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**Total Synthesis of Dihydrovitamin DHV₃ and Dihydrotachysterol DHT₃.
Application of the Low-Valent Titanium-Induced Reductive Elimination**

Guy Solladié* and Jean Hutt

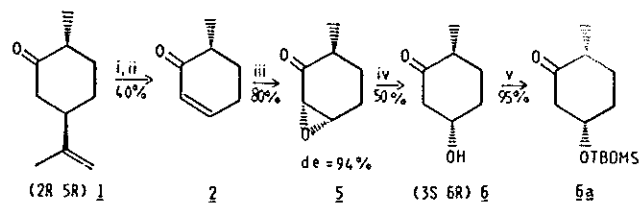
Ecole Européenne des Hautes Etudes des Industries Chimiques (U.A. 466), 67008 Strasbourg, France

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Optically active ring A synthons 6, 11, 13, and 14, precursors of DHV₃ and DHT₃, were synthesized from (-)- and (+)-carvone. Application of the low-valent titanium-induced reductive elimination gave a new synthetic approach to vitamin D₃ analogues, as shown by an efficient preparation of DHT₃.

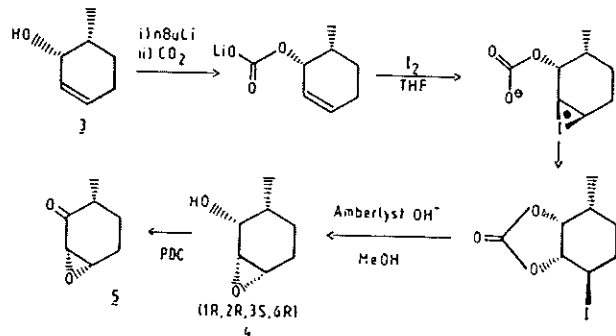
Synthetic efforts directed toward vitamin D₃ and its metabolites have been renewed since the discovery that specific hydroxylated derivatives are involved in a complex

control of calcification processes. In contrast to the traditional passive characterization of vitamin D₃ as a vitamin, it is known¹ that vitamin D₃ acts like other classical steroid

Scheme I^a

^a (i) O₃, MeOH, -78 °C; (ii) FeSO₄, Cu(OAc)₂; (iii) H₂O₂, K₂CO₃, MeOH, 0 °C; (iv) Al/Hg, NaHCO₃, EtOH, 90 °C; (v) *t*-BuMe₂SiCl, imidazole, DMF.

Scheme II



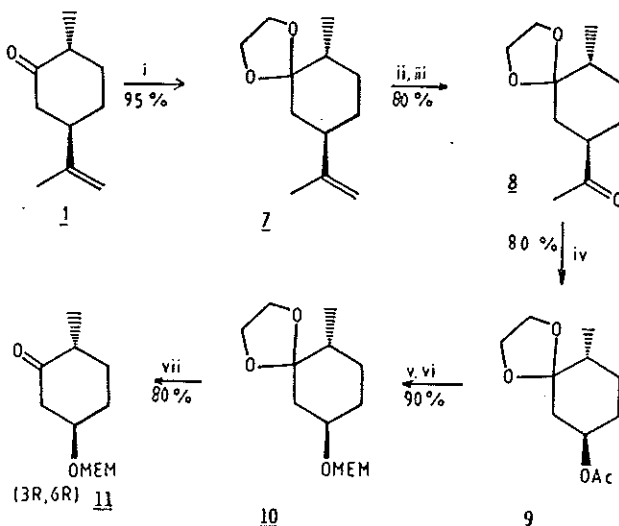
hormones: that is, its active form is synthesized in the liver and kidney in response to various stimuli and is transported to its site of action by a specific carrier protein.

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 dihydratachysterol and dihydrovitamin¹⁰ and only recently Okamura¹¹ 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 DHV₃ and DHT₃ stereoisomers using the low-valent titanium-induced reductive elimination to create the diene moiety.

We recently reported¹² 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 procedure¹³ from *trans*-dihydrocarvone

Scheme III^a

^a (i) HOCH₂CH₂OH, PPTS, PhH; (ii) O₃, MeOH, -30 °C; (iii) Me₂S; (iv) *m*-CPBA, NaHCO₃, CH₂Cl₂; (v) K₂CO₃, MeOH-H₂O; (vi) NaH, MeOCH₂CH₂OCH₂Cl, DME, 0 °C; (vii) Me₂CO, H₂O, PPTS.

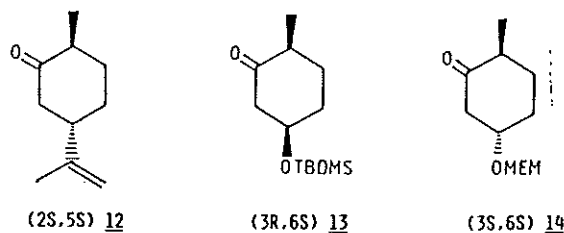
with a lower yield but a significantly higher rotatory power. Enone epoxidation with hydrogen peroxide afforded epoxide 5 in 94% de. The same diastereoselectivity but a lower yield (50%) was obtained with NaOCl in dioxane. Finally reductive opening of the epoxide with aluminium amalgam¹⁴ gave the hydroxy ketone (3*S*,6*R*)-6.

The configuration of the epoxide 5 was confirmed by independent synthesis using Cardillo's method¹⁵ (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 described¹² from (-)-carvone.



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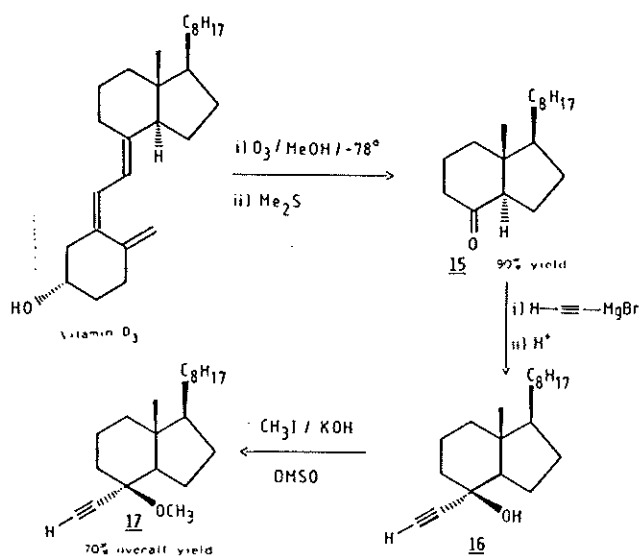
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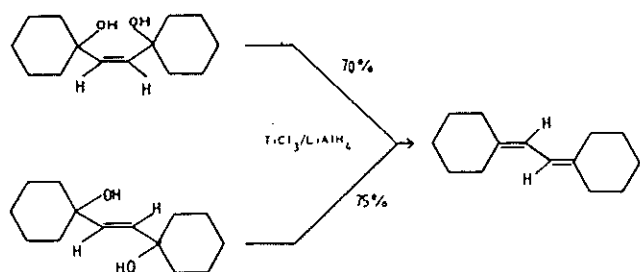
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Scheme IV



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 synthesize dihydrovitamin DHV₃ and dihydrotachysterol DHT₃.

The C/D moiety 17 was obtained by chemical degradation of natural vitamin D₃.

Ozonolysis¹⁶ of vitamin D₃ 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 NMR¹⁷.

Low-valent titanium was first used by Van Tamelen and his co-workers Schwartz¹⁸ and Hanzlik and Sharpless¹⁹ to effect reductive coupling of benzylic¹⁸ and allylic²⁰ alcohols. Subsequently low-valent titanium has been employed in

the pinacolic coupling of carbonyls to olefins²⁰ and in the reductive coupling of carbonyls to olefins.²⁰ Reductive elimination of 1,2-glycols to olefins²¹ as well as the cyclization of 1,3-glycols to cyclopropanes²² has also been reported. More recently Walborsky²³ 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 peculiarly 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 LiAlH₄ (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 TiCl₃ or TiCl₄ with metals^{20–22} such as magnesium, potassium, sodium, lithium, zinc-copper couple, or metal hydrides, particularly lithium aluminium hydride. A mixture of TiCl₃ and LiAlH₄ (4:1) is known as the McMurry reagent. However, Geise²⁴ has found that the TiCl₃/LiAlH₄ 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 LiAlH₄ in THF in the TiCl₃/LiAlH₄ 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 DHV₃ (5*Z*,7*E*) and DHT₃ (5*E*,7*E*); the 7*Z* geometry was never observed, probably because of severe interactions between hydrogens on C₆ and C₁₅. 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 DHV₃ and DHT₃ was stable in presence of low-valent titanium in refluxing THF.

The identification of DHV₃ and DHT₃ isomers was done by NMR according to the work of Okamura.^{25,26}

In DHV₃ 26 and 32 the methyl group on C₁₀ has an axial orientation (because of strong steric interaction between H₇ and the 10-CH₃ equatorial). Therefore, H₃ must be axial in 26, δ(H₃) 3.50 (lit.²⁵ δ 3.57), and equatorial in 32, δ(H₃) 4.00 (lit.²⁵ δ 4.02). Compounds 28 and 30 will have also the same conformation of the A-ring with the 10-CH₃ group axial. Therefore H₃ must be axial in 28, δ(H₃) 3.66, and equatorial in 30, δ(H₃) 3.85.

For DHT₃ the dienic moiety has no influence on the main conformation of the A-ring. Therefore in DHT₃ 27

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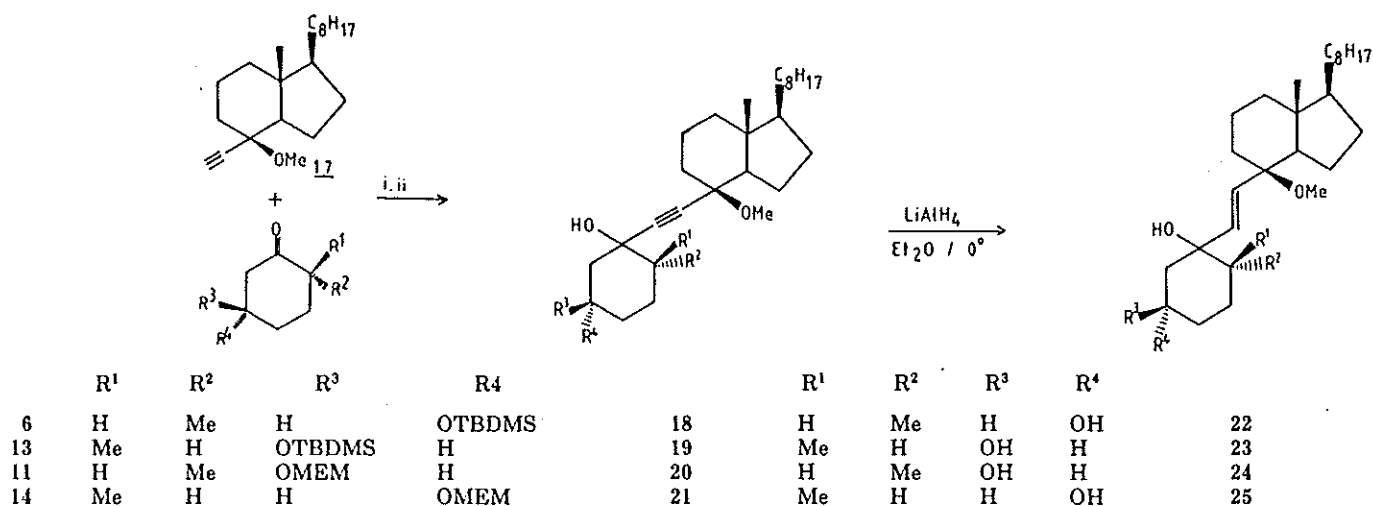
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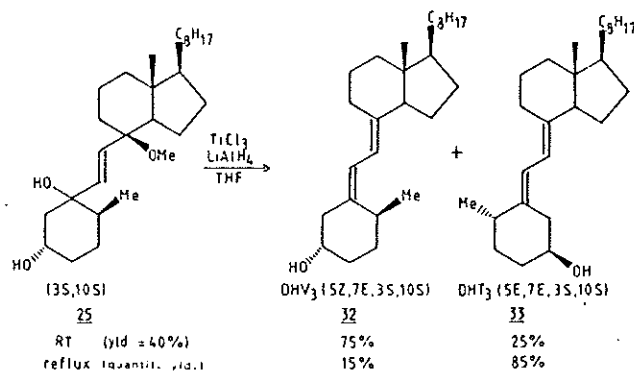
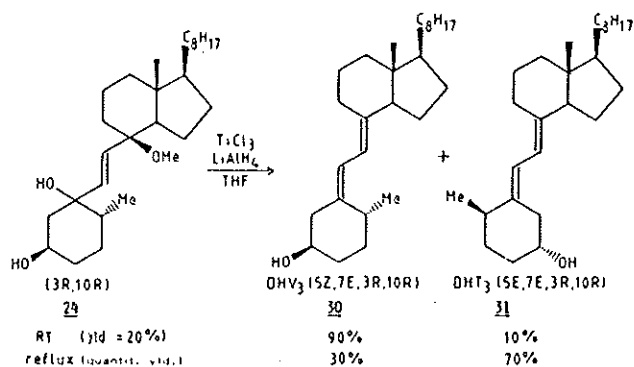
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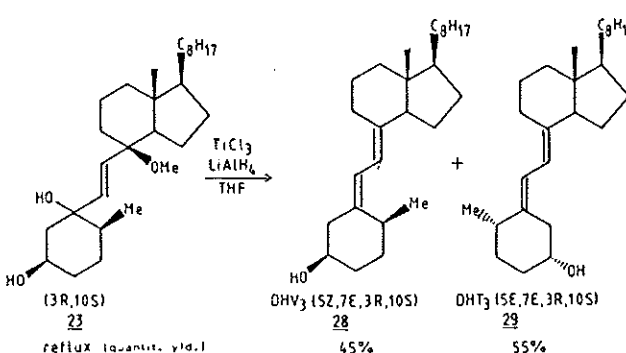
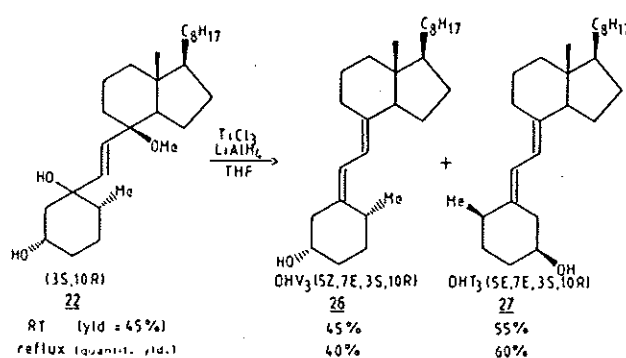
Scheme VI^a

^a (i) *n*-BuLi, THF; (ii) ZnBr₂, CH₂Cl₂ for 11 and 14, HF, CH₃CN for 6 and 13.

Scheme VII



Scheme VIII

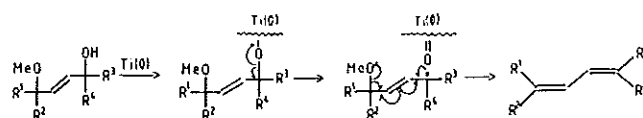


and 29, the *cis* configuration of the 2-substituents of the A-ring leads to the presence of two main conformations with about the same population, giving an average chemical shift for H₃: in 27, δ (H₃) 3.89 (lit.²⁵ δ 3.82), and in 29, δ (H₃) 3.73. In DHT₃ 31 and 33, the *trans* configuration of OH and CH₃ leads to a main conformation having the two substituents in equatorial orientation: in 33, δ (H₃) 3.65 (lit.²⁵ δ 3.61), and in 31, δ (H₃) 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 Walborsky²³ 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 sec-

Scheme IX

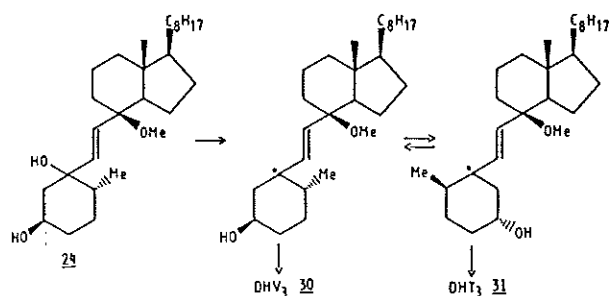


ondary diols, an (*E,E*)-diene is always obtained, suggesting a thermodynamic control of the reaction.

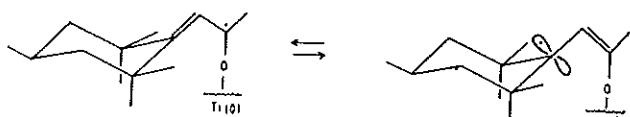
The application of this reductive elimination to the synthesis of DHV₃ and DHT₃ is rather complicated on the stereochemical point of view, the starting allylic diols being tertiary.

Let us consider first the reaction of compound 24. At room temperature, we observed mainly the formation of DHV₃ 30 (90%) in 20% yield. In refluxing THF, the reaction was quantitative and the main product was DHT₃ (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 DHT₃ in which the two substituents of the A-ring are equatorial, the driving force of this isomerization being the steric interactions between 10-CH₃ and H₇ 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 C₁ 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 approximately the same amount of DHV₃ and DHT₃, the reaction temperature influencing only the reaction yield. This result is consistent with the relative stability of DHV₃ 26 (or 28) and of DHT₃ 27 (or 29), the main conformations of these molecules having the 10-CH₃ axial and 3-OH equatorial.

The new approach to vitamin D₃ analogues has certainly some valuable contribution to the synthesis of such molecules.

Dihydrotachysterol DHT₃ 33 and DHT₂ (which differs only by the presence of a Δ²² double bond) have important biological properties,²⁵ DHT₃ being more active than DHT₂^{28,29} (DHT₂ was, however, marketed as early as 1934 under the trade name A.T.10 by Merck as antitetic agent). However, the synthesis reported in the literature started from vitamin D₃ with isomerization to 5*E* vitamin D₃ and reduction of the exocyclic double bond, giving a complex mixture of products.

DHT₃ 33 (or DHT₂) can be readily prepared by our methodology, the low-valent titanium reductive elimination giving in a quantitative yield a mixture containing 85%

of DHT₃ and 15% of the corresponding DHV₃ which is easily separated.

Experimental Section

(*R*)-6-Methylcyclohex-2-en-1-one (2). To a solution of (+)-*trans*-dihydrocarvone¹² (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, FeSO₄·7H₂O (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; [α]_D²⁵ +91° (neat), [α]_D²⁵ +70° (CHCl₃, c 3.0); ¹H NMR (200 MHz, CDCl₃) δ 1.15 (d, 3 H, *J* = 6.5 Hz, CH₃), 1.62–1.84 (m, 1 H, *J*_{gem} = -12.5 Hz, H₅), 2.00–2.15 (m, 1 H, H₅), 2.30–2.50 (m, 3 H, H₄ + H₆), 6.00 (td, 1 H, *J*_{2,3} = 10 Hz, *J*_{2,4} = 2 Hz, H₂), 6.94 (m, 1 H, *J*_{2,3} = 10 Hz, *J*_{3,4} = 4 Hz, *J*_{3,5} = 1 Hz, H₃).

(2*S*,3*S*,6*R*)-6-Methyl-2,3-epoxycyclohexan-1-one (5). (A) Saturated K₂CO₃ (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 Na₂SO₄. After evaporation of the solvent, the product was purified by chromatography (hexane/AcOEt, 80/20): yield 80%; [α]_D²⁵ +43° (CHCl₃, c 1.2); IR (CHCl₃) 1705, 1240, 875 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.99 (d, 3 H, *J* = 7 Hz, CH₃), 1.47–1.68 (m, 2 H, H₅), 1.85–2.31 (m, 3 H, H₄ + H₆), 3.26 (d, 1 H, *J*_{2,3} 4.5 Hz, H₂), 3.57 (td, 1 H, H₃). Anal. Calcd C₇H₁₀O₂: 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%; [α]_D²⁵ -3.2° (CHCl₃, c 1.1); IR (CHCl₃) 3610, 3440, 1705 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.03 (d, 3 H, *J* = 6.6 Hz, CH₃), 1.28 (m, 2 H, H₅), 1.56 (s, large, 1 H, OH), 1.90–2.34 (m, 3 H, H₄ + H₆), 2.59 (AB part of ABX, 2 H, *J*_{AB} = 13.0 Hz, *J*_{AX} = 5.0 Hz, *J*_{BX} = 2 Hz, *J*_{A6} = 2.2 Hz, Δν 73.4 Hz, H_A + H_B), 3.92 (sep, 1 H, H_X).

(3*S*,6*R*)-6-Methyl-3-[(*tert*-butyldimethylsilyloxy)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 NH₄Cl 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 MgSO₄, and evaporated. The product was purified by chromatography (hexane/AcOEt, 95/5): yield 95%; [α]_D²⁵ +7.9° (CHCl₃, c 2.2); IR (CHCl₃) 1705 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.07 (s, 3 H, CH₃Si), 0.08 (s, 3 H, CH₃Si), 0.89 (s, 9 H, *t*-BuSi), 1.02 (d, 3 H, *J* = 7 Hz, CH₃), 1.09–1.34 (m, 2 H, H₅), 1.71 (m, 1 H, H₂), 2.02 (m, 2 H, H₄), 2.50 (AB part of ABX, 2 H, *J*_{AB} = 13, 1 Hz, *J*_{AX} = 4.6 Hz, *J*_{A6} = 1.8 Hz, *J*_{BX} = 1.0 Hz, Δν = 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

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added, and the solvents were evaporated. The residue was treated with ether (50 mL) and 5% H₂SO₄ (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 MgSO₄, and evaporated. The product was finally purified by chromatography (hexane/AcOEt, 95/5): yield, 70%; [α]_D²⁵ +41° (neat, *d*₂₀²⁵ 0.956); IR (CCl₄) 3610, 3400, 1645 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.05 (d, 3 H, *J* = 6.0 Hz, CH₃), 1.22–1.81 (m, 3 H, H₅ + H₆), 2.03 (m, 2 H, H₄), 2.2 (m, 1 H, OH), 3.77 (m, 1 H, H₁), 5.50–5.9 (m, 2 H, H₂ + H₃).

Reduction with BBN or *n*-BuBH₃Li, 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); [α]_D²⁵ -36° (c 2.6, CHCl₃); IR (CHCl₃) 3560, 3420, 1240, 855, 825 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.99 (d, 3 H, *J* = 7 Hz, CH₃), 1.37–1.60 (m, 2 H, H₅), 1.63 (s, 1 H, OH), 1.69–1.91 (m, 3 H, H₆ + H₄), 3.27 (m, 1 H, H₃), 3.34 (m, 1 H, H₁), 3.50 (td, 1 H, *J*_{2,3} = *J*_{1,2} = 8 Hz, H₂). Anal. Calcd for C₇H₁₂O₂: 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 MgSO₄, and evaporated. The two epoxides diastereoisomers 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; [α]_D²⁵ +114° (c 2.4, CHCl₃); IR (CHCl₃) 3530, 3420, 1240, 860 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.95 (d, 3 H, *J* = 7 Hz, CH₃), 1.05–1.45 (m, 3 H, H₅ + H₆), 1.74 (m, 1 H, H₄), 2.01 (br s, 1 H, OH), 2.14 (m, 1 H, H₁), 3.38 (m, 2 H, H₁ + H₃), 3.91 (m, 1 H, H₂).

(2*R*,5*R*)-2-Methyl-5-isopropenyl-1-(1,3-dioxolan-2-yl)-cyclohexane (7). (+)-*trans*-dihydrocarvone (7): 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 MgSO₄; quantitative yield; [α]_D²⁵ -14° (neat, *d*₂₀²⁵ 0.998); ¹H NMR (200 MHz, CDCl₃) δ 0.95 (d, 3 H, *J* = 6.5 Hz, CH₃), 1.12–1.50 (m, 3 H, H₂ + H₃), 1.59–1.89 (m, 4 H, H₄ + H₆), 1.71 (s, 3 H, vinylic CH₃), 2.19 (tt, 1 H, *J*_{anti} = 12.5 Hz; *J*_{gauche} = 3.2 Hz, H₅), 3.96 (m, 4 H, OCH₂CH₂O), 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 MgSO₄, and evaporated; bp 110 °C (2.0 mm); yield, 80%; [α]_D²⁵ -17.5° (neat, *d*₂₀²⁵ 1.08); IR (CCl₄) 1710 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.79 (d, 3 H, *J* = 6.4 Hz, CH₃), 1.07–1.42 (m, 3 H, H₂ + H₃), 1.63 (m, 2 H, H₄), 1.83 (m, 2 H, H₆), 2.06 (s, 3 H, CH₃CO), 2.54 (tt, 1 H, *J*_{anti} = 12.3 Hz; *J*_{gauche} = 3.4 Hz, H₅), 3.87 (m, 4 H, OCH₂CH₂O).

(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), NaHCO₃ (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 NaHCO₃ solution, dried over MgSO₄, and evaporated. The product was purified by chromatography (hexane/acetone, 80/20): yield, 80%; IR (CHCl₃) 1720 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.86 (d, 3 H, *J* = 6.3 Hz, CH₃), 1.19–1.52 (m, 3 H, H₅ + H₆), 1.66 (m, 2 H, H₄), 1.97 (m, 1 H, H_{2a}), 2.02 (s, 3 H, CH₃CO), 2.14 (qd, 1 H, ²*J*_a = -12.2 Hz, ³*J*_{2,3} = 4.2 Hz, ⁴*J*_{2,6} = 2.1 Hz, H₂), 3.96 (m, 4 H, OCH₂CH₂O), 4.83 (m, 1 H, H₃).

(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 MgSO₄, and evaporated: yield, 98%; IR (CCl₄) 3630, 3440 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.89 (d, 3 H, *J* = 6.5 Hz, CH₃), 1.31–2.13 (m, 7 H, H₂), 2.36 (s, large, 1 H, OH); 3.82 (m, 1 H, CHOH), 3.95 (t, 2 H, *J* = 5.2 Hz, OCH₂CH₂O), 3.97 (t, 2 H, *J* = 5.2 Hz, OCH₂CH₂O).

(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 preceding 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 MgSO₄, and evaporated: quantitative yield; ¹H NMR (60 MHz, CCl₄) δ 0.8 (d, 3 H, *J* = 7.5 Hz, CH₃), 1.0–2.2 (m, 6 H, CH₂), 3.3 (s, 3 H, OCH₃), 3.5 (m, 5 H, OCH₂CH₂OCH₃ + CHO-MEM), 3.8 (br s, 4 H, OCH₂CH₂O), 4.6 (s, 2 H, OCH₂O).

(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 MgSO₄, and evaporated. The product was purified by chromatography (ether/hexane, 50/50): yield, 80%; [α]_D²⁵ +3.4° (CHCl₃, c 2.1); IR (CCl₄) 1715 cm⁻¹; ¹H NMR (60 MHz, CCl₄) δ 0.97 (d, 3 H, *J* = 6 Hz, CH₃), 1.0–3.0 (m, 7 H), 3.3 (s, 3 H, OCH₃), 3.5 (td, 4 H, OCH₂CH₂OCH₃), 3.8 (s, 1 H, CHOMEM), 4.6 (sd, 2 H, OCH₂O).

(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 D₃ (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 MgSO₄, 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-8 α -ethynylcholestan-8 β -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 NH₄Cl. The aqueous phase was extracted with ether (2 × 500 mL). The organic layers were washed with saturated NaCl, dried over MgSO₄, and evaporated. This crude product was used in the next step without further purification.

Methyl Ether of De-A,B-8 α -ethynylcholestan-8 β -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 Me₂SO. The reaction mixture was stirred for 15 min at room temperature, poured in 200 mL of water, and extracted with pentane (2 \times 50 mL). The organic phase was dried over MgSO₄ and evaporated. The crude product was purified by chromatography (hexane/AcOEt, 99/1): yield, 70% from ketone 15; mp 51–52 °C; [α]_D²¹ +4.0° (CHCl₃, c 2.0); IR (CHCl₃) 3310, 2870 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.9 (m, 12 H, CH₃), 1–2 (m, 20 H, CH₂ + CH), 2.38 (s, 1 H, CH), 3.31 (s, 3 H, CH₃O); ¹³C NMR (50 MHz, CDCl₃) 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 CH₂ + 3 C) 13.3, 18.5, 22.5, 22.8, 28.0, 35.4, 51.3, 56.8, and 57.1 (5 CH₃ + 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 NH₄Cl and extracted with ether (2 \times 20 mL). The organic phase was washed with saturated NaCl, dried over MgSO₄, 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 NaHCO₃ and extracted with ether (3 \times 10 mL). The organic layer was washed with saturated NaCl, dried over MgSO₄, and evaporated: quantitative yield; ¹H NMR (60 MHz, CCl₄) δ 0.9–2.1 (m), 3.2 (s, 3 H, OCH₃), 3.6 (m, 1 H, CHOH).

Hydroxy Ethers 20 and 21. ZnBr₂ (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 NaHCO₃ (100 mL). The solution became yellow, and a white precipitate formed. The aqueous phase was extracted with CH₂Cl₂ (2 \times 20 mL) and the organic layer dried over MgSO₄ and evaporated: quantitative yield; ¹H NMR (60 MHz, CCl₄) δ 1–2.2 (m), 3.2 (s, 3 H, OCH₃), 3.6 (m, 1 H, CHOH).

Reduction of Propargylic Alcohols 18–21. General Procedure. A titrated LiAlH₄ (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 \times 20 mL). The organic phase was washed with saturated NaCl (100 mL), dried over MgSO₄, and evaporated: quantitative yield; ¹H NMR (200 MHz,

CDCl₃) δ 0.9–2.1 (m), 3.3 (s, 3 H, OCH₃), 3.6 (m, 1 H, CHOH), 4.21 (2 AB systems, 2 H, *J*_{AB} = 12 Hz, $\Delta\nu$ = 28.6 Hz, vinylic H).

Low-Valent Titanium Reductive Elimination. General Procedure. A titrated solution of LiAlH₄ (8.3 mL, 6.4 mmol) in ether (0.77 M) was added to 1.97 g (12.8 mmol) of TiCl₃ 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 \times 20 mL). The organic layer was washed with water several times to remove the brown color, dried over MgSO₄, 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 (DHT₃ and DHTV₃) were then separated by preparative TLC (hexane/ether, 90/10). Yields of purified products after TLC separation are between 60% and 75%.

DHV₃ (5Z,7E,3S,10R)-26: ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.50 (m, 1 H, CHOH), 5.9 (m, 2 H, vinylic H).

DHT₃ (5E,7E,3S,10R)-27: [α]_D²¹ +0.5, [α]₃₆₅²¹ +2.4° (c 1.2, acetone); ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.89 (m, 1 H; CHOH), 6.0 (m, 2 H, vinylic H).

DHV₃ (5Z,7E,3R,10R)-30: ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.85 (m, 1 H, CHOH), 5.8 (m, 2 H, vinylic H).

DHT₃ (5Z,7E,3R,10R)-31: [α]_D²¹ +6.3°, [α]₃₆₅²¹ +19.4° (c 2.2, acetone); mp 92 °C; ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.65 (m, 1 H, CHOH), 6.61 (AB, *J*_{AB} = 11 Hz, $\Delta\nu$ = 33 Hz, vinylic H).

DHV₃ (5Z,7E,3R,10S)-28: ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.66 (m, 1 H, CHOH), 6.16 (AB, 2 H, *J*_{AB} = 10 Hz, $\Delta\nu$ = 7.5 Hz, vinylic H).

DHT₃ (5E,7E,3R,10S)-29: [α]_D²¹ +1.2°, [α]₃₆₅²¹ +4.8° (c 1.1, acetone); mp 92 °C; ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.73 (m, 1 H, CHOH), 6.24 (AB, 2 H, *J*_{AB} = 11.5 Hz, $\Delta\nu$ = 7 Hz).

DHV₃ (5Z,7E,3S,10S)-32: [α]_D²¹ +36.9; [α]₃₆₅²¹ +152° (c 0.4, acetone); ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 4.00 (m, 1 H, CHOH), 5.9 (m, 2 H, vinylic H).

DHT₃ (5E,7E,3S,10S)-33: [α]_D²¹ +5.2°, [α]₃₆₅²¹ +14.8° (c 1.1, acetone); ¹H NMR (200 MHz, CDCl₃) δ 1–2.5 (m), 3.65 (td, 1 H, CHOH), 6.03 (AB, 2 H, *J*_{AB} = 10 Hz, $\Delta\nu$ = 30 Hz, vinylic H).

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