# Synthesis of Vitamin D (Calciferol)

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## Contents



## I. Introduction

Vitamin D research from the viewpoint of its chemistry and pharmacology has expanded enormously in recent years with the discovery that 1α,25-dihydroxyvitamin $D_3$ (**1** (Figure 1), 1,25-$D_3$; also known as 1α,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. Norman, M. Thomasset, and R. Bouillon.[3] The steroid hormone 1,25-$D_3$ 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.

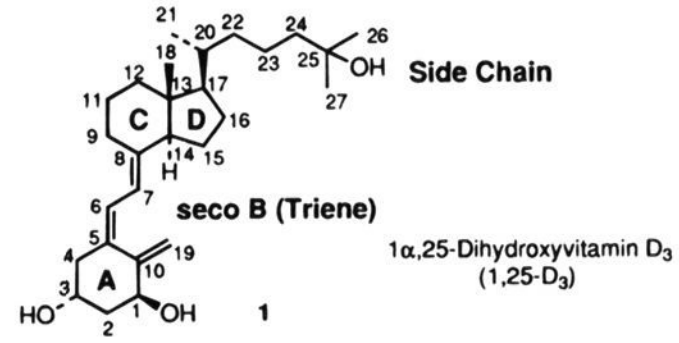



**Figure 1.**

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-$D_3$ 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-$D_3$ 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 $D_3$

The seco-B-steroid 1,25-$D_3$, an essential hormonal regulator in higher animals, is produced by the metabolic pathway shown in Figure 2. The natural vitamin $D_3$ (**5**, $D_3$) is produced in skin upon ultraviolet irradiation of 7-dehydrocholesterol (**2**, 7-DHC; also called provitamin $D_3$) 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 $D_3$ (**3**, Pre-$D_3$). The latter is likely a biologically inert compound, which is thought to spontaneously isomerize to $D_3$, 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-$D_3$ and $D_3$ with the latter

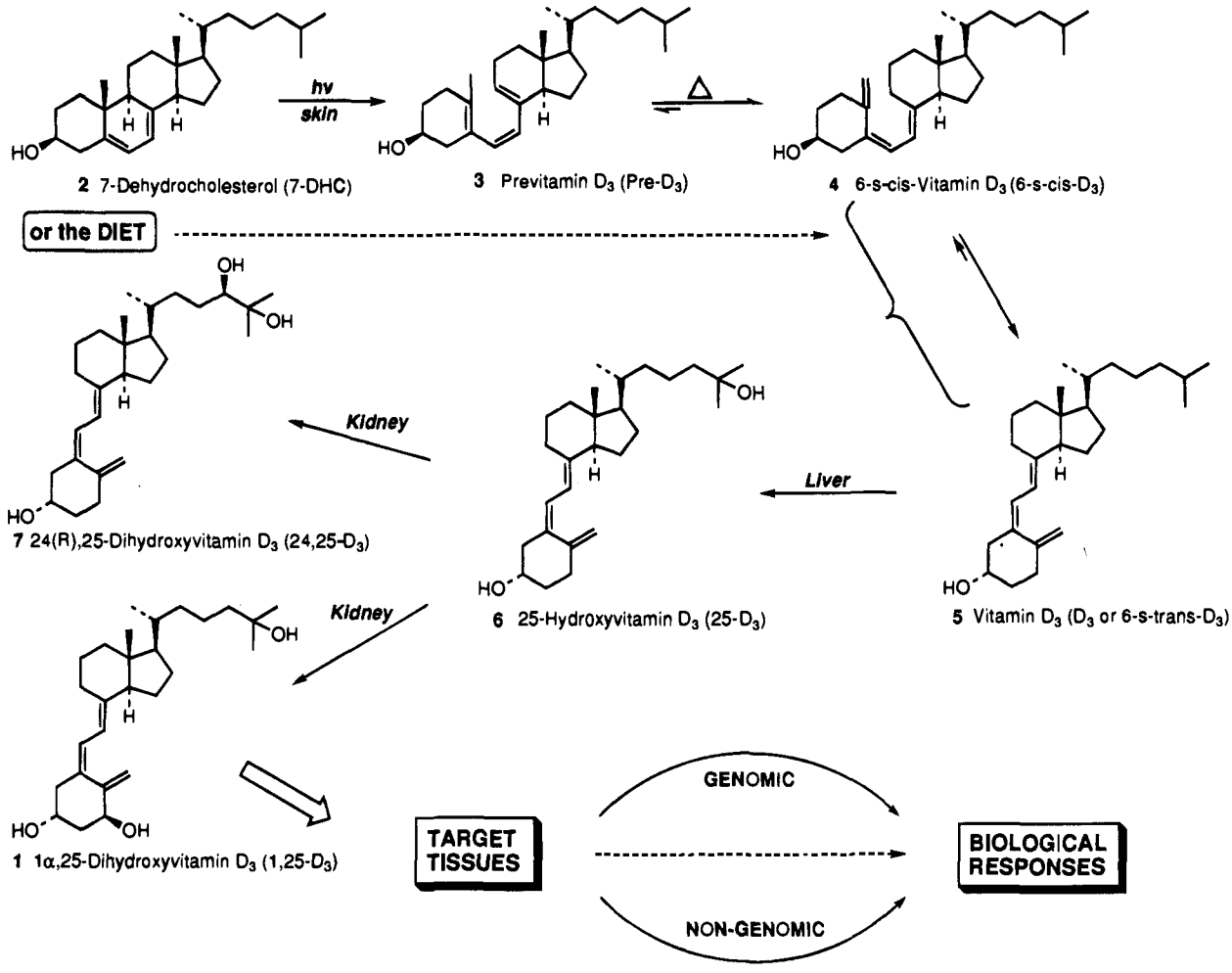



**Figure 2.**

predominating. This isomerization is markedly accelerated in other media such as the human skin,[59] the sea urchin *Psammechinus miliaris*,[60] phospholipid bilayers[61] as well as in an aqueous solution of β-cyclodextrin.[62] Entrapment of previtamin $D_3$ in its *s-cis,s-cis* conformation might be responsible for the enhanced conversion of previtamin $D_3$ to vitamin $D_3$.[63] A plasma protein, vitamin D binding protein (DBP), subsequently transports $D_3$ to the liver[64] where metabolic alteration required for hormonal function is initiated.[65] The conversion of $D_3$ to 25-hydroxyvitamin $D_3$ (**6**, 25-$D_3$) 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 $D_3$ hydroxylase,[67] which has recently been cloned.[68] The metabolite 25-$D_3$, the major circulating form of the vitamin D in serum, is then further metabolized to 1,25-$D_3$ in the kidney. This 1α-hydroxylation occurs exclusively in the renal mitochondrial fraction[69] except in the pregnant mammal in which the placenta can also perform the hydroxylation. 1α-Hydroxylation involves NADPH, a flavoprotein, an iron sulfur protein, and a cytochrome P-450.[70] Other major metabolites of 25-$D_3$ includes 24(*R*),25-dihydroxyvitamin $D_3$ (**7**, 24,25-$D_3$), which is also produced in the kidney.[31,32,41] The hormone 1,25-$D_3$ is transported via the plasma to target cells located for example in the intestine, kidney, and bone. In these target cells, 1,25-$D_3$ 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 1α,25-Dihydroxyvitamin $D_3$

It is currently believed[71] that the steroid hormone 1,25-$D_3$ generates biological responses via genomic or nongenomic pathways. In the genomic pathway, the nuclear receptor for 1,25-$D_3$ (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-$D_3$, 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-$D_3$ 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-$D_3$ has been observed both at the cellular and subcellular level. While an understanding of the mechanism of nongenomic actions of 1,25-$D_3$ 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-$D_3$ 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-$D_3$ 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-$D_3$ and its 1$\beta$-epimer, 1$\beta$,25-dihydroxyvitamin $D_3$, 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-$D_3$, m-VDR preferring the 6-*s-cis* conformation of 1,25-$D_3$ while n-VDR preferring its 6-*s-trans* conformation.[80]

## C. Structural Features of 1$\alpha$,25-Dihydroxyvitamin $D_3$[81]

*Structure Determines Biological Function.* The structurally dynamic hormone 1,25-$D_3$ 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-$D_3$ 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-$D_3$ was assessed primarily through $^1$H 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

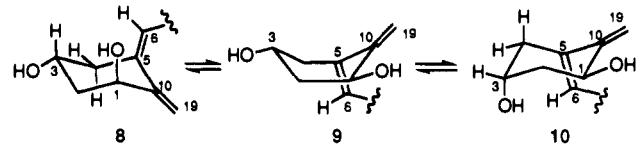


**Figure 3.**

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 $\Delta^{10,19}$

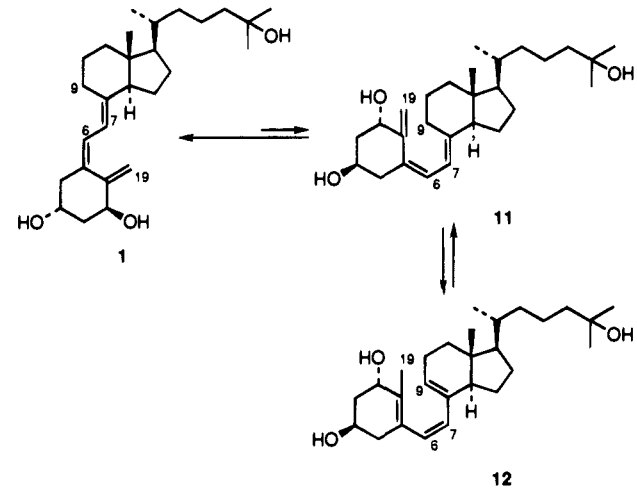


**Figure 4.**

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-$D_3$ to rotate about the $\Delta^{6,7}$-single bond must be extremely facile, possessing barriers similar to that observed for 1,3-butadiene. DeLaroff[83] first showed that the $\Delta^{6,7}$-single bond of $D_3$ in solution is transoid on the basis of $^1$H 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-$D_3$ 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-$D_3$ can equilibrate with the corresponding 1$\alpha$,25-dihydroxyprevitamin $D_3$ (**12**, 1,25-pre-$D_3$) 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-$D_3$ to afford 1,25-$D_3$ 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-$D_3$ molecule with restricted

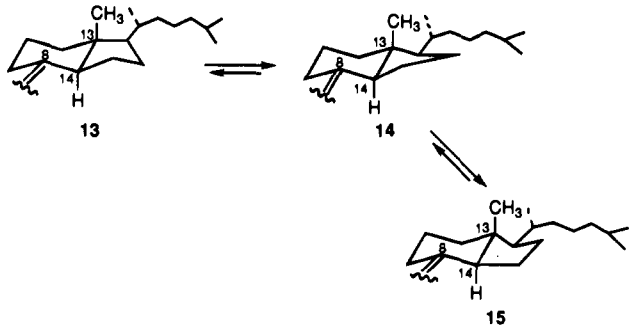



**Figure 5.**

dynamic behavior. To simplify matters, the CD ring of 1,25-$D_3$ 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-$D_3$. Six rotatable bonds (represented by the curved arrows in Figure 6) can lead to a large number of unique

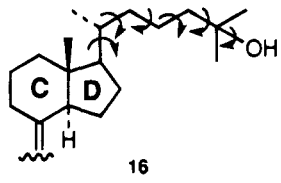



**Figure 6.**

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-$D_3$ 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-$D_3$ 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-$D_3$ molecule, there exists the possibility of a *mutually induced fit* between ligand and protein. An implication of the "mutally 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 gleaning 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-$D_3$ 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 1α,25-Dihydroxyvitamin $D_3$

### A. Overview

Some of the major synthetic routes utilized in recent years to synthesize the hormone 1,25-$D_3$ 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 $D_3$ and also after the industrial synthesis of the latter.[99,100] This entails the photochemical ring opening of a 1α-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-$D_3$ 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 Hopkins[109] 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 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 Trost[117] 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-$D_3$ skeleton.

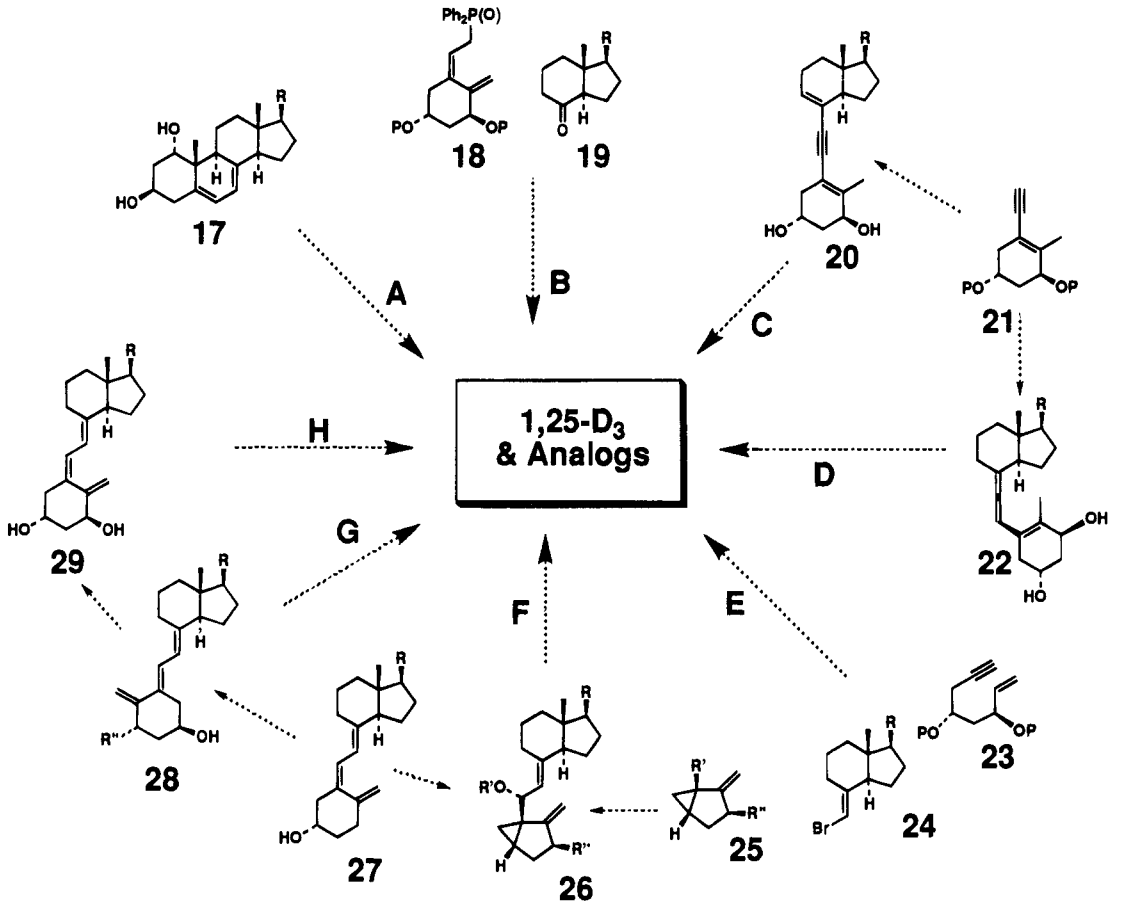



**Figure 7.**

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 1α,25-$D_3$ or analogues. Recent studies, particularly by the Hoffmann-La Roche[121] and Wilson[122] 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-$D_3$ 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-$D_3$ through the intermediacy of a previtamin form via thermal isomerization.[127] Method H entails the direct modification of 1,25-$D_3$ or an analogue, generalized as structure **29**, through use of suitable protecting groups, such as transition metal derivatives or by other chemical transformations directly on **29**. The latter method is now feasible because 1,25-$D_3$ 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-$D_3$ and still remains the main industrial procedure for conducting these syntheses. This approach, usually starting from an $\Delta^5$-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-

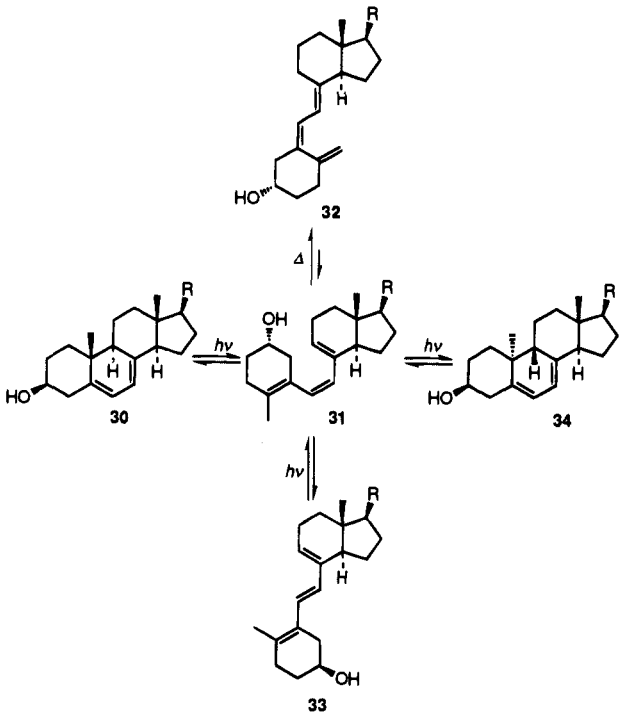



**Figure 8.**

thesis of biologically active metabolites and analogues. In general, the yield of previtamins **31**, and hence the vitamins **32**, obtained from the irradiation of the provitamins **30** is low, partly because of the photolytic conversion of the previtamins **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 1α-hydroxylated form of **32** was obtained on irradiation of 1α-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 1α-hydroxyvitamin $D_3$ (**32** 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 1α-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]

**Table 1**

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

| | | |
|---|---|---|
| **30** | hν, Hg medium pressure, 0°C | **30** (25%) + **31** (25%) + **33** (50%) |
| | chromatography | **31** + **33** |
| | EtOH, reflux | **33** + **32** |
| | chemical separation | **32** (9% yield) |

**Approach 2: Two Stage Irradiation**

| | | |
|---|---|---|
| **30** | hν, Hg medium pressure, 0°C | **30** (25%) + **31** (25%) + **33** (50%) |
| | chromatography | **31** + **33** |
| | hν, fluorenone, 0°C | **31** + **33** |
| | EtOH, reflux, separation | **32** (28%) |

**Approach 3: Wavelenth Controlled Irradiation**

| | | |
|---|---|---|
| **30** | 254 nm, 0°C | **30** (6%) + **31** (28%) + **33** (64%) +**34** (2%) |
| | 350 nm, 0°C | **30** (8%) + **31** (73%) + **33** (9%) + **34** (10%) |
| | Separation | **31** (66%) |
| | EtOH, reflux | **31** + **32** |
| | Separation | **32** (50%) |

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

There have been described at least five methods for introducing the 1α-hydroxy group to cholesterol. In method i (Figure 9), the $\Delta^5$ steroid was first transformed into **36** bearing a C-6 acetal[138–140] or 6β-alcohol[141,142] in the form of ketone **36**. Bromination of **36** followed by dehydrohalogenation afforded the $\Delta^1$-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**

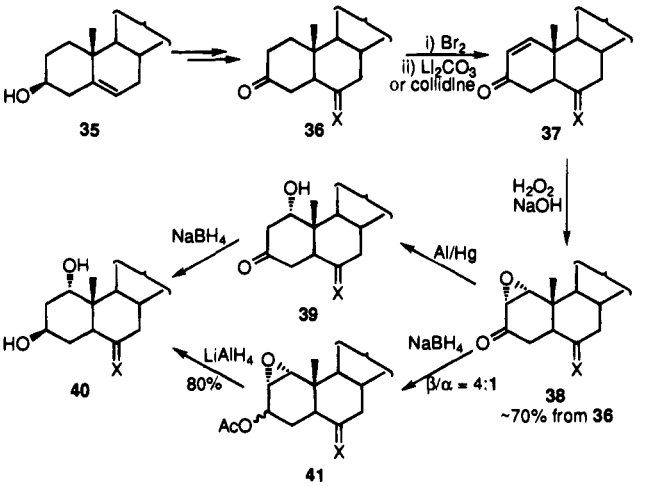



**Figure 9.**

is about 70%. Reduction of the epoxy ketone with $LiAlH_4$ gave a 1,3-diol, but with significant amounts of the 3α-isomer[142] or mainly the 3α-isomer.[138] However, epoxide cleavage using aluminum amalgam to β-hydroxy ketone **39** followed by $NaBH_4$ reduction gave the desired 1α,3β-diol **40**. Finally, the $\Delta^{5,6}$-double bond was regenerated by elimination of the 6β-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 1α-hydroxycholesterol.[140,141]

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

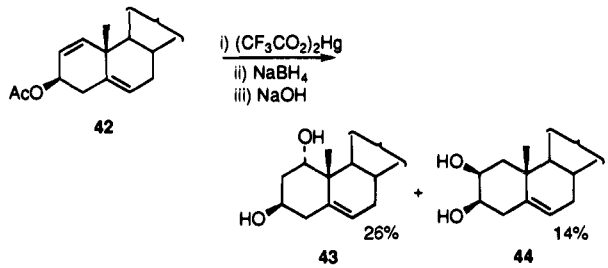



**Figure 10.**

The one-pot reduction of 1α,2α-epoxycholesta-4,6-dien-3-one (**45**) to 1α-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).

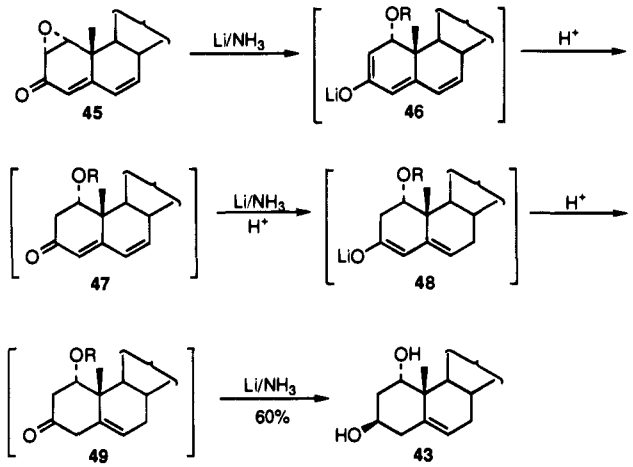



**Figure 11.**

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 1α,2α-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 1α,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

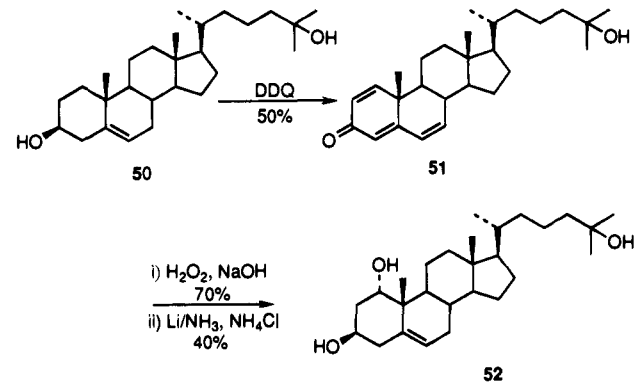



**Figure 12.**

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

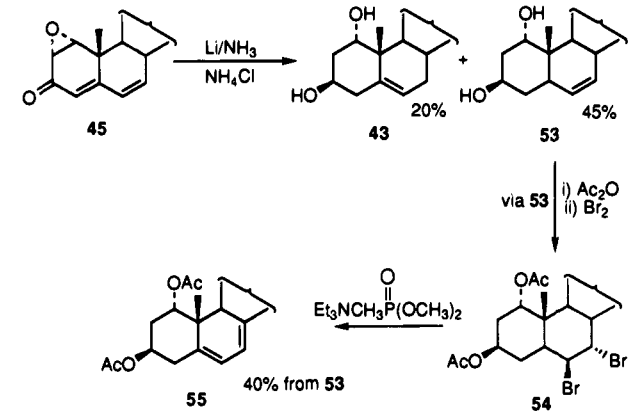



**Figure 13.**

Method v, perhaps a still earlier procedure for the preparation of 1α-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 1α-hydroxycholesterol derivative **59** (Figure 14).

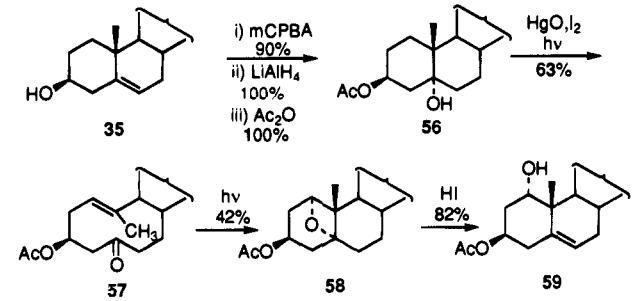



**Figure 14.**

The usual method for introduction of the $\Delta^{7,8}$-double bond to 1α-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 $(MeO)_3P$ in xylene[99,138,139] or collidine (in decalin or dioxane) typically affords about 40% of the desired 5,7-diene **62**

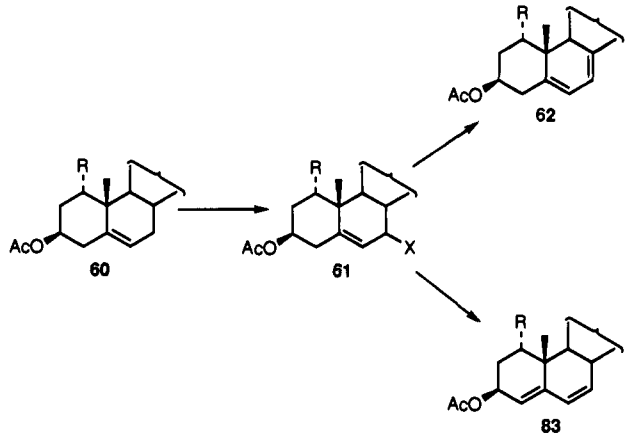



**Figure 15.**

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 $Bu_4NF{\cdot}H_2O$ 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-benzenesulfenic 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).

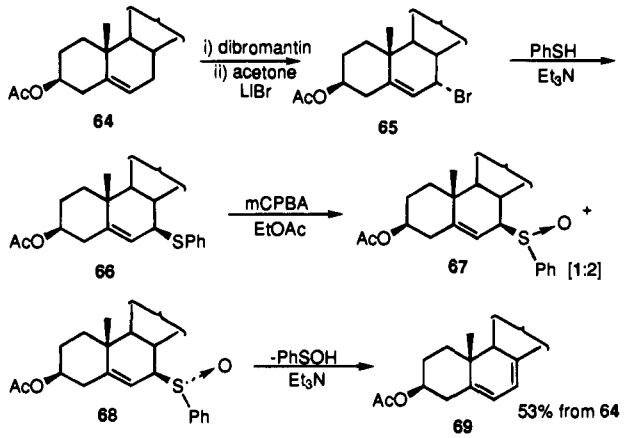



**Figure 16.**

Another possible alternative is the palladium-catalyzed elimination of allylic esters **61** (X = $O_2CCF_3$) (Figure 15).[156] Refluxing of 7α-allylic trifluoroacetate with $Pd_2(dba)_3$–$CHCl_3$, $PBu_3$, 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).

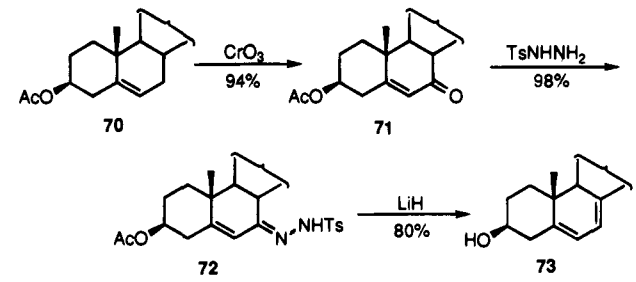



**Figure 17.**

The carbenoid route shown in Figure 17 features initial direct oxidation at C-7 of $\Delta^5$-ene-3β-acetate **70**[157–160] with $CrO_3$ and 3,5-dimethylpyrazole in pyridine.[161,162] This is followed by Bamford–Stevens elimination[163] 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 1α,2α-epoxide **79** and 1β,2β-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).

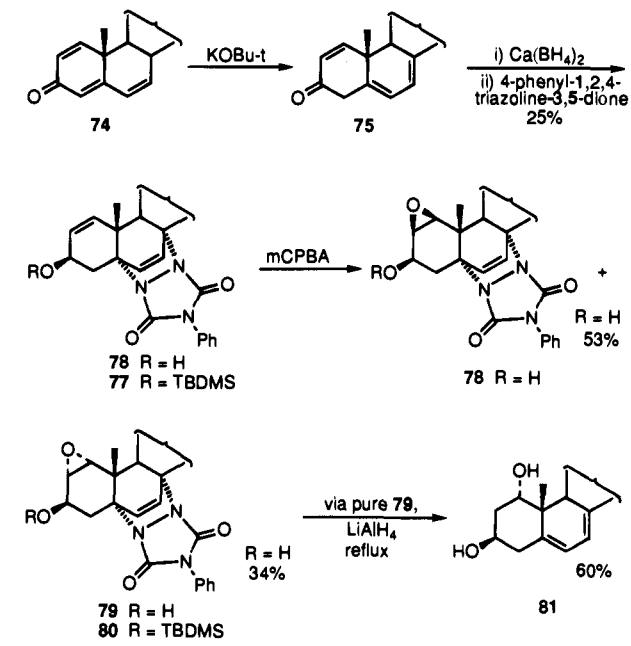



**Figure 18.**

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.

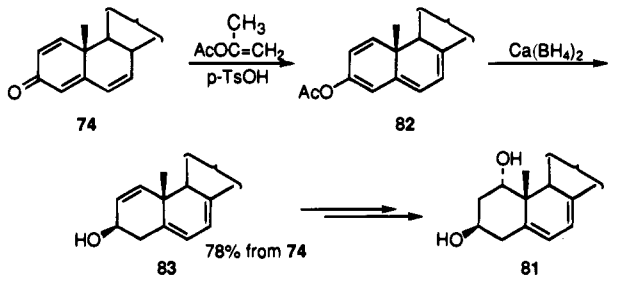



**Figure 19.**

### *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-trazoline-3,5-dione (**84**)[168,169] (Figure 20). In an improved

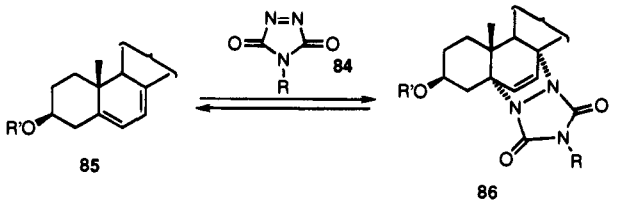



**Figure 20.**

version,[170] the ergosterol diene system **85** was reacted with 4-(*p*-nitrophenyl)-1,2,4-triazoline-3,5-dione (**84**, R = *p*-$O_2$NpH), 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 $D_3$[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-$D_3$ 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

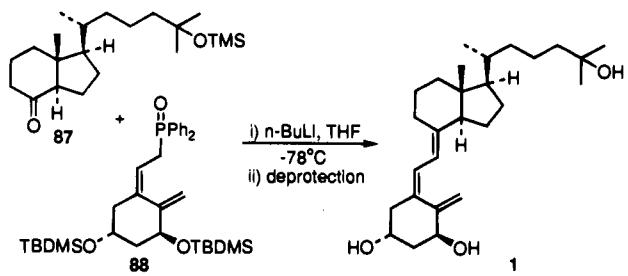



**Figure 21.**

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-$D_3$ 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.

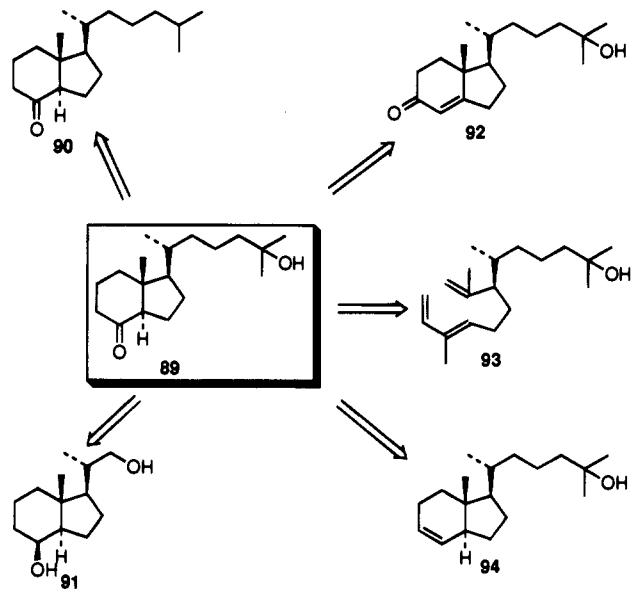



**Figure 22.**

The most practical approach to CD fragments is still the partial synthesis through $D_3$ degradation to **90** followed by direct 25-hydroxylation to **89**, or by side-chain modification of the Inhoffen–Lythgoe diol **91** (from vitamin $D_2$, 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

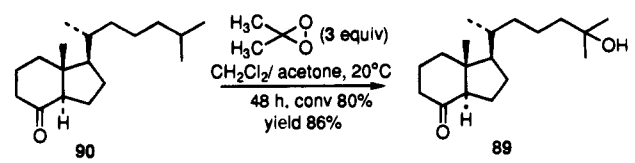



**Figure 23.**

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 group[176] 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

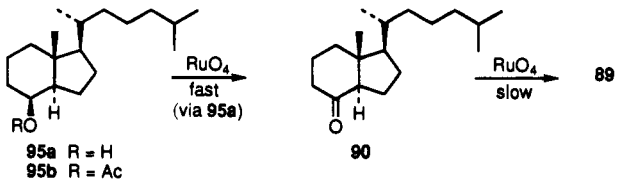



**Figure 24.**

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,

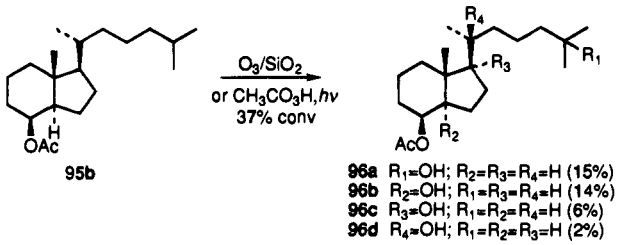



**Figure 25.**

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 ozonization 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

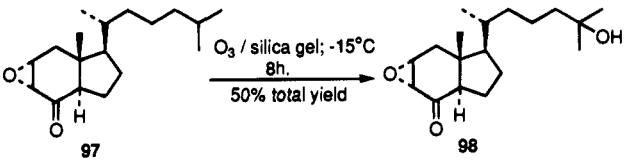



**Figure 26.**

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

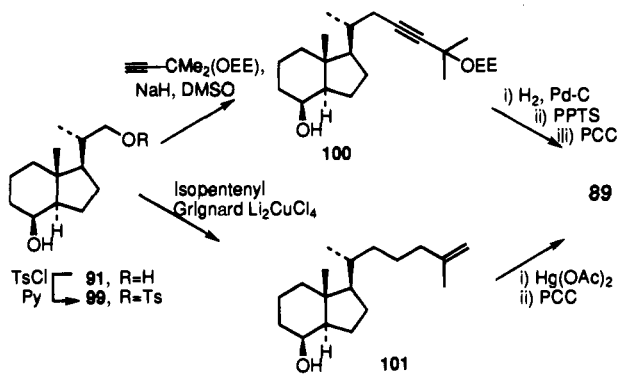



**Figure 27.**

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

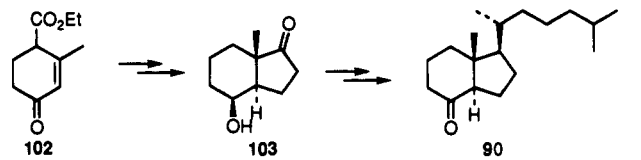



**Figure 28.**

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 $\gamma$-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-

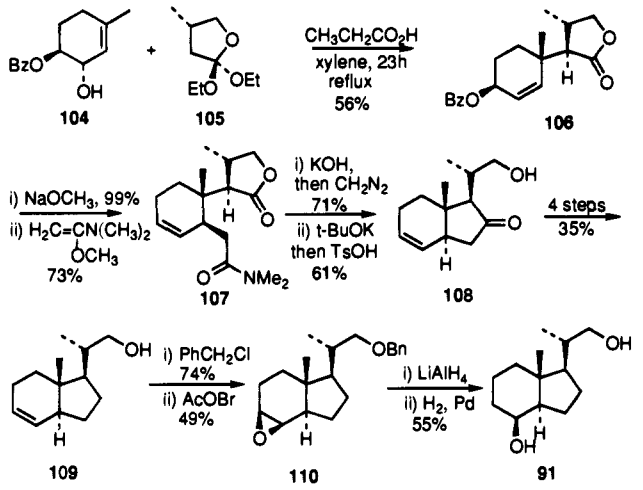



**Figure 29.**

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 $\beta$-epoxide **110**, which was reduced with $LiAlH_4$ and then hydrogenolyzed to give the desired Inhoffen–Lythgoe diol **91**.

Trost[188] 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

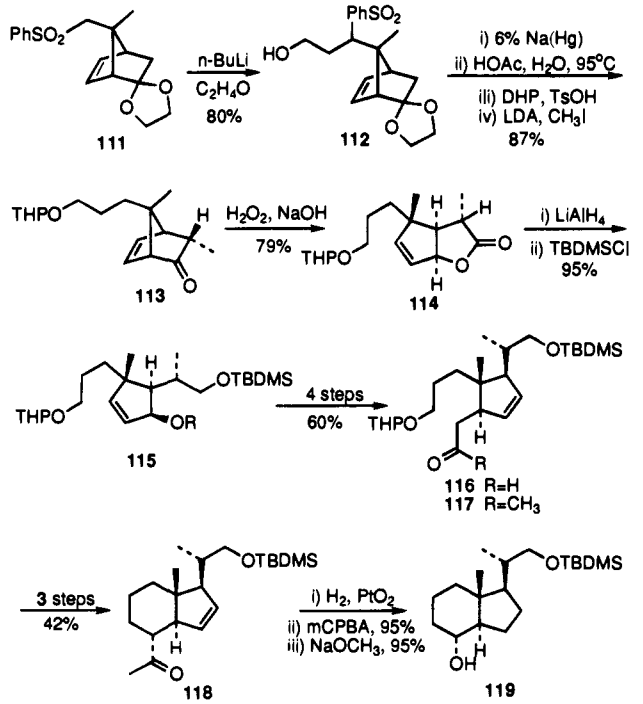



**Figure 30.**

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 hydrindene 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).

Johnson[190] 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).

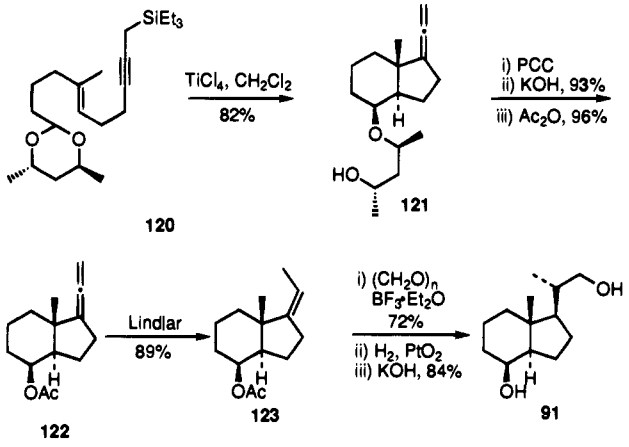



**Figure 31.**

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

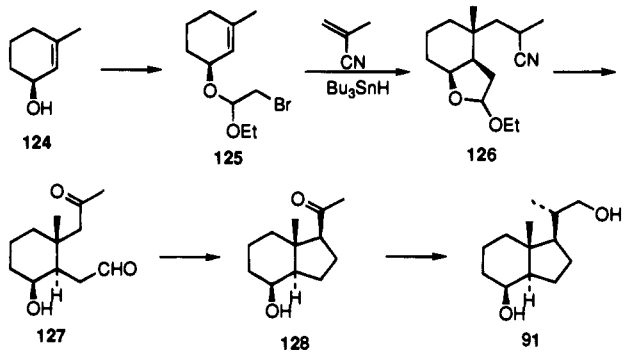



**Figure 32.**

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.

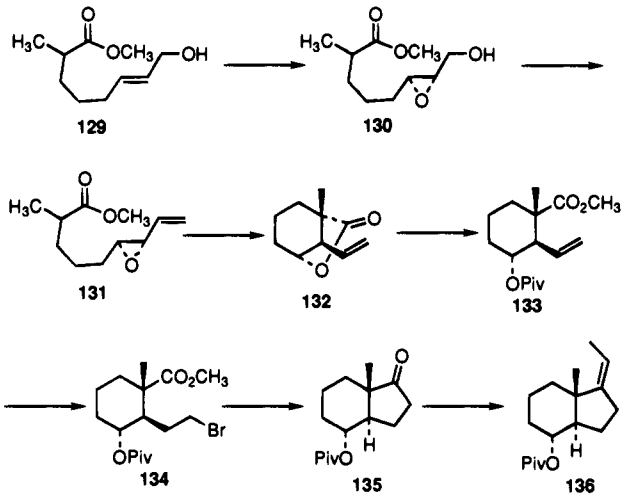



**Figure 33.**

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 $BF_3$–$Et_2O$ 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 condensation[195] 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

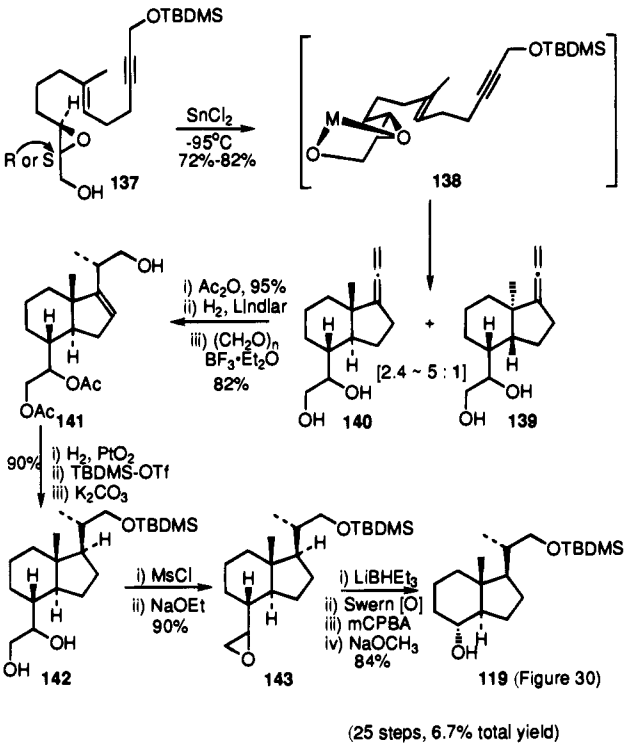



**Figure 34.**

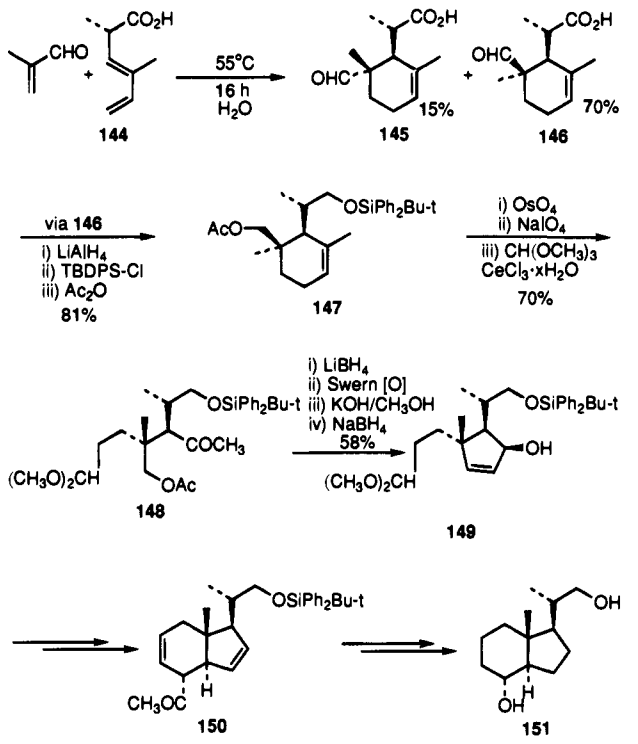



**Figure 35.**

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

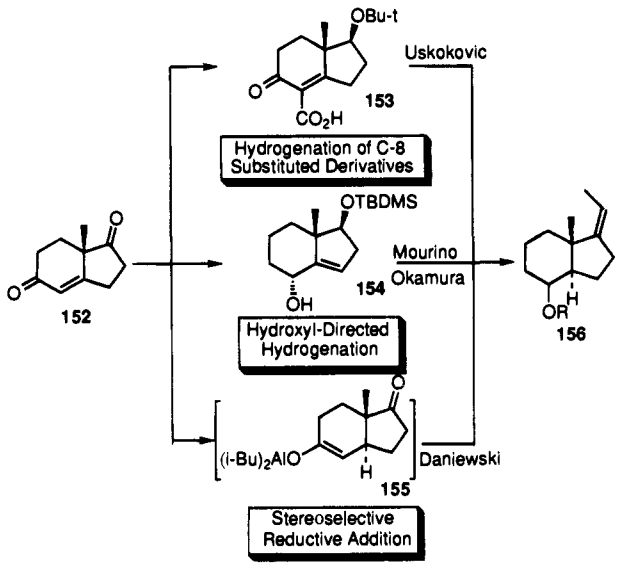



**Figure 36.**

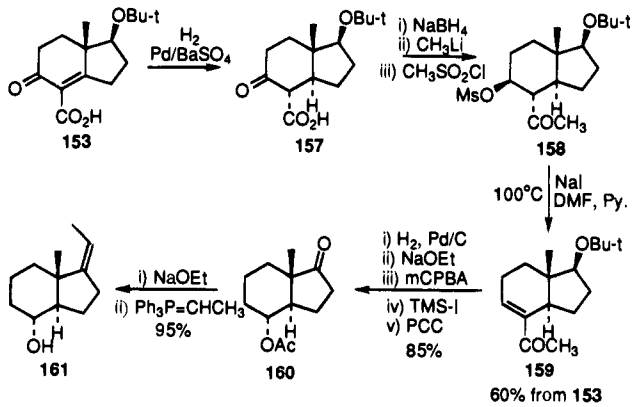



**Figure 37.**

synthesized from enedione **152**.[202,203] The starting keto acid **153** was hydrogenated highly stereoselectively to the corresponding *trans*-hydrindan derivative **157** ($H_2$, $Pd/BaSO_4$, 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 ethylidenetriphenylphosphorane 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 $BF_3{\cdot}Et_2O$ 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).

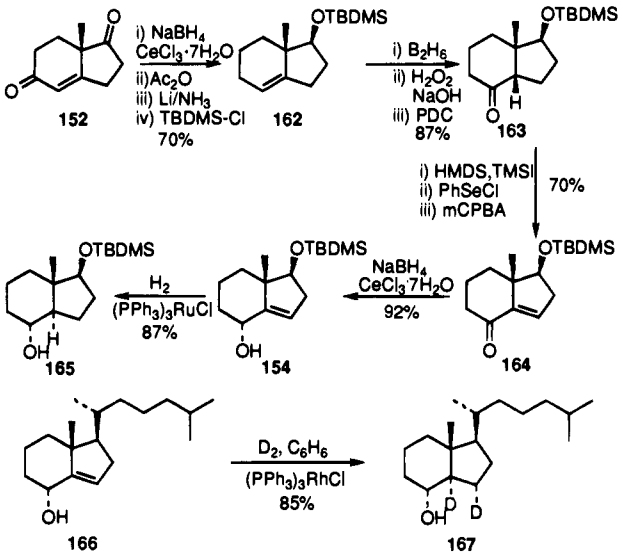



**Figure 38.**

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 procedure[206] through thermodynamic enol silylation, phenylselenyl 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 isooctyl 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 DIBAH,[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

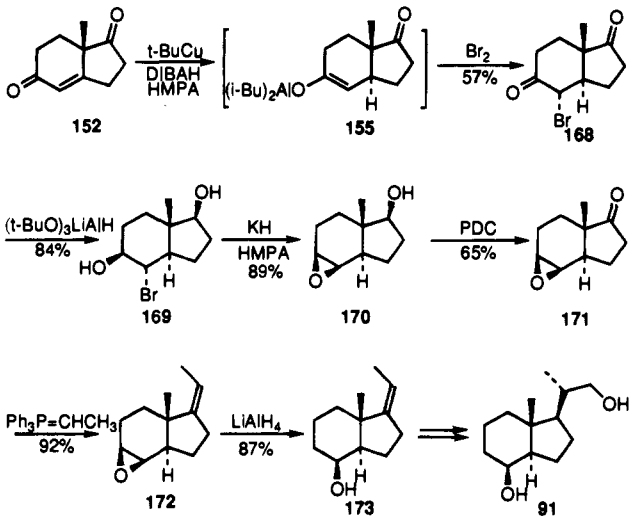


Figure 39.

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).

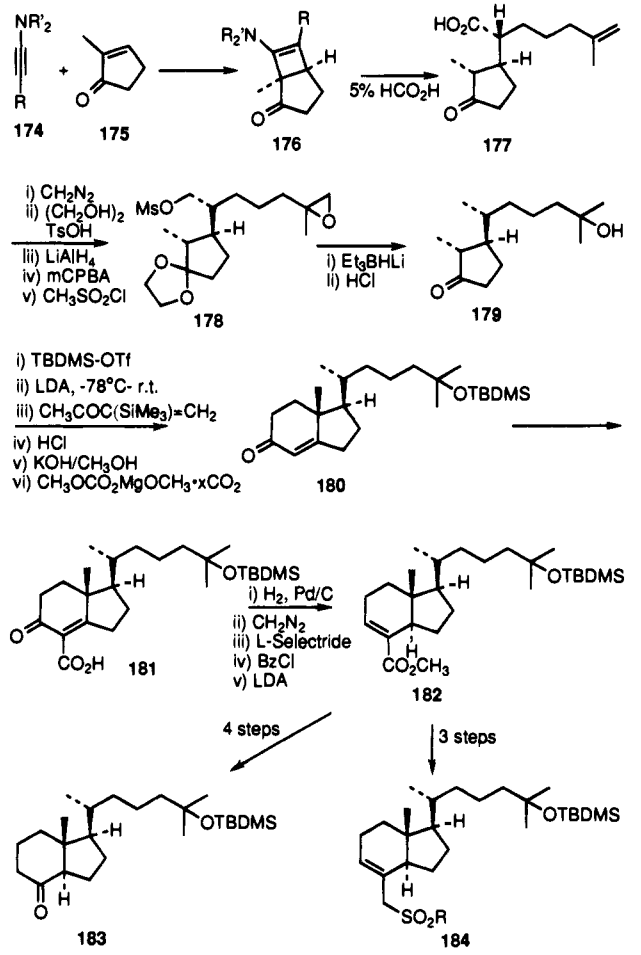


Figure 40.

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 (±)-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

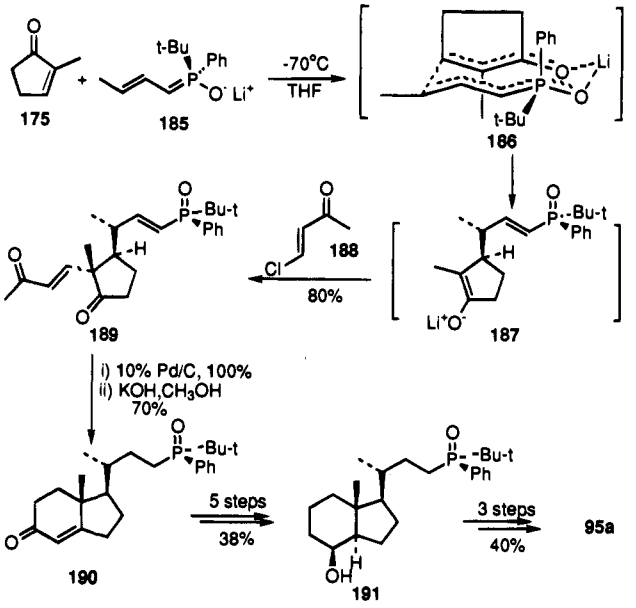


Figure 41.

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 hydrindenone 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 approach[217] (Figure 42). Hydrogenation of **195** at medium pressure (50–60 psi) is slow, giving a diastereomic 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

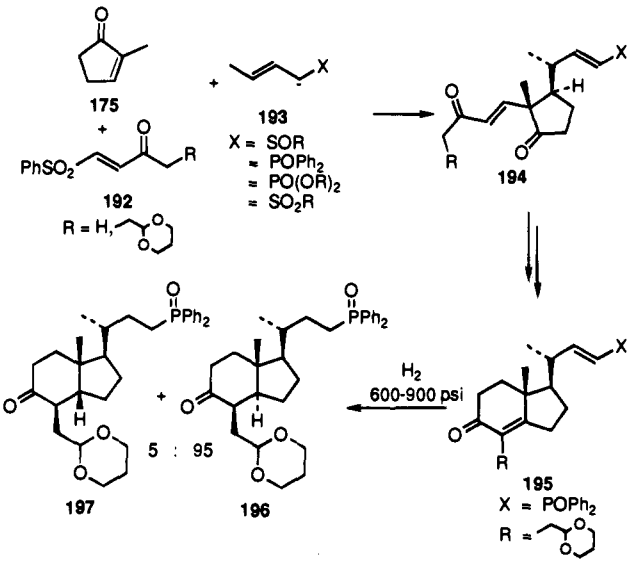


Figure 42.

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

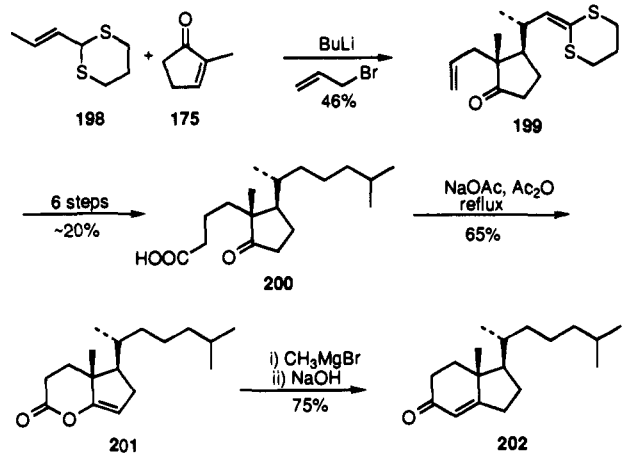


Figure 43.

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, $Ac_2O$, 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 $LiAlH_4$ 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 method[198] completes the synthesis in 19% overall yield.

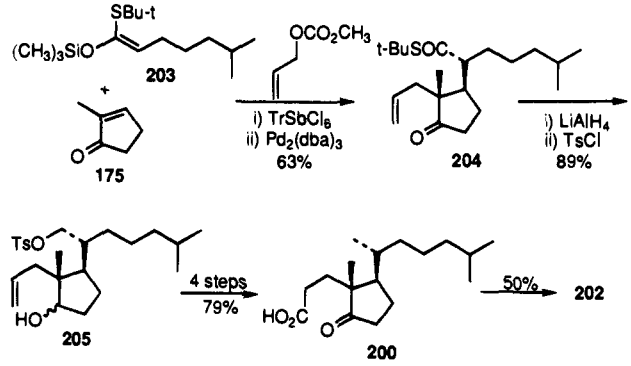


Figure 44.

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-

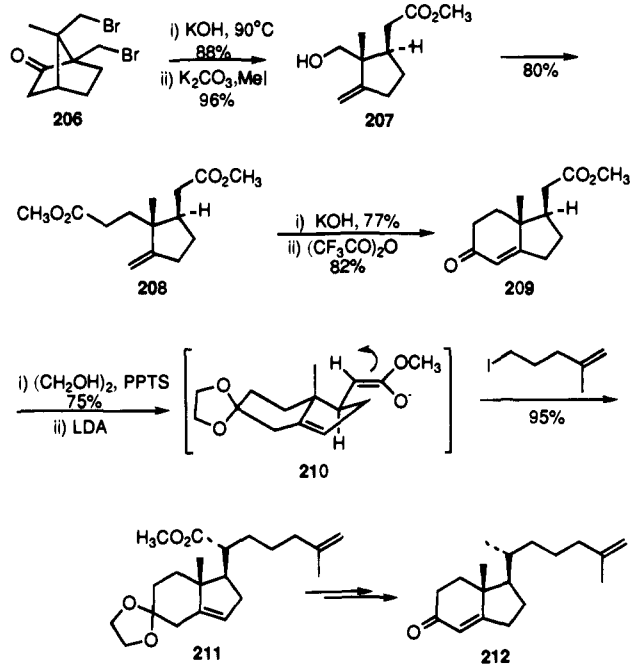


Figure 45.

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

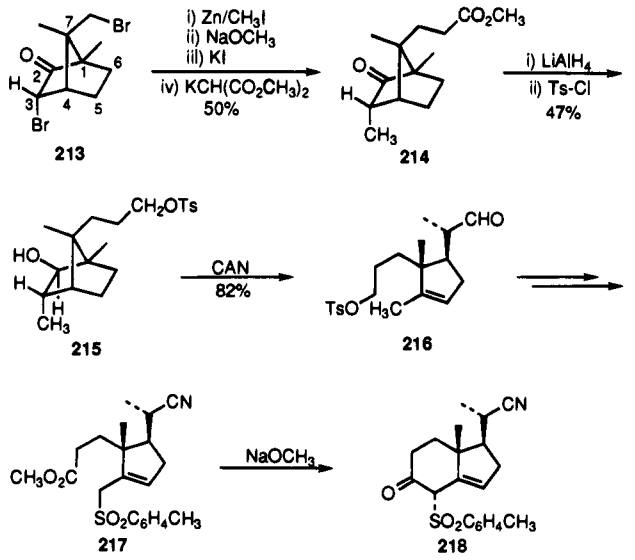



**Figure 46.**

as a single isomer, which is selectively tosylated to **215**. The fragmentation of the latter with ceric ammonium nitrate[226] 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*-toluenesulfinate leads to sulfone **217** which is cyclized ($CH_3ONa$) 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

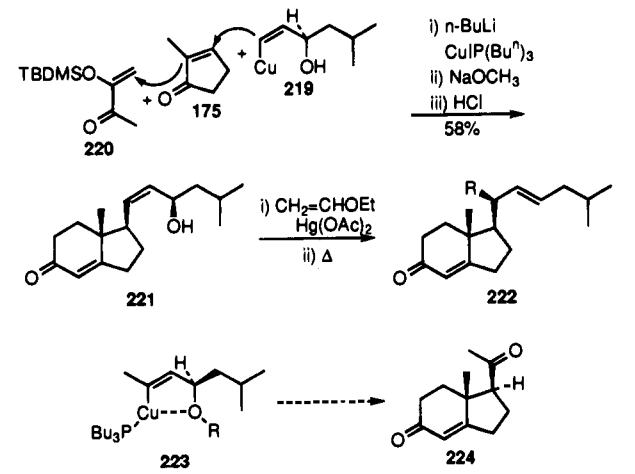



**Figure 47.**

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]

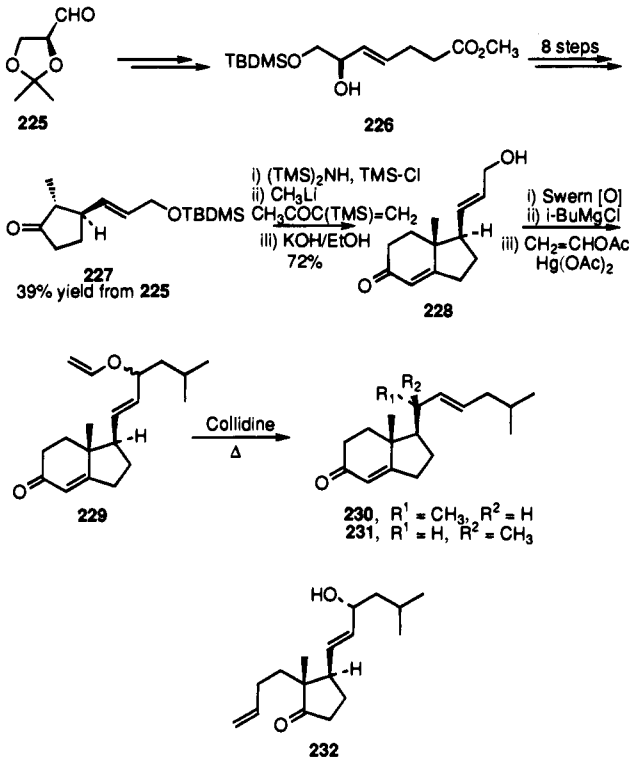



**Figure 48.**

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 monoepoxide[232] 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 indenedione **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 method[236] (Figure 50). Elaboration of the readily available Diels–Alder adduct **238** (both in racemic or optically pure form), in

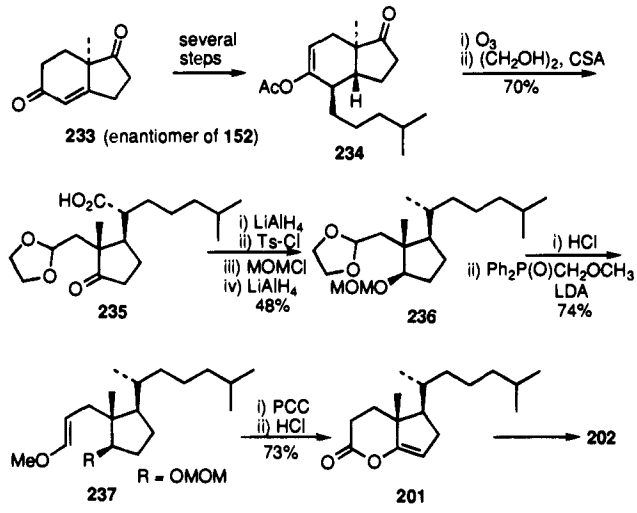



**Figure 49.**

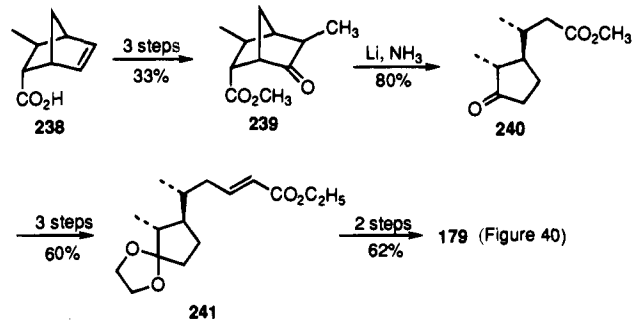



**Figure 50.**

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 laboratory[237] 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).

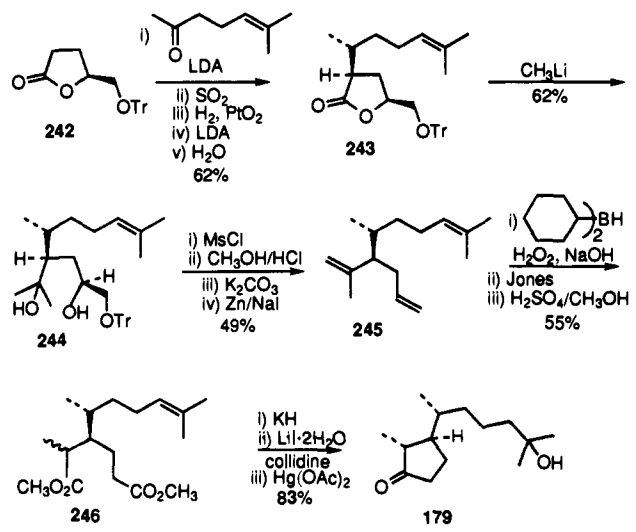



**Figure 51.**

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

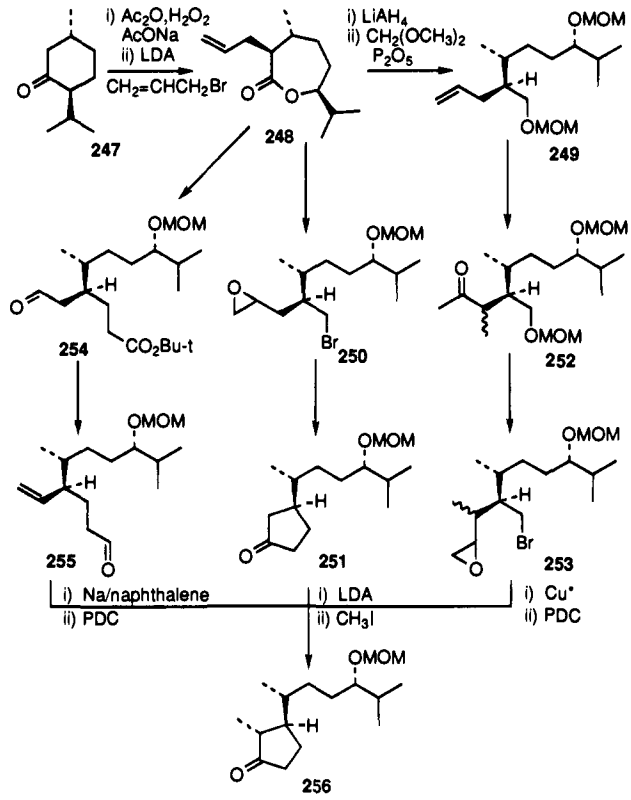



**Figure 52.**

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-workers[239] 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-

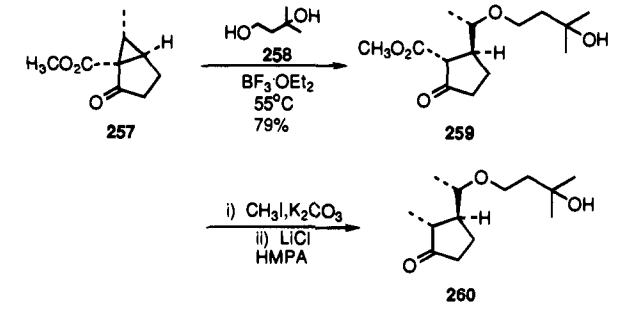



**Figure 53.**

propane **257** with 3-methyl-1,3-butanediol **258** in the presence of $BF_3$−$Et_2O$ 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).

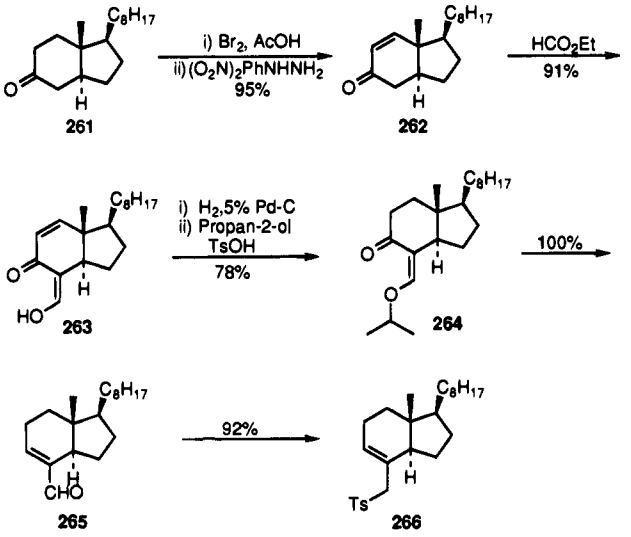



**Figure 54.**

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).

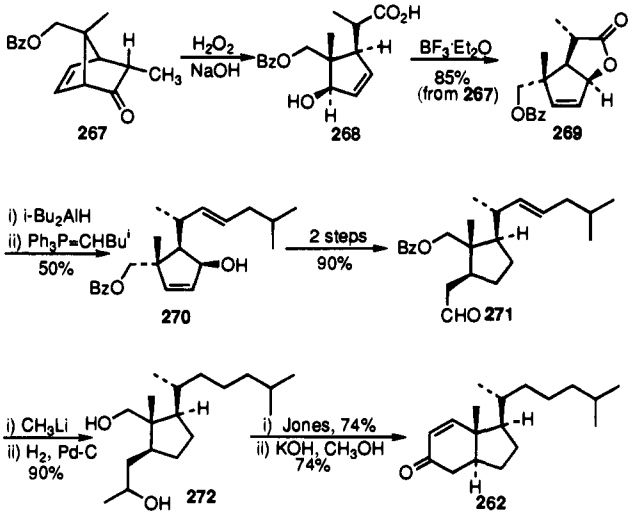



**Figure 55.**

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-

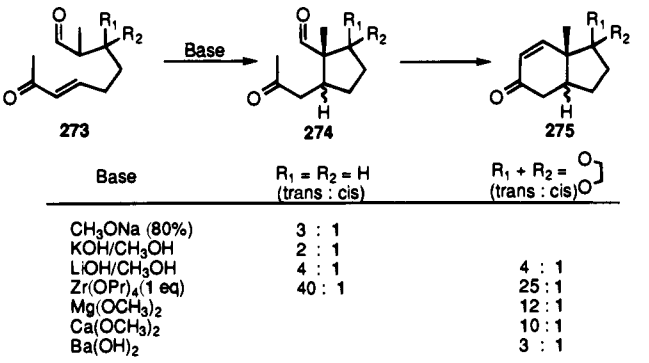



**Figure 56.**

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*-hydrindenones. 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*-hydrindenones 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).

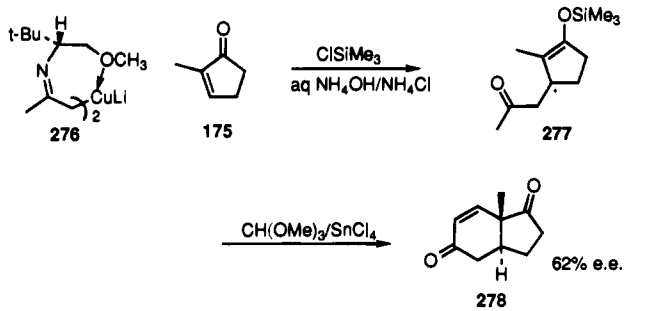



**Figure 57.**

$MeAlCl_2$-initiated ene cyclization of dienone **279** (Figure 58) provides the functionalized *trans*-fused hydrindenone **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 $MeAlCl_2$. 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-

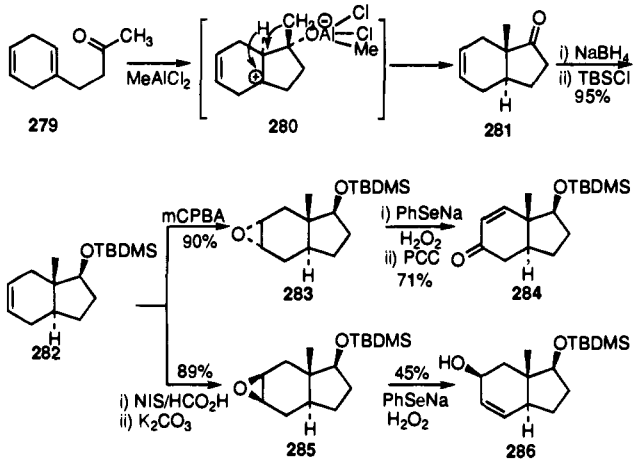


Figure 58.

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.

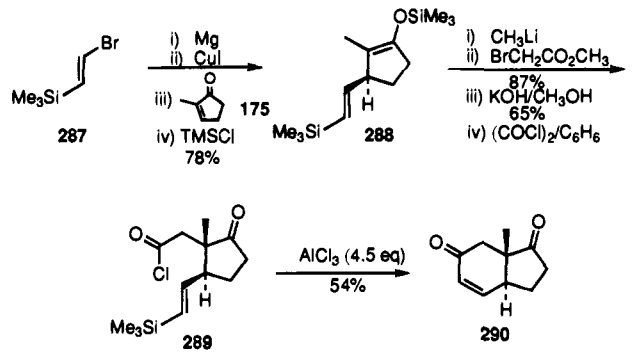


Figure 59.

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.

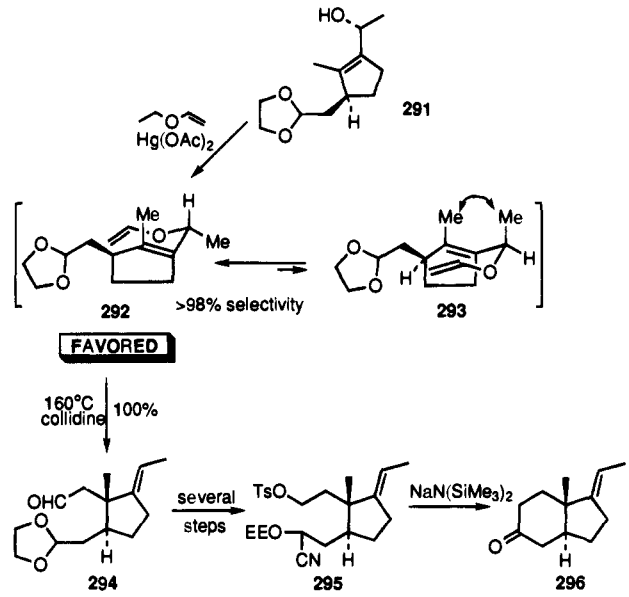


Figure 60.

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**

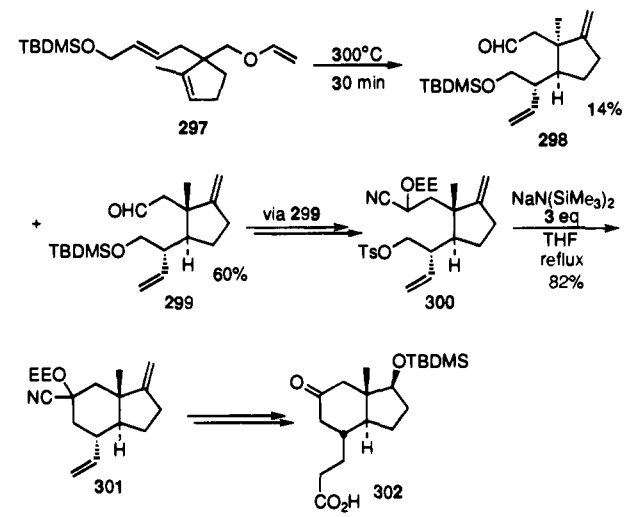
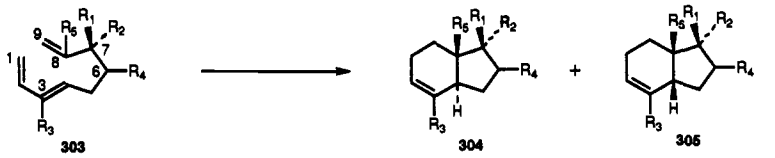


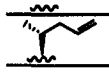
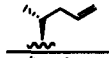
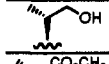
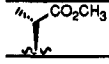
Figure 61.

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 |
| $-OCH_2CH_2CH_2O-$ | | 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 | $-CH_2C_6H_4-$ (-m-$OCH_3$) | OH | $CH_3$ | 160°C/20h | 96% | 80% | 20% | 261 |
|  | H | $-CH_2CH_2OH$ | 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 |
| $C_8H_{17}$ | H | $CH_3$ | H | $CH_3$ | 200°C/18h | 62% | 75% | 25% | 264 |
| $C_8H_{17}$ | H | Br | H | $CH_3$ | 200°C/60h | 71% | 58% | 42% | 264 |
| $C_8H_{17}$ | H | $SC_6H_5$ | H | $CH_3$ | 210°C/18h | 50% | 50% | 50% | 264 |
| $-SCH_2CH_2CH_2S-$ | | 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 Wilson[261] 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 dienal **307** was obtained through an Ireland–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 employing [3-[(triethylsilyl)oxy]-1,3-pentadienyl]lithium (**313**) instead of **311**, Wilson also reported a total synthesis of the 25-hydroxyvitamin $D_2$ CD precursor **317** through a similar intramolecular Diels–Alder reaction[270] (Figure 64). However, the stereochemistry of the Diels–Alder adduct at C-14 appeared not to be fully detailed.

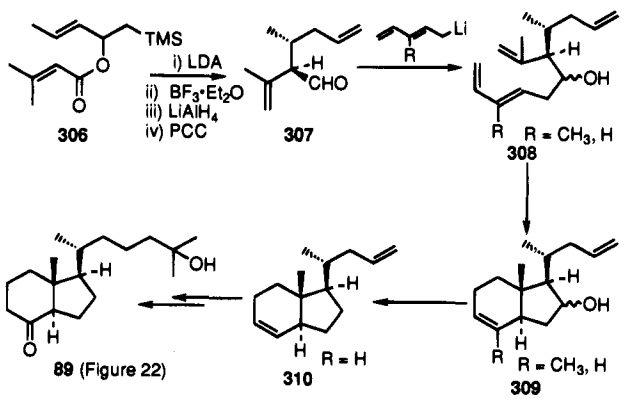



**Figure 62.**

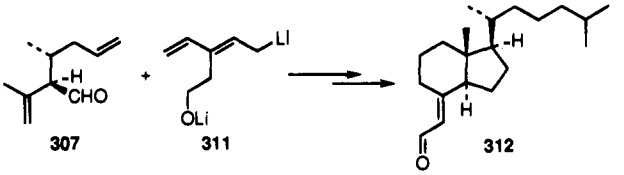



**Figure 63.**

In another approach, Parker[263] used the ester enolate Claisen rearrangement of **318** to generate the proper stereochemistry at C-17 and C-20. The con-

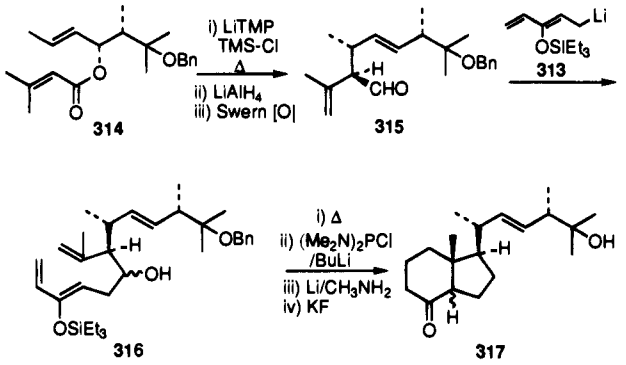


Figure 64.

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.

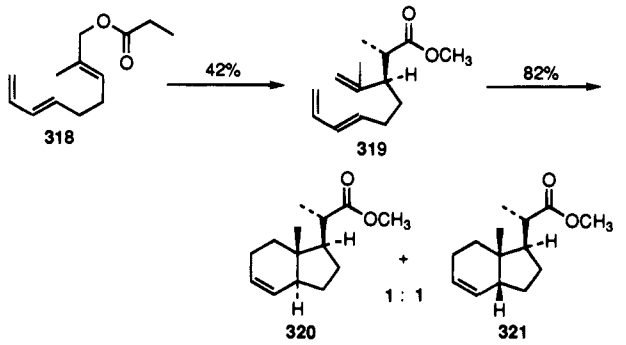


Figure 65.

*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 $\Delta^5$-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 fragment 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 = $C_8H_{17}$ as in Grundmann's ketone, **90**) (Figure 67).

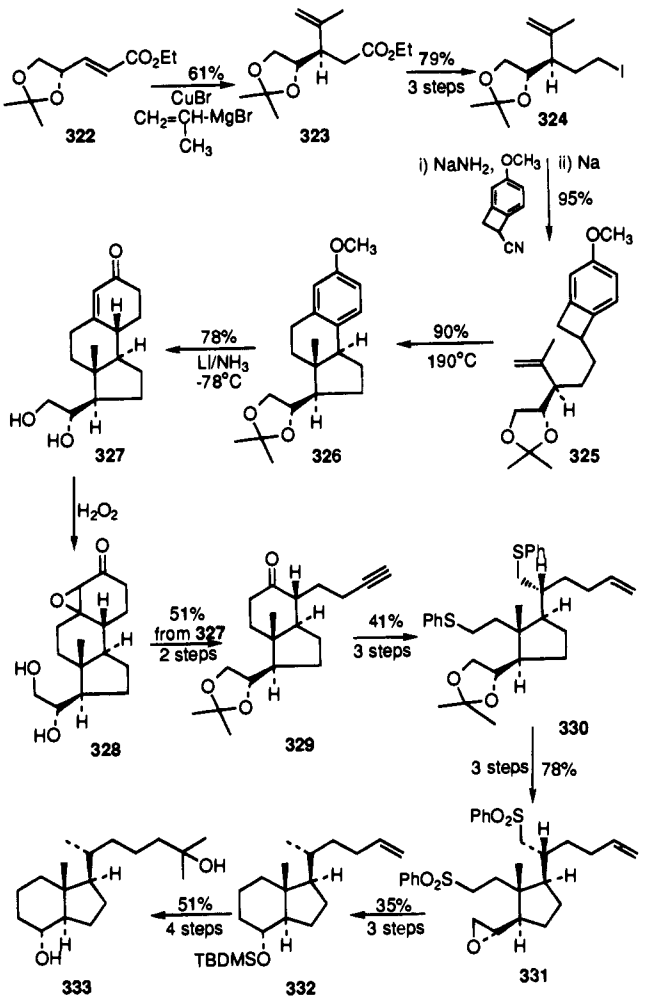


Figure 66.

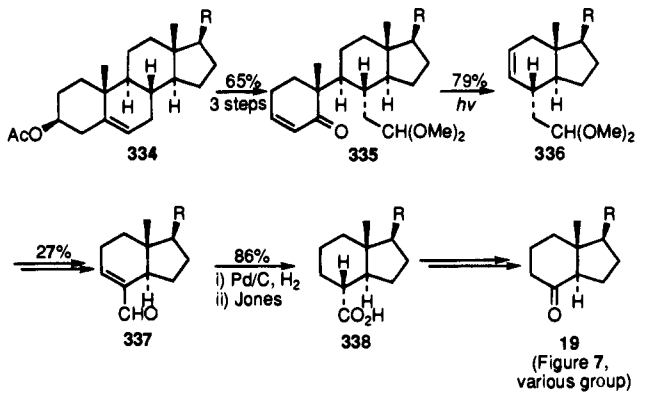


Figure 67.

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-

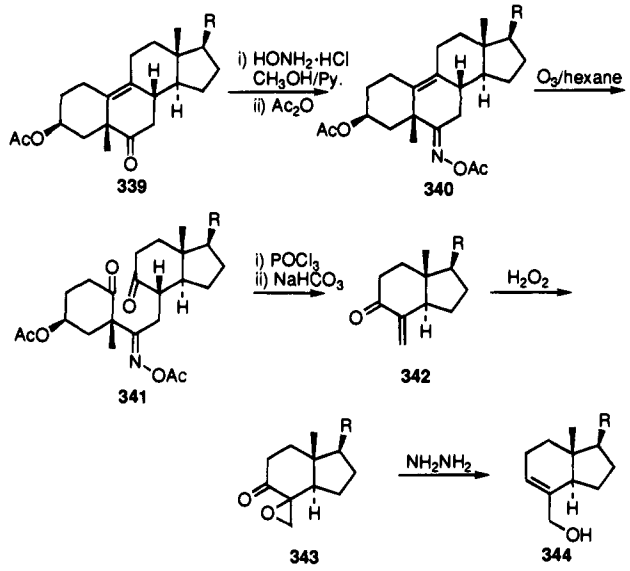



**Figure 68.**

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 $D_3$ followed by 25-hydroxylation (Figures 23 and 24) or the degradation of vitamin $D_2$ 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 $D_3$ (or vitamin $D_2$ with the ergosterol side chain) as shown in Figure 69.[106] From an economical point of view, Okamura's adaptation[277] of a previously described

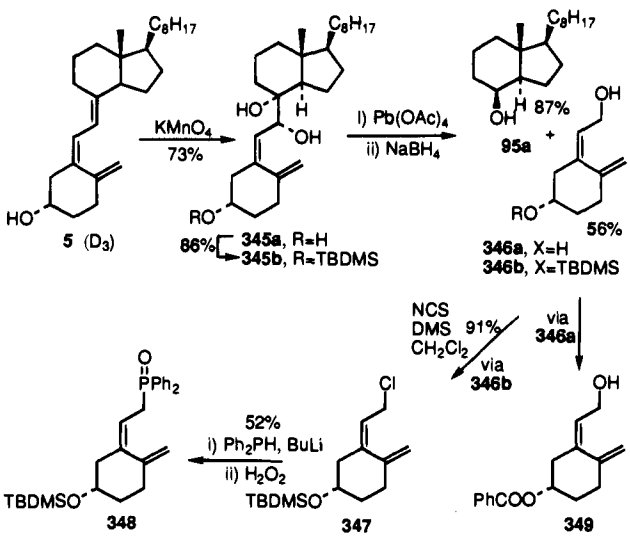



**Figure 69.**

procedure[278] using $KMnO_4$ as the initial oxidant is probably the most efficient one for selective $\Delta^{7\alpha,8\alpha}$-bis-hydroxylation of $D_3$ (**5**) (Figure 69). The C–C bond of 7α,8α-glycol **345** is easily cleaved via a lead tetraacetate oxidation–$NaBH_4$ 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]

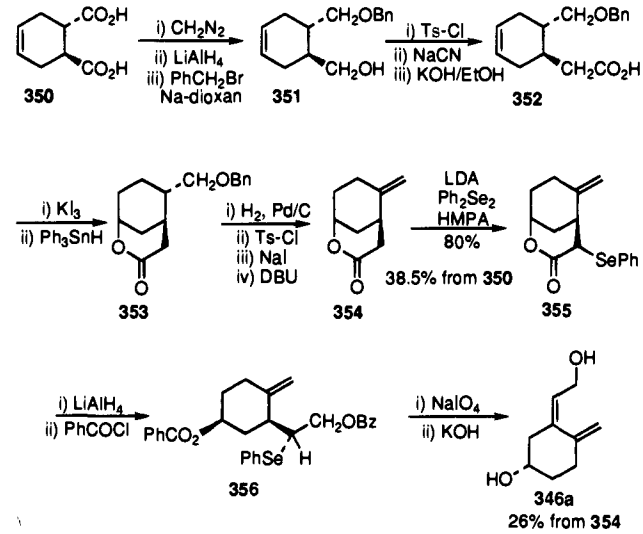



**Figure 70.**

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 $D_3$ to its 1α,25-dihydroxy metabolite[176] makes it possible to convert the vitamin $D_3$ (or $D_2$) degradation product **346b** directly to the 1α-hydroxylated phosphine oxide **88** (Figure 71). In this approach, the more reactive $\Delta^{5,6}$-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 $SeO_2$/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 Ganem[279] was reported to be productive for the regeneration of the $\Delta^{5,6}$-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%.

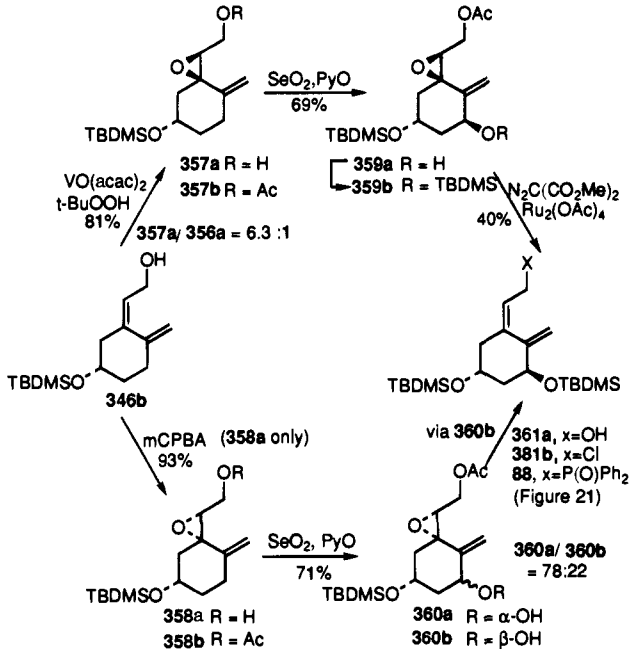



**Figure 71.**

*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 1α-hydroxy A-ring phosphine oxide **88** (Figure 72).

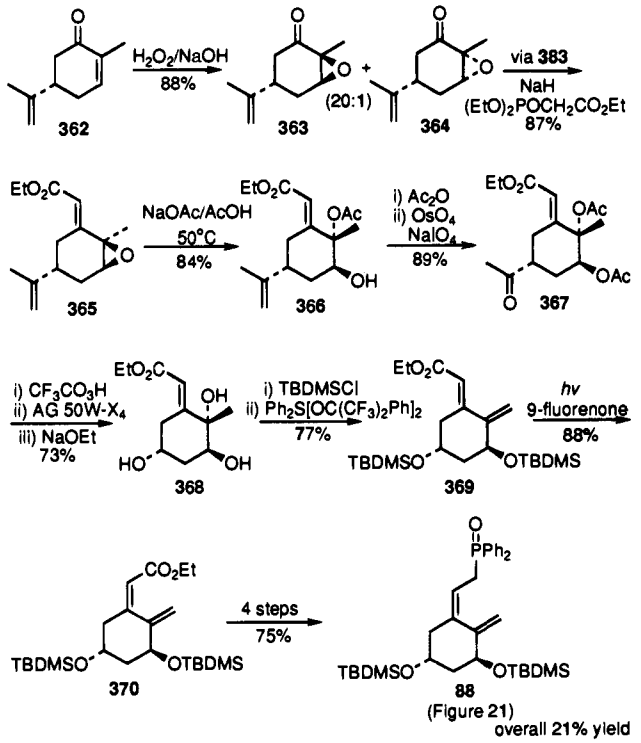



**Figure 72.**

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 dialkoxydiarylsulfurane 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 method[108] 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 reductive 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 1α-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**.

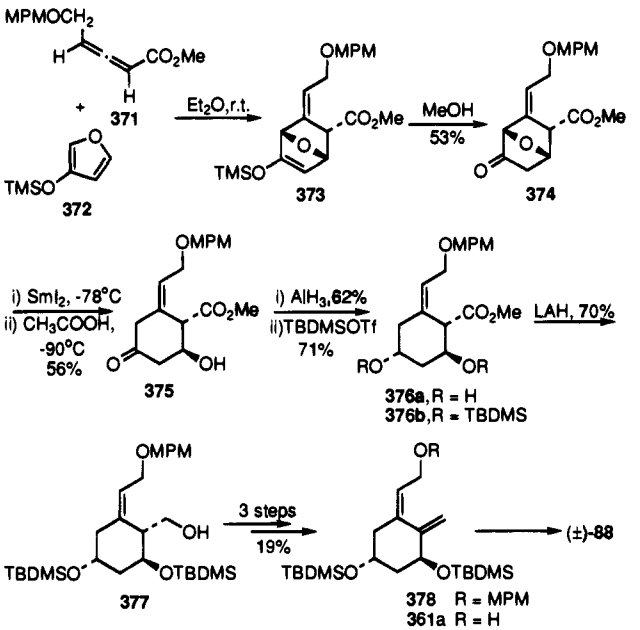



**Figure 73.**

Utilizing a Lewis acid-catalyzed [4 + 2] cycloaddition process, Posner[109] 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 dienoate esters. This tandem Claisen rearrangement–sulfoxide thermolysis of **385** produced

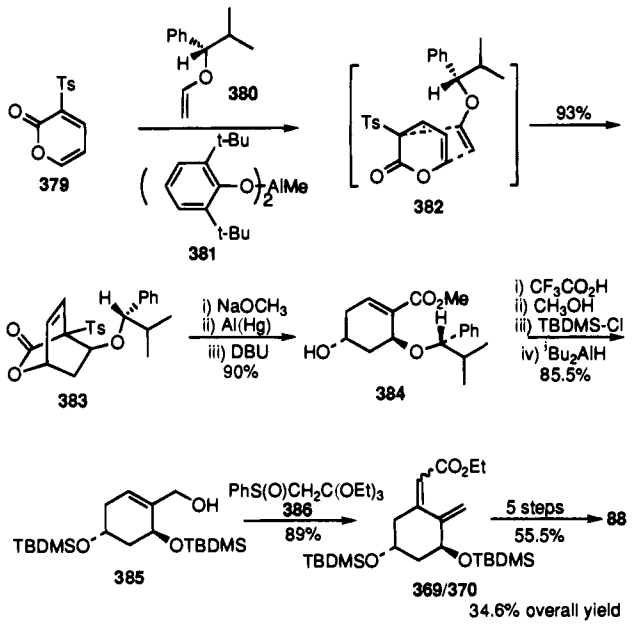



**Figure 74.**

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

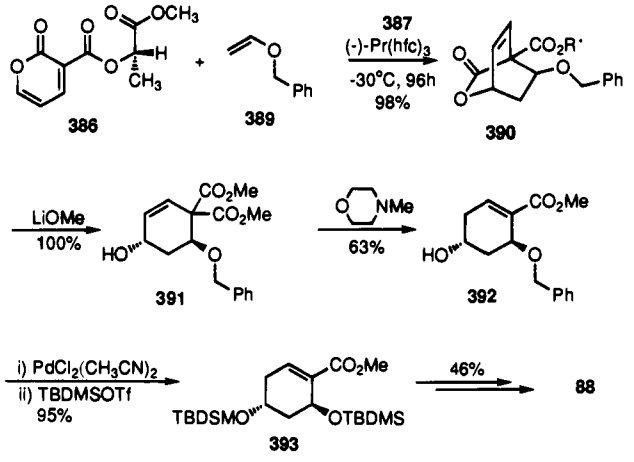



**Figure 75.**

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 debenzylation 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

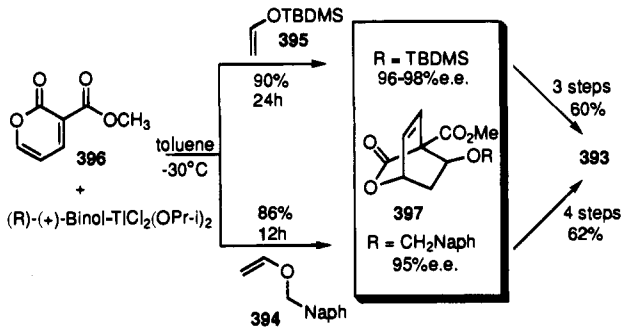



**Figure 76.**

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 procedure[285] involves the modification of an enzymatically resolved chiral monoester **409**

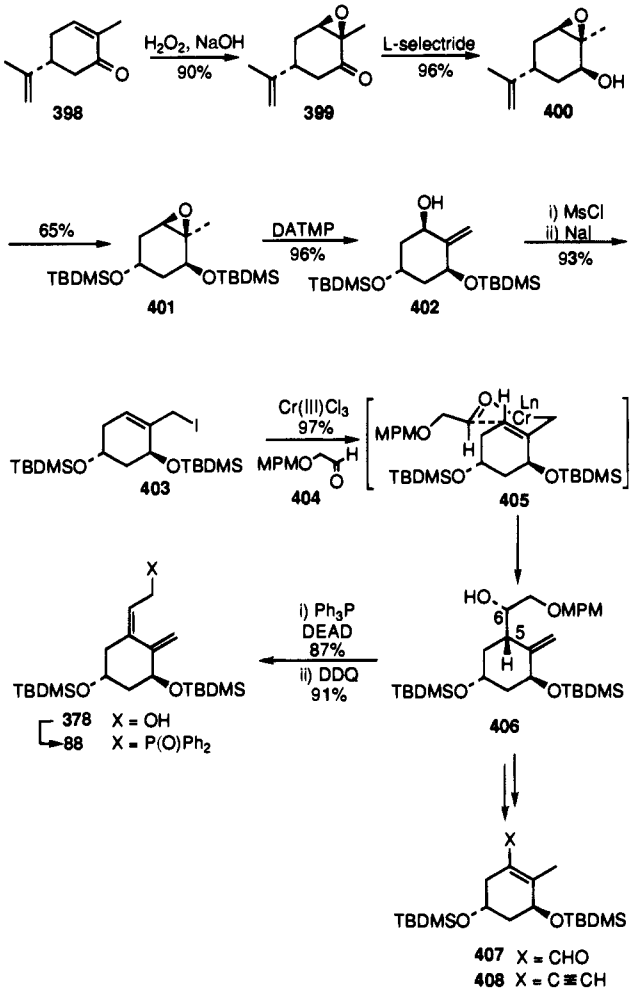


Figure 77.

(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-1α oxygenated synthon **413**, functional group modification including a selenoxide elimination step afforded the previously described **378** (from Figure 77).

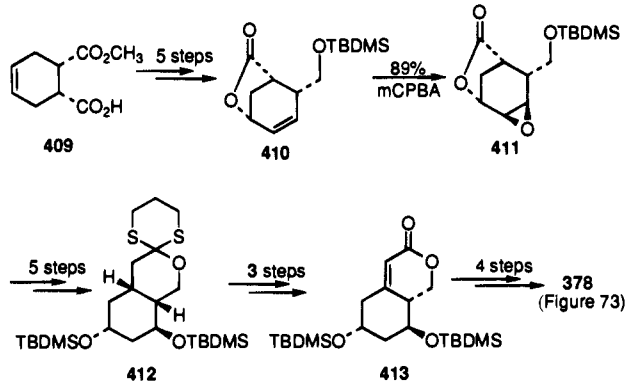


Figure 78.

*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 1α-hydroxyl was introduced through epoxidation–ring opening of the resulting double bond

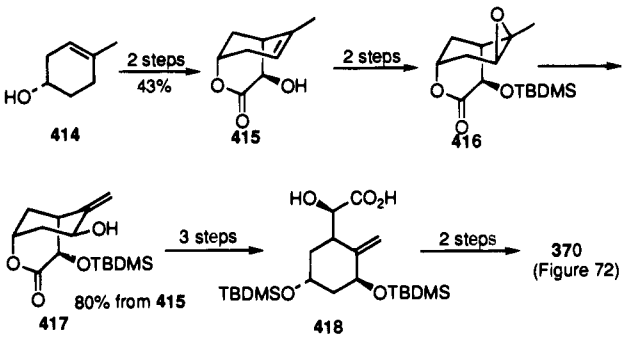


Figure 79.

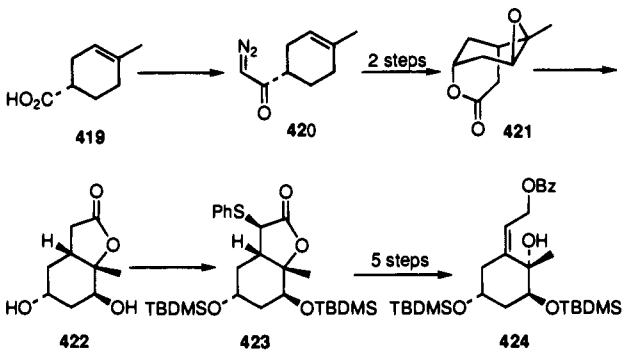


Figure 80.

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 developed[286] 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**

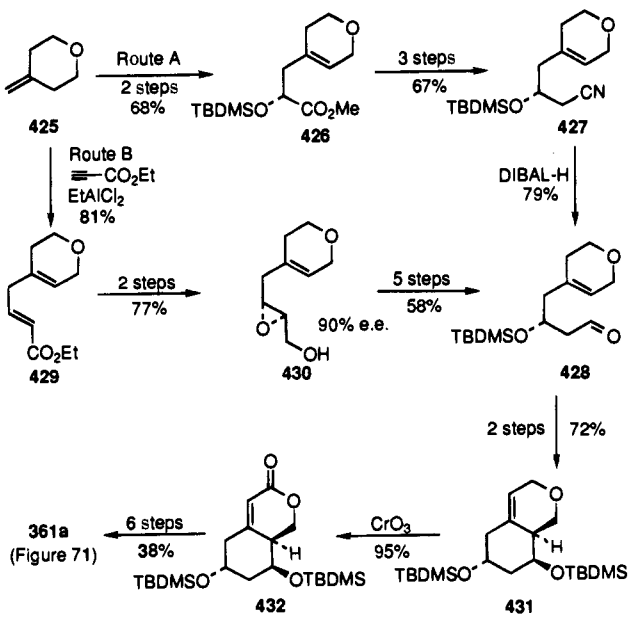


Figure 81.

were described. In the first procedure (route A), Mikami's catalytic system,[287,288] the Lewis acid system from $TiBr_2(OiPr)_2$, and (*R*)-(+)-1,1′-bi-2-napthol 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

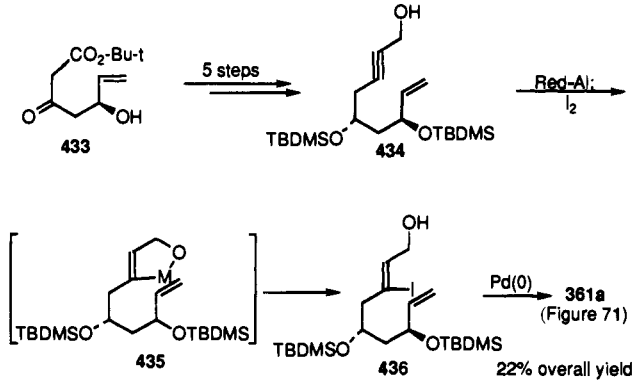



**Figure 82.**

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 % $Pd(PPh_3)_4$ and $Et_3N$ gave exclusively desired cyclization product **361a** (22% overall yield).

Shimizu's synthesis[118] 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

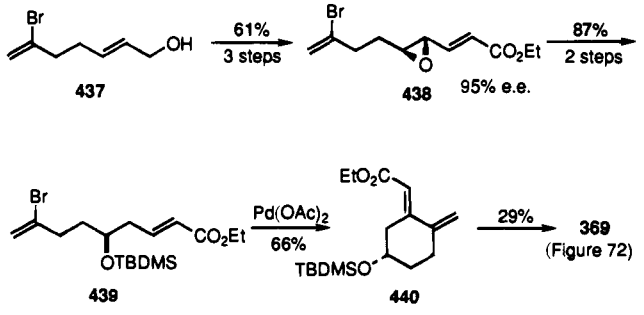



**Figure 83.**

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 epoxidation (95% ee), Swern oxidation, H··ner–Emmons reaction, palladium-catalyzed epoxide hydrogenolysis, and silylation. The cyclization of **439** to **440** was induced with 5 mol % $Pd(OAc)_2$–$PPh_3$ (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** [$Me_4NBH(OAc)_3$][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

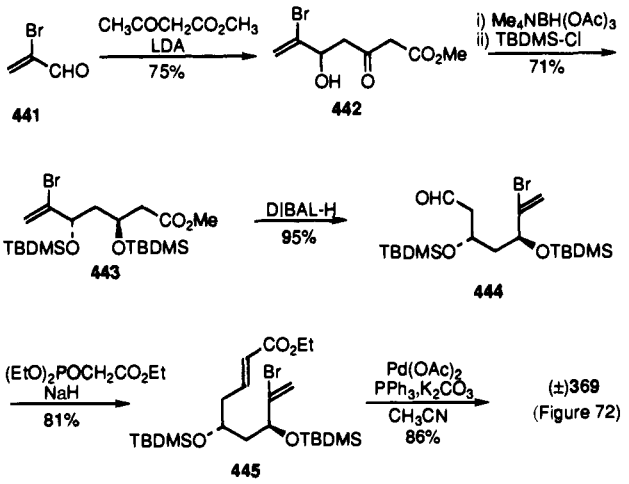



**Figure 84.**

**443** to racemic **369** was carried out conventionally and in parallel to that in Figure 83. The optically pure version of this synthesis[292] is outlined in Figure 85. Asymmetric aldol reaction of α-bromoacrolein

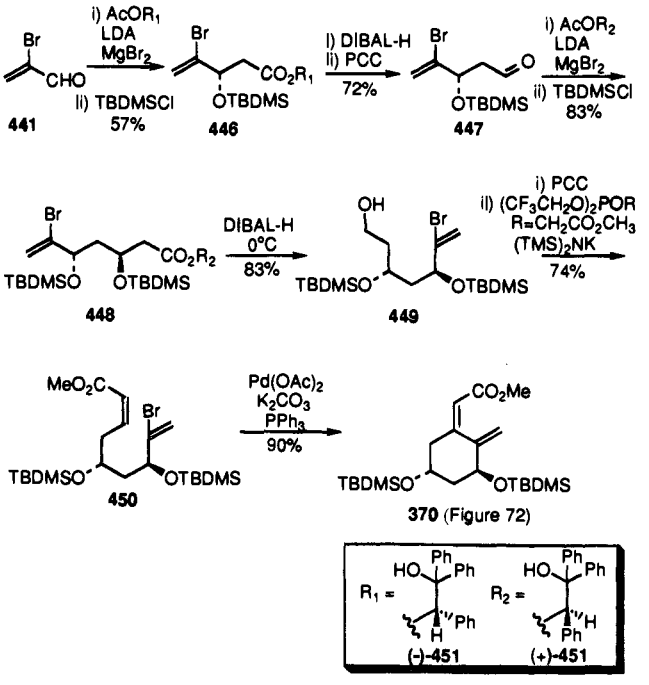



**Figure 85.**

(**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 $MeOH/CH_2Cl_2$ 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

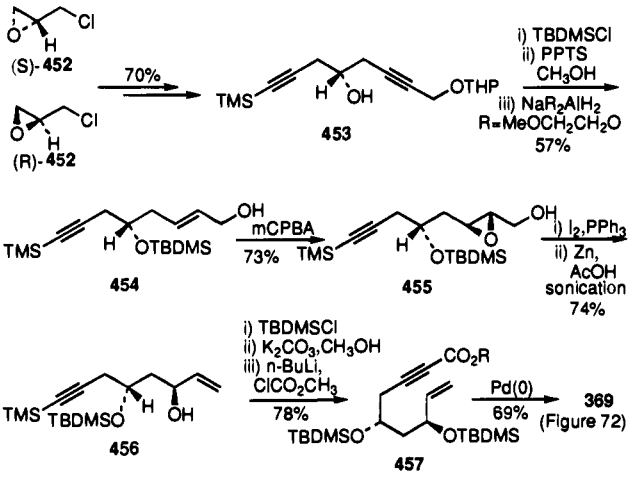



**Figure 86.**

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 [$Pd_2(dba)_3$ $CHCl_3$] 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*)-isopropyloxazolidinone (**458**) gave a single diastereoisomer **459**. Reductive removal of the unwanted chlorine atom followed by saponification with $LiO_2H$ 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** ($Bu_3SnH$, AIBN) generated **465** (94%). The latter was dehydrogenated to give a mixture of **369** and **370**. However, the bromide **464** could be efficiently converted

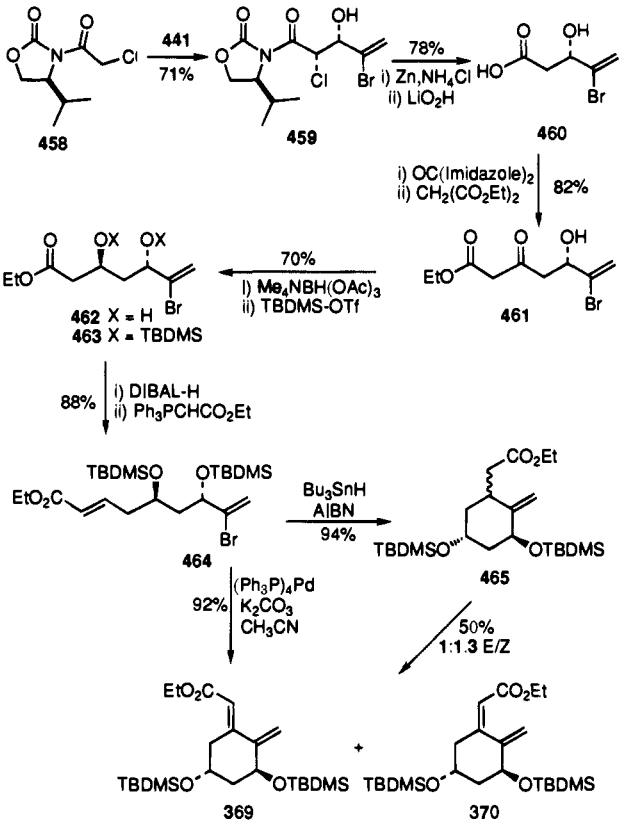



**Figure 87.**

to the single *E*-isomer **369** by palladium-catalyzed cyclization [$(Ph_3P)_4Pd$, $K_2CO_3$, $CH_3CN$, 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-

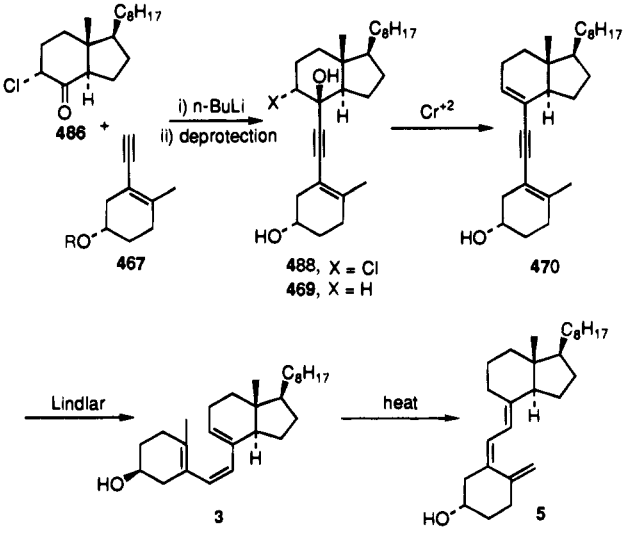



**Figure 88.**

chloro ketone **466** with the lithium derivative of enyne **467** to give, after deprotection, the vicinal chlorohydrin **468**. Elimination ($Cr^{2+}$) generated the $\Delta^{8,9}$-ene **470**, which was semihydrogenated over Lindlar's catalyst to give pre-$D_3$ (**3**, Figure 2). The latter undergoes thermal rearrangement to vitamin $D_3$ (**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

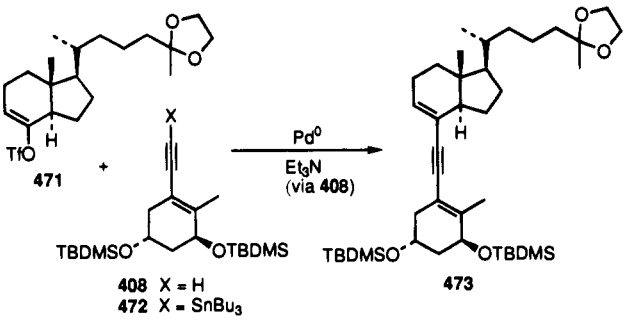



**Figure 89.**

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 $Pd(PPh_3)_2Cl_2$ (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 ($PhNTf_2$, 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

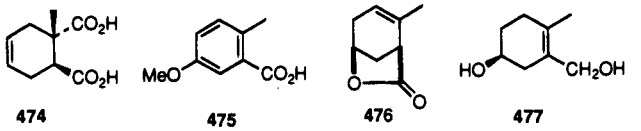



**Figure 90.**

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 1α-hydroxyl group, which characterizes the more active metabolites and analogues of vitamin D. For studies of thermal [1,7]-sigmatropic shifts of previtamin $D_3$ to vitamin $D_3$, a 12-step synthesis of the unlabeled (**486a**) or trideuteriated 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

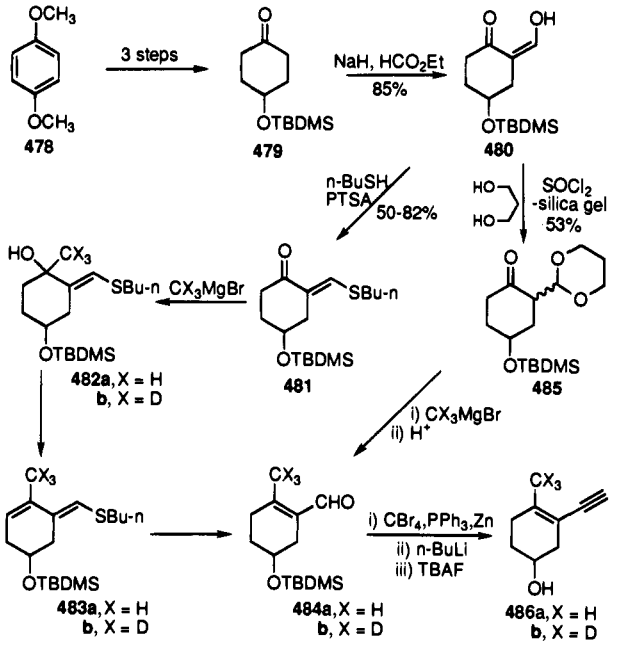



**Figure 91.**

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

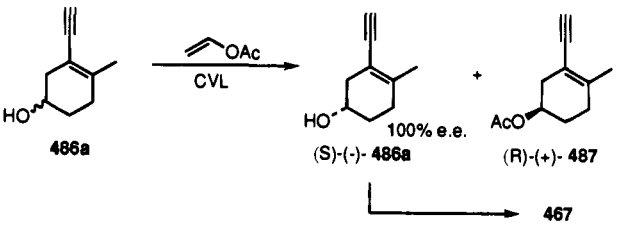



**Figure 92.**

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]

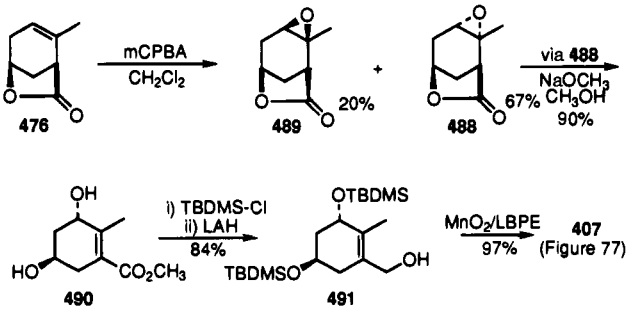



**Figure 93.**

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-

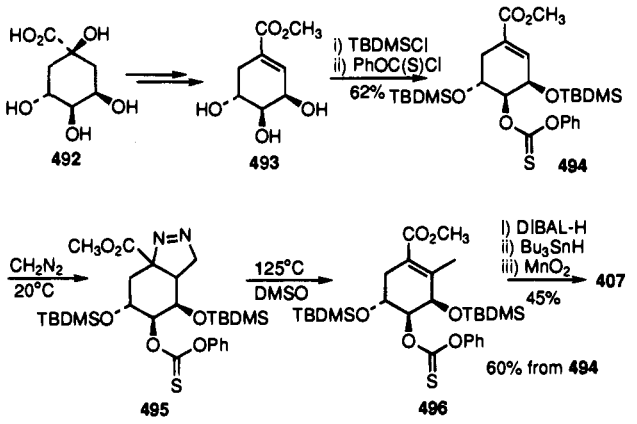



**Figure 94.**

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

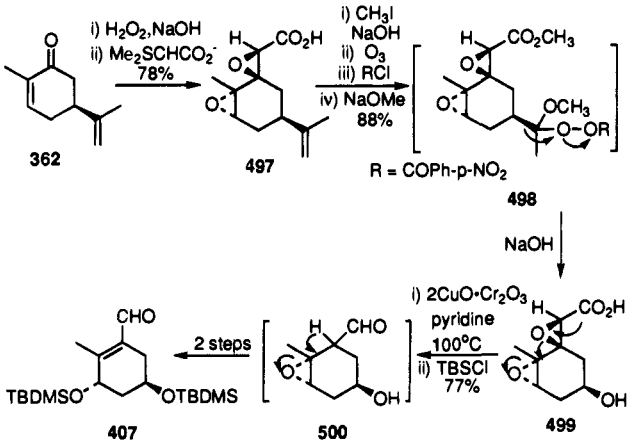



**Figure 95.**

involved the oxidative degradation of the isopropenyl side chain of the known carvone epoxide **363** to the reduced 3$\beta$-hydroxyl group and also by establishment of the suitable configuration of the 1$\alpha$-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 3$\beta$-hydroxy group by the Criegee-type procedure. The homologous alcohol

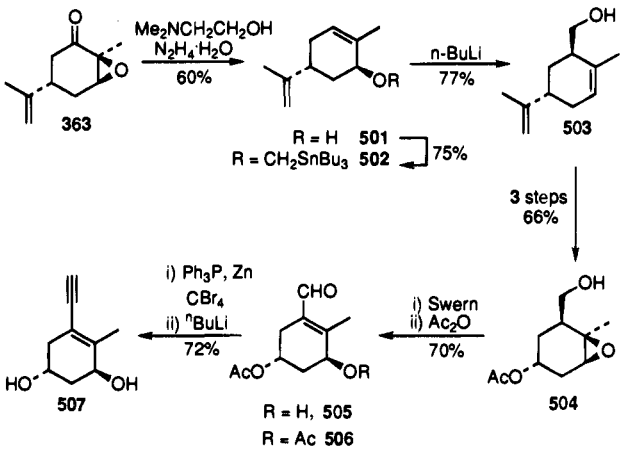



**Figure 96.**

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-

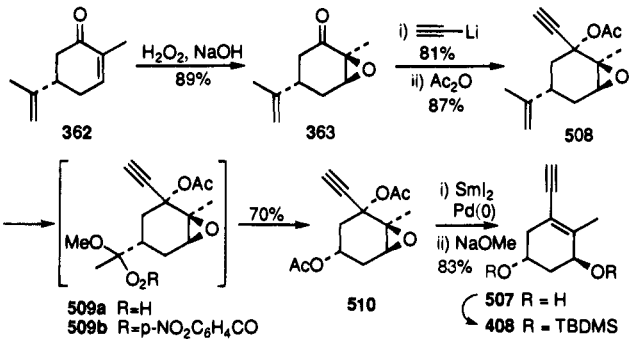



**Figure 97.**

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 rearrangement[308] of the resulting methoxy peroxyester afforded diacetate **510**, an easily purified, highly crystalline material. A novel $SmI_2$-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 group[314] as minor (11%) photoproducts of vitamin $D_3$ (Figure 98).

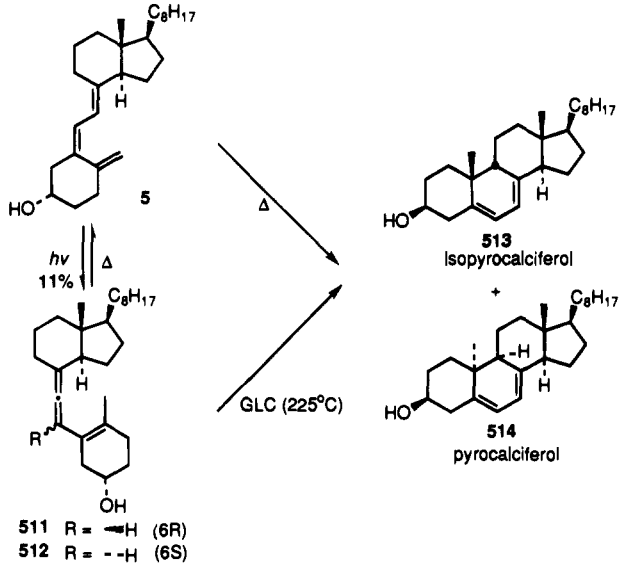



**Figure 98.**

Under gas chromatographic conditions (225 °C) the two vinylallenes were found to exhibit a chromatographic profile characteristic of vitamin $D_3$. Later Havinga's primary hypothesis that the vinylallenes undergo initial [1,5]-sigmatropic hydrogen shift to vitamin $D_3$, which then undergoes its characteristic thermal rearrangement to pyro- (**514**) and isopyrocalciferol (**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).

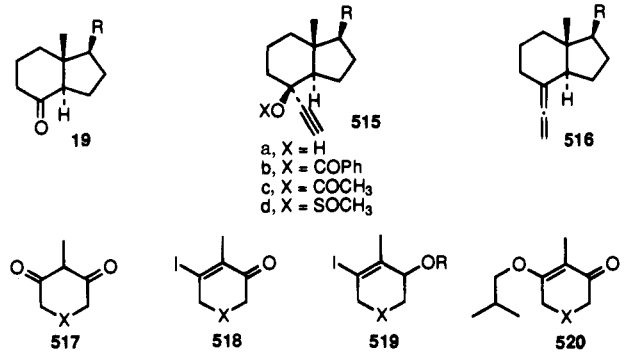



**Figure 99.**

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).

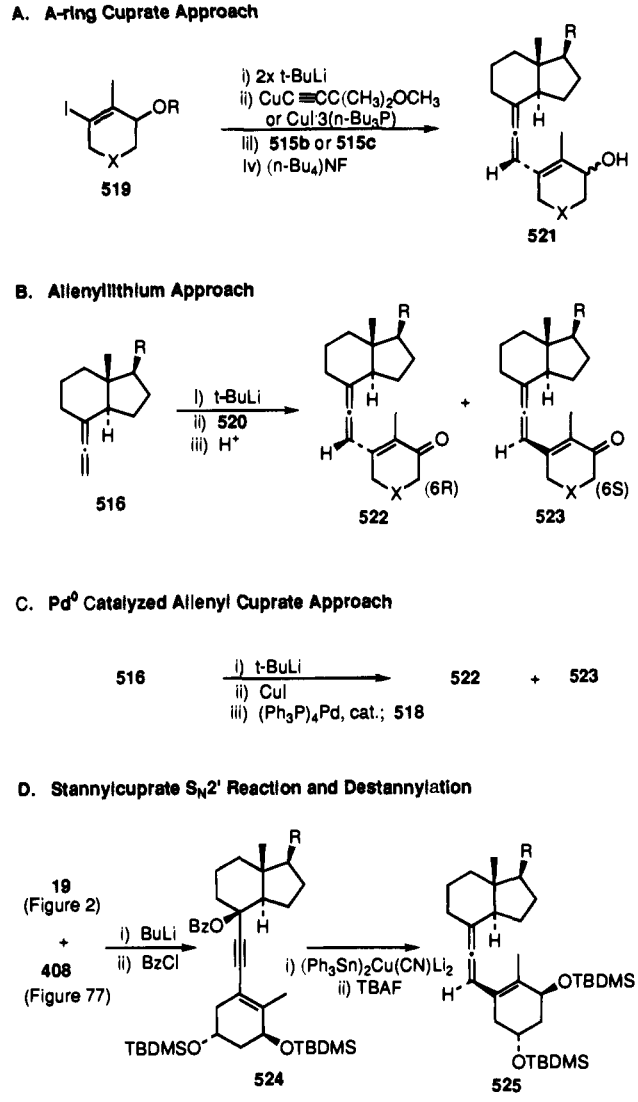



**Figure 100.**

The A-ring vinylcuprate route A[315–318] produced essentially exclusively the (6*R*)-allene **521**. The allenyllithium method B is less capricious than method A, but both (6*R*)-**522** and (6*S*)-**523** were produced.[316,319–322] However, exceptional large 6*R*/6*S* 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 6*R*/6*S* 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 (6*S*)-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 $\Delta^{9,11}$-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

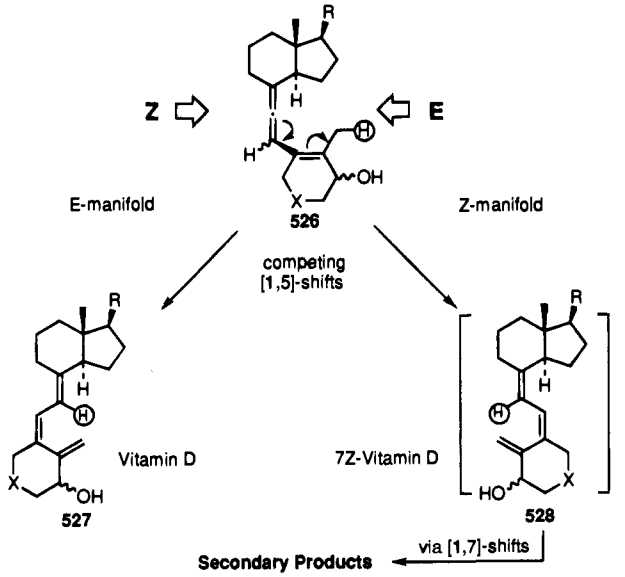



**Figure 101.**

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 1α-epimer **529b** afforded a 1:4.1 7*E*/7*Z* ratio, but this ratio was reversed (2.7:1) for the 1β-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

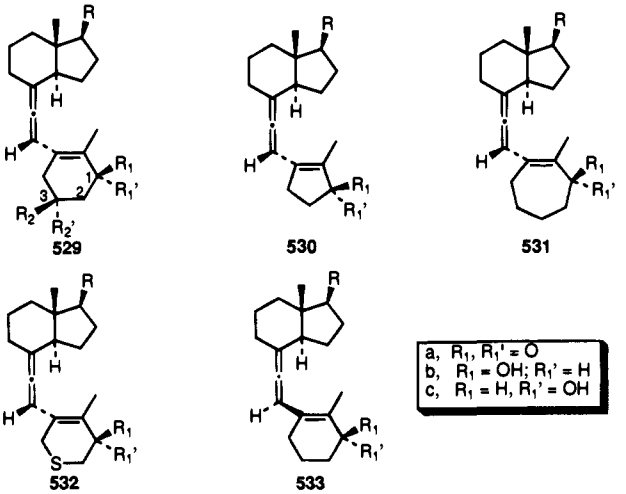



**Figure 102.**

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 terminii, $C_{19}$ and $C_7$, 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 1α,25-dihydroxy-9,11-dehydrovitamin $D_3$ (**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-

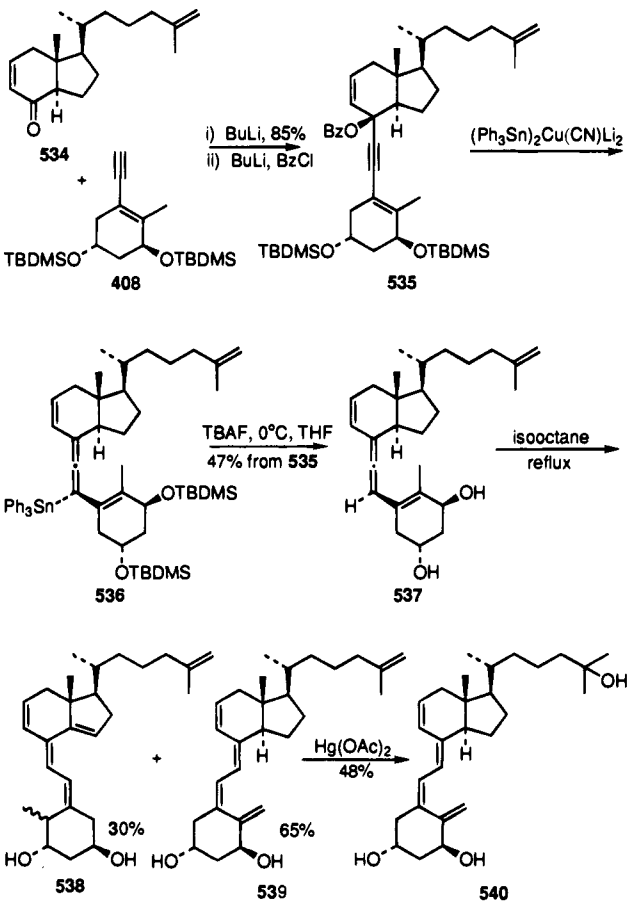



**Figure 103.**

ceeded stereoselectively to afford the 6β-stannylallene **536**. Simultaneous fluoride-induced destannylation and desilylation led to a 10:1 mixture of the desired 6β-vinylallenol **537** and its 6α-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 discovery[116] 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)$(CO)_3$Cr],[328–330] the Okamura laboratory has examined this same chromium(0)-mediated isomerization on the four diastereomeric vinylallenols **529bc** ($R_2 = R_2' = H$) 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)$(CO)_3$Cr in acetone, 38 °C, 4 h]. The results, summarized collectively for the four diastereomeric vinylallenes in Figure 104 and Table 3 provide new mechanistic

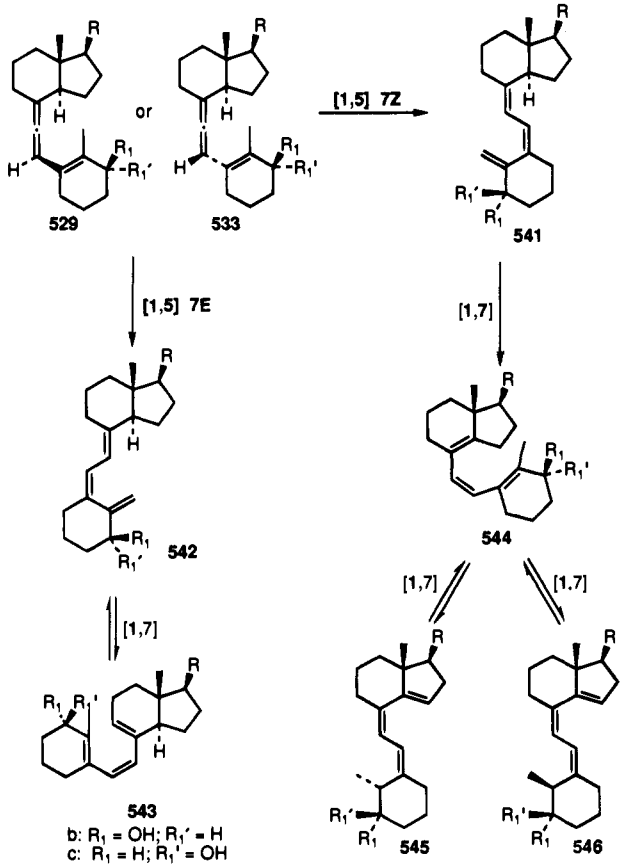



**Figure 104.**

**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 = $C_8H_{17}$ in all cases and, for **531**, $R_2 = R_2' = H$ (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 vinylallenols 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

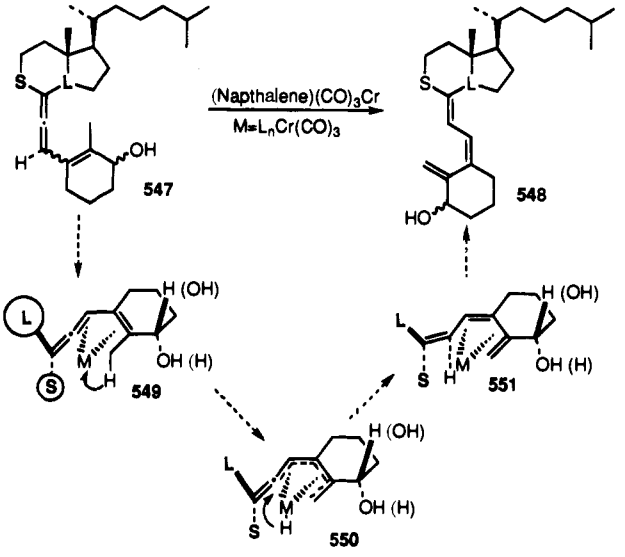



**Figure 105.**

envisaged that a chromium(0) species M metalates the vinylallene from its less hindered face to form the $\eta^4$-species **549**. Despite the presence of the $C_1$-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 $\eta^5$-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-$D_3$ and Its Geometric Isomers

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

$S_N2'$ displacement of a propargyl benzoate[115] 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

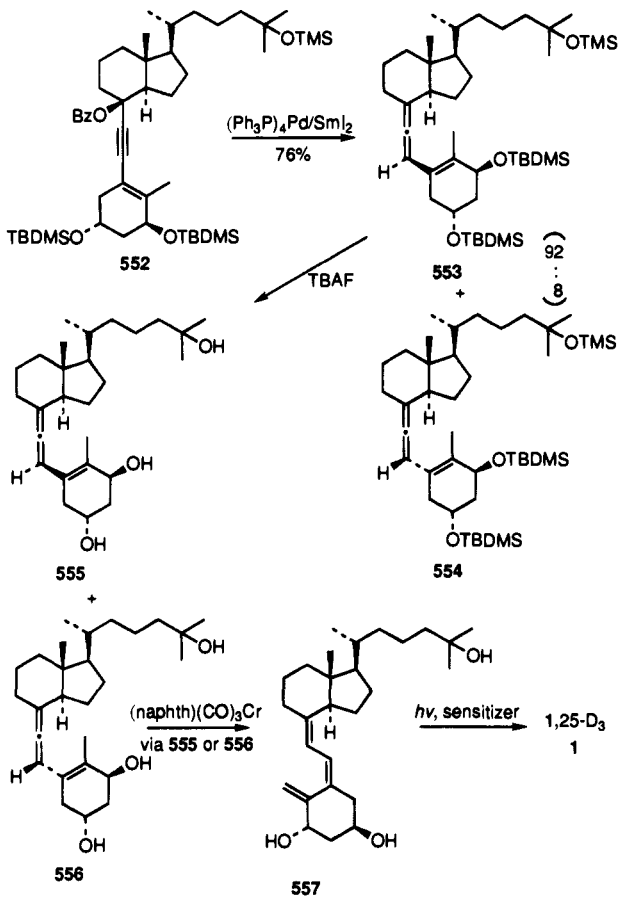



**Figure 106.**

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-acetylanthracene, 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-$(OH)_2D_3$ 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 cheleotropic addition–extrusion of sulfur dioxide, a known procedure, which will be discussed later in section II.H.2.

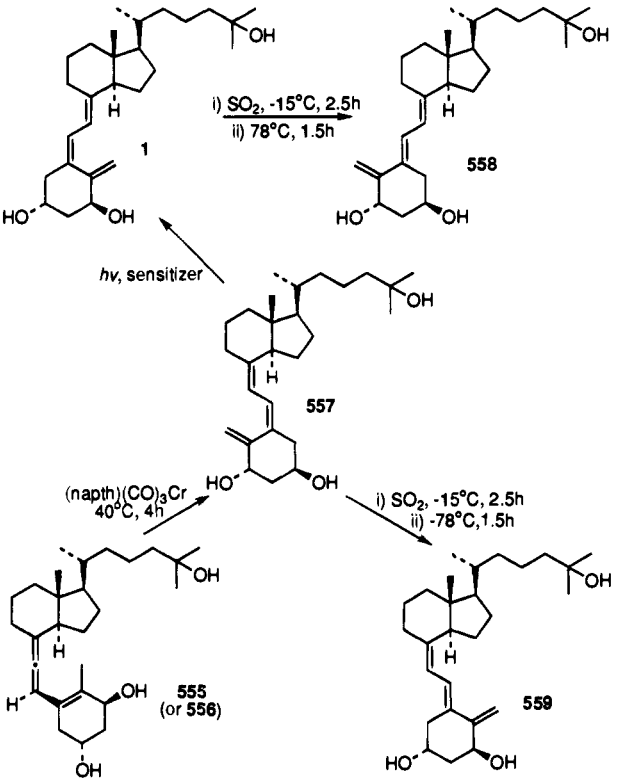



**Figure 107.**

## 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

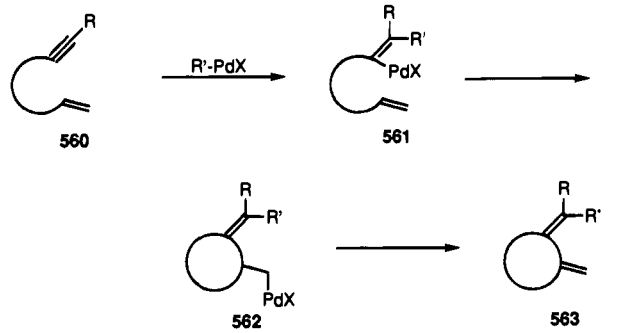



**Figure 108.**

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 acylic 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

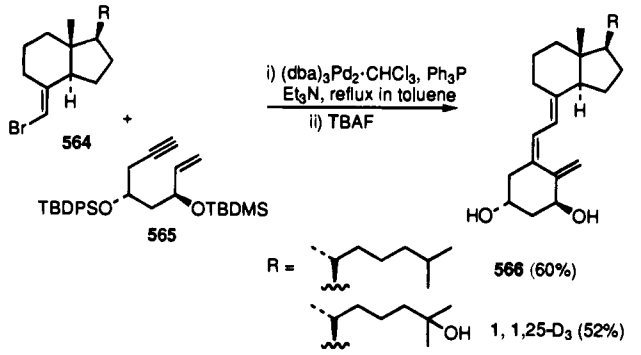



**Figure 109.**

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 $C_{10}-C_5$ bond (and the A-ring) and affords complete control over the $C_5-C_6$ olefin geometry. As depicted in Figure 110 the reaction proceeds through the same

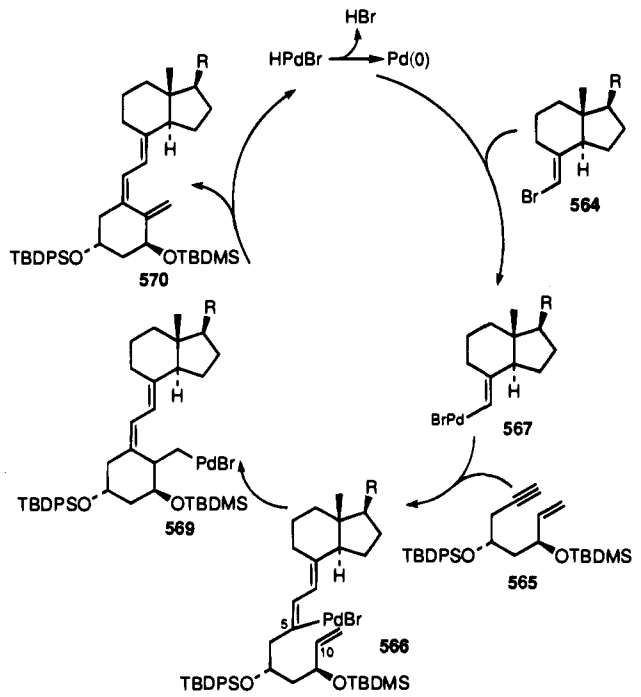



**Figure 110.**

mechanism as the general entry shown in Figure 108. Initial oxidative insertion of palladium(0) to the labile $C_7-Br$ bond of **564** forms intermediate **567** which is followed by *cis*-addition to the alkyne **565** to give second intermediate **568**. Bond formation between $C_{10}$ and $C_5$ 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

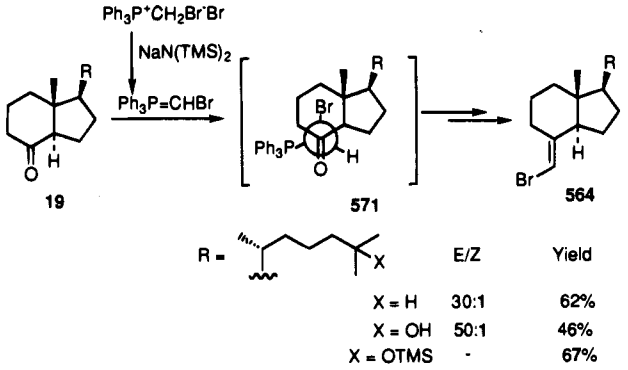



**Figure 111.**

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 bromomethylenation.

Figure 112 outlines an asymmetric synthesis of the enyne unit **565** from the monoacetal of maloaldehyde **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]

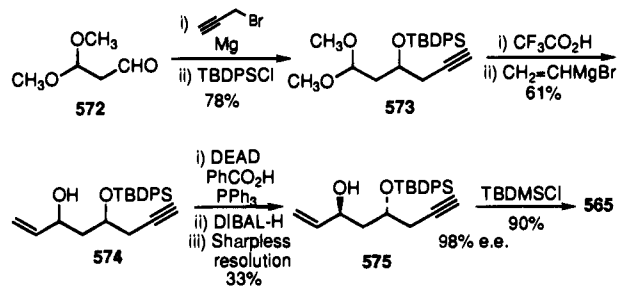



**Figure 112.**

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-chloroacetoacetate, 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.

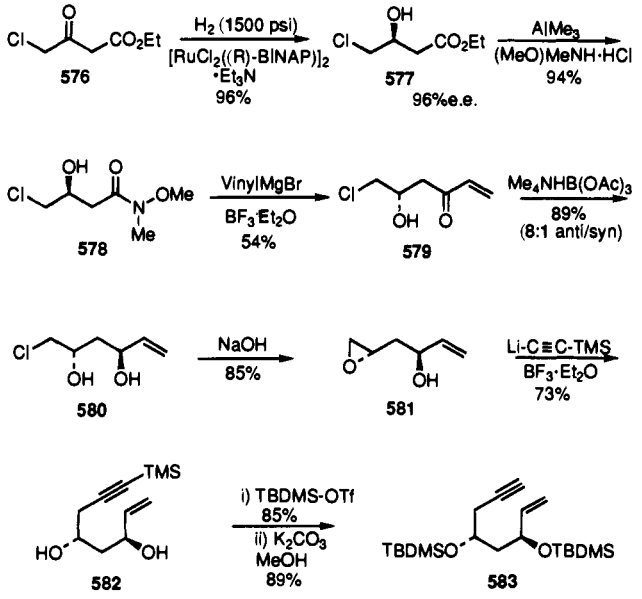



**Figure 113.**

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

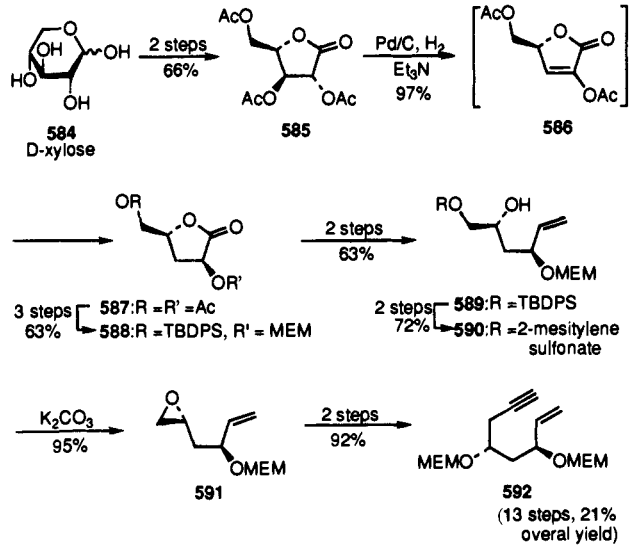



**Figure 114.**

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 $\beta$-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

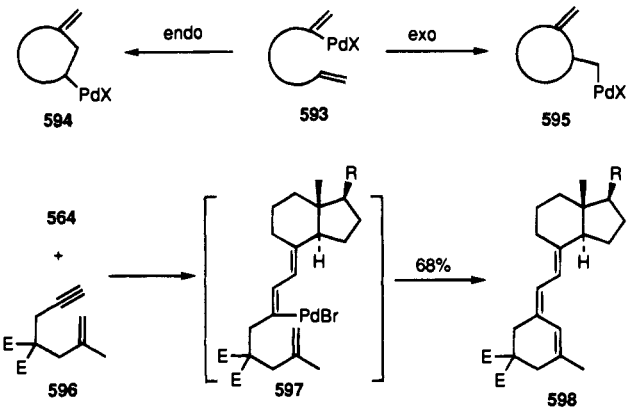
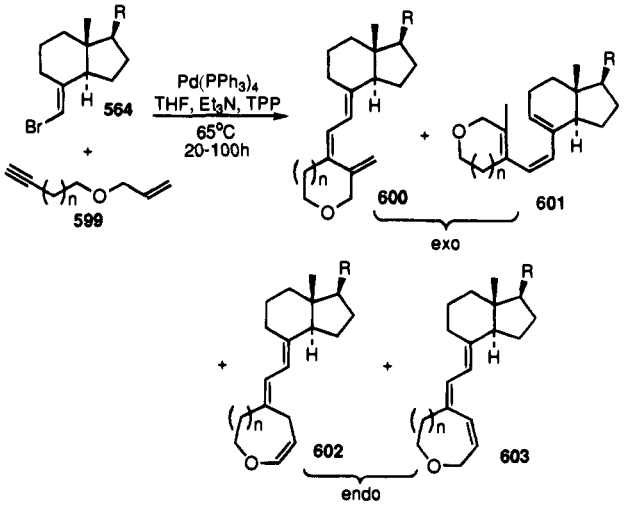



**Figure 115.**

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 carbometalation 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 $D_3$ 1$\alpha$-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' approach[341] 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

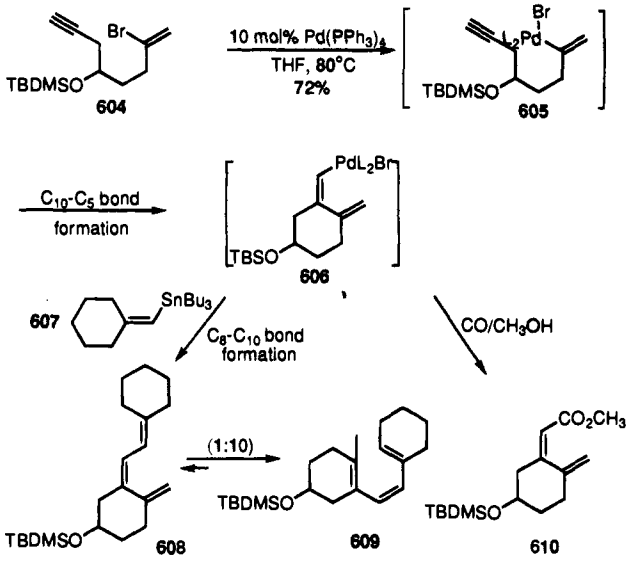



**Figure 117.**

$C_5-C_6$ 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.

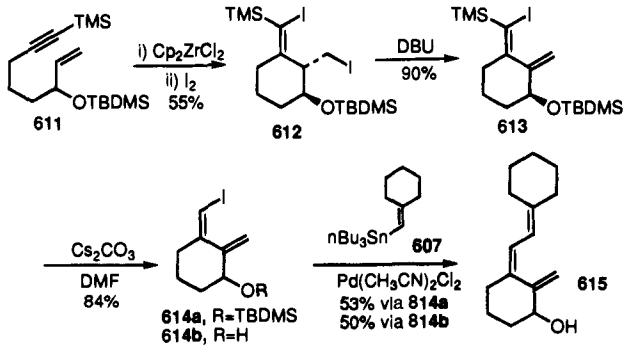



**Figure 118.**

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 **564** (Figure 110) failed to give the coupled product. However, using the trimethyltin derivative as the organometallic partner[343] 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, Mazur[119] uncovered the interesting interconversion between vitamin D and its *i*-steroid form, 3,5-cyclovitamin D. Treatment of vitamin $D_3$ 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 $D_3$ (**5**) and 5,6-*trans*-vitamin $D_3$ (**621**) in 80% yield (Figure 119). Analogous treatment of the

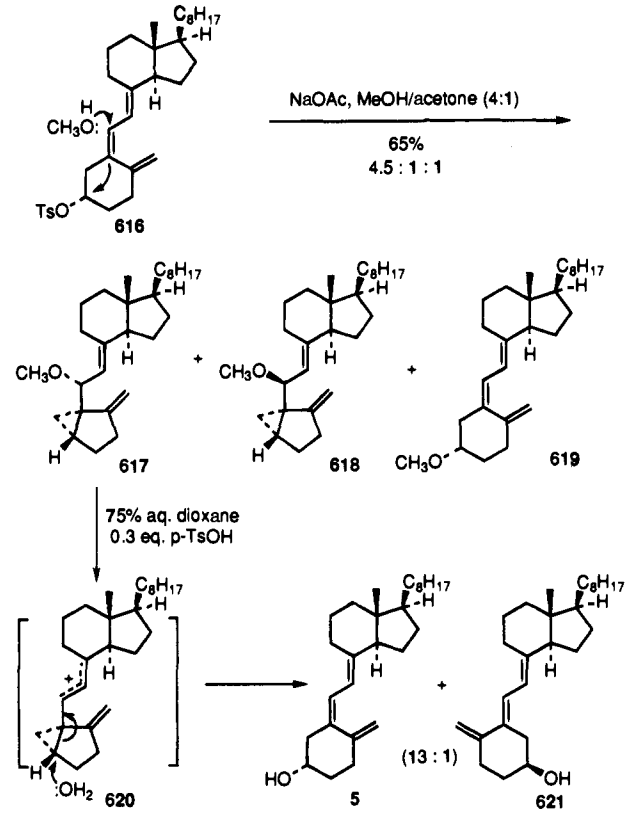



**Figure 119.**

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 $KHCO_3$, 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 $D_3$ [Okamura, Zhu; unpublished data]. The major alcohol **622** upon acid solvolysis rearranged back to vitamin $D_3$ (**5**) and 5,6-

*trans*-vitamin $D_3$ (**621**) in a 2.5:1 ratio (Figure 120).[344]

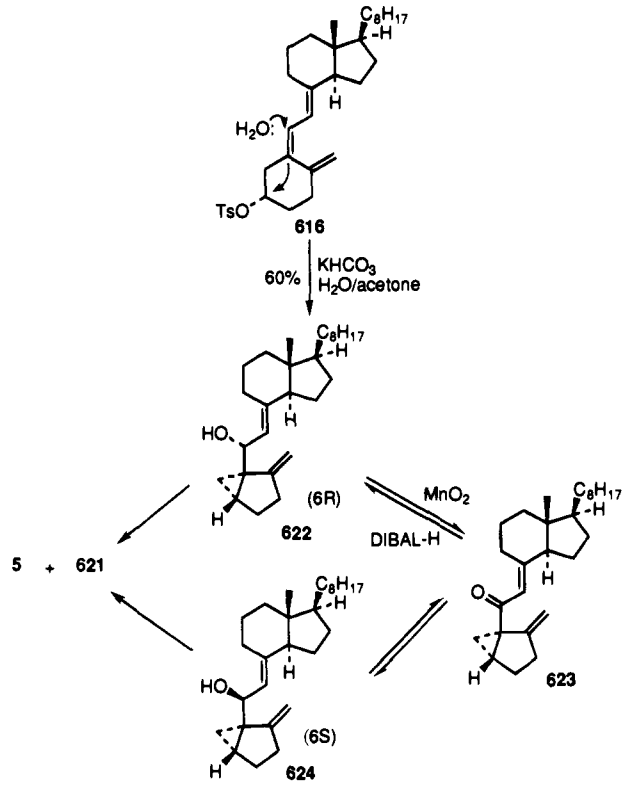



**Figure 120.**

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 6*R*/6*S*) of (6*R*)-alcohol **624**, yielded a 1:1 mixture of vitamin **5** and its 5,6-*trans* isomer **621**. In 1988, Wilson[345] elegantly established that the vinylogous model system **625** (Figure 121) behaved similarly to Mazur's system (Figures 119 and 120).

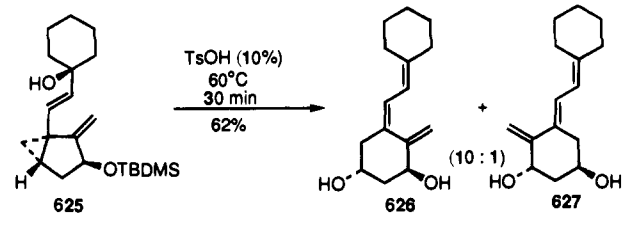



**Figure 121.**

Regarding the mechanism of the cyclovitamin–vitamin rearrangement (Figure 122), the acid catalyzed 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 cyclopropylcarbinyl cation with conformation **630** is preferred over **631**, starting from either of the two compounds.

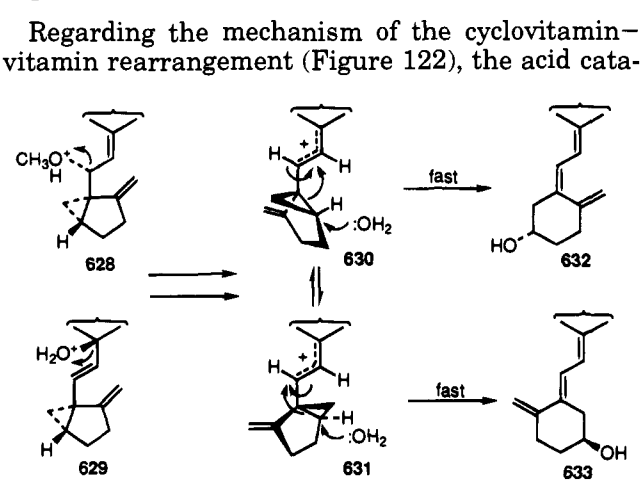
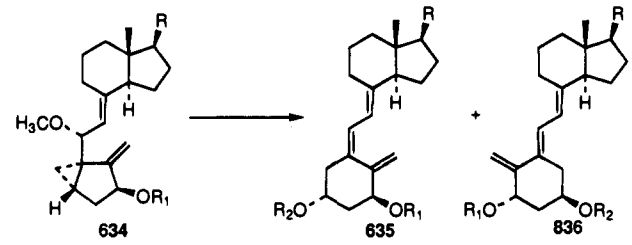


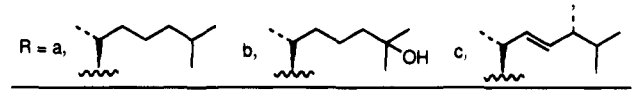

**Figure 122.**

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 1α-Functionalized Cyclovitamins**




| $R_1$ | catalyst/nucleophile | $R_2$ | % cis | % trans |
|---|---|---|---|---|
| $COCH_3$ | p-TsOH/$H_2O$ | H | 40 | 10 |
| $COCH_3$ | HOAc | $COCH_3$ | 52 | 18 |
| $COCH_3$ | i) $HCO_2H$, ii) $NaHCO_3$ | H | 46 | 22 |
| $COCH_3$ | p-TsOH/$Me_2SO$ | H | 42 | 8 |
| H | HOAc | $COCH_3$ | 55 | 20 |

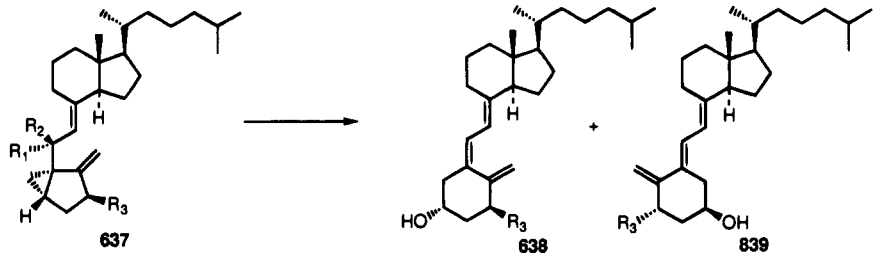



The higher *cis/trans* ratio (4:1) was obtained with water as the attacking nucleophile while lower ratios, 3:1 and 2:1, were produced with the weaker nucleophiles, acetic acid and formic acid. The structural influence of cyclovitamin D on the *cis/trans* ratios in the acid-catalyzed solvolysis has not 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 Cycloreversion of Some Cyclovitamins**




| $R_1$ | $R_2$ | $R_3$ | Conditions | % cis | % trans | yield | References |
|---|---|---|---|---|---|---|---|
| MeO | H | H | TsOH (0.3 eq), 1:3 $H_2O$/dioxane, 55°C, 2h | 93 | 7 | 80% | 119 |
| H | MeO | H | TsOH (0.3 eq), 1:3 $H_2O$/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, $H_2O$ / dioxane | 71 | 29 | - | 344 |
| ~OH | ~H | OMOM | TsOH, $H_2O$/dioxane, 55°C, 5 min | 100 | 0 | 77% | 347 |
| MeO | H | OAc | TsOH (0.2eq), 1:3 $H_2O$/dioxane, 65°C, 15 min | 80 | 20 | 50% | 120 |
| H | OH | H | TsOH, $H_2O$ / dioxane | 50 | 50 | - | 344 |

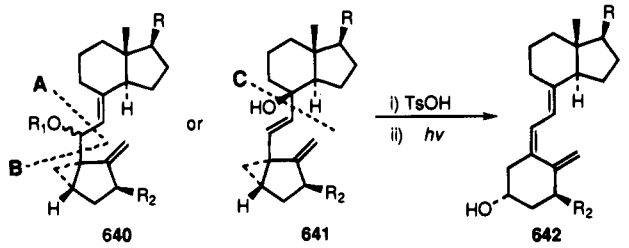



**Figure 123.**

*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 vinyllithium 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).

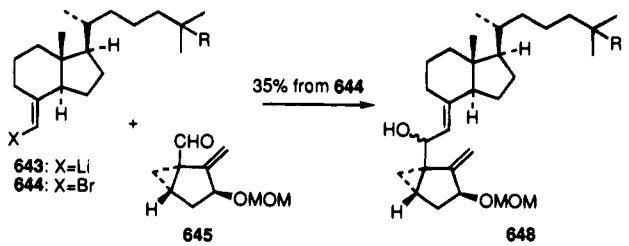



**Figure 124.**

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]

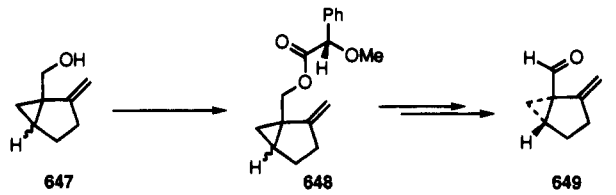



**Figure 125.**

The A-ring aldehyde with the 1α-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]

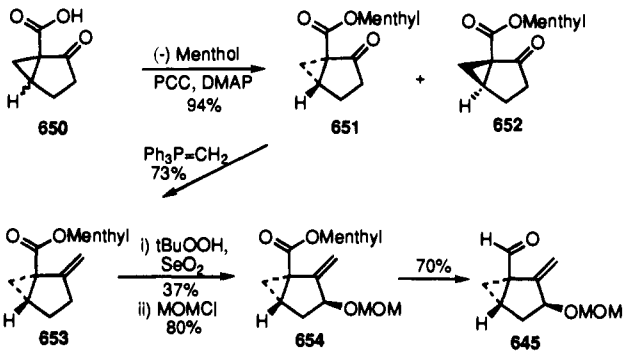



**Figure 126.**

*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

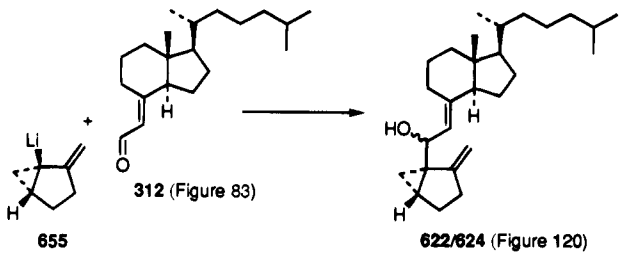



**Figure 127.**

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.

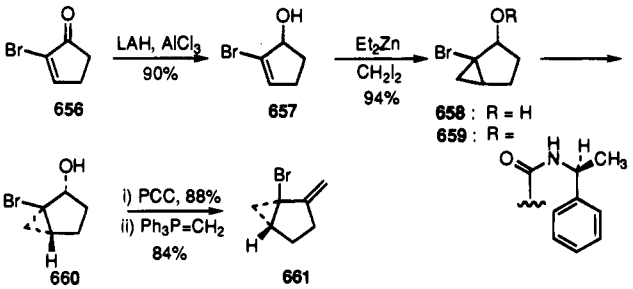



**Figure 128.**

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** was obtained by reduction of the propargyl alcohol using LAH modified with $NaOCH_3$. 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-$D_3$ as the sole product (64% yield).

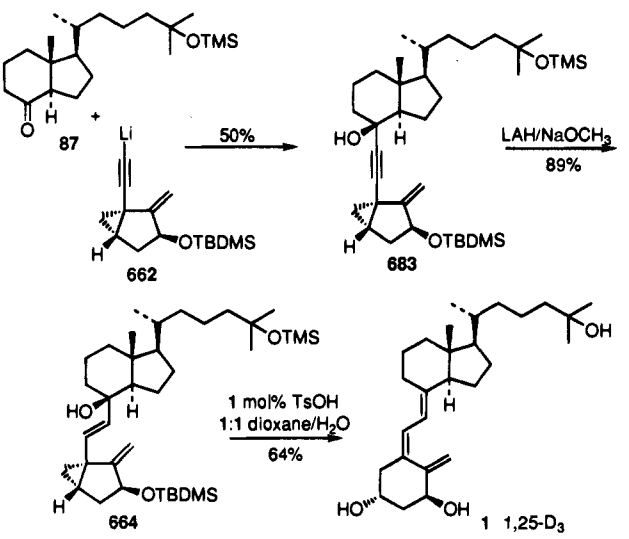



**Figure 129.**

Wilson's synthesis of A-ring **662** via **672** shown in Figure 130[122] involves the following key steps: (i) 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 diasteroisomers, **668** and **669** ($\Delta R_f = 0.11$ for NB). An alternative procedure for the intramolecular cyclopropanation was recently reported by Moriarty[353] using iodonium ylides (Figure 131). In

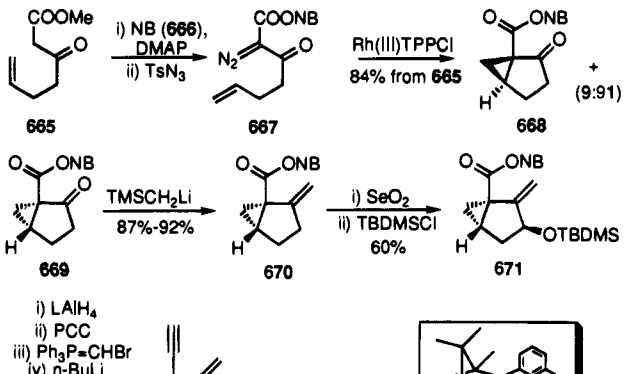



**Figure 130.**

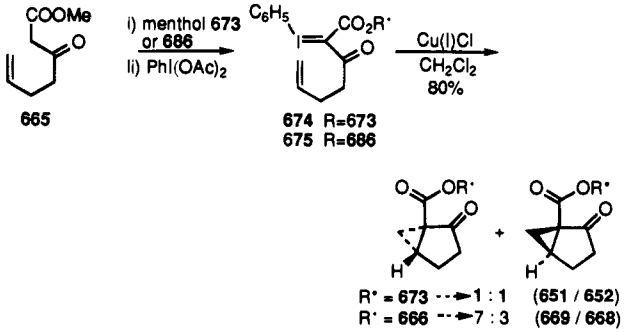



**Figure 131.**

Wilson's procedure the allylic oxidation of **670** with $SeO_2$ is reasonably effective, producing the desired 1α-hydroxy compound in over 60% yield. The cyclopropanation of the diazo keto ester with an established 1α-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

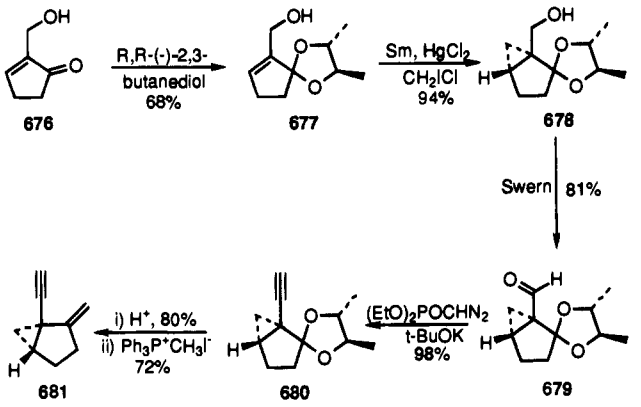



**Figure 132.**

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-

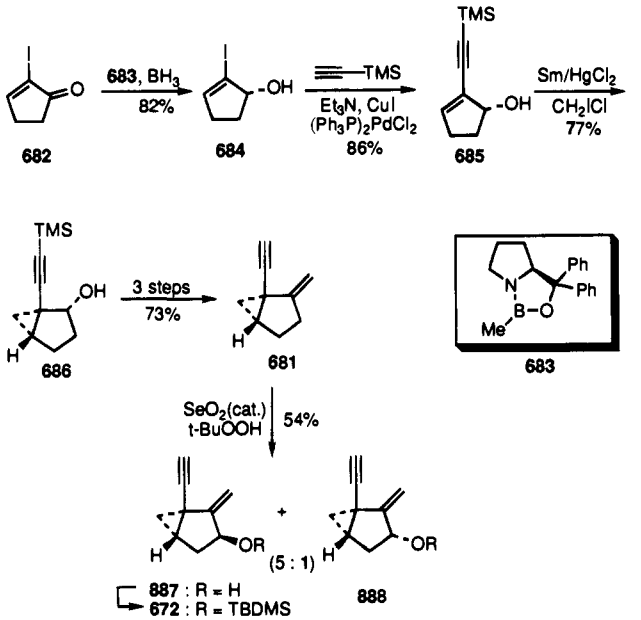



**Figure 133.**

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 $SeO_2$/*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

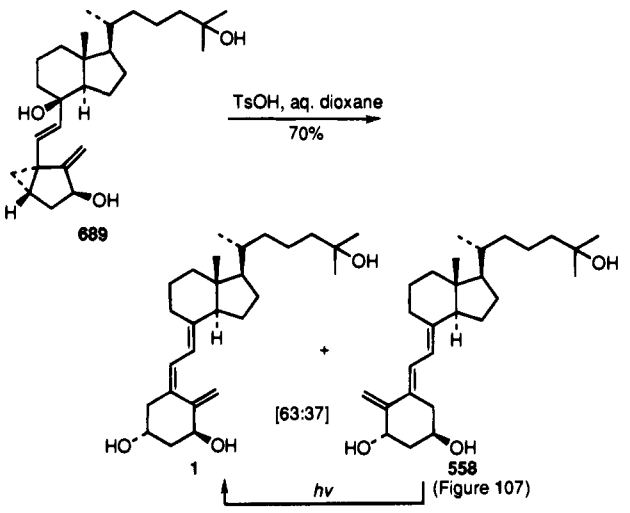



**Figure 134.**

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-cyclopentenecarboxylate (**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**

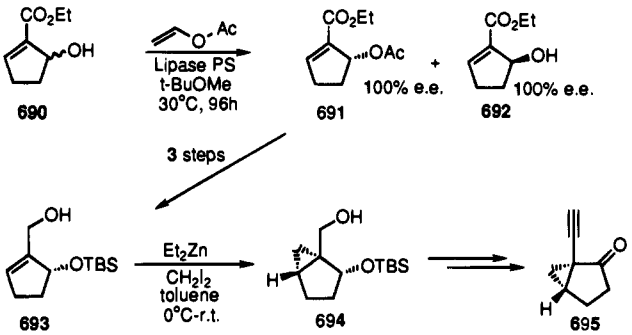



**Figure 135.**

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-cyclopentenol ((±)-**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*)-

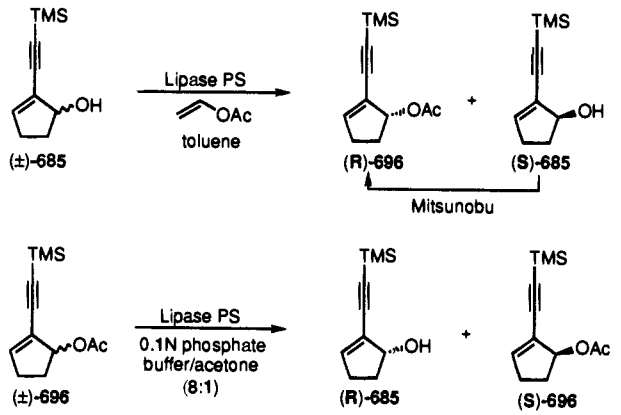



**Figure 136.**

**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 (±)-**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 $D_3$ and 3,5-cyclovitamin $D_3$ 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 1α-hydroxylated analogues in 20–25% overall yield (Figure 137).

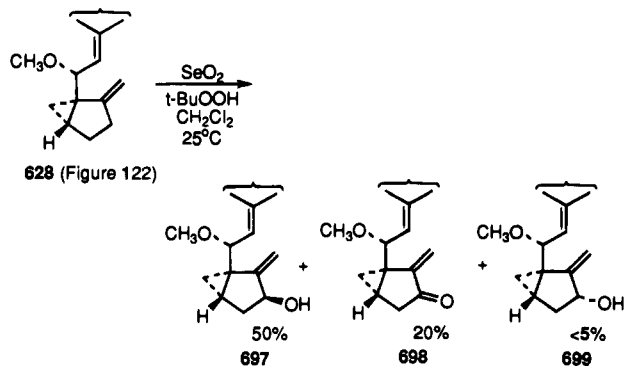



**Figure 137.**

Oxidation of cyclovitamin $D_3$ **628** with $SeO_2$/*t*-BuOOH afforded the desired 1α-hydroxycyclovitamin $D_3$ (**697**, 50%), oxidized ketone **698** (20%; which, upon hydride reduction gave the 1α-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** ($NaBH_4$, $LAlH_4$, or DIBALH) actually afforded the 1β-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 $D_3$ (20 times faster at 25 °C). The 1β-hydroxycyclovitamin $D_3$ 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-

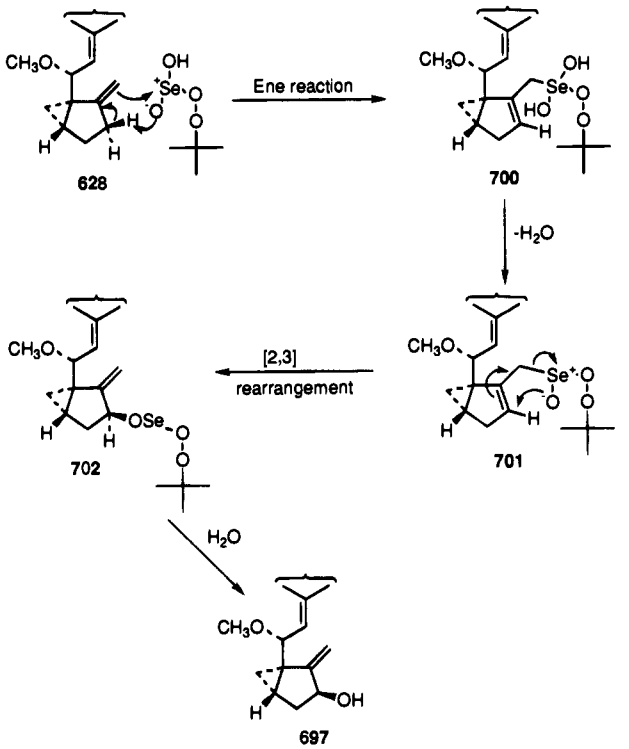



**Figure 138.**

termediate **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 1α-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 1α-hydroxyvitamin D analogues. As shown in the general conversion in Figure 139, application of this scheme to vitamin $D_3$, 25-

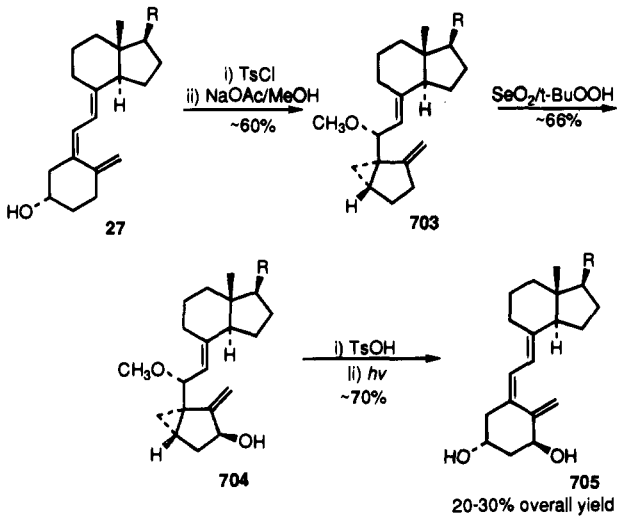



Figure 139.

hydroxyvitamin $D_3$, etc. has been shown to afford the 1α-hydroxy products in about 20% overall yield.[120] This approach has also been used in the recent years for synthesis of 1α,25-dihydroxy-10,19-dihydrovitamin $D_3$ isomers;[364] preparation of 25-hydroxy-1α-$^3$H-vitamin $D_3$,[365] 1β-hydroxyvitamin $D_2$ and $D_3$;[363,366,367] and 1α,25-dihydroxy-28-norvitamin $D_2$[368] and synthesis of ring A-stereoisomers of 1-hydroxyvitamin $D_3$,[369] the $\Delta^{22}$-unsaturated C-1-hydroxylated derivatives.[370]

*Selective Degradation of Vitamin D: Synthesis of 19-$^{13}$C-Labeled Vitamin D Analogues.* Treatment of the C-3 acetate of 25-$D_3$ (**6**) in pyridine with $OsO_4$ (1.2 equiv) afforded a 75% yield of 7,8-dihydroxylated compound **706**. The unique regiospecificity 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

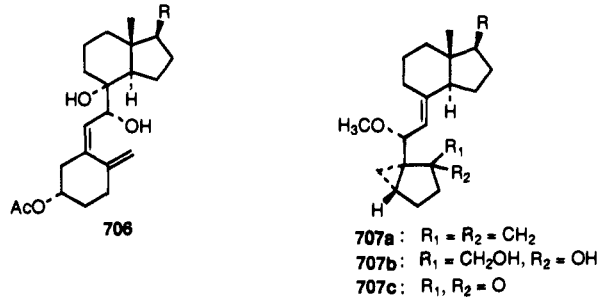



Figure 140.

reaction very rapidly afforded 10,19-dihydroxylated compound **707b**, which upon treatment with $NaIO_4$, led to the 19-oxo compound **707c**.[371] The pronounced change in the olefinic reactivity toward osmium tetraoxide 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-$^{13}$C]1α-hydroxyvitamin $D_3$ **709** through Wittig olefination[89] (Figure 141). Isotopically labeled vitamin D molecules will be discussed later in section IV.B.

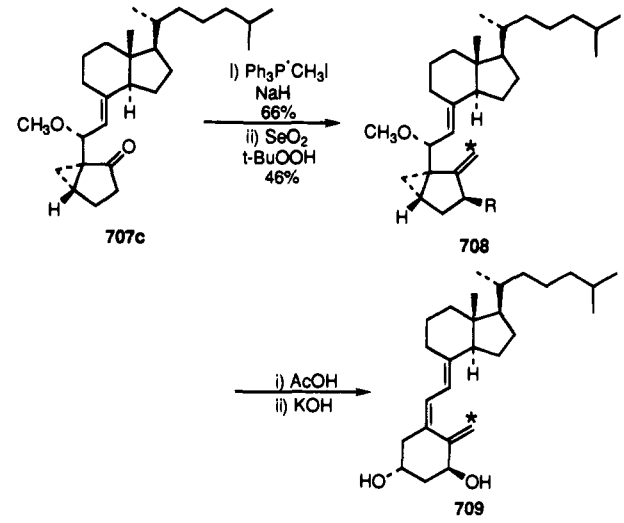



Figure 141.

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

### 1. Method G: Direct Hydroxylation of Vitamin D

Direct modification of $D_3$ (**5**), vitamin $D_2$, and 25-$D_3$ (**6**) is becoming more attractive for the synthesis of 1α,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 $D_3$ has thus far not been practical because of the difficulty in controlling the site, extent, and stereochemistry of the hydroxylation.[362] However, direct 1α-hydroxylation of a TBDMS protected 5,6-*trans* geometric isomer of vitamin D, which is available in high yield from vitamin D through cheleotropic addition of $SO_2$, thermal elimination of $SO_2$, and then silylation was reported to be very successful.[123,124] The details shown in Figure 142 for the specific case of vitamin $D_3$ (**5**) includes its initial reaction with $SO_2$ in benzene/water. The

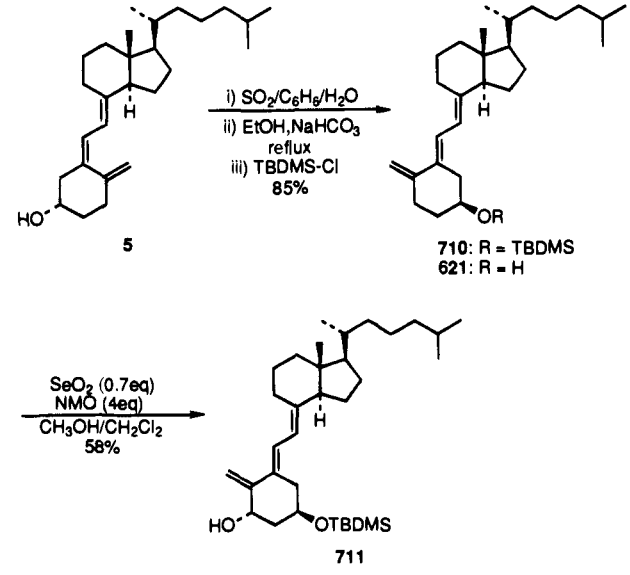



Figure 142.

resulting diastereomeric mixture of the adduct is heated in ethanolic $NaHCO_3$ to afford 5,6-*trans*-$D_3$ (**621**), which is then protected as the TBDMS ether **710** (85% yield for the three steps). The later oxidation [$SeO_2$(0.7 equiv), NMO (4 equiv) in methanol–$CH_2Cl_2$] affords the 1α-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 1α-hydroxyvitamin $D_3$ in 35% overall yield.

Oxidation of unprotected 5,6-*trans*-vitamin $D_3$ **621** under the same conditions is less selective, leading to a mixture of two isomers (1α/1β = 3:1). The silyl ether **710** was originally reported to lead to higher selectivity (1α/1β = 20:1).[123] The origin of this selectivity is suggested to be due to enforcement of conformation **712** rather than **713** (Figure 143) for

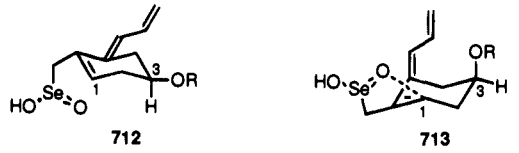



**Figure 143.**

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 1α- to 1β-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 $D_3$ was later reported by Reischl[374] (Figure 144). Treatment of vitamin $D_3$ with Hg-

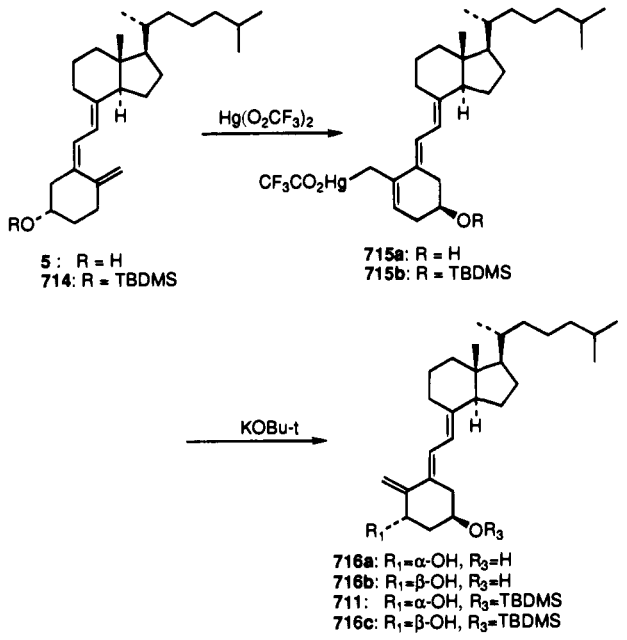



**Figure 144.**

$(OCOCF_3)_2$ 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, 1α/1β = 1:1). When TBDMS-protected vitamin $D_3$ (**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 1α-stereochemistry (1α/1β = 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 1α-hydroxyl derivatives with a competitive overall yield (30% from **714**).

Direct 25-hydroxylation of vitamin $D_3$ on a practical scale, to the best of our knowledge, has not yet been achieved. However, methyl(trifluoromethyl)dioxirane-mediated stepwise oxidation of vitamin $D_3$ was recently reported by Curci's laboratory (Figure 145).[175]

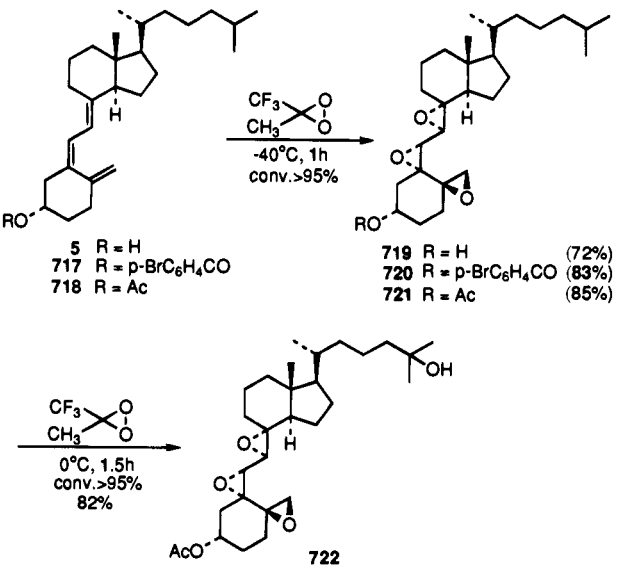



**Figure 145.**

Oxidation of vitamin $D_3$ 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 $D_3$ 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.

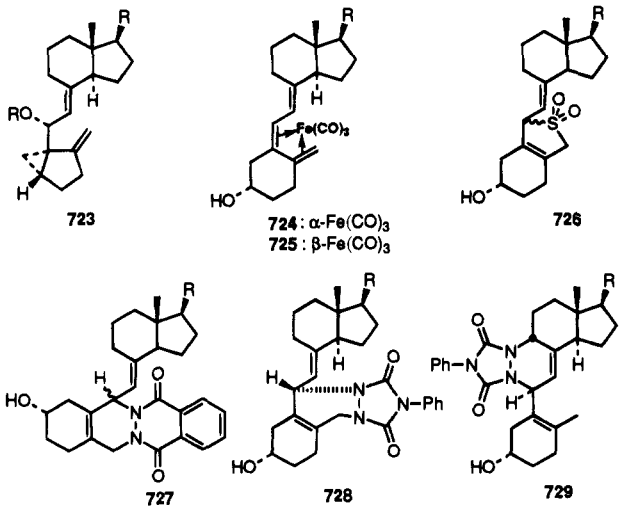



**Figure 146.**

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 1α-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 ($LAlH_4$) 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 $D_2$.[124]

The Yamada[376] and Zbiral[377] 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 $KOH/CH_3OH$ 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

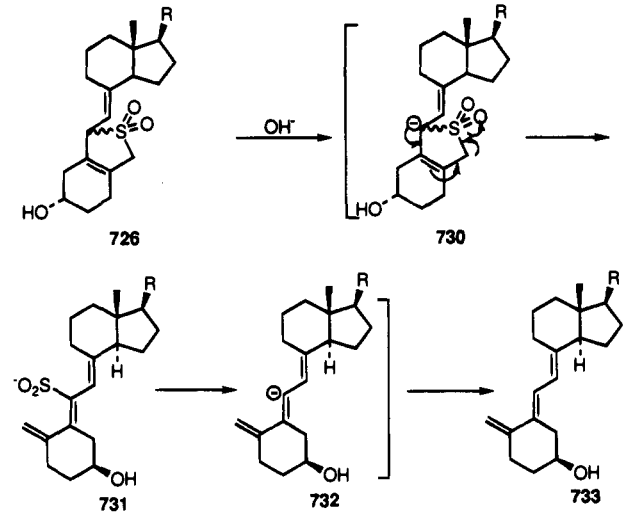



**Figure 147.**

vitamin D with high selectivity (ca. 95%) by photosensitized isomerization, the sulfur dioxide procedure has considerable potential. This protecting group is stable under various chemical transformation conditions such as radical conditions ($n\text{-}Bu_3SnH$, $h\nu$),[380] ozone oxidative conditions,[372,379,381] and acidic condition.[381] In **734** (Figure 148), sulfur dioxide not only

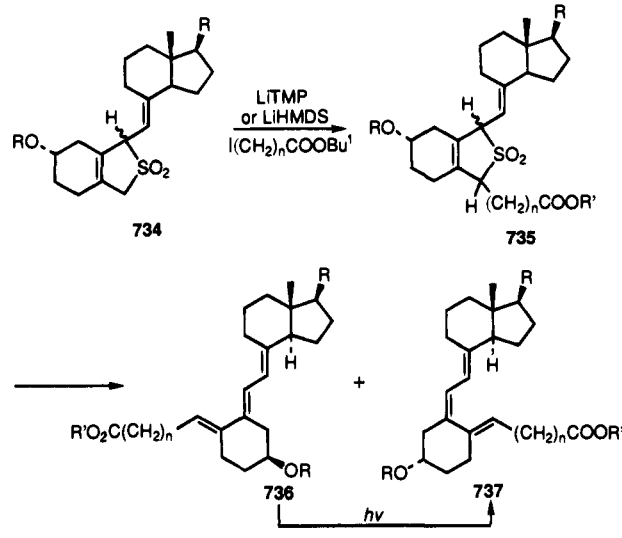



**Figure 148.**

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 $D_3$ 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

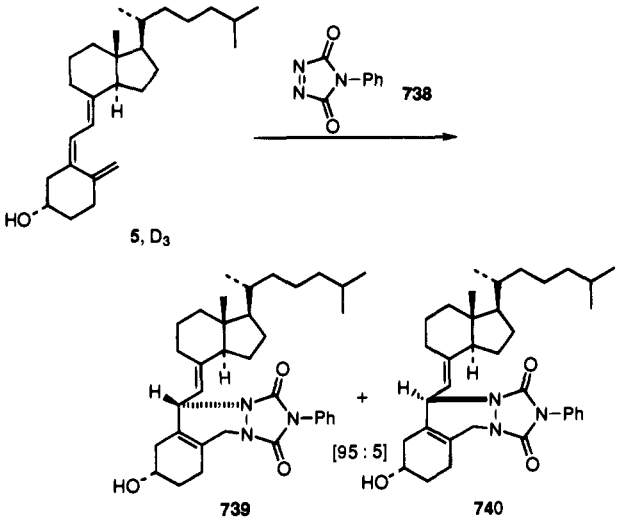



**Figure 149.**

glycol–water (100 °C), **739** or **740** affords 5,6-*trans*-vitamin $D_3$ (**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 $D_3$ (**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 $LiAlH_4$ (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 $D_2$ (**741**) and **738** under the reported conditions (KOH in refluxing ethylene glycol or in refluxing butanol) gave the corresponding 5,6-*trans*-vitamin $D_2$ (**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.

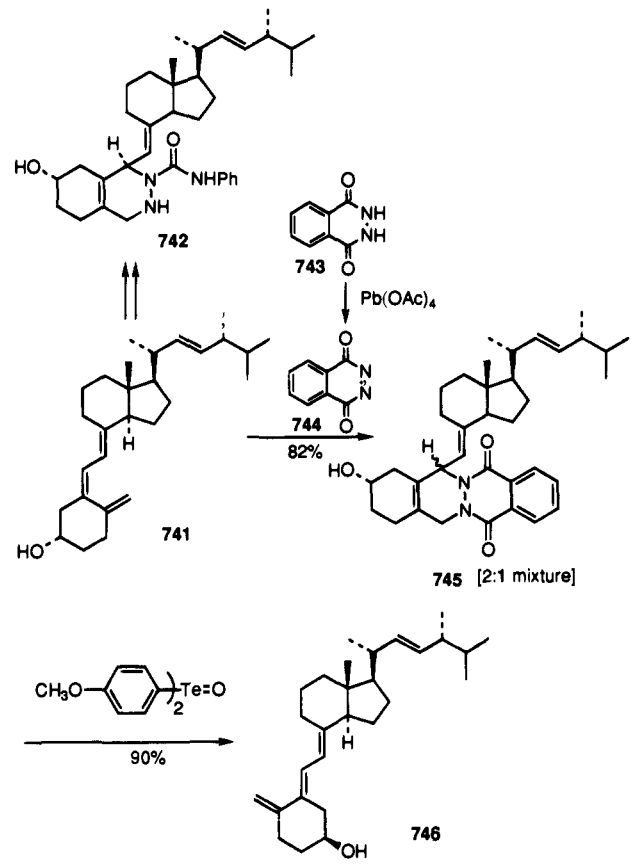



**Figure 150.**

Selective Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (**738**) with the $\Delta^{6,8}$-diene of previtamin $D_3$ generates a single adduct **747**, suitable for the stereoselective introduction of **748** bearing the 1α-hydroxyl group (Figure 151).[127,388-390] Cyclorever-

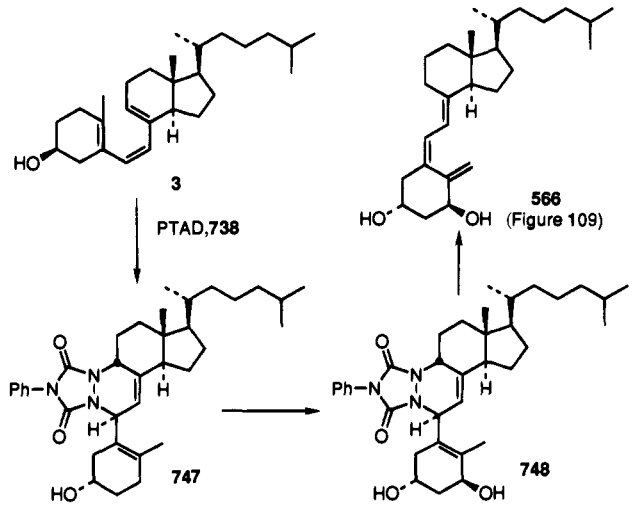



**Figure 151.**

sion of the modified adduct under basic conditions (KOH-MeOH, 80 °C, 24 h) leads to the desired previtamin $D_3$ and then to 1α-hydroxyvitamin $D_3$ (**566**) (Figure 109). The same sequence starting from 25-hydroxyprevitamin $D_3$ leads the hormone 1,25-$D_3$ (**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-$D_3$ (**1**) or its analogues. First, the Julia[391] 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 ketone[392] 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).

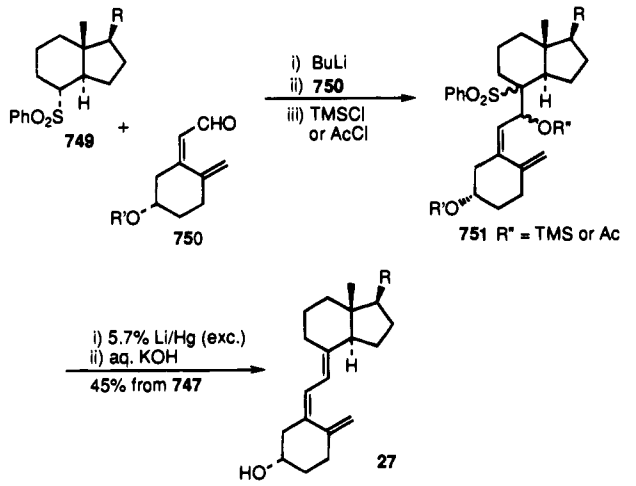



**Figure 152.**

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 $C_6$–$C_7$ 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 thermoisomerized to the natural vitamin D (Figure 153). Julia reductive elimination of keto

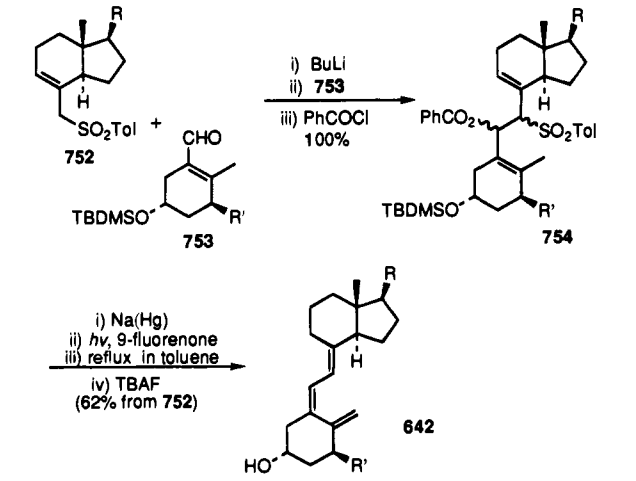



**Figure 153.**

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).

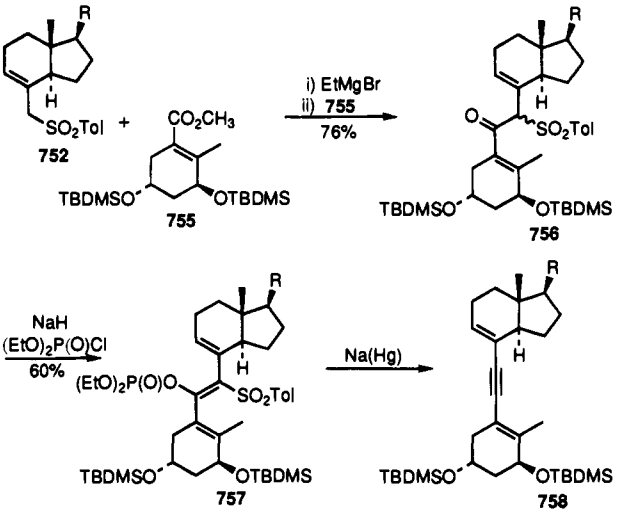



**Figure 154.**

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).

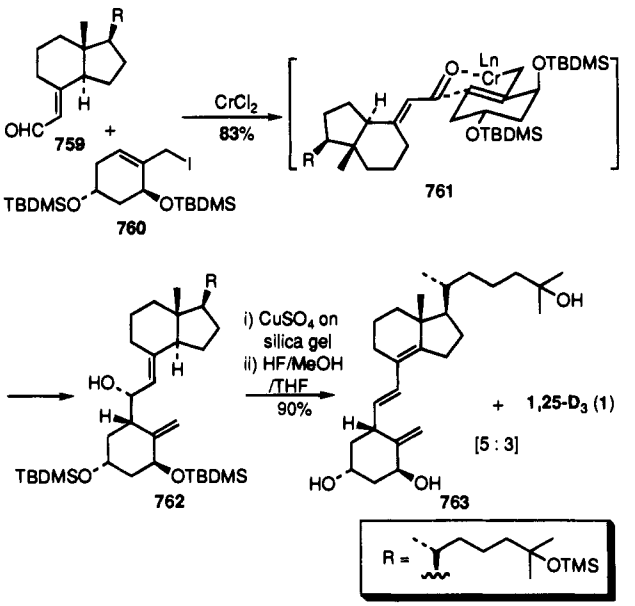



**Figure 155.**

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, Lythgoe[400] reported the first partial synthesis of vitamin $D_2$ (**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 $D_2$ (**741**) and its 3α-epimer **768** in which the epi isomer predominated (Figure 156).

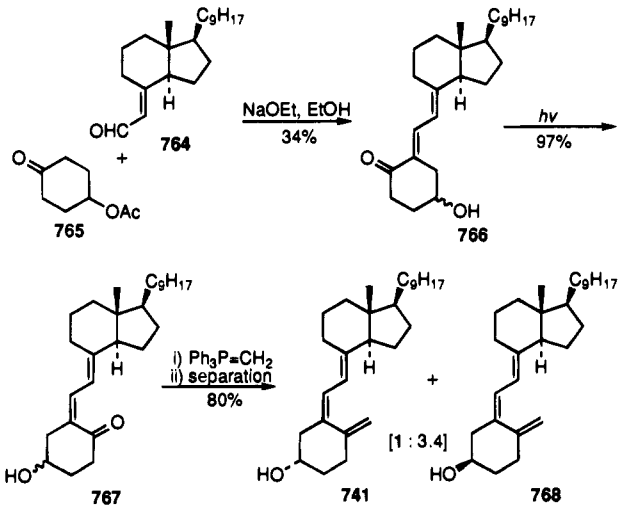



**Figure 156.**

## 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-$D_3$. 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

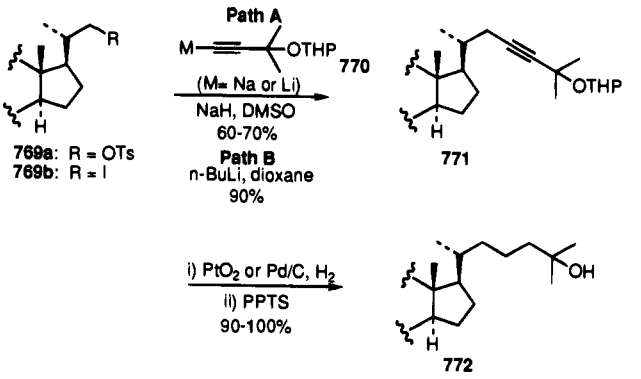



**Figure 157.**

**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

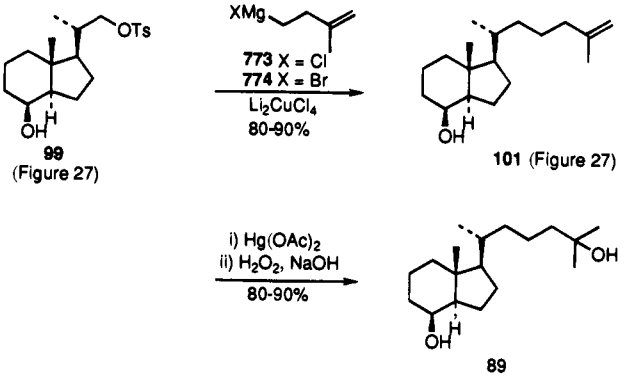



**Figure 158.**

later modified by Okamura.[318] The Grignard reagent **773** was coupled with tosylate **99** in either 8β-OH protected or unprotected forms[113] 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 $Li_2CuCl_4$ 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]

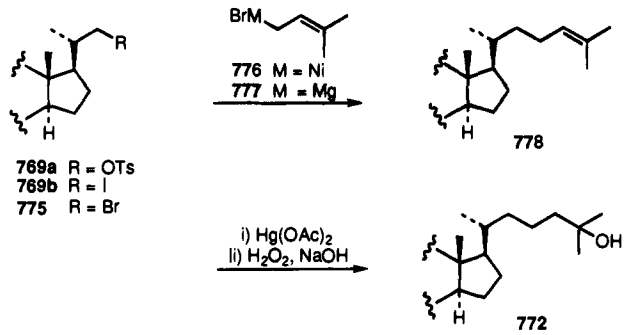



**Figure 159.**

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

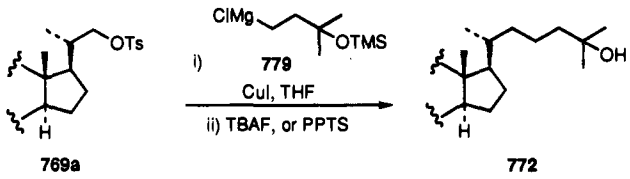



**Figure 160.**

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

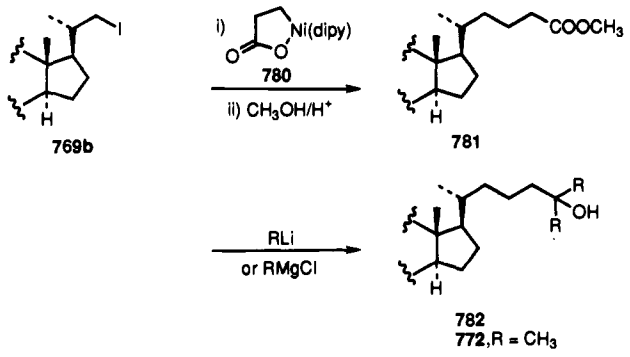



**Figure 161.**

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 = $CO_2CH_3$) 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 olefins[415] in reasonable or good yields. A clear advantage of this method over organometallic approaches[409] is its easy operation, including the use of aqueous reaction conditions. In general, polar substrates afford higher yields of product.

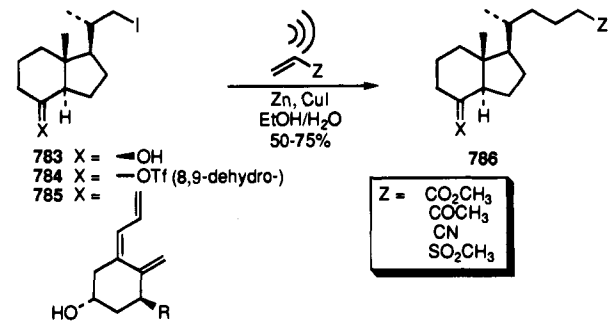



**Figure 162.**

### 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 bond[401] together with the 24-methyl group characteristic of ergosterol and vitamin $D_2$ as in **789** (Figure 163).[416,417] The reaction with

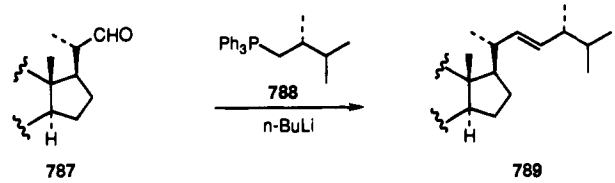



**Figure 163.**

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

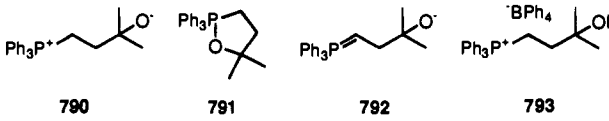



**Figure 164.**

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 $D_2$ 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]

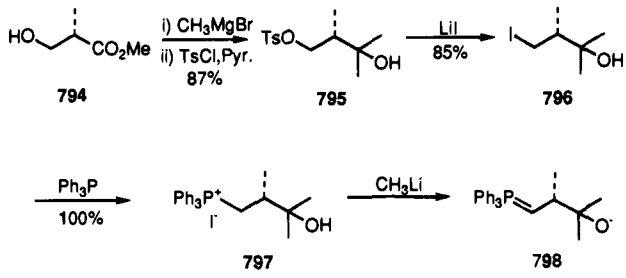



**Figure 165.**

*Julia Olefination.* The Julia olefination[391] approach (Figure 166), which was first utilized for

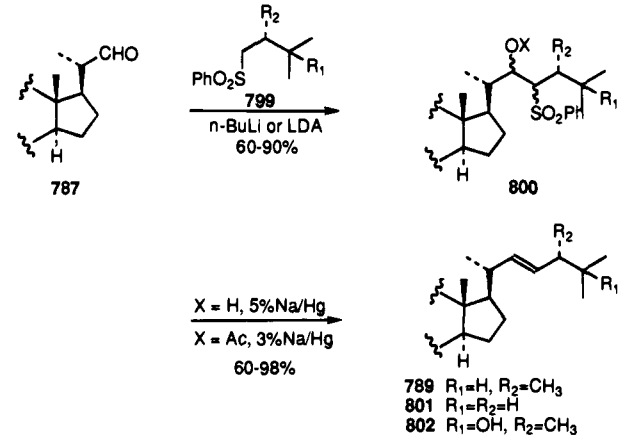



**Figure 166.**

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 $D_2$ 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 ethylidenetriphenylphosphorane (THF, 25 °C) gave the desired 17*Z*-olefin **804** (96:4,

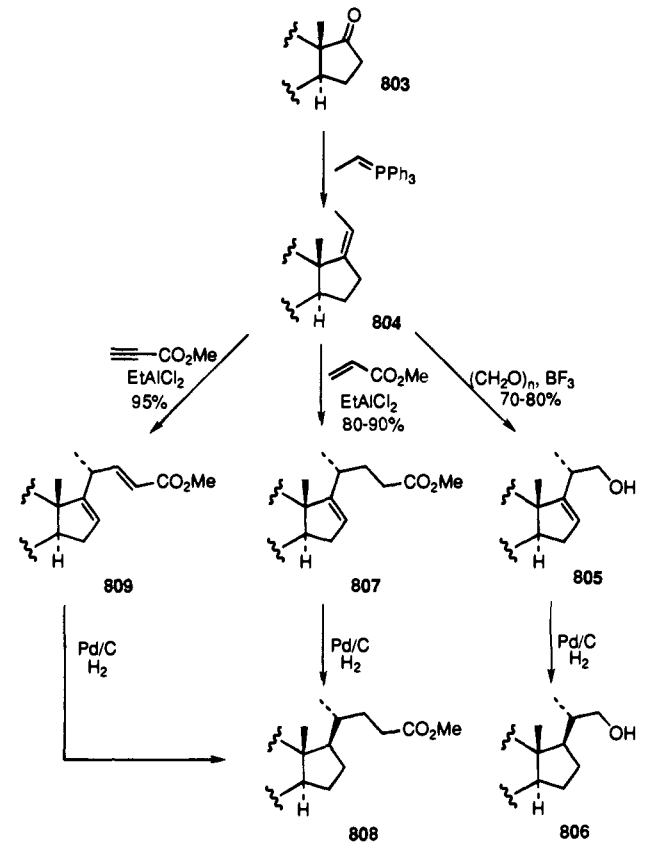



**Figure 167.**

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*)-ethylidene 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).

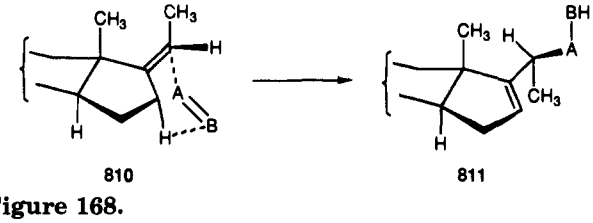


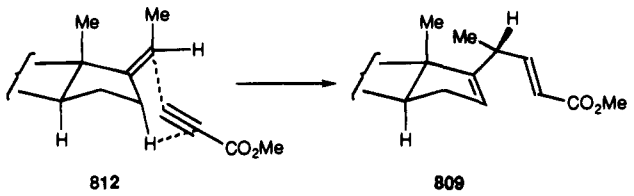

**Figure 168.**

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*)-ethylidene 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




812 809

**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-

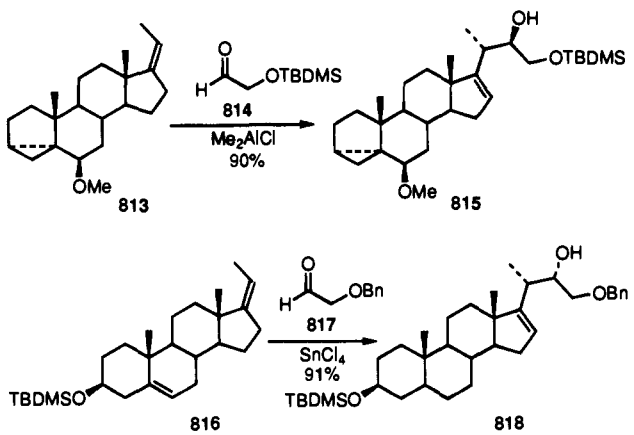



**Figure 170.**

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

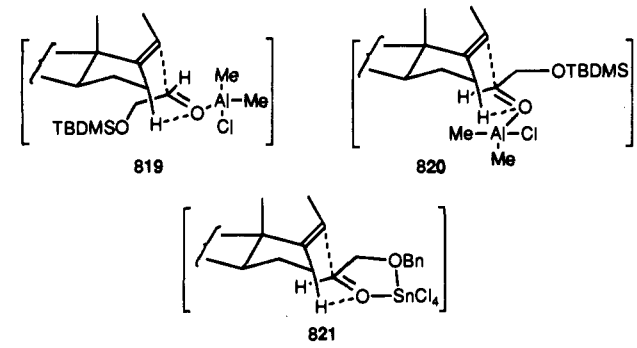



**Figure 171.**

reaction of the nonchelated α-siloxy 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

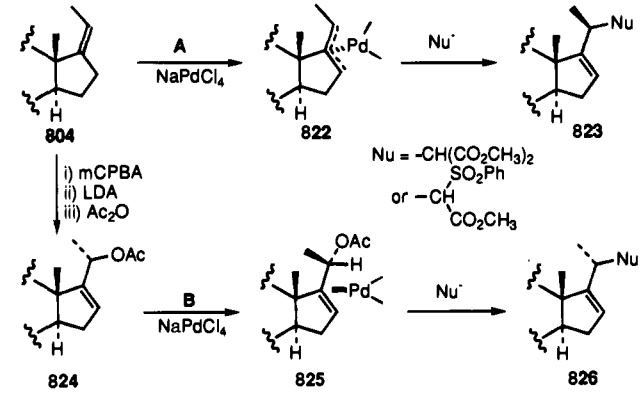



**Figure 172.**

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 $\pi$-allyl palladium complex chemistry.

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

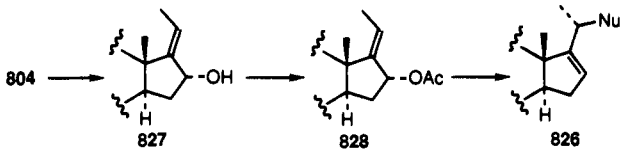



**Figure 173.**

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' procedure[443] 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

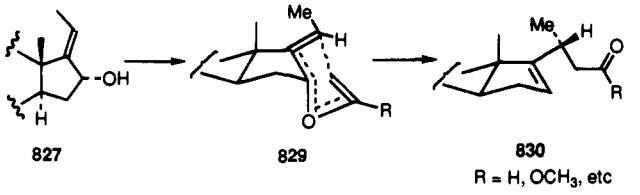



**Figure 174.**

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

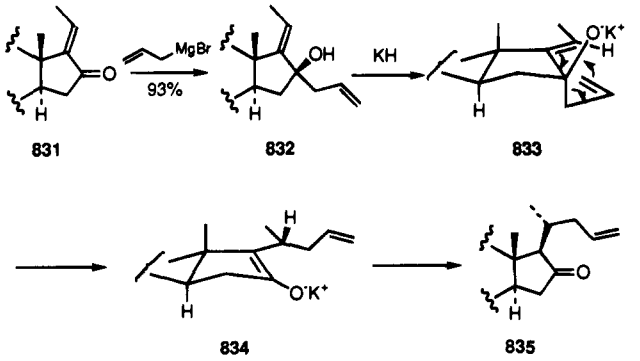



**Figure 175.**

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$\beta$-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 $\alpha$-face (Figure 176). Coupling of the borane derivative **836**

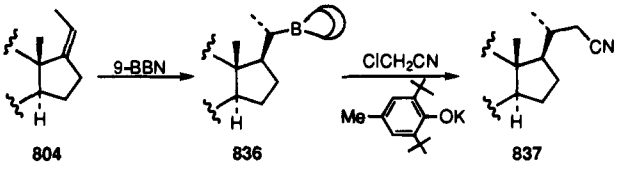



**Figure 176.**

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

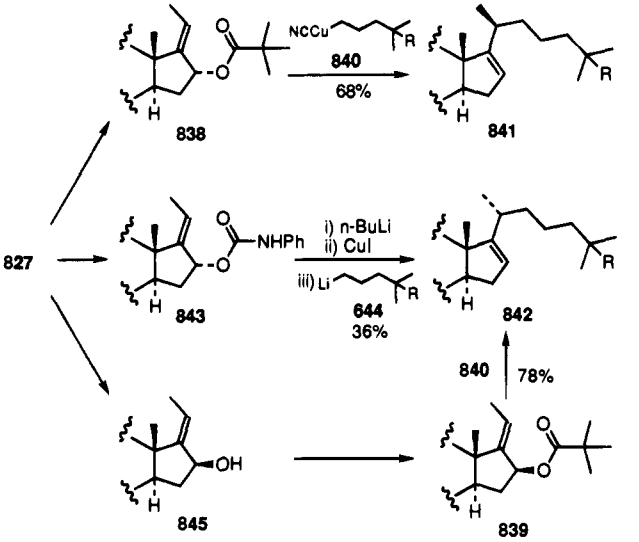



**Figure 177.**

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 (~5%) of the corresponding regioisomer could be discerned in the crude $^1$H 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$\alpha$-carbamate **843** is seen to give complementary stereochemical results to that from the 16$\alpha$-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-

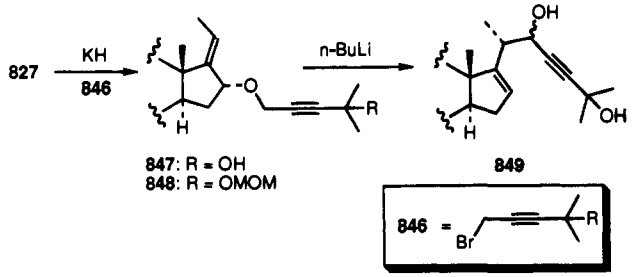



**Figure 178.**

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 $D_2$ or vitamin $D_3$ types.

### 4. Construction of the Vitamin $D_2$ Side Chain

*Claisen Rearrangement.* One of the most useful routes to construct the vitamin $D_2$ 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

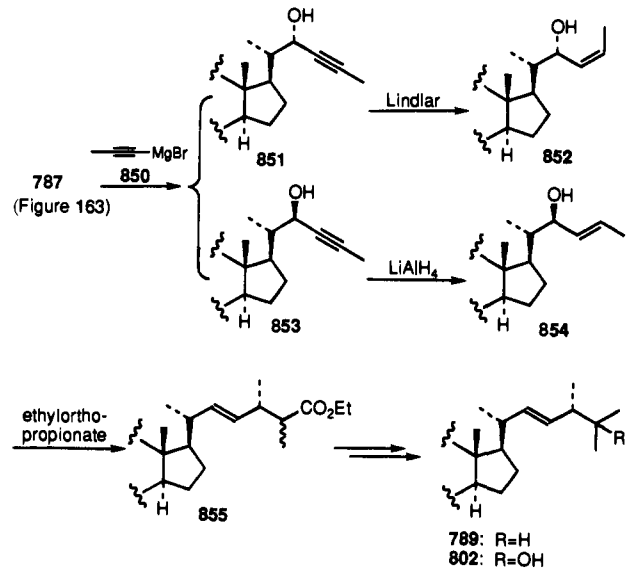



**Figure 179.**

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 $D_2$ 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-

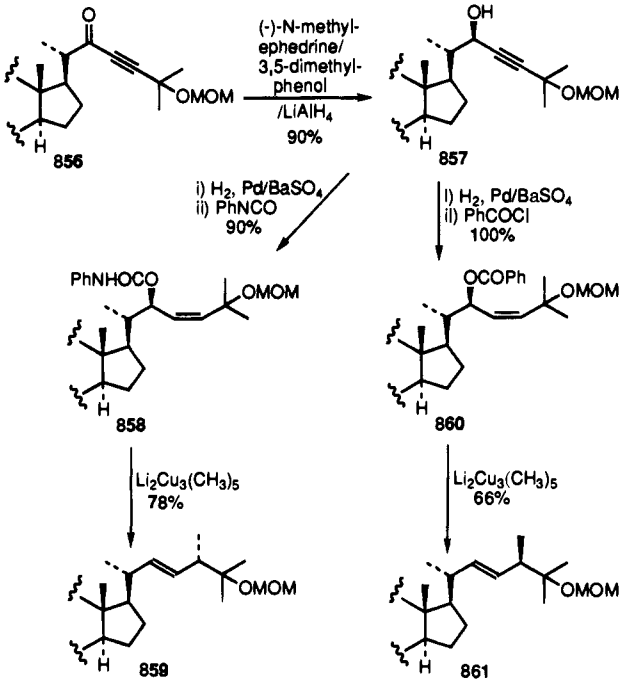



**Figure 180.**

placement of an allylic carbamate by cuprates [$Li_2Cu_3(CH_3)_5$], 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 $LiAlH_4$/(−)-*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 $Li_2Cu_3(CH_3)_5$ furnished the natural (24*S*) vitamin $D_2$ 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-

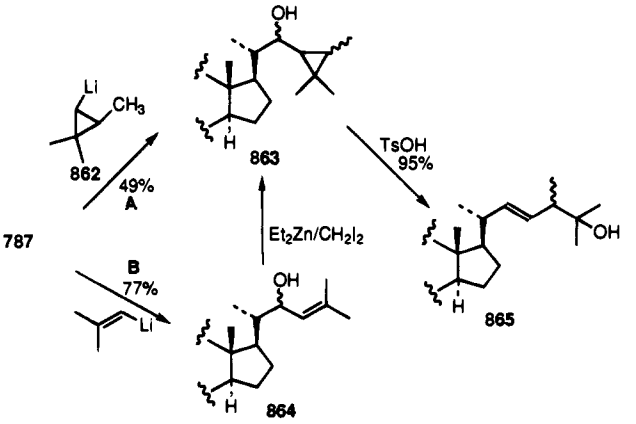



**Figure 181.**

vitamin $D_2$ 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 dimethylvinyllithium 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 position[461] 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

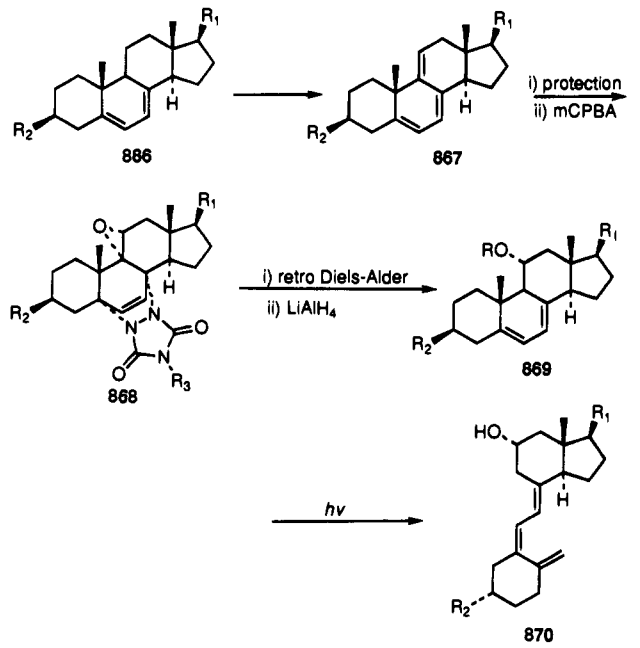



**Figure 182.**

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

Okamura's convergent approach[466] 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-8$\beta$-alcohol benzoate

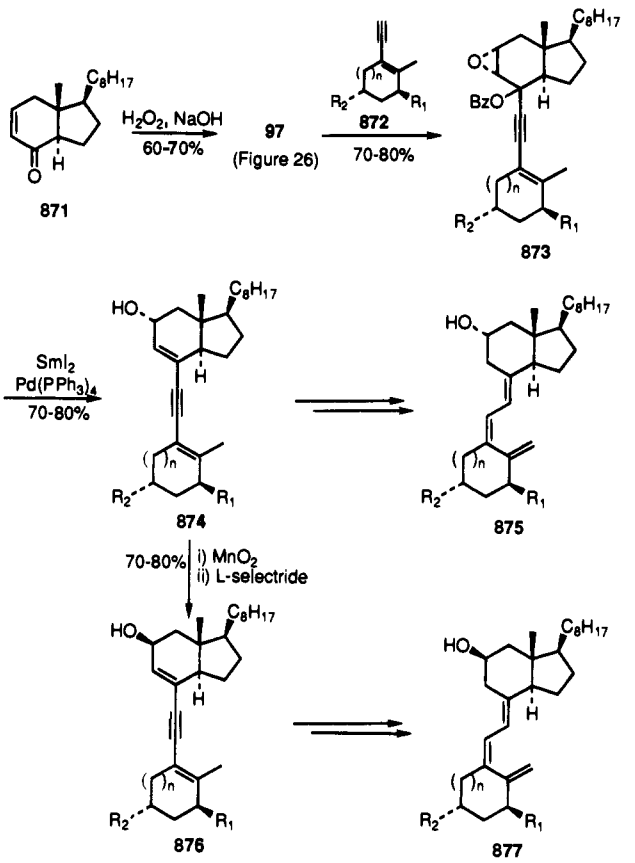



**Figure 183.**

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

In a synthesis of 11$\beta$-fluoro-1$\alpha$-hydroxyvitamin $D_3$ (**880**) (Figure 184), part of a quest for experimental

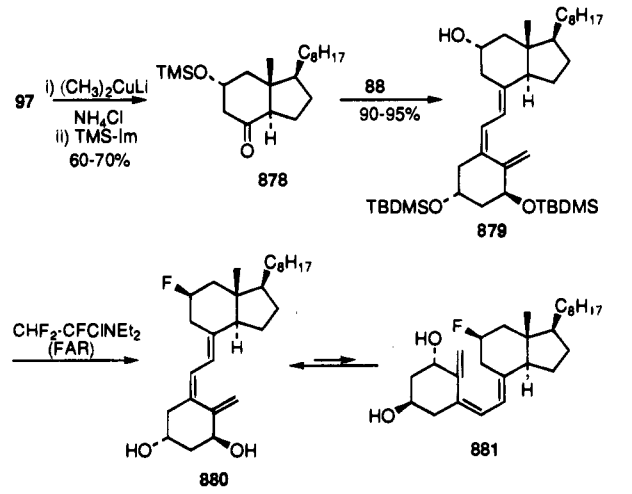



**Figure 184.**

evidence for the folded 6-*s*-*cis*-vitamin D conformation, the De Clercq laboratory in Belgium[95] synthesized 11$\alpha$-hydroxyvitamin D analogues through coupling of protected 11$\alpha$-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 Spain[467] and the De Clercq–Vandewalle laboratory in Belgium.[468,469] Mouriño's procedure (Figure 185)

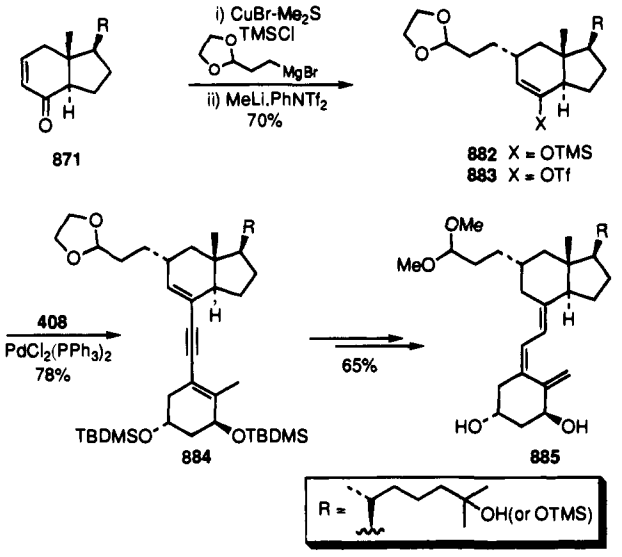



**Figure 185.**

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).

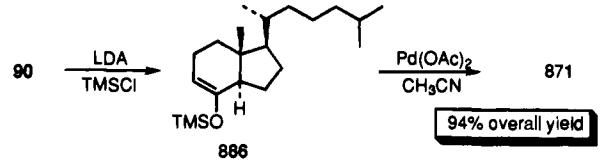



**Figure 186.**

The De Clercq–Vandewalle synthesis involves initial preparation of 11-substituted Grundmann's ketone for Wittig coupling and also allows preparation of 11$\beta$-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$\beta$ and $CH_3$-18 in 11$\alpha$-series (for **887** and **889**). The yields of the coupling to phosphine oxide **88**, in the 11$\alpha$-series varied from 70% to 90%. However, in the $\beta$-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 $\beta$-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$\beta$-substituents with the 18-methyl group.

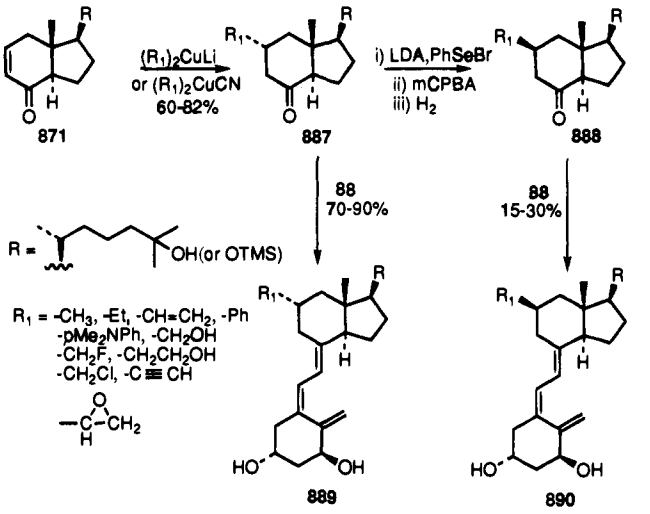



**Figure 187.**

### 2. C-14 Modification

Attempts to synthesize 14$\alpha$-fluoro- and 9$\alpha$-fluorovitamin D analogues have not succeeded (Figure 188).[471] Fluorination of the thermodynamic silyl enol

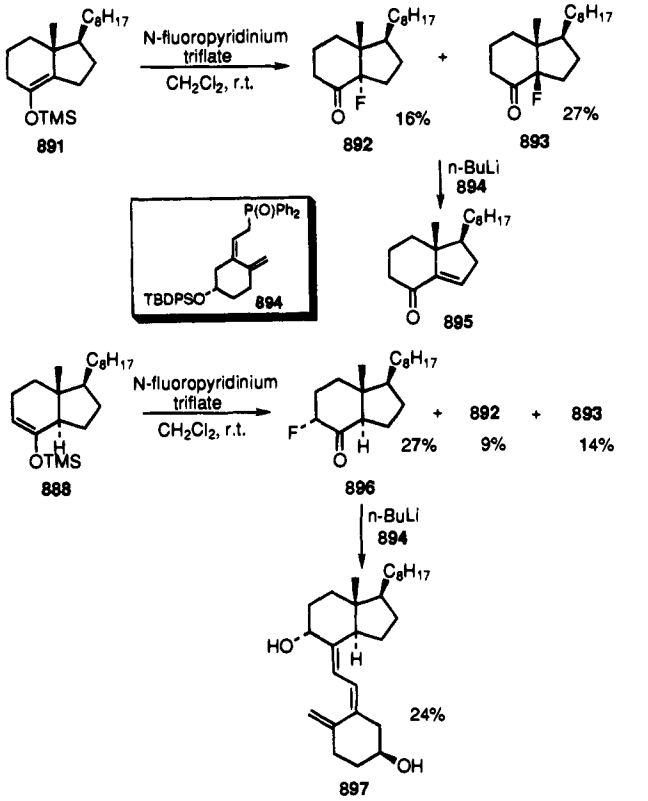



**Figure 188.**

ether **891** with *N*-fluoropyridinium triflate in refluxing methylene chloride gave 16% 14$\alpha$-fluoro Grundmann's ketone **892** and 27% of its 14$\beta$-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 $\alpha,\beta$-unsaturated ketone **895**. The reaction of the kinetic enol silyl ether **886** with *N*-fluoropyridinium triflate gave 9$\alpha$-fluoro Grundmann's ketone **896** in 27% yield together with 9% 14$\alpha$-fluoro **892** and 14% 14$\beta$-fluoro compound **893**. Horner–Wittig coupling of the 9$\alpha$-

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 synthesis[473] of 14α-methylvitamin $D_3$ started from *trans*-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (**898**), an intermediate in a terpene synthesis (Figure 189). Addition of

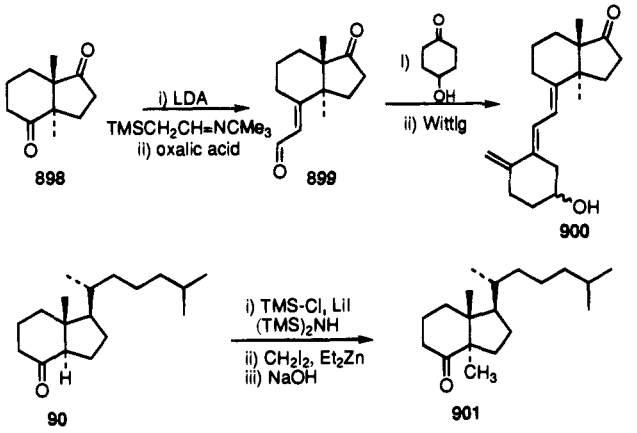



**Figure 189.**

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 14α-methylvitamin $D_3$ remains incomplete. However, a recent report by Corey[474] on the synthesis of 14α-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 14α,15α-methylene vitamin D analogues (Figure 190) relies on a hydroxyl directed Simmons–Smith

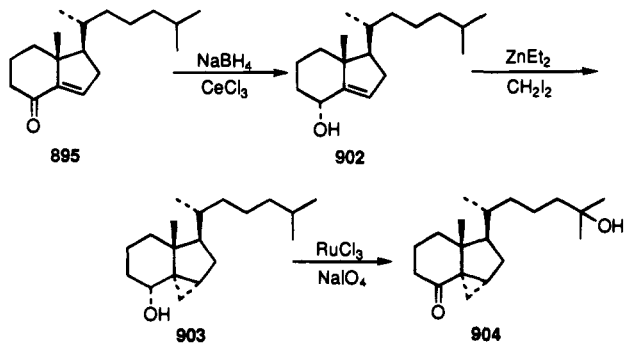



**Figure 190.**

cyclopropanation of 8α-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 laboratory[475] 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).

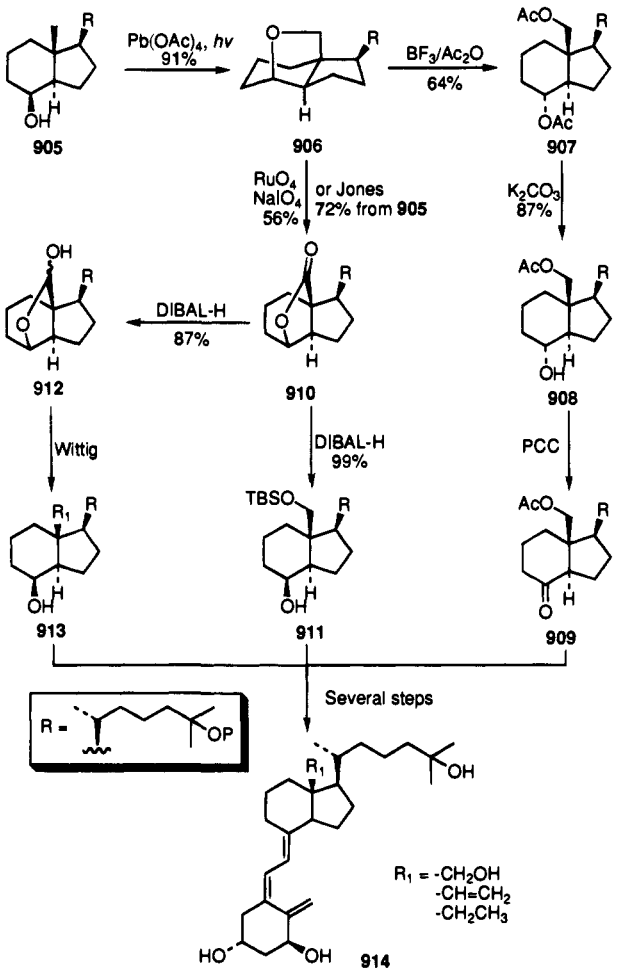



**Figure 191.**

The key feature of both syntheses involves the 8β-hydroxyl directed radical oxidation of the 18-methyl group to form the tetrahydrofuranyl 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, $BF_3{\cdot}Et_2O$ 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** (R = $CH_2OH$). In the Mouriño laboratory, the bridged ether **906** was oxidized with $RuO_4/NaIO_4$ 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**.

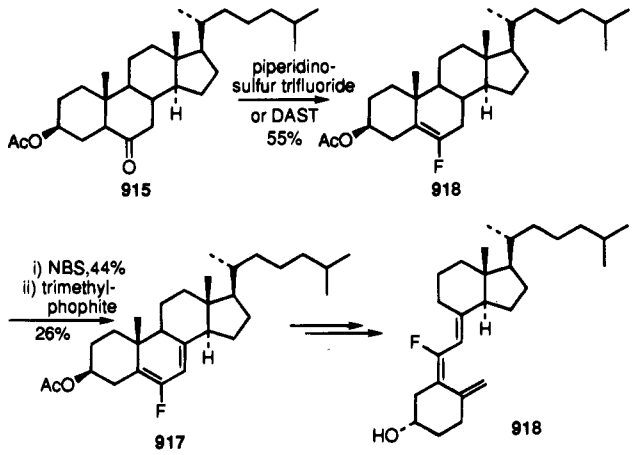



**Figure 192.**

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

### 1. C-6 Analogues

6-Fluorovitamin $D_3$[471,479] (Figure 192) is the first vitamin $D_3$ analogue lacking the C-1 and C-25 hydroxyls observed to bind significantly to the 1,25-$D_3$ 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 $D_3$ (**920**) was synthesized using the Mazur solvolysis approach (Figure 193).[480] Addition of

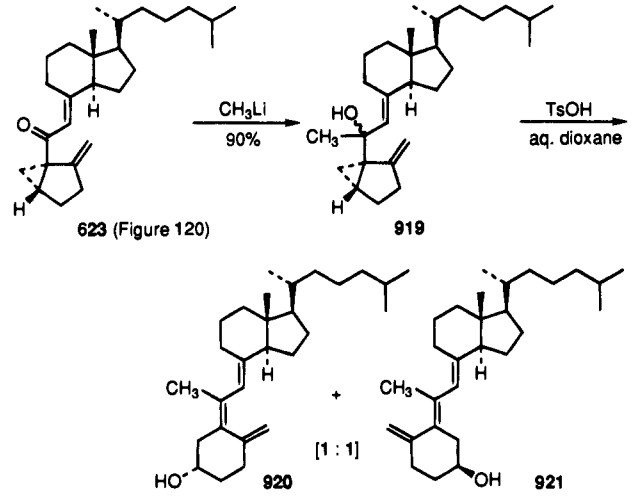



**Figure 193.**

methyllithium to 6-oxo-3,5-cyclovitamin $D_3$ **623**, obtained in three steps from vitamin $D_3$, 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 $D_3$ (**920**) and its 5,6-*trans* isomer **921**.

The diastereomeric vitamin $D_3$–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

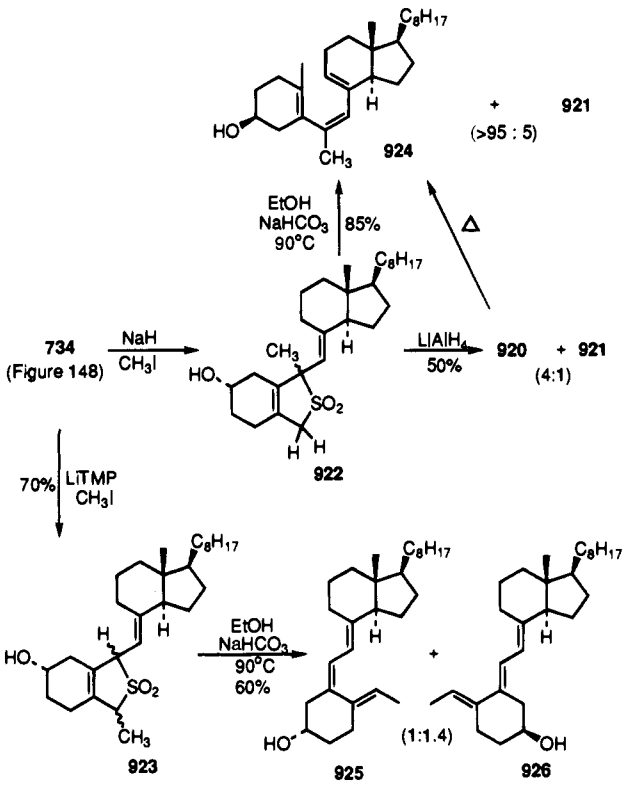



**Figure 194.**

mixture of 6-methyl adducts **922** ($LiAlH_4$, $Et_2O$, reflux) gave 40% 6-methylvitamin $D_3$ **920** together with 10% of its *trans*-isomer **921**. However, thermolysis of **922** (EtOH, $NaHCO_3$, 90 °C) yielded 6-methylprevitamin $D_3$ (**924**) as the major product (>95%) together with minor amounts of 6-methyl-5,6-*trans*-vitamin $D_3$ (**921**, <5%; 85% combined yield). Under thermolysis conditions, the predominantly formed primary product, 6-methylvitamin $D_3$ **920**, is isomerized completely to the thermodynamically more stable 6-methylprevitamin $D_3$ (**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 $D_3$ (**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-$D_3$ 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-$D_3$ 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-$D_3$.[17] The 19-nor analogue **929** was first synthesized by DeLuca[481] via oxidative

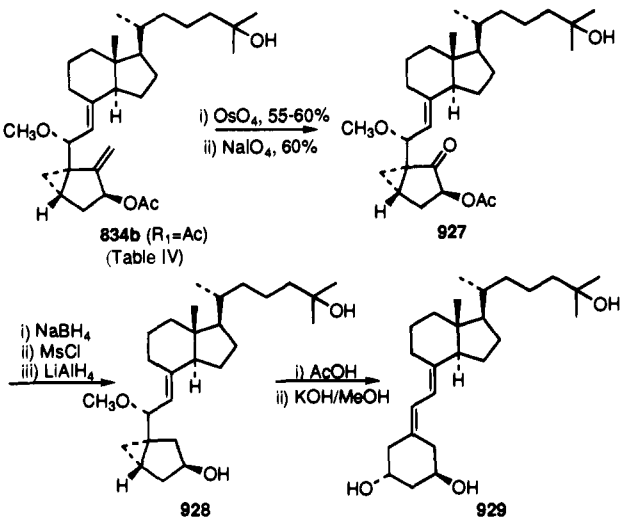



**Figure 195.**

degradation of a 1α-hydroxycyclovitamin D **634b** ($R_1$ = 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 DeLuca[482]

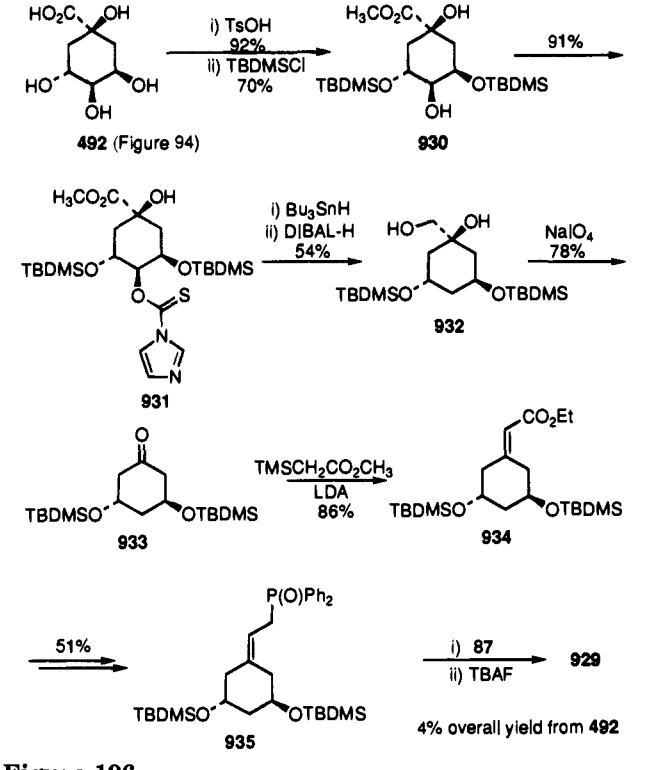



**Figure 196.**

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]

1α,25-Dihydroxy-19-nor previtamin $D_3$ **941** (Figure 197), an analogue of 1,25-$D_3$ locked into its previtamin form, was synthesized in Mouriño's laboratory[484] 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**.

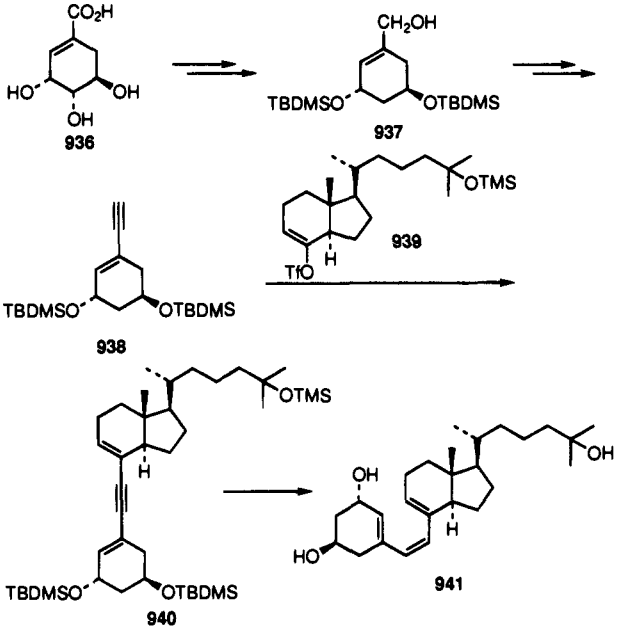



**Figure 197.**

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

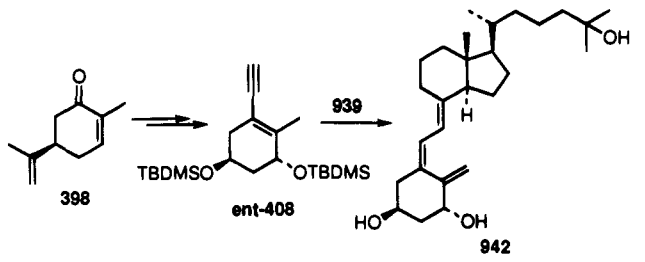



**Figure 198.**

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-$D_3$).[486] The 1α-fluoro derivative of 25-hydroxyvitamin $D_3$ (**946**, Figure 199) was

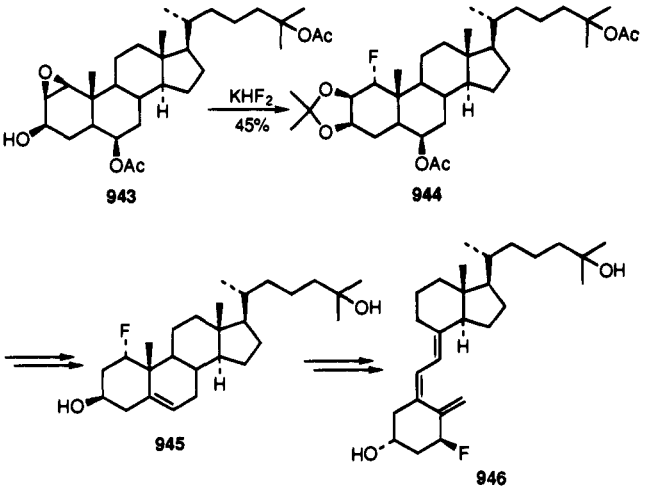



**Figure 199.**

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-

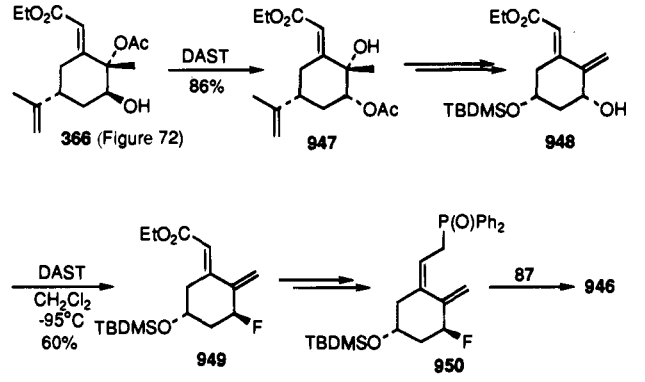



**Figure 200.**

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 +

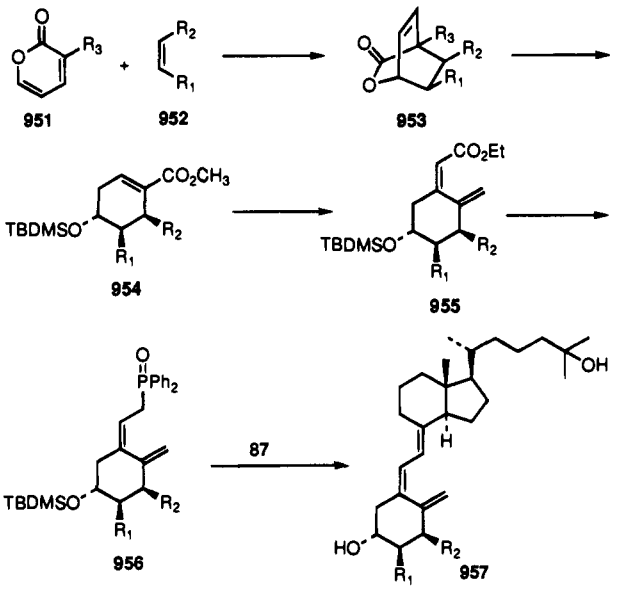



**Figure 201.**

2] cycloaddition of 3-bromo-2-pyrone (**951**, $R_3$ = Br) and acrolein (**952**, $R_1$ = H, $R_2$ = CHO) afforded adduct **953**, which was converted to 1α-analogues of 1,25-$D_3$ **957**.[82f,489–493] By starting with electron-rich dienophiles **952** ($R_1$ = alkoxy or alkyl; $R_2$ = alkoxy or silyloxy), the Diels–Alder reaction yielded adducts which were transformed to 2β-analogues of 1,25-$D_3$.[494,495] In principle, by replacing the ring oxygen of α-pyrone **951** with other heteroatoms (e.g., $NSO_2$-Tol), 3β-heteroatom-substituted 3β-deoxy analogues of 1,25-$D_3$ 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-hydroxyalkoxy[500] analogues, were synthesized through C-2 modification of steroid intermediates using the classical synthetic approach (method A, section II.B). Takahashi's synthesis[501] of 1α,2β-25-trihydroxyvitamin $D_3$ (**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 $BF_3$-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

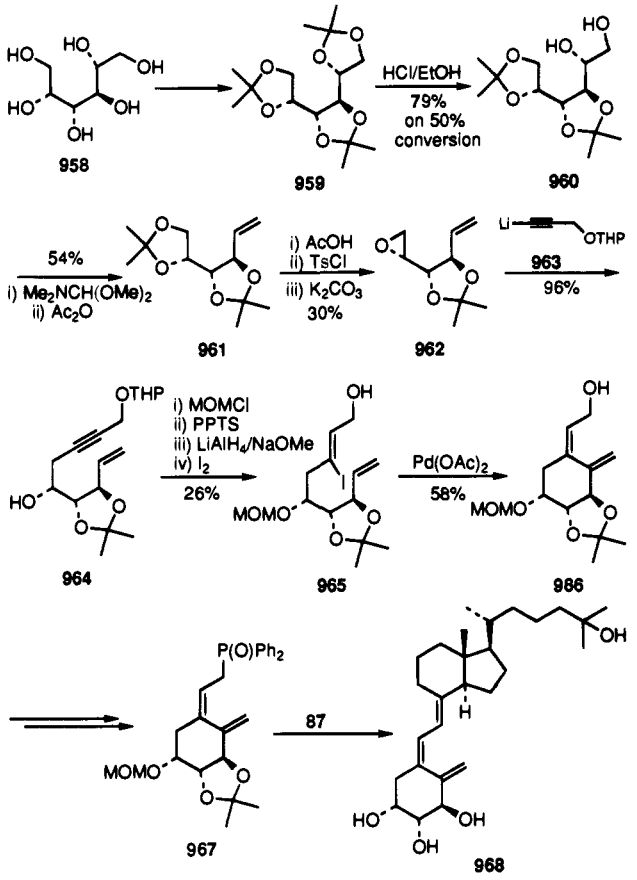



**Figure 202.**

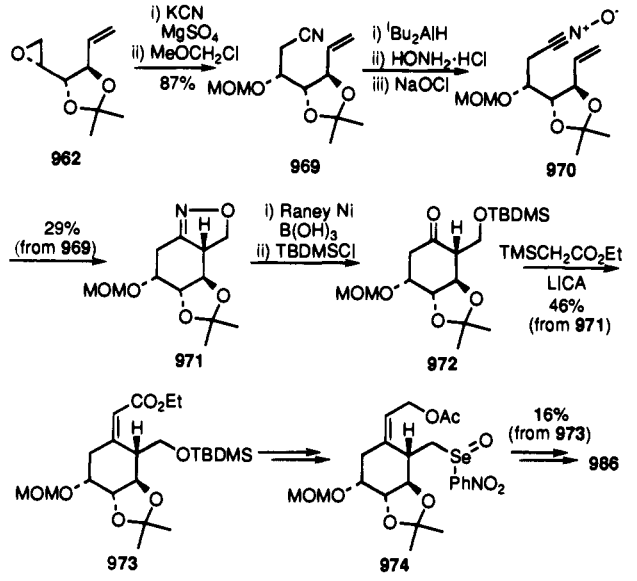



**Figure 203.**

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

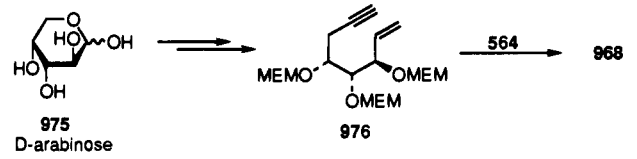



**Figure 204.**

Pd coupling to vinyl bromide **564** results in another alternative synthesis of 2$\beta$-analogue **968**.[503]

### 3. C-3 Analogues

Mitsunobu configurational inversion might be the most direct method for the synthesis of 3-epivitamin D analogues[504] while 3$\beta$-thiovitamin can be obtained through substitution of the tosylate of vitamin D with thiourea[505] or thiocyanate[506] followed by hydrolysis or reduction. Solvolysis[507] of 6($R$)-hydroxy-3,5-cyclovitamin $D_3$ (**624**, Figure 205) with HF, HCl and HBr

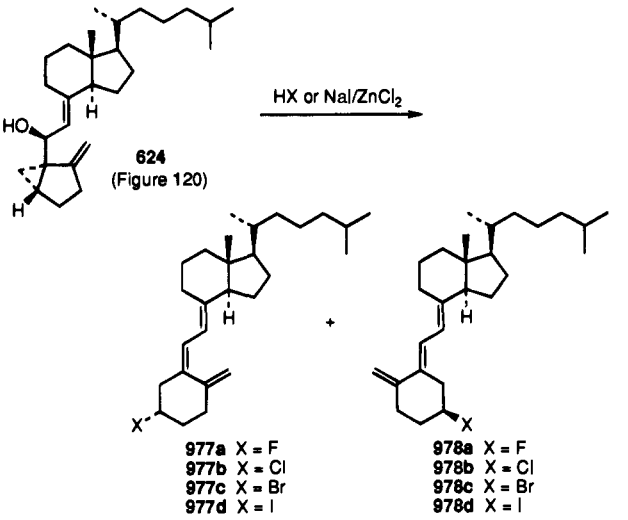



**Figure 205.**

in nonprotic solvents resulted in 3$\beta$-fluoro, 3$\beta$-chloro, and 3$\beta$-bromo analogues of $D_3$ together with 10% of 5,6-*trans*-isomers. The solvolysis with HI under the same conditions mainly led to elimination while rearrangement with $ZnCl_2$ 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 (diethylamido)sulfur trifluoride (DAST) gave 35% 3$\beta$-fluoro compound **979** with configurational retention (Figure 206).

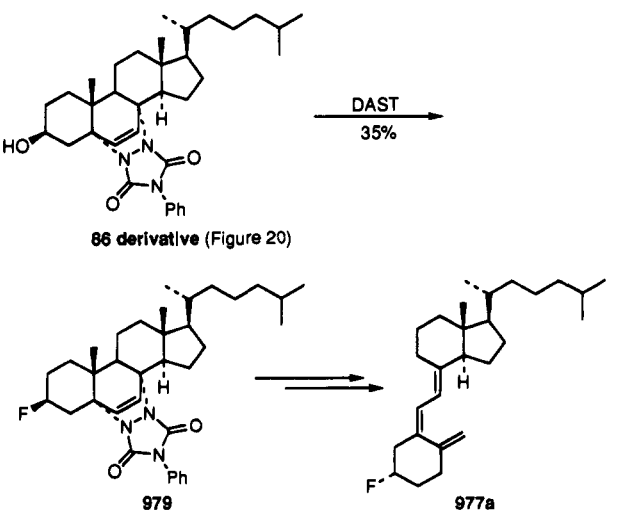



**Figure 206.**

## 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-$D_3$ 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

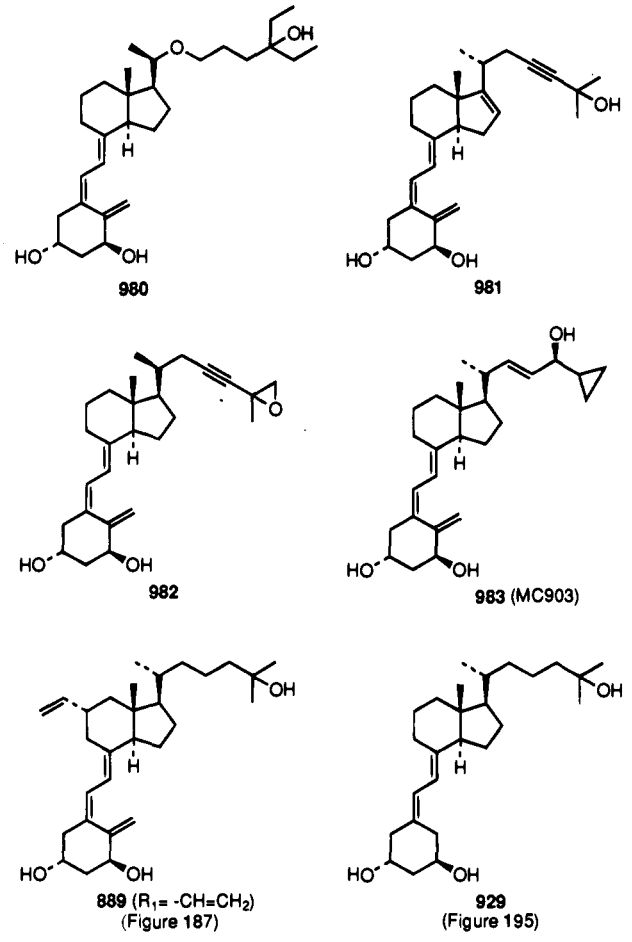



**Figure 207.**

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-$D_3$ 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-oxatrihomo-1α,25-dihydroxyvitamin $D_3$ analogue **980**, which possesses exceptionally high cell differentiation activity (20 000-fold higher than 1,25-$D_3$). This result has been questioned however.[17] (In a preliminary *in vitro* study 20(*R*)-1α,25-dihydroxy-26,27-dimethyl-22-thiavitamin $D_3$ was reported about 100 000 times as active as 1,25-$D_3$ to HL-60 cells).[508] Combination of 23-yne with either a 16-ene as in 1,25-$(OH)_2$-16-ene-23-yne-$D_3$ (**981**) or a 25,26-epoxide as in 1α-(OH)-25,26-epoxy-23-yne-20-epi-$D_3$ (**982**), results in a marked separation of calcemic and cell differentiating activities. The analogue 1α,24S-$(OH)_2$-22-ene-25,27-cyclopropyl-$D_3$ (**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-$D_3$ (**889**) and the 1,25-$(OH)_2$-19-nor-$D_3$ (**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-$D_3$ 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 transverses the endocrine maize, 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-$^{13}C$-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

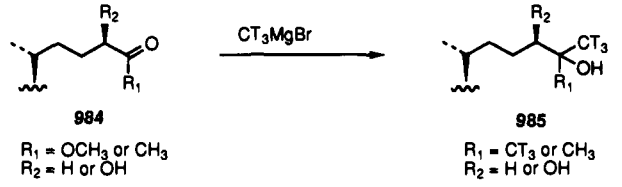



**Figure 208.**

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)

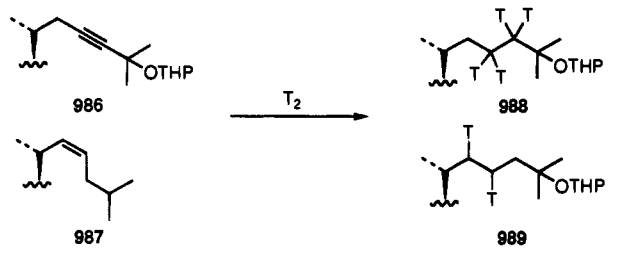



**Figure 209.**

with tritium gas has resulted in 23,24-$T_4$-**988** and 22,23-$T_2$-**989** vitamin D derivatives.[514,515] Labeled $NaBH_4$ reduction of a carbonyl group or removal of hydroxyl groups through reduction of tosylates or mesylates with labeled $LiAlH_4$ or super hydride are common procedures for introduction of tritium at various positions (24-T;[516] 1,2-T;[517] 1$\beta$-T;[518,519] 6-T;[520] 1$\alpha$-T and 1$\beta$-T).[365] Although $^{14}C$-labeled derivatives are known, only $^{13}C$-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 pentadeuteriated derivative of 1,25-$D_3$ **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-

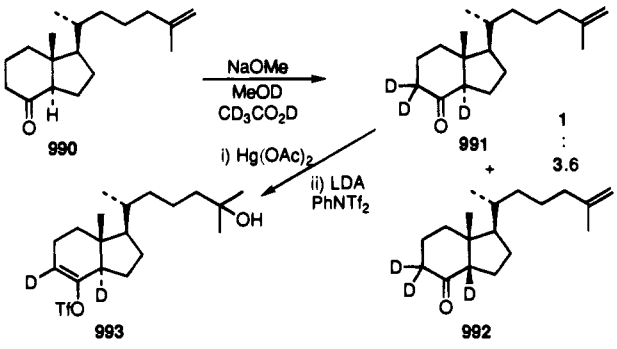



**Figure 210.**

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*-$d_1$ exchange followed by acetic acid-$d_4$ quench (three cycles)[521] gave the desired **991** (98% $D_3$) 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-

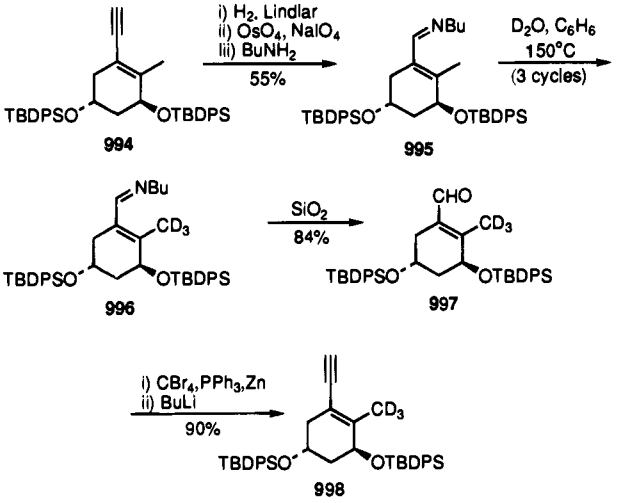



**Figure 211.**

A-ring enyne **998** was obtained via conversion of the easily accessible A-ring enyne **994** (related to **408**). Successive semihydrogenation (Lindlar), oxidative cleavage ($OsO_4$/$NaIO_4$) and *n*-butylamine treatment of **994** provided imine **995**, which underwent clean deuterium exchange ($D_2O$, 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

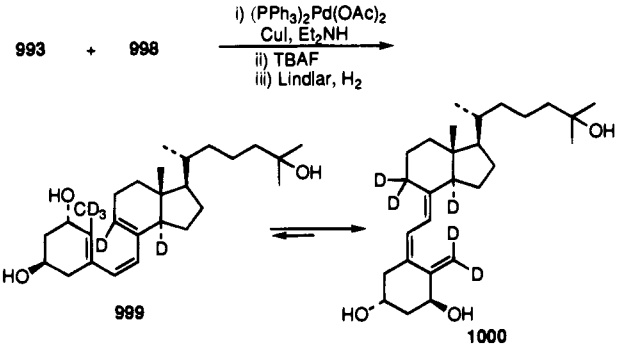



**Figure 212.**

[1,7]-sigmatropic deuterium shift at 25 °C to pentadeuteriated 1,25-$D_3$ **1000** (a normal primary kinetic isotope effect ($k_H/k_D$) of 5.5 was determined). Base-catalyzed (tBuOK) exchange of vitamin D–sulfur dioxide adducts of the type **1001** in anhydrous DMF–$D_2O$ (Figure 213), followed by thermal extrusion of $SO_2$ and photosensitized isomerization, provided 6,19,19-trideuteriovitamin D compounds of the type **1003** with >95% deuterium incorporation. The presence of a 1$\alpha$-hydroxy group ($R_3$ = 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's[527] have also been synthesized via known strategies of side chain construction.

### 3. Synthesis of $^{13}C$-Labeled Vitamin D Analogues

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

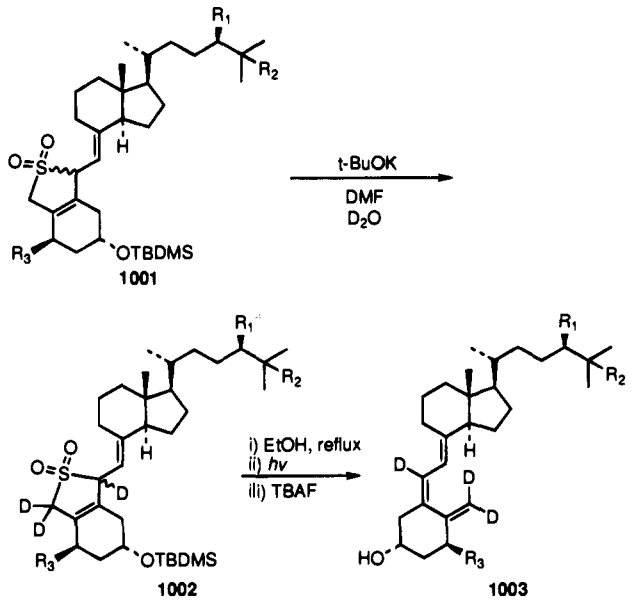



**Figure 213.**

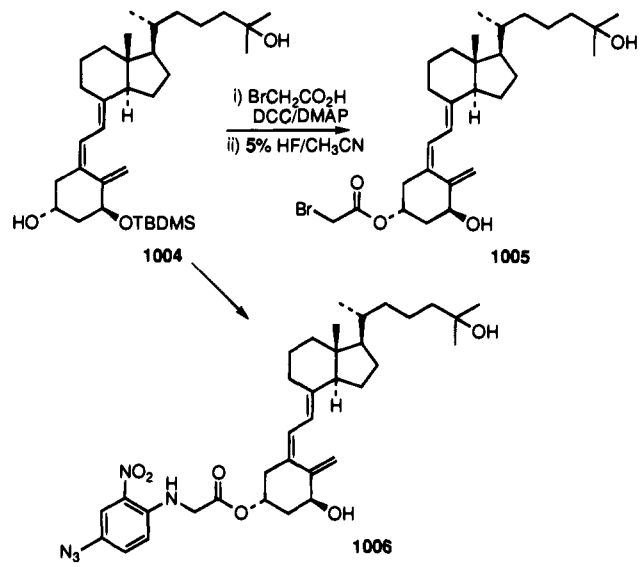



**Figure 214.**

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 spectroscopy[528] or detecting the NOE effect of the protons attached at $^{13}C$-labeled positions via heteronuclear-resolved half-filter experiments[529] could provide information on the binding conformation of vitamin D. To date, however, only the synthesis of 1α-[19-$^{13}C$]hydroxyvitamin $D_3$ has been reported through Wittig olefination of ketone **710** followed by 1α-hydroxylation[89] (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 D[530]

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. 1α,25-Dihydroxyvitamin $D_3$ 3β-bromoacetate **1005**, an affinity-labeled analogue for studies of 1,25-$D_3$ 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-$D_3$ 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 reported that this label containing the C-3 azido substiuent (**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-$D_3$ 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-$D_3$, 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-$D_3$ 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

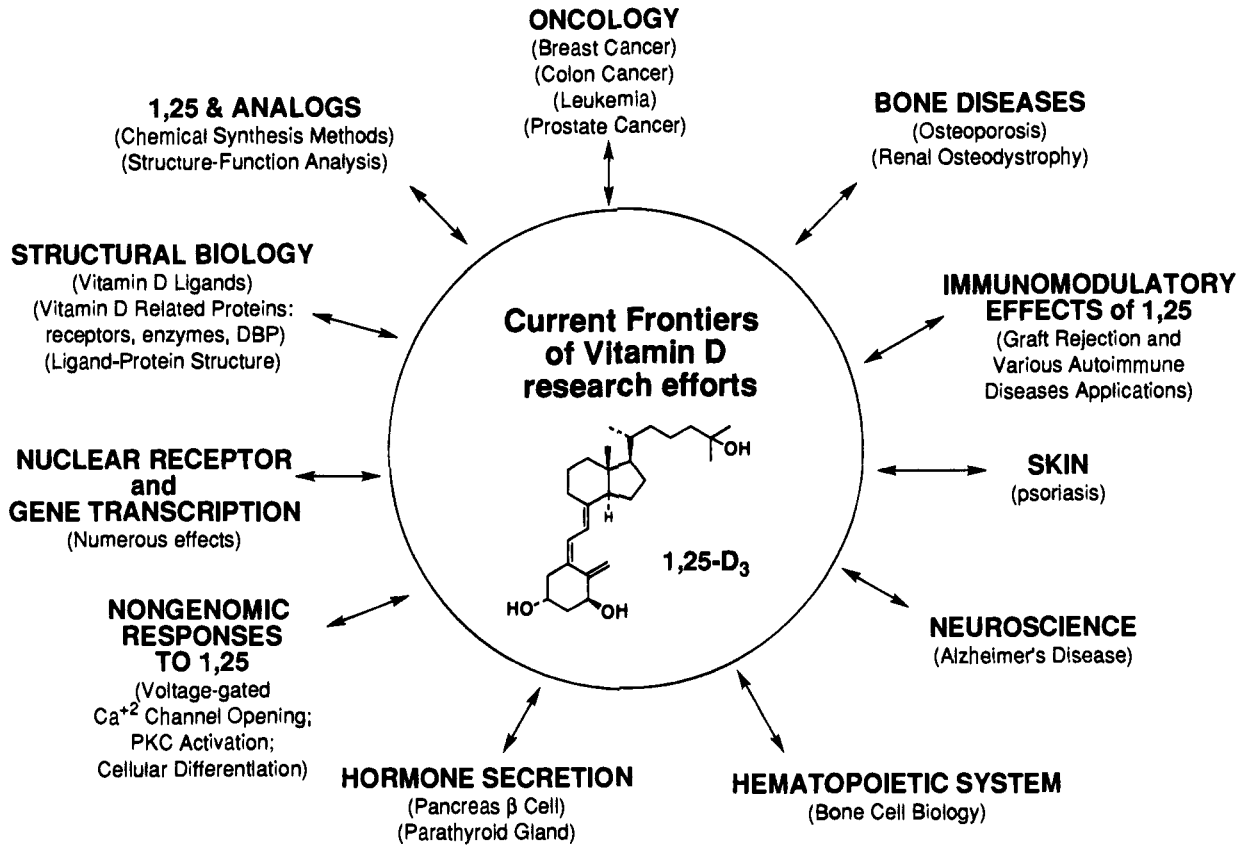



**Figure 215.**

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!

## VI. Acknowledgments

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