Organic Chemistry of Vitamin D Analogues (Deltanoids)

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An increasing number of synthetic vitamin D analogues (deltanoids) are now being used as sensitive molecular biology probes and also as new drug candidates and new drugs for treatment of various human diseases. The design and stereocontrolled synthesis of such new deltanoids are guided by considering catabolism inhibition and by using large steroidal chirons and small steroid-derived chirons.

Outline

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I. Introduction

When exposed to sunlight for even a few minutes, human skin converts 7-dehydrocholesterol into vitamin D_3 (Scheme 1).[1] Vitamin D binding protein (DBP) and hydroxylase enzymes in our kidneys and livers then produce the active hormone 1α,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$, calcitriol, Rocaltrol].[2] Synthetic organic chemists have altered the structure of $1,25(OH)_2D_3$ in various ways (see Scheme 2) with the goal of preparing vitamin D analogues (deltanoids) as sensitive molecular biology probes and as new drugs having a favorable therapeutic index (i.e., high efficacy and low toxicity).[3] Considerable success has been achieved in development of new deltanoid drugs. Table 1 shows deltanoids currently in use as drugs for chemotherapy of various human diseases, and Table 2 shows deltanoids currently in human clinical trials. This current drug development builds on the work of many researchers over the years; for example, Windaus received the Nobel Prize in 1928 for the study of sterols and their connection to vitamins.

The deltanoids Calderol, One-Alpha, Hectorol and Zemplar (Table 1) are prodrugs that require enzymatic 1- or 25-hydroxylation in vivo before becoming hormonally active. Many of the deltanoids in Tables 1 and 2 possess side-chain unsaturation that inhibits catabolic oxidation of the side chain and, thus, the in vivo half-lives of such deltanoids are prolonged.

II. Catabolism Inhibitors

Side-chain catabolism of the natural hormone $1,25(OH)_2D_3$ usually gives products that are medicinally less useful. Therefore, slowing or preventing such catabolic side-chain oxidation is an important goal for medicinal chemistry. Two publications that appeared simultaneously in 1993 were the first reports showing that remote structural/

Gary H. Posner, Scowe Professor of Chemistry, was mentored by E. J. Corey and William G. Dauben. He was a fellow of the Japan Society for the Promotion of Science sponsored by Ryoji Noyori, a Weizmann Institute Research Fellow sponsored by Mario Bachi, and a Fulbright Senior Fellow sponsored by Jean F. Normant. His research interests span the following areas: organocopper chemistry, asymmetric synthesis using sulfoxides, organic reactions on solid surfaces, inverse-electron-demand Diels−Alder cycloadditions, synthesis of new vitamin D analogues, and synthesis of new antimalarial trioxanes.

Mehmet Kahraman, currently a senior postdoctoral fellow in Gary H. Posner's research group, received his PhD degree guided by Michael Harmata at the University of Missouri, Columbia. His research is currently focused on the design and synthesis of new 1α,25-dihydroxyvitamin D_3 (calcitriol) analogues (deltanoids).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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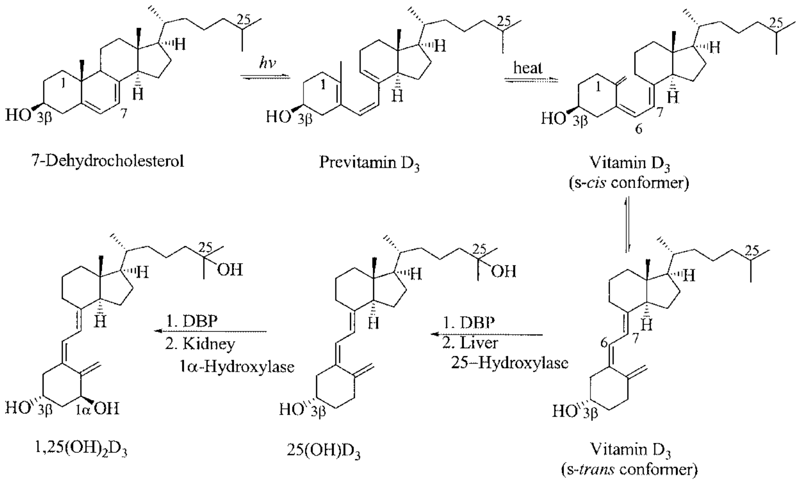
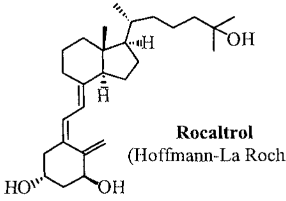
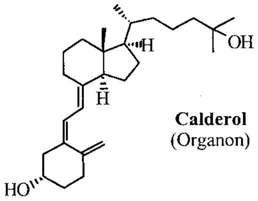
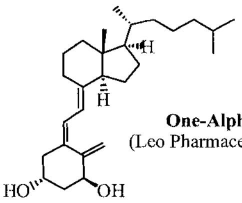
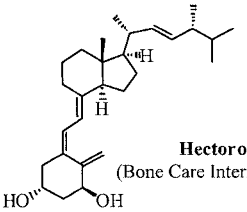
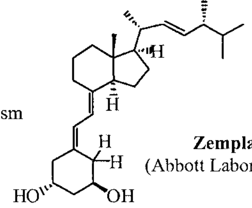
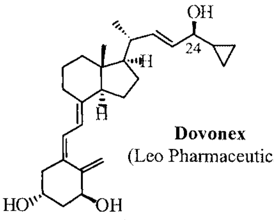
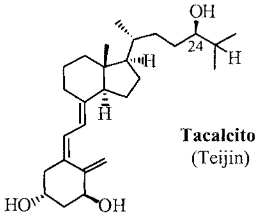
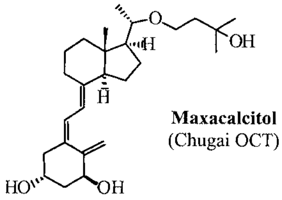
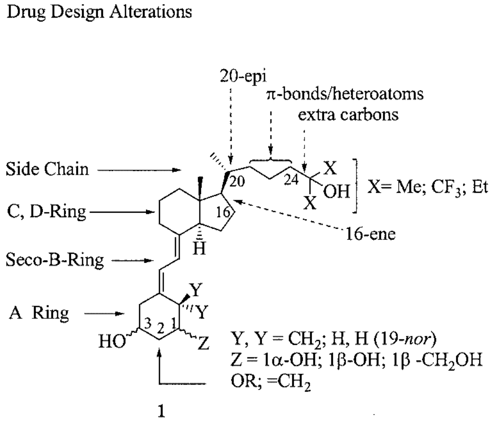


Scheme 1. Biosynthesis of 1α,25-dihydroxyvitamin D_3

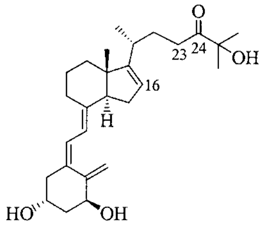
Table 1. Deltanoids in use as drugs

Deltanoid	Indications	Deltanoid	Indications
 **Rocaltrol** (Hoffmann-La Roche)	Secondary hyperparathyroidism Renal failure Osteoporosis		
 **Calderol** (Organon)	Renal failure Osteoporosis	 **One-Alpha** (Leo Pharmaceutical)	Secondary hyperparathyroidism Renal failure Osteoporosis
 **Hectorol** (Bone Care International)	Secondary hyperparathyroidism	 **Zemplar** (Abbott Laboratories)	Secondary hyperparathyroidism
 **Dovonex** (Leo Pharmaceutical)	Psoriasis	 **Tacalcitol** (Teijin)	Psoriasis
 **Maxacalcitol** (Chugai OCT)	Secondary hyperparathyroidism Psoriasis		



Scheme 2

functional changes can influence the rate of side-chain catabolic oxidation.[4,5] Hoffmann-La Roche's 16-en-24-oxo-$1,25(OH)_2D_3$ (**2**) resists enzymatic 23-hydroxylation,[4] and Johns Hopkins' homolog $1\text{-}CH_2OH\text{-}25(OH)_2D_3$ (**3**) resists 24-hydroxylation in human leukemic cells under the conditions in which natural $1,25(OH)_2D_3$ is easily 24-hydroxylated.[5] These two reports were the first indications that the presence of the 16-ene modification, as in the deltanoid **2**, and the presence of a very remote extra methylene group at the 1-position, as in the deltanoid **3**, could sufficiently alter the ligand−enzyme interactions and cause significant slowing in the rate of the enzymatic side-chain oxidation.



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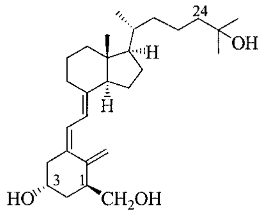
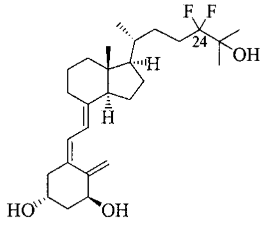
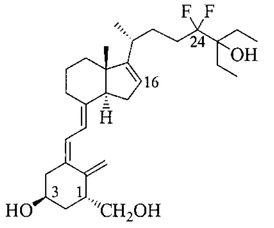


3

Falecalcitriol (Table 2) incorporates two side-chain CF_3 groups that prevent enzymatic C-26 oxidation. Replacing a C−H group by a C−F group, which is usually a miniscule change in a large deltanoid, leads to decreased catabolism because a C−F bond is much stronger and, therefore, less easily broken (i.e., oxidized) than is a C−H bond.[6] Thus, in the early 1980s, $24F_2\text{-}1,25(OH)_2D_3$ (**4**) and related 24-fluorinated deltanoids were prepared.[7,8] Although C-24 catabolic hydroxylation was indeed prevented in these compounds, they were disappointingly similar to $1,25(OH)_2D_3$ in terms of their undesirably high calcemic activity.[7,8] In sharp contrast, hybrid deltanoid Hopkins QW $1624F_2$-2 (**5**),[9] which is blocked toward C-24 hydroxylation by two fluorine atoms, but carries a desirable calcemia-lowering 1-CH_2OH group, is a selective agonist that inhibits mouse skin tumorigenesis without causing toxic hypercalcemia or animal weight loss over 4 months of treatment, whereas natural $1,25(OH)_2D_3$ is lethal under these conditions.[10] Large-scale synthesis of 24-difluorinated Hopkins QW $1624F_2$-2 (**5**) has been completed under the auspices of the NIH RAPID program and, thus, this hybrid deltanoid is now available to the scientific community for further studies as a molecular probe and as a drug candidate.



$24F_2\text{-}1,25(OH)_2D_3$ (**4**)

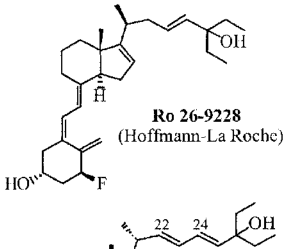
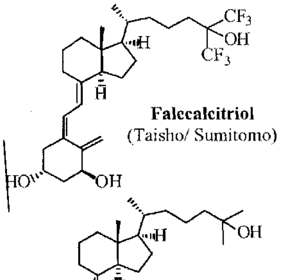
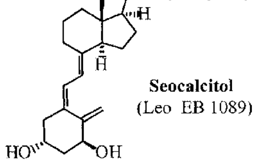
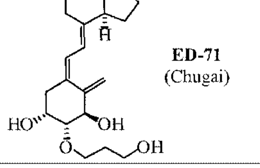


Hopkins QW $1624F_2$-2 (**5**)

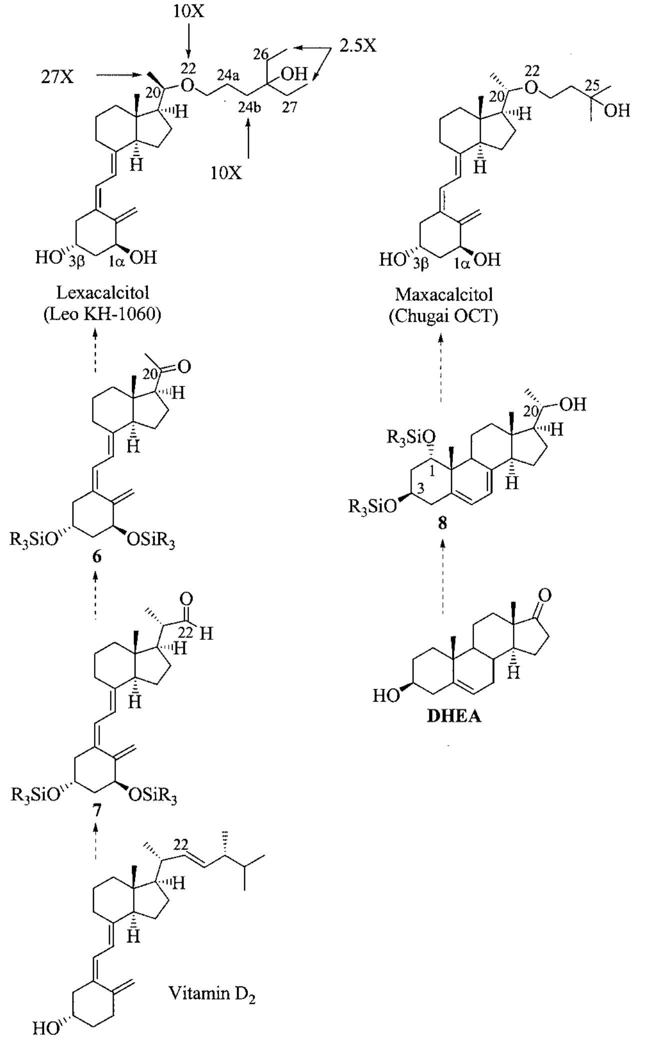
III. Synthesis Using Large Steroidal Chirons

Considerable research by pharmaceutical companies, relating chemical structures to biological activities (structure−activity relationship, SAR), has produced the potent 22-oxa deltanoids Leo KH-1060 and Chugai OCT (Scheme 3). Such SAR generalizations quantify the antiproliferative potency advantage (Scheme 3, Leo KH-1060, in-

Table 2. Deltanoids in clinical trials

Deltanoid	Indications	Deltanoid	Indications
 **Ro 26-9228** (Hoffmann-La Roche)	Osteoporosis	 **Falecalcitriol** (Taisho/ Sumitomo)	Secondary hyperparathyroidisr Osteoporosis
 **Seocalcitol** (Leo EB 1089)	Neoplasm Breast tumor Colon tumor Pancreas tumor	 **ED-71** (Chugai)	Osteoporosis

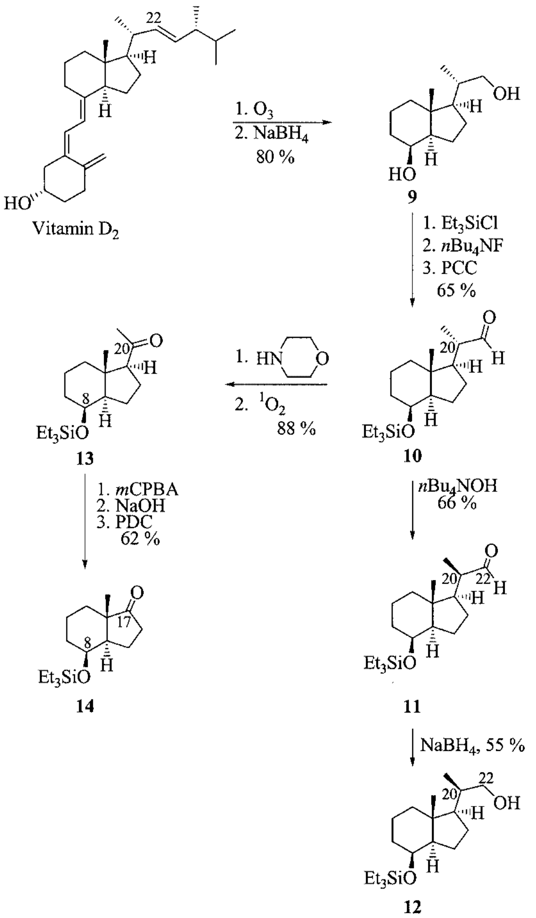
creases in antiproliferative activity are indicated) gained by altering the skeleton of natural 1,25(OH)$_2$D$_3$ by C-20 epimerization (27×), C-22 oxygenation (10×), and side chain homologation at C-24 and C-27 (2.5×).[3] Both 22-oxa deltanoids Leo KH-1060 and Chugai OCT are prepared typically from steroid precursors (Scheme 3). Thus, C-20 ketone **6** is derived from C-22 aldehyde **7**, which is prepared by ozonolysis of triene-protected steroidal vitamin D$_2$ followed, ultimately, by allylic 1-hydroxylation.[11] Likewise, C-20 alcohol **8** is prepared from the steroid dehydroepiandrosterone (DHEA).[12] The major advantage of preparing new deltanoids from almost whole steroid precursors is that most of the deltanoid skeleton, including its absolute stereochemistry, is available without needing costly and time-consuming multistep syntheses.



Scheme 3

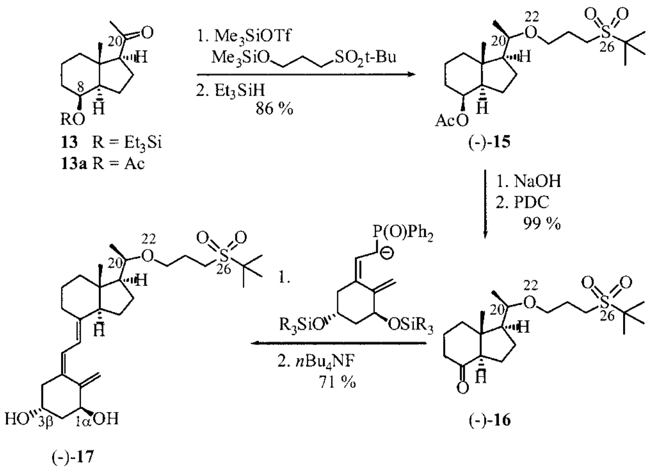
IV. Synthesis Using Small Steroid-Derived Chirons

The major advantage of using small parts of steroids for construction of new deltanoids is versatility. As shown in Scheme 4, oxidative cleavage, and then in situ reduction, of inexpensive and readily available vitamin D$_2$ (ergocalciferol) produces the versatile, enantiomerically pure deltanoid building block **9**.[13] This C,D-ring unit **9** can be converted readily into diastereoisomeric C-22 aldehydes **10** and **11** (differing only by their C-20 stereochemistry) and then into C-20-epi C-22 alcohol **12** and C-20 ketone **13**.[13] Ketone **13** can be converted into C-17 ketone **14** by sequential Baeyer−Villiger oxidation, hydrolysis, and C-17 oxidation (Scheme 4).[13c] These enantiomerically pure C,D-ring building blocks allow versatile attachment of diverse side chains, and also of A-ring portions by Lythgoe coupling.[14] For example, the C-20 ketone **13a** was converted by reductive etherification into the nonclassical side-chain sulfone deltanoid (−)-**17** (Scheme 5), a powerfully antiproliferative and transcriptionally active new deltanoid having desirably low-calcemic activity.[13]



Scheme 4

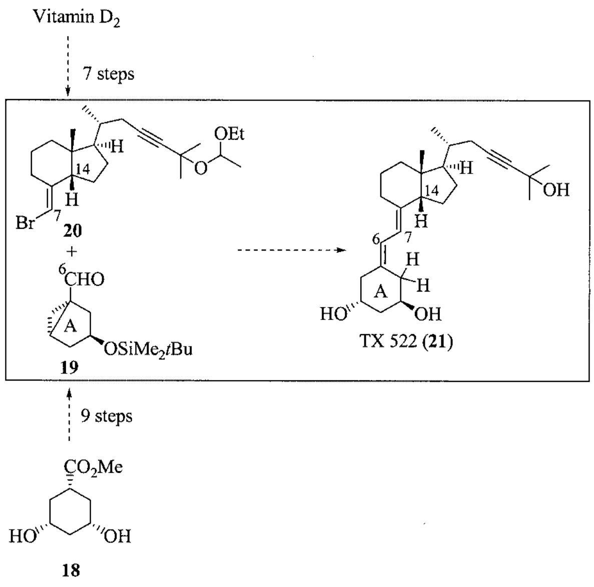
Multistep synthesis of key building blocks that can be joined to form new deltanoids has been reviewed.[14,15] Structurally and stereochemically complex deltanoid building blocks often offer serious synthetic challenges to organic chemists. Hybrid deltanoids, modified in two remote regions, are best prepared by joining small parts of natural steroids (typically the enantiomerically pure C,D-ring) with a nonclassical side chain and then with a nonclassical A-



Scheme 5

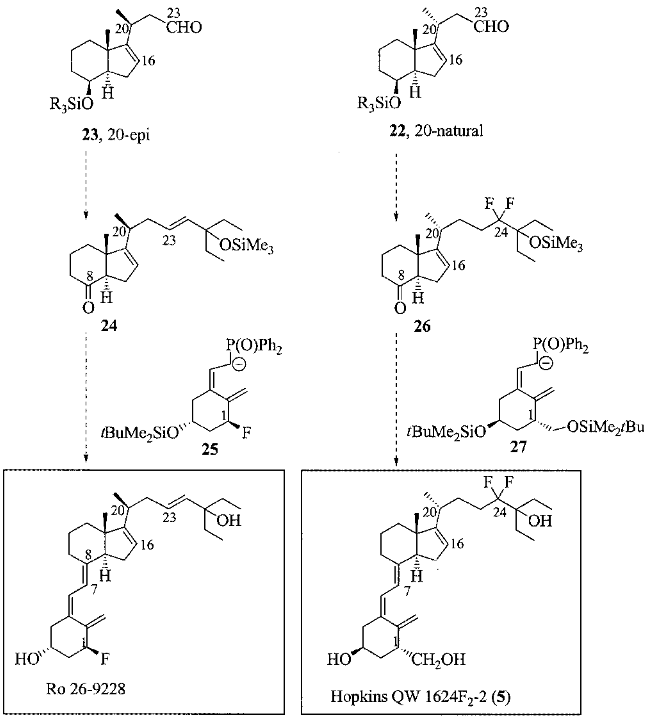
ring. Both the side chain and the A-ring are usually prepared by multistep syntheses. Such convergent synthesis allows much versatility in selecting the components to join and, in principle, allows small libraries of new deltanoids to be produced.[16] Three examples of multistep syntheses of therapeutically desirable hybrid deltanoids follow.

The Théramex 14-epi-19-nor-23-yne hybrid deltanoid **21** is in advanced clinical trials for treatment of psoriasis.[17,18] It was prepared by convergent coupling of the A-ring cyclopropane aldehyde **19** (prepared in nine steps from precursor cyclohexanediol **18**) and the C,D-ring bromo olefin **20** (prepared in about seven steps from vitamin D_2) (Scheme 6).



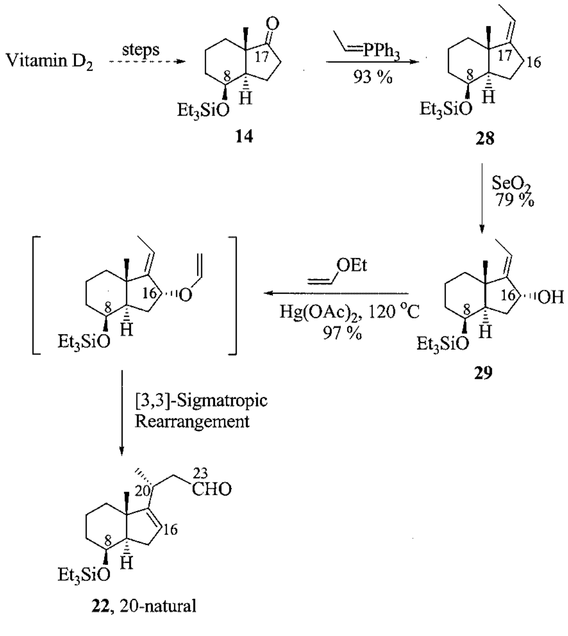
Scheme 6

1α-Fluoro-16,23-diene-20-epi hybrid deltanoid Ro 26-9228 is in human clinical trials for treatment of osteoporosis.[19,20] It was prepared by convergent coupling of the 16,23-diene 8-ketone **24** (prepared from 20-epi-23-aldehyde **23**) and the A-ring 1-fluorinated unit **25** (Scheme 7). Additionally, Hopkins QW-1624F_2-2 (**5**), a low-calcemic cancer-chemopreventive hybrid deltanoid,[10] was synthesized by coupling the 24-difluorinated C,D-ring 8-ketone **26** (prepared from 20-natural 23-aldehyde **22**) with the A-ring 1-homologated unit **27** (Scheme 7).[9]

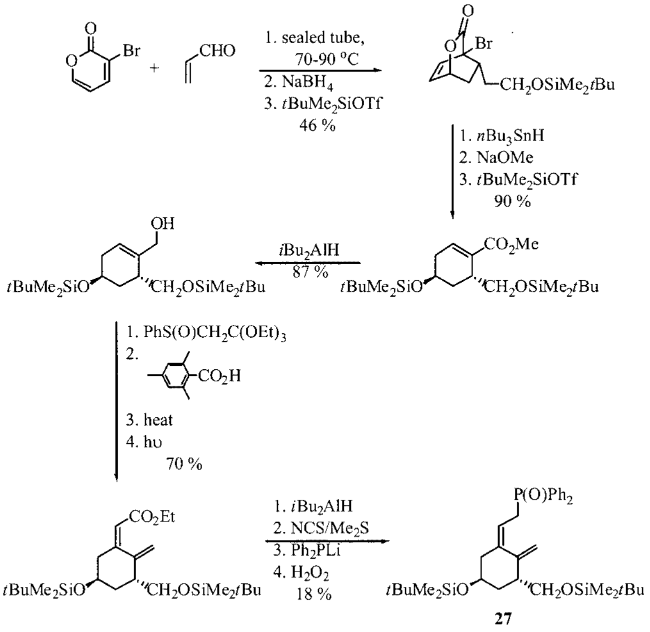


Scheme 7

20-Natural 23-aldehyde **22** was prepared from chiron C-17 ketone **14** by Wittig olefination and then a high-yielding stereocontrolled C-16 α-hydroxylation using selenium diox-



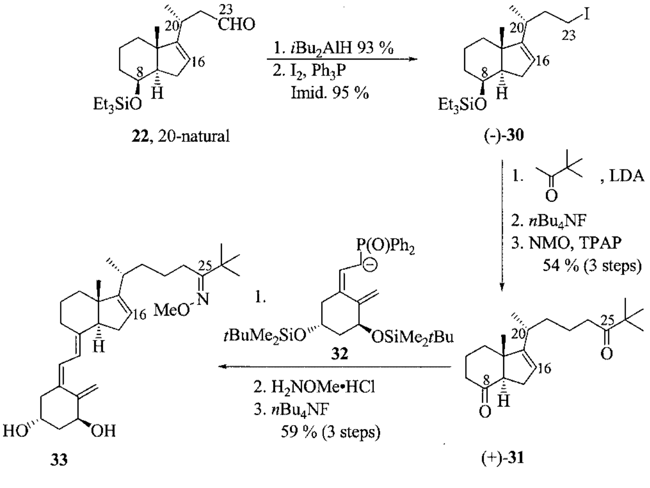
Scheme 8



Scheme 9

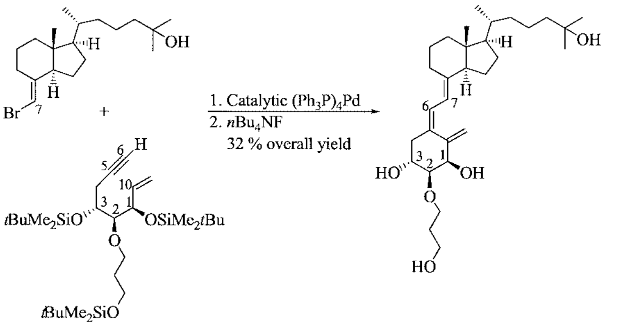
ide to form the allylic alcohol **29** (Scheme 8). A highly stereocontrolled [3,3]-sigmatropic rearrangement of an intermediate allyl vinyl ether then afforded the 23-aldehyde **22** with the desired 20-natural absolute stereochemistry.[21] A-Ring 1-homologated phosphane oxide unit **27** was prepared by stereocontrolled [4+2] cycloaddition of 3-bromo-2-pyrone with acrolein (Scheme 9).[22]

Although it is not a hybrid deltanoid, the conceptually new 16-ene-25-oxime deltanoid **33** has desirably low calcemic activity and is antiproliferatively and transcriptionally potent. Oxime deltanoid **33** was prepared also from the key 16-ene-23-aldehyde building block **22** (Scheme 10).[23] Noteworthy in its synthesis is the regiospecific joining of the A-ring nucleophile **32** with only the C-8 ketone group in the C-8,C-25-diketone (+)-**31**; also noteworthy is the oximation of the C-25 ketone group, which occurs without disturbing the sensitive conjugated triene unit.



Scheme 10

An important advance in synthetic methodology has been reported for the efficient construction of A-ring cyclohexane units directly by C-10 to C-5 bond formation in one operation from noncyclic precursors [Equation (1)].[24] This organometallic palladium-mediated approach to a C-6 vinylpalladium intermediate that couples in situ with C-7 vinylic bromides has been used successfully in some deltanoid syntheses [Equation (1)].[25]



(1)

V. Conclusions

The high value of deltanoids as fundamental molecular probes and as powerful drugs will continue to stimulate the design and synthesis of new deltanoids. In addition to producing selective, effective and safe new deltanoid drugs for prevention and treatment of various human illnesses, organic chemists will continue to design and prepare new deltanoids also as molecular probes to elucidate, in collaboration with molecular biologists, the fundamental details of the molecular machinery responsible for a deltanoid's selective biological profile. One such important collaborative finding with Hopkins' deltanoids is that a deltanoid's potency is not necessarily proportional to how strongly it binds to the nuclear vitamin D receptor.[26]

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