Studies on the Opening of Dioxanone and Acetal Templates and Application to the Synthesis of 1α,25-Dihydroxyvitamin D_2[1]

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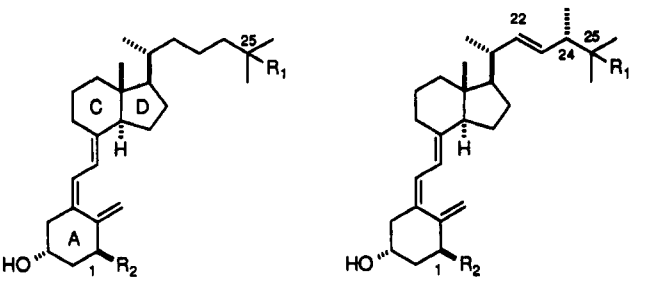
The Lewis-acid-mediated nucleophilic substitution of dioxanone and acetal templates for the construction of 25-hydroxylated side chains of vitamin D_2 metabolites and analogs has been studied. As an application a highly stereoselective synthesis of 1α,25-dihydroxyvitamin D_2 by the dienyne route is described.

Introduction

Research carried out during the last two decades has led to the discovery that vitamin D_3 (**1a**, Figure 1), the natural vitamin D, is transformed via successive hydroxylations in the liver and in the kidney into 1α,25-dihydroxyvitamin D_3 (**1b**). This metabolite, the hormonally active form of vitamin D_3, is an important factor in the regulation of mineral metabolism.[2] It has recently been discovered that **1b** is also involved in the regulation of cell proliferation and differentiation processes.[3] This finding has renewed the interest of chemists and biochemists in the vitamin D field due to the possibility of treating of several types of cancer and skin disorders with this hormone or its analogs.[4,5]

It has been assumed that the metabolism and biological activity of the nonnatural vitamin D_2 (**2a**) parallel those of vitamin D_3, and for this reason it has been administered to humans and commercially important mammals.[2a,6] However, although it is well-established that vitamin D_2 also undergoes double hydroxylation to 1α,25-dihydroxyvitamin D_2 (**2b**), differences in posterior metabolism and biological activity between **2b** and **1b** have also been identified.[7,8] Further details of the biological significance of 1α,25-dihydroxyvitamin D_2 remain largely unexplored due to the scarcity of synthetic material. Interest in the biological evaluation of vitamin D_2 metabolites has previously led us to synthesize 25-hydroxyvitamin D_2 (**2c**).[9] We now report our results on the synthesis of the more important 1α,25-dihydroxyvitamin D_2 (**2b**).



1a, $R_1 = R_2 = H$
1b, $R_1 = R_2 = OH$

2a, $R_1 = R_2 = H$
2b, $R_1 = R_2 = OH$
2c, $R_1 = OH$; $R_2 = H$

Figure 1.

Results and Discussion

Synthetic Strategy (Scheme I). Although considerable effort has been devoted to the synthesis of vitamin D_3 metabolites,[10] to date only two syntheses of 1α,25-hydroxyvitamin D_2 have been reported.[11] Our synthetic approach to the above metabolite (Scheme I) is based on previous findings of Lythgoe and co-workers, who were able to obtain the triene system of vitamin D from the corresponding dienyne precursor by partial hydrogenation

(1) (a) This article was taken in part from PhD thesis of Juan R. Granja (Universidad de Santiago, July 1988). (b) For preliminary communications describing part of this work, see: Castedo, L.; Granja, J.; Maestro, M. A.; Mouriño, E. *Tetrahedron Lett.* **1987**, *28*, 4589. (c) Mouriño, A.; Castedo, L.; Fernández, B. R.; Granja, J.; Maestro, M. A.; Mascareñas, J. L.; Sarandeses, L. A. *Vitamin D. Molecular, Cellular and Clinical Endocrinology*; Norman, A. W., Schaefer, K., Grigoleit, H. G., Herrath, D. v., Eds.; Walter de Gruyter: Berlin, New York, 1988; p 34.

(2) (a) Norman, A. W. *Vitamin D, The Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979. (b) De Luca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1. (c) Norman, A. W. *Vitamin D, Molecular Biology and Clinical Nutrition*; Marcel Dekker: New York, 1980. DeLuca, H. F.; Schnoes, H. K. *Ann. Rev. Biochem.* **1983**, *52*, 411. (d) Ikekawa, M. *Med. Chem. Rev.* **1987**, *7*, 333. (e) Dickson, I. *Nature* **1987**, *325*, 18.

(3) For reviews, see: (a) Ostrem, V. K.; DeLuca, H. F. *Steroids* **1987**, *40*, 74. (b) Holick, H. F. 1α,25-$(OH)_2$-D_3 a Novel Hormone with Unlimited Potential. *Kidn. Int.* **1987**, *32*, 912.

(4) For some analogs of 1α,25-$(OH)_2$-D_3 with promising properties for the treatment of psoriasis, see: Figadère, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. *J. Med. Chem.* **1991**, *34*, 2452 and references cited therein.

(5) For a summary of the role of the vitamin D endocrine system in health and disease see: (a) Reichel, H.; Koeffler, H. P.; Norman, A. W. *N. Engl. J. Med.* **1989**, *320*, 980. (b) DeLuca, H. F.; Burmester, J.; Darwish, H.; Krisinger, J. *Comprehensive Medicinal Chemistry*; Pergamon Press: New York, 1990; Vol. 3, p 1129.

(6) DeLuca, H. F. *Hanbd. Physiol.* **1978**, *7*, 265.

(7) (a) Jones, G.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1975**, *14*, 1250. (b) Norman, A. W.; Roth, J.; Orci, L. *Endocr. Rev.* **1982**, *3*, 331. (c) Reddy, G. S.; Tserng, K. *Biochemistry* **1986**, *25*, 5328 and references cited therein. (d) Koszewski, N. J.; Reinhardt, T. A.; Napoli, J. L.; Beitz, D. C.; Horst, R. L. *Biochemistry* **1988**, *27*, 5785.

(8) Interestingly, it has also been reported that vitamin D_2; and some of its metabolites are less toxic than the corresponding compounds of the vitamin D_3 series: (a) Hunt, R. D.; Garcia, F. G.; Wals, R. J. *J. Nutr.* **1972**, *102*, 957. (b) Sjoden, G.; Smith, C., Lindgren, U.; DeLuca, H. F. *Proc. Soc. Exp. Biol. Med.* **1985**, *178*, 432. (c) Tjellesen, L.; Christiansen, C.; Hummer, L. *Vitamin D: Chemical, Biochemical and Clinical Update*; Norman, A. W., Schaefer, K., Grigoleit, H. G., Herrath, D. v., Eds.; Walter de Gruyter: Berlin, 1985; pp 3-12. (d) Tjellensen, L.; Gotfredsen, A.; Christiansen, C. *Calcif. Tissue Int.* **1985**, *37*, 218.

(9) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264.

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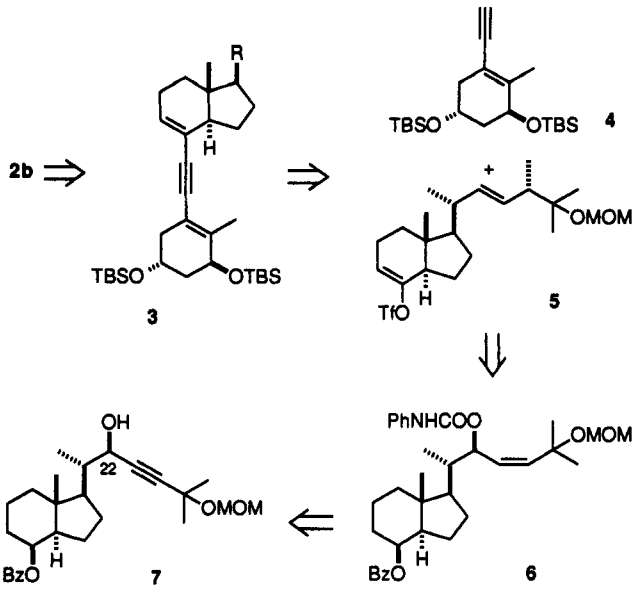
(11) (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098. (b) Sicinski, R. R.; Tanaka, Y.; Schnoes, H. K.; DeLuca, H. F. *Bioorganic Chem.* **1985**, *13*, 158. For syntheses of the 25-hydroxyvitamin D_2 side chain, see: (c) Wilson, S. R.; Davey, A. E.; Guazzaroni, M. E. *J. Org. Chem.* **1992**, *57*, 2007. (d) Hanekamp, J. C.; Rookhuizen, R. B.; Hevel, H.; Bos, H. J. T.; Brandsma, L. *Tetrahedron Lett.* **1991**, *32*, 5397.

0022-3263/93/1958-0124$04.00/0

Scheme I



and subsequent thermal isomerization.[12] The dienyne **3** is envisaged as the result of palladium-catalyzed coupling between the known enyne **4**[13] and the vinyl triflate **5**.[14] Our synthesis of vinyl triflate **5** was based on our previous work on the construction of 25-hydroxyvitamin D_2 side chain by stereospecific S_N2' syn displacement of carbamates with cuprates.[9,15] However, instead of stereoselectively reducing a propargyl ketone, which gives at best a 17:1 mixture of the desired 22*R*-alcohol **7** and its inseparable 22*S*-epimer,[9] we decided to explore an alternative route that could lead to **7** highly stereoselectively and more reproducibly.

Lewis-Acid-Mediated Nucleophilic Substitution of Dioxanone and Acetal Templates. For the construction of **7** and its 22*S*-isomer, we studied the Lewis-acid-assisted nucleophilic opening of chiral acetals and dioxanones discovered by Johnson[16] and Seebach,[17] respectively. These reactions have evolved as powerful methods for the stereoselective formation of carbon–carbon bonds.[16-18] The required known aldehyde **9a**[9,19] (Figure 2) was prepared in 95% yield from benzoate **8**[20] [(i) O_3, MeOH, CH_2Cl_2, py, (ii) $(EtO)_3P$].[1b] The acetals **10a–g** were prepared (82–97%) by reaction of the aldehyde **9a** with the corresponding diol in the presence of $BF_3{\cdot}OEt_2$.[21] The nonepimerization of the starting aldehyde **9a** at C(20) during acetal formation was demonstrated for **10a**, the ^1H NMR spectrum of which differed from that of its 20*R*-epimer **11**, which was prepared under the same reaction conditions from aldehyde **9b**.[22] Dioxanone **10h** was prepared in 95% yield by Noyori's procedure.[23] Treatment of aldehyde **9a** with the bis-silyl derivative of (*R*)-3-hydroxybutyric acid[24] in CH_2Cl_2 at −78 °C in the presence of 4% trimethylsilyl triflate and 2% 2,6-di-*tert*-butylpyridine.

Preliminary experiments were carried out using silylacetylene **12a** and acetals **10a** and **10b** in CH_2Cl_2 and in the presence of $TiCl_4$ (1.6 equiv, −78 °C, 5 min).[25] Although it has previously been reported that the reaction of similar substrates with simple silylacetylenes opens the acetal moiety to give almost exclusively the 22*R*-isomer,[26] in our cases no reaction took place. We therfore tried stronger nucleophilic reagents such as stannylacetylene **12b**.[1b,27] As previously reported,[1b] in the presence of $TiCl_4$, **12b** reacted with the chiral dioxane **10a** to give an 87:1 mixture of **13a** and **14a** (95% entry 1, Table I), in both of which the C(25)-OH group is deprotected.[28] Treatment of **10b** with **12b** under the same reaction conditions gave a 3:2 mixture of **13b** and **14b** (89%, entry 2), indicating that the stereogenic center at C(20) does not play an important role in inducing stereoselectivity.[29] Efforts to improve the stereoselectivity of the reaction by using Lewis acids other than $TiCl_4$ (including the recommended titanium blend [6/5 $TiCl_4$/Ti(O-*i*-Pr)$_4$][16c]) were unsuccessful (entries 3–6). The use of other stannylacetylenes to avoid deprotection of the hydroxyl group at C(25) was also unsuccessful (entries 7–10).

We next studied the reaction of **12b** with acetals **10c–e**. The reaction of acetal **10c** derived from (2*S*,4*S*)-2,4-pentanediol under the usual reaction conditions proceeded

(12) (a) Dawson, T. M.; Dixon, J.; Littleword, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc.* (c) **1971**, 2960. (b) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2654.

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(14) For related palladium-catalyzed couplings, see: (a) Castedo, L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1986**, *27*, 1523. (b) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. *Tetrahedron Lett.* **1988**, *29*, 1203. (c) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485. (d) Curtin, M. L.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 6958.

(15) Sardina, F. J.; Mouriño, A. Castedo, L. *Tetrahedron Lett.* **1983**, *24*, 4477.

(16) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D.; *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (c) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951. For reviews, see: (d) Seebach, D.; Imwinkelreid, R.; Weber, T. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Berlin, 1986, Vol. 4, p 125. (e) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

(17) (a) Seebach, D.; Imwinkelreid, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448. (b) Seebach, D.; Zimmerman, J.; Gysel, H.; Ziegler, R.; Ha, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.

(18) For recent reports of detailed mechanistic studies, see: (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (c) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (d) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (e) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997.

(19) (a) Inhoffen, H. H.; Quinkert, G.; Schütz, S.; Friedrich, G.; Tober, E. *Chem. Ber.* **1958**, *91*, 781. (b) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608.

(20) Benzoate **8** was prepared in 95% yield from the corresponding known alcohol (BzCl, py). For the preparation of this alcohol see: (a) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414. (b) Mascareñas, J. L.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1269.

(21) Efforts to prepare these acetals using PPTS and azeotropic removal of water in various solvents (benzene, CH_2Cl_3, toluene) were unsuccessful.

(22) The aldehyde **9b** was obtained by refluxing a solution of **9a** in *s*-collidine for 48 h, followed by reduction of the crude mixture with $NaBH_4$, separation of alcohols **18a** and **18b**, and further oxidation of **18b** with PDC to give **9b**.

(23) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, *27*, 2945. Pure dioxanone **10h** was obtained by crystallization from a solution of the resulting 20:1 mixture of **10h** and its trans isomer in Et_2O.

(24) For an economical method for the preparation of (*R*)-3-hydroxybutyric acid by depolymerization of inexpensive poly(hydroxybutanoate), see: (a) Seebach, D.; Züger, M. F. *Helv. Chim. Acta* **1982**, *65*, 495; (b) Seebach, D.; Züger, M. F. *Tetrahedron* **1984**, *25*, 2747.

(25) Increasing amounts of $TiCl_4$ (1–10 equiv) gave the starting aldehyde **9a** or a mixture of **9a** and its dimethoxy acetal.

(26) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

(27) This reagent has also recently been used for the opening of steroidal acetal templates: Yamamoto, Y.; Abe, H.; Nishii, S.; Yamada, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3253.

(28) The ratio of compounds **13a** and **14a** were determined by HPLC. In previous experiments,[1b] the ratio of these compounds was determined by ^1H NMR.

(29) For discussion of the opening of α-substituted chiral acetals, see ref 18b and references cited therein.

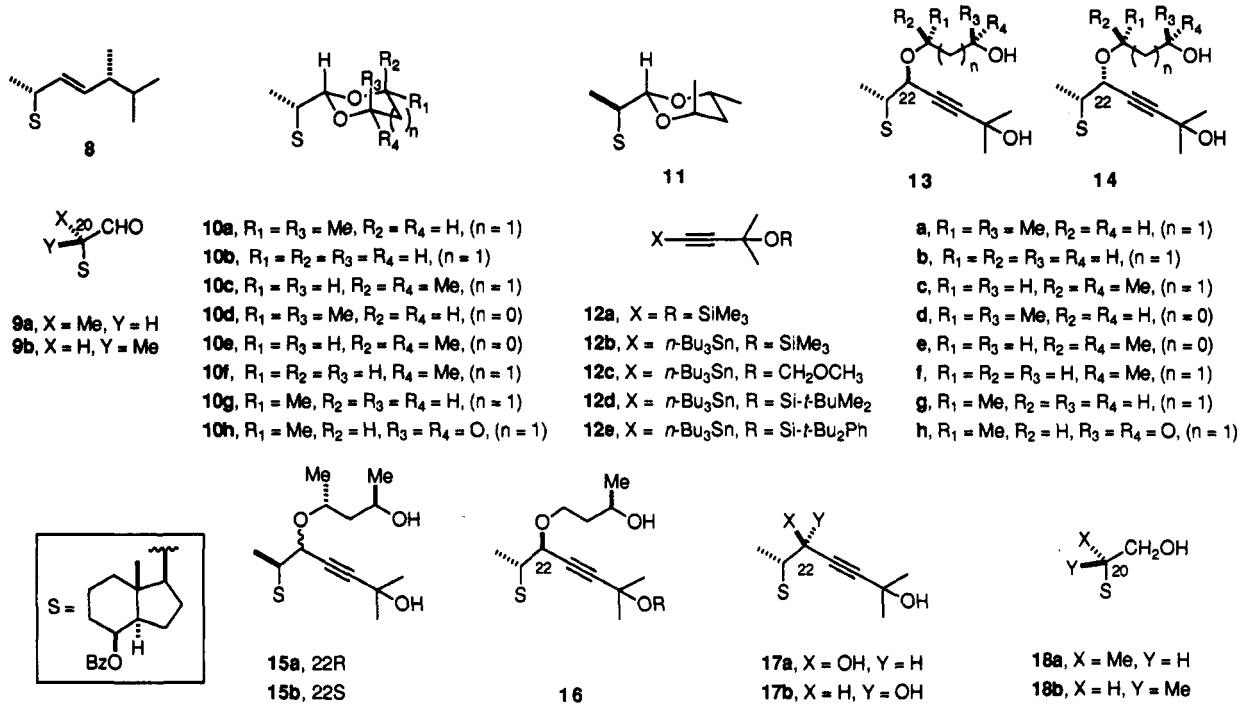


Figure 2.

Table I. Lewis-Acid-Mediated Opening of Dioxanones and Acetal Templates[a]

entry	substrate	reagent	Lewis acid	products (yield (%))	22*R*:22*S* ratio
1	**10a**	**12b**	$TiCl_4$	**13a, 14a** (95)	87:1[b]
2	**10b**	**12b**	$TiCl_4$	**13b, 14b** (89)	3:2[c]
3	**10b**	**12b**	$TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$	**13b, 14b** (85)	1:1[c]
4	**10b**	**12b**	$SnCl_4$		
5	**10b**	**12b**	$BF_3\text{-}Et_2O$		
6	**10b**	**12b**	$Ti(O\text{-}i\text{-}Pr)_4$		
7	**10b**	**12c**	$TiCl_4$		
8	**10b**	**12d**	$TiCl_4$	**13b, 14b** (69)	3:2[c]
9	**10b**	**12e**	$TiCl_4$	**13b, 14b** (78)	3:2[c]
10	**10b**	**12e**	$TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$		
11	**10c**	**12b**	$TiCl_4$	**13c, 14c** (94)	1:12[c]
12	**11**	**12b**	$TiCl_4$	**15a, 15b** (72)	8:1[d]
13	**10d**	**12b**	$TiCl_4$	**13d, 14d** (97)	5:1[e]
14	**10e**	**12b**	$TiCl_4$	**13e, 14e** (93)	1:9[e]
15	**10f**	**12b**	$TiCl_4$	**13f, 14f** (89)	1:2.6[c]
16	**10g**	**12b**	$TiCl_4$	**13g, 16** (82)	*f*
17	**10h**	**12b**	$TiCl_4$[g]	**13h, 14h** (87)	45:1[h]
18	**10h**	**12b**	$TiCl_4$		

[a] A 1 M solution of Lewis acid in CH_2Cl_2 (1.6 equiv) was added by syringe over 5 min to a cooled (−78 °C) 0.1 M solution of substrate in CH_2Cl_2. [b] Isomers ratio determined by integration of the HPLC peaks (UV detector) of the mixture of benzoates **17a–17b** resulting from removal of the chiral auxiliary (PDC, CH_2Cl_2; K_2CO_3, MeOH; 96%). [c] Ratio of isomers determined by ^1H NMR analysis of the crude mixture. The *R,S* configuration at C(22) was established by removal of the chiral auxiliary (PDC, CH_2Cl_2; K_2CO_3, MeOH; 75–95%). [d] Isomers ratio determined by ^1H NMR analysis of the crude mixture. The *R,S* configuration at C(22) was established by analogy with the results obtained above. [e] Isomers ratio determined by ^1H NMR analysis of the crude mixture. The *R,S* configuration at C(22) was established by removal of the chiral auxiliary (PDC, CH_2Cl_2; SmI_2, MeOH–THF; 73–79%). [f] ^1H NMR analysis of the crude mixture showed a 4:1 ratio of compounds **13g** and **16**. The *R* configuration of both compounds at C(22) was established by removal of the chiral auxiliary (PDC, CH_2Cl_2; K_2CO_3, MeOH, 80–90%). [g] A 0.1 M solution of $TiCl_4$ was used. [h] Isomer ratio determined by integration of the HPLC peaks (UV detector) of the mixture of benzoates **17a–17b** resulting from removal of the chiral auxiliary (2 equiv of LDA, THF, −78 °C → rt, 91%).

less diastereoselectively to give the 22*S*-isomer **14c** as the main product (entry 11). A similar degree of stereoselectivity was obtained when the acetal **11** was treated with the same stannylacetylene **12b** (entry 12). The lower ratio of the anti-Cram isomers (entries 11 and 12) with respect to their C(22) isomers can be explained in terms of the chirality dictated by the acetal template, which is the opposite of that dictated by the C(20) configuration, and by a predominant S_N2 Johnson-type mechanism that competes to some extent with an oxocarbenium pathway favored by the α-chiral center.[18]

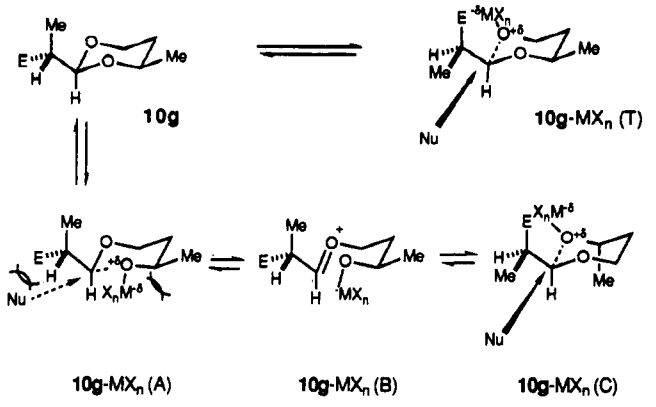
The cost of the (2*R*,4*R*)- and (2*S*,4*S*)-2,4-pentanediols led us to study the reactions of the acetals **10d–g** and the dioxanone **10h** with the same stannylacetylene **12b**. The five-membered ring acetals **10d** and **10e**, which were prepared from the corresponding chiral butanediols,[30] afforded 5:1 and 1:9 mixtures of 22*R*- and 22*S*-epimers, respectively (entries 13, 14). Surprisingly, the anti-Cram isomer **14e** (entry 14) was produced in a higher ratio than the Cram isomer **13d** (entry 13). Monosubstituted dioxanes **10f** and **10g** were prepared, respectively, from the readily available and less expensive (3*S*)- and (3*R*)-1,3-butanediols introduced by Johnson.[16b,31] Reaction of **10f** with **12b** under the usual conditions took place with low stereoselectivity to give the 22*S*-isomer **14f** as the main product, as expected (entry 15). Interestingly, opening the acetal **10g** afforded a 4:1 mixture of the isomers **13g** and **16**, which are both 22*R* isomers (entry 16). It is worth noting that removal of the chiral auxiliaries in the usual way from **13g** and **16** gave the propargyl alcohol **17a** as the sole product. The unexpected formation of **16** may be due to the establishment of equilibrium between the Lewis acid complex **10g**-MX_n (**A**) and the intimate ion pair **10g**-

(30) (a) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. (b) The (2*S*,3*S*)-2,3-butanediol was prepared (PTSA, EtOH; $LiAlH_4$, Et_2O; 40%) from 1,4-ditosyl-2,3-*o*-isopropylidene-L-threitol, which was obtained from L-tartaric acid: Carlmack, M.; Kelly, C. J. *J. Org. Chem.* **1968**, *33*, 2171.

(31) These diols can be prepared by reduction of the corresponding 3-hydroxybutyrate derivatives: Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117.

(32) The conformations of **10g** and of complexes **A**, **C**, and **T** are the results of MM2 molecular mechanics calculations.

Scheme II



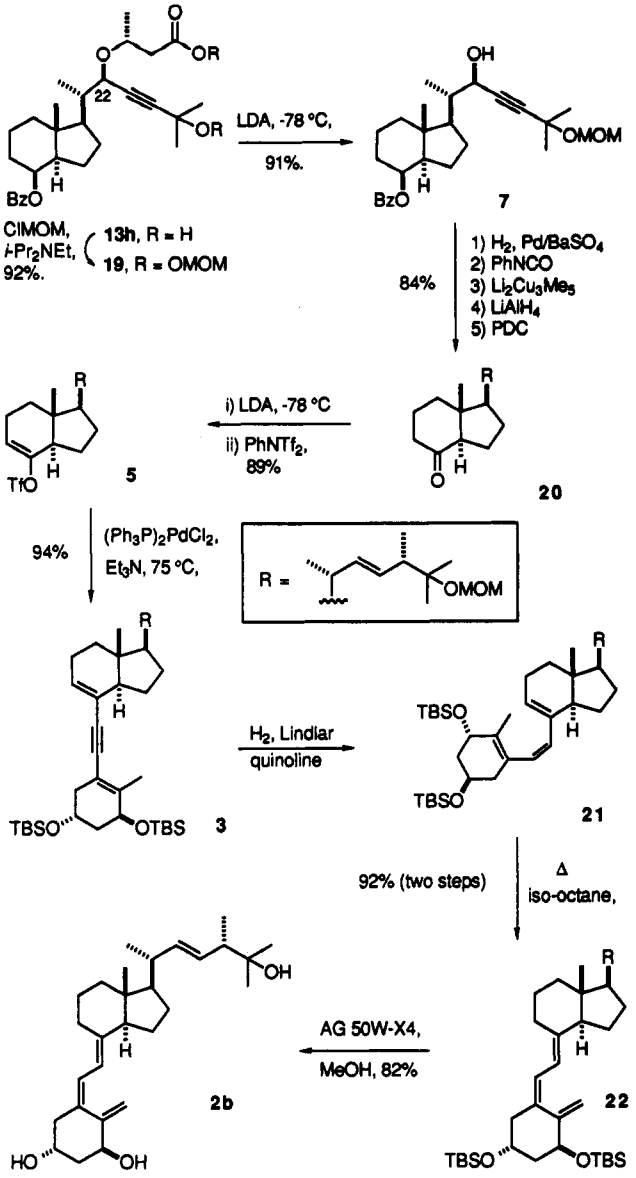
MX_n (C) via the external ion pair **10g**-MX_n (B),[18b] which avoids nonbonding interactions between the Lewis acid and the ring methyl group (Scheme II).[32] Nucleophilic attack on the complex **10g**-MX_n (C) would then give **16** with 22*R* stereochemistry, while nucleophilic attack on the Lewis acid complex **10g**-MX_n (T) would lead to **13g**. Finally, the dioxanone **10h** reacted highly stereoselectively to afford a 45:1 mixture of **13h** and **14h** (87%, entry 17). Interestingly, lower concentrations of $TiCl_4$ (0.1 M) and longer reaction times were required to complete the opening of the dioxanone.[33] The high stereoselectivity and inexpensiveness of the reaction with **13h** led us to use this compound as the appropriate intermediate for the synthesis of 1α,25-dihydroxyvitamin D_2.[34]

Syntheses of 1α,25-Dihydroxyvitamin D_2 (Scheme III). Protection of the acid **13h** with chloromethyl methyl ether under standard conditions[35] gave **19** in 92% yield. The chiral auxiliary was removed by treatment of **19** with LDA (2 equiv) in THF to give the alcohol **7** in 91% yield (de 95%). The alcohol **7** was transformed into ketone **20** following the procedure described previously.[9,15,36]

Construction of the triene was begun by treating **20** with LDA and trapping the kinetic enolate with $PhNTf_2$ to give vinyl triflate **5** (89%). Palladium-catalyzed cross-coupling between **5** and enyne **4**[13] afforded dienyne **3** (94%).[14] Partial hydrogenation (balloon pressure) of **3** in the presence of Lindlar palladium catalyst poisoned with quinoline in hexanes, with careful monitoring of the reaction by TLC to avoid overreduction, followed by thermal isomerization afforded a 88:12 mixture of the protected vitamin D **22** and previtamin D **21** (92%). Removal of the protecting groups by treatment with cation-exchange resin in deoxygenated methanol, followed by flash chromatography, gave the desired 1α,25-dihydroxyvitamin D_2 (**2b**, mp 159–161 °C (lit.[11a] mp 159–161 °C)), identical to that of an authentic sample (^{1}H NMR and HPLC).

In conclusion, the des-A,B-steroidal acetal **10g** (derived from (3*R*)-1,3-butanediol) and the less expensive dioxanone

Scheme III



10h (derived from (3*R*)-3-hydroxybutyric acid) are excellent intermediates for the preparation of 1α,25-dihydroxyvitamin D_2 (**2b**) by the dienyne route.

Experimental Section

General Procedures.[37] High-performance liquid chromatography (HPLC) was performed using a Zorbax-sil 10/250 column and a programmable multiwavelength detector.

(24*R*,22*E*)-Des-*A*,*B*-8β-(benzoyloxy)ergost-22-ene(8). Benzoyl chloride (10.2 mL, 58.4 mmol) was added to an ice-cooled solution of (24*R*,22*E*)-des-*A*,*B*-ergost-22-en-8β-ol[20] (8.13 g, 29.2 mmol) and DMAP (cat) in pyridine (45 mL). The resulting mixture was kept in the refrigerator for 14 h. Addition of ice gave a mixture that was extracted with EtOAc/hexanes (250 mL). The organic extracts were washed with HCl (5%, 100 mL), H_2O (100 mL), NH_4OH (5%, 100 mL), and H_2O (100 mL). The solution was dried, filtered, and concentrated to give a residue that was chromatographed on silica gel (3% EtOAc/hexanes) to give 10.87 g of 8 [95%, R_f 0.7 (10% EtOAc/hexanes), syrup]: ^{1}H NMR δ 8.10–7.40 (5 H, m, Bz), 5.40 (1 H, m, H-8), 5.18 (2 H, m, H-22 and H-23), 1.06 (3 H, s, CH_3-18), 1.03 (3 H, d, J = 6.6 Hz, CH_3-21 or CH_3-28), 0.91 (3 H, d, J = 6.8 Hz, 3 H, CH_3-21 or CH_3-28), 0.84 (3 H, d, J = 3.8 Hz, CH_3-26 or CH_3-27), 0.81 (3 H, d, J = 3.8 Hz,

(33) The high stereoselectivity observed can be explained by the S_N2-type substitution of the stereoelectronically polarized bond hypothesized by Seebach.[17b]

(34) To the best of our knowledge no reactions of stannylacetylenes or other stannyl nucleophiles with this type of dioxanones have been reported.

(35) Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190.

(36) The use of $Li_2Cu_3Me_5$ prepared from Cu_2I_2 purified by crystallization from an aqueous solution of KI (Kauffman, G. B., and Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9) to carry out the S_N2' syn displacement of carbamate **6** increases the yield of the reaction product from 78%[9] to 96%.

(37) For general procedures, see: Pérez Sestelo, J.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. *J. Org. Chem.*, preceding paper in this issue.

CH_3-26 or CH_3-27); ^{13}C NMR δ 166.3 (CO_2), 135.5 (CH), 132.6 (CH), 132.0 (CH), 131.0 (C), 129.5 (CH), 128.3 (CH), 72.1 (C-8), 56.3, 51.7, 42.7, 41.7, 39.8, 33.0, 30.5, 27.4, 22.6, 20.7, 19.8, 19.5, 17.9, 17.5, 13.6. Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.61; H, 10.03. Found: C, 81.53; H, 10.13.

Des-*A,B*-8β-(benzoyloxy)-23,24-dinorcholan-22-al (9a). A solution of 8 (1.72 g, 4.5 mmol) in MeOH (50 mL), CH_2Cl_2 (15 mL) and pyridine (1.5 mL) was placed in an ozonation vessel with a magnetic stirring bar. The solution was cooled to −78 °C while being purged with N_2. The N_2 flow was stopped, and a stream of ozone was passed until a gray-blue color appeared (25 min). The ozone flow was stopped, and the reaction mixture was purged with N_2 (−78 °C) until no ozone remained in solution (KI test). The resulting solution was concentrated. The residue was flash chromatographed (5% EtOAc/hexanes) to give aldehyde **9a**[9] [1.35 g, 95%, R_f 0.78 (20% EtOAc/hexanes)]: ^1H NMR δ 9.58 (1 H, d, J = 3.2 Hz, H-22), 8.10–7.40 (5 H, m, Bz), 1.14 (3 H, d, J = 6.9 Hz, CH_3-21), 1.07 (s, CH_3-18).

General Procedure for the Preparation of Acetals 10a–g. A solution of aldehyde **9a** (2.81 mmol) and the appropriate diol (3.11 mmol) in THF (30 mL) was treated at 0 °C with BF_3·OEt_2 (2.25 mmol, freshly distilled from CaH_2, under argon). The reaction mixture was stirred for 16 h at rt and quenched with MeOH (2 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc/hexanes (1:1, 3 × 50 mL). The combined organic extracts were dried, filtered, and concentrated. Flash chromatography of the residue (3% EtOAc/hexane) gave the acetals **10a–g** (85–97%).

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(4′*R*,6′*R*)-4′,6′-dimethyl-1′,3′-dioxan-2′-yl]pregnane (10a) [1.09 g, 97%, R_f 0.37 (10% EtOAc/hexanes), syrup]: ^1H NMR δ 4.85 (1 H, d, J = 2.1 Hz, H-2′), 1.34 (3 H, d, J = 6.9 Hz, CH_3-C-6′), 1.20 (3 H, d, J = 6.1 Hz, CH_3-C-4′), 1.04 (3 H, d, J = 3.8 Hz, CH_3-21), 1.02 (3 H, s, CH_3-18); ^{13}C NMR δ 166.4 (CO_2), 132.6 (CH), 130.9 (C), 129.5 (CH), 128.3 (CH), 94.8 (C-22), 72.0 (C-8), 67.6 (CH), 67.2 (CH), 52.0, 51.1, 41.8, 40.1, 39.7, 36.8, 30.6, 25.9, 22.6, 21.8, 17.9, 16.8, 13.3, 12.0; IR (CCl_4) 1730 (C=O, s) cm^{-1}. Anal. Calcd for $C_{25}H_{36}O_4$: 74.95: H, 9.06. Found: C, 75.16; H, 9.22.

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-(1′,3′-dioxan-2′-yl)pregnane (10b) [286 mg, 95%, R_f 0.33 (10% EtOAc/hexanes), foam]: ^1H NMR δ 4.50 (1 H, d, J = 2.0 Hz, H-2′), 4.11 (2 H, ddd, J = 11.4, 5.0 and 1.2 Hz, H-4′eq and H-6′eq), 3.84–3.65 (2 H, m, H-4′ax and H-6′ax), 1.04 (3 H, d, J = 3.8 Hz, CH_3-21), 1.03 (3 H, s, CH_3-18); ^{13}C NMR 166.4 (CO_2), 132.6 (CH), 130.8 (C), 129.5 (CH), 128.3 (CH), 103.5 (C-22), 71.9 (C-8), 66.9 (CH_2), 66.8 (CH_2), 51.8, 51.1, 41.7, 40.3, 39.6, 30.5, 26.1, 25.8, 22.5, 17.8, 13.2, 12.2; IR (KBr) 1715 (C=O, s) cm^{-1}.

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(4′*S*,6′*S*)-4′,6′-dimethyl-1′,3′-dioxan-2′-yl]pregnane (10c) [928 mg, 89%, R_f 0.8 (15% EtOAc/hexanes), crystallized from Et_2O/hexanes, mp 97–99 °C]: ^1H NMR δ 4.81 (1 H, d, J = 2.0 Hz, H-2′), 1.34 (3 H, d, J = 7.0 Hz, CH_3-C-6′), 1.18 (3 H, d, J = 6.1 Hz, CH_3-C-4′), 1.04 (3 H, s, CH_3-18), 1.01 (3 H, d, J = 3.8 Hz, CH_3-21); ^{13}C NMR δ 166.4 (CO_2), 132.6 (CH), 130.8 (C), 129.4 (CH), 128.3 (CH), 95.2 (C-22), 72.0 (C-8), 67.7 (CH), 67.2 (CH), 51.9, 51.0, 41.7, 40.1, 39.7, 36.8, 30.6, 25.9, 22.6, 21.8, 17.9, 16.8, 13.3, 12.0; IR (CCl_4) 1715 (C=O, s) cm^{-1}. Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.03; H, 9.17.

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(4′*R*,5′*R*)-4′,5′-dimethyl-1′,3′-dioxalan-2′-yl]pregnane (10d) [286 mg, 95%, R_f 0.37 (10% EtOAc/hexanes), crystallized from MeOH, mp 76–78 °C]: ^1H NMR δ 5.07 (1 H, d, J = 1.7 Hz, H-2′), 1.29 (3 H, d, J = 6.6 Hz, CH_3-C-4′), 1.22 (3 H, d, J = 6.8 Hz, CH_3-C-5′), 1.05 (3 H, s, CH_3-18), 0.98 (3 H, d, J = 6.6 Hz, CH_3-21); ^{13}C NMR δ 166.4 (CO_2), 132.6 (CH), 130.9 (C), 129.5 (CH), 128.3 (CH), 104.5 (C-22), 79.3 (CH), 78.6 (CH), 71.9 (C-8), 52.3, 51.0, 42.0, 39.6, 39.3, 30.5, 26.2, 22.6, 17.9, 17.3, 16.4, 13.2, 11.6; IR (KBr) 1730 (C=O, s) cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.20; H, 9.18.

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(4′*S*,5′*S*)-4′,5′-dimethyl-1′,3′-dioxalan-2′-yl]pregnane (10e) [195 mg, 82%, R_f 0.8 (30% EtOAc/hexanes), oil]: ^1H NMR δ 5.07 (1 H, d, J = 2.0 Hz, H-2′), 1.27 (3 H, d, J = 5.7 Hz, CH_3-C-4′ or CH_3-C-5′), 1.22 (3 H, d, J = 5.7 Hz, CH_3-C-4′ or CH_3-C-5′), 1.05 (3 H, s, CH_3-18), 0.96 (3 H, d, J = 5.6 Hz, CH_3-21); ^{13}C NMR δ 166.4 (CO_2), 132.6 (CH), 130.9 (C), 129.5 (CH), 128.3 (CH), 104.6 (C-22), 79.6 (CH), 78.4 (CH), 71.9 (C-8), 52.2, 50.9, 42.0, 39.6, 39.2, 30.4, 26.1, 22.6, 17.9, 17.2, 16.3, 13.1, 11.4; IR (film) 1715 (C=O, s) cm^{-1}.

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(2′*R*,4′*S*)-4′-methyl-1′,3′-dioxan-2′-yl]pregnane (10f) [532 mg, 91%, R_f 0.4 (10% EtOAc/hexanes), crystallized from EtOH, mp 94–96 °C]: ^1H NMR δ 4.48 (1 H, d, J = 2.2 Hz, H-2′), 1.20 (3 H, d, J = 6.1 Hz, CH_3-C-4′), 1.04 (3 H, s, CH_3-18), 1.02 (3 H, d, J = 6.6 Hz, CH_3-21); ^{13}C NMR 166.3 (CO_2), 132.5 (CH), 130.8 (C), 129.4 (CH), 128.2 (CH), 103.0 (C-22), 72.5, 71.9 (C-8), 66.3, 51.7, 51.0, 41.6, 40.1, 39.5, 33.0, 30.4, 26.0, 22.5, 21.6, 17.8, 13.2, 12.4; (KBr) 1705 (C=O, s) cm^{-1}.

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(2′*S*,4′*R*)-4′-methyl-1′,3′-dioxan-2′-yl]pregnane (10g) [512 mg, 85%, R_f 0.4 (10% EtOAc/hexanes), crystallized from MeOH, mp 104–106 °C]: ^1H NMR δ 4.51 (1 H, d, J = 1.9 Hz, H-2′), 1.22 (3 H, d, J = 6.2 Hz, CH_3-C-4′), 1.04 (3 H, d, J = 3.8 Hz, CH_3-21), 1.03 (3 H, s, CH_3-18); ^{13}C NMR 166.5 (CO_2), 132.7 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 103.0 (C-22), 72.5, 72.0 (C-8), 66.6, 52.1, 51.2, 41.8, 40.4, 39.7, 33.1, 30.6, 29.6, 26.2, 22.6, 21.7, 17.9, 13.3, 12.4; IR (CCl_4) 1720 (C=O, s) cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.32; H, 9.06.

(20*R*)-Des-*A,B*-8β-(benzoyloxy)-23,24-dinorcholan-22-al (9b). A solution of **9a** (350 mg, 1.1 mmol) in *s*-collidine (3 mL) was refluxed for 48 h. Concentration gave a residue that was dissolved in MeOH (10 mL). $NaBH_4$ (53 mg, 1.4 mmol) was added. The mixture was stirred for 15 min, quenched by addition of a few drops of water, and concentrated. The residue was dissolved in Et_2O (100 mL). The organic phase was washed with H_2O (3 × 50 mL), dried, filtered, and concentrated. The residue was flash chromatographed (2 × 30 cm, 25% EtOAc/hexanes) to give 83 mg of **18a**[11d] [24%, R_f 0.18 (25% EtOAc/hexanes)] and 218 mg of **18b** [62%, R_f 0.20 (25% EtOAc/hexanes), colorless liquid]. **18b**: ^1H NMR δ 3.76 (1 H, dd, J = 10.6 and 3.6 Hz, H-22), 3.49 (1 H, dd, J = 10.6 and 7.0 Hz, H-22), 1.07 (3 H, s, CH_3-18), 0.97 (3 H, d, J = 5.7 Hz, CH_3-21); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 131.0 (C), 129.6 (CH), 128.4 (CH), 72.1 (C-8), 66.8 (C-22), 52.8, 51.6, 41.8, 39.4, 37.5, 30.6, 26.3, 22.5, 18.0, 16.4, 13.9; IR (neat) 3400 (OH, br), 1730 (C=O, s) cm^{-1}. PDC (690 mg, 1.83 mmol) was added to a solution of alcohol **18b** (190 mg, 0.6 mmol) in CH_2Cl_2 (6 mL). The resulting suspension was stirred at rt overnight and then filtered through a path of Celite. The solution was concentrated to give a residue that the flash chromatographed (5% EtOAc/hexanes) to afford 172 mg of **9b** [91%, R_f 0.78 (20% EtOAc/hexanes)]: ^1H NMR δ 9.57 (1 H, d, J = 5.0 Hz, CHO), 1.06 (3 H, s, CH_3-18), 1.06 (3 H, d, J = 6.7 Hz, CH_3-21); ^{13}C NMR δ 205.4 (CHO), 166.4 (CO_2), 132.8 (CH), 130.8 (C), 129.6 (CH), 128.4 (CH), 71.6 (C-8), 52.2, 51.2, 48.4, 41.6, 38.7, 30.5, 25.3, 22.1, 17.7, 14.5, 13.3; IR (neat) 1720 (C=O, s) cm^{-1}.

(20*R*)-Des-*A,B*-8β-(benzoyloxy)-20-[(4′*R*,6′*R*)-4′-methyl-1′,3′-dioxan-2′-yl]pregnane (11). This compound was prepared as above [186 mg, 97%, R_f 0.40 (10% EtOAc/hexanes), syrup]: ^1H NMR δ 4.98 (1 H, d, J = 2.5 Hz, H-2′), 1.37 (3 H, d, J = 6.9 Hz, CH_3-C-6′), 1.18 (3 H, d, J = 6.1 Hz, CH_3-C-4′), 1.06 (3 H, s, CH_3-18), 0.92 (3 H, d, J = 6.4 Hz, CH_3-21); ^{13}C NMR δ 166.4 (CO_2), 132.6 (CH), 131.0 (C), 129.5 (CH), 128.3 (CH), 94.3 (C-22), 72.1 (C-8), 67.7 (CH), 66.9 (CH), 51.4, 51.2, 41.7, 39.0, 36.9, 30.6, 29.6, 25.7, 22.5, 21.8, 18.1, 17.4, 14.2, 11.6; IR (CCl_4) 1715 (C=O, s) cm^{-1}.

Trimethylsilyl (*R*)-3-[(Trimethylsilyl)oxy]butyrate. Dry hexamethyldisilazane (HMDS) (1.5 mL, 7.2 mmol, freshly distilled from CaH_2) was added dropwise to a solution of (*R*)-3-hydroxybutyric acid (680 mg, 6.53 mmol) in CH_2Cl_2 (30 mL) with formation of a white precipitate. The slurry was stirred overnight. Concentration gave a liquid that was bulb-to-bulb distilled (at 105–100 °C, 0.1 mmHg) to provide trimethylsilyl (*R*)-3-[(trimethylsilyl)oxy]butyrate[23b] (1.45 g, 89%, colorless liquid): ^1H NMR δ 4.29 (1 H, m, H-3), 2.48 (1 H, ABd, J = 15.2 and 7.6 Hz, H-2), 2.38 (1 H, ABd, J = 15.2, 5.6 Hz, H-2), 1.20 (3 H, d, J = 6.1 Hz, CH_3-4), 0.29 (9 H, s, TMS), 0.14 (9 H, s, TMS).

(20*S*)-Des-*A,B*-8β-(benzoyloxy)-20-[(2′*R*,6′*R*)-6′-methyl-4′-oxo-1′,3′-dioxan-2′-yl]pregnane (10h). 2,6-Di-*tert*-butylpyridine (8 μL) was added to a cooled (−78 °C) solution of trimethylsilyl (*R*)-3-[(trimethylsilyl)oxy]butyrate (520 g, 2.1 mmol) and **9a** (570 g, 1.82 mmol) in CH_2Cl_2 (6 mL). After 5 min, TMSTf (15 μL, 0.08 mmol) was added and the solution was stirred for 2 h. The reaction was quenched by addition of Et_3N (20 μL)

followed by MeOH (50 μL). The mixture was stirred at −78 °C for 5 min and then allowed to warm to rt. Concentration gave an oil that was flash chromatographed (20% EtOAc/hexanes) to give a 20:1 mixture of cis and trans dioxanone isomers. Pure **10h** was obtained by crystallization from Et_2O [692 mg, 95%, R_f 0.52 (40% EtOAc/hexanes), mp 133–135 °C]: ^1H NMR δ 5.32 (1 H, d, J = 1.6 Hz, H-2′), 2.67 (1 H, ABd, J = 17.7 and 4.1 Hz, H-5′), 2.40 (1 H, ABd, J = 17.7 and 10.9 Hz, H-5′), 1.34 (3 H, d, J = 6.1 Hz, CH_3-C-6′), 1.06 (3 H, d, J = 6.7 Hz, CH_3-21), 1.05 (3 H, s, CH_3-18); ^{13}C NMR δ 168.1 (CO_2), 166.4 (CO_2), 132.7 (CH), 130.9 (C), 129.5 (CH), 128.3 (CH), 104.6 (C-22), 71.8 (C-8), 70.2 (CH), 51.0, 50.7, 41.9, 40.1, 39.6, 37.8, 30.4, 26.0, 22.5, 21.0, 17.8, 13.3, 11.5; IR (KBr) 1745 (C=O, s), 1725 (C=O, s) cm^{-1}.

3-Methyl-3-[(trimethylsilyl)oxy]-1-butyne. TMSCl (6.5 mL, 50 mmol) was added to a solution of 3-butyn-2-methyl-3-ol (4.25 mL, 50 mmol), imidazole (10.34 g, 5 mmol) and Et_3N (10.5 mL, 75 mmol) in Et_2O (100 mL). The reaction mixture was stirred for 1 h, quenched with ice–water, and extracted with Et_2O (2 × 50 mL). The organic phase was dried, filtered, and distilled to afford $HC{\equiv}CCMe_2OTMS$[38] (5.11 g, 69%, bp 115–116 °C).

$Bu_3SnC{\equiv}CC(CH_3)_2OSiMe_3$ (12b). A solution of *n*-BuLi in hexane (5.9 mL, 2.13 M) was added dropwise to a cooled (−78 °C) solution of $HC{\equiv}CC(CH_3)_2OTMS$ (1.8 g, 12.6 mmol) in THF (15 mL). The mixture was stirred for 5 min, allowed to come to rt (30 min), and cooled again to −78 °C. Bu_3SnCl (3.4 mL, 12.6 mmol) was slowly added. The mixture was stirred at rt for 12 h and quenched with a few drops of water. Concentration gave a residue that was dissolved in EtOAc/hexanes (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried, and filtered. Concentration afforded a residue that was bulb-to-bulb distilled to give 4.76 g of **12b** [87%, at 85–90 °C (0.01 mmHg), colorless liquid]; ^1H NMR δ 1.48 (6 H, s, CH_3), 0.90 (9 H, t, J = 7.4 Hz, $CH_3(CH_2)_3Sn$), 0.19 (9 H, s, Me_3Si–); ^{13}C NMR 115.8, 85.1, 66.8, 33.4, 28.8, 26.8, 13.5, 10.8, 1.9.

Reaction of Acetals 10a–g and 11 with Stannylacetylene 12b. General Procedure. A solution of $TiCl_4$ (280 μL, 2.56 mmol, freshly distilled from Cu powder under argon) in CH_2Cl_2 (2.5 mL) was added to a cooled (−78 °C) solution of acetals **11a–g** (1.60 mmol) and **12b** (3.2 mmol, freshly distilled) in CH_2Cl_2 (20 mL). After being stirred for 5 min the reaction was quenched with MeOH (2 mL). The organic phase was washed with HCl (5%, 75 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was flash chromatographed (35–40% EtOAc/hexanes) to give the desired acetal (85–95%).

(22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[(1′*R*,3′*R*)-3′-hydroxy-1′-methylbutyl]oxy]-23-cholestyn-25-ol (13a) [736 mg, 95%, R_f 0.4 (40% EtOAc/hexanes)]: ^1H NMR δ 4.19 (1 H, d, J = 2.0 Hz, H-22), 1.52 (6 H, s, CH_3-26 and CH_3-27), 1.33 (3 H, d, J = 5.4 Hz, CH_3-4′), 1.19 (3 H, d, J = 6.2 Hz, CH_3-C-1′), 1.10 (3 H, d, J = 6.6 Hz, CH_3-21), 1.04 (3 H, s, CH_3-18); ^{13}C NMR δ 166.3 (CO_2), 132.6 (CH), 130.7 (C), 129.4 (CH), 128.2 (CH), 90.1 (C), 81.9 (C), 74.0 (CH), 71.6 (C-8), 64.6 (C-25), 64.2 (CH), 52.0, 51.2, 44.3, 42.0, 41.6, 39.4, 31.2, 30.2, 26.5, 23.5, 22.4, 20.2, 17.7, 13.9, 13.2; IR (neat) 3440 (OH, br), 1715 (C=O) cm^{-1}.

(22*R* and 22*S*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[(3′-hydroxypropyl)oxy]-23-cholestyn-25-ol (13b and 14b) [3:2 mixture (^1H NMR ratio) of **13b** and **14b** [296 mg, 89%, R_f 0.38 (45% EtOAc/hexanes), foam]]: ^1H NMR δ 4.18 (1 H, J = 1.9 Hz, H-22 of **13b**), 4.09 (1 H, d, J = 3.6 Hz, H-22 of **14b**), 1.54 (6 H, s, CH_3-26 and CH_3-27), 1.10 (3 H, d, J = 6.6 Hz, CH_3-21 of **13b**), 1.04 (3 H, s, CH_3-18 of **14b**), 1.04 (3 H, s, CH_3-18 of **13b**), 1.10 (3 H, d, J = 6.6 Hz, CH_3-21 of **14b**); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 130.9 (C), 129.5 (CH), 128.4 (CH), 92.0 (C) (**14b**), 91.2 (C) (**13b**), 80.8 (C) (**13b**), 78.6 (C) (**14b**), 73.3 (**14b**), 73.1 (**13b**), 72.1 (**13b**), 72.0 (C-8), 68.4, 67.5, 65.0 (C-25), 61.8, 61.4, 53.0, 52.3, 51.4, 51.3, 42.0, 41.7, 41.1, 40.4, 39.8, 39.6, 32.0, 31.9, 31.4, 30.4, 27.6, 26.4, 22.6, 22.5, 18.9, 17.9, 14.0, 13.6, 13.5, 13.4; IR (neat) 3390 (OH, br), 1715 (C=O) cm^{-1}. Anal. Calcd for $C_{24}H_{32}O_5$: C, 73.65; H, 8.83. Found: C, 73.66; H, 8.56.

(22*R* and 22*S*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[(1′*S*,3′*S*)-3′-hydroxy-1′-methylbutyl]oxy]-23-cholestyn-25-ol (13c and 14c) [1:12 mixture (^1H NMR ratio) of **13c** and **14c** [257, 94%, R_f 0.4 (40% EtOAc/hexanes), syrup]]: ^1H NMR δ 4.23 (1 H, J = 1.9 Hz, H-22 of **13c**), 4.20 (1 H, d, J = 3.5 Hz, H-22 of **14c**), 1.54 (6 H, s, CH_3-26 and CH_3-27), 1.28 (3 H, d, J = 6.4 Hz, CH_3-C-1′ or CH_3-4′), 1.18 (3 H, d, J = 6.2 Hz, CH_3-C-1′ or CH_3-4′), 1.07 (3 H, s, CH_3-18), 1.05 (3 H, d, J = 6.6 Hz, CH_3-21); ^{13}C NMR δ 166.6 (CO_2), 132.8 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 91.1 (C), 79.6 (C), 72.9 (CH), 72.0 (C-8), 71.6 (CH), 65.2 (C-25), 64.6, 53.0, 51.4, 44.0, 42.0, 40.8, 39.9, 31.5, 30.5, 26.6, 23.7, 22.7, 20.4, 17.9, 13.8, 13.6; IR (BrK) 3450 (OH, br), 1715 (C=O) cm^{-1}.

(22*R* and 22*S*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*R*,2′*R*)-2′-hydroxy-1′-methylpropyl]oxy]-23-cholestyn-25-ol (13d and 14d) [5:1 mixture (^1H NMR ratio) of **13d** and **14d** [258 mg, 97%, R_f 0.18 (30% EtOAc/hexanes), foam]]: ^1H NMR δ 8.10–7.40 (5 H, m, Bz), 4.20 (1 H, d, J = 1.9 Hz, H-22 of **13d**), 4.19 (1 H, J = 3.5 Hz, H-22 of **14d**), 3.61 (1 H, m, H-1′), 3.32 (1 H, m, J = 6.1 Hz, H-2′), 1.54 (6 H, s, CH_3-26 and CH_3-27), 1.25 (3 H, d, J = 6.2 Hz, CH_3-C-1′), 1.15 (3 H, d, J = 6.3 Hz, CH_3-3′), 1.10 (3 H, d, J = 6.6 Hz, CH_3-21), 1.06 (3 H, s, CH_3-18); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 90.1 (C), 82.5 (C), 81.2 (C), 72.4, 72.1, 71.3, 65.0 (C-25), 52.4, 51.5, 42.6, 41.9, 39.8, 31.4, 31.3, 30.4, 26.8, 22.6, 18.5, 17.9, 16.8, 14.0, 13.3; IR (neat) 3410 (OH, br), 1720 (C=O) cm^{-1}.

(22*R* and 22*S*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*S*,2′*S*)-2′-hydroxy-1′-methylpropyl]oxy]-23-cholestyn-25-ol (13e and 14e) [1:9 mixture (^1H NMR ratio) of **13e** and **14e** [87 mg, 93%, R_f 0.18 (30% EtOAc/hexanes]]: ^1H NMR δ 4.24 (1 H, J = 2.0 Hz, H-22 of **13e**), 4.16 (1 H, d, J = 3.5 Hz, H-22 of **14e**), 1.55 (6 H, s, CH_3-26 and CH_3-27), 1.21 (3 H, d, J = 6.2 Hz, CH_3-3′ or CH_3-C-1′), 1.15 (3 H, d, J = 6.3 Hz, CH_3-C-1′ or CH_3-3′), 1.08 (s, 3 H, CH_3-18), 1.06 (d, J = 6.2 Hz, 3 H, CH_3-21); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 130.8 (C), 129.5 (CH), 128.4 (CH), 91.1 (C), 80.3 (C), 79.6 (C), 72.5 (CH), 72.0 (C-8), 71.0 (CH), 65.0 (C-25), 52.8, 51.3, 42.0, 39.8, 31.4, 30.4, 26.5, 22.6, 18.5, 17.9, 16.8, 13.7, 13.5; IR (neat) 3440 (OH, br), 1715 (C=O) cm^{-1}.

(22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*S*)-3′-hydroxy-1′-methylpropyl]oxy]-23-cholestyn-25-ol (13f) and (22*S*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*S*)-3′-hydroxy-1′-methylpropyl]oxy]-23-cholestyn-25-ol (14f) [**13f** [39 mg, 25%, R_f 0.22 (40% EtOAc/hexanes)] and its C(22) epimer **14f** [100 mg, 64%, R_f 0.25 (40% EtOAc/hexanes)]]. **13f**: ^1H NMR δ 4.24 (1 H, d, J = 2.0 Hz, H-22), 1.54 (6 H, s, CH_3-26 and CH_3-27), 1.14–1.12 (6 H, m, CH_3-C-1′ and CH_3-21), 1.04 (3 H, s, CH_3-18); ^{13}C NMR δ 166.6 (CO_2), 132.7 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 91.1 (C), 81.5 (C), 72.1, 72.0, 69.6, 60.8, 51.8, 51.5, 41.7, 41.5, 39.6, 39.1, 31.4, 31.3, 30.5, 26.3, 22.6, 19.3, 17.9, 13.9, 13.4; IR (KBr) 3400 (OH, br), 1715 (C=O, s) cm^{-1}. **14f**: ^1H NMR δ 4.18 (1 H, d, J = 4.5 Hz, H-22), 1.54 (6 H, s, CH_3-26 and CH_3-27), 1.28 (3 H, d, J = 6.2 Hz, CH_3-C-1′), 1.08 (3 H, s, CH_3-18), 1.06 (3 H, d, J = 6.4 Hz, CH_3-21); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 130.8 (C), 129.5 (CH), 128.4 (CH), 91.1 (C), 79.5 (C), 73.7, 72.0 (C-8), 71.3, 65.0 (C-25), 60.2, 52.9, 51.3, 41.9, 40.7, 39.8, 38.4, 31.4, 30.4, 26.5, 22.6, 20.5, 17.8, 13.7, 13.5; IR (KBr) 3400 (OH, br), 1715 (C=O, s) cm^{-1}.

(22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*R*)-3′-hydroxy-1′-methylpropyl]oxy]-23-cholestyn-25-ol (13g) and (22*R*)-des-*A*,*B*-8β-(benzoyloxy)-22-[[(3′*R*)-3′-hydroxy-1′-butyl]oxy]-23-cholestyn-25-ol (16) [4:1 mixture (^1H NMR ratio) of the **13g** and **16** [82%, R_f 0.2 (40% EtOAc/hexanes), foam]]: ^1H NMR δ 4.18 (1 H, d, J = 1.9 Hz, H-22 of **13g**), 4.09 (1 H, d, J = 2.1 Hz, H-22 of **16**), 1.55 (6 H, s, CH_3-26 and CH_3-27 of **16**), 1.52 (6 H, s, CH_3-26 and CH_3-27 of **13g**), 1.33 (3 H, d, J = 5.4 Hz, CH_3-1′), 1.11 (3 H, d, J = 6.6 Hz, CH_3-21), 1.05 (3 H, s, CH_3-18 of **13g**), 1.04 (3 H, s, CH_3-18 of **16**); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 91.2 (C), 89.8 (C), 82.5 (C), 80.3 (C), 74.8, 73.1, 72.1 (C-8), 71.4, 68.6, 68.3, 65.0 (C-25), 60.0, 52.1, 51.5, 51.4, 42.3, 41.8, 40.6, 39.7, 38.7, 37.9, 31.4, 30.4, 29.6, 26.8, 26.5, 22.9, 22.6, 20.6, 17.9, 14.0, 13.3; IR (neat) 3400 (OH, br), 1715 (C=O, s) cm^{-1}.

(20*R*,22*R* and 20*R*,22*S*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*R*,3′*R*)-3′-hydroxy-1′-methylbutyl]oxy]-23-cholestyn-25-ol (15a and 15b) [8:1 mixture (^1H NMR ratio) of **15a** and **15b** [139 mg, 72%, R_f 0.30 (45% EtOAc/hexanes), foam]]: ^1H NMR δ 4.44 (1 H, d, J = 3.8 Hz, H-22 for **15b**), 4.44 (1 H, d, J = 2.9 Hz, H-22 for **15a**), 1.54 (6 H, s, CH_3-26 and CH_3-27 of **15a**), 1.53 (6 H, s, CH_3-26 and CH_3-27 of **15b**), 1.30 (3 H, d, J = 6.3 Hz, CH_3-4′), 1.20 (3 H, d, J = 6.2 Hz, CH_3-C-1′), 1.09 (3 H, s, CH_3-18),

(38) Visser, R. G.; Bos, H. J. T.; Brandsma, L. *Red. Trav. Chim. Pays-Bas.* **1981**, *100*, 34.

0.97 (3 H, d, J = 6.6 Hz, CH_3-21); ^{13}C NMR δ 166.5 (CO_2), 132.8 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 91.6 (C), 79.9 (C), 73.0 (CH), 72.0 (C-8), 71.0 (CH), 65.1 (C-25), 64.5, 52.5, 51.5, 44.0, 41.7, 39.7, 39.8, 31.5, 30.5, 26.2, 23.7, 22.4, 20.4, 18.0, 13.9, 13.4; IR (neat) 3420 (OH, br), 1715 (C=O, s) cm^{-1}.

(22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-22-[[(1′*R*)-2′-carboxy-1′-methylethyl]oxy]-23-cholestyn-25-ol (13h). A solution of $TiCl_4$ (70 μL, 0.65 mmol, freshly distilled from Cu powder under argon) in CH_2Cl_2 (200 μL) was added to a cooled solution (−78 °C) of acetal **10h** (240 mg, 0.6 mmol) and **12b** [543 mg, 1.22 mmol, freshly bulb-to-bulb distilled (at 110 °C, 0.1 mmHg)] in CH_2Cl_2 (12 mL). An additional amount of $TiCl_4$ (25 μL, 0.13 mmol) in CH_2Cl_2 (75 μL) was added after 1 h. The reaction mixture was stirred for 12 h, quenched by addition of MeOH (2 mL), and washed with HCl (5%, 75 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried, filtered, and concentrated. The residue was flash chromatographed (45% EtOAc/hexanes) to give 254 mg of **13h** [87%, R_f 0.30 (50% EtOAc/hexanes), foam]: ^1H NMR δ 4.21 (1 H, d, J = 1.5 Hz, H-22), 1.53 (6 H, s, CH_3-26 and CH_3-27), 1.31 (3 H, d, J = 6.2 Hz, CH_3-C-1′), 1.07 (3 H, d, J = 6.3 Hz, CH_3-21), 1.01 (3 H, s, CH_3-18); ^{13}C NMR δ 177.2 (CO_2H), 166.7 (CO_2), 132.8 (CH), 130.8 (C), 129.6 (CH), 128.4 (CH), 90.2 (C), 82.2 (C), 72.3 (CH), 71.8 (CH), 71.4 (CH), 65.2 (C-25), 51.7, 51.4, 42.2, 41.7, 39.6, 31.3, 30.5, 26.5, 22.6, 21.1, 19.0, 17.9, 13.9, 13.3; IR (neat) 3420 (OH, br), 1715 (C=O, s) cm^{-1}. Anal. Calcd for $C_{29}H_{40}O_6$: C, 71.83; H, 8.31. Found: C, 71.95; H, 8.76.

Removal of the Chiral Auxiliary and Determination of the *R*,*S* Configuration. Preparation of (22*S* and/or 22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-22,25-dihydroxycholest-23-yne (17a and/or 17b). General Procedure. PCC (6.25 mmol) was added to a solution of the diol or mixture of diols (605 mg, 1.25 mmol) in CH_2Cl_2 (25 mL). The resulting brown suspension was stirred at rt for 12 h and then filtered through a short column of Celite using EtOAc as eluent (4 × 10 mL). Concentration gave a residue that was directly used in the next step.

Removal of the Chiral Auxiliary. Method a. A suspension of the above crude mixture (1 mmol) and K_2CO_3 (6 mmol) in MeOH (10 mL) was stirred at rt for 3 h. Et_2O was added and the mixture washed with H_2O (75 mL) and HCl (5%, 50 mL), dried, filtered, and concentrated. The residue was flash chromatographed (38% EtOAc/hexanes) to give **17a** and/or **17b**. **17a**: ^1H NMR δ 4.51 (1 H, d, J = 2.0 Hz, H-22), 1.54 (6 H, s, CH_3-26 and CH_3-27), 1.13 (3 H, d, J = 6.5 Hz, CH_3-21), 1.06 (3 H, s, CH_3-18); ^{13}C NMR δ 166.5 (CO_2), 132.7 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 90.0 (C), 83.0 (C), 72.1 (C-8), 65.2 (C-25), 52.0, 51.5, 41.2, 39.7, 31.4, 30.5, 26.4, 22.5, 17.9, 13.4, 13.0; IR (neat) 3400 (OH, br), 1715 (C=O, s) cm^{-1}. **17b**: ^1H NMR δ 4.48 (1 H, d, J = 3.8 Hz, H-22), 1.55 (6 H, s, CH_3-26 and CH_3-27), 1.08 (3 H, s, CH_3-18), 1.07 (3 H, d, J = 6.5 Hz, CH_3-21); ^{13}C NMR δ 166.6 (CO_2), 132.7 (CH), 130.9 (C), 129.6 (CH), 128.4 (CH), 91.1 (C), 80.6 (C), 72.0 (C-8), 65.3 (CH), 65.2 (C-25), 53.4, 51.3, 42.2, 41.8, 40.0, 31.5, 30.5, 26.3, 22.6, 17.9, 13.7, 12.7; IR (neat) 3400 (OH, br), 1720 (C=O, s) cm^{-1}. **From 13a: 17a:17b** (87:1, HPLC, 304 mg, 96% two steps). **From 13b-14b: 17a:17b** [3.2 (^1H NMR), 121 mg, 84% two steps]. **From 13c–14c: 17a:17b** [1:12 (^1H NMR), 65 mg, 87% two steps]. **From 14f:17b** (46 mg, 77% two steps). **From 13g:17a** (51 mg, 58% two steps). **From 16:17a** (51 mg, 17% two steps).

Method b. A solution of 1,2-diiodoethane (2 mmol) in THF (1 mL) was added to a mixture of Sm powder (2 mmol) in THF (1 mL) at rt. The resulting olive-green slurry was stirred at rt for 1 h. The dark blue mixture of SmI_2 was cooled to −78 °C and treated with a solution of the crude mixture of ketones (1 mmol) in MeOH/THF (1:2, 3 mL). The brown mixture was stirred for 10 min at −78 °C and poured into saturated aqueous K_2CO_3. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined extracts were dried, filtered, and concentrated. The residue was flash chromatographed (35% EtOAc/hexanes) to give a mixture of diols **17a** and **17b**. **From 13d–14d: 17a:17b** [5:1 (^1H NMR), 114 mg, 79% two steps]. **From 13e:14e: 17a:17b** [1:9 (^1H NMR), 38 mg, 73% two steps].

(22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]-22-[[(1′*R*)-3′-oxo-3′-[(methoxymethyl)oxy]-1′-methylpropyl]-oxy]cholest-23-yne (19). ClMOM (325 μL, 4.39 mmol) was added to a cooled (0 °C) solution of **13h** (430 mg, 0.89 mmol), DMAP (cat.), and i-Pr_2NEt (940 μL, 5.25 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 18 h and quenched with H_2O. The resulting mixture was extracted with Et_2O (2 × 50 mL). The organic phase was washed with HCl (5%, 50 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL), dried, and filtered. Concentration afforded a residue that was flash chromatographed (10% EtOAc/hexanes) to give 468 mg of **19** [92%, R_f 0.63 (40% EtOAc/hexanes), syrup]: ^1H NMR δ 4.22 (1 H, d, J = 2.0 Hz, H-22), 4.09 (1 H, q, J = 6.1 Hz, H-1′), 1.52 (6 H, s, CH_3-26 and CH_3-27), 1.29 (3 H, d, J = 6.2 Hz, CH_3-C-1′), 1.08 (3 H, d, J = 6.4 Hz, CH_3-21), 1.03 (3 H, s, CH_3-18); ^{13}C NMR δ 171.0 (CO_2), 166.5 (CO_2), 132.7 (CH), 131.0 (C), 129.6 (CH), 128.4 (CH), 93.2 (CH_2), 90.4 (CH_2), 87.2 (C), 84.9 (C), 72.1 (C-8), 71.5 (CH) 71.0 (C-25), 57.6, 55.4, 51.8, 51.5, 42.1, 41.7 (CH_2), 39.7 (CH_2), 30.5 (CH_2), 30.1, 26.5 (CH_2), 22.7 (CH_2), 21.1, 17.9 (CH_2), 14.0, 13.4; IR (KBr) 1740 (C=O, s), 1715 (C=O, s) cm^{-1}. Anal. Calcd for $C_{33}H_{48}O_8$: C, 69.20; H, 8.45. Found: C, 69.01; H, 8.38.

(22*R*)-Des-*A*,*B*-8β-(benzoyloxy)-25-[(methoxymethyl)oxy]cholest-23-yn-22-ol (7). i-Pr_2NH (330 μL, 1.56 mmol) and THF (2 mL) were successively added dropwise to a cooled (−78 °C) solution of n-BuLi in hexane (4.2 mL, 2.3 M). The mixture was stirred at −78 °C for 10 min and at rt for 20 min and then cooled to −78 °C and added dropwise to a solution of **19** (450 mg, 0.78 mmol) in THF (5 mL) at the same temperature. The mixture was stirred for 30 min and warmed to rt overnight. The organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL), dried, and concentrated. Flash chromatography of the residue (10% EtOAc/hexanes) gave **7**[9] [314 mg, 91%, 22*R*:22*S* isomers (45:1, ratio determined by HPLC), syrup]: ^1H NMR δ 4.50 (1 H, d, J = 2.0 Hz, H-22), 1.52 (6 H, s, CH_3-26 and CH_3-27), 1.12 (3 H, d, J = 6.5 Hz, CH_3-21), 1.06 (3 H, s, CH_3-18).

(22*E*,24*S*)-Des-*A*,*B*-25-[(methoxymethyl)oxy]-8,22-ergostadien-8-yl Trifluoromethanesulfonate (5). Compound **5** was prepared from **20**[39] following a general procedure[37] [89%, R_f 0.5 (7% EtOAc/hexanes), colorless oil]: ^1H NMR δ 5.57 (1 H, dd, J = 6.8, 3.5 Hz, H-9), 5.32 (2 H, AB q, J = 14.8 Hz, $\Delta\gamma$ = 28 Hz, H-22 and H-23), 1.16 (3 H, s, CH_3-26 or CH_3-27), 1.13 (3 H, s, CH_3-26 or CH_3-27), 1.03 (3 H, d, J = 6.6 Hz, CH_3-21), 0.99 (3 H, d, J = 6.7 Hz, CH_3-28), 0.77 (3 H, s, CH_3-18); ^{13}C NMR δ 149.9 (C-8), 136.5 (CH), 130.4 (CH), 116.0 (C-9), 91.0 (CH_2), 78.1, 55.09, 54.1, 50.2, 46.6, 45.1, 40.2, 34.7, 28.4, 24.6, 23.8, 23.1, 21.4, 20.6, 15.1, 11.5.

1α-[(*tert*-Butyldimethylsilyl)oxy]-6,7-dihydro-25-[(methoxymethyl)oxy]previtamin D_2 *tert*-Butyldimethylsilyl Ether (3). Compound **3** was prepared by palladium-catalyzed coupling between **5** and **4** following the general procedure[37] [94%, oil that decomposed rapidly even at −10 °C but was stable in solution, R_f 0.45 (5% EtOAc/hexanes)]: ^1H NMR δ 5.97 (1 H, br d, J = 3.4 Hz, H-9), 5.32 (2 H, ABq, J = 14.8 Hz, $\Delta\gamma$ = 28 Hz, H-22 and H-23), 4.19 (1 H, m, H-1), 4.09 (1 H, m, H-3), 1.89 (3 H, br s, CH_3-19), 1.18 (3 H, s, CH_3-26 or CH_3-27), 1.14 (3 H, s, CH_3-26 or CH_3-27), 1.02 (3 H, d, J = 6.6 Hz, CH_3-21), 0.99 (3 H, d, J = 6.7 Hz, CH_3-28).

1α-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]previtamin D_2 *tert*-Butyldimethylsilyl Ether (21). Compound **21** was prepared from **3** following the general procedure for hydrogenation with Lindlar catalyst[37] [R_f 0.59 (5% EtOAc/hexanes)], which was used directly in the next step: ^1H NMR δ 5.87 and 5.74 (2 H, AB, J = 12.3 Hz, H-6 and H-7), 5.55 (1 H, br s, H-9), 5.32 (2 H, ABq, J = 14.8 Hz, $\Delta\gamma$ = 28 Hz, H-22 and H-23), 4.19 (2 H, br m, H-1 and H-3), 1.89 (3 H, br s, CH_3-19), 1.18 (3 H, s, CH_3-26), 1.14 (3 H, s, CH_3-27), 1.02 (3 H, d, J = 6.6 Hz, CH_3-21), 0.99 (3 H, d, J = 6.7 Hz, CH_3-28); UV (Et_2O) λ_{max} 259 nm (ϵ 8600), λ_{min} 232 nm.

1α-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]vitamin D_2 *tert*-Butyldimethylsilyl Ether (22). Compound **22** was prepared from **21** following the general procedure for the isomerization of previtamins D to vitamins D.[37] [Mixture of **22** and **21** (88:12 ^1H NMR ratio), 92%, R_f 0.59 (5% EtOAc/hexanes)]: ^1H NMR δ 6.24 and 6.01 (2 H, AB, J = 12.3 Hz, H-6 and H-7), 5.55 (1 H, br s, H-9), 5.27 (1 H, m, H-22 and H-23), 5.17 (1 H, br s, E-H-19), 4.86 (1 H, br s, Z-H-19), 4.19 (1 H, m, H-3), 1.17 (3 H, s, CH_3-26), 1.13 (3 H, s, CH_3-27), 1.01 (3

(39) For transformation of the alcohol **7** into the ketone **20** see ref 9.

H, d, J = 6.6 Hz, CH_3-21), 0.99 (3 H, d, J = 6.7 Hz, CH_3-28); ^{13}C NMR δ 148.5, 141.0, 137.4, 135.1, 129.7, 123.2, 118.0, 111.2, 90.9, 78.2, 72.0, 67.6, 56.4, 55.1, 46.6, 46.0, 45.7, 44.8, 40.5, 28.8, 27.8, 25.8, 24.7, 23.4, 23.0, 22.6, 22.1, 20.8, 18.2, 15.1, 12.2, -4.3, -4.7, -4.9, -5.2; UV (Et_2O) λ_{max} 264 nm (ϵ 12 950), λ_{min} 228 nm.

1α,25-Dihydroxyvitamin D_2 (2b). A solution of **22** (50 mg, 0.071 mmol) in deoxygenated MeOH (5 mL) was stirred with ion-exchange resin (AG 50W-X4, 700 mg, prewashed with MeOH) at rt for 48 h in the dark. Filtration and concentration gave a residue that was flash chromatographed (50% EtOAc/hexanes) to afford 25 mg of pure 1α,25-dihydroxyvitamin D_2 [82%, crystallized from Et_2O, mp 159–161 °C (lit.[11a] mp 159–161 °C)]: ^1H NMR δ 6.38 and 6.01 (2 H, AB, J = 11.1 Hz, H-6 and H-7), 5.32 (2 H, ABq, J = 14.8 Hz, $\Delta\gamma$ = 28 Hz, H-22 and H-23), 5.32 (br s, 1 H, E-H-19), 5.00 (1 H, br s, Z-H-19), 4.45 (m, 1 H, H-1), 4.26 (1 H, m, H-3), 1.17 (3 H, s, CH_3-26), 1.13 (3 H, s, CH_3-27), 1.03 (3 H, d, J = 6.6 Hz, CH_3-21), 0.98 (3 H, d, J = 6.9 Hz, CH_3-28), 0.55 (s, 3 H, CH_3-18); UV (Et_2O) λ_{max} 264 nm (ϵ 18 500), λ_{min} 228 nm.

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Supplementary Material Available: Spectral and analytical data (^1H NMR, ^{13}C NMR, IR, UV, MS, HRMS, and elemental analyses) and ^1H and ^{13}C NMR spectra for compounds **2b, 3, 5, 8, 9a, 10a-h, 11, 12b, 13–14(a-h), 15, 17a–b, 18b, 19, 21,** and **22** (32 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.