An enantiospecific strategy to all four diastereomers of A-ring enyne synthon of 1α,25-dihydroxyvitamin D₃

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Enantiospecific syntheses of derivatives all the four diastereomers of A-ring enyne synthon of 1α,25-dihydroxyvitamin D₃ (5-ethynyl-4-methylcyclohex-4-en-1,3-diol) have been described starting from the abundantly available monoterpene (R)-carvone, exploiting the isopropenyl group of carvone as an equivalent of an hydroxy group. A combination of Criegee rearrangement and Mitsunobu reactions has been strategically employed.

Keywords: Vitamin D₃, calcitriol, Criegee rearrangement, A-ring enyne synthon, carvone
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Like a chameleon, vitamin D has changed its colours many times over the past 70 years. To the nutritionist who discovered and named it, vitamin D appeared as an essential nutritional factor carrying out some fundamental role in bone. Biochemists showed it to be a sterol derived from 7-dehydrocholesterol 1 in the skin and therefore not a vitamin. To the physiologists working with the molecule in the early seventies, vitamin D revealed itself as a prohormone giving rise to an active principle 1α,25-dihydroxyvitamin D₃ 2, and as such playing a major role in calcium homeostasis. The elegant work of Haussler and Pike has showed that 1α,25-dihydroxyvitamin D₃ 2 to possess a specific nuclear receptor in target cells and thus to be a true steroid hormone. Through all of these different visions stretching over 80 years of research, the function of vitamin D has not deviated from that of a 'calcemic factor' responsible for maintaining a healthy skeleton. Its actions at the intestine to stimulate calcium and inorganic phosphate absorption, and at the bone, in juxtaposition with parathyroid hormone to stimulate bone resorption, are well established. Most recently vitamin D, through its active form 1α,25-dihydroxyvitamin D₃ 2, may have exhibited its latest 'colour' as a potent differentiating agent involved in the recruitment and maturation of bone marrow derived cells into osteoclasts.

In recent years, research activity in the synthesis of vitamin D₃ 3 and its analogues has grown exponentially owing to the discovery that 1α,25-dihydroxyvitamin D₃ (calcitriol) 2, the hormonally active metabolite of vitamin D₃ and its analogues have much broader spectrum of activity than originally thought, in addition to the classical role of regulating calcium and phosphorous metabolism. Significant numbers of vitamin D analogues are being used as drugs and several of the analogues are at various stages of clinical trials, as drugs, for the treatment of various human disorders ranging from osteoporosis, psoriasis, leukemia, Alzheimer's disease, AIDS and various cancers. Owing to these biological activities, the synthetic activity in the research of vitamin D₃ and its analogues continues to flourish and several research groups have developed synthesis of vitamin D₃ and its analogues¹.

The synthetic approaches to vitamin D₃ 3 and its analogues can be broadly classified into two types, viz. (i) Semisynthesis: The classical approach is patterned after the biosynthetic route leading to vitamin D₃ 3 and also offer the industrial synthesis of the latter; and (ii) Convergent synthesis: An attractive synthetic approach, originally developed by Lythgoe², is based on the coupling of an appropriate CD-ring fragment with a suitable A-ring fragment. In his pioneering work on vitamin D₃ synthesis, Lythgoe developed three A-ring synthons viz. the phosphine oxide 4, the cyclohexenaldehyde 5 and the enyne 6. Subsequently, many research groups have reported synthesis of A-ring synthons of vitamin D₃ analogues employing a variety of novel and innovative strategies³.
The two approaches, which have gained maximum attention, are: (i) The phosphine oxide coupling approach; and (ii) The enyne coupling approach. In the first approach, the phosphine oxide and an appropriate derivative of Grundmann's ketone, such as (a CD-ring fragment) are directly coupled to produce analogues of vitamin D3 (Eqn. 1). In the second approach, an A-ring enyne synthon, e.g., and a suitable derivative of Grundmann's ketone are coupled to generate dienynes of the type, which are then transformed into the vitamin D3 analogues (Eqn. 2).

The success of the enyne approach to efficiently assemble vitamin D skeleton spurred interest in the synthesis of A-ring enyne synthons. As a result, several research groups have reported synthesis of A-ring enynes and analogues. In our laboratory, utilisation of monoterpenes, in particular (R)-carvone, for the synthesis of various natural products and their part structures is an area of active pursuit. In continuation, synthesis of both enantiomers of A-ring enyne synthon viz. 1R,3S-12 and 1S,3R-13 of vitamin D3, starting from (R)-carvone 11 has been explored. Several research groups have employed (S)-carvone as the chiral starting material for the synthesis of A-ring enyne derivatives of vitamin D3 (ref. 1). In contrast, we embarked on the synthesis of both enantiomeric forms of A-ring enyne synthons of 1α,25-dihydroxyvitamin D3 and its analogues starting from abundantly available (R)-carvone 11. It is of interest to us to synthesise both enantiomers of natural products starting from single enantiomer of carvone.

To begin with, synthesis of the 1R,3S-enyne 12 was addressed. The retrosynthetic analysis is depicted in Scheme I. Since the isopropenyl group could be considered as equivalent to hydroxy group at the C-3 position in the A-ring of vitamin D3, β-ethynylcarvone was contemplated as the key intermediate, and a 1,3-enone transposition methodology was conceived for converting (R)-carvone into β-ethynylcarvone.

Thus, sonochemical irradiation of a suspension of lithium acetylide-ethylenediamine complex and (R)-carvone in THF for one and half-hours furnished the 1,2-addition product, tertiary alcohol, which on oxidation with a mixture of pyridinium chlorochromate (PCC) and silica gel in methylene chloride at room temperature for ten hours furnished β-ethynylcarvone in 70% yield (two steps). The well established stereo- and regioselective reduction of 5-substituted cyclohexenones was exploited for the stereoselective creation of the syn alcohol. Thus, reduction of β-ethynylcarvone with lithium aluminium hydride (LAH) in ether at -70°C quantitatively furnished the syn analogue via degradation of the isopropenyl group. The hydroxy group in ethynylcarvone was protected as its benzoate, m.p. 74°C, by reacting with benzooyl chloride, pyridine and a catalytic amount of DMAP in
methylene chloride at room temperature for ten hours in almost quantitative yield. It was anticipated that the isopropenyl group could be converted into an acetoxy group employing a one pot, controlled ozonation followed by Criegee rearrangement sequence. Accordingly, controlled ozonation of the benzoate in 1:5 methanol-methylene chloride at -70°C followed by treatment of the intermediate methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of DMAP in refluxing benzene furnished an ~3:1 mixture of the acetate and the ketone, which were separated by silica gel column chromatography. The ketone was found to be ~3:1 epimeric mixture at the C-5 carbon, probably due to the base catalysed isomerisation of the acetyl group. The structure of the acetate rests secured from its spectral data. The molecular ion at m/z 298 (C_{18}H_{18}O_{4}) in the mass spectrum and an absorption band at 1720 cm\(^{-1}\) due to two carbonyls of acetate and benzoate groups in the IR spectrum revealed the formation of the acetate. In the \(^1\)H NMR spectrum, a triplet at \(\delta\) 5.68 and a multiplet at 5.10-5.00 ppm due to the CHO\(\text{Bz}\) and CHO\(\text{Ac}\) protons, respectively, established the structure of the 1S,3S-acetate, which was confirmed by the \(^{13}\)C NMR spectrum.

After successful synthesis of the 1S,3S-enyne, attention was turned towards synthesis of the 1R,3S-enyne. For the conversion of the alcohol into the 1R,3S-enyne, it was obvious that the stereochemistry at the C-1 carbon atom needs to be inverted. The highly dependable Mitsunobu reaction was exploited for this conversion. Thus, treatment of the alcohol with triphenylphosphine, diethyl azodicarboxylate (DEAD) and benzoic acid in THF at room temperature for ten hours furnished the benzoate, m.p. 103-104°C, whose structure rests secured.
from its spectral data in comparison with the epimeric benzoate 18. Controlled ozonation of the benzoate 20 in 1:5 methanol-methylene chloride at -70°C followed by treatment of the intermediate methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of DMAP in refluxing benzene furnished an ~ 2:1 mixture of the acetate 21 and the ketone 22, which was separated by column chromatography on silica gel. The structures of the acetate 21 and the ketone 22 were established from their spectral data. Presence of the molecular ion at m/z 298 (C_{18}H_{18}O_{4}) in the mass spectrum and presence of two carbonyl absorption bands at 1735 and 1715 cm\(^{-1}\) due to the ester groups in the IR spectrum revealed the formation of the acetate 21. In the \(^1\)H NMR spectrum, presence of a triplet at \(\delta\) 5.73 due to the \(\text{C}-\text{H}^\text{OBz}\) proton, a multiplet at \(\delta\) 5.25-5.15 due to the \(\text{C}-\text{H}^\text{OAc}\) proton, a singlet at \(\delta\) 3.14 due to the acetylenic proton and two singlets at \(\delta\) 2.05 and 1.97 ppm due to the acetoxy and olefinic methyl groups, respectively, established the structure of the acetate 21. In the \(^{13}\)C NMR spectrum, presence of two resonances at \(\delta\) 170.1 and 165.9 due to the acetate and benzoate carbonyl carbons, respectively, two peaks at \(\delta\) 82.4 and 81.7 due to the acetylenic carbons, two signals at \(\delta\) 70.6 and 66.4 due to the \(\text{CHOBz}\) and \(\text{CHOAc}\) carbons and two methyl signals at \(\delta\) 21.2 and 18.5 ppm due to the acetyl and olefinic methyl groups, respectively, further confirmed the structure of the acetate 21.

After successfully developing a short route to the calcitriol A-ring synthon 1\(R,3\)S-eneyne 21, which is enantiomeric to that present in natural vitamin D\(_3\) and its analogues, attention was then turned towards the synthesis of natural series, 1\(S,3\)R-eneyne 13. Even though repetition of the same sequence of reactions with (S)-carvone will provide the shortest route to the A-ring synthon 1\(S,3\)R enantiomer of the enyne 21, a strategy was conceived from (R)-carvone 11 itself via inversion at the C-5 carbon instead of at the C-1 carbon. First, the hydroxy group in the allyl alcohol 16 was protected, which is stable to basic conditions. Consequently, reaction of the alcohol 16 with \(t\)-butyldimethylsilyl chloride (TBDMSCl) and imidazole in the presence of a catalytic amount of DMAP in methylene chloride at room temperature for four hours, quantitatively furnished the TBDMS ether 23. Ozonolysis of the isopropenyl group in the ether 23 in a 1:5 mixture of methanol-methylene chloride followed by Criegee rearrangement of the intermediate methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of DMAP in refluxing benzene furnished the acetate 24 in 34% yield. Presence of a carbonyl absorption band at 1740 cm\(^{-1}\) due to the acetate group in the IR spectrum suggested the formation of the acetate 24. In the \(^1\)H NMR spectrum, presence of two multiplets at \(\delta\) 4.95-4.80 and 4.29 due to the \(\text{C}-\text{H}^\text{OAc}\) and \(\text{C}-\text{H}^\text{OTBDMS}\) protons, respectively, a singlet at \(\delta\) 3.02 due to the acetylenic proton, two singlets at \(\delta\) 2.04 and 1.90 due to the acetate and olefinic methyl groups, three singlets at \(\delta\) 0.90, 0.10 and 0.09 ppm due to the TBDMS group established the structure of the acetate 24, which was further confirmed by the \(^{13}\)C NMR spectrum. For the conversion of the enyne derivative 24 into the 1\(S,3\)R-eneyne derivative, hydrolysis of the acetate group and Mitsunobu
inversion of resultant hydroxy group was explored. Thus, reaction of the acetate 24 with potassium carbonate in methanol at room temperature for two hours furnished the alcohol 25, m.p. 81-82°C, in 93% yield. Mitsunobu reaction of the alcohol 25 with triphenylphosphine, DEAD and benzoic acid in THF at room temperature for four hours cleanly furnished the benzoate 26, m.p. 98-99°C, in 80% yield, whose structure rests secured from its spectral data. Presence of an absorption band at 1720 due to the benzoate group, absorption bands at 3100 and 2100 cm\(^{-1}\) due to the acetylenic moiety in the IR spectrum along with a fragment ion at m/z 312 (M - CMe\(_3\)) in the mass spectrum clearly indicated the formation of the benzoate 26. In the \(^1\)H NMR spectrum, presence of a doublet at \(\delta\) 8.01 and two triplets at 7.54 and 7.43 due to the aromatic protons, respectively, a singlet at 3.03 due to the acetylenic proton and two singlets at 0.93 and 0.12 ppm due to the TBDMS group established the structure of the benzoate 26. It was further confirmed by the 18 lines \(^{13}\)C NMR spectrum, which exhibited characteristic signals at \(\delta\) 165.6 due to the ester carbonyl carbon, at \(\delta\) 143.9, 132.8, 130.6, 129.7 (2 C), 128.3 (2 C) and 113.2 due to the aromatic and olefinic carbons, at \(\delta\) 83.2 and 80.3 due to the acetylenic carbons, two methane carbons at \(\delta\) 68.8 and 67.5 due to the CHO\(_{2}\) and CHOTBDMS carbons in addition to peaks at \(\delta\) 25.9, 18.2, -4.2 and -4.7 ppm due to the TBDMS group. It is worth mentioning that in the 1S,3R A-ring synthon 26, the two hydroxy groups are differentially protected.

In conclusion, enantiospecific syntheses of both enantiomers of A-ring precursors of 1\(\alpha\),25-dihydroxy-vitamin D\(_3\) and its analogues have been achieved starting from (R)-carvone 11 employing 1,3-enone transposition methodology, Mitsunobu inversion and one pot ozonation followed by Criegee rearrangement as the key reactions.

**Experimental Section**

Melting points were recorded using a Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. \(^1\)H (300 MHz) and \(^{13}\)C (75 MHz) NMR spectra were recorded on a JNM\(\lambda\)-300 spectrometer. The chemical shifts (\(\delta\) ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for \(^1\)H) or the central line (77.0 ppm) of CDCl\(_3\) (for \(^{13}\)C). In the \(^{13}\)C NMR spectra, the nature of the carbons (C, CH, CH\(_2\) or CH\(_3\)) was determined by recording the DEPT-135 spectra, and is given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet mode. Relative intensities are given in parentheses. Elemental analyses were carried out using Carlo Erba 1106 CHN analyser. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electrospray ionisation. Ozonolysis experiments were carried out using Fischer 502 ozone generator and the oxygen flow and the current were regulated to generate 1 mmole of ozone for 4 minutes. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and [\(\alpha\)]\(_D\) values are given in units of 10\(^{-1}\) deg cm\(^2\) g\(^{-1}\).

\(+\)-(5S)-3-Ethynyl-5-isopropenyl-2-methylcyclohex-2-ene 14. A suspension of (R)-carvone 11 (450 mg, 3 mmoles) and lithium acetylide-ethylenediamine complex (550 mg, 6 mmoles) in dry THF (5 mL) was sonochemically irradiated in an ultrasonic cleaning bath for 1.5 hr. The reaction was then quenched with saturated aq. NH\(_4\)Cl solution and extracted with ether (2 \(\times\) 10 mL). The ether extract was washed with brine and dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent furnished the tertiary alcohol 15. To a magnetically stirred solution of the tertiary alcohol 15 in 5 mL of CH\(_2\)Cl\(_2\) was added a homogeneous mixture of PCC (1.29 g, 6 mmoles) and silica gel (1.29 g), and stirred vigorously for 10 hr at RT. The mixture was then filtered through a small silica gel column and the column was eluted with excess of CH\(_2\)Cl\(_2\). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-
hexane (1:20) as eluent furnished the enone 14 (365 mg, 70%, for two steps) as an oil. [α]D25 40.3 (c 3.60, CHCl3); IR (neat): 3280, 2100, 1670, 1600, 890 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 4.83 (1 H, s) and 4.77 (1 H, s) [C=CH2], 3.77 (1 H, s, C≡CH), 2.80-2.30 (5 H, m), 1.98 (3 H, s) and 1.76 (3 H, s) [2 × olefinic CH2]; 13C NMR (75 MHz, CDCl3): δ 198.4 (C=O), 145.9, 140.2, 135.4, 110.9 (C=CH2), 90.6 (C≡CH), 82.1 (C≡CH), 42.7, 41.4, 35.8, 20.4, 13.7; Mass: m/z 174 (M+, C12H16O, 3%), 158 (19), 143 (10), 133 (29), 132 (100).

(+)-(1S,5S)-3-Ethynyl-5-isopropenyl-2-methylcyclohex-2-enyl benzoate 18. To a magnetically stirred solution of the alcohol 16 (145 mg, 0.82 mmole) in 2 mL of dry CH2Cl2 were added successively pyridine (0.13 mL, 1.6 mmoles), benzoyl chloride (0.18 mL, 1.55 mmoles) and a catalytic amount of DMAP. The reaction mixture was stirred at RT for 10 hr. It was then diluted with 5 mL of water and extracted with CH2Cl2 (3 × 5 mL). The combined organic extract was washed successively with 3 M aqueous HCl, saturated aqueous NaHCO3 and brine, and dried (Na2SO4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the benzoate 18 (226 mg, 98%), m.p.: 74°C; [α]D25 18.4 (c 2.5, CHCl3); IR (neat): 3293, 1717, 1646, 893 cm⁻¹; 1H NMR (300 MHz, CDCl3 + CH2Cl2): δ 8.04 (2 H, d, J=−7.5 Hz), 7.55 (1 H, t, J=−7.5 Hz), 7.43 (2 H, t, J=−7.5 Hz), 5.72 (1 H, m, CHOBz), 4.75 (2 H, s, C=CH2), 3.10 (1 H, s, C≡CH), 2.50-2.15 (4 H, m), 1.93 (3 H, s) and 1.75 (3 H, s) [2 × olefinic CH2], 1.62 (1 H, d of t, J=12.0 and 11.0 Hz), 13C NMR (75 MHz, CDCl3 + CH2Cl2): δ 165.8 (C, O=O), 147.1 (C), 140.9 (C), 133.0 (CH), 130.4 (C), 129.8 (2 C, CH), 128.4 (2 C, CH), 118.2 (C), 110.2 (CH2, C=CH2), 83.2 (C, C≡CH), 81.2 (CH, C≡CH), 73.5 (CH, CHOBz), 39.5 (CH, C-5), 35.3 (CH2) and 33.6 (CH2) [C-4 and 6], 20.6 (CH2), 17.4 (CH3); Mass: m/z 280 (M+, 1%), 237 (40), 159 (15), 143 (55), 128 (50), 117 (30), 115 (30), 106 (40), 105 (100), 91 (20), 77 (100); Anal.: Caled. for C19H20O2: C, 81.40; H, 7.19%. Found: C, 81.52; H, 7.28%.

(−)-(1S, 5R)-5-Acetoxy-3-ethynyl-2-methylcyclohex-2-enyl benzoate 17 and (1S,5S)- and (1S,5R)-5-acetyl-3-ethynyl-2-methylcyclohex-2-enyl benzoate 19. Pre-cooled dry ozone in oxygen gas was passed through a cold (−70°C) suspension of the benzoate 18 (150 mg, 0.54 mmole) and NaHCO3 (pinch) in 1.5 mL MeOH-CH2Cl2 (3 mL) for ca. 2 min. Excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo and the residue dissolved in dry benzene (3 mL). To this mixture was added triethylamine (0.50 mL, 3.6 mmoles), acetic anhydride (0.34 mL, 3.6 mmoles) and a catalytic amount of DMAP and stirred at RT for 1 hr. The reaction mixture was then refluxed for 6 hr. It was then cooled, diluted with 5 mL of water and extracted...
with ether (3 \times 5 mL). The ether extract was washed with 3N aq. HCl, water and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished, first, the unreacted benzoate 18 (15 mg, 10%). Further elution of the column with ethyl acetate-hexane (1:10) as eluent furnished the acetate 17 (47 mg, 29%). \[ \alpha \]$_{D}^{25}$: -63.0 (c 1.27, CHCl$_3$); IR (neat): 3270, 1720, 1600, 1580 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 8.04 (2 H, d, J=7.2 Hz), 7.55 (1 H, t, J=7.5 Hz), 7.43 (2 H, t, J=7.2 Hz), 5.60 (1 H, br s, CHO$_2$Bz), 4.76 (1 H, s) and 4.72 (1 H, s) [C=CH$_2$], 3.19 (1 H, s, C=CH), 2.55-2.35 (2 H, m), 2.15-2.05 (2 H, m), 1.96 (3 H, s) and 1.72 (3 H, s) [2 \times olefinic CH$_3$], 1.80-1.65 (1 H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.1 (C, O-C=O), 147.6 (C), 138.7 (C), 133.0 (CH), 130.3 (C), 129.6 (2 C, CH), 128.4 (2 C, CH), 119.9 (C), 109.8 (CH$_2$, C=CH$_2$), 83.0 (C, C=CH), 81.6 (CH, C=CH), 71.0 (CH, CHO$_2$Bz), 36.0 (CH, C$_5$), 35.3 (CH$_3$), 33.3 (CH$_2$), 20.8 (CH$_2$), 19.1 (CH$_3$); Mass: m/z 280 (M$^+$, 1%), 237 (6), 143 (7), 128 (5), 105 (100), 77 (24); HRMS: m/z for C$_{19}$H$_{20}$O$_2$: Calcd.: 280.1463. Found: 280.1452; Anal.: Calcd. for C$_{19}$H$_{20}$O$_2$: C, 80.95; H, 7.30%. Further elution of the column gave unreacted starting alcohol 16 (58 mg, 40%).

(+)-(1R, 5S)-5-Acetoxy-3-ethyl-2-methylcyclohex-2-enyl benzoate 21 and (+)-(1R,5S)-5-acetyl-3-ethyl-2-methylcyclohex-2-enyl benzoate 22. Pre-cooled dry ozone in oxygen gas was passed through a cold (−70°C) suspension of the benzoate 20 (150 mg, 0.55 mmole) and NaHCO$_3$ (pinch) in 1:5 MeOH-CH$_2$Cl$_2$ (3 mL) for ca. 2 min. Excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo and the residue dissolved in dry benzene (4 mL). To this mixture was added triethylamine (0.50 mL, 3.6 mmoles), acetic anhydride (0.34 mL, 3.6 mmoles) and a catalytic amount of DMAP and stirred at RT for 1 hr. The reaction mixture was then reflu xen for 6 hr. It was then cooled, diluted with 5 mL of water and extracted with ether (3 \times 5 mL). The ether extract was washed with 3N aq. HCl, water and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished, first, the unreacted benzoate 20 (18 mg, 12%). Further elution of the column with ethyl acetate-hexane (1:10) furnished the acetate 21 (40 mg, 25%) as an oil. \[ \alpha \]$_{D}^{24}$: 13.0 (c 1.0, CHCl$_3$); IR (neat): 3280, 1735, 1715 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 8.07 (2 H, d, J=7.5 Hz), 7.61 (1 H, t, J=7.5 Hz), 7.44 (2 H, t, J=7.5 Hz), 5.73 (1 H, t, J=4.8 Hz, CHO$_2$Bz), 5.25-5.15 (1 H, m, CHOAc), 3.14 (1 H, s, C=CH), 2.72 (1 H, dd, J=17.4 and 3.9 Hz), 2.26 (1 H, dd, J=17.4 and 7.8 Hz), 2.20-2.00 (2 H, m), 2.05 (3 H, s, OCOCH$_3$), 1.97 (3 H, s, olefinic CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 170.1 (C, OCOCH$_3$), 165.9 (C, OCOPh), 139.5 (C), 133.1 (CH), 130.1 (C), 129.9
Further elution of the column with ethyl acetate-hexane (1:5) gave ketone 22 (18 mg, 12%). [α]D24: 101.0 (c 1.00, CHCl3); IR (neat): 3280, 1710, 1600 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 8.05 (2 H, d, J=7.5 Hz), 7.59 (1 H, t, J=7.5 Hz), 7.46 (2 H, t, J=7.5 Hz), 5.62 (1 H, br s, CH2O), 3.23 (1 H, s, C=H), 2.95-2.80 (1 H, m), 2.53 (1 H, d with fine splitting, J=12.3 Hz), 2.50-2.30 (1 H, m), 2.27 (1 H, d with fine splitting, J=14.4 Hz), 2.19 (3 H, s, COCH3), 1.98 (3 H, s, olefinic CH3), 1.81 (1 H, ddd, J=15.0, 13.5 and 4.2 Hz); 13C NMR (75 MHz, CDCl3): δ 209.4 (C, COCH3), 165.9 (C, C=O), 138.8 (C), 133.2 (CH), 130.0 (C), 129.7 (2 C, CH), 128.4 (2 C, CH), 118.6 (C), 82.1 (C, C=CH), 80.3 (C, C=CH), 79.8 (CH, olefinic CH2), 79.8 (CH, olefinic CH2), 79.4 (CH, olefinic CH), 69.9 (CH, CHO), 30.4 (CH2), 28.1 (CH3, COCH3), 19.1 (CH3, olefinic CH3); Mass: m/z 298 (M⁺, 1%), 238 (35), 177 (10), 133 (33), 117 (80), 116 (45), 115 (45), 106 (60), 105 (100), 91 (22), 77 (100); HRMS: m/z for C18H18O4, Calcd.: 298.1205. Found: 298.1219.

(+)-(1S,5S)-3-Ethynyl-5-isopropenyl-2-methyloclohex-2-ynyl tert-butylmethysilyl ether 23. To a magnetically stirred solution of the alcohol 16 (270 mg, 1.53 mmoles) in dry CH2Cl2 (3 mL) were added imidazole (125 mg, 1.84 mmoles), TBDMSI (277 mg, 1.84 mmoles) and a catalytic amount of DMAP, and stirred for 4 hr at RT. The reaction mixture was then diluted with CH2Cl2 (10 mL), washed with brine and dried (Na2SO4). Evaporation of the solvent furnished the TBDMS ether 23 (100 mg, 0.34 mmole) in the presence of NaHCO3 (pinch) for ca. 2 min followed by Criegee rearrangement of the ozonide with triethylamine (0.39 mmole, amine) and purification of the products on a silica gel column using ethyl acetate-hexane (1:20) as eluent gave first, unreacted starting TBDMS ether 23 (10 mg, 10%). Further elution of the column with ethyl acetate-hexane (1:10) as eluent furnished the acetate 24 (36 mg, 34%) as an oil. [α]D20: 30.7 (c 1.14, CHCl3); IR (neat): 3300, 1740 cm⁻¹; 1H NMR (300 MHz, CDCl3+CCl4): δ 4.95-4.80 (1 H, m, CH2OAc), 4.29 (1 H, m, CH2OSi), 3.02 (1 H, s, C=CH), 2.49 (1 H, d, J=16.2 and 4.2 Hz), 2.35-2.10 (2 H, m), 2.04 (3 H, s, OCOCH3), 1.90 (3 H, s, olefinic CH3), 1.72 (1 H, d of t, J=11.7 and 9.3 Hz), 0.90 (9 H, s, (CH3)2C), 0.10 (3 H, s) and 0.09 (3 H, s) [Si(CH3)2]; 13C NMR (75 MHz, CDCl3+CCl4): δ 170.1 (C, OCOCH3), 145.3 (C), 112.6 (C), 83.1 (C, C=CH), 80.3 (CH, C=CH), 69.9 (CH, CH2OAc), 67.2 (CH, CHOSi), 38.1 (CH2), 35.4 (CH2), 25.9 (3 C, CH3, (CH3)2Si), 21.3 (CH3, COCH3), 18.2 (C, CH3), 17.9 (CH3, olefinic CH3), –4.1 (CH3) and –4.8 (CH3) [Si(CH3)2]; Mass: m/z 249 (M – OAc, C15H28OSi, 2%), 248 (2), 117 (30), 116 (15), 115 (20), 91 (8), 75 (100).

(+)-(1S,5S)-5-(tert-Butyldimethylsilyloxy)-3-epsilonnyl-4-methylcyclohex-3-enyl acetate 24. Ozonation of the TBDMS ether 23 (100 mg, 0.34 mmole) in 1:5 MeOH-CH2Cl2 (3 mL) in the presence of NaHCO3 (pinch) for ca. 2 min followed by Criegee rearrangement of the ozonide with triethylamine (0.39 mmole, amine) and a catalytic amount of DMAP in dry benzene (3 mL) as described for the compound 18, and purification of the products on a silica gel column using ethyl acetate-hexane (1:20) as eluent gave first, unreacted starting TBDMS ether 23 (10 mg, 10%). Further elution of the column with ethyl acetate-hexane (1:10) as eluent furnished the acetate 24 (36 mg, 34%) as an oil. [α]D20: 30.7 (c 1.14, CHCl3); IR (neat): 3300, 1740 cm⁻¹; 1H NMR (300 MHz, CDCl3+CCl4): δ 4.95-4.80 (1 H, m, CH2OAc), 4.29 (1 H, m, CH2OSi), 3.02 (1 H, s, C=CH), 2.49 (1 H, d, J=16.2 and 4.2 Hz), 2.35-2.10 (2 H, m), 2.04 (3 H, s, OCOCH3), 1.90 (3 H, s, olefinic CH3), 1.72 (1 H, d of t, J=11.7 and 9.3 Hz), 0.90 (9 H, s, (CH3)2C), 0.10 (3 H, s) and 0.09 (3 H, s) [Si(CH3)2]; 13C NMR (75 MHz, CDCl3+CCl4): δ 170.1 (C, OCOCH3), 145.3 (C), 112.6 (C), 83.1 (C, C=CH), 80.3 (CH, C=CH), 69.9 (CH, CH2OAc), 67.2 (CH, CHOSi), 38.1 (CH2), 35.4 (CH2), 25.9 (3 C, CH3, (CH3)2Si), 21.3 (CH3, COCH3), 18.2 (C, CH3), 17.9 (CH3, olefinic CH3), –4.1 (CH3) and –4.8 (CH3) [Si(CH3)2]; Mass: m/z 249 (M – OAc, C15H28OSi, 2%), 248 (2), 117 (30), 116 (15), 115 (20), 91 (8), 75 (100).
C≡CH), 2.40-2.20 (2 H, m), 1.97 (1 H, t of d, J=13.5 and 4.5 Hz), 1.89 (3 H, s, olefinic CH3), 1.80 (1 H, dd, J=13.5, 4.5 and 2.4 Hz), 0.82 (9 H, s, (CH3)2), 0.07 (3 H, s) and 0.05 (3 H, s) [Si(CH3)2]; 13C NMR (75 MHz, CDCl3): δ 142.3 (C), 113.7 (C), 83.6 (C, C=CH), 80.4 (CH, C=CH), 69.1 (CH, CHOSi), 64.6 (CH, CHO), 38.8 (CH2), 37.2 (CH2), 25.7 (3 C, CH3, (CH3)2Si), 19.3 (CH3, olefinic CH3), 17.9 (C, CMe3), −4.4 (CH3) and −4.9 (CH3) [Si(CH3)2]; Mass: m/z 266 (M+, 1%), 209 (21), 191 (9), 177 (24), 75 (100); Anal.: Calcd. for C15H30O3Si: C, 71.31; H, 9.84%. Found: C, 68.11; H, 10.06%.

(-)-(1R,5S)-5-(tert-Butyldimethylsilyloxy)-3-ethyl-5-methylcyclhexox-3-ethyl benzoate 26. Mitsunobu reaction of alcohol 25 (26 mg, 0.1 mmole) with triphenylphosphine (39 mg, 0.15 mmole), benzoic acid (13 mg, 0.11 mmole) and DEAD (0.02 mL, 0.13 mmole) in 1 mL of THF, as described for the compound 20, for 4 hr and purification of the product on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the benzoate 26 (29 mg, 80%) as a white solid, which was recrystallised from a mixture of hexane and ether. m.p.: 98-99°C; [α]23D = -41.7 (c 1.15, CHCl3); IR (neat): 3300, 2100, 1720, 1600 cm−1; 1H NMR (300 MHz, CDCl3 + CCl4): δ 8.01 (2 H, d, J=7.5 Hz), 7.54 (1 H, t, J=7.5 Hz), 7.43 (2 H, t, J=7.5 Hz), 5.41 (1 H, m, CHOBr), 4.31 (1 H, m, CHOTBDMS), 3.03 (1 H, s, C≡CH), 2.73 (1 H, d with fine coupling, J=18.0 Hz), 2.35 (1 H, dd, J=18.0 and 6.0 Hz), 2.05-1.95 (2 H, m), 1.98 (3 H, s, olefinic CH3), 0.93 (9 H, s, (CH3)2), 0.12 (6 H, s, Si(CH3)2); 13C NMR (75 MHz, CDCl3 + CCl4): δ 165.6 (C, O-C=O), 143.9 (C), 132.8 (CH), 130.6 (C), 129.7 (2 C, CH), 128.3 (2 C, CH), 113.2 (C), 83.2 (C, C≡CH), 80.3 (CH, C≡CH), 68.8 (CH, CHOBz), 67.5 (CH, CHOTBDMS), 37.0 (CH2), 35.2 (CH2), 25.9 (3 C, CH3, Si(CH3)2), 18.9 (CH2), 18.2 (C, CMe3), −4.2 (CH3) and −4.7 (CH3) [Si(CH3)2]; Mass: m/z 312 (M – CMe3, 16%), 247 (58), 179 (50), 178 (100), 117 (68), 105 (100); Anal.: Calcd. for C22H30O3Si: C, 71.31; H, 8.16%. Found: C, 71.10; H, 8.19%.

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References

6 Atom numbers 1 and 3 refer to the carbons corresponding to those in vitamin D3 and analogues. For a preliminary communication, see: Srikrishna A, Gharpure S J & Kumar P R, Tetrahedron Lett, 41, 2000, 3177.
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