5.92 (dd, J = 15.5, 7.5 Hz, 1 H), 6.65 (dt, 1 H), 9.36 (d, J = 7.5 Hz, 1 H).

(3*Z*,5*E*)-3,5-Tetradecadien-1-ol (9). To a suspension of **8** (240 mg, 0.495 mmol) in THF (2 mL) was added dropwise *n*-BuLi (1.36 N hexane solution, 0.37 mL) at -30 °C. After the mixture was stirred for 1 h, HMPA (2 mL) was added, and then the aldehyde **7a** (67 mg, 0.40 mmol) was added at the same temperature. After being stirred for 1 h, the resulting mixture was quenched with water (4 mL) and extracted with petroleum ether, dried over sodium sulfate, and evaporated. To this concentrated solution was added methanol (10 mL) and HCl (2 N, 4 mL). The resulting solution was stirred at room temperature for 20 h and then shaken with $NaHCO_3$, and the organic layer was washed with water until neutral, dried over sodium sulfate, and evaporated. The crude product was purified by TLC (silica gel) eluting with 8:2 petroleum ether–ethyl acetate to afford 70 mg (80%) of **9**.

(3*Z*,5*E*)-3,5-Tetradecadien-1-ol Acetate (1). A solution of the dienol **9** (86 mg, 0.41 mmol), pyridine (1 mL), and acetic anhydride (50 mg) was stirred at 5–10 °C for 8 h and worked up. The crude mixture was purified by flash chromatography to give as an oil **1** (99 mg, 96%). This oil consists of three peaks (94.9%, 2.3%, 2.8%) in GC. MS data of these three components were shown as isomers [192 (M^+ - 60, 100%)]. The main isomer (3*Z*,5*E*)-**1** was identified by ^1H NMR: IR (film) 3032, 2936, 1763, 1234, 980, 945 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, H-14), 1.27 (m, 12 H, H-8,9,10,11,12,13), 2.04 (s, 3 H, H-2′), 2.08 (m, 2 H, H-7), 2.50 (dt, 2 H, H-2), 4.09 (t, J = 7.0 Hz, 2 H, H-1), 5.26 (dt, $J_{3,4}$ = 10.9 Hz, $J_{2,3}$ = 8.0 Hz, 1 H, H-3), 5.69 (dt, $J_{5,6}$ = 14.7 Hz, $J_{6,7}$ = 6.5 Hz, 1 H, H-6), 6.06 (dd, $J_{3,4}$ = 10.9 Hz, $J_{4,5}$ = 10.9 Hz, 1 H, H-4), 6.28 (dd, $J_{5,6}$ = 14.7 Hz, $J_{4,5}$ = 10.9 Hz, 1 H, H-5) [decoupling of H-2 and H-7 transformed H-3 to a doublet, $J_{3,4}$ = 10.9 Hz (cis), and H-6 to a doublet, $J_{5,6}$ = 14.7 Hz (trans)].

(5*Z*,7*E*)-5,7-Dodecadien-1-ol (2). The reaction conditions used for the Wittig transformation of **10** with **7b** were the same as described above. The crude product was mixed with potassium hydroxide (50 mg) in aqueous ethanol (3 mL, H_2O/EtOH = 1:2) and stirred at room temperature for 24 h. The reaction mixture was neutralized with 0.1 N HCl, extracted with ether, and washed with brine. The organic layer was dried over sodium sulfate and filtered, and the filtrate was concentrated in vacuo to afford a yellow oil. this crude product was purified by column chromatography (silica gel), eluting with 20% ethyl acetate–petroleum ether to afford a colorless oil (105 mg, 68%). The purity of the desired product **2** (5*Z*,7*E* form) determined by GC and GC/MS was 92%: MS, m/z 182 (M^+); IR (film) 3330 (br), 981, 950 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3 H, H-12), 1.26–1.68 (m, 9 H, H-2,3,10,11, OH), 2.06–2.26 (m, 4 H, H-4,9), 3.66 (t, J = 6 Hz, 2 H, H-1), 5.30 (dt, $J_{5,6}$ = 10.8 Hz, $J_{4,5}$ = 7.0 Hz, 1 H, H-5), 5.68 (dt, $J_{7,8}$ = 15.1 Hz, $J_{8,9}$ = 6 Hz, 1 H, H-8), 5.98 (dd, $J_{5,6}$ = 10.8 Hz, $J_{6,7}$ = 10.6 Hz, 1 H, H-6), 6.30 (dd, $J_{7,8}$ = 15.1 Hz, $J_{6,7}$ = 10.6 Hz, 1 H, H-7).

(5*Z*,7*E*)-5,7-Dodecadien-1-ol Acetate (3). The mixture of **2** (11 mg, 0,06 mmol), Ac_2O (12 mg, 0.11 mmol), and pyridine (1 mL) was stirred at 10 °C for 1 h. The resulting crude product was concentrated in vacuo and purified by TLC (silica gel), eluted with 20% ethyl acetate–petroleum ether, to afford as a colorless oil **3** (13 mg, 96%): IR (film) 1740, 1260, 1180, 990, 950 cm^{-1}; MS, m/z (relative intensity) 224 (M^+, 23); ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3 H, H-12), 1.20–1.72 (m, 8 H H-2,3,10,11), 2.05 (s, 3 H, H-2′), 2.09–2.26 (m, 4 H, H-4,9), 4.07 (t, J = 6.5 Hz, 2 H, H-1), 5.28 (dt, $J_{5,6}$ = 10.8 Hz, $J_{4,5}$ = 7.2 Hz, 1 H, H-5), 5.68 (dt, $J_{7,8}$ = 15.1 Hz, $J_{8,9}$ = 7.0 Hz, 1 H, H-8), 5.96 (dd, $J_{5,6}$ = 10.8 Hz, $J_{6,7}$ = 10.9 Hz, 1 H, H-6), 6.30 (dd, $J_{7,8}$ = 15.1 Hz, $J_{6,7}$ = 10.9 Hz, 1 H, H-7).

(5*E*,7*Z*)-Dodecadien-1-ol (12). The reaction conditions used for the Wittig transformation of **11** to **12** were the same as described for the prepartion of **9**. The purity of the desired **12** (5*E*,7*Z* isomer 92%) determined by GC and GC/MS as the same as in **1** was 92%, The other two isomers were 2% and 4%, respectively. ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3 H, H-12), 1.26–1.68 (m, 9 H, H-2,3,10,11, OH), 2.06-2.26 (m, 4 H, H-4,9), 3.66 (t, J = 6 Hz, 2 H, H-1), 5.30 (dt, $J_{5,6}$ = 10.8 Hz, $J_{4,5}$ = 7 Hz, 1 H, H-5), 5.68 (dt, $J_{7,8}$ = 15.1 Hz, $J_{8,9}$ = 6 Hz, 1 H, H-8), 5.98 (dd, $J_{5,6}$ = 10.8 Hz, $J_{6,7}$ = 10.6 Hz, 1 H, H-6), 6.30 (dd, $J_{7,8}$ = 15.1 Hz, $J_{6,7}$ = 10.6 Hz, 1 H, H-7).

(5*E*,7*Z*)-5,7-Dodecadienal (4). To a suspension of PCC (60 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) solution was added **12** (31 mg, 0.17 mmol) quickly. The mixture was stirred at room temperature. After the mixture was stirred for 2 h, ether (10 mL) was added. The resulting mixture was filtered on a short column of silica gel (petroleum ether–ethyl acetate, 95:5) to give the product (21 mg, 68%). The purity of the desired isomer (5*E*,7*Z* form) **4**, identified by GC and GC/MS, was 96%. The other isomers were 2% and 2%, respectively. MS, M^+ of the three isomers were the same; IR (film) 1725, 985, 995 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3 H, H-12), 1.26–1.40 (m, 4 H, H-10,11), 1.75 (m, 2 H, H-3), 2.16 (m, 4 H, H-4, 9), 2.45 (dt, 2 H, H-2), 5.35 (dt, $J_{8,9}$ = 7.2 Hz, $J_{7,8}$ = 10.9 Hz, 1 H, H-8), 5.60 (dt, $J_{4,5}$ = 7.1 Hz, $J_{5,6}$ = 15.1 Hz, 1 H, H-5), 5.94 (dd, $J_{7,8}$ = 10.9 Hz, $J_{6,7}$ = 10.5 Hz, 1 H, H-7), 6.33 (dd, $J_{5,6}$ = 15.1 Hz, $J_{6,7}$ = 10.5 Hz, 1 H, for H-6), 9.77 (t, J = 1.7 Hz, 1 H for H-1).

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Registry No. **1**, 61360-84-7; **2**, 73416-71-4; **3**, 78350-11-5; **4**, 75539-65-0; **5**, 103698-50-6; **6a**, 124-19-6; **6b**, 110-62-3; **6c**, 124-19-6; **7a**, 53448-07-0; **7b**, 18829-55-5; **7c**, 78350-09-1; **8**, 70665-02-0; **9**, 102488-79-9; **10**, 83085-84-1; **11**, 21406-61-1; **12**, 72922-18-0; $THPO(CH_2)_5OH$, 76102-74-4; $BrCH_2CHO$, 17157-48-1; Ph_3As, 603-32-7.

Total Synthesis of Dihydrovitamin DHV_3 and Dihydrotachysterol DHT_3. Application of the Low-Valent Titanium-Induced Reductive Elimination

Guy Solladié* and Jean Hutt

Ecole Europeenne des Hautes Etudes des Industries Chimiques (U.A. 466), 67008 Strasbourg, France

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Optically active ring A synthons **6**, **11**, **13**, and **14**, precursors of DHV_3 and DHT_3, were synthetized from (-)- and (+)-carvone. Application of the low-valent titanium-induced reductive elimination gave a new synthetic approach to vitamin D_3 analogues, as shown by an efficient preparation of DHT_3.

Synthetic efforts directed toward vitamin D_3 and its metabolites have been renewed since the discovery that specific hydroxylated derivatives are involved in a complex control of calcifiction processes. In contrast to the traditional passive characterization of vitamin D_3 as a vitamin, it is known[1] that vitamin D_3 acts like other classical steroid

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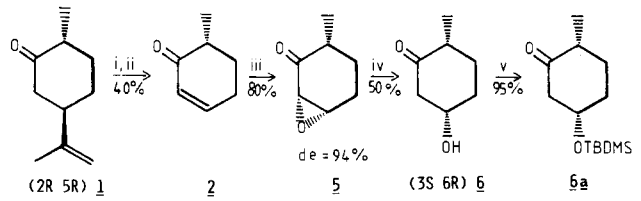
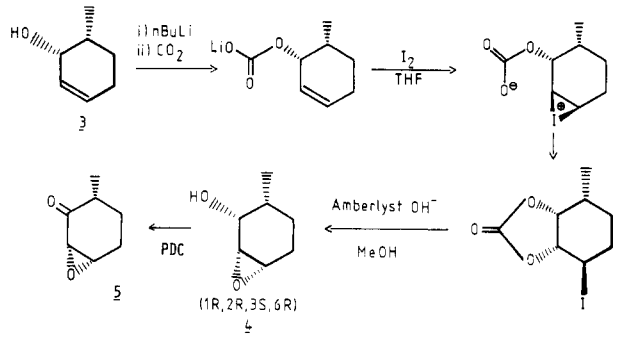
Scheme I[a]



[a] (i) O_3, MeOH, −78 °C; (ii) $FeSO_4$, $Cu(OAc)_2$; (iii) H_2O_2, K_2CO_3, MeOH, 0 °C; (iv) Al/Hg, $NaHCO_3$, EtOH, 90 °C; −15 °C; (v) *t*-$BuMe_2SiCl$, imidazole, DMF.

Scheme II



hormones: that is, its active form is synthetized in the liver and kidney in response to various stimuli and is transported to its site of action by a specific carrier protein.

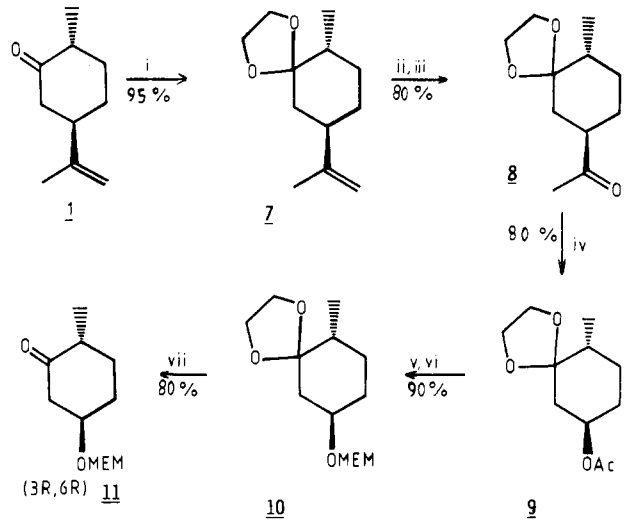
Many total syntheses of vitamin D and related molecules have been reported in the literature.[2-7] Till now the diene part was obtained by three main routes: a Wittig coupling reaction,[3,7] a sigmatropic rearrangement of vinylallenes,[4,5] and a reductive elimination of acyloxysulfones.[8,9] Very little has been done in the field of dihydrotachysterol and dihydrovitamin[10] and only recently Okamura[11] described the structural characteristics of all the possible stereoisomers.

We describe in this paper the synthesis of the four optically active stereoisomers of ring A synthons **6**, **11**, **13**, and **14** and their transformation into DHV_3 and DHT_3 stereoisomers using the low-valent titanium-induced reductive elimination to create the diene moiety.

We recently reported[12] a large-scale stereospecific synthesis of (+)-(2*R*,5*R*)-*trans*-dihydrocarvone (**1**) from (−)-carvone. The two chiral ring A synthons **6** and **11** are now readily prepared from molecule **1** (Schemes I and III).

Optically active methylcyclohexenone **2** was obtained by the literature procedure[13] from *trans*-dihydrocarvone with a lower yield but a significantly higher rotatory power. Enone epoxidation with hydrogen peroxide afforded epoxide **5** in 94% de. The same diastereoselectivity but a lower yield (50%) was obtained with NaOCl in dioxane. Finally reductive opening of the epoxide with aluminium amalgam[14] gave the hydroxy ketone (3*S*,6*R*)-**6**.

Scheme III[a]



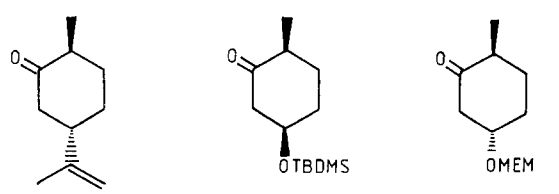
[a] (i) $HOCH_2CH_2OH$, PPTS, PhH; (ii) O_3, MeOH, −30 °C; (iii) Me_2S; (iv) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (v) K_2CO_3, MeOH–H_2O; (vi) NaH, $MeOCH_2CH_2OCH_2Cl$, DME, 0 °C; (vii) Me_2CO, H_2O, PPTS.

The configuration of the epoxide **5** was confirmed by independent synthesis using Cardillo's method[15] (Scheme II). Direct epoxidation of the alcohol **3** with *m*-CPBA or *tert*-butyl hydroperoxide gave a mixture of the two diastereoisomeric epoxides in the ratio 45/55.

The trans isomer **11** was prepared by another methodology (Scheme III).

The carbonyl of *trans*-dihydrocarvone (**1**) was protected without any epimerization of the chiral center and the acetal **7** submitted to ozonolysis in order to obtain ketone **8**. Baeyer–Villiger oxidation with *m*-CPBA gave the desired acetate **9** with complete retention of configuration (oxidation with trifluoroperacetic acid hydrolyzed the acetal and gave 12% of epimerization of carbon 2). After saponification of the acetate and protection of the OH group as a MEM ether, the acetal was hydrolyzed with PPTS (hydrolysis of the acetal in presence of the free hydroxylic group gave mainly the elimination product, the α,β-unsaturated ketone).

The two last molecules **13** and **14**, enantiomers of **6** and **11**, were prepared by the same procedure from (−)-(2*S*,5*S*)-*trans*-dihydrocarvone (**12**) which was prepared from commercially available (+)-carvone by the methodology already described[12] from (−)-carvone.



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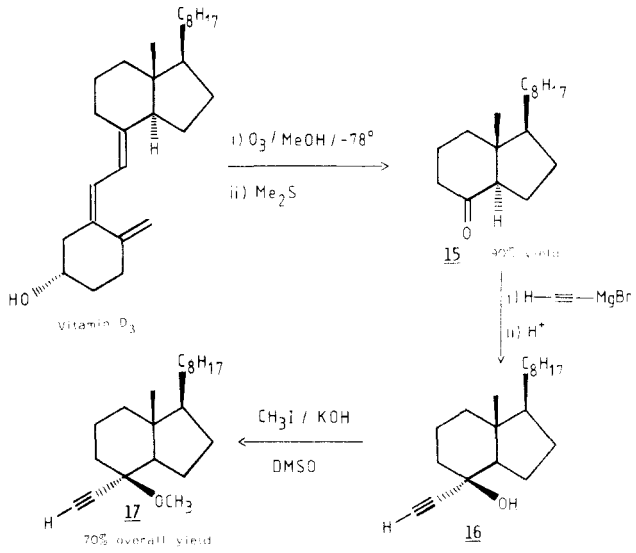
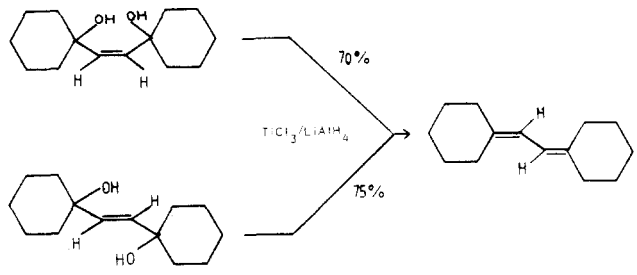
Scheme IV



Scheme V



Comparison of the rotatory powers of all the compounds prepared from (−)- and (+)-carvone showed that commercially available (+)-carvone was not optically pure; the ee was about 80%.

The four stereoisomers **6**, **11**, **13**, and **14**, readily prepared from (−)- and (+)-carvone will be used to synthetize dihydrovitamin DHV_3 and dihydrotachysterol DHT_3.

The C/D moiety **17** was obtained by chemical degradation of natural vitamin D_3.

Ozonolysis[16] of vitamin D_3 gave Grundmann's ketone **15** in 90% yield. Addition of acetylenic Grignard and methylation of the resulting alcohol gave compound **17** in 70% yield (Scheme IV).

Compound **16** was obtained as a pure diastereoisomer as a result of Grignard addition on the α side. The structure of the product was confirmed by NMR[17].

Low-valent titanium was first used by Van Tamelen and his co-workers Schwartz[18] and Hanzlik and Sharpless[19] to effect reductive coupling of benzylic[18] and allylic[20] alcohols. Subsequently low-valent titanium has been employed in the pinacolic coupling of carbonyls to olefins[20] and in the reductive coupling of carbonyls to olefins.[20] Reductive elimination of 1,2-glycols to olefins[21] as well as the cyclization of 1,3-glycols to cyclopropanes[22] has also been reported. More recently Walborsky[23] showed that low-valent titanium reacted with 2-ene-1,4-diols to yield 1,3-dienes by a 1,4-reductive elimination. One result was pecurliarly interesting: (*E*)- or (*Z*)-1,2-bis(1-hydroxycyclohexyl)-ethylene reacted with an excess of low-valent titanium to give dicyclohexylideneethane in 75% and 70% yields respectively (Scheme V).

Since dicyclohexylideneethane is a key moiety of vitamin D, this result suggested that this mode of generating 1,3-dienes might be effectively used in the synthesis of vitamin D and analogues.

Therefore, compounds **6**, **11**, **13**, and **14** were condensed with molecule **17** in presence of *n*-BuLi, the hydroxyl-protecting group on A ring was hydrolyzed and the triple bond reduced with $LiAlH_4$ (Scheme VI). These three steps gave quantitative yields. Compounds **18**–**21** are a mixture of two diastereoisomers resulting from a nonstereospecific addition to the carbonyl group.

Low-valent titanium reagents can be prepared by reduction of $TiCl_3$ or $TiCl_4$ with metals[20-22] such as magnesium, potassium, sodium, lithium, zinc–copper couple, or metal hydrides, particularly lithium aluminium hydride. A mixture of $TiCl_3$ and $LiAlH_4$ (4:1) is known as the McMurry reagent. However, Geise[24] has found that the $TiCl_3/LiAlH_4$ ratio of 2:1 is most effective in the coupling of ketones. This reagent was also used by Walborsky.[23]

In this study, the low-valent titanium reagent was prepared from a titrated solution of $LiAlH_4$ in THF in the $TiCl_3/LiAlH_4$ ratio of 2:1. Compounds **22**–**25** were submitted to the reaction. As shown in Schemes VII and VIII, we obtained in all cases a mixture of DHV_3 (5*Z*,7*E*) and DHT_3 (5*E*,7*E*); the 7*Z* geometry was never observed, probably because of severe interactions between hydrogens on C_6 and C_{15}. At room temperature, the reaction was not completed; it was necessary to heat the reaction mixture under reflux for 1 h to have a quantitative yield. It is interesting to remark (Scheme VII) that essentially in the cases of compounds **22** and **25** the isomer ratios were not the same at room temperature and under reflux. We checked that a mixture of DHV_3 and DHT_3 was stable in presence of low-valent titanium in refluxing THF.

The identification of DHV_3 and DHT_3 isomers was done by NMR according to the work of Okamura.[25,26]

In DHV_3 **26** and **32** the methyl group on C_{10} has an axial orientation (because of strong steric interaction between H_7 and the 10-CH_3 equatorial). Therefore, H_3 must be axial in **26**, $\delta(H_3)$ 3.50 (lit.[25] δ 3.57), and equatorial in **32**, δ (H_3) 4.00 (lit.[25] δ 4.02). Compounds **28** and **30** will have also the same conformation of the A-ring with the 10-CH_3 group axial. Therefore H_3 must be axial in **28**, $\delta(H_3)$ 3.66, and equatorial in **30**, $\delta(H_3)$ 3.85.

For DHT_3 the dienic moiety has no influence on the main conformation of the A-ring. Therefore in DHT_3 **27**

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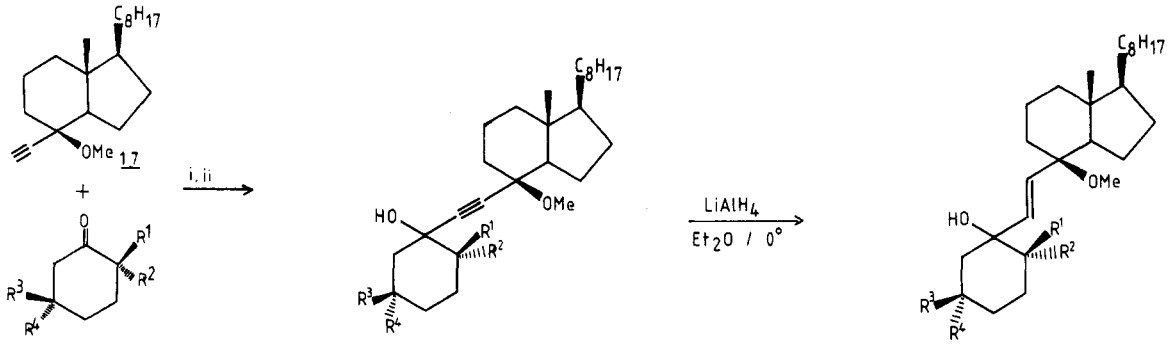
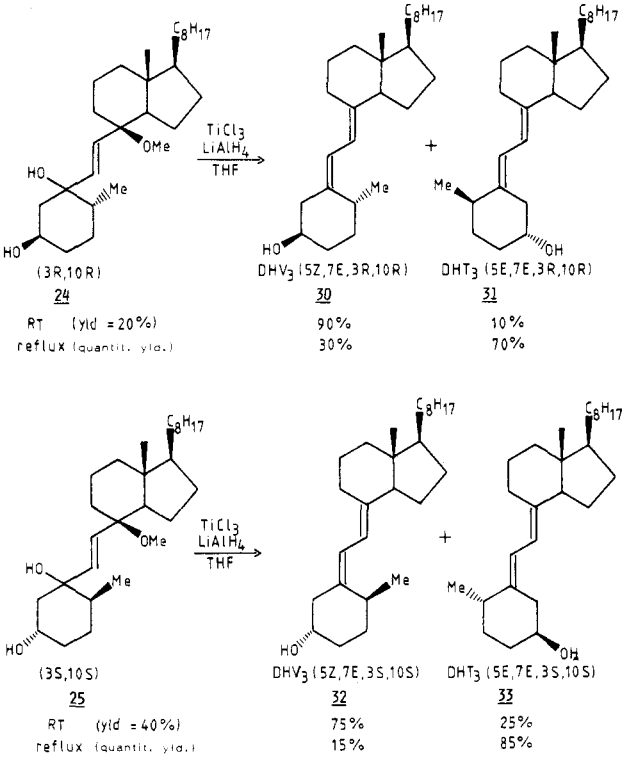
Scheme VI[a]



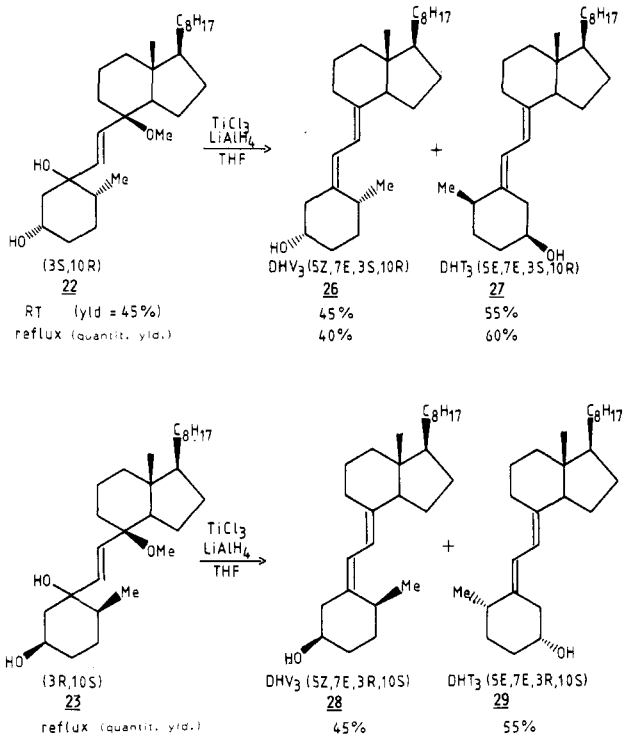
	R^1	R^2	R^3	R4		R^1	R^2	R^3	R^4	
6	H	Me	H	OTBDMS	18	H	Me	H	OH	22
13	Me	H	OTBDMS	H	19	Me	H	OH	H	23
11	H	Me	OMEM	H	20	H	Me	OH	H	24
14	Me	H	H	OMEM	21	Me	H	H	OH	25

[a] (i) *n*-BuLi, THF; (ii) $ZnBr_2$, CH_2Cl_2 for **11** and **14**, HF, CH_3CN for **6** and **13**.

Scheme VII



Scheme VIII

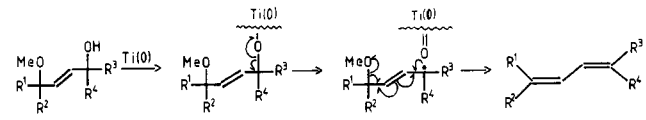


and **29**, the cis configuration of the 2-substituents of the A-ring leads to the presence of two main conformations with about the same population, giving an average chemical shift for H_3: in **27**, $\delta(H_3)$ 3.89 (lit.[25] δ 3.82), and in **29**, $\delta(H_3)$ 3.73. In DHT_3 **31** and **33**, the trans configuration of OH and CH_3 leads to a main conformation having the two substituents in equatorial orientation: in **33**, $\delta(H_3)$ 3.65 (lit.[25] δ 3.61), and in **31**, $\delta(H_3)$ 3.65.

It is generally believed[20-22,24,25] that the low-valent species generated in these reductions is Ti(0) and that the reaction occurs on the Ti(0) surface by single electron transfer. The reductive elimination of allylic diols or ethers reported by Walborsky[23] could therefore be rationalized by the formation of an allylic radical which undergoes a reductive elimination to give the diene (Scheme IX).

The geometry *E* or *Z* of the double bond in the allylic diol or ether has no influence on the stereochemistry of the product. As shown by Walborsky in the case of secondary diols, an (*E*,*E*)-diene is always obtained, suggesting a thermodynamic control of the reaction.

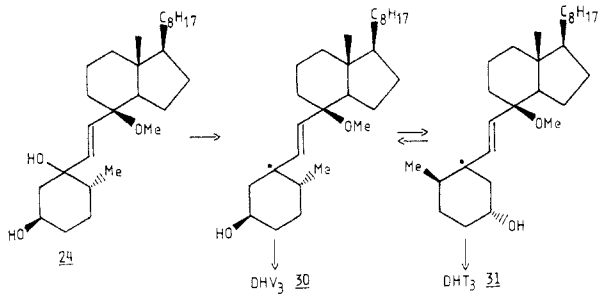
Scheme IX



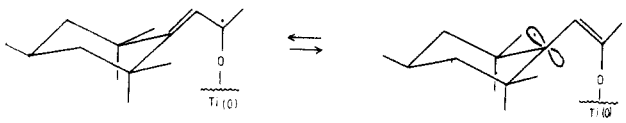
The application of this reductive elimination to the synthesis of DHV_3 and DHT_3 is rather complicated on the stereochemical point of view, the starting allylic diols being tertiary.

Let us consider first the reaction of compound **24**. At room temperature, we observed mainly the formation of DHV_3 **30** (90%) in 20% yield. In refluxing THF, the reaction was quantitative and the main product was DHT_3 (70%) (Scheme X).

Scheme X



Scheme XI



This result can be explained by rotation of the radical, before the elimination step, leading to the more stable DHT_3 in which the two substituents of the A-ring are equatorial, the driving force of this isomerization being the steric interactions between 10-CH_3 and H_7 in the first conformation of the intermediate. This result, due to a thermodynamic control of the reaction, is closely related to the recent observation of Walborsky.[27] He compared the cross-coupling of chiral (*R*)-(4-methylcyclohexylidene)acetone with acetone on a Ti(0) surface and that of (*S*)-(2,2,4,6,6-pentamethylcyclohexylidene)acetone in the same conditions. The first molecule gave the adduct with a high degree of retention of configuration, while the second molecule gave only racemic product. This striking difference is due to hindrance exerted by the 2,2,6,6-tetramethyl groups. These groups provide a steric inhibition to the delocalization of the allyl radical system and in order to relieve the steric interaction, the radical resides at C_1 of the cyclohexane ring, intermediate having a plane of symmetry (Scheme XI).

A similar result was obtained with compound **25**.

In sharp contrast molecules **22** and **23** gave always approximatively the same amount of DHV_3 and DHT_3, the reaction temperature influencing only the reaction yield. This result is consistent with the relative stability of DHV_3 **26** (or **28**) and of DHT_3 **27** (or **29**), the main conformations of theses molecules having the 10-CH_3 axial and 3-OH equatorial.

The new approach to vitamin D_3 analogues has certainly some valuable contribution to the synthesis of such molecules.

Dihydrotachysterol DHT_3 **33** and DHT_2 (which differs only by the presence of a Δ^{22} double bond) have important biological properties,[25] DHT_3 being more active than DHT_2[28,29] (DHT_2 was, however, marketed as early as 1934 under the trade name A.T.10 by Merck as antitetanic agent). However, the synthesis reported in the literature started from vitamin D_3 with isomerization to 5*E* vitamin D_3 and reduction of the exocyclic double bond, giving a complex mixture of products.

DHT_3 **33** (or DHT_2) can be readily prepared by our methodology, the low-valent titanium reductive elimination giving in a quantitative yield a mixture containing 85% of DHT_3 and 15% of the corresponding DHV_3 which is easily separated.

Experimental Section

(*R*)-6-Methylcyclohex-2-en-1-one (2). To a solution of (+)-*trans*-dihydrocarvone[12] (**1**; 4.7 g, 30.8 mmol) in methanol (200 mL), to cooled −30 °C, was added ozone till a blue color persisted. Then the solution was flushed with argon till the color disappeared. The reaction mixture was then allowed to warm to −20 °C, and copper(II) acetate monohydrate (12.3 g, 61.6 mmol, 2 equiv) was added. After 15 min, $FeSO_4 \cdot 7H_2O$ (8.5 g, 37 mmol, 1.2 equiv) was added in small portions. The green solution was maintained at −20 °C for 8 h and at room temperature for 3 h. After the addition of 200 mL of water, the solution was extracted with ether (5 × 100). The organic layer was then washed with a saturated sodium bicarbonate solution (100 mL) and with a saturated sodium chloride solution (10 mL) and finally dried over sodium sulfate. After evaporation of the solvent, the product was distilled: bp 33–35 °C (2.5 mm); 40% yield; $[\alpha]^{21}_D$ +91° (neat), $[\alpha]^{21}_D$ +70° ($CHCl_3$, *c* 3.0); ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, 3 H, J = 6.5 Hz, CH_3), 1.62–1.84 (m, 1 H, J_{gem} = −12.5 Hz, H_5), 2.00–2.15 (m, 1 H, H_5), 2.30–2.50 (m, 3 H, H_4 + H_6), 6.00 (td, 1 H, $J_{2,3}$ = 10 Hz, $^4J_{2,4}$ = 2 Hz, H_2), 6.94 (m, 1 H, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 4 Hz, $^4J_{3,5}$ = 1 Hz, H_3).

(2*S*,3*S*,6*R*)-6-Methyl-2,3-epoxycyclohexan-1-one (5). (A) Saturated K_2CO_3 (5 mL) was slowly added to a cold solution (0 °C) containing enone **2** (6.57 g, 59.6 mmol), methanol (100 mL), a 30% hydrogen peroxide solution (1.5 mL, 140 mmol, 2 equiv), and water (50 mL). The reaction mixture was stirred at 0 °C for 1 h. After the addition of 300 mL of water and extraction with ether (5 × 100 mL), the organic layer was washed with a saturated NaCl solution (100 mL) and dried over Na_2SO_4. After evaporation of the solvent, the product was purified by chromatography (hexane/AcOEt, 80/20): yield 80%; $[\alpha]^{21}_D$ +43° ($CHCl_3$, *c* 1.2); IR ($CHCl_3$) 1705, 1240, 875 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (d, 3 H, J = 7 Hz, CH_3), 1.47–1.68 (m, 2 H, H_5), 1.85–2.31 (m, 3 H, H_4 + H_6), 3.26 (d, 1 H, $J_{2,3}$ 4.5 Hz, H_2), 3.57 (td, 1 H, H_3). Anal. Calcd $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 68.74; H, 8.14.

(B) Oxidation of the Epoxy Alcohol 4. PDC (6.2 g, 16.4 mmol, 7 equiv) was added at 0 °C to a solution of epoxy alcohol **4** (300 g, 2.3 mmol) in DMF (13 mL). The mixture was stirred at 0 °C for 6 h, diluted by 150 mL of water, and extracted with a mixture of ether–hexane (50/50, 5 × 50 mL). The organic layer was washed with water (2 × 100 mL) and a saturated NaCl solution (100 mL). The product isolated by chromatography showed the same characteristics as above: yield, 95%.

(3*S*,6*R*)-6-Methyl-3-hydroxycyclohexan-1-one (6): Obtained by reduction of epoxy ketone **5** with aluminium–amalgam according to the published procedure;[14] yield, 50%; $[\alpha]^{21}_D$ −3.2° ($CHCl_3$, *c* 1.1); IR ($CHCl_3$) 3610, 3440, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (d, 3 H, J = 6.6 Hz, CH_3), 1.28 (m, 2 H, H_5), 1.56 (s, large, 1 H, OH), 1.90–2.34 (m, 3 H, H_4 + H_6), 2.59 (AB part of ABX, 2 H, J_{AB} = 13.0 Hz, J_{AX} = 5.0 Hz, J_{BX} = 2 Hz, $^4J_{A6}$ = 2.2 Hz, $\Delta\nu$ 73.4 Hz, H_A + H_B), 3.92 (sep, 1 H, H_X).

(3*S*,6*R*)-6-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]cyclohexan-1-one (6a). *tert*-Butyldimethylsilyl chloride (78 mg, 0.52 mmol, 1.2 equiv) and imidazole (73 mg, 1.1 mmol, 2.5 equiv) were added at room temperature to a solution of **6** (56 mg, 0.43 mmol) in DMF (100 mL) and stirred for 4 h. After the addition of a saturated NH_4Cl solution (100 mL), the reaction mixture was extracted with a mixture ether–hexane (50/50, 3 × 50 mL). The organic phase was washed with water (3 × 50 mL), dried over $MgSO_4$, and evaporated. The product was purified by chromatography (hexane/AcOEt, 95/5): yield 95%; $[\alpha]^{21}_D$ + 7.9° ($CHCl_3$, *c* 2.2); IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 3 H, CH_3Si), 0.08 (s, 3 H, CH_3Si), 0.89 (s, 9 H, *t*-BuSi), 1.02 (d, 3 H, J = 7 Hz, CH_3), 1.09–1.34 (m, 2 H, H_5), 1.71 (m, 1 H, H_6), 2.02 (m, 2 H, H_4), 2.50 (AB part of ABX, 2 H, J_{AB} = 13, 1 Hz, J_{AX} = 4.6 Hz, $^4J_{A6}$ = 1.8 Hz, J_{BX} = 1.0 Hz, $\Delta\nu$ = 48.5 Hz, H_A + H_B), 3.86 (X part of ABX, 1 H, H_X).

(1*R*,6*R*)-6-Methylcyclohex-2-en-1-ol (3). A 1 M DIBAL solution in hexane (35.4 mmol) was added at 0 °C to a solution of ketone **2** (3.25 g, 29.5 mmol) in anhydrous benzene (100 mL). After the mixture was stirred for 30 min, methanol (100 mL) was

(27) Reddy, S. M.; Duraisamy, M.; Walborsky, H. M. *J. Org. Chem.* **1986**, *51*, 2361.
(28) Van de Vliervoet J. L. J.; Westernof, P.; Keverling-Buisman, J. A.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 1179.
(29) Hibberd, K.; Norman, A. W., *Biochem. Pharmacol.* **1969**, *18*, 2347.

added, and the solvents were evaporated. The residue was treated with ether (50 mL) and 5% H_2SO_4 (50 mL). After separation, the aqueous phase was extracted with ether (50 mL) and the organic layer washed with a saturated solution of NaCl (50 mL), dried over $MgSO_4$, and evaporated. The product was finally purified by chromatography (hexane/AcOEt, 95/5): yield, 70%; $[\alpha]^{21}_D$ +41° (neat, d^{20} 0.956); IR (CCl_4) 3610, 3400, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, 3 H, J = 6.0 Hz, CH_3), 1.22–1.81 (m, 3 H, $H_5 + H_6$), 2.03 (m, 2 H, H_4), 2.2 (m, 1 H, OH), 3.77 (m, 1 H, H_1), 5.50–5.9 (m, 2 H, $H_2 + H_3$).

Reduction with BBN or *n*-$BuBH_3Li$, gave a mixture of the two diastereoisomers in a cis/trans ratio = 80/20 or 60/40, respectively. The *1S,6R* trans isomer showed in NMR a doublet of δ 0.96 for the methyl group.

(1*R*,2*R*,3*S*,6*R*)-6-Methyl-2,3-epoxycyclohexan-1-ol (4). Allylic alcohol **3** (2.14 g, 19.1 mmol) was transformed into the corresponding cyclic iodocarbonate by Cardillo's method,[15] which was hydrolyzed to the corresponding epoxide with Amberlyst OH.[15] The product was purified by chromatography (hexane/AcOEt, 60/40): yield, 20%; mp 62 °C; R_f 0.23 (hexane/AcOEt, 60/40); $[\alpha]^{21}_D$ – 36° (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 3560, 3420, 1240, 855, 825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (d, 3 H, J = 7 Hz, CH_3), 1.37–1.60 (m, 2 H, H_5), 1.63 (s, 1 H, OH), 1.69–1.91 (m, 3 H, $H_6 + H_4$), 3.27 (m, 1 H, H_3), 3.34 (m, 1 H, H_1), 3.50 (td, 1 H, $J_{2,3} = J_{1,2}$ = 8 Hz, H_2). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.69; H, 9.49.

Epoxidation of the Allylic Alcohol 3. A benzene solution of *tert*-butyl hydroperoxide–vanadyl acetoacetate (1.04 M, 21 mL, 18 mg, 0.0005 equiv) was added to the allylic alcohol **3** (1.55 g, 13.8 mmol). After 24 h at room temperature under stirring, the mixture was washed with an aqueous solution of sodium thiosulfate and extracted with ether. The organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$, and evaporated. The two epoxides diastereosimers were separated by chromatography (hexane/AcOEt, 60/40).

Cis epoxide **4**: R_f 0.23; 55% yield; compound shows all the characteristics described above.

Trans epoxide **5**: R_f 0.33; 45% yield; $[\alpha]^{21}_D$ +114° (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) 3530, 3420, 1240, 860 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, 3 H, J = 7 Hz, CH_3), 1.05–1.45 (m, 3 H, $H_5 + H_6$), 1.74 (m, 1 H, H_4), 2.01 (br s, 1 H, OH), 2.14 (m, 1 H, H_4), 3.38 (m, 2 H, $H_1 + H_3$), 3.91 (m, 1 H, H_2).

(2*R*,5*R*)-2-Methyl-5-isopropenyl-1-(1,3-dioxolan-2-yl)-cyclohexane (7). (+)-*trans*-dihydrocarvone (**1**; 8.93 g, 58.6 mmol), ethyleneglycol (7.3 g, 117 mmol, 2 equiv), PPTS (1.46 g, 0.1 equiv), and benzene (150 mL) were refluxed in a Dean–Stark apparatus for 1 h. After evaporation, the residue was diluted by 100 mL of ether and 100 mL of water. The organic phase was washed with a saturated solution of NaCl and dried over $MgSO_4$: quantitative yield; $[\alpha]^{21}_D$ –14° (neat, d^{20} 0.998); ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, 3 H, J = 6.5 Hz, CH_3), 1.12–1.50 (m, 3 H, $H_2 + H_3$), 1.59–1.89 (m, 4 H, $H_4 + H_6$), 1.71 (s, 3 H, vinylic CH_3), 2.19 (tt, 1 H, J_{anti} = 12.5 Hz; J_{gauche} = 3.2 Hz, H_5), 3.96 (m, 4 H, OCH_2CH_2O), 4.70 (s, 2 H, vinylic H).

(2*R*,5*R*)-2-Methyl-5-acetyl-1-(1,3-dioxolan-2-yl)cyclohexane (8). Ozone was added to a solution of the acetal **10** (11.52 g, 58.7 mmol) in methanol (300 mL) at –30 °C till the formation of a persistent blue color. Then argon was flushed into the reaction mixture till the disappearance of the blue color. Dimethyl sulfide (20 mL) was finally added and the mixture stirred at room temperature for 8 h. After evaporation of the solvent, the residue was diluted with 100 mL of ether and 100 mL of water. The aqueous layer was extracted with ether (2 × 50 mL) and the organic phase washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated; bp 110 °C (2.0 mm); yield, 80%; $[\alpha]^{21}_D$ – 17.5° (neat, d^{20} 1.08); IR (CCl_4) 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.79 (d, 3 H, J = 6.4 Hz, CH_3), 1.07–1.42 (m, 3 H, $H_2 + H_3$), 1.63 (m, 2 H, H_4), 1.83 (m, 2 H, H_6), 2.06 (s, 3 H, CH_3CO), 2.54 (tt, 1 H, J_{anti} = 12.3 Hz, J_{gauche} = 3.4 Hz, H_5), 3.87 (m, 4 H, OCH_2CH_2O).

(3*R*,6*R*)-6-Methyl-3-acetyl-1-(1,3-dioxolan-2-yl)cyclohexane (9). A mixture of ketone **9** (2 g, 10 mmol), *m*-CPBA (6.5 g, 30 mmol), $NaHCO_3$ (1 g, 12 mmol), and dichloromethane (30 mL) was stirred at room temperature for 24 h. The resulting white solid was filtered over Celite and washed with 100 mL of dichloromethane. The filtrate was washed with a sodium sulfite solution and then with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. The product was purified by chromatography (hexane/acetone, 80/20): yield, 80%; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 3 H, J = 6.3 Hz, CH_3), 1.19–1.52 (m, 3 H, $H_5 + H_6$), 1.66 (m, 2 H, H_4), 1.97 (m, 1 H, H_{2a}), 2.02 (s, 3 H, CH_3CO), 2.14 (qd, 1 H, ^2J_a = –12.2 Hz, $^3J_{2,3}$ = 4.2 Hz, $^4J_{2,6}$ = 2.1 Hz, H_2), 3.96 (m, 4 H, OCH_2CH_2O), 4.83 (m, 1 H, H_3).

(3*R*,6*R*)-6-Methyl-3-[(2-methoxyethoxy)methoxy]-1-(1,3-dioxolan-2-yl)cyclohexane (10). (1) The acetate group in compound **9** was hydrolyzed by stirring acetate **9** (7 g, 32.7 mmol) and potassium carbonate (9.0 g, 65.3 mmol) in water (100 mL) and methanol (100 mL) for 3 h at room temperature. After dilution with 200 mL of water, the reaction mixture was extracted with ether (5 × 100 mL); the organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$, and evaporated: yield, 98%; IR (CCl_4) 3630, 3440 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3 H, J = 6.5 Hz, CH_3), 1.31–2.13 (m, 7 H, CH_2), 2.36 (s, large, 1 H, OH); 3.82 (m, 1 H, C*H*OH), 3.95 (t, 2 H, J = 5.2 Hz, OCH_2CH_2O), 3.97 (t, 2 H, J = 5.2 Hz, OCH_2CH_2O).

(2) The OH group was then protected as a MEM ether by adding (2-methoxyethoxy)methyl chloride (1.44 mL, 12.6 mmol) to a suspension of the preceeding alcohol (2.68 g, 12.5 mmol) and NaH (0.36 g, 15.0 mmol) in DME (20 mL) at 0 °C. After 2 h at 0 °C, the reaction mixture was hydrolyzed with 80 mL of water and diluted with 40 mL of ether. The aqueous phase was saturated with sodium chloride and extracted with ether (3 × 40 mL). The organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$, and evaporated: quantitative yield; ^1H NMR (60 MHz, CCl_4) δ 0.8 (d, 3 H, J = 7.5 Hz, CH_3), 1.0–2.2 (m, 6 H, CH_2), 3.3 (s, 3 H, OCH_3), 3.5 (m, 5 H, $OCH_2CH_2OCH_3$ + C*H*O-MEM), 3.8 (br s, 4 H, OCH_2CH_2O), 4.6 (s, 2 H, OCH_2O).

(3*R*,6*R*)-6-Methyl-3-[(2-methoxyethoxy)methoxy]cyclohexan-1-one (11). A mixture of PPTS (3.14 g, 12.5 mmol) and acetal **10** (3.25 g, 12.5 mmol) in acetone containing 10% of water (150 mL), was refluxed for 4 h. After evaporation, the residue was diluted with 100 mL of water and 100 mL of ether. The aqueous phase was extracted with ether (2 × 50 mL). The organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$, and evaporated. The product was purified by chromatography (ether/hexane, 50/50): yield, 80%; $[\alpha]^{21}_D$ +3.4° ($CHCl_3$, *c* 2.1); IR (CCl_4) 1715 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.97 (d, 3 H, J = 6 Hz, CH_3), 1.0–3.0 (m, 7 H), 3.3 (s, 3 H, OCH_3), 3.5 (td, 4 H, $OCH_2CH_2OCH_3$), 3.8 (s, 1 H, C*H*OMEM), 4.6 (sd, 2 H, OCH_2O).

(2*S*,5*S*)-*trans*-Dihydrocarvone was prepared from (+)-carvone by the procedure already described.[12] Compounds **13** and **14** were prepared by the same reactions used for the enantiomeric series. All the physical and spectroscopic characteristics are the same as those of the enantiomers already described. However, the rotatory powers are lower because of the optical purity of the starting (+)-carvone, which was assumed to be around 80%.

De-A,B-cholestan-8-one (Grundmann's Ketone; 15). Vitamin D_3 (3 g, 7.8 mmol) in methanol (350 mL) was treated at –78 °C by ozone till a blue color persisted. Then the solution was flushed with argon till the blue color disappeared. Dimethyl sulfide (4 mL, 54.4 mmol, 7 equiv) was added and the reaction mixture stirred at room temperature for 8 h. Two-thirds of the methanol was then evaporated and 500 mL of water added. The mixture was extracted with pentane (3 × 100 mL), dried over $MgSO_4$, and evaporated. The product was purified by chromatography (hexane/ether, 95/5) and used rapidly in the next step (this molecule cannot be stored because of its epimerization): yield, 1.82 g (90%).

De-A,B-8α-ethynylcholestan-8β-ol (16). A solution of ethylmagnesium bromide (from 0.34 g of Mg, 1.24 mL of ethyl bromide, 30 mL of THF) was added at –78 °C to 150 mL of THF saturated with acetylene. Then ketone **15** (1.82 g, 6.9 mmol) was added at room temperature, with acetylene still bubbling into the solution. The reaction mixture was stirred at room temperature for 2 h and hydrolyzed with 100 mL of saturated NH_4Cl. The aqueous phase was extracted with ether (2 × 500 mL). The organic layers were washed with saturated NaCl, dried over $MgSO_4$, and evaporated. This crude product was used in the next step without further purification.

Methyl Ether of De-A,B-8α-ethynylcholestan-8β-ol (17). Alcohol **16** (6.9 mmol) and methyl iodide (0.87 mL, 14 mmol) were added to a solution of KOH (1.57 g, 28 mmol) in 14 mL of Me_2SO. The reaction mixture was stirred for 15 min at room temperature, poured in 200 mL of water, and extracted with pentane (2 × 50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography (hexane/AcOEt, 99/1): yield, 70% from ketone **15**; mp 51-52 °C; $[\alpha]^{21}_D$ +4.0° ($CHCl_3$, *c* 2.0); IR ($CHCl_3$) 3310, 2870 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9 (m, 12 H, CH_3), 1-2 (m, 20 H, CH_2 + CH), 2.38 (s, 1 H, C*H*), 3.31 (s, 3 H, CH_3O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 20.9, 23.8, 26.7, 34.4, 35.9, 39.5, 40.3, 42.6, 71.8, 74.7, 76.4, 77.0, and 77.6 (8 CH_2 + 3 C) 13.3, 18.5, 22.5, 22.8, 28.0, 35.4, 51.3, 56.8, and 57.1 (5 CH_3 + 5 CH).

Coupling Reaction of Alkyne 17 with Ketones 6, 11, 13, and 14. General Procedure. *n*-BuLi (1.25 mL; 1.32 M in hexane) was added to 500 mg (1.6 mmol) of product **17** in 5 mL of anhydrous THF. After 5 min at room temperature, 1.6 mmol of ketone in 5 mL of THF was added. After 1 h at room temperature, the reaction mixture was hydrolyzed with 10 mL of saturated NH_4Cl and extracted with ether (2 × 20 mL). The organic phase was washed with saturated NaCl, dried over $MgSO_4$, and evaporated. The crude product (80% yield) was used in the next step without purification.

Hydroxy Ethers 18 and 19. The TBDMS ether of **18** or **19** (0.61 mmol) in acetonitrile (10 mL) was treated by 1 mL of 40% FH for 30 min. The solution was then washed with saturated $NaHCO_3$ and extracted with ether (3 × 10 mL). The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated: quantitative yield; ^1H NMR (60 MHz, CCl_4) δ 0.9-2.1 (m), 3.2 (s, 3 H, OCH_3), 3.6 (m, 1 H, C*H*OH).

Hydroxy Ethers 20 and 21. $ZnBr_2$ (1.1 g, 5 mmol) was added to a solution of 1.0 mmol of the MEM ether of **20** or **21** in 20 mL of dichloromethane. The dark reaction mixture was stirred for 8 h and then hydrolyzed with saturated $NaHCO_3$ (100 mL). The solution became yellow, and a white precipitate formed. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the organic layer dried over $MgSO_4$ and evaporated: quantitative yield; ^1H NMR (60 MHz, CCl_4) δ 1-2.2 (m), 3.2 (s, 3 H, OCH_3), 3:6 (m, 1 H, C*H*OH).

Reduction of Propargylic Alcohols 18-21. General Procedure. A titrated $LiAlH_4$ (2.4 mL, 1.8 mmol, 3 equiv) solution (0.77 M) in ether was added at 0 °C to a solution of 0.61 mmol of propargylic alcohol in 20 mL of ether. After 1 h at 0 °C, the reaction mixture was hydrolyzed with 2 mL of EtOAc and 20 mL of 5% HCl and extracted with ether (3 × 20 mL). The organic phase was washed with saturated NaCl (100 mL), dried over $MgSO_4$, and evaporated: quantitative yield; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9-2.1 (m), 3.3 (s, 3 H, OCH_3), 3.6 (m, 1 H, C*H*OH), 4.21 (2 AB systems, 2 H, J_{AB} = 12 Hz, Δν = 28.6 Hz, vinylic H).

Low-Valent Titanium Reductive Elimination. General Procedure. A titrated solution of $LiAlH_4$ (8.3 mL, 6.4 mmol) in ether (0.77 M) was added to 1.97 g (12.8 mmol) of $TiCl_3$ in 10 mL of THF under argon. A black suspension formed. The reaction mixture was stirred at room temperature for 30 min. Then 1.6 mmol of allylic hydroxy ether in 5 mL of THF was added and the reaction mixture refluxed for 1 h, hydrolyzed with 50 mL of 2 N HCl, and extracted with chloroform (3 × 20 mL). The organic layer was washed with water several times to remove the brown color, dried over $MgSO_4$, and evaporated.

The diastereoisomer ratio was determined by NMR on the crude product from the signals of the proton α to the hydroxyl group.

The products (DHT_3 and $DHTV_3$) were then separated by preparative TLC (hexane/ether, 90/10). Yields of purified products after TLC separation are between 60% and 75%.

DHV_3 (5*Z*,7*E*,3*S*,10*R*)-**26**: ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.50 (m, 1 H, C*H*OH), 5.9 (m, 2 H, vinylic H).

DHT_3 (5*E*,7*E*,3*S*,10*R*)-**27**: $[\alpha]^{21}_D$ +0.5, $[\alpha]^{21}_{365}$ +2.4° (*c* 1.2, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ -2.5 (m), 3.89 (m, 1 H; C*H*OH), 6.0 (m, 2 H, vinylic H).

DHV_3 (5*Z*,7*E*,3*R*,10*R*)-**30**: ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.85 (m, 1 H, C*H*OH), 5.8 (m, 2 H, vinylic H).

DHT_3 (5*Z*,7*E*,3*R*,10*R*)-**31**: $[\alpha]^{21}_D$ +6.3°, $[\alpha]^{21}_{365}$ +19.4° (*c* 2.2, acetone); mp 92 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.65 (m, 1 H, C*H*OH), 6.61 (AB, J_{AB} = 11 Hz, Δν = 33 Hz, vinylic H).

DHV_3 (5*Z*,7*E*,3*R*,10*S*)-**28**: ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.66 (m, 1 H, C*H*OH), 6.16 (AB, 2 H, J_{AB} = 10 Hz, Δν = 7.5 Hz, vinylic H).

DHT_3 (5*E*,7*E*,3*R*,10*S*)-**29**: $[\alpha]^{21}_D$ +1.2°, $[\alpha]^{21}_{365}$ +4.8° (*c* 1.1, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.73 (m, 1 H, C*H*OH), 6.24 (AB, 2 H, J_{AB} = 11.5 Hz, Δν = 7 Hz).

DHV_3 (5*Z*,7*E*,3*S*,10*S*)-**32**: $[\alpha]^{21}_D$ +36.9; $[\alpha]^{21}_{365}$ +152° (*c* 0.4, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 4.00 (m, 1 H, C*H*OH), 5.9 (m, 2 H, vinylic H).

DHT_3 (5*E*,7*E*,3*S*,10*S*)-**33**: $[\alpha]^{21}_D$ +5.2°, $[\alpha]^{21}_{365}$ +14.8° (*c* 1.1, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 1-2.5 (m), 3.65 (td, 1 H, C*H*OH), 6.03 (AB, 2 H, J_{AB} = 10 Hz, Δν = 30 Hz, vinylic H).

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Synthetic Approaches to Nogalamycin-Related Anthracyclines. An Approach to a Western Synthon[1]

Thomas H. Smith* and Helen Y. Wu

Bio-Organic Chemistry Laboratory, SRI International, Menlo Park, California 94025

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A synthetic approach to the "western" portion of nogalamycin is described. The synthesis of the 3-aminoglucose synthon **21** and its utilization in the stereocontrolled glycosidation of the D-ring synthon **9** is reported. The resulting glycoside **24** was converted to the 5′,6′-olefin **36**. The formation of the 2,5′-C-C bond was attempted via an intramolecular cation induced olefinic cyclization approach. While model intermolecular studies were successful, the intramolecular reaction failed presumably due to insufficient nucleophilicity of the aromatic moiety.

The clinical utility of the anthracycline antibiotics daunorubicin (**1**) and doxorubicin (**2**)[2] in the treatment of cancer has prompted the development of so-called second generation anthracyclines which include both natural products and their semisynthetic analogues. Therapeutic

* Address correspondence to this author at: American Bionetics, Inc., 21377 Cabot Blvd., Hayward, CA 94545.

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