Tetrahedron Vol. 47, No.20/21, pp. 3485-3498, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

PALLADIUM-CATALYSED COUPLING OF VINYL TRIFLATES WITH ENYNES AND ITS APPLICATION TO THE SYNTHESIS OF 1α,25-DIHYDROXYVITAMIN D_3[1,2]

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(*Received in UK* 14 *January* 1991)

Abstracts. We describe a general approach, based on the palladium-catalysed coupling of enynes with vinyl triflates, for the construction of dienynes related to vitamin D metabolites and analogues. As an application of this method, an efficient convergent synthesis of 1α,25-dihydroxyvitamin D_3 starting from the Inhoffen-Lythgoe diol (**6a**) and natural carvones has been carried out (11 steps, 28% overall yield from **6a**). This strategy allows labelling of the side chain in the final steps of the synthesis

Introduction

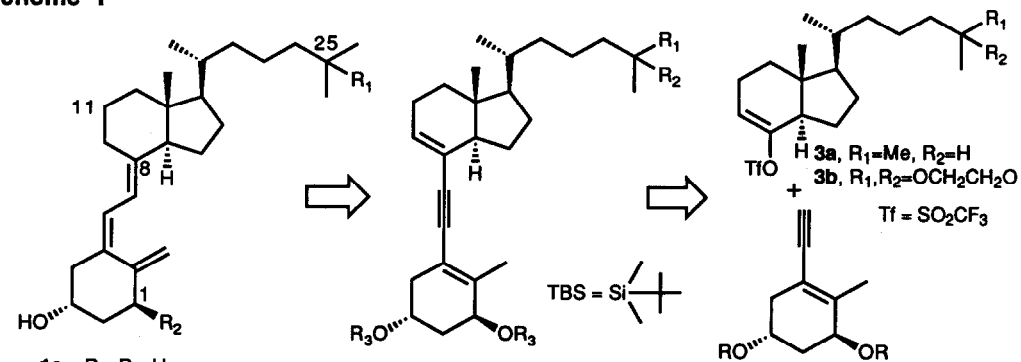
Vitamin D_3 (**1a**), before fulfilling classical biological functions such as intestinal calcium absorption and bone calcium mobilization, must undergo hydroxylation at C-25 and C-1 to produce 1α,25-dihydroxyvitamin D_3 [**1b**, 1α,25-$(OH)_2$-D_3]. This metabolite is thought to be the active form of vitamin D_3, and its mode of action resembles that of the steroid sex hormones.[3] Great interest has recently been attracted in the vitamin D field by the discovery that in addition to playing an important role in the medical treatment of a wide spectrum of human diseases,[3c] 1α,25-$(OH)_2$-D_3 is also able to induce cell differentiation and to inhibit cell proliferation in several lines of cancer cells.[4]

Several reports of syntheses of 1α,25-$(OH)_2$-D_3 have appeared.[5] Most of these approaches follow the long and tedious classical method in which the low-yielding electrocyclic photochemically induced opening of steroidal 5,7-dienes is the key step (~18-23 steps, ~0.2-1 % overall yield).[6] More recently, partial syntheses from 25-OH-D_3[7] or from the inexpensive vitamin D_2,[8] and a convergent approach based on the Wittig-Horner coupling of ketones with allylic phosphine oxides,[9] have also been reported.

Lythgoe and coworkers have shown that semihydrogenation of dienynes of type **2** (Scheme I), followed by thermolysis of the resulting previtamins, affords the corresponding vitamin D derivatives in good yield.[10] However, this approach has three drawbacks: (i) many steps are required for the preparation of the chloroketone corresponding to the CD fragment, (ii) low yield (~3 %) is obtained in the A ring fragment, and (iii) low yield in dienyne (20 %) is obtained by successive coupling between the chloroketone and an acetylenic fragment corresponding to ring A followed by formal elimination of ClOH.

We have recently reported convenient syntheses of dienynes related to vitamin D metabolites and analogues in which the key step is the palladium-catalysed coupling of enynes and vinyl triflates (Scheme I).[2b,11] We now describe details of this procedure and its application to an efficient synthesis of 1α,25-$(OH)_2$-D_3 following the retrosynthetic analysis depicted in Scheme I. This approach also allows labelling of the hydroxylated side chain in the final steps of the synthesis, and is flexible enough to permit preparation of several C-11-substituted analogues of potential interest for (i) the construction of affinity columns for the isolation and purification of the receptor of the hormone, (ii) the construction of photolabile probes for studying the active site of the receptor, and (iii) the generation of specific monoclonal 1α,25-$(OH)_2$-D_3 antibodies.

Scheme I



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

2a , R_1=Me, R_2=R_3=H
2b , R_1,R_2=OCH_2CH_2O, R_3=TBS

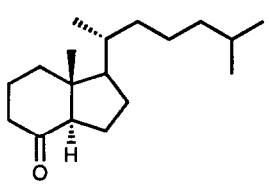
4a , R=H
4b , R=TBS

Syntheses of CD side chain fragments

In preliminary experiments to determine the effectiveness of the coupling reaction between vinyl triflates and the A-ring fragments **4a** and **4b**, we focussed our attention on the simple vinyl triflate **3a** (Scheme I), which had already proved to be a useful model in similar reactions with other A-ring derivatives.[11] Compound **3a** was obtained in around 90 % yield (several runs) by reacting Grundmann's ketone (**5**)[12] (Chart I) with lithium di-isopropylamide (LDA) to form the kinetic enolate, followed by quenching with N-phenyltriflimide[13] (Tf_2NPh).

For the synthesis of the hormone **1b** we chose the vinyl triflate **3b** (Scheme I), since the 25-masked carbonyl would allow labelling in the last steps of the synthesis. This compound was efficiently prepared from the Inhoffen-Lythgoe diol (**6a**) (44 %, 6 steps, chart I) as follows: monotosylation of **6a** and treatment of the resulting tosylate **6b**[14] with sodium iodide afforded **6c** (96 %). The key step for the construction of the side chain was the sonication of a mixture of iodide **6c**, methyl vinyl ketone, CuI and Zn in H_2O:EtOH (3:7) following Luche's method,[15] which provided the known ketoalcohol **7a**[17] in 76 % yield (this interesting procedure avoids the need to protect the hydroxyl group).[16] Ketalization and oxidation of the resulting ketal **7b**, as previously reported, afforded the protected ketone **7c**[17] (72 %). Finally, reaction of **7c** with LDA and trapping of the resulting kinetic enolate with Tf_2NPh gave the desired vinyl triflate **3b** (Scheme I) in 90 % yield.

Chart I



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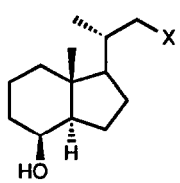
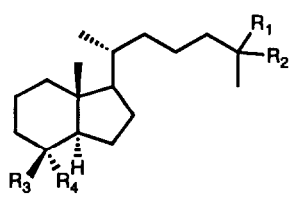


6a , X=OH
6b , X=OTs
6c , X=I



7a , R_1=R_2=O, R_3=OH, R_4=H
7b , R_1+R_2=OCH_2CH_2O, R_3=OH, R_4=H
7c , R_1+R_2=OCH_2CH_2O, R_3=R_4=O

Syntheses of A-ring fragments

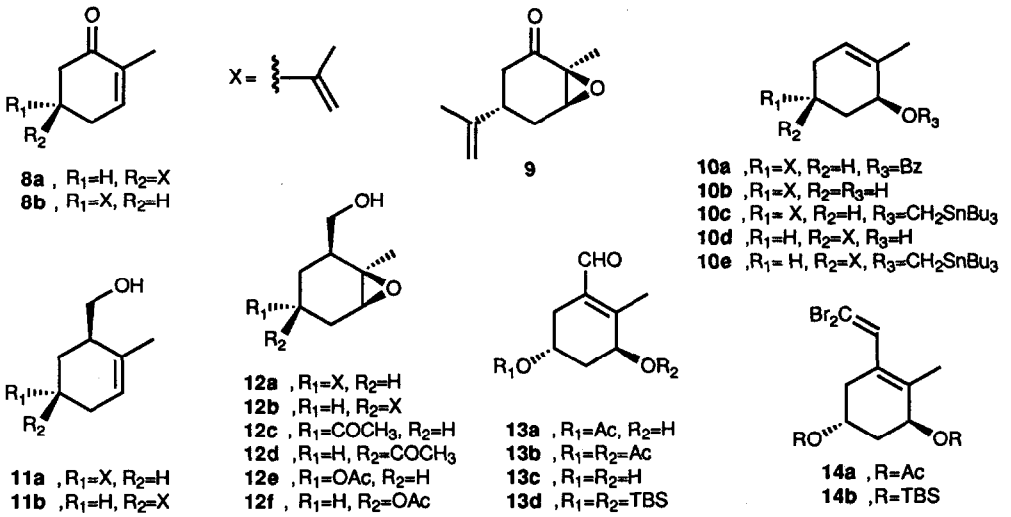
Diol **4a** and protected diol **4b** (Scheme I) were synthesized either from (R)-(-)-carvone (**8a**, l-carvone) or from (S)-(+)-carvone (**8b**, d-carvone) (Chart II). Sodium borohydride reduction of **8a** under Luche conditions[18] afforded an inseparable mixture of *cis*-carveol[19c] and its *trans*-epimer in a ratio of ca. 12:1 as shown by ^{1}H NMR analysis (91 %). This mixture was subjected to the Mitsunobu procedure[20] to provide, after column chromatography filtration, the crude benzoate **10a**, which without further purification was hydrolysed by means of methanolic potassium hydroxide to a mixture of the desired *trans*-carveol **10b**[19b] together with approximately 8 % of its epimer, as shown by ^{1}H NMR analysis (70 % yield).

Snags arising during the purification of benzoate **10a** from byproducts, and the expense of the above method, induced us to seek an alternative procedure for the preparation of *trans*-carveol **10b**. Stereoselective epoxidation of d-carvone (**8b**) was conveniently accomplished using modified Ohloff conditions (30 % H_2O_2, LiOH, MeOH) to give the epoxy ketone **9**[21,19d] in 88 % yield after kugelrohr distillation. Wharton reaction on **9** (NH_2NH_2•H_2O, $Me_2NCH_2CH_2OH$)[22] afforded a mixture of *trans*-carveol **10b** and the corresponding minor product *cis*-carveol in 60-70 % yield after conventional chromatography and kugelrohr distillation. Gas chromatographic analysis of this mixture showed it to contain 4 % *cis*-carveol. Potassium hydride deprotonation of alcohol **10b** in THF followed by alkylation with ICH_2SnBu_3[23] afforded the stannane **10c**, which after column chromatography filtration was rapidly treated with n-BuLi in THF to produce the homoallylic alcohol **11a** in 72 % yield through [2,3]-sigmatropic rearrangement[24] of the resulting primary carbanion; we were able to accomplish this transformation in similar yield in a one-pot reaction without isolating the stannyl derivative. Hydroxy-directed epoxidation of freshly distilled **11a** under Sharpless' conditions [$VO(acac)_2$, TBHP][25] provided the desired epoxy alcohol **12a** [86 %, ^{1}H NMR δ 3.05 (1H, t, J=2.3 Hz, H-6)] and its epoxy diastereomer [7 %, ^{1}H NMR δ 3.30 (1H, t, J=2.1 Hz, H-6)], which were separated by flash chromatography[26] Oxidative cleavage of **12a** (OsO_4, KIO_4) followed by flash chromatography gave pure **12c** in 88 % yield [^{1}H NMR δ 3.08 (1H, t, J=2.2 Hz, H-6)]. At this stage traces of a compound of closely similar Rf, which according to ^{1}H NMR analysis of the crude (δ 2.98, d) made up approximately 4% of the total mass, were also separated. As is argued below, this byproduct was assigned as the enantiomer of **12d**, derived from the diastereomer of the epoxy carvone **9**. Conversion of **12c** into acetate **12e** was then accomplished in 89 % yield by Baeyer-Villiger oxidation (*m*-CPBA, $CHCl_3$).

In order to check the purity of **12e** and to ensure that no epimerization had taken place at C-4 during the last two steps, *cis*-carveol **10d** obtained from d-carvone (**8b**) under Luche's conditions was subjected to the same sequence of reactions as above (**10d**→**10e**→**11b**→**12b**→**12d**→**12f**) to afford acetate **12f** in 30 % overall yield. The ^{1}H NMR of **12d** shows a doublet centred at δ 2.97 identical with that observable as a small signal in the ^{1}H NMR spectrum of crude **12c** (see above). In view of the synthetic sequence, this suggests that the material separated as traces from **12c** is the enantiomer of **12d**.

Swern oxidation[28] of **12e** under appropriate conditions opened the epoxy ring to afford the hydroxy acetate **13a**, which was acetylated to the diacetate **13b**[10a] in 83 % yield (two steps). Chain extension[29] to diol **4a** (Scheme I) was accomplished in 73 % yield by conversion to the vinyl dibromide **14a** (Zn, CBr_4, Ph_3P, pyridine) and subsequent elimination with n-BuLi. Standard protection with *tert*-butyldimethylsilyl chloride afforded the desired enyne **4b**[30] (16 % overall yield from d-carvone, 12 steps).

Chart II



Alternatively, it was also possible to obtain the enyne **4b** from the hydroxy acetate **13a** as follows. Sodium methoxide saponification of **13a** to the hydroxy aldehyde **13c**,[31] followed by protection with *tert*-butyldimethylsilyl chloride, afforded **13d**[31,32] in 82 % yield. Chain extension to vinyl dibromide **14b** and subsequent elimination as above afforded **4b** (Scheme I) in 84 % yield (16.5 %, 12 steps from d-carvone).

Coupling Experiments

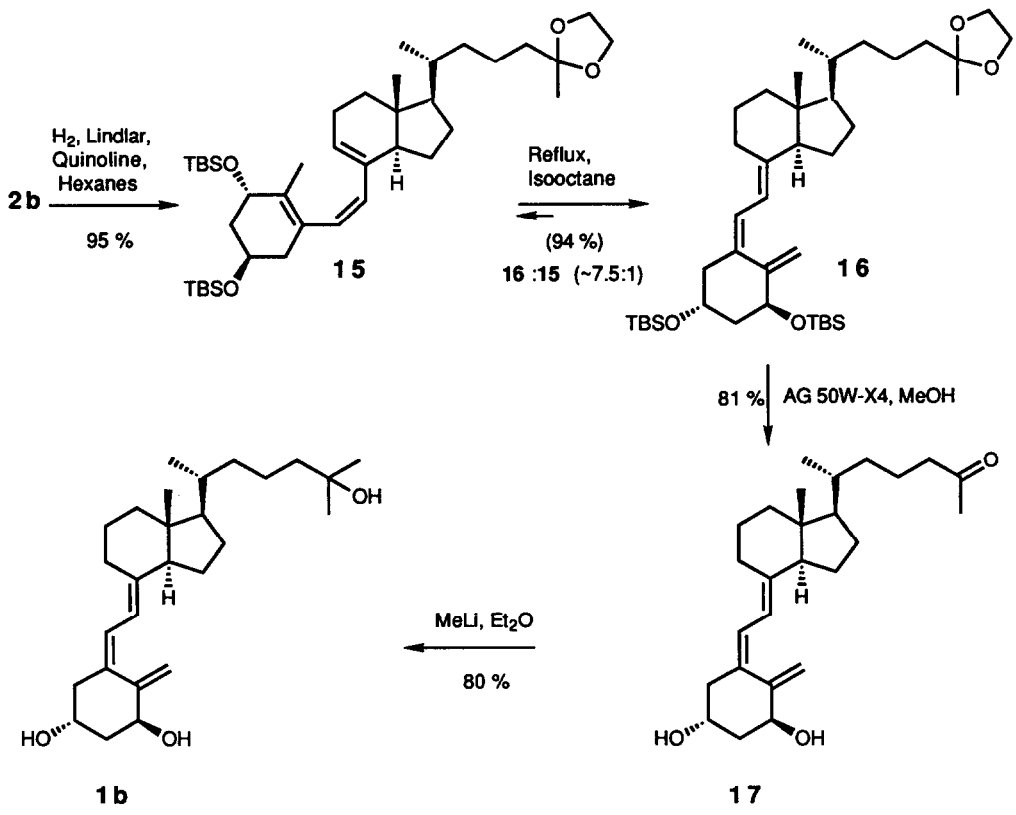
We first investigated the synthesis of unprotected dienyne **2a** starting from the enyne diol **4a** and the simple vinyl triflate **3a** (Scheme I). The coupling reaction between **3a** and **4a** in the presence of a catalytic amount of bis(triphenylphosphine)palladium (II) chloride [$(Ph_3P)_2PdCl_2$] under previously reported conditions (NEt_3, DMF, 75 °C)[34] afforded the dienyne diol **2a** in 54% yield. This unprotected dienyne was fairly unstable, and for this reason and in view of published precedents,[11] we decided to prepare the protected dienyne **2b**, the precursor of the natural hormone **1b**, starting from the protected enyne **4b**. Coupling between the tert-butyldimethylsilyl-protected A-ring fragment **4b** and the 25-carbonyl-protected vinyl triflate **3b** under the above reaction conditions furnished the desired dienyne **2b** in 91% yield after chromatography.

Synthesis of 1α,25-dihydroxyvitamin D_3 (Scheme II)

Semihydrogenation of dienyne **2b** in hexane with Lindlar palladium catalyst poisoned with quinoline, with careful monitoring of the reaction by TLC to avoid over-reduction of the triple bond, afforded **15** in 95 % yield after flash chromatography. The previtamin **15** was refluxed in iso-octane for 4 h to bring about equilibration to the vitamin **16**. Flash chromatograpy of the crude product afforded a mixture of **15** and **16** (94 % combined yield) in a ratio of approximately 12:88 (^{1}H NMR analysis). Treatment of this previtamin-vitamin mixture with H^+ cation exchange resin in methanol followed by flash chromatography afforded the pure keto vitamin **17** (81 % yield from **16**). Finally,

reaction of **17** with methyllithium in diethyl ether provided the desired 1α,25-dihydroxyvitamin D_3 metabolite **1b** in 80 % yield [28 % overall yield from the Inhoffen-Lythgoe diol (**6a**)].

Scheme II



Experimental Section

General. All dry solvents were distilled under argon. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride was distilled from phosphorus pentoxide. Pyridine was distilled from potassium hydroxyde. Di-isopropylamine from Aldrich was distilled and then redistilled from calcium hydride. Dimethylformamide (DMF, from Merck) was stored under Type 4A molecular sieves. All reactions were conducted under an argon atmosphere unless otherwise stated. Boiling points and melting points (open capillary tubes) are uncorrected. Kugelrohr distillation boiling points refer to the external air bath temperature. All 250 MHz ^{1}H NMR spectra were recorded in a Bruker WM-250 apparatus, using $CDCl_3$ as solvent. Chemical shifts are given in δ units with respect to tetramethylsilane as internal standard. Mass spectra were measured in a Kratos MS-50 apparatus, using electron impact at 70 eV. Mass spectra data are given as m/z (intensity expressed as percentage of total ion current). Flash chromatography was performed by Still's method.[35] Sonications were carried out in a BANDELIN type RK102H apparatus.

(1S,4S,6S)-1-Methyl-4-(1-methylethenyl)-7-oxabicyclo (4.1.0) heptan-2-one (9). A mixture of $LiOH.H_2O$ (25%, 16 mL) and methanol (500 mL) was stirred for 5 min. (S)-(+)-Carvone (**8b**, 9.6 g, 64 mmol, 10 mL) and hydrogen peroxide (30%, 100 mL, 0.96 mol) were successively added at 0 °C, and the resulting mixture was stirred for 2.5 h and then poured into water (60 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic extracts were washed with brine and then dried over Na_2SO_4. After filtration, the solvent was evaporated and the crude residue was bulb to bulb distilled to afford 9.3 g of the epoxide **9**[21,19d] (88 %, bp 70 °C / 0.6 mm) as a colourless oil. ^1H NMR δ 1.40 (3 H, s, C_1-CH_3), 1.72 (3 H, s, vinyl CH_3), 1.7-2.2 and 2.3-2.8 (5 H, two m), 3.45 (1 H, dd, J= 0.9 and 3 Hz, H-6), 4.72 and 4.80 (2 H, two br s, vinyl H's).

(1S,5R)-2-Methyl-5-(1-methylethenyl)-cyclohex-2-en-1-ol (10b). A mixture of the epoxy ketone **9** (5.5 g, 33.1 mmol), N,N-dimethylethanolamine (15 mL) and $NH_2NH_2.H_2O$ (1 mL, 0.93 g, 18.5 mmol) was stirred at room temperature for 12 h. More hydrazine (1 mL) was added and the resulting mixture stirred for 10 h. Concentration with a rotary evaporator and purification of the residue through a short column of silica gel (10% EtOAc/hexanes) gave 3.4 g of the allyl alcohol **10b**[19b] (70 %, colourless viscous liquid), which was further purified by kugelrohr distillation (bp 80 °C/0.1 mm). ^1H NMR δ 1.75 (3 H, br s, vinyl CH_3), 1.80 (3 H, br s, C_2-CH_3), 4.02 (1 H, m, H-1), 4.73 (2 H, m, vinyl H's), 5.60 (1 H, m, H-3). A weak signal at δ 4.19 (approx. 4 % intensity relative to the signal at 4.02) was assigned to H-1 of the epimer at C-1. G. C. analysis (Column: 6 ft, 3 % OV-17. 170 °C) of the distilled reaction product showed the same isomer ratio.

(1R,5R)-2-Methyl-5-(1-methylethenyl)-cyclohex-2-en-1-ol [(-)-*cis*-carveol, epimer of 10b at C-1]. (R)-(-)-carvone (**8a**,10 g, 66.6 mmol) and $CeCl_3{\cdot}7H_2O$ (25.3 g, 68 mmol) were dissolved in dry MeOH (100 mL). The solution was cooled to 0 °C, and $NaBH_4$ (2.5 g, 68 mmol) was added in portions. After stirring for 30 min at room temperature, water was carefully added and the resulting mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and filtered. Concentration in the rotary evaporator afforded 9.1 g of crude epimer[19c] of **10b**, which was subjected to the Mitsunobu inversion. ^1H NMR δ 1.74 and 1.76 (6 H, two br s, vinyl CH_3's), 4.19 (1 H, m, H-1), 4.73 (2 H, br s, vinyl H's), 5.50 (1 H, m, H-3). The weak signal at δ 4.02 (approx. 8 % intensity relative to the signal at 4.19) is attributed to H-1 of **10b**.

(1S,5R)-2-Methyl-5-(1-methylethenyl)-cyclohex-2-en-1-ol (10b). To a stirred mixture of the above crude *cis*-carveol (1g, 6.6 mmol), $PhCO_2H$ (1.6 g, 13.1 mmol) and Ph_3P (3.5 g, 13.2 mmol, crystallized from hexane) in THF (70 mL) was slowly added a solution of diethylazodicarboxylate (2.1 mL, 2.3 g, 13.1 mmol) in THF (13 mL). The mixture was stirred for 15 h, topped up with more Ph_3P (3.5 g, 13.2 mmol), $PhCO_2H$ (1.6 g, 13.1 mmol) and diethylazodicarboxylate (2.1 mL), and stirred for an additional 20 h. The mixture was rotary evaporated to a small volume, diluted with hexane/Et_2O (1:1) and washed with brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was filtered through a column of silica gel (2% EtOAc/hexanes) to give 1.23 g of the epimeric benzoate (72%), which was subjected to the next reaction. ^1H NMR δ 1.74 and 1.75 (6H, two br s, vinyl CH_3's), 4.73 (2H, two br s, vinyl H's), 5.51 (1H, m, H-3), 5.81 (1H, m, H-1), 7.40-7.60 (5H, m, Ar).

To a solution of the benzoate obtained as above in MeOH (10 mL) was added KOH (28 g, 0.7 mol) dissolved in MeOH (200 mL). The mixture was stirred for 14 h and the solvent removed in vacuo. The residue was diluted in Et_2O (150 mL) and the resulting solution washed with brine. The aqueous layer was extracted again with Et_2O (90 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified through a columnn of silical gel (5% EtOAc/hexanes) to give 3.1 g of **10b** (95%), whose ^1H NMR spectrum was similar to that of the product obtained previously, although now there was approx. 8% contamination by the epimer.

Bu_3SnCH_2I. Zn-Cu couple prepared by Smith's[36] procedure (10 g) and dry THF (20 mL) were placed in a three-necked round-bottomed flask equipped with a thermometer, a dropping funnel and a reflux condenser. CH_2I_2 (4.91 mL,16 g, 59.6 mmol) was dissolved in THF (14 mL) in the dropping funnel. The reaction was initiated by the addition of a few drops of the CH_2I_2 solution, and then this solution was added dropwise at a rate which maintained the temperature between 38 and 40 °C. The mixture was stirred for 1.5-2 h, cooled in an ice bath, and filtered through a Schlenk-type apparatus into another dry three-necked flask equipped with a thermometer and dropping funnel. To the white filtrate, a solution of freshly distilled Bu_3SnCl (18 mL, 21 g, 64 mmol) in THF (20 mL) was added dropwise over 30 min from the dropping funnel. After stirring for 12 h, the reaction mixture was poured into an aqueous solution of HCl (10 %, 100 mL) and extracted with hexanes. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in the rotary evaporator to give a residue which was filtered through a column of silica gel (hexanes) to afford liquid Bu_3SnCH_2I,[23] which was further purified by kugelrohr distillation [24 g, 93 %, bp 110-120 °C/0.1 mm; Rf: 0.90 (hexanes)]. ^1H NMR δ 1.94 (2 H, s, $-CH_2Sn-$).

(1R,5R)-2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-methanol (11a). An excess of KH (35 % dispersion in mineral oil) was washed with hexanes (3 x 20 mL) and THF (15 mL) by magnetic stirring and decantation, and dried in high vacuum. To a stirred suspension of dried KH (2.1 g, 52 mmol) in THF (80 mL) was added a solution of **10b** (4.6 g, 30 mmol, freshly distilled in the kugelrohr) in THF (26 mL). After stirring at room temperature for 5 h, the mixture was cooled at 0 °C and Bu_3SnCH_2I (15 mL, 21.5 g, 50 mmol, freshly distilled in the kugelrohr) was added. The reaction mixture was stirred for 12 h, and MeOH (3 mL) and water (50 mL) were added. The resulting solution was concentrated in the rotary evaporator to a small volume. Extraction with hexanes (3 x 75 mL), washing with brine, drying (Na_2SO_4) and concentration in the rotary evaporator afforded an oily residue which was filtered through a column of silica gel (hexanes) to give 12.4 g of stannane **10c** (90 %, colourless oil), which was inmediately subjected to the next reaction.^1H NMR δ 1.75 (6 H, br s, vinyl CH_3's), 3.38 (1 H, br s, H-1), 3.55 and 3.95 (2 H, AB, J= 10 Hz, $-OCH_2Sn-$), 4.73 (2 H, m, vinyl H's), 5.54 (1 H, m, H-3). To a stirred solution of stannane **10c** (12.4 g, 27.2 mmol) in THF (80 mL) at -78 °C was added a solution of n-butyllithium i hexane (17.5 mL, 2.1 M, 36.5 mmol). The reaction mixture was allowed to come to room temperature and was stirred for an additional hour. Several drops of water were added and the solvent removed in the rotary evaporator. The residue was diluted with Et_2O (100 mL) and the organic layer washed with brine, dried (Na_2SO_4) and filtered. Concentration in the rotary evaporator and flash chromatography (5-10 % EtOAc/hexanes) afforded, after concentration in vacuo and high vacuum drying, 3.58 g of the homoallyl alcohol **11a**: $[\alpha]^{25}_D$ -18.5° (*c* 0.77, $CHCl_3$); (80 %, 90-100 °C/0.5 mm, viscous colourless liquid). ^1H NMR δ 1.72 and 1.74 (6 H, two br s, vinyl CH_3's), 3.61 (1 H, dd, J= 8 and 11 Hz, -CHHOH), 3.74 (1 H, dd, J= 11 and 3.5 Hz, -CHHOH), 4.73 (2 H, br s, vinyl H's), 5.56 (1 H, m, H-3); MS, m/z 166 (M^+, 7), 151 (M^+-CH_3, 6), 148 (M^+-H_2O, 9), 135 (15), 133 (17), 119 (11), 107 (40), 105 (26), 93 (100), 91 (41); HRMS calcd for $C_{11}H_{18}O$ 166.1353, found 166.1354. **11b**: $[\alpha]^{25}_D$ +11.4° (*c* 0.65, $CHCl_3$).

(1R,2S,4R,6S)-2-Hydroxymethyl-1-methyl-4-(methylethenyl)-7-oxabicyclo [4.1.0] heptane (12a). To a solution of the freshly kugelrohr distilled alcohol **11a** (1.55 g, 9.3 mmol) in dry benzene (75 mL) was added vanadyl acetyl acetonate (100 mg), and the resulting mixture was stirred at 50 °C for 5 min. After cooling to room temperature, the reaction mixture was treated dropwise with a solution of anhydrous *tert*-butylhydroperoxide in toluene (4.3 mL, 3 M, 13 mmol). The green solution turned deep red as the t-BuOOH was added. The reaction was monitored by TLC (30 % EtOAc/hexanes) and judged complete after 3 h, by which time the deep red colour had turned to yellow. The reaction mixture was poured on a saturated solution of $NaHCO_3$ (70 mL) and extracted with Et_2O (3 x 60 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in the rotary evaporator, and the residue was purified by flash chromatography (10-15 %, EtOAc/hexanes) to afford, after concentration in vacuo and high vacuum drying, 1.45 g

of the desired **12a** (86 %) and 130 mg of the epoxydiastereomer (7 %, less polar compound) as colourless oils. Compound **12a** : $[\alpha]^{25}_D$ - 6.4°, (*c* 1.08, $CHCl_3$);^{1}H NMR δ 1.40 (3 H, s, C_1-CH_3), 1.71 (3 H, br s, vinyl CH_3), 3.05 (1 H, t, J= 2.3 Hz, H-6), 3.82 (2 H, d, J= 5.8 Hz, -CH_2OH), 4.68 and 4.74 (2 H, two s, vinyl H's); IR ($CHCl_3$) 1450, 1370, 1040, 900 cm^{-1}; MS, m/z 182 (M^+, 2), 167 (M^+-CH_3, 4), 164 (M^+-H_2O, 8) 149 (M^+-CH_3-H_2O, 14), 133 (20), 121 (23), 109 (30), 107 (48), 105 (27), 93 (49), 83 (52), 67 (83), 55 (59), 43 (100). HRMS calcd for $C_{11}H_{18}O_2$ 182.1302, found 182.1303. Epoxydiastereomer of **12a** ^{1}H NMR δ 1.44 (3 H, s, C_1-CH_3), 1.71 (3 H, br s, vinyl CH_3), 3.30 (1 H, t, J= 2.1 Hz, H-6), 3.91 (2 H, br s, -CH_2OH), 4.68 and 4.75 (2 H, two s, vinyl H's). **12b**: $[\alpha]^{25}_D$ + 4.2°, (*c* 2.5, $CHCl_3$).

(1R,2S,4R,6S)-2-Hydroxymethyl-4-acetyl-1-methyl-7-oxabicyclo [4.1.0] heptane (12c). To a mixture of **12a** (2.15 g, 11.8 mol) in THF-water (1:1, 160 mL) were added an aqueous solution of osmium tetroxide (1 %, 2.3 mL) and finely powdered potassium periodate (6.9 g, 30 mmol). After stirring at room temperature for 3 h, additional amounts of OsO_4 (1 %, 1 mL) and KIO_4 (2 g, 8 mmol) were added and the reaction mixture was stirred for a further 12 h. The resulting solution was concentrated in the rotary evaporator, and the residue was diluted with brine (75 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in the rotary evaporator, and the resulting residue was purified by flash chromatography (30-50 % EtOAc/hexanes) to afford, after concentration in vacuo and high vacuum drying,1.9 g of the pure ketone **12c** (88 %, colourless oil) and traces of a compound of slightly smaller Rf for which we attribute the structure of the enantiomer of **12d**, on the basis of caracteristic signals observed in the ^{1}H NMR of the reaction crude. Compound **12c**, ^{1}H NMR δ 1.40 (3 H, s, C_1-CH_3), 2.16 (3 H, s, CH_3CO), 2.64-2.77 (1 H, m, H-4), 3.08 (1 H, t, J= 2.2 Hz, H-6), 3.77-3.90 (2 H, m, -CH_2OH); IR ($CHCl_3$) 3400 (br), 1700, 1350, 1040 cm^{-1}; MS, m/z 184 (M^+, 40), 169 (M^+-CH_3, 18), 166 (M^+-H_2O, 64), 155 (60), 153 (85), 151 (100), 148 (72); HRMS calcd for $C_{10}H_{16}O_3$ 184.1116, found 184.1107. Enantiomer of **12d** : ^{1}H NMR δ 2.98 (d).

(1R,2S,4R,6S)-2-Hydroxymethyl-4-acetoxy-1-methyl-7-oxabicyclo [4.1.0] heptane (12e). Purified *m*-CPBA (2.6 g, 15.1 mmol) was added to an ice cooled solution of ketone **12c** (1.6 g, 8.7 mmol) in $CHCl_3$ (80 mL). An aqueous buffer of pH 7.8 (NaH_2PO_4-Na_2HPO_4, 70 mL) was added and the resulting mixture stirred for 3h. An additional amount of *m*-CPBA (2.7 g, 15.7 mmol) was added. After further stirring for 22 h, the reaction mixture was transferred into a separating funnel containing a solution of $NaHCO_3$ (60 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 70 mL) and the combined organic extracts were dried (Na_2SO_4) and filtered. Concentration in the rotary evaporator afforded a residue which was purified by flash chromatography (70 %, EtOAc/hexanes) to give, after concentration in vacuo and high vacuum drying, 1.55 g of acetate **12e** (89 %, colourless oil). ^{1}H NMR δ 1.44 (3 H, s, C_1-CH_3), 2.04 (3 H, s, AcO), 2.96 (1 H, d, J= 4 Hz, H-6), 3.80 (1 H, dd, J= 4.4 and 11.0 Hz, -CHHOH), 3.95 (1 H, dd, J= 5.2 and 11.0 Hz, -CHHOH), 4.98 (1 H, m, H-4); IR ($CHCl_3$) 3000, 1730, 1260,1050 cm^{-1}. MS, m/z 182 (M^+-H_2O, 1), 157 (M^+-CH_3CO, 12), 141 (13), 140 (100), 125 (35), 122 (88), 110 (33), 109 (58), 95 (51), 84 (32), 82 (90). HRMS calcd for $C_{10}H_{16}O_4$ -CH_3CO 157.0885, found 157.0874.

(3S,5R)-5-Acetoxy-3-hydroxy-2-methylcyclohex-1-ene-1-carboxaldehyde (13a). To a stirred solution of oxalyl chloride (0.164 mL, 1.9 mmol) in CH_2Cl_2 (15 mL) at -60 °C was added Me_2SO (0.27 mL, 3.8 mmol). The mixture was stirred for 5 min and then a solution of alcohol **12e** (300 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added within 5 min; stirring was continued for an additional 15 min. TEA (2.1 mL, 15 mmol) was added and the reaction was allowed to reach 0-10 °C. After stirring for 5 h at that temperature, water (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The organic layer was washed with brine. The aqueous layer was re-extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in the rotary evaporator. The residue was flash chromatographed (25-35 % EtOAc/hexanes) to afford, after concentration in vacuo and high vacuum drying, 260 mg of

aldehyde **13a** (88 %, light yellow oil). ^{1}H NMR δ 2.04 (3 H, s, Ac), 2.30 (3 H, s, C_2-CH_3), 4.38 (1 H, t, J= 3.8 Hz, H-3), 5.18 (1 H, m, H-5), 10.16 (1 H, s, HCO); IR (Film) 3440 (br), 2940, 2870, 1740, 1680, 1250 cm^{-1}; MS m/z 198 (M^+, 1), 168 (1), 155 (1), 152 (8), 136 (7), 135 (50), 134 (100), 119 (80), 105 (95).

(3S,5R)-3,5-Diacetoxy-2-methylcyclohex-1-en-1-carboxaldehyde (13b). Acetic anhydride (0.083 mL, 82 mg, 0.8 mmol, freshly distilled) and dimethylaminopyridine (50 mg) were successively added to a solution of alcohol **13a** (100 mg, 0,5 mmol) in pyridine (2 mL). The mixture was stirred at 25 °C for 6 h and then diluted with EtOAc (50 mL). The resulting solution was washed with brine, dried (Na_2SO_4), filtered and concentrated in the rotary evaporator to give 115 mg of **13b**[10b] (95 %, yellow oil), which was used directly in the next step. ^{1}H NMR δ 2.05 (3 H, s, C_5-Ac), 2.14 (3 H, s, C_3-Ac), 2.15 (3 H, s, C_2-CH_3), 5.13 (1 H, m, H-5), 5.57 (1 H, t, J= 4 Hz, H-3), 10.17 (1 H, s, HCO); IR (film) 2940,1735,1720, 1670, 1370, 1230, 1040 cm^{-1}; MS, m/z 211 (M^+-HCO, 1), 198 (10), 197 (M^+-CH_3CO, 100), 180 (15), 179 (20), 168 (8), 155 (90).

(3S,5R)-3,5-Dihydroxy-1-ethynyl-2-methylcyclohex-1-ene (4a). To a mixture of zinc dust (192 mg, 2.94 mmol) and Ph_3P (764 mg, 2.94 mmol) in CH_2Cl_2 (20 mL) at room temperature was added CBr_4 (960 mg, 2.94 mmol), and the resulting mixture was stirred for 15 min. Pyridine (0.4 mL) and aldehyde **13b** (115 mg, 0.48 mmol) in CH_2Cl_2 (4 mL) were successively added. After stirring for 30 min, Et_2O (20 mL) was added and the resulting suspension filtered through a short pad of silica gel [Et_2O (2 x 25 mL) and EtOAc (20 mL)]. Concentration of the filtrate in the rotary evaporator afforded the crude vinyl dibromide **14a** , which was used in the next step without further purification. ^{1}H NMR δ 1.66 (3 H, s C_2-CH_3), 2.05 (3H, s, C_5-Ac), 2.09 (3 H, s, C_3-Ac), 5.03-5.17 (1 H, m, H-5), 5.42 (1 H, t, J= 3.5 Hz, H-3), 6.94 (1 H, s, vinyl H). MS, m/z 396 (M^+, 1), 394 (2), 392 (1), 337 (30), 335 (50), 333 (30), 313 (10),311 (20), 309 (10), 396 (70), 294 (100), 292 (70).

The crude product of the previous reaction was dissolved in dry THF (6 mL) and cooled to -78 °C under an atmosphere of argon. A solution of n-butyllithium in hexane (1.6 mL, 2.1 M, 3.5 mmol) was slowly added to a solution of the dibromide **14a** in THF (6 mL) at -78 °C. The resulting deep red mixture was warmed to room temperature and quenched with a saturated aqueous solution of NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in the rotary evaporator to give a residue which was purified by flash chromatography (80 % EtOAc/hexanes) to give 53 mg of the enynediol **4a** (73 % yield from **13b**), as a viscous oil that decomposed on standing at room temperature. ^{1}H NMR δ 2.01 (3 H, br s, 1/2 W= 12 Hz, C_2-CH_3), 3.10 (1 H, s, sp-CH), 4.13 (1 H, m, H-5), 4.25 (1 H, t, J=4.3 Hz, H-3).

(3S,5R)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylcyclohex-1-en-1-carboxaldehyde (13d). The hydroxyacetate **13a** (480 mg, 2.42 mmol) was dissolved in MeOH (4 mL) and the solution was cooled to 0 °C and treated with a solution of sodium methoxide in MeOH (14 mL, 0.2 M, 2.80 mmol). After stirring for 5 h at room temperature, acetic acid (0.5 mL) was added. Concentration in the rotary evaporator gave a residue which was purified by flash chromatography (80 % EtOAc/hexanes) to afford, after concentration in vacuo and high vacuum drying, 300 mg of deprotected diol **13c**[31] (90 %, oil). ^{1}H-NMR δ 2.27 (3 H, br s, C_2-CH_3), 4.17 (1 H, m, H-5), 4.40 (1 H, t, J= 3.5 Hz, H-3), 10.17 (1 H, s, HCO).

A solution of this diol in CH_2Cl_2 (10 mL) was treated with *tert*-butyldimethylsilyl chloride (610 mg, 4.03 mmol) and imidazole (580 mg, 8.4 mmol). After stirring at room temperature for 20 min, additional amounts of *tert*-butyldimethylsilyl chloride (300 mg, 2 mmol) and imidazole (280 mg, 4 mmol) were added. The reaction mixture was stirred for 10 h, and then quenched by the addition of water (30 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 30 mL), dried (Na_2SO_4), filtered and concentrated in the rotary evaporator to gave a residue which was purified by flash chromatography (0-5 %

EtOAc/hexanes) to afford 720 mg of the protected aldehyde **13d**[31,32] (90 %, syrup). ^{1}H NMR δ 0.05 and 0.07 (6 H, two s, Me_2Si), 0.13 and 0.15 (6 H, two s, Me_2Si), 0.87 (9 H, s, Me_3CSi), 0.92 (9 H, s, Me_3CSi), 2.17 (3 H, s, C_2-CH_3), 4.10 (1 H, m, H-5), 4.34 (1 H, br s, H-3), 10.14 (1 H, s, HCO). IR ($CHCl_3$) 2910, 1675, 1460, 1255, 1080, 840 cm^{-1}.

(3S,5R)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-1-ethynyl-2-methylcyclohex-1-ene (4b). To a mixture of zinc dust (290 mg, 4.4 mmol) and Ph_3P (1.14 g, 4.35 mmol) in dry CH_2Cl_2 (20 mL) at room temperature was added CBr_4 (1.3 g, 4.0 mmol) and the resulting mixture was stirred for 15 min. Pyridine (1.4 mL) was then added, followed by a solution of aldehyde **13d** (280 mg, 0.73 mmol) in CH_2Cl_2 (6 mL). After stirring for 30 min, Et_2O (20 mL) was added and the resulting suspension filtered through a short pad of silica gel [Et_2O (2 x 25 mL)]. Concentration of the filtrate gave a crude which was purified by flash chromatography (hexanes) to afford, after concentration in vacuo and high vacuum drying, 368 mg of dibromide **14b** (92 %, mp: 62-64 °C, yellowish solid). ^{1}H NMR δ 0.06 and 0.10 (12 H, two br s, two Me_2Si), 0.88 and 0.90 (24 H, two s, two Me_3CSi),1.66 (3 H, br s, C_2-CH_3), 4.03-4.13 (1 H, m, H-5), 4.14 (1 H, br t, J= 3.2 Hz, H-3), 6.98 (1 H, s, vinyl H). IR (CCl_4) 1070, 1250 cm^{-1}. MS, m/z 542 (M^+, 1.3), 540 (2.3), 538 (1.1), 527 (10), 525 (17), 523 (8), 483 (44), 408 (74), 352 (72), 327 (96), 271 (58), 248 (49), 189 (60), 147 (74), 133 (70), 111 (76), 69 (100). HRMS calcd for $C_{21}H_{40}O_2Si_2Br_2$ 540.0915, found 540.0920.

A solution of n-butyllithium in hexane (0.6 mL, 2.3 M, 1.38 mmol) was added dropwise to a solution of the above dibromide **14b** in THF (6 mL) at -78 °C and the resulting deep red mixture was warmed to room temperature and quenched with a saturated aqueous solution of NH_4Cl (5 mL). The resulting mixture was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in the rotary evaporator to give a residue which was purified by flash chromatography (80 % EtOAc/hexanes), affording, after concentration in vacuo and high vacuum drying, 230 mg of the enyne **4b**, identical in all respects to the material obtained by bis-t-butylsilylation of **4a** and t an authentic specimen obtained by Okamura's procedure[30] (91 %, colourless oil). ^{1}H NMR δ 0.07 (6 H, s, Me_2Si), 0.11 (6 H, s, Me_2Si), 0.89 (9H, s, Me_3CSi), 0.91 (9H, s, Me_3CSi), 1.93 (3 H, br s, C_2-CH_3), 3.06 (1 H, s, sp-CH), 4.04-4.15 (1 H, m, H-5), 4.21 (1H, t, J=4 Hz, H-3). IR (CCl_4) 3310, 2085, 1260, 835 cm^{-1}; MS, m/z 380 (M^+, 3), 365 (M^+-CH_3, 25), 323 (80), 248 (100), 192 (44), 165 (50), 115 (9), 73 (75). HRMS calcd for $C_{21}H_{40}O_2Si_2$ 380.2567, found 380.2547.

De-A,B-cholest-8-en-8-yl Trifluoromethanesulphonate (3a). Lithium di-isopropylamide (LDA) was prepared by the addition of di-isopropylamine (0.16 mL, 1.14 mmol) to a solution of n-BuLi in hexane (0.4 mL, 2.56 M, 1.02 mmol) and THF (1 mL) at -78 °C. After stirring for 10 min at -78 °C and 15 min at room temperature, the solution was again cool to -78 °C and Grundmann's ketone (214 mg, 0.81 mmol) in THF (2 mL) was added dropwise via a cannula. After stirring f 15 min, the enolate solution was warmed to room temperature over 2 h and then recooled to -78 °C. N-phenyltriflimide (320 mg, 0.9 mmol) was dissolved in THF (2 mL) and added to the enolate at - 78 °C. The reaction mixture was warmed to °C and stirred for 10 h. The resulting solution was poured into water and extracted with Et_2O. The organic phase was drie ($MgSO_4$), filtered and concentrated in the rotary evaporator. The residue was purified by chromatography (hexanes) to afford, after concentration in vacuo and high vacuum drying, 300 mg of **3a** (86 %, colourless oil). ^{1}H NMR δ 0.75 (3 H, s, C_{18}-CH_3), 0.85 and 0.88 (6 H, two br s, $C_{26,27}$-CH_3), 0.93 (3 H, d, J= 6.4 Hz, C_{21}-CH_3), 5.57 (1 H, m, H-9).

De-A,B-22-Iodo-23,24-dinorcholestan-8β-ol (6c). A mixture of tosylate **6b**[14] (1 g, 2.7 mmol), acetone (50 mL, freshly purified with $KMnO_4$ and distilled from K_2CO_3) and NaI (1.5 g, 10 mmol) was stirred in the dark at 60-70 °C for 6 h. Water (10 mL) was added, the resulting solution was concentrated in the rotary evaporator to a small volume, and this residue was extracted with Et_2O (3 x 45 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated in the rotary evaporator to give a crude product which was purified by chromatography (5-10 % EtOAc/hexanes) to afford 0.84 g of the iodide **6c** (96 %, viscous colourless liquid). ^{1}H NMR δ 0.97 (3 H, s, C_{18}-CH_3), 1.00

(3 H, d, J= 5.5 Hz, C_{21}-CH_3), 3.18 (1 H, dd, J= 4.8 and 9.5 Hz, -CHHI), 3.32 (1 H, dd, J= 2.1 and 9.5 Hz, -CHHI), 4.09 (1 H, m, H-8). MS, m/z 322 (M^+, 1), 307 (M^+-CH_3, 6), 177 (77), 135 (29), 111 (100). HRMS calcd for $C_{13}H_{23}OI$: 322.0797, found 322.0794.

De-A,B-27-norcholestan-8β-ol-25-one (7a). To a sonicated (150 W) solution of iodide **6c** (140 mg, 0.44 mmol) and methyl vinyl ketone (65 μL, 0.8 mmol) in deoxygenated 7:3 EtOH/H_2O (6 mL) were added Zn dust (110 mg, 1.7 mmol, freshly purified and dried[36]) and CuI (42 mg, 0.44 mmol, freshly purified and dried[37]). The mixture was sonicated under argon at room temperature for 20 min, and then additional amounts of Zn (55 mg, 0.85 mmol) and CuI (42 mg, 0.23 mmol) were added. After further sonication for 30 min, Et_2O (10 mL) was added. The resulting mixture was filtered, and the solids were washed with Et_2O (3 x 30 mL). The filtrate was washed with brine and the aqueous phase was extracted with Et_2O (15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in the rotary evaporator. Flash chromatography of the crude (5 % EtOAc/hexanes) afforded, after concentraton in vacuo and high vacuum drying, 87 mg of the ketone **7a** (76%), identical with an authentic sample (TLC, ^1H NMR) obtained by an alternative route.[17]

De-A,B-25,25-(ethylenedioxy)-27-norcholest-8-en-8-yl trifluoromethanesulphonate (3b). The same procedure as for the preparation of **3a** was used to obtain **3b** (90 %, colourless oil). ^1H NMR δ 0.75 (3 H, s, C_{18}-CH_3), 0.93 (3 H, d, J= 6.7 Hz, C_{21}-CH_3), 1.32 (3 H, s, C_{26}-CH_3), 3.93 (4 H, m, OCH_2CH_2O), 5.57 (1 H, dd, J= 6 and 3.5 Hz, H-9); IR ($CHCl_3$) 2940, 1410, 1245, 1145, 880 cm-1; MS, m/z 425 (M^+-CH_3, 7), 381 (1), 87 (100), 69 (6), 43 (12); HRMS calcd for $C_{20}H_{31}O_5F_3S$ -CH_3 425.1609, found 425.1618.

5,7-Dehydro-1α-hydroxyprevitamin D_3 (2a). A mixture of enynediol **4a** (32 mg, 0.211 mmol), triflate **3a** (93 mg, 0.234 mmol), Et_3N (0.115 mL, 0.805 mmol), bis-triphenylphosphine palladium dichloride (4 mg, 0.005 mmol) and DMF (2 mL) was heated at 75 °C for 10 h and then was cooled to room temperature. Et_2O was added and the ether layer was washed successively with water and brine, dried ($MgSO_4$) and filtered. Concentration in the rotary evaporator gave a residue which was purified by flash chromatography (40-50 % EtOAc/hexanes) to afford, after concentration in vacuo and high vacuum drying, 45 mg of the dienyne **2a** (54 %, viscous liquid); ^1H NMR δ 0.69 (3 H, s, C_{18}-CH_3), 1.98 (3 H, t, J= 1.8 Hz, C_{19}-CH_3), 4.08-4.13 (1 H, m, H-3), 4.24 (1 H, t, J= 4 Hz, H-1), 5.97 (1 H, t, J= 3.2 Hz, H-9); MS m/z 398 (M^+, 2), 397 (8), 396 (28), 380 (M^+-H_2O, 8), 379 (28), 378 (100), 361 (8), 360 (30). HRMS calcd for $C_{27}H_{42}O_2$-H_2O 380.3079, found 380.3078.

1α-*tert*-Butyldimethylsilyloxy-6,7-dehydro-25,25-(ethylenedioxy)-27-norprevitamin D_3 *tert*-butyldimethylsilyl ether (2b). A mixture of enyne **4b** (80 mg, 0.21 mmol), triflate **3b** (90 mg, 0.20 mmol), Et_3N (0.08 mL, 0.56 mmol), bis-triphenylphosphine palladium dichloride (4 mg, 0.005 mmol) and DMF (1.5 mL) was heated at 75 °C for 1.5 h and then cooled to room temperature. The reaction mixture was diluted with Et_2O and the resulting mixture was washed with water and brine. Drying ($MgSO_4$), filtration and concentration in the rotary evaporator gave a residue which was purified by flash chromatography (2-4 % Et_2O/hexanes) to afford, after concentration in vacuo and high vacuum drying, 123 mg of the dienyne **2b** (91 %, a viscous liquid that decomposes rapidly even at -10 °C but is stable in solution in the refrigerator). ^1H NMR δ 0.06 and 0.090 (12 H, two s, Me_2Si), 0.69 (3 H, s, C_{18}-CH_3), 0.88 and 0.89 (24 H, two s, Me_3CSi), 1.32 (3 H, s, C_{26}-CH_3), 1.90 (3 H, s, C_{19}-CH_3), 3.94 (4 H, m, OCH_2CH_2O), 4.13 (1 H, m, H-3), 4.19 (1 H, t, J= 3.6 Hz, H-1), 5.97 (1 H, d, J= 3 Hz, H-9); MS, m/z 572 (48), 554 (M^+-HSiMe$_2$*t*-Bu, 100), 538 (64), 513 (19), 422 (23), 355 (57), 301 (35). HRMS calcd for $C_{40}H_{70}O_4Si_2$-HSiMe$_2$*t*-Bu 554.3793, found 554.3782.

1α-*tert*-Butyldimethylsilyloxy-25,25-(ethylenedioxy)-27-norprevitamin D_3 *tert*-butyldimethylsilyl ether (15). To a solution of dienyne **2b** (100 mg, 0.15 mmol) in hexane (5 mL) was added 0.5 mL of a solution of quinoline in hexane (100 μL of quinoline in 5 mL of hexane). Lindlar's catalyst from Aldrich (60 mg, previously dried at 60 °C for 4 h in high vacuum) was added, and the resulting solution was exposed to hydrogen gas at slightly positive H_2 pressure. After stirring for 45 min, TLC (2 % EtOAc/hexanes) indicated that all the starting material had been converted to a product with a slightly higher Rf; it is prudent to follow the reaction by TLC in order to avoid over-hydrogenation. After filtration and concentration in the rotary evaporator, the residue was purified by flash chromatography (1-3 % Et_2O/hexane) to give, after concentration in vacuo and high vacuum drying, 95 mg of protected previtamin **15** (95 %, colourless oil). ^{1}H NMR δ 0.06 and 0.09 (12 H, two s, two Me_2Si), 0.69 (3 H, s, C_{18}-CH_3), 0.89 (18 H, br s, two Me_3CSi), 0.95 (3 H, d, J= 6.4 Hz, C_{21}-CH_3),1.32 (3 H, s, C_{26}-CH_3), 1.65 (3 H, s, C_{19}-CH_3), 3.94 (4 H, m, OCH_2CH_2O), 4.11 (2 H, br s, H-1,3), 5.55 (1 H, br s, H-9), 5.72 and 5.88 (2 H, AB, J= 12.1 Hz, H-6,7); UV (Et_2O) λ_{max} 253 nm (ε 7800 nm).

1α-*tert*-Butyldimethylsilyloxy-25,25-(ethylenedioxy)-27-norvitamin D_3 *tert*-butyldimethylsilyl ether (16). Previtamin **15** (75 mg, 0.11 mmol) was dissolved in dry iso-octane (5 mL) and heated under reflux in the dark for 4 h. Concentration in the rotary evaporator at room temperature gave a residue which was purified by flash chromatography (2-4 % Et_2O/hexanes) to afford, after concentration in vacuo and high vacuum drying, 71 mg of an 88:12 mixture (NMR ratio) of **16** and **15** (94 % combined yield, 82 % of vitamin **16**). The mixture was inmediately subjected to deprotection. ^{1}H NMR of the mixture: δ 0.06 (12 H, br s, two Me_2Si), 0.52 (3 H, s, C_{18}-CH_3), 0.87-0.91 (18 H, br s, two Me_3CSi), 0.93 (3 H, d, J= 6 Hz, C_{21}-CH_3),1.32 (3 H, s, C_{26}-CH_3), 3.94 (4 H, m, OCH_2CH_2O), 4.17-4.23 (1 H, m, H-3), 4.36 (1 H, m, H-1), 4.86 (1 H, br s, *Z* - H-19), 5.17 (1 H, br s, *E* - H-19),6.01 and 6.24 (2 H, AB, J= 11.8 Hz, H-6,7); UV (Et_2O) λ_{max}263 nm (ε 12500 nm); MS, m/z 672 (M^+, 20), 657 (M^+-CH_3, 10), 646 (6), 540 (24), 355 (15), 311 (20), 211 (22), 163 (29), 113 (35), 108 (35), 108 (40), 104 (100), 87 (52).

1α-Hydroxy-25-oxo-27-norvitamin D_3 (17). A solution of the above mixture of **15** and **16** (65 mg, 0.09 mmol) in MeOH (5 mL) and CH_2Cl_2 (0.6 mL) was stirred with AG 50W-X4 resin (1.5 g, prewashed with MeOH) at room temperature for 12 h in the dark. An additional amount of resin (0.5 g) was added and the stirring continued for 12 h. Filtration, concentration in the rotary evaporator and purification of the crude product by flash chromatography (50-70 % EtOAc/hexanes) afforded, after concentration in vacuo and high vacuum drying, 30 mg of pure ketone **17** (81 % from the mixture, white syrup). ^{1}H NMR δ 0.54 (3 H, s, C_{18}-CH_3), 0.94 (3 H, d, J= 6.2 Hz, C_{21}-CH_3), 2.14 (3 H, s, C_{26}-CH_3), 4.23 (1H, m, H-3), 4.44 (1 H, t, J= 4.6 Hz, H-1), 5.01 (1 H, br s, H-19 *E*), 5.32 (1 H, m, H-19 *Z*), 6.01 and 6.37 (2 H, AB, J= 11.3 Hz, H-6,7); UV (Et_2O) λ_{max} 264 nm (ε 20000); IR (film) 3360 (br), 2900, 1690, 1340, 1040 cm^{-1}; MS, m/z 382 (M^+, 86), 145 (18), 131 (20), 87 (39), 55 (36), 43 (100); HRMS calcd for $C_{26}H_{38}O_2$ 382.2872, found 382.2874.

1α,25-Dihydroxyvitamin D_3 (1b). A solution of methyllithium in diethyl ether (0.33 mL,1.3 M, 0.43 mmol), was added dropwise to a cooled -78 °C solution of **17** (30 mg, 0.08 mmol) in diethyl ether (6 mL). After stirring for 20 min, the reaction was quenched with water (1 mL). Concentration in the rotary evaporator at room temperature (in the dark) gave a residue which was diluted with $CHCl_3$ and transferred to a separating funnel. Water was added and the aqueous phase was extracted with $CHCl_3$ (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in the rotary evaporator as above. The resulting crude product was flash chromatographed (70 % EtOAc/hexane) to give, after concentration in vacuo and high vacuum drying, 25 mg (80 %) of 1α,25-dihydroxyvitamin D_3 (**1b**). Crystallization from benzene/EtOAc afforded white crystals [mp 94-96 °C (Lit.[7b] mp 94-96 °C)]. ^{1}H NMR δ 0.54 (3 H, s, C_{18}-CH_3), 0.94 (3 H, d J= 6.2 Hz, C_{21}-CH_3), 1.26 (6 H, s, $C_{26,27}$-CH_3), 4.23 (1 H, m, H-3), 4.43 (1 H, m, H-1), 5.00 (1 H, br s, H-19 *E*), 5.33 (1 H, m, H-19 *Z*), 6.01 and 6.37 (2 H, AB, J= 12.4 Hz, H-6,7).

Acknowledgement. This research was supported by Doctoral Research Fellowships (FPI) to J.L.M. and L.A.S. and by Grants (CAICYT and DGICYT-PB87-0478) by the Spanish Ministerio de Educación y Ciencia. We thank Hoffmann la Roche (Basel) for the generous gift of vitamin D_2 and vitamin D_3

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