[1,7]-Sigmatropic Hydrogen Shifts of A-Norvitamin D Analogues: Ring Size and Substituent Effects on the Previtamin D–Vitamin D Equilibrium[1]

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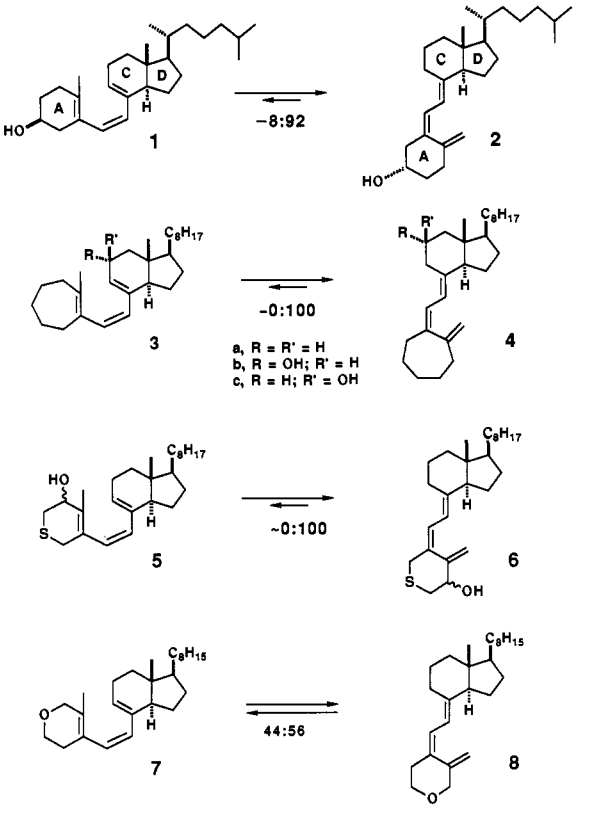
Abstract: The [1,7]-sigmatropic hydrogen shift of the 11α-OH-*A*-norprevitamin D analogue **9** and its 11β-epimer **10** to the vitamin forms **24** and **25**, respectively, was determined to be ~20 and ~10 times faster than that of previtamin D_3 (**1**) to vitamin D_3 (**2**). In addition, the location or absence of the hydroxyl group relative to the triene moiety of *A*-norprevitamins **9–12** was determined to have diverse effects on the position of the previtamin–vitamin equilibrium. Together with the results for the oxa analogues **53/54** and **55/56** and our earlier results for **3/4**, **5/6**, and **7/8**, it appears that the smaller A-ring size favors the previtamin structure and the larger A-ring favors the vitamin form, but small structural changes can readily influence the equilibrium (e.g., the 11-OH group in the *A*-nor series **9/24** and **10/25**). While the observed equilibrium changes can be rationalized on the basis of nonbonded substituent steric effects superimposed upon ring size (strain) effects, the origin of the observed rate enhancements of the [1,7]-shift in the *A*-nor series compared to the six-membered A-ring, natural series is less clear.

Introduction

At 25 °C, the [1,7]-sigmatropic hydrogen shift[2] mediated previtamin D_3 (**1**)–vitamin D_3 (**2**) equilibrium ratio is 8:92 favoring the vitamin (Scheme I).[3] Over 1 week at room temperature is required to reach this equilibrium starting with **1**; more specifically, $t_{1/2}$ (25 °C) = 70 h for the transformation of **1** to **2**.[3] From our own studies, the enlargement of the A-ring of **1** as in **3** has been shown to affect the previtamin–vitamin equilibrium. In the three cases **3a–c** studied,[1,4] it has been shown that these *A*-homo previtamins rearrange completely to the side of the corresponding vitamin **4**. The dynamics for the transformation of **3** to **4** was particularly striking in that the transformation of **3b** or **c** to **4b** or **c**, respectively, occurs ~300 times more rapidly than does **1** to **2** at room temperature [$t_{1/2}$ (25 °C) < 15 min].[1]

In an earlier study of several heterocalciferols, it was shown on the one hand that the sulfur analogue **5/6** completely favors the vitamin form **6** at equilibrium.[5] On the other hand, for the oxacalciferol derivatives **7/8**, nearly equal proportions of **7** and **8** are found to be in equilibrium at ambient temperature.[6,7] The thia–calciferol system **5/6** resembles the ring enlarged case **3/4** in the sense that the thia six-membered ring resembles a seven-membered ring in its effect on the previtamin–vitamin equilibrium position. That is, because of the longer carbon–sulfur single bond distance (1.81 Å)[8] compared to the carbon–carbon single bond distance (1.54 Å), the A-ring of **5/6** more nearly resembles the seven-membered A-ring of *A*-homo analogue **3/4** than the parent system **1/2**. The oxa–calciferol system **7/8**, whose A-ring bears two carbon–oxygen single bonds of 1.41 Å each,[8] which is shorter than the carbon–carbon single bond, exists to a greater extent than

Scheme I



1/2 in the previtamin form. This suggests that A-ring contraction could very well lead to a shift in equilibrium to the previtamin form at the expense of the vitamin form. In order to test the idea that A-ring contraction leads to a preference for the previtamin form and that larger A-rings prefer the vitamin form, it became of interest to synthesize and examine the behavior of a series of *A*-norcalciferols. An earlier attempt at preparing such *A*-nor systems by using our vinylallene [1,5]-sigmatropic hydrogen shift strategy[9] had proven unsatisfactory, and thus a new method had to be developed.

It is the purpose of this paper to describe the successful preparation and study of such a series, namely previtamins **9–12** listed

(1) This is paper 38 in the series Studies on Vitamin D (Calciferol) and Its Analogues. For paper 37, see: Enas, J. D.; Palenzuela, J. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 1355.

(2) (a) Hoeger, C. A.; Johnston, A. D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690. (b) Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 268. (c) Wu, K.-W.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 4025.

(3) Hanewald, K. H.; Rappoldt, M. P.; Roborgh, J. R. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1003.

(4) (a) Sine, S. M.; Conklin, T. E.; Okamura, W. H. *J. Org. Chem.* **1974**, *39*, 3797. See, also: (b) Gerdes, J. M.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 4030. (c) Gerdes, J. M.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1981**, *46*, 599.

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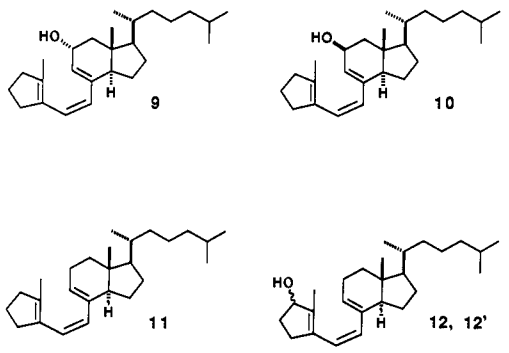
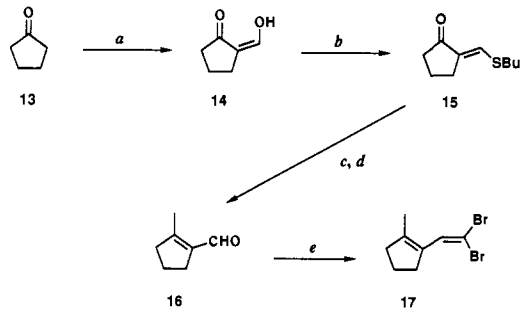
Chart I



Scheme II[a]



[a] Reagents: (a) KH, HCOOEt (56%); (b) *n*-BuSH, *p*-TsOH, $MgSO_4$ (81%); (c and d) MeMgI; $HgCl_2$, $CdCO_3$ (50%); (e) PPh_3, CBr_4, Zn (68%).

in Chart I. Besides these substrates, we also describe an investigation of a series of A-ring analogues bearing oxygen functionality to compliment not only the studies of **9–12** but also our earlier studies of the homo analogues **3**/**4**[1,4] and the heteroanalogs **5**/**6**[5] and **7**/**8**.[6,7]

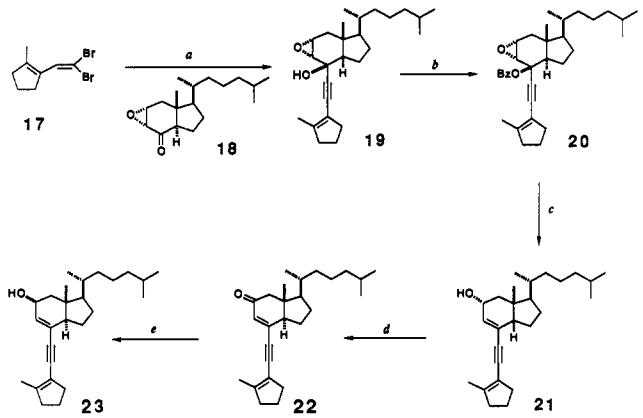
Results and Discussion

The 11-hydroxy-*A*-nor analogues **9** and **10** were targeted for study first because they could be directly compared to the analogous *A*-homo compounds **3b** and **3c** recently reported by this laboratory.[1] In fact, the procedure successfully used for preparing the latter 11-hydroxy-A-homo analogues could be applied here. The construction of the requisite A-ring fragment, enal **16**, was similar to that reported by Bernstein[10] for the synthesis of related 3-substituted derivatives (Scheme II). Enal **16** was then transformed to the dibromide **17** via a Wittig reaction (15.4% overall yield from cyclopentanone).[11]

Following the Corey–Fuchs protocol,[11a] the A-ring dibromide **17** was treated with 2 equiv of *n*-BuLi to generate the lithium acetylide followed by its in situ coupling with the known CD epoxy ketone **18** to afford the epoxy propargyl 8β-alcohol **19** as a single diastereomer (Scheme III). The alcohol **19** was transformed to the benzoate **20** (79%), which was converted in good yield to the key intermediate 11α-dienynol **21** by treatment with Sm(II) iodide in the presence of Pd(0).[12] The synthesis of the 11β-epimer **23** was then relatively straightforward. Allylic oxidation of **21** afforded dienynone **22**, which upon L-Selectride reduction resulted in selective formation of only the 11β-dienynol **23** in 64% yield for the two steps (Scheme III).

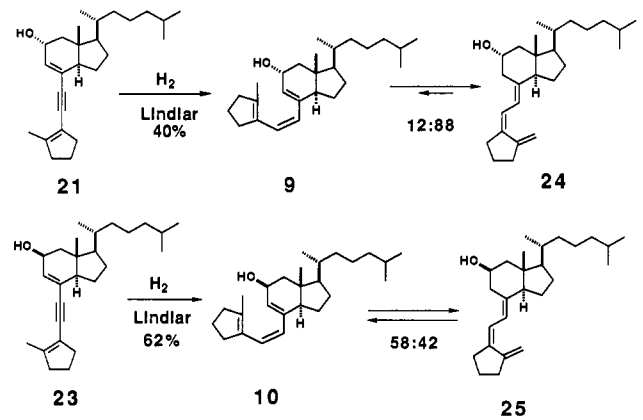
Semihydrogenation of the 11α-dienynol **21** under Lindlar conditions afforded the 11α-OH previtamin **9** in 40% yield

Scheme III[a]



[a] Reagents: (a) *n*-BuLi; **18** (77%); (b) *n*-BuLi; PhCOCl (79%); (c) SmI_2; $Pd(PPh_3)_4$ (89%); (d) MnO_2 (70%); (e) L-Selectride (91%).

Scheme IV



(Scheme IV). The mean rate constant at 25.4 °C for the previtamin-to-vitamin rearrangement of **9** to **24** was determined to be 5.34×10^{-5} s^{-1}. This corresponds to a half-life of 3.6 h and represents an approximate 20-fold rate enhancement when compared to the corresponding [1,7]-sigmatropic shift of previtamin D_3 ($t_{1/2} \approx 70$ h at 25 °C).[3] The HPLC purified previtamin was allowed to equilibrate with the vitamin **24** at 25.4 °C. To ensure that complete equilibration had been achieved, the purified vitamin **24** was also allowed to equilibrate with the previtamin **9** at the same temperature from the opposite direction (see the Experimental Section and supplementary material for details). The previtamin/vitamin ratio (**9**:**24**) at equilibrium was determined to be 12:88. This result was unexpected since, as was discussed in the Introduction, the anticipated trend was that the equilibria of vitamin D analogues with A-rings smaller than the six-membered ring of the parent previtamin D_3 (**1**) would be shifted mainly toward the previtamin form.

The 11β-dienynol **23** was also subjected to semihydrogenation in the presence of Lindlar catalyst to afford the 11β-OH previtamin **10** in 62% yield (Scheme IV). The mean rate constant at 25.4 °C for the previtamin-to-vitamin rearrangement was determined to be 2.65×10^{-5} s^{-1}, within a factor of two of that of the 11α-epimer **9**. This corresponds to a half-life of 7.3 h and represents an approximate 10-fold rate enhancement when compared to the [1,7]-sigmatropic shift of previtamin D_3 to vitamin D_3.[3] As in the case of the 11α-epimer **9**, the purified previtamin was allowed to equilibrate with the vitamin **25** and likewise the purified vitamin with the previtamin (see the Experimental section and the supplementary material for details). The previtamin–vitamin ratio (**10**/**25**) was determined to be 58:42 at 25.4 °C. Thus, inverting the carbinol center at C_{11} from 11α-OH to 11β-OH caused a significant shift in the position of the previtamin–vitamin equilibrium, favoring the vitamin form in the 11α-OH case and favoring slightly the previtamin form in the 11β-OH

(10) (a) Bernstein, P. R. *Tetrahedron Lett.* **1979**, 1015. (b) Eaton, P. E.; Jobe, P. G. *Synthesis* **1983**, 796. (c) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 1324.

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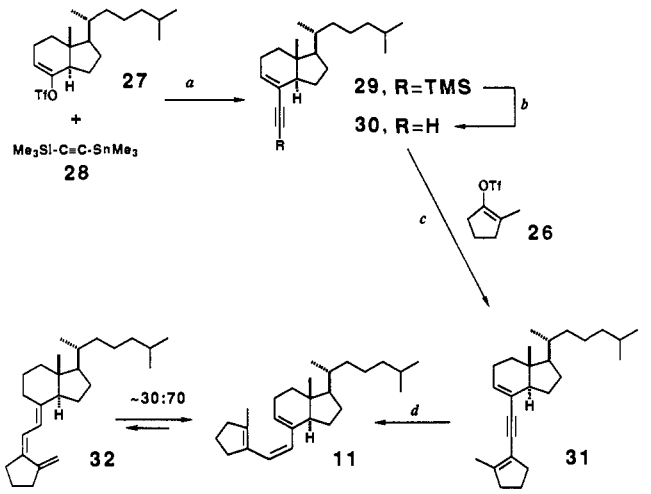
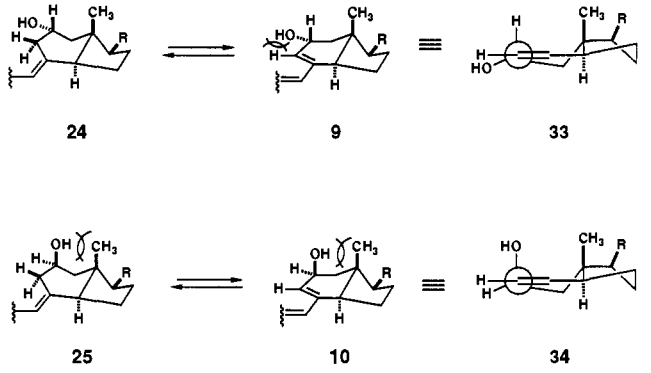
Scheme V[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, LiCl (86%); (b) TBAF, THF (68%); (c) $(PPh_3)_2Pd(OAc)_2$, CuI, Et_2NH, DMF (95%); (d) H_2, Lindlar (67%).

Scheme VI

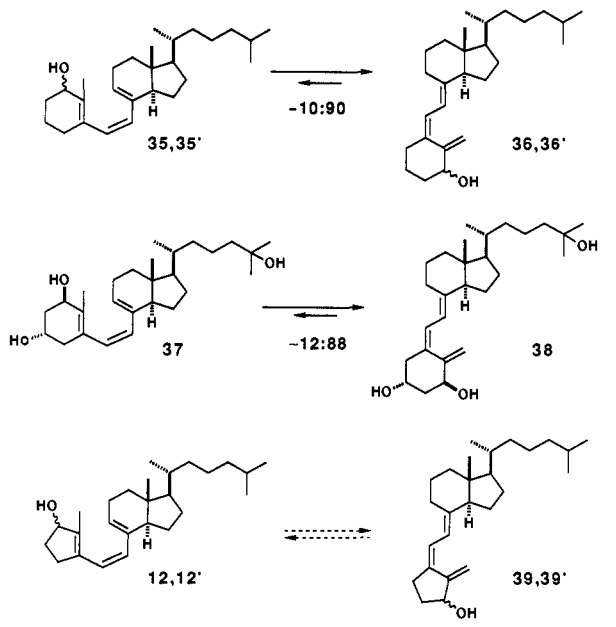


example. By contrast, there was no observable effect by the C_{11} hydroxyl group on the previtamin–vitamin equilibria of the A-homo analogues **3b** and **3c**,[1] both existing entirely in the vitamin form **4b** and **4c**. These unexpected results thus prompted a study of an *A*-norprevitamin D analogue lacking a hydroxyl altogether.

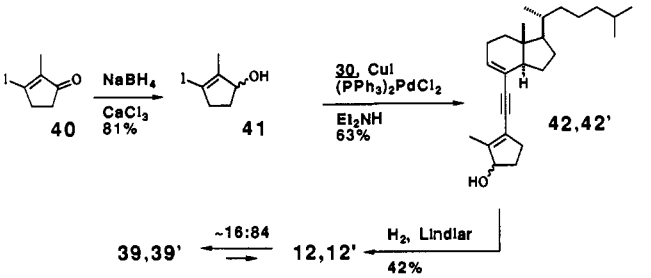
The enolate of commercially available 2-methylcyclopent-2-enone generated by its treatment with L-Selectride at −78 °C was reacted with $PhNTf_2$ to afford the volatile enol triflate **26** as the requisite A-ring fragment in 42% yield.[13a-d] Scheme V details the synthesis of the desired desoxy-*A*-nor analogue **11**. The known triflate **27** was coupled with stannyl silyl acetylene **28** under Stille conditions to afford the TMS-enyne **29**, which upon deprotection gave the CD fragment **30**. The A- and CD-fragments **26** and **30** were coupled to afford dienyne **31** in 95% yield by using the procedure of Cacchi.[14] The dienyne **31** was then semihydrogenated to afford the previtamin **11** and vitamin **32** as a nonpolar, inseparable mixture in 67% yield. The purified previtamin–vitamin mixture was allowed to equilibrate at 25.4 °C as described in the Experimental Section and supplementary material. The previtamin–vitamin equilibrium ratio was determined to be 70:30, and, as noted above, the equilibrium between the *A*-homo hydrocarbons **3a** and **4a** completely favors the latter.

To summarize the previtamin–vitamin equilibrium results described to this point, the intrinsic thermodynamic preference of the *A*-norprevitamin is to exist mainly in the previtamin form at equilibrium (K_{eq} = 70:30) as exemplified by the desoxy system

Scheme VII



Scheme VIII



11/32. However, when a hydroxyl group is introduced at the 11α position as in **9**, the equilibrium shifts to favor the vitamin form **24** (K_{eq} = 12:88). This is proposed to be due to developing $A_{1,2}$-strain[15] between the pseudoequatorial 11α-hydroxyl group and H_9 of the previtamin **9** which is relieved in the vitamin **24** as depicted in Scheme VI. The Newman projection of the CD ring **33** is drawn from the perspective of looking down the C_9–C_{11} single bond of the 11α-OH-previtamin **9**. From this view it is evident that the C_{11}-hydroxyl group and the C_9-hydrogen are nearly in an eclipsed relationship with one another ($A_{1,2}$-strain).

It is instructive to compare **9** and **24** with the 11-unsubstituted previtamin–vitamin system **11/32**, respectively. In the latter pair, the 11α-OH is absent as is the resulting $A_{1,2}$-strain. The equilibrium thus favors the previtamin **11** (70%) as suggested above for A-ring analogues with ring sizes smaller than that of the parent, six-membered ring vitamins.

The intermediate K_{eq} = 42:58 value observed for **25/10** is not so simply rationalized. Note that there exists a 1,3-diaxial interaction between the C_{11}-hydroxyl and the C_{18}-angular methyl group in the vitamin **34**, but this is also present in the previtamin **10**. This interaction may perhaps be more easily relieved in the previtamin **10** which possesses a more flexible half-chair C-ring (**34**). This can be envisaged to bend the 11β-C–O bond in **10** into the plane defined by $C_{8,9}$–H_9, and the consequent development of partial $A_{1,2}$-strain could account for the higher population of the vitamin form **25** (42%) than for the parent *A*-norvitamin **32** (30%). These effects are small however, and in light of the unexpected trend in these previtamin–vitamin equilibria, it is instructive to compare the *A*-nor series to other related compounds in the six-membered A-ring previtamin–vitamin series such as the 1-hydroxylated analogue **35/36** (Scheme VII),[16] a reasonable

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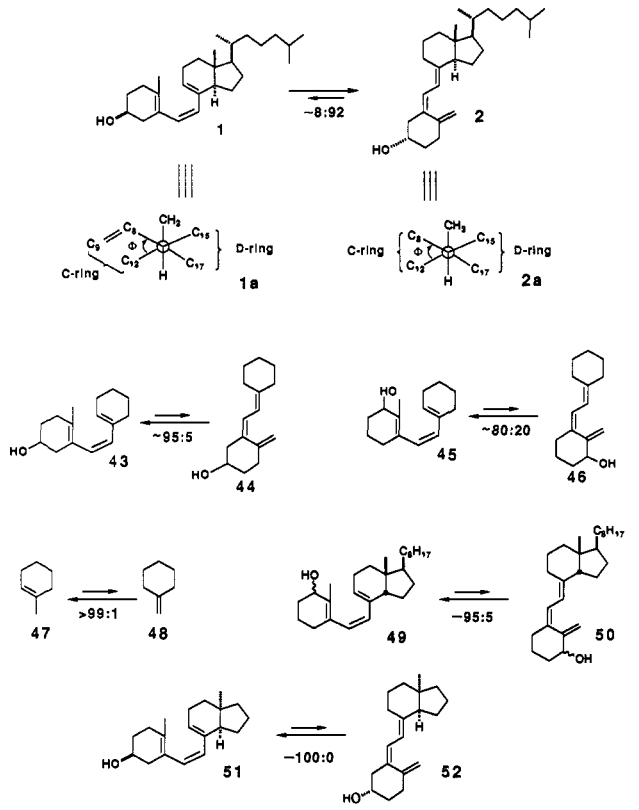
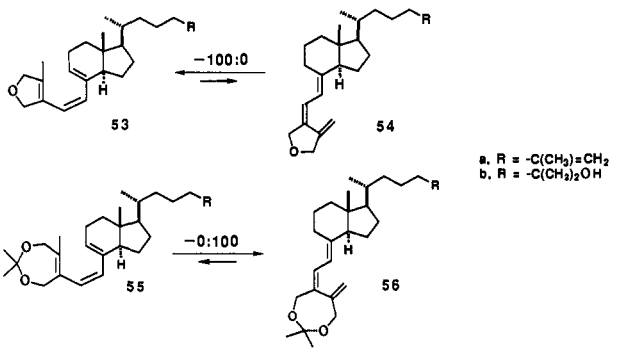
Scheme IX



model system for the hormonally active form of vitamin D (namely 1α,25-dihydroxyvitamin D_3 (**38**) and its previtamin form (**37**)[17]) and the oxacalciferol system **7**/**8** described earlier. It may be recalled that the surprising 1:1 equilibrium ratio observed between **7** and **8** was the reason for undertaking this *A*-nor project in the first place. Thus, the next goal was the synthesis and study of **12** (**12′**) and its vitamin form **39** (**39′**) as well as several oxygen containing A-ring analogues (vide supra).

The known iodo enone **40**[18] was reduced under Luche conditions[19] to afford the racemic iodo alcohol **41** (81%), which was coupled[20] to the enyne **30** (Scheme VIII) to afford the inseparable mixture of dienynols **42** and **42′** in 63% yield. The latter dienynol mixture was then semihydrogenated over Lindlar's catalyst to afford the separable epimeric vitamins **39** and **39′** and the inseparable mixture of previtamins **12** and **12′** in 42% yield. The purified previtamin mixture **12** and **12′** was allowed to equilibrate with the vitamin forms **39** and **39′** at 25.4 °C as described in the Experimental Section and supplementary material. Only one of the diastereomeric vitamins **39** or **39′** was obtained pure and was allowed to equilibrate separately with its previtamin form **12** or **12′**. In both instances, the mixture (**12** and **12′** and **39** and **39′**) and the purified vitamin (**12** or **12′** and **39** or **39′**), the previtamin–vitamin ratio at equilibrium was determined to be 84:16. The equilibrium position of the 1-OH-*A*-norprevitamins **12** and **12′** is shifted even further toward the previtamins when compared to **11**, i.e., 84/16 (Scheme V) versus 70/30 (Scheme VIII). This small shift in the equilibrium may be due to the presence of $A_{1,3}$-strain[15] present in vitamins **39** and **39′** between the C_1-hydroxyl group and the C_{19}-exocyclic methylene syn-hydrogen. This interaction is absent in desoxyvitamin **32**.

Scheme X



The predominance of the vitamin form in the equilibrium between natural vitamin and previtamin is attributed to CD ring (trans ring junction) strain present in previtamin. As shown in Scheme IX, when the D ring of the parent vitamin D_3 (**2**) and previtamin D_3 (**1**) (92:8 ratio) is removed, the resulting trienols **43** and **44** exist at equilibrium in a ratio of ~95:5 favoring previtamin type trienol **43**.[21] Moving the hydroxyl group to one of the allylic positions affords similarly the trienols **45** and **46** with an equilibrium ratio of ~80:20 also favoring the former previtamin-like isomer.[22] Havinga[21] has rationalized these phenomena by using 1-methylcyclohexane (**47**) as a reference compound. The double bond in 1-methylcyclohexene almost exclusively prefers to be endocyclic as in **47** rather than exocyclic as in **48** (**47**:**48** >99:1). Thus, the equilibrium results for **43** and **44** and **45** and **46** are not unexpected since they merely reflect this inherent thermodynamic bias.[23]

However, fusion of the D-ring onto trienol **43** and, particularly, formation of a *trans*-hydrindane system to afford the previtamin D–vitamin D structures **1** and **2**, creates torsional strain about the C_{13}–C_{14} bond.[21] In Scheme IX, a Newman projection viewed down the C_{14}–C_{13} bond is depicted for both the previtamin **1a** and the vitamin **2a**. The dihedral angle Φ for an unsubstituted cyclohexane is 55°. Fusion of the five-membered D-ring trans onto ring C in steroids tends to increase this angle slightly ($\Phi \approx 60°$), wherein as reference, the internal five-membered ring dihedral angle (C_{15}–C_{14}–C_{13}–C_{17}) has been estimated to be ~40°.[21] Introduction of the $\Delta^{8,9}$-double bond in the previtamin (**1a**) tends to decrease the angle Φ toward the 45° dihedral angle found in an unsubstituted cyclohexene. The result is that previtamin D_3 suffers significant strain about the angular positions. The previtamin relieves this strain by isomerizing the $\Delta^{8,9}$-double bond to the exocyclic position affording the observed predominance of the vitamin form (wherein Φ for methylenecyclohexane is ~53°)[21] in the previtamin D–vitamin D equilibrium. If the CD ring junction of the previtamin **1** is changed to the *cis*-hydrindane ring system as in **49**, no unusual strains is imposed on the C-ring by the endocyclic $\Delta^{8,9}$-double bond, and the previtamin–vitamin equilibrium now shifts in favor of the previtamin in a ratio of ~95:5 (**49**:**50**)[24] as in the case of **43**–**48**. Havinga has previously also shown that the *cis*-*C*/*D*-previtamin **51** shows no tendency to exist in the vitamin form **52**.[21]

In order to better evaluate the finding that **7** and **8** exist as a rapidly equilibrating 1:1 mixture of previtamin (**7**) and vitamin

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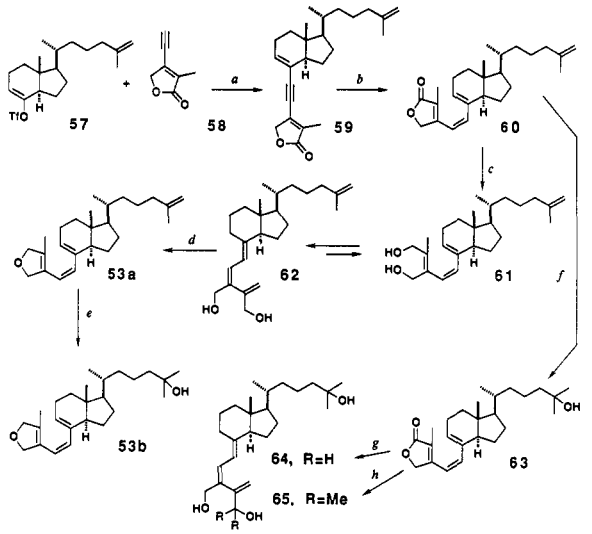
Scheme XI[a]



[a] Reagents: (a) $(PPh_3)_2PdCl_2$, Et_3N, DMF (86%); (b) H_2, Lindlar, quinoline, hexanes (64%); (c) Dibal-H (90%); (d) *n*-BuLi; TsCl; *n*-BuLi/THF (67%); (e) $Hg(OAc)_2$, THF-H_2O; $NaBH_4$, NaOH, MeOH (72%); (f) reagent (e) (70% plus 27% recovered **60**); (g) reagent (c) (56%); (h) MeLi, ether (56%).

(**8**) forms, particularly in connection with the hypothesis that this result is merely a reflection of a ring size effect, we next turned to a study of the oxa analogues **53**/**54** and **55**/**56**. These analogues were of particular interest since the oxacalciferol analogue **7**/**8** as their 25-hydroxylated counterparts proved to be exceedingly potent inhibitors of the enzyme 25-hydroxyvitamin D_3-1α-hydroxylase,[7] which is involved in the final step of the metabolic activation of vitamin D_3 to **38**. In short, **53**/**54** has been determined to exist primarily if not exclusively as the previtamin **53**, whereas **55**/**56** was observed to exist solely as the vitamin form **56** (Scheme X). These observations are consistent with the hypothesis that the smaller ring size favors the previtamin form, whereas the larger ring size favors the vitamin form. Schemes XI and XII outline the preparation of both the precursor unsaturated side-chain forms **53a**/**54a** and **55a**/**56a** as well as their 25-hydroxylated forms **53b**/**54b** and **55b**/**56b**, respectively. The biological evaluation of **53b** and **56b** will be described elsewhere.

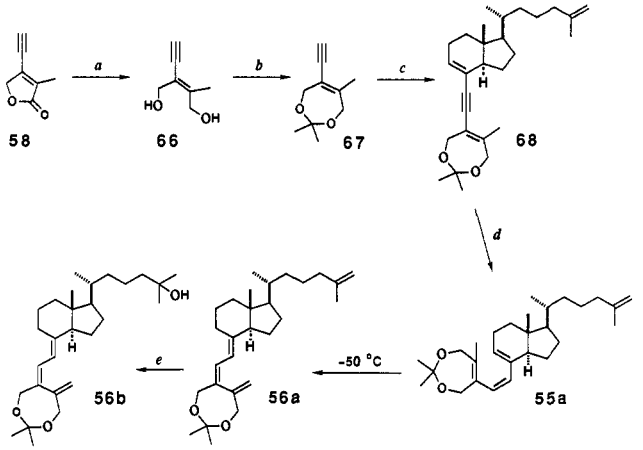
As shown in Scheme XI, cross coupling of the known CD[6] and A-ring fragments,[6,25] **57** and **58**, respectively, followed by semihydrogenation of the diene **59** afforded the key previtamin lactone **60** in a manner analogous to the preparation of **7**/**8**. The reduction of **60** afforded diol **61** which upon standing at ambient temperature completely isomerized to the secovitamin form **62**. Upon ring closure there resulted only the previtamin structure **53a**. The latter could then be oxymercurated–demercurated to the desired 25-hydroxy counterpart **53b**. As a compliment to our earlier studies, the lactone **60** could also be oxymercurated–demercurated to the 25-hydroxy lactone **63** which in turn could be reduced to additional A-seco vitamins **64** and **65**. We were unable to transform **62** directly to **64**.

Scheme XII outlines a similar scheme used to synthesize the *A*-homo dioxa analogues **56a** and **56b**. In this scheme, the known lactone **58** was first reduced to the exceptionally water soluble diol **66**, whose acetonide could be transformed to **68** and then **55a** through a similar cross coupling/semihydrogenation sequence described in Scheme XI. The previtamin structure **55a** slowly isomerized completely to the corresponding vitamin form **56a** on standing at room temperature. Analogous oxymercuration–demercuration then completed the synthesis of **56b**.

Summary

The rearrangement of 11α-OH-*A*-norprevitamin D analogue **9** to its vitamin form **24** was determined to be ~20 times faster than that of previtamin D_3 (**1**) to vitamin D_3 (**2**). Similarly, the transformation of the 11β-OH-*A*-norprevitamin **10** was determined

Scheme XII[a]



[a] Reagents: (a) Dibal-H (69%); (b) acetone, $FeCl_3$ (78%); (c) **57**, $(PPh_3)_2PdCl_2$, DMF (79%); (d) H_2, Lindlar, quinoline, hexanes (~96%, crude); (e) $Hg(OAc)_2$, THF-H_2O; $NaBH_4$, NaOH, MeOH (62%).

to be ~10 times faster than that of the same parent previtamin D_3 (**1**). In addition, the position of the hydroxyl group relative to the triene moiety of *A*-norprevitamins **9**–**12** was determined to have diverse effects on the position of the previtamin–vitamin equilibrium. Together with the results for the oxa analogues **53**/**54** and **55**/**56** and our earlier results for **3**/**4**, **5**/**6**, and **7**/**8**, it appears that the smaller A-ring size favors the previtamin structure and the larger A-ring favors the vitamin form, but small structural changes can readily influence the equilibrium (e.g., the 11-OH group in the *A*-nor series). While the observed equilibrium changes are explicable on the basis of a nonbonded substituent steric effects superimposed upon ring size (strain) effects, the origin of the observed rate enhancements of the [1,7]-shift in the *A*-nor series compared to the six-membered A-ring natural series is less clear. Computations to determine whether or not conformational factors are influencing the rates of the [1,7]-sigmatropic hydrogen shifts of the *A*-nor previtamin D analogues versus previtamin D_3 are in progress.[26]

Experimental Section[27]

(6*Z*)-*A*-Nor-9,10-secocholesta-5(10),6,8-trien-11α-ol (9) and (5*Z*,7*E*)-*A*-Nor-9,10-secocholesta-5,7,10(19)-trien-11α-ol (24). A mixture of dienynol **21** (10 mg, 0.027 mmol), Lindlar catalyst (41 mg), and quinoline (0.13 mL, 0.17 M solution in hexanes) in hexanes (3 mL) was exposed to hydrogen gas for 2 h (room temperature, ~1 atm).

(25) Bilinski, V.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 1734.

(26) It has become apparent that presently available molecular mechanics programs will need to be more satisfactorily parameterized to handle conjugated hexatrienes such as those present in the vitamin D/previtamin D system. We thank Professor M. M. Midland of this department for collaborative input on this matter.

(27) More comprehensive spectral and other analytical data along with a detailed description of the kinetic studies are presented in the supplementary material section. All experiments involving air- and/or moisture-sensitive materials were carried out under a nitrogen or argon atmosphere, which was dried prior to use by passage through a column of KOH layered with $CaSO_4$. Tetrahydrofuran, ether, and benzene were distilled from sodium benzophenone ketyl immediately prior to use. Hexanes was distilled from CaH_2. Unless otherwise indicated for workup procedures, organic solutions were dried over $MgSO_4$, filtered, and then finally concentrated on a rotary evaporator at reduced pressure. High-pressure liquid chromatography (HPLC) was performed by using a Rheodyne 7125 sample injector, Waters 6000A or 510 pump, a Waters R401 refractive index detector, and a Rainin Dynamax 60A silica column, or Whatman Partisil M9 column unless otherwise noted. Flash chromatography was performed by using silica gel (EM Science, 230–400 mesh), and thin-layer chromatography (TLC) was run on a plastic plate precoated with silica gel (Kodak, 0.25 mm) and developed by spraying with a 15% ethanol solution of phosphomolybdic acid. The purity of all new compounds was judged by a combination of HPLC and ^1H and ^{13}C NMR analysis before mass spectral determination. Satisfactory combustion analyses were also obtained for selected compounds. For other new compounds, the level of purity is indicated by the inclusion of copies of NMR spectra presented in the supplementary material.

Filtration of the reaction mixture through Celite followed by concentration afforded a residue which was kept under vacuum overnight and then subjected to HPLC purification (10% EtOAc/hexanes) to yield the previtamin **9** (1 mg, 10%, eluted first) and the vitamin **24** (3 mg, 30%, eluted second) as colorless oils: ^{1}H NMR ($CDCl_3$) (88/12 vitamin/previtamin mixture at equilibrium). Vitamin: δ 0.58 (3 H, $C_{18}CH_3$, s), 0.86 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.4$ Hz), 0.95 (3 H, $C_{21}CH_3$, d, $J \sim 6$ Hz; overlapping with previtamin $C_{21}CH_3$), 3.17 (1 H, $H_{9\beta}$, dd, $J \sim 12.8$ Hz, 4.7 Hz), 3.89 (1 H, H_{11}, $W \sim 28$ Hz), 5.15 (1 H, $H_{19E \text{ or } Z}$, br s), 5.29 (1 H, $H_{19Z \text{ or } E}$, br s), 6.28 (1 H, H_7, $J \sim 11.4$ Hz), 6.41 (1 H, H_6, d, $J \sim 11.4$ Hz). Previtamin: δ 0.74 (3 H, $C_{18}CH_3$, s), 0.86 (6 H, $C_{26,27}2CH_3$, buried underneath $C_{26,27}$ d of vitamin form), 0.97 (3 H, $C_{21}CH_3$, d, $J \sim 6$ Hz), 2.55 (1 H, $H_{12\alpha \text{ or } 12\beta}$, dd, $J \sim 12.7$ Hz, 7.3 Hz), 4.46 (1 H, H_{11}, br m, $W \sim 24$ Hz), 5.37 (1 H, H_9, br s, $W \sim 7$ Hz), 5.68 (1 H, $H_{6 \text{ or } 7}$, d, $J \sim 12.1$ Hz), 6.16 (1 H, $H_{7 \text{ or } 6}$, d, $J \sim 12.1$ Hz).

The thermal [1,7]-hydrogen rearrangement of the previtamin to the vitamin was followed by 300-MHz ^{1}H NMR analysis until complete equilibration had occurred. The same equilibration experiment was carried out on the vitamin. Both experiments afforded essentially the same equilibrium value: previtamin/vitamin ratio = 12/88 (25.4 °C). The experimental details are presented in the supplementary material.

(6*Z*)-*A*-Nor-9,10-secocholesta-5(10),6,8-trien-11β-ol (10) and (5*Z*,7*E*)-*A*-Nor-9,10-secocholesta-5,7,10(19)-trien-11β-ol (25). The dienynol **23** (6.4 mg, 0.017 mmol) with Lindlar catalyst (30 mg) and quinoline (0.08 mL, 0.17 M solution in hexanes) in hexanes (3 mL) was reduced and then worked up (HPLC, 10% EtOAc/hexanes) as in the preceding experiment to yield the mixture of **10** (eluted first) and **25** (eluted second) (4 mg total, 62%) as a colorless oil: ^{1}H NMR ($CDCl_3$) (42/58 vitamin/previtamin mixture at equilibrium). Vitamin: δ 0.79 (3 H, $C_{18}CH_3$, s), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.5$ Hz, overlaps with $C_{26,27}2CH_3$ of previtamin), 0.95 (3 H, $C_{21}CH_3$, d, $J \sim 6.1$ Hz), 2.93 (1 H, $H_{9\beta}$, br d, $J \sim 14.4$ Hz), 4.25 (1 H, $H_{11\alpha}$, br, $W \sim 15$ Hz), 5.17 (1 H, $H_{19E \text{ or } Z}$, br s), 5.33 (1 H, $H_{19Z \text{ or } E}$, br s), 6.42 (1 H, H_7, d, $J \sim 12$ Hz), 6.46 (1 H, H_6, d, $J \sim 12$ Hz). Previtamin: δ 0.85 (3 H, $C_{18}CH_3$, s, overlaps with $C_{26,27}2CH_3$ signal), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.5$ Hz, overlaps with $C_{26,27}2CH_3$ of vitamin), 0.99 (3 H, $C_{21}CH_3$, d, $J \sim 6.4$ Hz), 1.76 (3 H, $C_{19}CH_3$, s), 4.38 (1 H, $H_{11\alpha}$, $W \sim 13$ Hz), 5.50 (1 H, H_9, br, $W \sim 7$ Hz), 5.73 (1 H, $H_{6 \text{ or } 7}$, d, $J \sim 12.2$ Hz), 6.18 (1 H, $H_{7 \text{ or } 6}$, d, $J \sim 12.2$ Hz).

The thermal [1,7]-hydrogen rearrangement of the previtamin to the vitamin as well as that of vitamin to previtamin were followed by 300-MHz ^{1}H NMR analysis until complete equilibration had occurred. Both experiments afforded essentially the same equilibrium value: previtamin–vitamin ratio = 58:42 (25.4 °C). The experimental details are presented in the supplementary material.

(6*Z*)-*A*-Nor-9,10-secocholesta-5(10),6,8-triene (11) and (5*Z*,7*E*)-*A*-Nor-9,10-secocholesta-5,7,10(19)-triene (32). Dienynol **31** (6 mg, 0.017 mmol) with Lindlar catalyst (60 mg) and quinoline (0.08 mL, 0.17 M solution in hexanes) in hexanes (4 mL) was reduced and then worked up as above to afford a residue which was subjected to HPLC purification (hexanes). An inseparable mixture of trienes **11** and **32** (4 mg, 67%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) (30/70 vitamin/previtamin mixture at equilibrium). Vitamin: δ 0.58 (3 H, $C_{18}CH_3$, s), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.4$ Hz), 0.94 (3 H, $C_{21}CH_3$, d, $J \sim 6.4$ Hz), 2.85 (1 H, $H_{9\beta}$, br d, $J \sim 12$ Hz), 5.16 (1 H, $H_{19Z \text{ or } E}$, br s), 5.33 (1 H, $H_{19E \text{ or } Z}$; superimposed on H_9 of previtamin), 6.25 (1 H, H_7, d, $J \sim 11.4$ Hz), 6.43 (1 H, H_6, d, $J \sim 11.4$ Hz). Previtamin: δ 0.73 (3 H, $C_{18}CH_3$, s), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.4$ Hz), 0.96 (3 H, $C_{21}CH_3$, d, $J \sim 6.6$ Hz), 1.76 (3 H, $C_{19}CH_3$, s), 5.33 (1 H, H_9, br s; overlaps with a H_{19} of vitamin), 5.72 (1 H, $H_{7 \text{ or } 6}$, d, $J \sim 12.0$ Hz), 6.10 (1 H, $H_{6 \text{ or } 7}$, d, $J \sim 12.0$ Hz).

The previtamin–vitamin ratio at equilibrium (25.4 °C) was determined to be 70:30 (300-MHz ^{1}H NMR spectral analysis). Because of the inseparability of the hydrocarbon (previtamin–vitamin) mixture, the equilibration could be followed from only one direction. However, the equilibration time was estimated to be sufficient based on the reaction times required for the 11α- and 11β-hydroxy compounds. The details are presented in the supplementary material section.

(6*Z*)-*A*-Nor-9,10-secocholesta-5(10),6,8-trien-1-ol (12 and 12′) and (5*Z*,7*E*)-*A*-Nor-9,10-secocholesta-5,7,10(19)-trien-1-ol (39 and 39′). Dienynols **42** and **42′** (13 mg, 0.035 mmol) with Lindlar catalyst (106 mg) and quinoline (0.05 mL, 0.17 M solution in hexanes) in hexanes (5 mL) was hydrogenated and then worked up as described above. The crude materials was subjected to HPLC purification (10% EtOAc/hexanes) to yield the previtamin–vitamin mixture **12** and **12′** and **39** and **39′** (5.5 mg, 42%) as a colorless oil. One epimeric vitamin was eluted first (vitamin isomer A) followed by the second epimer (vitamin isomer B) under normal phase HPLC conditions. The epimeric previtamin mixture was then eluted third as an inseparable mixture. ^{1}H NMR ($CDCl_3$) (a mixture of both C-1 epimers of vitamin and previtamin). Vitamin: δ 0.58 (3 H, $C_{18}CH_3$, s), 2.85 (1 H, $H_{9\beta}$, d with fine structure, $J \sim 11.5$ Hz), 4.53 (1 H, H_1, m, partially buried under H_1 of the previtamin), 5.36 (1 H, $H_{19E \text{ or } Z}$; buried under H_9 of previtamin), 5.48 (1 H, $H_{19Z \text{ or } E}$, br s), 6.24 (1 H, H_7, d, $J \sim 11.6$ Hz), 6.47 (1 H, H_6, d, $J \sim 11.6$ Hz). Previtamin: δ 0.71 (3 H, $C_{18}CH_3$, s), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.6$ Hz), 0.95 (3 H, $C_{21}CH_3$, d, $J \sim 6.4$ Hz), 1.80 (3 H, $C_{19}CH_3$, s), 4.59 (1 H, H_1, br, $W \sim 16$ Hz), 5.36 (1 H, H_9, br s, $W \sim 11$ Hz), 5.85 (1 H, $H_{7 \text{ or } 6}$, d, $J \sim 12.0$ Hz), 6.06 (1 H, $H_{6 \text{ or } 7}$, d, $J \sim 12.0$ Hz).

In order to determine the equilibrium constant for the 1-OH previtamin–vitamin interconversion, the mixture of previtamins **12** and **12′** and vitamin isomer A were isolated separately. The thermal [1,7]-hydrogen rearrangement of the epimeric mixture of previtamins **12** and **12′** to the vitamin mixture (isomers A and B) was followed by 300-MHz ^{1}H NMR analysis until complete equilibration had occurred. The same equilibration experiment was carried out on the separate sample of HPLC purified vitamin isomer A. Both experiments afforded the same equilibrium value (previtamin vitamin ratio = 84:16 at 25.4 °C) as presented in the supplementary material.

2-(Hydroxymethylene)cyclopentanone (14). This compound was prepared following a known procedure.[10b] The keto aldehyde **14** was obtained in 56% yield as a yellow solid sufficiently pure for the next step. A sample for spectral characterization was prepared by subjecting the α-formyl ketone to HPLC purification (25% EtOAc/hexanes): white solid, mp 70–72 °C (lit.[10b] mp 74–76 °C).

2-((*n*-Butylthio)methylene)cyclopentanone (15). To a solution of **14** (3.038 g, 0.027 mmol) in benzene (50 mL) was added *n*-butanethiol (3.76 mL, 0.035 mmol), $MgSO_4$ (4.21 g, 0.035 mmol), and *p*-toluenesulfonic acid (0.103 g, 2 mol %). The mixture was stirred at room temperature for 7 h and then filtered. The filtrate washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL) and then dried. Concentration afforded a red-brown oil which was flash chromatographed (7% EtOAc/hexanes) to afford the thioether **15** (4.04 g, 81%) as a yellow oil sufficiently pure for use in the next step. A sample for spectral characterization was prepared by HPLC purification of the oil (10% EtOAc/hexanes): ^{1}H NMR ($CDCl_3$) δ 0.92 (3 H, CH_3, t, $J \sim 7.1$ Hz), 1.42 (2 H, sextet, $J \sim 7.3$ Hz), 1.7 (2 H, m), 1.9 (2 H, m), 2.31 (2 H, m), 2.50 (2 H, td, $J \sim 7.1$ Hz, 2.5 Hz), 2.83 (2 H, t, $J \sim 7.3$ Hz), 7.37 (1 H, t, $J \sim 2.5$ Hz).

2-Methyl-1-cyclopentenecarboxaldehyde (16). The synthesis of this compound was achieved following a known procedure for the corresponding 3-substituted derivatives.[10a] The aldehyde **16** was isolated in ~50% yield (from ketone **15**) as a volatile oil. The aldehyde was not completely free of solvent, but the material was adequately pure for the next step.

1-(2,2-Dibromoethenyl)-2-methylcyclopent-1-ene (17). To a mixture of zinc dust (1.68 g, 25.7 mmol) and triphenylphosphine (6.74 g, 25.7 mmol, recrystallized from ether) in dry CH_2Cl_2 (25 mL) was added CBr_4 (8.52 g, 25.7 mmol) in dry CH_2Cl_2 (25 mL) via cannula at room temperature. The resulting suspension was stirred for 24 h at room temperature. The aldehyde **16** (0.429 g, 3.9 mmol) in CH_2Cl_2 (2 mL) was then introduced via syringe to the reaction mixture, and then the latter was stirred for 1 h at room temperature. Workup was accomplished by dilution of the mixture with pentane (200 mL), filtration through Celite to remove the insoluble material, and evaporation of the pentane/CH_2Cl_2. The insoluble material was subjected to additional cycles (4×) of CH_2Cl_2 extraction and pentane precipitation to remove the olefinic product. After concentration of the pentane extract, the resulting oil was taken up in hexanes and passed through a short column of silica gel (7 × 1.5 cm) to afford after evaporation of solvent the dibromoolefin **17** (0.170 g, 68%) as a colorless volatile oil which turned yellow readily upon standing. A sample for spectral characterization was prepared by subjecting the dibromoolefin to HPLC purification (hexanes): ^{1}H NMR ($CDCl_3$) δ 1.71 (3 H, CH_3, s), 1.81 (2 H, CH_2, apparent quintet, $J \sim 7.5$ Hz), 2.25 (2 H, pseudo t, $J \sim 7.2$ Hz), 2.80 (2 H, pseudo t, $J \sim 6.0$ Hz), 7.21 (1 H, vinyl, s).

De-*A*,*B*-9α,11α-oxidocholestan-8-one (18). The preparation of this substance was achieved in 63% yield as described previously.[1]

***A*-Nor-9α,11α-oxido-9,10-secocholest-5(10)-en-6-yn-8β-ol (19).** To a solution of dibromoolefin **17** (0.356 g, 1.33 mmol) in dry THF (5 mL) at −78 °C was added *n*-BuLi (1.66 mL, 1.61 M solution in hexanes, 2.67 mmol) dropwise. The resulting orange solution was stirred at −78 °C for 30 min and at room temperature for 1 h. The solution was again cooled to −78 °C, and the epoxy ketone **18** (0.263 g, 0.95 mmol) in THF (2 mL) was added via cannula. The solution was warmed to room temperature and stirred for 30 min. The reaction was quenched with water and extracted with ether (1 × 25 mL). The ether layer was washed with saturated $NaHCO_3$ and dried. Concentration afforded a dark orange oil which was purified by HPLC (10% EtOAc/hexanes) to yield the propargyl alcohol **19** (0.282 g, 77%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.8–0.9 (12 H, $C_{18,21,26,27}4CH_3$, overlapping singlets and doublets), 1.82

(3 H, $C_{19}CH_3$, s), 2.3–2.5 (4 H, $C_{1,3}2CH_2$, m), 3.28 (2 H, $H_{9,11}$, m).

A-Nor-9α,11α-oxido-9,10-secocholest-5(10)-en-6-yn-8β-yl Benzoate (20). To a solution of epoxy propargyl alcohol **19** (0.251 g, 0.65 mmol) in dry THF (5 mL) at −78 °C was added *n*-BuLi (0.88 mL, 1.61 M solution in hexanes, 1.41 mmol) dropwise via syringe. The solution was warmed to room temperature and stirred for 1 h. After recooling the solution to −78 °C, benzoyl chloride (0.18 mL, 1.6 mmol) was added as a neat liquid. The solution was then brought to room temperature and stirred for 30 min. Water (5 mL) and ether (20 mL) were added, the layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and dried. Concentration of the ethereal solution afforded an orange oil which was purified by HPLC (5% EtOAc/hexanes) to yield the epoxy propargyl benzoate **20** (0.251 g, 79%) as an amorphous white foam: ^1H NMR ($CDCl_3$) δ 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.6$ Hz), 0.91 (3 H, $C_{21}CH_3$, d, $J \sim 6.5$ Hz), 0.99 (3 H, $C_{18}CH_3$, s), 1.82 (3 H, $C_{19}CH_3$, s), 2.3–2.5 (4 H, m), 3.27 (1 H, H_{11}, dd, $J \sim 5.3$ Hz, 3.1 Hz), 4.19 (1 H, H_9, d, $J \sim 3.1$ Hz), 7.4–7.6 (3 H, m), 8.0 (2 H, m).

A-Nor-9,10-secocholesta-5(10),8-dien-6-yn-11α-ol (21). To a suspension of samarium powder (0.451 g, 3.0 mmol) in dry THF (5 mL) was added a solution of 1,2-diiodoethane (0.724 g, 2.57 mmol) in THF (5 mL) under argon at room temperature via cannula. After stirring for 1 h, a deep blue solution was obtained, and a solution of epoxy propargyl benzoate **20** (0.251 g, 0.51 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.018 g, 3 mol %) in THF (7 mL) was added via cannula. The deep blue color persisted, and the solution was stirred for 1 h. Water (5 mL) was added, and the mixture was stirred until it became yellow. Solid Na_2CO_3 was added to separate the layers, the entire mixture was extracted with ether (2 × 25 mL), and the organic layers were combined and dried. Concentration gave a dark orange oil which was subjected to HPLC purification (10% EtOAc/hexanes) to give the dienynol **21** (0.168 g, 89%) as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.72 (3 H, $C_{18}CH_3$, s), 0.85 (6 H, $C_{26,27}2CH_3$, overlapping d, $J \sim 6.7$ Hz), 0.95 (3 H, $C_{21}CH_3$, d, $J \sim 6.2$ Hz), 1.84 (3 H, $C_{19}CH_3$, s), 4.41 (1 H, H_{11}, ddd, $J \sim 12.9$ Hz, 7.0 Hz, 3.1 Hz), 5.91 (1 H, H_9, dd, $J \sim 3.1$ Hz, 3.1 Hz).

A-Nor-9,10-secocholesta-5(10),8-dien-6-yn-11-one (22). To a suspension of MnO_2 (156 mg, 1.79 mmol) in hexanes (8 mL) under argon was added dienynol **21** (34 mg, 0.09 mmol) in hexanes (4 mL) at room temperature. The mixture was stirred for 1.5 h and then filtered through Celite. Concentration afforded the dienynone **22** (24 mg, 70%) as a viscous oil sufficiently pure for use in the next step. A sample for spectral characterization was prepared by HPLC purification (5% EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 0.82 (3 H, $C_{18}CH_3$, s), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.3$ Hz), 0.92 (3 H, $C_{21}CH_3$, d, $J \sim 5.7$ Hz), 1.90 (3 H, $C_{19}CH_3$, s), 2.31 (1 H, $H_{12\alpha \text{ or } 12\beta}$, d, $J \sim 16.6$ Hz), 2.4–2.6 (4 H, m), 2.69 (1 H, H_{14}, ddd, $J \sim 12.4$ Hz, 7.1 Hz, 2.9 Hz), 2.83 (1 H, $H_{12\alpha \text{ or } 12\beta}$, d, $J \sim 16.6$ Hz), 6.14 (1 H, H_9, d, $J \sim 2.9$ Hz).

A-Nor-9,10-secocholesta-5(10),8-dien-6-yn-11β-ol (23). To a solution of dienynone **22** (2.2 mg, 0.006 mmol) in dry THF (1 mL) at −78 °C was added L-Selectride (0.012 mL, 1.0 M in THF, 0.012 mmol) dropwise. The solution was stirred for an additional 2 h at −78 °C and then warmed to 0 °C. A solution of NaOH (1 M, 0.015 mL) and 30% H_2O_2 (0.015 mL) were added successively, and the mixture was brought to room temperature. Water (5 mL) and ether (5 mL) were added, and the layers were separated. The aqueous phase was extracted once with ether, and the combined organic layers were dried. Concentration afforded **23** (2.0 mg, 91%) as a viscous oil, sufficiently pure for use in the next step. A sample for spectral characterization was obtained by HPLC purification (10% EtOAc/hexane): ^1H NMR ($CDCl_3$) δ 0.84 (3 H, $C_{18}CH_3$, s), 0.87 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.6$ Hz), 0.97 (3 H, $C_{21}CH_3$, d, $J \sim 6.4$ Hz), 1.86 (3 H, $C_{19}CH_3$, s), 2.25 (1 H, d, $J \sim 14.4$ Hz), 2.3–2.5 (4 H, m), 4.39 (1 H, H_{11}, br peak, $W \sim 15$ Hz), 6.04 (1 H, H_9, dd, $J \sim 3.4$ Hz, 3.4 Hz).

2-Methylcyclopent-1-en-1-yl Trifluoromethylsulfonate (26). The triflate **26** was obtained in 42% yield as a colorless, volatile oil by using a known procedure.[13a-d]

De-A,B-cholest-8-en-8-yl Trifluoromethylsulfonate (27). The enol triflate **27**[11c] was obtained in 85% yield as a colorless oil according to a previously published procedure.[11b]

Trimethyl[(trimethylstannyl)ethynyl]silane (28). The silylstannylacetylene **28** (bp 50 °C, 1.5 mm) was obtained in 88% yield as a light yellow oil following the procedure of Stille.[13e,f]

De-A,B-8-[(trimethylsilyl)ethynyl]cholest-8-ene (29). The TMS-enyne **29** was obtained in 86% yield as a colorless oil as previously described.[16a]

De-A,B-8-ethynylcholest-8-ene (30). The enyne **30** was obtained in 68% yield as a colorless oil as described previously.[11c]

A-Nor-9,10-secocholesta-5(10),8-dien-6-yne (31). To a solution of enyne **30** (0.142 g, 0.52 mmol) and vinyl triflate **26** (0.137 g, 0.60 mmol) in DMF (1 mL) and Et_2NH (1 mL) was added $(PPh_3)_2Pd(OAc)_2$ (8 mg, 0.011 mmol, 2 mol %) and CuI (10 mg, 0.052 mmol, 10 mol %). After stirring the mixture at room temperature for 1.5 h, water (5 mL) and ether (10 mL) were added, and then the layers were separated. The aqueous phase was extracted with ether (1 × 10 mL), and the combined organic layers were dried. Concentration and then chromatographic purification (silica gel, 7 × 1.5 cm, hexanes) afforded **31** (0.174 g, 95%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.73 (3 H, $C_{18}CH_3$, s), 0.88 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.4$ Hz), 0.96 (3 H, $C_{21}CH_3$, d, $J \sim 6.3$ Hz), 1.85 (3 H, $C_{19}CH_3$, s), 2.3–2.5 (4 H, m), 5.95 (1 H, H_9, apparent d, $J \sim 2.4$ Hz).

3-Iodo-2-methylcyclopent-2-en-1-one (40). The iodo enone **40** was obtained as a white solid which was recrystallized from hexanes to afford white needles (69% yield, mp 54–56 °C; lit.[18] mp 52–53 °C).

3-Iodo-2-methylcyclopent-2-en-1-ol (41). To an ice cold solution of iodo enone **40** (0.444 g, 2.0 mmol) in 0.4 M $CeCl_3$/MeOH (5 mL) was added $NaBH_4$ (0.076 g, 2.0 mmol) in portions. After addition was complete, the mixture was warmed to room temperature and stirred for 30 min. Water (10 mL) was added, and the mixture was extracted with ether (2 × 20 mL). The combined organic layers were washed with water and dried. Concentration followed by refrigeration afforded the iodo alcohol **41** (0.362 g, 81%) as a white crystalline solid (mp 37–38 °C): ^1H NMR ($CDCl_3$) δ 1.77 (1 H, m), 1.79 (3 H, CH_3, s), 2.3 (1 H, m), 2.5 (1 H, m), 2.7 (1 H, m), 4.5 (1 H, m).

A-Nor-9,10-secocholesta-5(10),8-dien-6-yn-1-ol (42 and 42′). To a solution of enyne **30** (115 mg, 0.42 mmol) and iodo alcohol **41** (95 mg, 0.42 mmol) in dry Et_2NH (3 mL) under argon was added $(PPh_3)_2PdCl_2$ (29 mg, 0.041 mmol) and CuI (16 mg, 0.084 mmol) together in one portion. After the mixture was stirred in the dark for 3 h at room temperature, the solvent was removed, and then water (5 mL) and ether (10 mL) were added. The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic layers were dried. Concentration and then HPLC purification (20% EtOAc/hexanes) gave dienynols **42** and **42′** (98 mg, 63%) as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.70 (3 H, $C_{18}CH_3$, s), 0.86 (6 H, $C_{26,27}2CH_3$, d, $J \sim 6.4$ Hz), 0.94 (3 H, $C_{21}CH_3$, d, $J \sim 6.4$ Hz), 1.87 (3 H, $C_{19}CH_3$, s), 4.6 (1 H, H_1, m), 5.99 (1 H, H_9, ddd, $J \sim 3$ Hz, 3 Hz, 3 Hz).

(6Z)-9,10-Seco-A-nor-2-oxacholesta-5(10),6,8,25-tetraene (53a). To a solution of the diol **62** (34.6 mg, 0.093 mmol) in THF (0.5 mL) at 0 °C was added *n*-BuLi (64 μL, 1.6 M in hexanes, 0.10 mmol) and the mixture was stirred for 30 min. A solution of *p*-toluenesulfonyl chloride (18.6 mg, 0.098 mmol) in THF (0.5 mL) was added dropwise via syringe. After stirring for 1 h, *n*-BuLi (64 μL, 1.6 M in hexanes, 0.10 mmol) was added again with ice cooling. The resulting solution was then heated (oil bath) at 60 °C for 4 h. After cooling, the solution was diluted with ether and washed with H_2O (5 mL). The aqueous layer was extracted with ether (5 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated, and then the crude residue was flash chromatographed (silica gel, 2.5% EtOAc/hexanes). The less polar fractions were combined and further purified by HPLC (5% EtOAc/hexanes) to afford after removal of solvent 22.2 mg of the ether **53a** (67%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.70 (3 H, $C_{18}CH_3$, s), 0.95 (3 H, $C_{21}CH_3$, d, $J \sim 6.3$ Hz), 1.71 (3 H, $C_{27}CH_3$, s), 1.76 (3 H, $C_{19}CH_3$, s), 4.51 (2 H, br s), 4.68 (4 H, br s), 5.32 (1 H, H_9, br s), 5.81 (1 H, H_7, d, $J \sim 11.7$ Hz), 6.02 (1 H, H_6, d, $J \sim 11.7$ Hz).

(6Z)-9,10-Seco-A-nor-25-hydroxy-2-oxacholesta-5(10),6,8-triene (53b). Mercuric acetate (7.0 mg, 0.022 mmol) dissolved in water (0.7 mL) and THF (0.7 mL) were added to give a fine yellow suspension. The yellow suspension was then added via cannula to a stirred solution of **53a** (7.1 mg, 0.02 mmol) in THF (0.7 mL) at room temperature under argon. After 5 h, 0.5 mL of 1 M NaOH followed by 0.5 mL of 0.5 M $NaBH_4$ in 1 M NaOH was added. After stirring for 1 min, ether (5 mL) was added, the organic layer was separated, and the aqueous layer was extracted with ether (4 × 7 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue in ether (5 mL) was passed through a short column of silica gel. The concentrated product was subjected to HPLC purification (30% EtOAc/hexanes) to afford 5.4 mg of **53b** (72%) as an oil: ^1H NMR ($CDCl_3$) δ 0.70 (3 H, $C_{18}CH_3$, s), 0.96 (3 H, $C_{21}CH_3$, d, $J \sim 6.3$ Hz), 1.22 (6 H, $C_{26,27}2CH_3$, s), 1.76 (3 H, $C_{19}CH_3$, s), 4.51 (2 H, br s), 4.69 (2 H, br s), 5.32 (1 H, H_9, br s), 5.82 (1 H, H_7, d, $J \sim 11.7$ Hz), 6.02 (1 H, H_6, d, $J \sim 11.7$ Hz).

(6Z)-9,10-Seco-A-homo-3,3-dimethyl-2,4-dioxacholesta-5(10),6,8,25-tetraene (55a) and A-Homo-3-deoxy-25,26-didehydro-3,3-dimethyl-2,4-dioxavitamin D_3 (56a). Trienyne **68** (32 mg, 0.078 mmol) with Lindlar's catalyst (29 mg, 5% Pd content) and quinoline (~0.6 mg) in hexanes (4 mL) was subjected to semihydrogenation and then workup as described above for the preparation of **9/24**. Vacuum drying afforded 31 mg (~96%) of a mixture of **55a** and its rearranged product **56a**. The ^1H NMR spectrum of the crude mixture showed a ratio of approximately 80:20 for **55a**:**56a**. The previtamin **55a** exhibited a characteristic AB pattern at δ 5.72 (H_7, d, $J \sim 11.7$ Hz) and 5.91 (H_6, d, $J \sim 11.7$ Hz),

another vinylic signal at δ 5.60 (H_9, br m), and a methyl signal at δ 0.70 ($C_{19}Me$, s). The vitamin **56a** exhibited peaks at δ 6.36 (H_7, d, $J \sim 11.2$ Hz), 6.01 (H_6, d, $J \sim 11.2$ Hz), 5.26 ($H_{19Z \text{ or } E}$, br s), 5.09 ($H_{19E \text{ or } Z}$, d, $J \sim 2.4$ Hz), 2.82 ($H_{9\beta}$, d, $J \sim 11.5$ Hz), and 0.54 ($C_{18}Me$, s). The disappearance of peaks assigned to previtamin **55a** and the concomitant increase in peaks due to vitamin **56a** was observed when the mixture was heated at 50 °C (by ^1H NMR monitoring). The crude product was subjected to oxymercuration–demercuration directly without further purification or characterization. The 25-hydroxylated product was considerably more easily purified and characterized.

***A*-Homo-3-deoxy-3,3-dimethyl-2,4-dioxa-25-hydroxyvitamin D_3 (56b).** Mercuric acetate (35.9 mg, 0.113 mmol) dissolved in water (0.5 mL) and THF (0.5 mL) were mixed to give a fine yellow suspension. A solution of **55a/56a** (31 mg, 0.075 mmol) in THF (0.5 mL) was added dropwise via cannula to the well-stirred yellow suspension under argon at room temperature. After 24 h, 0.5 mL of 1 M NaOH followed by 0.5 mL of 0.5 M $NaBH_4$ in 1 M NaOH was added. After standing for 1 min, ether (5 mL) was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ether (5 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residual product was again diluted with ether and passed through a short column of silica gel. After removal of ether, the crude product was subjected to HPLC purification (15% EtOAc/hexanes, 4.5 mL/min flow rate) to afford 20 mg of the vitamin **56b** (62%) as a viscous residue. There was no indication of the back equilibration of the vitamin **56b** to the previtamin form as judged by ^1H NMR analysis (200 MHz) at 50 °C or at room temperature: ^1H NMR ($CDCl_3$) δ 0.54 (3 H, $C_{18}CH_3$, s), 0.93 (3 H, $C_{21}CH_3$, d, $J \sim 5.9$ Hz), 1.22 (6 H, $C_{26,27}2CH_3$, s), 1.38 (6 H, C_32CH_3, s), 2.82 (1 H, $H_{9\beta}$, d, $J \sim 11.2$ Hz), 4.12 (2 H, s), 4.14 (2 H, s), 5.09 (1 H, H_{19}, d, $J \sim 2.0$ Hz), 5.26 (1 H, $H_{19'}$, br s), 6.01 (1 H, H_7, d, $J \sim 11.2$ Hz), 6.37 (1 H, H_6, d, $J \sim 11.2$ Hz).

De-*A*,*B*-cholesta-8,25-dien-8-yl Trifluoromethylsulfonate (57) and 3-Ethynyl-2-methyl-5-oxacyclopent-2-en-1-one (58). These substances were prepared in satisfactory yield as previously described.[6a]

9,10-Seco-*A*-nor-2-oxacholesta-5(10),8,25-trien-6-yn-1-one (59). To a solution of the lactone **58** (56.7 mg, 0.464 mmol) and bis(triphenylphosphine)palladium dichloride (6.2 mg, 0.009 mmol, $Pd(PPh_3)_2Cl_2$) in DMF (1 mL) was added triethylamine (0.21 mL, 1.5 mmol) under argon at room temperature. The mixture was then heated to 75 °C, and the triflate **57** (175 mg, 0.442 mmol) in DMF (1 mL) was added dropwise via cannula. The reaction mixture was allowed to stir at 75 °C for 5 h. After cooling to room temperature, the mixture was diluted with ether and then washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and passed through a short column of silica gel. After removal of solvent, the crude product was subjected to flash column chromatography (10% EtOAc/hexanes) to afford 140 mg of **59** (86%) as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.71 (3 H, $C_{18}CH_3$, s), 0.96 (3 H, $C_{21}CH_3$, d, $J \sim 6.3$ Hz), 1.72 (3 H, $C_{27}CH_3$, s), 1.97 (3 H, $C_{19}CH_3$, t, $J \sim 2.0$ Hz), 4.6–4.8 (4 H, $2H_3$ and $2H_{26}$, m), 6.21 (1 H, H_9, ddd, $J \sim 2.9$ Hz, 2.9 Hz, 2.9 Hz).

(6*Z*)-9,10-Seco-*A*-nor-2-oxacholesta-5(10),6,8,25-tetraen-1-one (60). The dienyne lactone **59** (147 mg, 0.40 mmol) with quinoline (~3 mg) and Lindlar's catalyst (127 mg) in hexanes (16 mL) was subjected to semihydrogenation and workup as described above for the preparation of **9/24**. The crude product was subjected to HPLC purification (Whatman Partisil, M10/50 column, 15% EtOAc/hexanes) to afford 94 mg of **60** (64%) as an oil: ^1H NMR ($CDCl_3$) δ 0.72 (3 H, $C_{18}CH_3$, s), 0.97 (3 H, $C_{21}CH_3$, d, $J \sim 6.3$ Hz), 1.71 (3 H, $C_{27}CH_3$, s), 1.90 (3 H, $C_{19}CH_3$, s), 4.7 (2 H, $2H_{26}$, m), 4.87 (2 H, narrow m), 5.53 (1 H, H_9, narrow m), 6.16 and 6.23 (2 H, $H_{6,7}$, AB pattern, $J \sim 11.9$ Hz).

1,3-Seco-2,4-dinor-25,26-didehydro-1-hydroxyvitamin D_3 (61 and 62). To a solution of the lactone **60** (20.4 mg, 0.055 mmol) in dried hexanes (0.8 mL) at 0 °C under argon was added dropwise DIBAL-H (0.22 mL, 1 M in hexanes, 0.22 mmol) via syringe. The solution was stirred for 20 min at 0 °C, and then the ice bath was removed. After additional stirring for 30 min at ambient temperature, the solution was diluted with ether (4 mL) and then poured into a beaker with 5 mL of ice water. After stirring for 30 min, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were then dried over $MgSO_4$. After removal of solvent, the residue was subjected to flash column chromatography (silica gel, 10% then 40% EtOAc/hexanes) to afford 18.5 mg of vitamin form **62** (90%) as an oil: ^1H NMR ($CDCl_3$) δ 0.53 (3 H, $C_{18}CH_3$, s), 0.93 (3 H, $C_{21}CH_3$, d, $J \sim 5.9$ Hz), 1.71 (3 H, $C_{27}CH_3$, s), 2.83 (1 H, $H_{9\beta}$, d, $J \sim 11.4$ Hz), 4.21 (4 H, $C_{1,3}2CH_2$, s), 4.67 (2 H, $2H_{26}$, br s), 5.07 (1 H, H_{19E}, d, $J \sim 1.5$ Hz), 5.40 (1 H, H_{19Z}, d, $J \sim 1.5$ Hz), 5.85 (1 H, H_7, d, $J \sim 11.2$ Hz), 6.53 (1 H, H_6, d, $J \sim 11.2$ Hz).

(6*Z*)-9,10-Seco-*A*-nor-25-hydroxy-2-oxacholesta-5(10),6,8-trien-1-one (63). Mercuric acetate (34 mg, 0.11 mmol) was dissolved in water (0.5 mL), and then THF (0.5 mL) was added to give a fine yellow suspension. Lactone **60** (29.4 mg, 0.08 mmol) in THF (0.5 mL) was added dropwise via cannula to the stirred yellow suspension (N_2, room temperature). After 5 h, 0.5 mL of 1 M NaOH and 0.5 mL of 0.5 M sodium borohydride in 1 M NaOH were added successively. After standing for 1 min, sodium chloride was added to saturate the aqueous layer. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were then washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. The concentrated, crude product was flash chromatographed (40% EtOAc/hexanes) to afford 7.9 mg of recovered **60** (27%) and 21.6 mg of the alcohol **62** (70%) as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.72 (3 H, $C_{18}CH_3$, s), 0.97 (3 H, $C_{21}CH_3$, d, $J \sim 6.3$ Hz), 1.22 (6 H, $C_{26,27}2CH_3$, s), 1.90 (3 H, $C_{19}CH_3$, br t, $J \sim 2.0$ Hz), 4.88 (2 H, $2H_3$, narrow m), 5.53 (1 H, H_9, br s), 6.16 and 6.24 (2 H, $H_{6,7}$, AB pattern, $J \sim 12.7$ Hz).

1,3-Seco-2,4-dinor-1,25-dihydroxyvitamin D_3 (64). To a solution of the hydroxy lactone **63** (25.6 mg, 0.066 mmol) in benzene (0.3 mL) and hexanes (0.5 mL) was added dropwise DIBAL-H (0.27 mL, 1 M in hexanes, 0.27 mol) via syringe at 0 °C under an argon atmosphere. After stirring for 30 min, the ice water bath was removed, and the mixture was stirred for an additional 30 min. Ether (10 mL) was added, and the mixture was then poured into ice water (10 mL). After 30 min stirring, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, the solvent was removed, and the residue was flash chromatographed (75% EtOAc/hexanes) to afford 14.5 mg of triol **64** (56%) as an amorphous solid: ^1H NMR ($CDCl_3$) δ 0.53 (3 H, $C_{18}CH_3$, s), 0.94 (3 H, $C_{21}CH_3$, d, $J \sim 5.9$ Hz), 1.22 (6 H, $C_{26,27}2CH_3$, s), 2.83 (1 H, $H_{9\beta}$, d, $J \sim 11.2$ Hz), 4.22 (4 H, $C_{1,3}2CH_2$, s), 5.08 (1 H, H_{19}, d, $J \sim 1.5$ Hz), 5.40 (1 H, $H_{19'}$, d, $J \sim 1.5$ Hz), 5.86 (1 H, H_7, d, $J \sim 11.2$ Hz), 6.54 (1 H, H_6, d, $J \sim 11.2$ Hz).

2,3-Seco-4-nor-1,25-dihydroxy-1-methylvitamin D_3 (65). To a solution of the lactone **63** (5.5 mg, 0.014 mmol) in dry ether (0.3 mL) was added dropwise MeLi (30 μL, 1.5 M in ether, 0.045 mmol) via syringe at room temperature under an argon atmosphere. After stirring for 30 min, water (0.5 mL) was added to quench the reaction. Ether (10 mL) and water (5 mL) were added, and the organic layer was separated. The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was subjected to HPLC (50% EtOAc/hexanes) to afford 3.4 mg of triol **65** (56%) as an amorphous solid: ^1H NMR ($CDCl_3$) δ 0.51 (3 H, $C_{18}CH_3$, s), 0.93 (3 H, $C_{21}CH_3$, d, $J \sim 5.9$ Hz), 1.21 (6 H, $C_{26,27}2CH_3$, s), 1.43 (6 H, C_12CH_3, s), 2.8 (1 H, $H_{9\beta}$, m), 4.22 (2 H, $2H_3$, s), 4.88 (1 H, H_{19}, d, $J \sim 1.5$ Hz), 5.34 (1 H, $H_{19'}$, d, $J \sim 1.5$ Hz), 5.73 (1 H, H_7, d, $J \sim 11.2$ Hz), 6.54 (1 H, H_6, d, $J \sim 11.2$ Hz).

(2*Z*)-3-(Hydroxymethyl)-2-methylpent-2-en-4-yn-1-ol (66). To a solution of the lactone **58**[25] (1.95 g, 16.0 mmol) in dry benzene (25 mL) was added dropwise DIBAL-H (51 mL, 1 M in toluene, 51 mmol) via syringe at 5 °C under argon. The mixture was stirred for 10 min at 5 °C and 30 min at room temperature and then poured into 30 mL of ice water. After adding 10 mL of 1 M H_2SO_4 to the mixture, the organic layer was separated, and the aqueous layer was extracted with ether (2 × 40 mL). The organic extracts were combined and washed with $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Meanwhile, the combined aqueous layers were continuously extracted with ether for 2 days. The ether extract was dried over $MgSO_4$ and concentrated, and the residue was combined with the original crude product. The crude product was purified by flash chromatography (10% EtOAc/hexanes and then 50% EtOAc/hexanes) to afford the diol **66** (1.37 g, 69%) as a thick oil: ^1H NMR ($CDCl_3$) δ 2.06 (3 H, s), 3.24 (1 H, s), 4.18 (2 H, s), 4.21 (2 H, s).

2-Ethynyl-1,5,5-trimethyl-4,6-dioxacycloheptan-1-ene (67). To a solution of the diol **66** (50.0 mg, 0.396 mmol) in dry acetone (10 mL) was added $FeCl_3$ (18 mg, 0.11 mmol) under argon at room temperature. After 24 h at room temperature, a solution of 10% K_2CO_3 (2.5 mL) was added to quench the reaction. After removal of the acetone solvent, the residue was extracted with $CHCl_3$ (3 × 10 mL). The organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed, and the crude product was then subjected to flash chromatography (silica gel, 8% EtOAc/hexanes) to afford 52 mg of **67** (78%) as a thick oil: ^1H NMR ($CDCl_3$) δ 1.41 (6 H, C_52CH_3, s), 1.84 (3 H, C_1CH_3, s), 3.13 (1 H, s), 4.23 (2 H, br s), 4.28 (2H, m).

9,10-Seco-*A*-homo-3,3-dimethyl-2,4-dioxacholesta-5(10),8,25-trien-6-yne (68). To a solution of acetonide **67** (113.9 mg, 0.685 mmol) and bis(triphenylphosphine)palladium dichloride (9.2 mg, 0.013 mmol, $Ph\text{-}(PPh_3)_2Cl_2$) in DMF (2 mL) was added triethylamine (0.31 mL, 2.2 mmol) under argon at room temperature. The resulting mixture was heated to 75 °C, and the triflate **57** (257.5 mg, 0.652 mmol) in DMF (1.5 mL) was added dropwise via cannula. The reaction mixture was allowed to stir at 75 °C for 30 h. After ether (10 mL) and water (10 mL) were added to the cooled mixture, the organic layer was separated,

and the aqueous layer was extracted with ether (5 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was subjected to flash chromatography (silica gel, 5% EtOAc/hexanes) to afford 210 mg of **68** (79%) as an amorphous solid: ^1H NMR ($CDCl_3$) δ 0.69 (3 H, $C_{18}CH_3$, s), 0.94 (3 H, $C_{21}CH_3$, d, $J \sim$ 6.8 Hz), 1.41 (6 H, C_32CH_3, s), 1.71 (3 H, $C_{27}CH_3$, s), 1.82 (3 H, $C_{19}CH_3$, s), 4.23 (2 H, br s), 4.27 (2 H, m), 4.67 (2 H, $2H_{26}$, br s), 5.93 (1 H, H_9, m).

Acknowledgment. This study was generously supported by the NIH Grant DK-16595, the UC Riverside Intramural Fund, and the Chancellor's Patent Fund. Duphar (Weesp, The Netherlands) provided generous quantities of vitamin D_3 utilized as starting material in this study. We also acknowledge Professor M. M. Midland for helpful discussions.

Supplementary Material Available: Spectral data for all new compounds and general experimental details (34 pages). Ordering information is given on any current masthead page.

Photoemission Probes of Hydrocarbon–DNA Interactions: A Comparison of DNA Influences on the Reactivities of (±)-*trans*-7,8-Dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene, Benzo[*a*]pyrene 4,5-Oxide, and Benz[*a*]anthracene 5,6-Oxide

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Abstract: Time-resolved fluorescence and UV photoelectron measurements have been employed to examine the influence of calf thymus DNA on the reactivities of epoxides derived from benzo[*a*]pyrene (BP) and benz[*a*]anthracene (BA). By monitoring the increase in fluorescence intensity, which accompanies reaction at 23 °C, overall, pseudo-first-order rate constants have been measured for reactions of the highly carcinogenic bay region epoxide (±)-*trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (BPDE) and of two less carcinogenic K region epoxides benzo[*a*]pyrene 4,5-oxide (BPO) and benz[*a*]anthracene 5,6-oxide (BAO). Overall rate constants for hydrolysis and rearrangement reactions have been measured for BPDE, BPO, and BAO in buffer alone (1.0 mM sodium cacodylate, pH 7.1). The rate constants increase in the order BPO ($(3.8 \pm 0.1) \times 10^{-6}$ s^{-1}) < BAO ($(5.7 \pm 2.6) \times 10^{-5}$ s^{-1}) < BPDE ($(7.2 \pm 1.0) \times 10^{-4}$ s^{-1}). These results have been compared with overall rate constants for reactions, carried out in calf thymus DNA, which result in catalyzed hydrolysis and rearrangement, as well as DNA adduct formation. In DNA, the ordering of the rate constants for BPO and BAO changes from that observed in buffer alone. The rate constants increase in the order BAO ($(2.8 \pm 0.1) \times 10^{-3}$ s^{-1}) < BPO ($(1.2 \pm 0.2) \times 10^{-2}$ s^{-1}) < BPDE ($\sim 1 \times 10^{-1}$ s^{-1}). This ordering is the same as the ordering of association constants for the reversible binding to DNA of the fluorescent diols *trans*-7,8-dihydroxy-7,8-dihydro-BP (BP78D), *trans*-4,5-dihydroxy-4,5-dihydro-BP (BP45D) and *cis*-5,6-dihydroxy-5,6-dihydro-BA (BAD), which are model compounds of BPDE, BPO, and BAO, respectively. For the model compounds, the association constants for intercalation increase in the order BAD ($(3.6 \pm 0.9(\times 10^2$ M^{-1}) < BP45D ($(9.6 \pm 0.5) \times 10^3$ M^{-1}) < BP78D ($(3.4 \pm 0.1) \times 10^4$ M^{-1}). This ordering is consistent with the ordering of the association constants of BPDE ($(2.5 \pm 0.3) \times 10^4$ M^{-1}) and of BPO ($(6.0 \pm 1.0) \times 10^3$ M^{-1}). The temperature dependence of the association constants of the model compounds demonstrates that, for the intercalation of the BP diols into DNA, differences in the enthalpy of binding contribute significantly to differences in the free energy of binding. UV photoelectron data and results from ab initio molecular orbital calculations on BPDE, BPO, and BAO indicate that, for these three epoxides, the association constants increase as the ionization potentials decrease and the polarizabilities increase. The percentage of epoxide reaction that yields DNA adducts has been compared under varying conditions. For long reaction times (>1 h) in systems containing native, calf thymus DNA at low salt concentrations, the ordering of adduct yields is BPO (14.9 ± 1.1%) > BPDE (10.1 ± 3.0%) > BAO (3.6 ± 0.4%). For short reaction times (10 min) in systems containing native DNA stabilized with 0.10 mM Mg^{2+}, the ordering of adduct yields is BPDE (7.3 ± 1.9%) > BPO (1.3 ± 0.1%) > BAO (0.1 ± 0.1%). These results suggest that the ability of an epoxide to form adducts with exposed DNA during long reaction times is less indicative of the genotoxic potency of the epoxide than its ability to form adducts with stabilized DNA during short reaction times.

Introduction

Among the mutagenic and carcinogenic metabolites of benzo[*a*]pyrene (BP) and benz[*a*]anthracene (BA), the K region epoxides and the bay region diol epoxides have been the most carefully examined.[1-5] Early investigations of BP and BA metabolism focused on K region epoxides.[6-9] This interest shifted when cell cultures treated with parent hydrocarbons showed that major DNA adducts did not form from reactions of K region epoxides[7,10] but instead from reactions of bay region diol epoxides.[11]

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