Inhibitors of 25-Hydroxyvitamin D_3-1α-Hydroxylase: A-Ring Oxa Analogs of 25-Hydroxyvitamin D_3[1]

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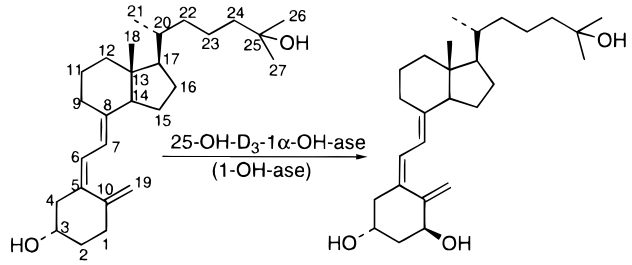
The most potent inhibitor known of 25-hydroxyvitamin D_3 1α-hydroxylase (1-OHase), a cytochrome P-450 mixed function oxidase involved in the production of the steroid hormone 1α,25-dihydroxyvitamin D_3 (**2**), is 25-hydroxy-3-deoxy-2-oxavitamin D_3 (**3b**). The latter, prepared previously in relatively low yield, is unusual because it coexists in nearly equal proportions with its [1,7]-sigmatropic shifted, previtamin D_3 tautomer **4b**. A more efficient synthesis of this potent inhibitor was developed by applying Trost's enyne Pd(0) cyclization strategy. Besides succeeding in improving the synthesis of **3b**/**4b**, extension of this approach to the synthesis of other related A-ring oxacycles for structure−function studies of the 1-OHase system has been successful. This venture has resulted not only in oxacycles **4a**, **3b**/**4b**, and **3c** but also their 9,11-didehydro counterparts **5a**, **5b**, and **5c**. The analog **5b** was anticipated to be of particular interest because it represents an analog of the potent inhibitor **3b**, but the presence of the 9,11-double bond renders it incapable of undergoing a [1,7]-sigmatropic shift to a form resembling **4b**. Biological evaluation of **5b** revealed it to be a more potent inhibitor of 1-OHase than **3b**/**4b**, suggesting that **3b** is the likely form of the inhibitor **3b**/**4b**. Initial kinetic experiments indicate that the analogs (**3b**, **3c**, and **5b**) tested do not inhibit by direct mechanism-based enzyme inactivation, revealing rather that inhibition of 1-OHase is competitive. Finally, it should be noted that the synthetic studies described herein provide new information regarding the scope and limitations of the palladium(0)-mediated enyne cyclization strategy leading to vitamin D molecules.

Introduction

From a biomedical standpoint there are now many examples of pathological disruption of the normal state in which a drug form of vitamin D (an analog or metabolite) is proposed to be a potentially useful form of therapy, e.g., in treating various cancers, bone and kidney diseases, skin diseases, neurological disorders (Alzheimer's disease), problems associated with the immune system (graft rejection and several autoimmune diseases), and also AIDS.[2] In order to understand the behavior of any analog of the hormone 1α,25-dihydroxyvitamin D_3 (**2**, 1,25-D3), they need to be understood in terms of how they potentially affect the endogenous hormone metabolic machinery. The final step in the metabolic activation of 1,25-D3 (**2**) is its formation in the kidney from 25-hydroxyvitamin D_3 (**1**, 25-D3), a process catalyzed by the mitochondrial enzyme, 25-hydroxyvitamin D_3 1α-hydroxylase (1-OHase), a cytochrome P-450 mixed function oxidase (Scheme 1).[3] Inhibitory analogs of this enzyme would serve as useful biochemical research tools to develop an understanding of its mechanism of action by providing discrete information about its structure, particularly its active site, and also to provide a means for developing affinity labels for its more detailed molecular characterization. Our laboratories have recently reported what has emerged as the best 1-OHase inhibitor yet identified, namely the heterocalciferol[4] 2-oxa-3-deoxy analog **3b** (Scheme 2).[5] The recent studies indicated that analog **3b** is 6-fold more potent as an inhibitor of the 1-OHase than 1,25-D3.

Scheme 1



1 (25-D3) **2** (1,25-D3)

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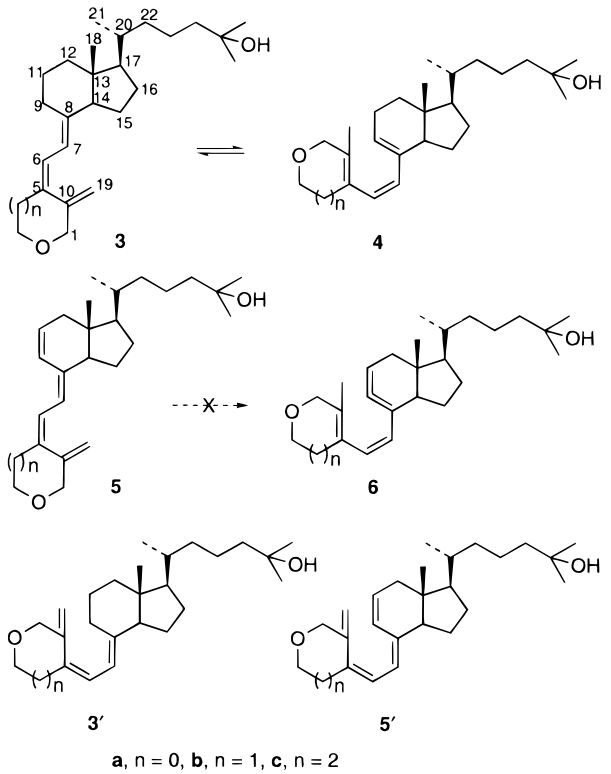
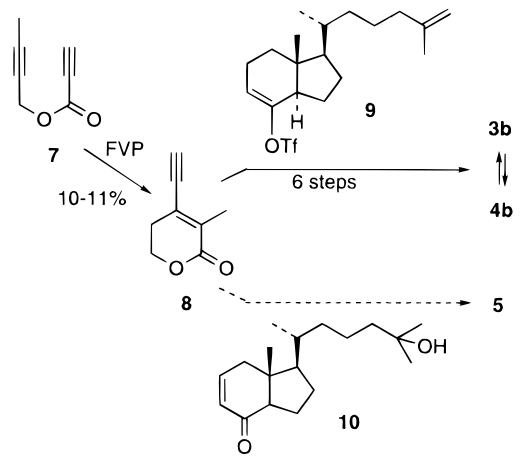
Scheme 2



Scheme 3



The inhibitor **3b** is highly unusual in two respects. First, this analog has the unusual property of existing in dynamic equilibrium with its previtamin form **4b**, formed via a [1,7]-sigmatropic shift of **3b** involving migration of a hydrogen atom from carbon 9 to 19. This sigmatropic shift must occur via the intermediacy of the 6-*s*-*cis* conformer of **3b**, namely **3′b**.[5] A second unusual feature of inhibitor **3b** is that while the natural substrate for this enzyme (i.e., 25-D3) possesses a 3-hydroxyl group, it does not. It is unclear whether the active inhibitory form of this 2-oxa analog is actually the previtamin structure **4b** with which it is in dynamic equilibrium or even the 6-*s*-*cis* conformer **3′b**.[5a,b,6] It was reasoned that by introducing a double bond in the $\Delta^{9,11}$ position as in the analog **5b**, the previtamin structure **6b** would be suppressed because the C_9 hydrogen is now at an sp^2 carbon.[7] It is highly unlikely that **5b** would undergo a [1,7]-sigmatropic shift to previtamin structure **6b** analogous to the related isomerization of **3b** to **4b** since **6b** would possess a highly strained cyclic allene moiety. Thus, it became of interest to synthesize and study analog **5b**. It should be noted, however, that the introduction of the C-ring double bond at the 9,11-position does not preclude **5b** from rotating into its 6-*s*-*cis* form **5′b**, which of course topologically resembles the putative **6b** as well as **4b**.[6] Nevertheless, the synthesis and evaluation of **5b** was deemed of significant interest because of its certain inability to produce the previtamin structure **6b**.

It should also be noted that **3b** has a 6-membered oxa-ring. Because a C−O bond is shorter than a C−C bond, this ring size is slightly smaller than the native 6-membered carbon-ring. It is possible that this ring size plays a part in the inhibition of the 1-OHase. To test this, **3c**, containing a 7-membered oxa-ring, was also synthesized and studied.

An equally important goal was to develop a more effective chemical synthesis of **3b**, which involved a rather tedious synthetic scheme. The original scheme involved[5b] the low yield flash vacuum pyrolysis of the diyne ester **7** to afford the key synthon **8**, which is obtained in only 10−11% yield (Scheme 3). Moreover, some six steps were required to transform **8** into the desired analog **3b**, which as indicated above is in rapid equilibrium with **4b**. As for the preparation of **5b** some brief attempts were made to transform **8** into **5b** through coupling with unsaturated ketone **10**, but this has not succeeded.[4e]

While the latter route via **10** was in progress, Trost[8] reported the synthesis of the natural hormone **2** by a

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(7) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. Synthesis and Biological Activity of 9,11-Dehydrovitamin D_3 Analogues: Stereoselective Preparation of 6*β*-Vitamin D Vinylallenes and a Concise Enynol Synthesis for Preparing the A-Ring. *J. Org. Chem.* **1989**, *54*, 4072−4083.

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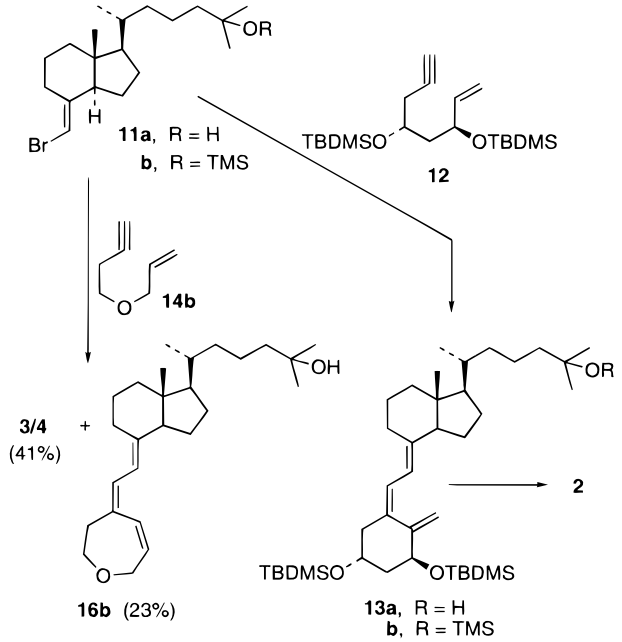
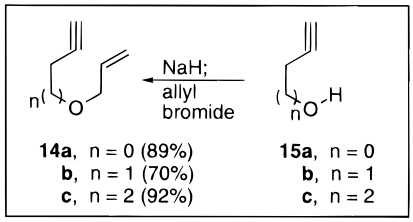
Scheme 4

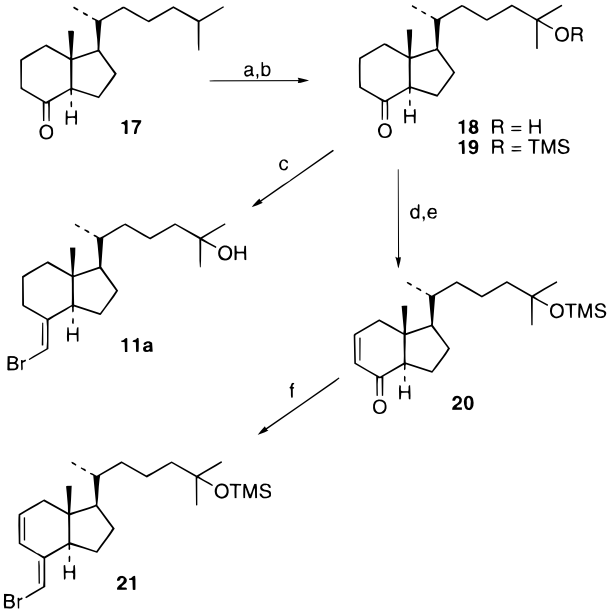




palladium-mediated cascade cyclization strategy involving the convergent coupling of the vinyl bromide **11** with **12** (Schemes 4 and 5).[9−11] It was easy to envisage that coupling of **11** to the structurally related ether **14b** (prepared by the Williamson ether synthesis approach using the alkoxide derived from **15b** and allyl bromide)[12] to afford **3b/4b** in an analogous fashion. In the event we determined that this route provides an expeditious synthesis of the desired analog **3b** (41% yield), but the novel A-homo analog **16b** was also concomitantly produced (23% yield) (Schemes 4 and 6).

It is the purpose of this paper to elaborate on the details of this more efficient production of **3b** and also to describe a more systematic study of a similar coupling leading to both A-nor and A-homo analogs that might provide some insight into the production of these inhibitors and to better define the scope of the Trost methodology[8] for producing new A-ring oxa analogs such as **5b**. Biological assays[5a] were performed on the 1-OHase, isolated from kidney mitochondria, using the analogs **3b**, **3c**, and **5b**. These assays allowed us to investigate the inhibitory effects of these analogs, as well as to gain some insight into the mechanism of this inhibition.

Scheme 5[a]



[a] Key: (a) see ref 10; (b) see ref 11; (c) see ref 8a−c; (d) LDA, −78 °C, PhSeCl, THF, 2 h; (e) *m*-CPBA, CH_2Cl_2, 0 °C, 15 min (75%); (f) $Ph_3P^+CH_2BrBr^-$, $NaN(TMS)_2$, THF, −78 °C (40%).

Results and Discussion

As described above, our general strategy for these analogs utilized the tandem palladium coupling of the appropriate vinyl bromide **11a** or **21** and the corresponding enyne (Schemes 4 and 5).[8] This approach was chosen since it was envisioned to lend ready access to the desired analogs and allow examination of the scope and limitation of this method for synthesizing oxa A-ring vitamin D analogs.

Synthesis of the CD Vinyl Bromides and Enynes. The readily available Grundmann's ketone **17**[9] served as the common precursor to both vinyl bromides **11a** and **21** (Scheme 5). Ruthenium-catalyzed hydroxylation of the ketone **17**[10] gave alcohol **18**, which underwent a Wittig coupling as described previously by Trost[8] to give the vinyl bromide **11a**. For preparation of vinyl bromide **21**, the alcohol **18** was first protected as the TMS ether **19**.[11] Formation of the kinetic enolate of ketone **19** with LDA followed by trapping with phenylselenenyl chloride resulted in the phenylselenium intermediate.[7] This intermediate, without purification, was then oxidized with *m*-CPBA to give the enone **20** in 75% yield from **19**. A Wittig reaction was performed on the enone **20** using bromomethyltriphenylphosphonium bromide to provide the desired vinyl bromide **21** in 40% yield. Enynes **14a−c** were prepared by reacting the corresponding alkynols **15a−c** with sodium hydride, and the resulting alkoxides were then quenched with allyl bromide (Scheme 4).[12]

Palladium Coupling. The vinyl bromides **11a** and **21** were allowed to react under inert argon atmosphere with the different enynes **14a−c** using 20 mol % tetrakis(triphenylphosphine)palladium(0) in toluene or THF as

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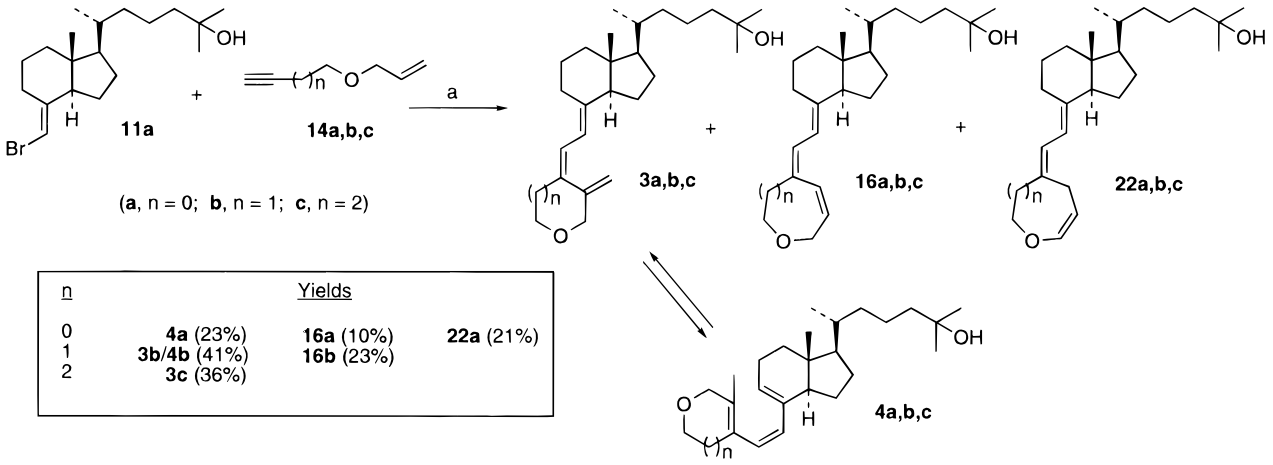
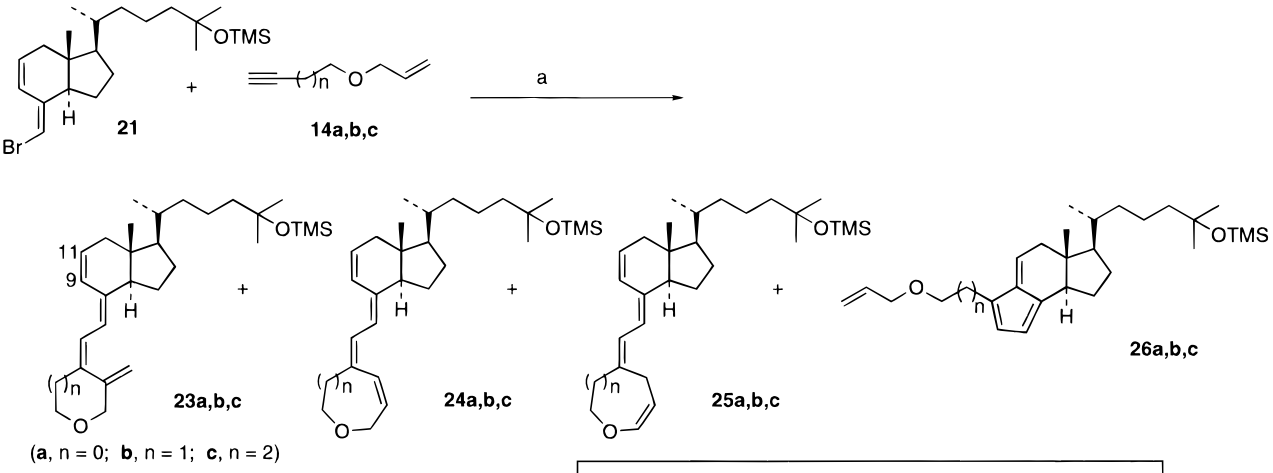
Scheme 6[a]



n	Yields		
0	**4a** (23%)	**16a** (10%)	**22a** (21%)
1	**3b/4b** (41%)	**16b** (23%)	
2	**3c** (36%)		

[a] Key: (a) 20 mol % $Pd(Ph_3P)_4$, TPP, THF, Et_3N, 40-65 °C, 40−100 h.

Scheme 7[a]



n	Yields			
0	**23a** (12%)	**24a** (8%)	**25a** (23%)	**26a** (12%)
1	**23b** (27%)	**24b** (16%)	**26b** (18%)	
2	**23c** (13%)	**26c** (17%)		

[a] Key: (a) 20 mol % $Pd(Ph_3P)_4$, TPP, toluene, Et_3N, 80 °C, 4−20 h.

solvent. Different times and temperatures were used depending on the structure of the vinyl bromide or length of the enyne in an effort to obtain the optimum yield of coupled products. The reaction conditions and ratio of products obtained are summarized in Schemes 6 and 7. In some cases uncyclized intermediates were obtained in addition to the coupled product but they were not further characterized. As shown in Scheme 6, the number of discernible byproducts that resulted from the coupling of vinyl bromide **11a** decreased with increasing length of the corresponding enyne reacted. In particular, enyne **14a** gave in addition to the desired five membered A-ring product **4a**, two six-membered A-ring byproducts **16a** and **22a** resulting from endo attack in the final cyclization. The desired product exists only as the previtamin form **4a**, resulting from a [1,7]-sigmatropic hydrogen shift.[6] As mentioned in the Introduction, the use of enyne **14b** gave 41% of an almost 1:1 equilibrium mixture of the previtamin and vitamin form **3b**/**4b**. This yield represents a significant improvement compared to that of our previous synthesis;[5b] in particular, it is much more succinct. We also obtained 23% of the seven-membered A-ring byproduct **16b** resulting from endo attack. Enyne **14c** gave only the desired A-homo product **3c** although in a modest 36% yield, and it was observed to exist by proton NMR only in the vitamin form. It is interesting to note that for the equilibrium between the previtamin and vitamin form, the proportion of the latter increases as the size of the oxa A-ring containing the exocyclic double bond increases. This result is in accord with our previous study of the effect of the A-ring size on the [1,7]-sigmatropic hydrogen shift in the vitamin D series.[4]

Similarly, Scheme 7 shows that the number of byproducts obtained from the coupling of vinyl bromide **21** decreased with increasing length of the enyne. However, an additional byproduct (as compared with the 9,11-dihydrovinyl bromide **11a**) was formed in each case resulting from final closure onto the 9,11 double bond of the CD ring portion of **21**. For example, enyne **14a** gave the desired five-membered A-ring product **23a**, two six-membered A-ring coupled byproducts **24a** and **25a** from final endo closure, and the de-A-ring byproduct **26a** that resulted from final closure onto the 9,11 double bond of

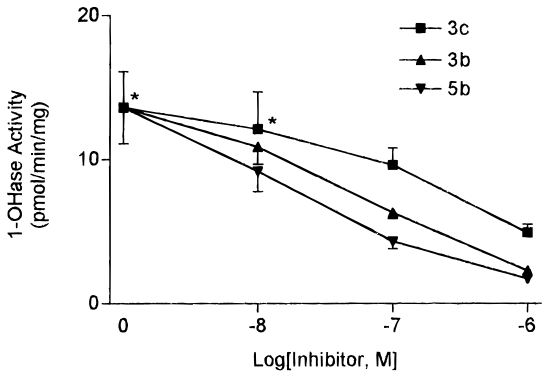


Figure 1. 1-OHase activity in chick kidney mitochondria was assayed in the presence of increasing inhibitor concentrations. Results represent the mean (*, $n = 3$; all others, $n = 4$) ± the standard deviation. Where no error bars are visible, they are smaller than the symbol.

the CD ring.[13] In the case of enyne **14b**, coupling with vinyl bromide **21** gave three coupled products. The desired product **23b** was obtained in 27% yield along with the seven-membered A-ring byproduct **24b** and the de-A-ring byproduct **26b**. Enyne **14c** provided two coupled products when reacted with vinyl bromide **21**; in addition to the desired product **23c**, the de-A-ring product **26c** was obtained.

The TMS protecting groups of the tetraenes **23**−**c** were then removed with TBAF to provide the free 25-hydroxy tetraene A-ring exocyclic double bond analogs **5a** (70%), **b** (75%), and **c** (81%), respectively. Although the five-membered-ring tetraene **5a** can be isolated and characterized if handled under an inert atmosphere, exposure to air for a short period (∼5 min) leads to rapid decomposition. The instability of tetraene **5a** may be due to the cumulative effect of the small A-ring size (five membered), the shorter bond length of the carbon−oxygen single bond (1.41 Å) compared to the carbon−carbon single bond (1.54 Å), and the presence of the two exocyclic double bonds.

To summarize, the tandem palladium coupling approach proved synthetically useful since it enables rapid access to all the desired A-ring oxa analogs, albeit in low to modest yields and production of mixtures. Modification of the reaction conditions of the method described herein, or using completely different oxa-A ring preparative strategies as reviewed recently[2b,4e] (e.g., a Wittig−Horner process of the Lythgoe type), will be necessary for producing larger quantities of these analogs. Nevertheless, sufficient quantities of analogs have become available for biological assay, and this study has been useful for identifying a possible limitation of the Trost methodology at least for synthesizing oxa A-ring analogs.

Biological Evaluation. In order to study the inhibitory effects of **3b**, **3c**, and **5b**, 1-OHase assays[5a] were performed using mitochondria isolated from kidney tissue of 3-week old, vitamin D deficient chicks. As is evident from Figure 1 **5b** proved to be even more potent than **3b**, while **3c**, although less inhibitory, did exhibit some activity. Since the latter **3c** is the least potent of these inhibitors and contains a larger oxa-ring than **3b**, the ring size does play a role in the inhibition of the 1-OHase. The analog **5b**, on the other hand, is the most potent inhibitor of the three and contains the smaller, 6-membered oxa-ring. In addition, unlike **3b**, it cannot undergo a sigmatropic shift (C9 to C19) due to the presence of a double bond in the $\Delta^{9,11}$ position. Thus, it is locked into the vitamin form, suggesting that, for **3b**, it exerts its inhibitory activity through **3b** rather than **4b**.

Table 1. 1-OHase Activity Assayed with Preincubations at Varying Times and Concentrations of the Inhibitor 5b

preincubation (min)	[**5b**] (M)	% control activity[a]
0	10^{-6}	20 ± 5*
12	10^{-6}	15 ± 4
0	10^{-6}	16 ± 2
12	10^{-6}	18 ± 3
0	10^{-7}	58 ± 6
12	10^{-7}	63 ± 19
0	10^{-8}	100 ± 9
12	10^{-8}	95 ± 13
0	10^{-6}	18 ± 2
10	10^{-6}	11 ± 2
20	10^{-6}	15 ± 7

[a] Results represent the mean (*, $n = 3$; all others, $n = 4$) ± the standard deviation.

Initial kinetic experiments showed that the inhibition by **5b** of the 1-OHase is competitive. Other analogs of 25-D3 have also been previously shown to be competitive inhibitors.[5a] Several experiments were carried out to determine if the inhibition was due to irreversible enzyme inactivation. In mechanism-based enzyme inactivation the inhibitor, mimicking the substrate, is converted by the enzyme into a compound that irreversibly inhibits it.[14] If inhibitor **5b** is a mechanism-based enzyme inactivator, then inhibition should increase with preincubation in a time-dependent manner. To test this, preincubations at various time points were performed. As shown in Table 1 varying the time of preincubation had little or no effect on the inhibition by **5b**, indicating that **5b** is not a mechanism-based enzyme inactivator. To determine whether a mechanism-based enzyme inactivator could be identified at submaximal inhibitor concentrations, several experiments at various inhibitor concentrations were carried out. This also had little or no effect on the inhibition by **5b**, again supporting the view that the inhibition is not due to enzyme inactivation. The analogs **3b** and **3c** were also shown to not inhibit by enzyme inactivation (data not shown).

Summary

Besides providing new information regarding the scope and limitations of Trost's Pd(0)-mediated enyne cyclization strategy leading to vitamin D, and affording a more efficient synthesis of the potent 1-OHase inhibitor **3b**/**4b**, new A-ring oxacyclic analogs of vitamin D have been synthesized and biologically evaluated. Most interestingly, one of the new analogues, the 9,11-didehydro derivative **5b**, has proven to be even more biologically potent as a 1-OHase inhibitor than **3b**/**4b**. Since **5b** is incapable of tautomerizing via a [1,7]-sigmatropic shift to the putative cyclic allene **6b**, it seems that the analogue **3b**/**4b** (a ∼1:1 tautomeric mixture) probably exerts its inhibitory activities via **3b**. The greater inhibitory activity of **5b** can perhaps be rationalized on the basis that it exists solely in the vitamin D form. The

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biological assay results indicate that the analogs tested do not inhibit by direct enzyme inactivation, initial kinetic experiments revealing that inhibition of 1-OHase is competitive.

Experimental Section[15]

25-Hydroxy-3-deoxy-2-oxavitamin D_3 (3b)−25-Hydroxy-3-deoxy-2-oxaprevitamin D_3 (4b) Equilibrium Mixture and A-Homo-19-nor-3-deoxy-3-oxa-1(10)-didehydro-25-hydroxyvitamin D_3 (16b). A solution of tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.016 mmol, 20%), triphenylphosphine (6.1 mg, 0.023 mmol, 30%), THF (0.25 mL), and triethylamine (0.5 mL) was prepared in a vial under argon at room temperature. A solution of vinyl bromide **11a** (28 mg, 0.078 mmol) in THF (0.25 mL) and enyne **14b** (13 mg, 0.12 mmol, 15 μL) were then added successively via syringe. The vial was capped, and the mixture was heated with stirring under argon at 65 °C for 40 h. The reaction mixture was cooled to room temperature and filtered through a short column of silica gel. The filtrate was concentrated, and flash chromatography (25% ethyl acetate/hexanes) was performed to remove the remaining palladium. The products were then separated by HPLC (25% ethyl acetate/hexanes) to give two major peaks **A** and **B**. Peak **A** was identified as an equilibrium mixture of 25-hydroxy-3-deoxy-2-oxavitamin D_3 and 25-hydroxy-3-deoxy-2-oxaprevitamin D_3 (**3b**−**4b**, 12.5 mg, 41%). Peak **B** was identified as A-homo-19-nor-3-deoxy-3-oxa-1(10)-didehydro-25-hydroxyvitamin D_3 (**16b**, 7.1 mg, 23%). **3b**/**4b**: ^{1}H-NMR (the ^{1}H-NMR spectrum corresponds to the equilibrium mixture of the vitamin D and previtamin D forms (~55/45) as previously described) δ 0.54 (3H, C_{18}-CH_3, s), 0.93 (3H, C_{21}-CH_3, d, J = 6.1 Hz), 2.82 (1H, $H_{9\beta}$, d, J = 12.2 Hz), 4.07 (2H, $2H_1$, pseudo-d, J = 5.0 Hz), 5.01 (1H, H_{19E}, s), 5.13 (1H, H_{19Z}, s), 6.03 (1H, H_6, d, J = 11.2 Hz), 6.27 (1H, H_7, d, J = 11.2 Hz). The assignable signals for the previtamin are as follows: 0.69 (3H, C_{18}-CH_3, s), 0.95 (3H, C_{21}-CH_3, d, J = 6.4 Hz), 4.01 (2H, $2H_1$, br s), 5.51 (1H, H_9, br s), 5.72 and 5.96 (2H, $H_{6\text{ and }7}$, AB pattern, J = 12.0 Hz). **16b**: ^{1}H-NMR δ 0.55 (3H, C_{18}-CH_3, s), 0.93 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 2.65 (2H, H_{4a}, t, J = 5.4 Hz), 2.81 (1H, dd, J = 11.9 Hz, 3.5 Hz), 3.82 (1H, H_4, br s), 3.82 (1H, H_4, m), 4.29 (2H, $2H_2$, dd, J = 3.8 Hz, 1.3 Hz), 5.68 (1H, H_1, ddd, J = 12.3 Hz, 4.1 Hz, 4.1 Hz), 5.96 (1H, $H_{6\text{ or }7}$, d, J = 11.5 Hz), 6.24 (1H, $H_{7\text{ or }6}$, d, J = 11.5 Hz), 6.63 (1H, H_{10}, d, J = 12.1 Hz); ^{13}C-NMR δ 12.1, 18.8, 20.8, 22.2, 23.6, 27.6, 28.9, 29.2, 29.4, 36.1, 36.4, 40.1, 40.5, 44.4, 46.0, 56.51, 56.54, 68.9, 70.3, 71.1, 116.0, 125.1, 127.2, 129.8, 133.6, 144.0.

A-Homo-3-deoxy-2-oxa-25-hydroxyvitamin D_3 (3c). A solution of tetrakis (triphenylphosphine)palladium(0) (14 mg, 0.012 mmol, 20%), triphenylphosphine (4.8 mg, 0.018 mmol, 30%), THF (0.25 mL), and triethylamine (0.5 mL) was prepared under argon at room temperature in a vial. A solution of vinyl bromide **11a** (22 mg, 0.061 mmol) in THF (0.25 mL) and enyne **14c** (8.3 mg, 0.067 mmol, 10 μL) were introduced successively via syringe. The vial was then capped, and the stirred mixture was heated under argon for 100 h at 65 °C. The reaction mixture was cooled to room temperature and filtered through a short column of silica gel. After the filtrate was concentrated, the remaining palladium was removed by a short flash chromatography (25% ethyl acetate/hexanes). The crude residue was then purified by HPLC (20% ethyl acetate/hexanes) to give three main peaks in the order of elution **A**, **B**, and then **C**. The products corresponding to peaks **A** and **B** were probably CD coupled, but uncyclized A-ring products (6.5 and 4.3 mg, respectively) were not further characterized. Peak **C** was identified as A-homo-3-deoxy-2-oxa-25-hydroxyvitamin D_3 (**3c**, 8.8 mg, 36%). **3c**: ^{1}H-NMR δ 0.54 (3H, C_{18}-CH_3, s), 0.93 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 2.41 (2H, t, J = 5.6 Hz), 2.82 (1H, d, J = 12.0 Hz), 3.76 (2H, $2H_3$, overlapping m), 4.26 (2H, $2H_1$, s), 5.02 (1H, $H_{19Z\text{ or }E}$, s), 5.16 (1H, $H_{19E\text{ or }Z}$, s), 6.02 (1H, H_7, d, J = 11.0 Hz), 6.36 (1H, H_6, d, J = 11.0 Hz); ^{13}C-NMR δ 12.0, 18.8, 20.8, 22.3, 23.6, 27.7, 29.1, 29.2, 29.3, 32.4, 36.1, 36.4, 37.0, 40.5, 44.4, 45.9, 56.3, 56.5, 71.1, 73.6, 75.6, 114.5, 118.5, 124.4, 139.4, 142.1, 147.4.

19-Nor-3-deoxy-3-oxa-1,2-didehydro-25-hydroxyvitamin D_3 (22a), (6Z)-9,10-seco-A-nor-25-hydroxy-2-oxacholesta-5(10),6,8-triene (4a), and 19-Nor-3-deoxy-3-oxa-1(10)-didehydro-25-hydroxyvitamin D_3 (16a). A solution of tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.011 mmol, 20%), triphenylphosphine (4.4 mg, 0.017 mmol, 30%), THF (0.20 mL), and triethylamine (0.40 mL) was prepared under argon at room temperature in a vial. A solution of vinyl bromide **11a** (20 mg, 0.056 mmol) in THF (0.20 mL) and then enyne **14a** (8 mg, 0.084 mmol, 10 μL) were introduced successively by syringe. The vial was then capped, and the mixture was heated at 40−45 °C with stirring for 40 h. The reaction mixture was cooled to room temperature and filtered through a short column of silica gel. After removal of the solvent, the remaining palladium was removed by flash chromatography (25% ethyl acetate/hexanes). The crude residue was purified by HPLC (18% ethyl acetate/hexanes) to give three major peaks: **A**, **B**, and **C**. Peak **A** was identified as 19-nor-3-deoxy-3-oxa-1,2-didehydro-25-hydroxyvitamin D_3 (**22a**, 4.3 mg, 21%). Peak **B** was identified as (6*Z*)-9,10-seco-A-nor-25-hydroxy-2-oxacholesta-5(10),6,8-triene (**4a**, 4.7 mg, 23%). Peak **C** was identified as 19-nor-3-deoxy-3-oxa-1(10)-didehydro-25-hydroxyvitamin D_3 (**16a**, 2.1 mg, 10%). **4a**: ^{1}H-NMR δ 0.70 (3H, C_{18}-CH_3, s), 0.96 (3H, C_{21}-CH_3, d, J = 6.4 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 1.76 (3H, C_{19}-CH_3, s), 4.51 (2H, $2H_{3\text{ or }1}$, br s), 4.69 (2H, $2H_{1\text{ or }3}$, br s), 5.32 (1H, H_9, br s), 5.81 (1H, H_7, d, J = 12.3 Hz), 6.01 (1H, H_6, d, J = 11.9 Hz); ^{13}C-NMR δ 10.3, 11.2, 18.7, 20.8, 23.4, 24.6, 28.4, 29.2, 29.4, 36.0, 36.1, 36.4, 42.1, 44.4, 51.2, 54.3, 71.1, 76.9, 78.4, 118.6, 125.1, 129.8, 130.8, 134.5, 136.9; **16a**: ^{1}H-NMR δ 0.54 (3H, C_{18}-CH_3, s), 0.93 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.22 (6H, $C_{26,27}$-$2CH_3$, s), 2.82 (1H, dd, J = 12.0 Hz, 3.6 Hz), 4.22 (2H, $2H_{4\text{ or }2}$, s), 4.46 and 4.54 (2H, $2H_{2\text{ or }4}$, AB pattern, J = 14.1 Hz), 5.72 (1H, $H_{6\text{ or }7}$, d, J = 11.9 Hz), 5.80 (1H, H_1, dt, J = 10.3 Hz, 3.1 Hz), 6.15 (1H, $H_{7\text{ or }6}$, d, J = 11.9 Hz), 6.24 (1H, H_{10}, d, J = 10.0 Hz); ^{13}C-NMR 12.0, 18.8, 20.8, 22.1, 23.6, 27.6, 28.9, 29.2, 29.4, 36.1, 36.4, 40.4, 44.4, 46.1, 56.5, 65.0, 65.6, 71.1, 77.2, 114.9, 121.2, 126.0, 128.2, 129.6, 145.3. **22a**: ^{1}H-NMR δ 0.54 (3H, C_{18}-CH_3, s), 0.93 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.22 (6H, $C_{26,27}$-$2CH_3$, s), 2.80 (2H, overlapping m), 4.56 and 4.60 (2H, $2H_4$, AB pattern, J = 12.1 Hz), 4.73 (1H, H_1, dt, J = 6.0 Hz, 3.3 Hz), 5.85 (1H, $H_{6\text{ or }7}$, d, J = 11.4 Hz), 6.39 (1H, H_2, dt, J = 6.0 Hz, 2.1 Hz), 6.44 (1H, $H_{7\text{ or }6}$, d, J = 11.5 Hz); ^{13}C-NMR δ 12.0, 18.8, 20.8, 22.2, 23.5, 27.6, 28.8, 29.2, 29.4, 29.7, 36.1, 36.4, 40.4, 44.4, 45.8, 56.3, 56.5, 64.3, 71.1, 77.2, 100.7, 114.5, 121.6, 128.8, 143.9.

A-Nor-3-deoxy-2-oxa-9(11)-didehydro-25-hydroxyvitamin D_3 (5a). The TMS-protected tetraene **23a** (4.6 mg, 0.010 mmol) was placed under argon in a 5 mL round-bottom flask with a stirring bar. Tetrahydrofuran (0.50 mL) was added followed by a solution of TBAF (60 μL, 1.0 M in THF). After 1.25 h, all starting protected tetraene was shown by TLC to be consumed. The reaction mixture was filtered on a short column of SiO_2 that was eluted with 25% ethyl acetate/hexanes (nitrogen pressure). The filtrate was concentrated, avoiding exposure to air. The crude product was purified by HPLC (20% ethyl acetate/hexanes) and the solvent removed, avoiding exposure to air to give the deprotected tetraene **5a** (2.6 mg, 70%) as a colorless oil. The product was shown to be highly unstable, exposure to air over 5 min affording a white solid that was insoluble in acetone. Decanting the NMR sample solution into a flask also gave a white insoluble precipitate. **5a**: ^{1}H-NMR (C_6D_6) δ 0.63 (3H, C_{18}-CH_3, s), 0.91 (3H, C_{21}-CH_3, d, J = 6.4 Hz), 1.08 (6H, $C_{26,27}$-CH_3, s), 2.05 (1H, H_{12}, d, J = 18.2 Hz), 2.25 (1H, H_{12}, dd, J = 18.1 Hz, 6.1 Hz), 2.31 (1H, m), 4.41 (2H, $2H_{1\text{ or }3}$, t, J = 2.0 Hz), 4.44 (2H, $2H_{3\text{ or }1}$, s), 4.97 (1H, $H_{19E\text{ or }Z}$, br s), 5.58 (1H, $H_{19Z\text{ or }E}$, br s), 5.68 (1H, H_{11}, m),

(15) More complete spectral data are given in the supporting information. Selected ^{1}H-NMR (300 MHz) and ^{13}C NMR (75.5 MHz) signals (in $CDCl_3$ except as noted) are also presented in the Experimental Section. The purity of all major isomers or intermediates was estimated by a combination of HPLC and NMR analysis. The level of purity is indicated by the inclusion of copies of ^{1}H-NMR spectra and ^{13}C NMR spectra in the supporting information unless otherwise noted.

6.45 and 6.54 (2H, $H_{6\text{ and }7}$, AB pattern, J = 12.0 Hz), 6.59 (1H, H_9, dd, J = 9.8 Hz, 1.8 Hz).

3-Deoxy-2-oxa-9(11)-didehydro-25-hydroxyvitamin D_3 (5b). The TMS-protected tetraene **23b** (23 mg, 0.050 mmol) was placed under argon in a 5 mL round-bottom flask with a stirring bar. Tetrahydrofuran (0.75 mL) and then a solution of TBAF (0.5 mL, 1.0 M in THF) were added. TLC taken 45 min later showed all starting material was consumed. The mixture was then filtered through a short SiO_2 column with 25% ethyl acetate/hexanes. After the filtrate was concentrated, the residue was purified by HPLC (20% ethyl acetate/hexanes) to give the product **5b** (14.5 mg, 75%) as a colorless oil. **5b**: ^{1}H-NMR δ 0.57 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.22 (6H, $C_{26,27}$-2CH_3, s), 2.44 (2H, $2H_4$, t, J = 5.3 Hz), 3.81 (2H, $2H_3$, t, J = 5.5 Hz), 4.09 (2H, $2H_1$, AB pattern, J = 12.7 Hz), 5.05 (1H, $H_{19E\text{ or }Z}$, d, J = 1.5 Hz), 5.16 (1H, $H_{19E\text{ or }Z}$, d, J = 0.6 Hz), 5.74 (1H, H_{11}, m), 6.10 (1H, $H_{6\text{ or }7}$, d, J = 11.5 Hz), 6.41 (1H, $H_{7\text{ or }6}$, d, J = 11.6 Hz), 6.61 (1H, H_9, d, J = 9.7 Hz); ^{13}C-NMR δ 11.8, 18.4, 20.8, 22.8, 28.0, 29.2, 29.4, 35.9, 36.3, 37.8, 42.9, 43.4, 44.4, 51.8, 56.5, 68.8, 71.1, 73.5, 113.8, 119.5, 121.0, 123.6, 129.4, 135.1, 138.3, 142.3.

A-Homo-3-deoxy-2-oxa-9(11)-didehydro-25-hydroxyvitamin D_3 (5c). The TMS-protected tetraene **23c** (9 mg, 0.019 mmol) was placed under argon in a 5 mL round-bottom flask with a stirring bar. Tetrahydrofuran (0.75 mL) was added followed by a solution of TBAF (0.11 mL, 1.0 M in THF). After 1.5 h, all starting tetraene was shown by TLC to be consumed. The reaction mixture was filtered on a short column of SiO_2 that was eluted with 25% ethyl acetate/hexanes. After the filtrate was concentrated, the crude residue was purified by HPLC (20% ethyl acetate/hexanes) to give the deprotected tetraene **5c** (6.2 mg, 81%) as a colorless oil. **5c**: ^{1}H-NMR δ 0.67 (3H, C_{18}-CH_3, s), 0.92 (3H, C_{21}-CH_3, d, J = 6.4 Hz), 1.07 (6H, $C_{26,27}$-2CH_3, s), 3.54 (2H, $2H_3$, t, J = 5.3 Hz), 4.20 (2H, $2H_1$, br s), 5.08 (1H, $H_{19E\text{ or }Z}$, d, J = 0.6 Hz), 5.18 (1H, $H_{19Z\text{ or }E}$, s), 5.70 (1H, H_{11}, m), 6.46 (2H, $H_{6\text{ or }7}$, d, J = 11.2 Hz), 6.65 (1H, $H_{7\text{ or }6}$, d, J = 11.2 Hz), 6.79 (1H, H_9, dd, J = 10.2 Hz, 1.0 Hz).

3-(2-Propenyloxy)-1-propyne (14a). Sodium hydride (2.81 g, 70.0 mmol, ~60% in mineral oil) was washed with THF (3 × 10 mL) under argon. A mixture of diethyl ether and THF (1:1 v/v, 20 mL) was added and the heterogeneous mixture stirred at 0 °C. A solution of 2-propyn-1-ol (2.0 g, 35.6 mmol) in 5 mL of THF was added dropwise via syringe and left to stir for 45 min. Allyl bromide (5.18 g, 42.7 mmol) was then added, and the mixture was left to stir overnight at room temperature. The reaction mixture was then cooled to 0 °C and quenched slowly with H_2O (20 mL). The mixture was extracted with ether (3 × 30 mL), and the combined organic layers were washed with brine and then dried over Na_2SO_4. Removal of the drying agent and solvent gave a light yellow oil that was fractionally distilled (90−100 °C) to give enyne **14a** (3.0 g, 89%) as a colorless oil. **14a**: ^{1}H-NMR δ 2.41 (1H, sp C-H, t, J = 2.0 Hz), 4.04 (2H, $2H_{1'}$, d, J = 5.6 Hz), 4.12 (2H, $2H_3$, d, J = 2.0 Hz), 5.19 (1H, $H_{3'}$, d, J = 10.5 Hz), 5.28 (1H, $H_{3'}$, dd, J = 17.3 Hz, 0.9 Hz), 5.87 (1H, $H_{2'}$, ddt, J = 16.5 Hz, 10.8 Hz, 5.7 Hz); ^{13}C-NMR δ 56.9, 70.4, 74.3, 79.5, 117.8, 133.8.

4-(2-Propenyloxy)-1-butyne (14b). Sodium hydride (2.00 g, 50.0 mmol, ~60% in mineral oil) was washed with THF (3 × 10 mL) under argon. Another 10 mL of THF was added and the heterogeneous mixture was stirred at 0 °C. A solution of 3-butyn-1-ol (2.0 g, 28.5 mmol) in 4 mL of THF was added dropwise via syringe and the mixture left to stir for 45 min. Allyl bromide (4.14 g, 34.2 mmol) was then added, and the mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C and quenched slowly with H_2O (20 mL). The mixture was extracted with ether (3 × 30 mL), and the combined organic layers were washed with brine and then dried over Na_2SO_4. Removal of the drying agent and solvent gave a light yellow oil that was distilled under aspirator pressure at 80 °C to give the enyne **14b** (2.2 g, 70%) as a colorless oil. **14b**: ^{1}H-NMR δ 1.98 (1H, sp C-H, t, J = 2.6 Hz), 2.47 (2H, $2H_3$, td, J = 6.9 Hz, 2.6 Hz), 3.56 (2H, $2H_4$, t, J = 6.9 Hz), 4.02 (2H, $2H_{1'}$, dd, J = 4.5 Hz, 1.2 Hz), 5.19 (1H, $H_{3'}$, dd, J = 10.3 Hz, 1.2 Hz), 5.28 (1H, $H_{3'}$, dd, J = 17.2 Hz, 1.5 Hz), 5.90 (1H, $H_{2'}$, ddt, J = 17.2 Hz, 10.7 Hz, 5.4 Hz); ^{13}C-NMR δ 19.6, 67.9, 69.1, 71.6, 80.9, 116.8, 134.3.

5-(2-Propenyloxy)-1-pentyne (14c). Sodium hydride (1.66 g, 41.6 mmol, ~60% in mineral oil) was washed with 3 × 5 mL of THF under argon, 10 mL of THF was added, and the heterogeneous mixture was stirred at 0 °C. A solution of 4-pentyn-1-ol (2.0 g, 23.7 mmol) in 3 mL of THF was added dropwise via syringe and the mixture left to stir for 45 min. Allyl bromide (3.44 g, 2.46 mL, 28.4 mmol) was then added, and the mixture was left to stir overnight at room temperature. The reaction mixture was then cooled to 0 °C and quenched slowly with H_2O (20 mL). The mixture was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine and then dried over Na_2SO_4. Removal of the drying agent and solvent gave a light yellow oil that was distilled (Kugelrohr, aspirator pressure, 85 °C) to give enyne **14c** (2.70 g, 92%) as a colorless oil. **14c**: ^{1}H-NMR δ 1.75 (2H, H_4 quintet, J = 6.6 Hz), 1.90 (1H, sp C-H, apparent t, J = 2.0 Hz), 2.25 (2H, $2H_3$, td, J = 7.0 Hz, 2.6 Hz), 3.48 (2H, $2H_5$, t, J = 6.2 Hz), 3.92 (2H, $2H_{1'}$, d, J = 5.3 Hz), 5.12 (1H, $H_{3'}$, apparent d, J = 10.2 Hz), 5.22 (1H, $H_{3'}$, apparent d, J = 17.3 Hz), 5.86 (1H, $H_{2'}$, ddt, J = 16.6 Hz, 10.6 Hz, 5.3 Hz); ^{13}C-NMR δ 15.2, 28.6, 68.4, 68.5, 71.8, 83.8, 116.6, 134.8.

De-A,B-25-[(trimethylsilyl)oxy]cholest-9(11)-en-8-one (20). A solution of *n*-BuLi (1.32 M in hexanes, 954 μL, 1.26 mmol) was added dropwise via syringe to a stirred solution of diisopropylamine (129 mg, 1.26 mmol) in THF (3 mL) at 0 °C. This was left to stir for 15 min and then cooled to −78 °C. A solution of ketone **19** (375 mg, 1.06 mmol) in THF (2 mL) was then added dropwise via syringe, and the resulting light yellow solution was stirred at −78 °C for 1 h. To this solution was added a solution of phenylselenenyl chloride (241 mg, 1.26 mmol) in THF (1.5 mL), and the mixture changed from light yellow to green. After 1 h, solid NH_4Cl (~4 g) was added, and then the mixture was allowed to warm to room temperature. The deep yellow solution was filtered with ether through a short column of neutral alumina and the filtrate concentrated to give crude selenide as a yellow oil (593 mg). The crude selenide was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C with stirring. *m*-CPBA (454 mg, 2.1 mmol, 80%) was added in several portions over 10 min. The resulting white cloudy mixture was stirred for another 15 min at 0 °C, and then solid $NaHCO_3$ (~4 g) was added. The mixture was allowed to warm to room temperature and then filtered with ether through a short column of neutral alumina. The filtrate was concentrated, and then the residue was purified by flash chromatography to give 279 mg (75%) of a colorless oil that solidified upon cooling in a freezer to a soft, white solid. **20**: ^{1}H-NMR δ 0.09 (9H, $SiMe_3$, s), 0.74 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.20 (6H, $C_{26,27}$-2CH_3, s), 5.98 (1H, H_9, dd, J = 9.9 Hz, 2.9 Hz), 6.75 (1H, H_{11}, ddd, J = 9.7 Hz, 5.7 Hz, 2.2 Hz); ^{13}C-NMR δ 2.6, 11.9, 18.3, 19.3, 20.6, 27.4, 29.8, 29.9, 35.3, 36.1, 42.9, 45.0, 47.4, 56.7, 59.1, 73.9, 129.4, 147.4, 201.8.

De-A,B-8-(*trans*-bromomethylene)-25-[(trimethylsilyl)-oxy]cholest-9(11)-ene (21). (Bromomethylene)triphenylphosphonium bromide (3.12 g, 7.15 mmol) was placed into a 50 mL two-neck round-bottom flask and dried overnight under vacuum at 70 °C. After the compound was cooled under argon to room temperature, THF (16 mL) was added and the resulting suspension was cooled to −78 °C with stirring. Sodium hexamethyldisilazide (1 M in THF, 7.0 mL, 7.0 mmol) was then added dropwise, and the yellow suspension was allowed to stir at −78 °C for 2 h. A solution of enone **20** (375 mg, 1.06 mmol) in THF (2 mL) was added dropwise. The cooling bath was removed and the mixture allowed to warm to room temperature over a 3 h period. This brown mixture was filtered through a short column of SiO_2 (10% ethyl acetate/hexanes), and the residue after solvent removal was purified by HPLC (0.25% ethyl acetate/hexanes) to give vinyl bromide **21** (180 mg, 40%) as a colorless oil that turned slightly yellow upon storage. **21**: ^{1}H-NMR δ 0.10 (9H, $SiMe_3$, s), 0.58 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 6.2 Hz), 1.20 (6H, $C_{26,27}$-2CH_3, s), 2.37 (1H, H_{12}, dd, J = 18.2 Hz, 5.7 Hz), 5.76 (1H, CHBr, br s), 5.89 (1H, H_{11}, m), 6.45 (1H, H_9, dd, J = 9.6 Hz,

2.0 Hz); ^{13}C-NMR δ 2.6, 11.7, 18.4, 20.8, 22.4, 28.0, 29.8, 29.9, 35.8, 36.3, 42.5, 43.5, 45.2, 52.1, 55.9, 74.1, 100.3, 124.5, 132.3, 141.4.

19-Nor-3-deoxy-3-oxa-1,2,9(11)-tetradehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (25a), De-A-(B-nor)-19-(2′-propenoxy)-25-[(trimethylsilyl)oxy]cholesta-5(10),6(8),9-(11)-triene (26a), 19-Nor-3-deoxy-3-oxa-1(10),9(11)-tetradehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (24a), and A-Nor-3-deoxy-2-oxa-9(11)-didehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (23a). A solution of tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.0087 mmol, 15%), triphenylphosphine (4 mg, 0.015 mmol, 26%), toluene (0.25 mL), and triethylamine (0.5 mL) was prepared under argon at room temperature in a vial. A solution of CD vinyl bromide **21** (25 mg, 0.058 mmol) and enyne **14a** (9 mg, 0.094 mmol, 11 μL), in toluene (0.25 mL) was added via syringe. The vial was then capped, and the mixture was heated at 80 °C for 4 h. The mixture was cooled to room temperature and filtered through a short column of silica gel. After removal of the solvent, the remaining palladium was removed by flash chromatography (10% ethyl acetate/hexanes). The crude residue was purified by HPLC (0.5% ethyl acetate/hexanes) to give four major peaks: **A**, **B**, **C**, and **D**. Peak **A** was identified as 19-nor-3-deoxy-3-oxa-1,2,9(11)-tetradehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (**25a**, 6 mg, 23%). Peak **B** was identified as de-A-(B-nor)-19-(2′-propenoxy)-25-[(trimethylsilyl)oxy]cholesta-5(10),6(8),9(11)-triene (**26a**, 3 mg, 12%). Peak **C** was identified as 19-nor-3-deoxy-3-oxa-1(10),9(11)-tetradehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (**24a**, 2 mg, 8%). Peak **D** was identified asA-nor-3-deoxy-2-oxa-9(11)-didehydro-25-[(trimethylsilyl)oxy]-vitamin D_3 (**23a**, 3.0 mg, 12%). **23a**: ^{1}H-NMR δ 0.10 (9H, $SiMe_3$, s), 0.59 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 5.8 Hz), 1.20 (6H, $C_{26,27}$-$2CH_3$, s), 4.49 (2H, $2H_{1\text{ or }3}$, s), 4.52 (2H, $2H_{3\text{ or }1}$, s), 5.18 (1H, $H_{19E\text{ or }Z}$, br s), 5.47 (1H, $H_{19Z\text{ or }E}$, br s), 5.81 (1H, H_{11}, m), 6.28 (1H, $H_{6\text{ or }7}$, d, J = 12.1 Hz), 6.56 (2H, H_9 and $H_{7\text{ or }6}$, overlapping m). **24a**: ^{1}H-NMR δ 0.103 and 0.104 (9H, $SiMe_3$, two s), 0.57 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 6.0 Hz), 1.20 (6H, $C_{26,27}$-$2CH_3$, s), 4.24 (2H, $2H_4$, br s), 4.55 and 4.49 (2H, $2H_2$, AB pattern, J = 14.0 Hz), 5.81 (3H, m), 6.27 (2H, m), 6.59 (1H, d, J = 10.3 Hz); ^{13}C-NMR δ 2.6, 11.8, 18.4, 20.9, 22.8, 28.0, 29.8, 29.9, 35.9, 36.3, 43.0, 43.6, 45.2, 52.0, 56.7, 64.9, 65.6, 74.1, 117.3, 120.6, 123.3, 126.6, 128.2, 130.3, 130.4, 140.1. **25a**: ^{1}H-NMR δ 0.11 (9H, $SiMe_3$, s), 0.58 (3H, C_{18}-CH_3, s), 0.95 (3H, C_{21}-CH_3, d, J = 6.0 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 2.80 (2H, br s), 4.60 (2H, $2H_4$, AB pattern, J = 12.8 Hz), 4.75 (1H, H_1, dt, J = 5.9 Hz, 3.2 Hz), 5.76 (1H, H_{11}, m), 5.92 (1H, $H_{6\text{ or }7}$, d, J = 11.8 Hz), 6.41 (1H, H_2, dt, J = 6.0 Hz, 2.1 Hz), 6.58 (2H, H_9 and $H_{7\text{ or }6}$, two overlapping d's, J = 11.1 Hz); ^{13}C-NMR δ 2.6, 11.8, 18.4, 20.9, 22.8, 28.0, 29.79, 29.84, 29.9, 35.9, 36.3, 42.9, 43.4, 45.2, 51.8, 56.7, 64.2, 74.1, 77.2, 100.6, 116.8, 121.1, 123.3, 130.0, 139.1, 143.9. **26a**: ^{1}H-NMR δ 0.11 (9H, $SiMe_3$, s), 0.61 (3H, C_{18}-CH_3, s), 0.95 (3H, C_{21}-CH_3, d, J = 5.7 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 1.97 (2H, m), 2.32 (1H, H_{12}, d, J = 18.2 Hz), 2.58 (1H, m), 2.70 (1H, H_{12}, dd, J = 18.4 Hz, 6.4 Hz), 4.02 (2H, $2H_{1'}$, dt, J = 6.8 Hz, 1.2 Hz), 4.30 (2H, $2H_{19}$, br s), 5.18 (1H, $H_{3'}$, d with fine structure, J = 11.0 Hz), 5.29 (1H, $H_{3'}$, dq, J = 17.2 Hz, 1.6 Hz), 5.96 (3H, H_{11}, $H_{2'}$ and $H_{5\text{ or }6}$, overlapping m), 6.41 (1H, $H_{6\text{ or }5}$, d, J = 6.0 Hz); ^{13}C-NMR δ 2.6, 12.1, 18.6, 20.9, 23.1, 28.5, 29.9, 30.0, 35.9, 36.5, 43.2, 45.2, 48.4, 49.0, 55.3, 67.9, 71.2, 74.1, 115.7, 116.9, 122.0, 135.0, 135.1, 139.5, 144.7, 145.0.

De-A-(B-nor)-19-[(2″-propenoxy)methyl]-25-[(trimethylsilyl)oxy]cholesta-5(10),6(8),9(11)-triene (26b), 3-Deoxy-2-oxa-9(11)-didehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (23b), and 19-Nor-A-homo-3-deoxy-3-oxa-1(10),9(11)-tetradehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (24b). Tetrakis(triphenylphosphine)palladium(0) (7 mg, 0.006 mmol) and triphenylphosphine (3 mg, 0.011 mmol) were added to a vial under argon. Triethylamine (0.5 mL) and toluene (0.25 mL) were then added followed by a solution of vinyl bromide **21** (24 mg, 0.056 mmol) and enyne **14b** (8.5 mg, 0.077 mmol, 10 μL) in toluene (0.25 mL). The vial was capped, and the mixture was heated for 4 h at 80 °C. After being cooled to room temperature, the reaction mixture was filtered through a plug of SiO_2, and then flash chromatography was performed on the concentrated filtrate to remove the remaining palladium. The products were separated by HPLC (1% ethyl acetate/hexanes) to give four major peaks: **A**, **B**, **C**, and **D**. Peak **A** was identified as de-A-(B-nor)-19-[(2″-propenoxy)-methyl]-25-[(trimethylsilyl)oxy]cholesta-5(10),6(8),9(11)-triene (**26b**, 4.5 mg, 18%). Peak **B** was tentatively assigned as an uncyclized A ring product (5.4 mg) but was not characterized further. Peak **C** was identified as 3-deoxy-2-oxa-9(11)-didehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (**23b**, 6.7 mg, 27%). Peak **D** was idenified as 19-nor-A-homo-3-deoxy-3-oxa-1(10),9(11)-tetradehydro-25-[(trimethylsilyl)oxy]vitamin D_3 (**24b**, 4 mg, 16%). **23b**: ^{1}H-NMR δ 0.10 (9H, $SiMe_3$, s), 0.58 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 6.1 Hz), 1.20 (6H, $C_{26,27}$-$2CH_3$, s), 2.44 (2H, $2H_4$, t, J = 5.3 Hz), 3.81 (2H, $2H_3$, t, J = 5.5 Hz), 4.09 (2H, $2H_1$, AB pattern, J = 12.6 Hz), 5.05 (1H, $1H_{19E\text{ or }Z}$, d, J = 0.9 Hz), 5.16 (1H, $1H_{19E\text{ or }Z}$, d, J = 1.6 Hz), 5.75 (1H, H_{11}, m), 6.11 (1H, $H_{6\text{ or }7}$, d, J = 11.5 Hz), 6.41 (1H, $H_{7\text{ or }6}$, d, J = 11.6 Hz), 6.61 (1H, H_9, d, J = 9.9 Hz). **24b**: ^{1}H-NMR δ 0.10 (9H, Si-Me_3, s), 0.58 (3H, C_{18}-CH_3, s), 0.94 (3H, C_{21}-CH_3, d, J = 6.0 Hz), 1.20 (6H, $C_{26,27}$-$2CH_3$, s), 2.68 (2H, $2H_{4a}$, t, J = 5.4 Hz), 3.83 (2H, $2H_4$, t, J = 5.5 Hz), 4.30 (2H, $2H_2$, d, J = 2.5 Hz), 5.74 (2H, H_{11} and H_1, overlapping m with H_1 discernible as a dt, J = 12.3, 3 Hz, centered at δ 5.72), 6.03 (1H, $H_{6\text{ or }7}$, d, J = 11.9 Hz), 6.38 (1H, $H_{7\text{ or }6}$, d, J = 11.9 Hz), 6.59 (1H, H_9, d, J = 9.8 Hz), 6.66 (1H, H_{10}, d, J = 12.1 Hz). **26b**: ^{1}H-NMR δ 0.10 (9H, $SiMe_3$, s), 0.63 (3H, C_{18}-CH_3, s), 1.06 (3H, C_{21}-CH_3, d, J = 5.9 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 2.72 (2H, $2H_{19}$, t, J = 6.6 Hz), 3.03 (2H, $2H_{12}$, s), 3.53 (2H, $2H_{1'}$, t, J = 7.1 Hz), 3.98 (2H, $2H_{1''}$, d, J = 4.8 Hz), 5.16 (1H, $H_{3''}$, d, J = 10.2 Hz), 5.26 (1H, $H_{3''}$, d, J = 17.9 Hz), 5.71 (1H, H_{11}, br s), 5.90 (1H, $H_{2''}$, ddt, J = 16.7 Hz, 10.7 Hz, 5.6 Hz), 6.29 (1H, $H_{6\text{ or }5}$, d, J = 9.8 Hz), 6.44 (1H, $H_{5\text{ or }6}$, d, J = 9.7 Hz).

De-A-(B-nor)-19-[2′-(2″-propenoxy)ethyl]-25-[(trimethylsilyl)oxy]cholesta-5(10),6(8),9(11)-triene (26c) and A-Homo-3-deoxy-2-oxa-9(11)-didehydro-25-[(trimethylsilyl)-oxy]vitamin D_3 (23c). A solution of tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.020 mmol, 20%), triphenylphosphine (7.7 mg, 0.029 mmol, 30%), toluene (0.50 mL), and triethylamine (1.00 mL) was prepared under argon at room temperature in a vial. A solution of CD-vinyl bromide **21** (42 mg, 0.098 mmol) in toluene (0.50 mL) and then enyne **14c** (18.2 mg, 0.15 mmol, 2.2 μL) were added successively to the catalyst solution. The vial was then capped and the mixture was heated at 80 °C for 20 h. After being cooled to room temperature, the reaction mixture was filtered through a short column of silica gel. The filtrate was concentrated and the remaining palladium removed by flash chromatography (10% ethyl acetate/hexanes). After removal of the solvent, the crude residue was purified by HPLC (0.5% ethyl acetate/hexanes) to give three major peaks **A**, **B**, and **C**. Peak **A** was identified as de-A-(B-nor)-19-[2′-(2″-propenoxy)ethyl]-25-[(trimethylsilyl)oxy]cholesta-5(10),6(8),9(11)-triene (**26c**, 8.0 mg, 17%). Peak **B** was apparently uncyclized A-ring product (8.6 mg), which was not examined further. Peak **C** was identified as A-homo-3-deoxy-2-oxa-9(11)-didehydro-25-[(trimethylsilyl)-oxy]vitamin D_3 (**23c**, 6.1 mg, 13%). **23c**: ^{1}H-NMR δ 0.10 (9H, $SiMe_3$, s), 0.57 (3H, C_{18}-CH_3, s), 0.93 (3H, C_{21}-CH_3, d, J = 6.0 Hz), 1.20 (6H, $C_{26,27}$-$2CH_3$, s), 3.77 (2H, $2H_3$, t, J = 5.2 Hz), 4.27 (2H, $2H_1$, s), 5.05 (1H, $H_{19E\text{ or }Z}$, br s), 5.18 (1H, $H_{19Z\text{ or }E}$, br s), 5.72 (1H, H_{11}, m), 6.10 (1H, $H_{6\text{ or }7}$, d, J = 11.4 Hz), 6.51 (1H, $H_{7\text{ or }6}$, d, J = 11.4 Hz), 6.60 (1H, H_9, d, J = 10.2 Hz); ^{13}C-NMR δ 2.6, 11.8, 18.4, 20.9, 22.8, 28.0, 29.8, 29.9, 32.3, 36.0, 36.3, 37.0, 43.0, 43.4, 45.2, 51.8, 56.7, 73.7, 75.5, 77.2, 114.8, 121.1, 123.8, 124.0, 129.0, 137.7, 140.6, 147.4. **26a**: ^{1}H-NMR δ 0.10 (9H, $SiMe_3$, s), 0.63 (3H, C_{18}-CH_3, s), 1.06 (3H, C_{21}-CH_3, d, J = 6.3 Hz), 1.21 (6H, $C_{26,27}$-$2CH_3$, s), 2.50 (2H, $H_{12\text{ or }19}$, t, J = 7.4 Hz), 2.98 (2H, $H_{19\text{ or }12}$, m), 3.38 (2H, $2H_{2'}$, t, J = 6.5 Hz), 3.94 (2H, $2H_{1''}$, dt, J = 5.6 Hz, 1.3 Hz), 5.16 (1H, $H_{3''}$, dq, J = 10.3 Hz, 1.3 Hz), 5.26 (1H, $H_{3''}$, dq, J = 17.2 Hz, 1.6 Hz), 5.69 (1H, H_{11}, d, J = 1.62 Hz), 5.92 (1H, $H_{2''}$, ddt, J = 16.5 Hz, 10.4 Hz, 5.8 Hz), 6.28 (1H, $H_{6\text{ or }7}$, d, J = 9.8 Hz), 6.41 (1H, $H_{7\text{ or }6}$, d, J = 9.9 Hz); ^{13}C-NMR δ 2.6, 14.6, 18.8, 20.9, 22.2, 24.8, 29.4, 29.8, 29.9, 30.2, 36.3, 36.6, 43.1, 45.2, 46.2, 50.1, 50.5, 69.7, 71.9, 74.1, 116.7, 118.5, 120.2, 135.0, 136.6, 139.4, 140.0, 146.8.

Inhibition Assay. 1-OHase assays were performed using

mitochondria (3−4 mg protein/mL) from 3-week old, vitamin D deficient chicks as previously described.[5a] Mitochondria were isolated from kidney tissue by differential centrifugation in 10% 0.25 M sucrose. The 1-OHase assay was carried out at 37 °C, for 10 or 12 min, in a final volume of 2 mL containing 10 mM malate, 75 mM sucrose, 28 mM Tris-Cl, 16.8 mM KCl, and 6.72 mM $MgCl_2$. Reactions were started by adding 5 μL of the substrate, 10^{-7} M 25-OH-[26,27-^{3}H]vitamin D_3 (40 mCi/mmol), and 5 μL of vehicle (ethanol) or appropriate analog (10^{-8}, 10^{-7}, or 10^{-6} M). The reaction was stopped by the addition of $CHCl_3$ methanol (1:2, v/v). Metabolites were measured using normal phase HPLC after lipid separation by a modified Bligh and Dyer method.

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Supporting Information Available: Spectral and analytical data (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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