Asymmetric Synthesis via Acetal Templates. 6.[1] A Stereoselective Approach to a Key Intermediate for the Preparation of Vitamin D Metabolites

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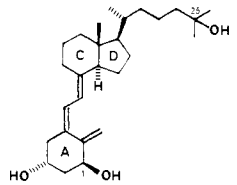
Calcium metabolism is controlled by the hormone[2] 1α,25-dihydroxyvitamin D_3 (**1**) (calcitriol[3]), a metabolite of vitamin D_3,



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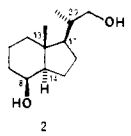

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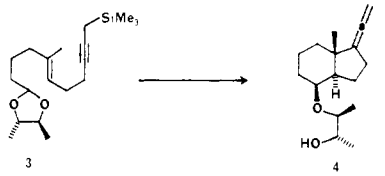
formed by successive hepatic and renal hydroxylations at C-1 and C-25. Certain liver or kidney disorders, often a consequence of the aging process, interrupt formation of calcitriol resulting in serious diseases, e.g., osteodystrophy. Since the treatment of these conditions may only be achieved with the appropriate metabolite, the practical synthesis of this hormone has become an issue of major concern. Among the various synthetic approaches which exist, those based upon Lythgoe–Inhoffen methodology[4] are particularly attractive since they provide for convergent Wittig coupling of the A-ring and C/D-ring fragments, leading directly to the conjugated triene system.

The preparation of potential C/D ring fragments has already been the inspiration of some highly imaginative syntheses.[4-7] The Inhoffen–Lythgoe diol **2** has been prepared in this context[8] and has proved to be a useful precursor for elaboration of the side chain of calcitriol (**1**).[7] While diol **2** can be obtained by degradation (O_3, LAH) of vitamin D_2,[9] total synthetic approaches remain of importance.[8] The present paper discloses a total synthesis of **2**, the heart of which is the efficient cyclization **9** → **10a** involving the highly selective, asymmetric generation of a trans-bicyclic nucleus with three new chiral centers.

Initially we envisaged using the Lewis-acid-catalyzed cyclization of optically active acetal **3** to provide **4**. This plan derived from

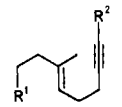


3 **4**

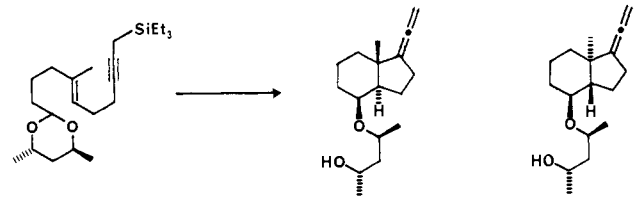
the established stereoselective cyclization of the (2*R*,3*R*)-butanediol acetal of (5*E*)-5,9-dimethyldeca-5,9-dienal,[10] the results of which show that the *S*,*S* acetal **3** would be required to give the predominant absolute configuration, as shown, for the major (axial alkoxy) product **4**. There is also precedent[11] that cyclizations terminated by the propargylsilane function (as in **3**) lead to steroidal structures with the trans-fused, five-membered D ring and a 17-vinylidene residue (as in **4**). Furthermore, it was anticipated that the allenic moiety present in **4** would provide for facile elaboration of the C-17 side chain of **2**.

Since the *R*,*R* enantiomer of 2,3-butanediol is the more readily accessible, our preliminary experiments were performed with enantiomeric **3**. Cyclization ($SnCl_4$, $EtNO_2$, −78 °C, 0.5 h) gave in high yield a 9:1 mixture of axial and equatorial alkoxy isomers, which were readily separable by chromatography. The ^1H NMR and IR spectra of the major component were entirely consistent with the expected bicyclic allene, enantiomeric **4**. The GC indicated the presence of two diastereomers in the ratio of approximately 4:1 which were presumed, on the basis of the earlier work,[10a] to be enantiomeric **4** and its 13β,14α isomer, respectively. Attempts to remove the chiral auxiliary were unpromising,[12] therefore, our attention turned to the use of the acetal **9** derived from (2*S*,4*S*)-pentanediol[13] since removal of the side chain from the anticipated major product **10a** seemed almost certain to be a facile, high-yield process.[14]

The acetal **9** was synthesized as follows:[15,16] (a) **5** was prepared according to the modified Julia method for making a homologue (**5**, R^1 = Br, R^2 = CH_3);[17] (b) the lithium salt of **5** was alkylated



5 R^1 = Br R^2 = H
6 R^1 = Br R^2 = CH_2SiEt_3
7 R^1 = CH_2CO_2Me R^2 = CH_2SiEt_3
8 R^1 = CH_2CHO R^2 = CH_2SiEt_3



9 **10a** **10b**

with triethylsilylmethyl triflate[18] to give **6**; (c) **6** was converted into **7** via a malonic ester chain-extension sequence; (d) reduction of **7** with diisobutylaluminum hydride gave aldehyde **8**; (e) finally, oxalic acid catalyzed reaction of **8** with (2*S*,4*S*)-pentanediol[13] in THF containing Linde 4A molecular sieves afforded acetal **9**[19b,20]

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(12) Procedures involving oxidation of **3** to the ketone followed by treatment with alkali metrals (cf. ref 10a) resulted in simultaneous reduction of the allenic function.
(13) Both enantiomeric forms of 2,4-pentanediol are readily available through the asymmetric hydrogenation of acetylacetone. See: Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3367–3368.
(14) Cf. ref 1, 10b, and: Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904–2905.
(15) A summary of the complete scheme together with spectroscopic and analytical data for all intermediates is given in the supplementary material.
(16) This route to aldehyde **8** (the precursor of **9**) was chosen in part because it was straightforward and also because some of the intermediates were already in hand from other work in our laboratory. In view of the success of the conversion of **9** into **2**, the development of an improved, convergent route to **8** is warranted.
(17) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274–4282.
(18) Cf.: Ambasht, S.; Chiu, S. K.; Peterson, P. E.; Queen, J. *Synthesis* **1980**, 318.
(19) (a) The crude product was homogeneous with respect to GC and TLC. (b) The product was purified by low-pressure column chromatography using "Merck silica gel 60 H for thin-layer chromatography".
(20) The ^1H NMR, IR, and mass spectra were consistent with the assigned structure. A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

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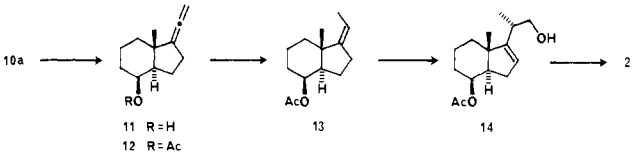
in 48% overall yield from **5**.

The best conditions found for the cyclization **9** → **10a** were as follows: titanium tetrachloride (0.24 mL, 2.18 mmol) was added to a stirred solution of 0.45 g (1.19 mmol) of acetal **9** in anhydrous dichloromethane (25 mL), containing 2,4,6-trimethylpyridine (0.16 mL, 1.21 mmol) at −78 °C under argon. After 5 min the mixture was treated with methanol (1 mL) then warmed to room temperature, and finally excess 1 M hydrochloric acid was added. The crude product contained **10a**:**10b** in the ratio 87:13 by GC.[21] Column chromatography[19b] easily separated the mixture to give **10a**[20] (82% yield) and **10b**[22] (9% yield).

The chiral auxiliary was removed from **10a** by oxidation[23] to the corresponding ketone[19a,20] followed by base-catalyzed β-elimination[24] to give alcohol **11**[19b,20] in 93% overall yield from **10a**. The optical purity of **11**, $[\alpha]^{25}_D$ −13° (*c* 0.4, CCl_4), was determined to be 92% by conversion to the (+)-MTPA ester.[25] The alcohol **11** was acetylated (Ac_2O/pyridine/10% DMAP, 70 °C, 3 h) to give **12**[19a,20] in 96% yield. The compound **12** was then subjected to semihydrogenation[26] over Lindlar catalyst.[27] As anticipated the addition occurred from the more exposed face of the terminal double bond of the allene, to give **13**[20] (89% yield) with no de-



tectable amount of the *E* double-bond isomer (^{1}H NMR spectroscopy and GC).[28] Olefin **13** is the C-8 epimer of an intermediate known to be convertible to the C/D unit of calcitriol.[4] Completion of the synthesis of the Inhoffen-Lythgoe diol **2** followed known methodology.[29] Reaction of **13** with paraformaldehyde catalyzed by BF_3·Et_2O gave **14**[19b,20] stereospecifically (72% yield).[30] Finally stereospecific hydrogenation of **14** (H_2/PtO_2) followed by deacetylation (THF/MeOH/2 M aqueous KOH, 1:1:1, 48 h, 25 °C) gave **2** in 84% overall yield from **14** (39% overall yield from **9**). ^{1}H NMR, IR, and mass spectroscopy as well as GC coinjection established the identity of **2** with an authentic sample prepared by degradation of vitamin D_2,[9] $[\alpha]^{25}_D$ +40.5 (*c* 0.38, MeOH).[31] The $[\alpha]^{25}_D$ +37.1° (*c* 0.38, MeOH) found for the synthetic material was in excellent agreement with the value calculated for a sample of 92% optical purity. A single crystallization of synthetic **2** from hexane gave optically pure material as colorless needles, $[\alpha]^{25}_D$ +40.6, mp 110-111 °C (mixture mp with authentic **2**, 110-111 °C) (lit. 113-114,[6] 109-110 °C[9]).

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research. We also express our appreciation to Dr. A. Tai of the Institute of Protein Research, Osaka University, for the gift of a generous sample of (2*S*,4*S*)-pentanediol.

Supplementary Material Available: Spectroscopic (^{1}H NMR, IR, MS) and analytical data (8 pages). Ordering information is given on any current masthead page.

(21) GC (15 m SE-54 capillary column) separation of **10a** and its 8α,13α,14β isomer was not possible though under less favorable cyclization conditions (i.e., in which a larger proportion of the latter isomer was formed, e.g., $SnCl_4$/fluorobenzene −40 °C, 4 h) the minor diastereomer appeared as a shoulder on the major GC peak.

(22) The ^{1}H NMR spectrum was consistent with the structural assignment. The predominant absolute configuration at C-8, C-13, and C-14 was assumed on the basis of earlier work (see ref 10a).

(23) Pyridinium chlorochromate (1.5 mol equiv), CH_2Cl_2, 25 °C, 18 h. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-2650.

(24) THF/MeOH/7.5 M aqueous KOH (4:2:1), 24-48 h, 25 °C; see ref 10b.

(25) Determined by GC analysis (base-line separation on a 15-m SE-54 capillary column) of (*R*)-(+)-MTPA esters. See: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

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(27) Available from Aldrich Chemical Co.

(28) The hydrogenation was accompanied by approximately 5% overreduction to the fully saturated compound as determined by GC (15-m SE-54 capillary column).

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(30) ^{1}H NMR and GC (15-m SE-54 capillary column) indicated that **14** was diastereomerically pure at C-20.

(31) The reported rotation is +36.5° (*c* 1, MeOH).[6]

Deuterium Isotope Effect on the Heme-Coordinated CO Vibration Band of Ferrous Cytochrome *c* Peroxidase-CO

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The question of distal effects as mediators of ligand binding in heme proteins has resulted in efforts to discern the role of the distal histidine at position E-7 in the primary amino acid sequence.[2-15] This amino acid is situated closest to the ligand binding site in heme globins,[3,7] but a similarly positioned "distal histidine" is present in cytochrome *c* peroxidase (EC 1.11.1.5; CcP), a native ferriheme enzyme.[15] For CcP this histidine has been implicated in the peroxidase catalytic mechanism.[16]

Ferrous heme globins bind both molecular oxygen and carbon monoxide, and evidence has been presented which suggests that nature takes advantage of the potential multifunctionality of the distal histidine.[2-5] For example, distal histidine hydrogen bonding has been reported for heme-coordinated dioxygen,[3,4,15] whereas the absence of neutron density between histidine E-7 and heme-bound CO was noted for carbonylmyoglobin.[7] In CO-ligated heme proteins, it has been suggested that the role of the distal histidine is primarily steric,[2] although evidence has been presented in support of a strong hydrogen bond between heme-coordinated CO and protein in the heme enzyme carbonylhorseradish peroxidase (EC 1.11.1.7; HRP).

In addition to structural evidence,[3,7] one of the primary arguments against hydrogen bonding involving heme-coordinated CO in hemoglobins and myoglobins has been the absence of a spectroscopically detectable deuterium isotope effect. The reasoning

(1) (a) University of New Mexico; Fellow of the Alfred P. Sloan Foundation. (b) Northern Illinois University.

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