of r_{CH} was used to interpret their ^{13}C T_1 data.[1,2] We hope that the results presented in this report will lead to a general re-evaluation of the choice of r_{CH} in ^{13}C relaxation studies.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE 76-17572).

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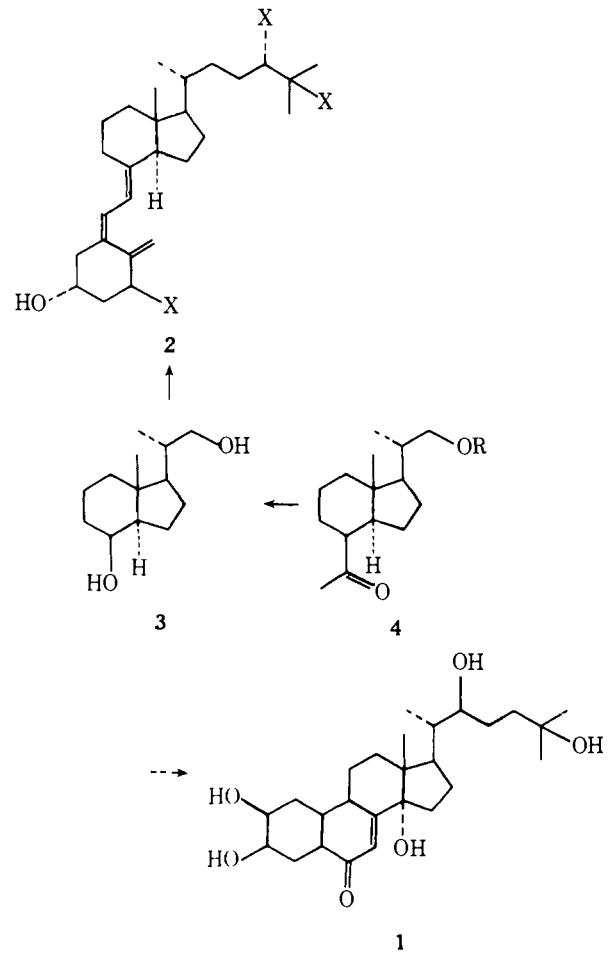
A Stereocontrolled Approach toward Vitamin D Metabolites. A Synthesis of the Inhoffen–Lythgoe Diol

Sir:

Steroids and their transformation products possessing modified side chains such as the molting hormones (e.g., ecdysones **1**)[1] and the metabolites of vitamin D_3 (e.g., **2**)[2] have spurred much research concerned with the synthesis of systems incorporating a functionalized side chain.[3,4] The vitamin D_3 problem is further complicated by conversion of the steroid nucleus into the seco system. Of the synthetic approaches, only Lythgoe's[5] and more recently Okamura's[6] directly construct the conjugated triene system. Thus, a strategy which produces a C,D unit incorporating the asymmetric center at C(20) (steroidal numbering) and which is suitably functionalized for elaboration into these biologically important systems as well as various analogues appears to represent a useful synthetic goal. We describe a synthesis of such a unit, e.g., **4**, which, by conversion into the Inhoffen–Lythgoe diol **3**, effects a formal total synthesis of both vitamin D_3 and some of its metabolites.[5]



2 **3** **4** **1**

As outlined in Scheme I, the starting material for the sequence is the hydroxy ketal **5**, which is readily available in 45% overall yield from 3-carboxytricyclo[2.2.1.$0^{2,6}$]heptan-5-one.[7] The sulfone **6**[8] is prepared from the iodide by displacement with sodium benzenesulfinate.[9] Conversion into its anion in a THF–HMPA mixture and then addition of a 10% (w/v) solution of ethylene oxide in ether led to the hydroxyethylated product **7**.[8] Desulfonylation with $Li/C_2H_5NH_2$ was plagued by double-bond reduction and with unbuffered Na(Hg)[10] by formation of undefined byproducts, whereas desulfonylation by 6% Na(Hg) buffered with Na_2HPO_4 proceeded quantitatively.[11] The desulfonylated product was directly converted into the THP derivative of the bishomologated hydroxy ketone **8**.[8] Methylation proceeds highly stereoselectively from the less hindered endo face to give **9**[8] (>30:1). NMR shows a single doublet, δ 1.01 for **9**, whereas the exo methyl isomer, obtained by partial equilibration of **9**, shows this methyl group at δ 1.20. At this point, all four critical centers corresponding to C(13), C(14), C(17), and C(20) in steroid numbering have been created with the correct relative configuration.

Baeyer–Villiger oxidation using basic hydrogen peroxide gives initially the unrearranged hydroxy acid which upon direct subjection to TsOH in benzene is converted into the rearranged lactone **10**:[8] IR 1780, 1655 cm^{-1}; NMR δ 5.43 (d, J = 7 Hz, 1 H), 4.55 (br S, 1 H), 1.28 (d, J = 7 Hz, 3 H), 1.11 (s, 3 H). After reduction to the diol, reaction with 1 equiv of *tert*-butyldimethylsilyl chloride allowed selective protection of the primary alcohol. Transposition of the chirality of the allyl alcohol unit to an allylic inverted carbon unit envisioned the use of allylic alkylation via organopalladium chemistry[12,13] or [3.3]-sigmatropic rearrangement. Attempts to effect a modified Claisen rearrangement (Claisen–Johnson[14] ortho ester or Claisen–Ireland–Arnold[15] enolate) failed presumably because of steric crowding. On the other hand, the much less

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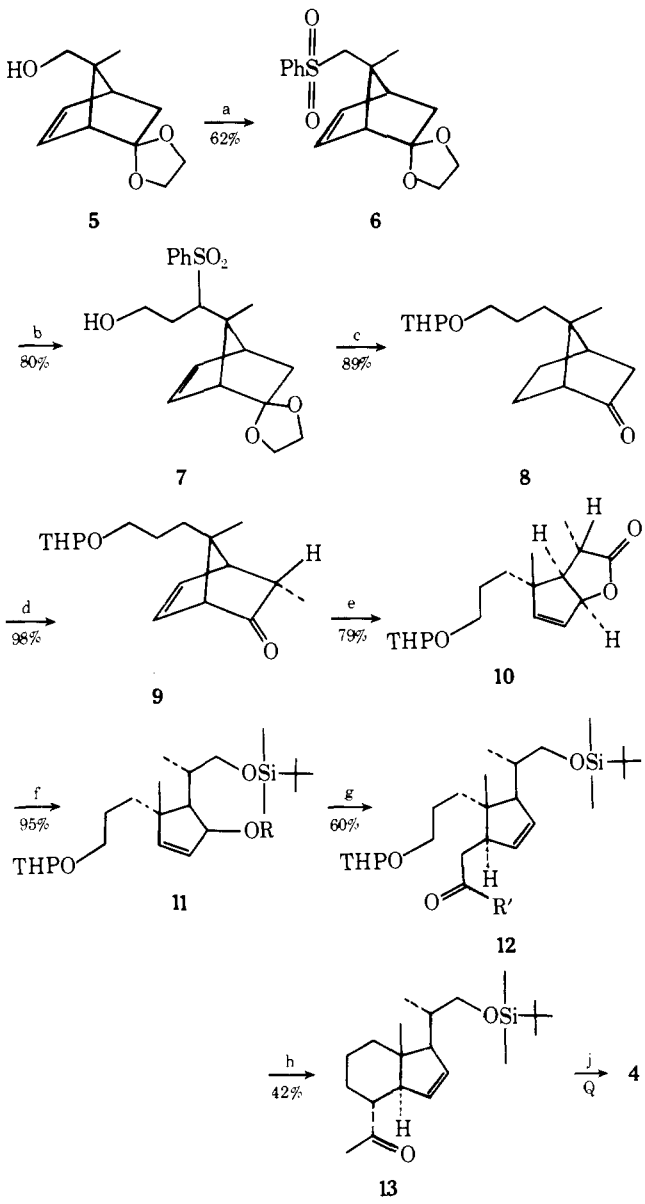
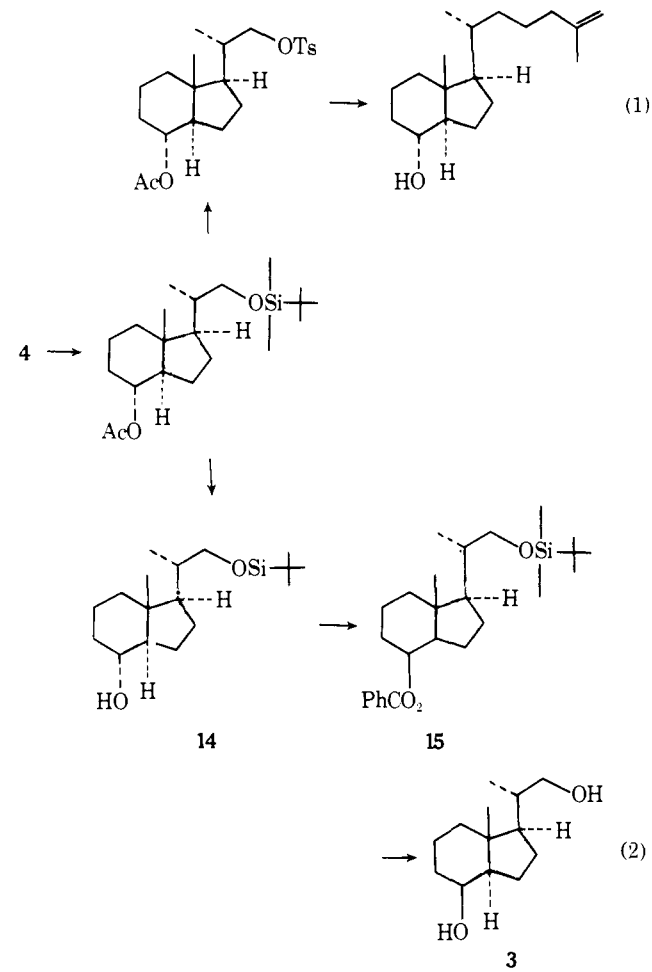
Scheme I. Preparation of 1β-[(*R**)-2-*tert*-Butyldimethylsiloxy-1-methylethyl]-4α-acetyl-7aβ-methyl-3aα,4,5,6,7,7aβ-hexahydroindan[a,b]



[a] Reference 4. a: [b] (i) TsCl, C_5H_5N, 0 °C; (ii) NaI, MEK, reflux; (iii) $PhSO_2Na$, DMF, 137 °C. b: C_4H_9Li, THF, HMPA, −70 °C and then C_2H_4O, ether, −20 °C. c: (i) 6% Na(Hg), Na_2HPO_4, CH_3OH, 25 °C; (ii) HOAc, H_2O, 95 °C; (iii) DHP, TsOH, CH_2Cl_2, RT. d: LDA, THF, −78 to 0 °C. e: (i) H_2O_2, NaOH, CH_3OH, H_2O, 25 °C; (ii) TsOH, PhH, RT. f: (i) $LiAlH_4$, ether, reflux; (ii) TBDMS−Cl, imidazole, DMF, RT. g: (i) $C_2H_5OCH{=}CH_2$, $Hg(OAc)_2$, RT; (ii) FVP, 500 °C; (iii) CH_3Li, ether, −70 °C; (iv) PCC, CH_2Cl_2, NaOAc, RT. h: (i) C_5H_5NHOTs, C_2H_5OH, RT; (ii) TsCl, C_5H_5N, 0 °C; (iii) KOC_4H_9-*t*, ether, 0 °C. (j) 1 atm of H_2, PtO_2, THF.

sterically demanding normal Claisen reaction of **11** (R = CH = CH_2) proceeded cleanly in >85% yield using a flash vacuum pyrolysis technique.[16] The lability of the aldehyde led us to convert it directly into the methyl ketone **12**[8] (R′ = CH_3), which was isolated in 60% yield based on **11** (R = H). The critical stereochemistry of this sequence stemmed from the cis fused lactone **10** and the concerted nature of the Claisen reaction. Correlation with an authentic sample at a later stage confirmed these anticipations. Selective removal of the THP utilized acetal exchange.[17] The yield of 70% represented a minimum since the major byproduct is the diol in which both the THP and silyl groups are removed. *trans*-Hydrindene



formation to **13**[8] was accomplished by intramolecular alkylation of the keto tosylate[18] which was subsequently hydrogenated to give **4.** Since the cyclization is performed under epimerizing conditions, the stereochemistry of the acetyl group is assigned as equatorial. The proton at C(4) appears as a td (J = 12, 3.8 Hz) at δ 2.71 to support this assignment.

Compound **4** is ideal for going toward either the ecdysones or vitamin D. With a view toward the latter, **4** was subjected to a Baeyer–Villiger oxidation (MCPBA, CH_2Cl_2, RT, 95%). The steroid side chain can be easily introduced via an organocuprate reaction (eq 1) (i, TsOH, CH_3OH, RT; ii, TsCl, C_5H_5N 0 °C; iii, $CH_2{=}C(CH_3)CH_2CH_2MgI$, Li_2CuCl_4, ether–THF, −78 °C to RT)[8] and the hydroxylated vitamin D side chain with correct stereochemistry has been introduced from this type of system.[5,19] Introduction of the remaining portions of the vitamin incorporating the acetyl carbons is envisioned for future work. On the other hand, methanolysis ($NaOCH_3$, CH_3OH, RT) gave the alcohol **14**[8] in 95% yield with the primary alcohol still protected. Using the method of Lythgoe, this intermediate can be converted into various vitamin D's.[5] To confirm the structural assignment, **14** was converted into diol **3** by hydroxy inversion[20] via **15** and then removal of both the *tert*-butyldimethylsilyl and benzoate groups (i, Ph_3P, $C_2H_5O_2CN{=}NCO_2C_2H_5$, $PhCO_2H$, PhH, 60–65 °C; ii, TsOH, CH_3OH, RT; iii, $LiAlH_4$, THF, RT).[8] The racemic diol thus obtained was identical with an authentic sample by TLC, ^1H and ^{13}C NMR, and IR spectroscopy.

Thus, **14** represents a differentiated basic building block of special use for modified vitamin D's. The ability to form **14** in over 8% overall yield from **5** compares quite favorably with the alternative approach to the closely related system[5] (epimeric at the secondary hydroxyl). Starting with optically pure **5,** the sequence was repeated to give all of the intermediates (see the

appendix, which appears in the microfilm edition, for selected data), **14** ($[\alpha]^{24}_D$ 7.6° (*c* 1.0, CH_2Cl_2)), and **3** in optically pure form. The latter was compared spectrally as well as by melting point (113–114 °C, lit.[5] 114 °C), mixture melting point (113–114 °C), and rotation ($[\alpha]^{24}_D$ 36.2° (*c* 0.395, CH_3OH) (authentic, $[\alpha]^{24}_D$ 36.5° (*c* 1.0, CH_3OH)) with an authentic sample.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We especially thank Professor B. Lythgoe for a generous sample of diol **3** and Sandoz, Ltd., for very generous supplies of starting materials.

Supplementary Material Available: Key spectral data for compounds **4**, **6**, **8**, and **10–14** (2 pages). Ordering information is given on any current masthead page.

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(8) All new compounds have been characterized by spectroscopic means and elemental composition, either by high resolution mass spectroscopy and/or elemental analysis. For some key spectral data, see the appendix which appears in the microfilm version.
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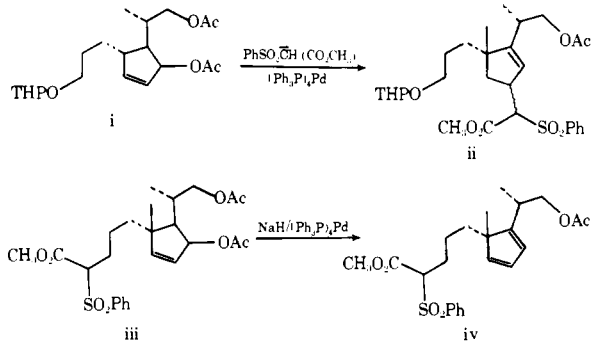

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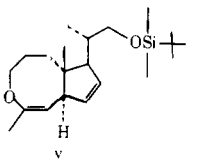

v

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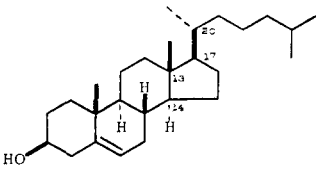
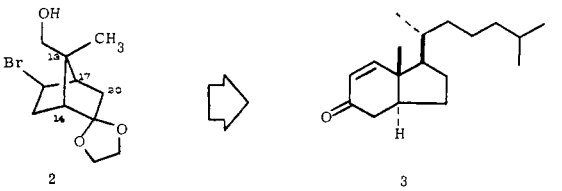
Bicyclo[2.2.1]heptanes in Organic Synthesis. Stereocontrolled Approach to Sterol Side-Chain Construction: Synthesis of De-*AB*-cholest-11-en-9-one

Sir:

The vast majority of sterols, including insect and crustacean moulting hormones, and the active metabolites of vitamin D possess the *R* configuration at C(20) (cf. cholesterol (**1**)). The



problems associated with generating and controlling chirality in acyclic systems have primarily been responsible for the limited success recorded to date for elaborating the stereochemistry at C(17) and at C(20) of sterol side chains.[1,2] A potential solution to this problem is embodied in the bicyclo[2.2.1]heptane derivative **2** whose conformational rigidity allows for elaboration of not only the chirality at C(20), but also that encountered at C(13), C(14), and C(17). We detail below the conversion of (−)-**2** into (+)-de-*AB*-cholest-11-en-9-one (**3**), a known precursor to tachysterol[3] and precalciferol[3].



2 3

The synthetic plan centered around the key bicyclic lactone **4** in which the carbonyl unit of the lactone serves to introduce the remaining carbon atoms of the side chain (cf. **4** → **5**). The oxygen function at C(16) (steroid numbering) provides a handle for establishing the stereochemistry at C(14) via a C–O → C–C chirality transfer (cf. **5** → **6**).

Alcohol **7**, $[\alpha]^{25}_D$ −115° (*c* 1.01, $CHCl_3$), obtained in near-quantitative yield by dehydrohalogenation (DBU, DMF, 170–180 °C, 1 h) of (−)-bromo alcohol **2**,[3] was subjected to (a) benzylation (NaH, $C_6H_5CH_2Br$, Bu_4NI, benzene–Me_2SO (20:1)) and (b) hydrolysis (10% HCl, THF) giving rise (~86% overall yield) to the bicyclo[2.2.1]heptenone **8**: $[\alpha]^{25}_D$ −479°

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