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Synthesis and X-ray crystallography of (1R,3aR,7aR)-1-((S)-1-((2R,5S)-5-(3-hydroxypentan-3-yl)tetrahydrofuran-2-yl)ethyl)-7a-methyloctahydro-4*H*-inden-4-one

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ABSTRACT

The crystal of the title compound, $C_{21}H_{36}O_3$ contains an oxolane ring, and six defined stereocenters which are unambigously established by the crystallography study. A three dimensional supramolecular architecture is ensured by hydrogen bonds from the hydroxy group which is both engaged in inter (O-H···O2) and intramolecular C-H···O-H) hydrogen bonds. Weak C-H···O=C hydrogen bonds are involved also into the consolidation of the network.

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1. Introduction

Our constant interest in the chemistry of heterocyclic compounds and particularly in the synthesis of vitamin D analogues, has led us to develop several methods for the synthesis of these compounds [1,2]. We also considered their biological activities which are studied in the literature [3]. Recently, we reported the synthesis of a new vitamin D2 analogue and the evaluation of its biological activity on colon cancer [4]. In the continuation of our work on the analogues of vitamin D, we synthesized two new molecules of calcitriol from an oxolane ring and its side chains [5]. In this study, we present the structure of a new analog of calcitriol with six stereo centers. The crystal structure allowed elucidating the absolute configuration of the stereo centers.

2. Experimental

2.1. Materials and physical methods

Diol and pyridinium dichromate (PDC) were purchased from Aldrich and used without further purification. The IR spectrum was recorded as KBr discs on a Bruker IFS-66 V spectrophotometer (4000-400 cm^{-1}). Mass spectrometry was carried out with a Hewlett Packard 5988A spectrometer. The ^1H and ^{13}C NMR spectra of the compound **1** were recorded in $CDCl_3$ on a BRUKER 500 MHz spectrometer at room temperature using TMS as internal reference.

2.2. Crystal structure determination

Crystallographic data were collected at room temperature using a Bruker Smart 6000 CCD detector and Cu-Kα radiation (λ = 1.54178 Å) generated by a Incoatec microfocus source equipped with Incoatec Quazar MX optics. The software APEX3 [6] was used for collecting frames of data, indexing reflections and the determination of lattice parameters, SAINT [6] for integration of intensity of reflections, and SADABS [6] for scaling and empirical absorption correction. The structure was solved by dual-space methods using the program SHELXT [7].

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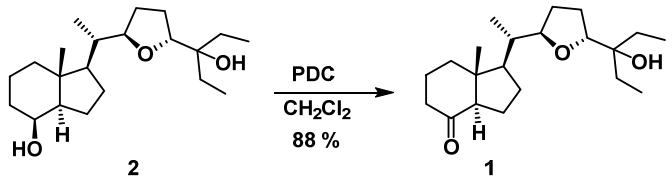

Scheme 1

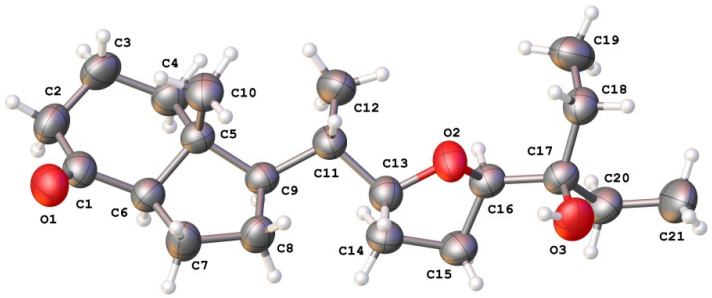

Figure 1. Crystal structure of the compound **1**.

All non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least-squares calculations on F^2 using the program SHELXL [8]. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters except for the hydrogen atom of the hydroxyl group. Drawings were produced with PLATON [9].

2.3. Synthesis of compound 1

To a solution of diol (**2**) (0.18 mmol) in CH_2Cl_2 (5 mL), pyridinium dichromate (PDC) (0.37 mmol) was added and the mixture stirred at room temperature for 12 h, then the solvent was evaporated and the residue was chromatographed on sılica gel using (10%, EtOAc:hexane, *v*:*v*) to afford ketone (**1**) (Scheme 1). The title compound was recrystallized using a mixture of hexane:ethyl ether (1:1, *v*:*v*).

(1R, 3aR, 7aR)-1-((S)-1-((2R, 5S)-5-(3-hydroxypentan-3-yl)tetrahydrofuran-2-yl)ethyl)-7a-methyloctahydro-4H-inden-4-one (**1**): Color: White solid. M.p: 80-82 °C. Yield: 88%. R_f: 0.42 (30%, EtOAc:hexane, *v*:*v*). $[\alpha]_D^{19}$ = +26.27 (c 1.0, $CDCl_3$). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 3.99 (1H, td, *J* = 10.1, 5 Hz, H-5'), 3.81 (1H, dd, *J* = 9.8, 5.7 Hz, H-2'), 2.42 (1H, dd, *J* = 11.2, 7.4 Hz, H-3a), 2.37-1.70 (12H, m, 6 x CH_2) , 1.69-1.24 (9H, m, 3 x CH_2 + H-1 + H-1' + HO), 0.93 (3H, d, *J* = 6.7 Hz, CH_3-21), 0.87 (6H, td, *J* = 7.5, 5.3 Hz, CH_3-Et), 0.66 (3H, s, CH_3-18). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ, ppm): 211.91 (C=O), 83.49 (CH-2'), 81.78 (CH-5'), 74.76 (C-3''), 61.43 (CH-14), 54.23 (CH-17), 50.30 (CH-13), 41.02 (CH_2), 38.94 (CH_2), 38.93 (CH-20), 28.79 (CH_2), 26.91 (CH_2), 26.35 (CH_2), 25.92 (CH_2), 25.89 (CH_2), 24.05 (CH_2), 19.26 (CH_2), 12.69 (CH_3-21), 12.50 (CH_3-18), 7.99 (CH_3-Et), 7.60 (CH_3-Et). IR (NaCl, ν, cm^{-1}): 3491, 3361, 2964, 2879, 2347, 1713, 1460, 1381, 1245, 1145, 958, 890, 755. MS (ESI^+) (*m*/*z*, (%)): 359.25 ($(M^+Na)^+$, 47), 319.26 ($(M-OH)^+$, 100). HRMS (ESI^+): Calculated for $C_{21}H_{36}NaO_3$, 359.25567 g/mol; Found: 359.25562 g/mol.

3. Results and discussion

The compound **1** was prepared by a facile oxidation of compound **2** with pyridinium dichromate in dichloromethane (Scheme 1). Suitable X-ray crystals diffraction was obtained after recrystallization of compound **1** in a mixture of hexane:ethyl ether (1:1, *v*:*v*). The afforded compound is soluble in common organic solvent such as chloroform. The mass spectrum of the compound **1** present a peak at 359.25562 amu corresponding to the molecular ion of $[\mathbf{1}+Na]^+$. The infrared spectrum of the compound shows absorption band pointed at 1713 cm^{-1} which is assigned to the ν(C=O) vibration confirming the oxidation of the secondary alcohol function of compound **2**. In addition the ^{13}C NMR spectrum recorded in deuterated chloroform shows a characteristic signal at δ 211.91 ppm which is assigned to the C=O.

The molecular structure of the title compound is shown in Figure 1. Crystallographic data, selected bond lengths and angles, hydrogen-bond geometry and atomic displacement parameters are listed respectively in Table 1-4. The compound crystallizes in the non-centrosymmetric space group $P2_1$ and the absolute structure was unambiguously established. The molecule contains a cyclopentane ring trans-fused to a cyclohexanone ring. The lateral chain contains an oxolane ring. The cyclohexanone ring adopts a chair conformation. The cyclopentane ring is an envelope (Flap atom = C5) and the tetrahydrofuran ring is twisted about C13-O2. The configurations of the stereogenic centres are C5(*R*), C6(*R*), C9(*R*), C11(*S*), C13(*R*) and C16(*R*). There is an intramolecular O-H···O hydrogen bond involving the hydroxyl group (O3-H3) and an oxolane O atom (O2), generating an S(5) ring motif (Figure 1 and Table 4). The bond lengths and angles are normal and comparable to those observed in compounds containing the bicyclic moiety fragment (1S,3aR,7aR)-1-ethyl-7a-methyl-octahydroinden-4-one); specially in our recent work [10], which concerns an isomer of the title compound, adopting a very similar crystal structure.

In the crystal, weak C2-H2B···O1=C hydrogen bonds (Table 4, Figure 2) link the molecules into C(4) chains, which propagate parallel to [101]. The chains are linked through extremely weak hydrogen bonds. Comparison of the crystal structure with that of the recent isomer we reported [10], shows that the two isomers adopt similar supramolecular architecture: hydrogen bonds linking molecules into chains, which propagate parallel to [101]. In both structures, the chains are linked by very weak H bonds.

Table 1. Crystal data and structure refinement for compound **1**.

Empirical formula	$C_{21}H_{36}O_3$
Formula weight	336.50
Temperature (K)	296(2)
Crystal shape / color	Block/Colorless
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	12.4156(19)
b (Å)	6.3672(6)
c (Å)	12.7186(12)
α (°)	90
β (°)	90.509(5)
γ (°)	90
Volume (Å^3)	1005.4(2)
Z	2
ρ_{calc} (g/cm^3)	1.112
μ (mm^{-1})	0.562
F(000)	372.0
Crystal size (mm^3)	0.111 × 0.107 × 0.053
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection (°)	6.95 to 143.848
Index ranges	$-15 \le h \le 15$, $-7 \le k \le 7$, $-15 \le l \le 15$
Reflections collected	12352
Independent reflections	3777 [R_{int} = 0.0296, R_{sigma} = 0.0278]
Data/restraints/parameters	3777/1/221
Goodness-of-fit on F^2	1.065
Final R indexes [I≥2σ (I)]	R_1 = 0.0370, wR_2 = 0.1009
Final R indexes [all data]	R_1 = 0.0384, wR_2 = 0.1039
Largest diff. peak/hole (e Å^{-3})	0.18/-0.13

Table 2. Bond lengths for compound **1**.

Atom	Atom	Length (Å)	Atom	Atom	Length (Å)
O1	C1	1.213(3)	C7	C8	1.542(3)
O2	C16	1.437(2)	C8	C9	1.551(3)
O2	C13	1.447(3)	C9	C11	1.538(3)
O3	C17	1.431(3)	C11	C12	1.522(4)
C1	C6	1.501(3)	C11	C13	1.540(3)
C1	C2	1.504(3)	C13	C14	1.528(3)
C2	C3	1.519(4)	C14	C15	1.525(3)
C3	C4	1.531(3)	C15	C16	1.519(3)
C4	C5	1.532(3)	C16	C17	1.529(3)
C5	C10	1.539(3)	C17	C20	1.528(3)
C5	C9	1.551(3)	C17	C18	1.531(3)
C5	C6	1.553(3)	C18	C19	1.506(4)
C6	C7	1.514(3)	C20	C21	1.522(4)

Table 3. Bond angles for compound **1**.

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C16	O2	C13	109.87(16)	C5	C9	C8	103.55(16)
O1	C1	C6	123.5(2)	C12	C11	C9	114.17(19)
O1	C1	C2	123.2(2)	C12	C11	C13	111.22(18)
C6	C1	C2	113.3(2)	C9	C11	C13	109.33(17)
C1	C2	C3	113.63(19)	O2	C13	C14	105.57(17)
C2	C3	C4	113.8(2)	O2	C13	C11	110.18(18)
C3	C4	C5	111.88(19)	C14	C13	C11	116.21(18)
C4	C5	C10	110.61(19)	C15	C14	C13	102.53(19)
C4	C5	C9	117.21(17)	C16	C15	C14	101.03(18)
C10	C5	C9	111.04(17)	O2	C16	C15	104.17(17)
C4	C5	C6	106.79(17)	O2	C16	C17	107.87(16)
C10	C5	C6	111.02(18)	C15	C16	C17	118.20(19)
C9	C5	C6	99.50(15)	O3	C17	C20	106.00(18)
C1	C6	C7	119.95(19)	O3	C17	C16	109.04(17)
C1	C6	C5	111.81(17)	C20	C17	C16	109.75(19)
C7	C6	C5	105.13(17)	O3	C17	C18	108.45(18)
C6	C7	C8	103.97(17)	C20	C17	C18	112.73(19)
C7	C8	C9	107.11(16)	C16	C17	C18	110.69(18)
C11	C9	C5	119.18(17)	C19	C18	C17	116.4(2)
C11	C9	C8	112.71(17)	C21	C20	C17	114.7(2)

The title isomer is characterized by the presence of an intramolecular hydrogen bond and the molecules in the chains are linked by weak H bonds. On the contrary, in the previously reported isomer, there is no intramolecular H bond and the molecules in the chains are strongly linked. It should be mentioned that the crystal structure change between the two isomers affected mainly the unit cell lattice, but not the crystal system (monoclinic), nor the space group symmetry ($P2_1$). Indeed, the unit cell volume expands from the precedent isomer to the title isomer (979.3 to 1005.3 Å^3). This expansion resulted from contraction in the *c* parameter and the increase of the *a* parameter, so that the *c*/*a* ratio and the β angle decreased from 1.8° to 1.0° and 104.2 to 90.5 °, respectively. The *b* parameter remains almost unchanged.

4. Conclusion

The titled compound having an oxolane moiety in his side chain was synthesized successfully and its structure has been determined by X-ray single crystallography. One of his stereo-isomer was previously synthetized and reported by our group.

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for compound **1**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	84.8(11)	73.9(11)	58.6(9)	5.9(8)	7.4(8)	-0.2(9)
O2	79.6(10)	49.9(8)	55.5(8)	10.5(7)	15.0(7)	10.9(7)
O3	54.1(8)	99.9(14)	69.2(9)	-1.4(10)	-7.4(7)	-4.6(9)
C1	64.2(12)	50.8(12)	60.3(12)	-0.1(10)	10.6(10)	2.5(9)
C2	55.6(12)	72.6(15)	80.1(15)	2.6(13)	14.0(11)	-3.9(11)
C3	51.9(12)	77.9(16)	90.0(17)	-3.0(14)	3.0(11)	-13.8(12)
C4	53.3(11)	69.7(14)	65.3(12)	-1.8(11)	-4.6(9)	-7.1(11)
C5	47.8(10)	46.6(10)	53.4(10)	1.5(9)	0.0(8)	-1.7(9)
C6	51.2(10)	51.5(11)	55.2(11)	-0.5(9)	2.6(8)	-1.2(9)
C7	55.7(12)	91.1(18)	54.4(11)	-8.7(12)	0.9(9)	-8.4(12)
C8	49.1(10)	72.7(14)	58.0(11)	-1.3(11)	1.9(8)	-6.4(10)
C9	49.4(10)	43.7(10)	51.7(10)	1.9(8)	0.3(8)	-1.2(8)
C10	75.8(15)	50.5(12)	72.4(14)	6.3(10)	10.3(12)	2.8(11)
C11	61.9(12)	45.8(10)	54.2(10)	1.6(9)	6.5(9)	-1.7(9)
C12	87.3(17)	81.1(18)	61.6(13)	-13.9(13)	5.7(12)	-24.3(14)
C13	58.9(11)	53.9(12)	52.3(10)	2.6(10)	5.4(9)	1.4(9)
C14	68.5(13)	47.4(11)	65.8(13)	-4.0(9)	6.2(11)	-2.6(10)
C15	74.0(14)	47.5(11)	62.8(12)	4.5(10)	4.6(10)	-6.5(10)
C16	55(1)	45.3(10)	55.5(10)	7.5(8)	-1.9(8)	-1.2(8)
C17	50.7(10)	52.7(11)	53.2(10)	5.7(9)	-2.6(8)	-4.3(9)
C18	63.8(12)	52.2(11)	63.2(12)	6.4(10)	8(1)	2.4(10)
C19	81.3(17)	70.5(16)	92.6(19)	-22.7(15)	-2.2(14)	-9.7(14)
C20	82.4(16)	56.4(13)	64.6(13)	10.5(11)	5.7(12)	-12.0(12)
C21	116(2)	91(2)	71.2(16)	7.6(16)	25.6(16)	-26.4(19)

Table 5. Hydrogen bonds for compound **1**.

D	H	A	d(D-H) (Å)	d(H-A) (Å)	d(D-A) (Å)	D-H-A (°)
O3	H3	O2	0.82	2.34	2.766(2)	112.6
C2	H2B	O1[1]	0.97	2.55	3.267(4)	130.7

[1] 1-*x*, -1/2+*y*, -*z*.

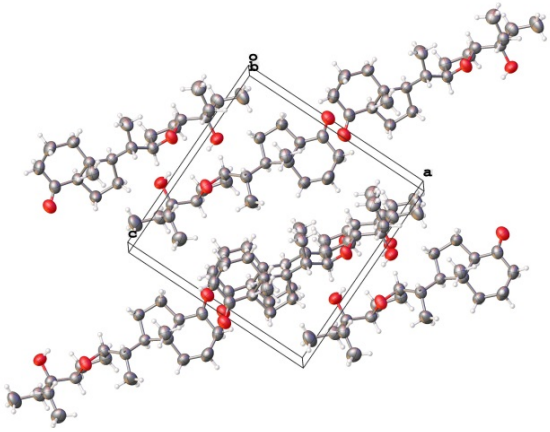

Figure 2. Three dimensional network of compound **1**.

In future, the biological activities of these two calcitriol analogues will be studied.

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Supplementary material

Crystallographic data for the structure reported in this article have been deposited with Cambridge Crystallographic Data Center, CCDC-1555293. The data can be obtained free of charge at http://www.ccdc.cam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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