**, *25*, 4729–4733. Photoaffinity Labeling of the Rat Plasma Vitamin D Binding Protein with [26,27-³H]-25-Hydroxyvitamin D₃ 3β -[N-(4-Azido-2-nitrophenyl)glycinate].
- (536) Ray, R.; Bouillon, R.; Van Baelen, H.; Holick, M. F. *Biochemistry* **1991**, *30*, 4809–4813. Synthesis of 25-Hydroxyvitamin D₃ 3β -3'-[N-(4-Azido-2-nitrophenyl)amino]propyl Ether, A Second-Generation Photoaffinity Analogue of 25-Hydroxyvitamin D₃: Photoaffinity Labeling of Rat Serum Vitamin D Binding Protein.
- (537) Kutner, A.; Link, R. P.; Schnoes, H. K.; DeLuca, H. F. *Bioorg. Chem.* **1986**, *14*, 134–147. Photoactivable Analogs for Labeling 25-Hydroxyvitamin D₃ Serum Binding Protein and for 1,25-Dihydroxyvitamin D₃ Intestinal Receptor Protein.
- (538) Link, R. P.; Kutner, A.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1987**, *26*, 3957–3964. Photoaffinity Labeling of Serum Vitamin D Binding Protein by 3-Deoxy-3-azido-25-hydroxyvitamin D₃.
- (539) Verboven, Ch.; De Bondt, H.; De Ranter, C.; Bouillon, R.; Van Baelen, H. Crystallization and Preliminary X-Ray Investigation of Vitamin D-Binding Protein from Human Serum. In *Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1994; pp 107–108. See also: Verboven, C. C.; De Bondt, H. L.; De Ranter, C.; Bouillon, R.; Van Baelen, H. *J. Steroid Biochem. Mol. Biol.* **1995**, *54*, 11–14. Crystallization and X-ray Investigation of Vitamin D-binding Protein from Human Serum. Identification of the Crystal Content.
- (540) Ray, R.; Bouillon, R.; Van Baelen, H.; Holick, M. F. *Biochemistry* **1991**, *30*, 7638–7642. Photoaffinity Labeling of Human Serum Vitamin D Binding Protein and Chemical Cleavages of the Labeled Protein: Identification of an 11.5-kDa Peptide Containing the Putative 25-Hydroxyvitamin D₃ Binding Site.