Research Article

Synthesis of a New Type of *Trans*-Decalin Vitamin D Analogue through a Dyotropic Ring Expansion

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A new vitamin D analogue with a *trans*-fused decalin as the CD-ring system and containing a sulphur atom in the side chain has been synthesized in our research group. The obtention of this analogue is based on a recently discovered transformation of hydrindane cores into decalins through a dyotropic ring expansion in very mild conditions.

1. Introduction

Calcitriol 1 (Figure 1) or $1\alpha,25$ -dihydroxyvitamin D₃, the biologically active form of vitamin D₃, has a potential application as a therapy agent in the treatment of different pathologies related to antiproliferative and cell differentiation activity [1–8]; however, it shows as the main limitation its calcemic effects. Actually, there is great interest in the obtention of new calcitriol analogues with less calcemic toxicity.

Facing this goal, an interesting research area is the synthesis of nonsteroidal analogues where the CD fragment is modified, substituting the natural *trans*-fused hydrindane bicyclic system for a monocyclic moiety such as five- [9, 10] or six-membered rings [11–14].

In fact, one of the most used modifications is the replacement of the *trans*-hydrindane core for a *trans*-decalin core (Figure 1).

Decalins are bicyclic carbon frameworks that can be found in numerous polyterpenoid and steroid natural products with interesting biological activity [15–23]. In our laboratory, we recently reported a very useful stereospecific methodology to convert hydrindane moieties into decalin derivatives through a new type of dyotropic reaction involving a mesylate group in mild conditions with high yields (Scheme 1) [24].

These decalin cores have been recently used as the building block to obtain interesting functionalized decalins which represents a challenging task for organic chemists such as chiral thioethers [25].

Thus, we can access disulphide 5 by displacement of mesylate 4 with potassium thioacetate. Alkylation of 5 with an electrophile [26, 27] using sodium borohydride afforded (between others) compound 6, our precursor in the synthesis of a new *trans*-decalin vitamin D analogue (Scheme 2).

From chiral building block 6 as the initial substrate, we report on easy synthesis of a novel type of *trans*-decalin vitamin D analogue with a sulphur atom as the linker between the side chain and CD fragment as depicted in Scheme 3 (compound 7).

2. Results and Discussion

The synthesis is based on a convergent route which involves the construction of Grundmann's ketone 8 followed by Wittig–Horner coupling using phosphine oxide 9 to afford the triene system, as shown in the retrosynthetic scheme (Scheme 3).

First, compound 6 was deprotected using a TBAF solution 1.0 M in THF and heating at 65°C several days to transform both silyl ethers into hydroxyl groups, affording diol 10 with 97% yield as shown in Scheme 4.

FIGURE 1: Structure of calcitriol 1 and *trans*-decalin vitamin D analogue 2.

SCHEME 1: Ring expansion of 3 via the dyotropic ring expansion to afford decalin 4.

SCHEME 2: Obtention of key intermediate 6 from mesylate 4.

SCHEME 3: Retrosynthetic scheme for the obtention of a new *trans*-decalin vitamin D analogue with a sulphur atom.

SCHEME 4: Synthetic sequence to obtain Grundmann's ketone 8.

An oxidant such as PDC was used to convert diol 10 into Grundmann's ketone derivative 11 with 91% yield which was protected with TMS-imidazole in THF, obtaining Grundmann's ketone synthon 8 with 85% yield.

Compound 8 was converted into 12 via the Wittig-Horner reaction [28, 29] with phosphine oxide 9 with 55% yield. Removal of the TBS-protecting groups in 12 gave analogue 7 with 99% yield as shown in Scheme 5.

SCHEME 5: Obtention of final analogue 7.

3. Conclusions

In conclusion, we have demonstrated how this dyotropic expansion reaction to convert a hydrindane into a decalin scaffold under very mild conditions can be a powerful tool to an easy access to vitamin D analogues with a *trans*-decalin core in its structure as the CD fragment. Work is now in progress towards the synthesis of new similar analogues as well as their biological evaluation.

4. Experimental Section

For experimental procedures, characterization data and copies of ^1H and ^{13}C spectra of all compounds were used; see the Supplementary Materials (available here).

General: solvents were purified and dried by standard procedures before use. Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer (400 MHz for ^1H NMR and 100.61 MHz for ^{13}C NMR) using TMS as the internal standard (chemical shifts in δ values, J in Hz). Flash chromatography (FC) was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm); mass spectra (FAB and EI) were recorded using Fisons VG, and electron spray ionization (ESI-MS) spectroscopy was recorded using Bruker FTMS APEXIII. Melting points were obtained in open capillary tubes and were not corrected. Optical rotations were obtained using a Jasco P-2000 polarimeter. IR spectra were recorded with a Jasco FT/I(R)-6100 spectrophotometer.

Synthesis of (1*S*,4*aS*,5*R*,6*R*,8*aR*)-5-((3-hydroxy-3-methylbutyl)thio)-4*a*,6-dimethyldecahydronaphthalen-1-ol (10): TBAF 1.0M solution in THF (0.92 ml, 0.92 mmol) was added to another solution of 6 (122 mg, 0.23 mmol) in THF (4 ml),

and the mixture was stirred at 65°C for 3 days. After that time, 4 equivalents of TBAF were added, and the mixture was stirred in these conditions for another 3 days. After that time, the reaction was concentrated under reduced pressure. The residue was purified by column chromatography with EtOAc/hexane (30%) as the eluent, affording 10 (67 mg, 97%) as colourless oil; Rf: 0.40 (50% EtOAc/hexane). IR (ATR, cm^{-1}): 3434, 3385, 2963, 2922, 2865, 1458, 1377, 1240, 915. $[\alpha]_{\text{D}}^{23} = +21.71$ (c 1.00, CHCl_3). ^1H -NMR (CDCl_3 , δ): 3.83 (1H, d, $J = 2.6$ Hz, H-1), 2.58 (2H, m, H-1'), 2.25 (2H, m), 2.12 (1H, d, $J = 3.1$ Hz, H-5), 1.79 (5H, m), 1.63 (3H, m), 1.48 (3H, m), 1.27 (2H, m), 1.25 (6H, s, CH_3 -4'), 1.22 (3H, s, CH_3 -10), 1.17 (1H, m), 1.06 (3H, d, $J = 6.6$ Hz, CH_3 -9) ppm. ^{13}C -NMR (CDCl_3 , δ): 71.8 (CH-1), 70.8 (C-3'), 67.7 (CH-5), 43.6 (CH_2), 41.4 (CH), 39.6 (C-8a), 36.7 (CH_2), 33.7 (CH_2), 31.2 (CH), 31.0 (CH_2), 30.5 (CH_2), 29.4 (CH_3 -4'), 29.3 (CH_3 -4'), 25.7 (CH_2), 21.6 (CH_3 -10), 21.0 (CH_3 -9), 16.8 (CH_2) ppm. MS (ESI) ($[m/z]$, %): 283.20 ($[\text{M}-\text{OH}]^+$, 100), 301.22 ($[\text{M}+1]^+$, 55). HRMS (ESI): 301.2196 calculated for $\text{C}_{17}\text{H}_{33}\text{O}_2\text{S}$ and found 301.2191.

Synthesis of (4*aS*,5*R*,6*R*,8*aR*)-5-((3-hydroxy-3-methylbutyl)thio)-4*a*,6-dimethyloctahydronaphthalen-1(2*H*)-one (11): PDC (245 mg, 0.65 mmol) was added to a solution of alcohol 10 (65 mg, 0.21 mmol) in CH_2Cl_2 (3 ml), and the mixture was stirred at room temperature for 3 hours. Then, it was filtered, and the solvent was evaporated. The residue was purified by column chromatography with EtOAc/hexane (50%) as the eluent, affording 11 (58 mg, 91%) as colourless oil; Rf: 0.34 (50% EtOAc/hexane). IR (ATR, cm^{-1}): 3503, 2963, 2931, 2853, 1708, 1455, 1366, 1248, 1039, 838. $[\alpha]_{\text{D}}^{22} = +7.95$ (c 1.00, CHCl_3). ^1H -NMR (CDCl_3 , δ): 2.68 (2H, m, H-1'), 2.59 (1H, m), 2.50 (1H, dd, $J = 11.8/4.0$ Hz), 2.32 (3H, m), 2.17 (1H, m), 2.01 (1H, m), 1.91 (1H, m), 1.79 (2H, ddd, $J = 9.3/6.6/2.2$ Hz), 1.52 (5H, m), 1.31 (1H, m), 1.26 (6H, s, CH_3 -4'), 1.07 (3H, d, $J = 6.5$ Hz, CH_3 -9), 0.96 (3H, s, CH_3 -10) ppm. ^{13}C -NMR (CDCl_3 , δ): 213.4 (C=O), 70.7 (C-3'), 65.0 (CH-8a), 51.3 (CH-5), 45.4 (C-4a), 43.7 (CH_2), 41.3 (CH_2), 36.2 (CH_2), 30.9 (CH), 30.8 (CH_2), 29.4 (CH_3 -4'), 29.3 (CH_3 -4'), 28.9 (CH_2), 22.6 (CH_2), 20.7 (CH_3 -9), 20.7 (CH_2), 18.9 (CH_3 -10) ppm. MS (ESI) ($[m/z]$, %): 179.15 (100), 298.20 ($[\text{M}]^+$, 19). HRMS (ESI): 298.1967 calculated for $\text{C}_{17}\text{H}_{30}\text{O}_2\text{S}$ and found 298.1974.

Synthesis of (4*aS*,5*R*,6*R*,8*aR*)-4*a*,6-dimethyl-5-((3-methyl-3-((trimethylsilyl)oxy)butyl)thio)octahydronaphthalen-1(2*H*)-one (8): to a solution of ketone 11 (60 mg, 0.2 mmol) in THF (3 mL), TMS-Im (300 μL , 2.0 mmol) was added, and the mixture was stirred at room temperature for 3 days. Then, it was quenched with H_2O (5 mL), and the mixture was extracted with EtOAc (2×10 mL). The combined organic phases were dried over Na_2SO_4 , filtered, and concentrated to give a residue which was chromatographed on silica gel using EtOAc/hexane (2%) as the eluent, affording compound 8 (63 mg, 85%) as colourless oil; Rf: 0.55 (20% EtOAc/hexane). IR (ATR, cm^{-1}): 2963, 2930, 2852, 1708, 1455, 1367, 1250, 1038, 838. $[\alpha]_{\text{D}}^{23} = +17.68$ (c 1.00, CHCl_3). ^1H -NMR (CDCl_3 , δ): 2.75 (1H, td, $J = 13.4/4.8$ Hz), 2.57 (3H, m), 2.31 (3H, m), 2.16 (1H, m), 1.97 (2H, m), 1.72 (2H, ddd, $J = 9.4/6.4/2.0$ Hz), 1.62 (1H, m), 1.51 (3H, m), 1.31 (1H, m), 1.24 (6H, s, CH_3 -4'), 1.07 (3H, d, $J = 6.4$ Hz,

CH₃-9), 0.96 (3H, s, CH₃-10) ppm. ¹³C-NMR (CDCl₃, δ): 213.8 (C = O), 73.4 (C-3'), 64.3 (CH-8a), 51.3 (CH-5), 45.5 (C-4a), 45.0 (CH₂), 41.3 (CH₂), 36.1 (CH₂), 30.8 (CH), 30.5 (CH₂), 29.9 (CH₃-4'), 29.8 (CH₃-4'), 28.9 (CH₂), 22.7 (CH₂), 20.7 (CH₃-9), 20.7 (CH₂), 18.9 (CH₃-10) ppm. MS (ESI) ([m/z], %): 283.24 (50), 371.24 ([M+1]⁺, 100). HRMS (ESI): 371.2434 calculated for C₂₀H₃₉O₂SSi and found 371.2426.

Synthesis of (((1*R*,3*S*,*Z*)-5-(2-((4*aS*,5*R*,6*R*,8*aS*,*E*)-4*a*,6-dimethyl-5-((3-methyl-3-((trimethylsilyl)oxy)butyl)thio)octahydronaphthalen-1(2*H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diyl)bis(oxy))bis(*tert*-butyldimethylsilyl)ane) (12): *n*-BuLi solution 2.5M in hexane was added dropwise to another solution of phosphine oxide 9 (347 mg, 0.595 mmol) in THF (2 ml) at -78°C, and the deep red mixture was stirred for 1 h. A solution of ketone 8 (25 mg, 0.067 mmol) in THF (1 mL) was added at the same conditions via the cannula and stirred for 17 h. A saturated aqueous solution of NH₄Cl (5 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 × 5 mL). The organic phase was dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography with EtOAc/hexane (1%) as the eluent, affording 12 (27 mg, 55%) as colourless oil; Rf: 0.95 (10% EtOAc/hexane). IR (ATR, cm⁻¹): 2960, 2935, 2851, 1487, 1357, 1210, 1037, 852. [α]_D²¹ = +32.70 (c 1.00, CHCl₃). ¹H-NMR (CDCl₃, δ): 6.25 (1H, d, *J* = 11.0 Hz, H-8''), 6.02 (1H, d, *J* = 11.0 Hz, H-7''), 5.21 (1H, d, *J* = 1.7 Hz, H₂C=C-4''), 4.88 (1H, d, *J* = 2.0 Hz, H₂C=C-4''), 4.39 (1H, m, H-3''), 4.21 (1H, m, H-1''), 2.89 (1H, d, *J* = 12.9 Hz, H-5), 2.53 (3H, m), 2.17 (4H, m), 1.81 (7H, m), 1.58 (2H, m), 1.41 (2H, m), 1.24 (6H, s, CH₃-4'), 1.22 (2H, m), 1.09 (3H, d, *J* = 6.4 Hz, CH₃-9), 0.90 (12H, s, CH₃-^{*t*}Bu), 0.89 (6H, s, CH₃-^{*t*}Bu), 0.86 (3H, s, CH₃-10), 0.14 (9H, s, CH₃-Si/TMS), 0.09 (12H, s, CH₃-Si/TBS) ppm. ¹³C-NMR (CDCl₃, δ): 148.4 (C-4''), 142.4 (C-1), 135.1 (C-5''), 123.6 (CH-7''), 118.0 (CH-8''), 111.4 (H₂C=C-4''), 73.6 (C-3'), 72.1 (CH-3''), 67.5 (CH-1''), 65.5 (CH-8a), 46.0 (CH₂), 45.1 (CH₂), 44.8 (CH₂), 44.3 (CH), 43.0 (C-4a), 37.6 (CH₂), 37.6 (CH₂), 31.1 (CH), 30.8 (CH₂), 30.2 (CH₂), 29.9 (CH₃-4'), 29.9 (CH₃-4'), 25.9 (CH₃-^{*t*}Bu), 25.8 (CH₃-^{*t*}Bu), 24.4 (CH₂), 23.4 (CH₂), 20.9 (CH₃-9), 18.8 (CH₃-10), 18.3 (C-^{*t*}Bu), 18.2 (C-^{*t*}Bu), 2.6 (CH₃-Si/TMS), -4.6 (CH₃-Si/TBS), -4.7 (CH₃-Si/TBS), -4.8 (CH₃-Si/TBS), -5.1 (CH₃-Si/TBS) ppm. MS (ESI) ([m/z], %): 735.50 ([M+1]⁺, 100), 757.48 ([M+Na]⁺, 7). HRMS (ESI): 735.5058 calculated for C₄₁H₇₉O₃SSi₃ and found 735.5063.

Synthesis of (1*R*,3*S*,*Z*)-5-(2-((4*aS*,5*R*,6*R*,8*aS*,*E*)-5-((3-hydroxy-3-methylbutyl)thio)-4*a*,6-dimethyloctahydronaphthalen-1(2*H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (7): TBAF 1.0M solution in THF (0.120 ml, 0.120 mmol) was added to another solution of 12 (17 mg, 0.023 mmol) in THF (2 ml), and the mixture was stirred at r.t. for 24 h. After that time, 2 equivalents of TBAF were added, and the mixture was stirred in these conditions for another 24 h. Then, the reaction was concentrated under reduced pressure. The residue was purified by column chromatography with EtOAc/hexane (80%) as the eluent, affording 7 (10 mg, 99%) as colourless oil; Rf: 0.60 (EtOAc). IR (ATR, cm⁻¹): 3367, 3318, 2958, 2937, 2851, 1490, 1355, 1208, 1037. [α]_D²³ = +2.58 (c 1.00, CHCl₃). ¹H-NMR (CDCl₃, δ): 6.38 (1H,

d, *J* = 11.1 Hz, H-8''), 6.01 (1H, d, *J* = 11.2 Hz, H-7''), 5.34 (1H, d, *J* = 1.9 Hz, H₂C=C-4''), 5.00 (1H, d, *J* = 2.0 Hz, H₂C=C-4''), 4.45 (1H, dd, *J* = 7.6/4.4 Hz, H-3''), 4.25 (1H, m, H-1''), 2.89 (1H, m), 2.59 (4H, m), 2.32 (3H, m), 2.05 (4H, m), 1.79 (4H, m), 1.57 (1H, m), 1.42 (2H, m), 1.26 (6H, s, CH₃-4'), 1.19 (1H, m), 1.08 (3H, d, *J* = 6.5 Hz, CH₃-9), 0.89 (1H, m), 0.87 (3H, s, CH₃-10) ppm. ¹³C-NMR (CDCl₃, δ): 147.6 (C-4''), 144.5 (C-1), 133.1 (C-5''), 125.4 (CH-7''), 117.3 (CH-8''), 112.1 (H₂C=C-4''), 70.9 (CH-3''), 70.9 (C-3'), 66.8 (CH-1''), 66.1 (CH-8a), 45.3 (CH₂), 44.4 (CH), 43.6 (CH₂), 43.1 (C-4a), 42.8 (CH₂), 37.6 (CH₂), 31.1 (CH₂), 31.0 (CH), 30.0 (CH₂), 29.9 (CH₂), 29.4 (CH₃-4'), 29.3 (CH₃-4'), 24.5 (CH₂), 23.4 (CH₂), 20.9 (CH₃-9), 18.8 (CH₃-10) ppm. MS (ESI) ([m/z], %): 186.22 (100), 435.29 ([M+1]⁺, 85), 457.27 ([M+Na]⁺, 83). HRMS (ESI): 435.2927 calculated for C₂₆H₄₃O₃S and found 435.2916.

Data Availability

The data used to support the findings of this study are available in supplementary materials.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

The supplementary data contain experimental procedures, characterization data, and copies of ¹H and ¹³C spectra of all compounds. (*Supplementary Materials*)

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