ORGANIC COMPOUNDS

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The S_P Diastereomer of a Dinucleoside Methylphosphonate Methanol Solvate Containing Thymine and N^3-Methyl-4-thiothymine Bases

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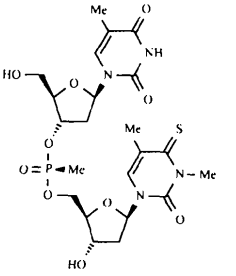
Abstract

The structure of the non-self-complementary dinucleotide analogue (3′-deoxythymidin-3′-yl) (N^3-methyl-4-thio-5′-deoxythymidin-5′-yl) methylphosphonate (1) [1-(3,5-dimethyl-2-oxo-4-thio-1,2,3,4-tetrahydro-1-pyrimidinyl)-2,5-dioxoxy-β-D-ribofuranos-5-yl (5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-2,3-dideoxy-β-D-ribofuranos-3-yl methylphosphonate], Tp(Me)msT, $C_{22}H_{31}N_4O_{10}PS.CH_4O$, has been determined and its absolute configuration at the phosphorus centre shown to be *S*. The 2′-deoxyribose rings of the thymidine and N^3-methyl-4-thiothymidine moieties adopt ${}_3T^2$ (C3′-*exo*/C2′-*endo*) and ${}^2T_3$ (C2′-*endo*/C3′-*exo*) conformations, respectively. Both heterocyclic bases are oriented *anti* relative to the sugar rings. The deoxyribose–phosphonate backbone has an extended conformation with the bases completely unstacked and tilted away from being parallel by 16 (1)°.

Comment

Spectroscopic studies together with molecular-mechanics and molecular-dynamics calculations indicate that an absolute configuration at the phosphorus centre of chiral oligonucleotide analogues can significantly influence stability of the formed duplexes (Bower *et al.*, 1987) and may also modulate some conformational transitions in helical structures (Callahan *et al.*, 1986; Swarna Latha & Yathindra, 1991). The biological activity of chiral oligonucleotide analogues (*e.g.* methylphosphonates) and their potential applications in the antisense strategy for the artificial control of gene expression has stimulated wide interest in this class of compounds (Englisch & Gauss, 1991; Miller, 1989). In contrast, only three solid-state structures of dinucleoside methylphosphonates are known to date, namely S_P-dAp(Me)T (Chacko, Lindner, Saenger & Miller, 1983), R_P-dCp(Me)G (Han *et al.*, 1990) and S_P-Tp(Me)sT (where sT is 4-thiothymidine) (Szabó, Noréus, Norrestam & Stawiński, 1993).

The title compound, (thymidin-3′-yl) (N^3-methyl-4-thiothymidin-5′-yl) methylphosphonate (1), [Tp(Me)msT], was obtained by the condensation of (5′-*O*-*tert*-butyldiphenylsilylthymidin-3′-yl) methylphosphonate (1.67 eq.) with 3′-*O*-*tert*-butyldiphenylsilyl-N^3-methyl-4-thiothymidine (1 eq.) in pyridine using 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane (5 eq.) as coupling reagent and 4-methoxypyridine 1-oxide (5 eq.) as catalyst. The protected R_P and S_P diastereomers were separated by high-performance liquid chromatography (Dynamax silica column) using a linear gradient of ethyl acctate (50–100%) in toluene. Deprotection of the slower eluting isomer (resonating in ^{31}P NMR downfield from the faster eluting isomer) with tetrabutylammonium fluoride in tetrahydrofuran furnished (1) (HRMS: found $M^+ = 575.1550$; $C_{22}H_{32}O_{10}N_4SP$ requires $M = 575.1577$). Crystals were grown from a dilute solution of (1) in methanol. Details of the preparation of (1) will be published elsewhere (Clivio, Fourrey, Szabó & Stawiński, 1994).



(1)

Fig. 1 shows molecule (1) and the labelling scheme used (*cf.* Table 1). The atoms included in the pyrimidine rings are almost coplanar (r.m.s. deviation 0.02 Å) but the substituents C1′*T*, C1′*msT*, O4*T*, S4*msT* and C3*msT* are displaced significantly (0.10–0.13 Å) from the least-squares planes. The effect of 'locking' the tautomeric form of the N^3-methyl-4-thiothymine moiety in (1) does not shorten the C4*msT*—S4*msT* and C2*msT*—O2*msT* bond lengths [1.67 (2) and 1.22 (2) Å, respectively], which are identical to those in the non-*N*-methylated Tp(Me)sT

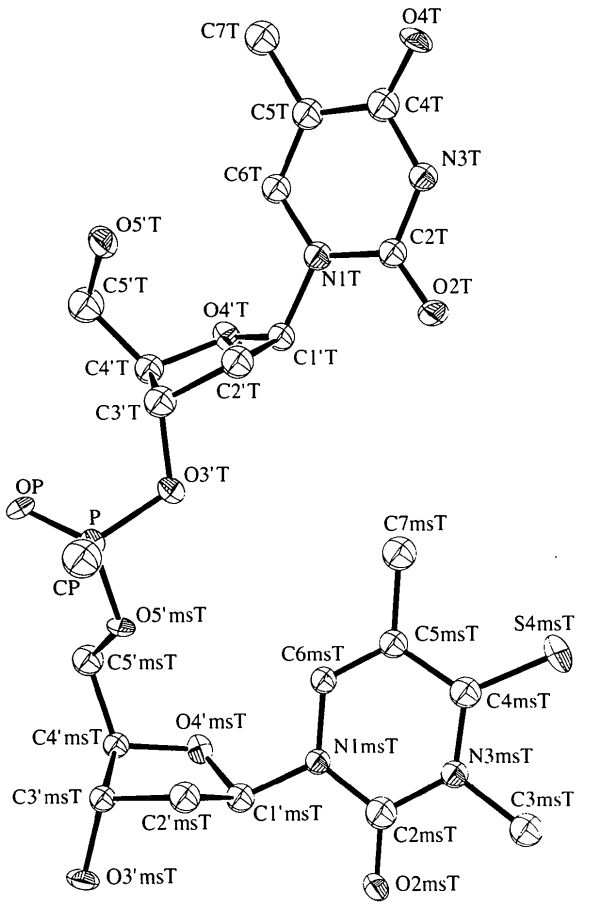


Fig. 1. Displacement ellipsoid plot of the title compound showing the labelling of atoms with ellipsoids drawn at the 50% probability level. H atoms are omitted for clarity.

counterpart (Szabó *et al.*, 1993). This indicates that the thiothymine rings in Tp(Me)sT and in (1) are in the same tautomeric thiono–keto form. The heterocyclic bases are tilted away from being parallel with an angle between the normals to the ring planes of 16 (1)°.

The values of the endocyclic torsion angles together with the pseudorotational parameters (Altona & Sundaralingam, 1972) for the deoxyribose rings of (1) are given in Table 3. Both sugar moieties have *S* conformations but with a different degree of ring puckering. The thymidine deoxyribose is rather flat ($\psi = 22°$, ${}_3T^2$ conformation) with the C2′*T* and C3′*T* atoms displaced from the plane defined by atoms C1′*T*, O4′*T*, C4′*T* by 0.14 (2) (*endo*) and 0.21 (2) Å (*exo*), respectively, while the N^3-methyl-4-thiothymidine deoxyribose moiety is more puckered ($\psi = 40°$, ${}^2T_3$ conformation) and the corresponding displacements of the C2′*msT* and C3′*msT* atoms are 0.55 (2) (*endo*) and 0.09 (2) Å (*exo*), respectively. The large difference in the deoxyribose ring puckering parameters previously found in Tp(Me)sT is preserved in (1). This most likely arises from crystal-packing forces and similarities in hydrogen bonding (see below) in the two crystal structures. The N-glycosidic torsion angles χ in both nucleosidic units are in the *anti* range (Table 3).

The absolute configuration at the phosphorus centre in (1) is *S*. The atoms around this centre form a distorted tetrahedron with bond lengths and angles similar to those found in the crystal structures of the other dinucleoside methylphosphonates (Chacko *et al.*, 1983; Han *et al.*, 1990; Szabó *et al.*, 1993). The compound adopts an extended completely unstacked conformation with a distance between the two anomeric C atoms of 7.71 (2) Å. The torsion angles that characterize the overall geometry of (1) are given in Table 3, together with the corresponding values for the non-*N*-methylated methylphosphonate compound S_P-Tp(Me)sT. Similarities between the two compounds are clearly visible in Fig. 2 where both structures are superimposed (r.m.s. deviation 0.4 Å). The most significant difference is in the values of the α angles [$-111°$ in (1) *versus* $-123°$ in S_P-Tp(Me)sT]. Thus, the torsion angle C5′*msT*—O5′*msT*—P—O*P* in (1) is $\simeq 12°$, causing a staggered conformation with respect to S_P-Tp(Me)sT where the C5′*sT* and the non-esterified phosphonyl O atoms are completely eclipsed (C5′*sT*—O5′*sT*—P—O*P* $\simeq$ 0°). The torsion angles β, γ and δ in (1) are in the typical range for a nucleic acid fragment (Saenger, 1984), while angles α, ε and γ deviate substantially from the standard values and are closer to those found in some nucleic acid analogues with an

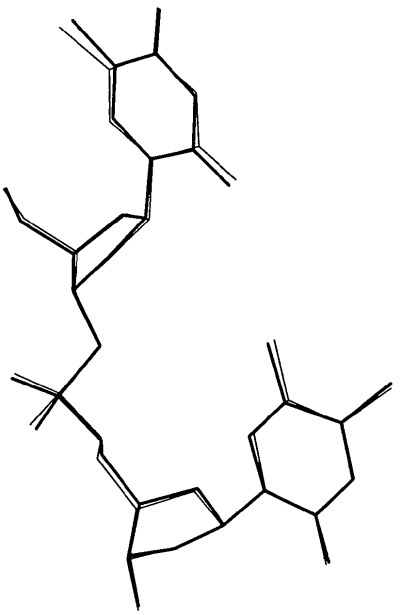


Fig. 2. Superposition of (1) (thick lines) and the S_P-Tp(Me)sT dimer.

extended phosphate-backbone conformation (Cruse *et al.*, 1986; Dickerson, Kopka & Drew, 1982).

Except for the methanol solvent molecule, the patterns of intermolecular hydrogen bonding between the methylphosphonate molecules in the crystal structures of (1) and S_P-Tp(Me)sT (Szabó *et al.*, 1993) are similar (*cf.* Table 4). The methanol C atom is disordered in the crystal lattice with two partially occupied sites, *CM'* 68 (3) and *CM''* 32 (3)%. The most notable differences between (1) and S_P-Tp(Me)sT are obviously due to elimination of one hydrogen-donor centre in the methylphosphonate (1) because of methylation of the N^3 position. The role of the methanol molecule is different in the two crystal structures. In S_P-Tp(Me)sT, the methanol acts as both a hydrogen donor and hydrogen acceptor while in the crystal structure of (1), the methanol molecule only acts as a donor for a bond to the O2*T* atom (Fig. 3). This atom is involved as an acceptor in another hydrogen bond from O5'*T* of an adjacent molecule. In the methylphosphonate S_P-Tp(Me)sT, a similar role as double hydrogen-acceptor centre is played by the phosphonyl O atom, while the O2*T* atom is only involved in a single hydrogen bond involving the O5' atom. Despite different patterns of hydrogen bonding between the phosphonate and the solvent molecule in (1) and S_P-Tp(Me)sT, both structures are very similar. This may indicate that interactions with methanol are of minor importance and do not induce significant conformational changes in the methylphosphonate molecules. All hydrogen bonds are confined within the infinite stacked layers of molecules held together by packing forces of, most likely, van der Waals and/or weaker electrostatic character. In each layer, the methylphosphonate molecules are arranged in an anti-parallel manner with the S atom positioned over the thymine ring of the other molecule with a partial overlap of the C4*T*—O4*T* bond with the N^3-methyl-4-thiothymine ring (*cf.* Fig. 3). It is possible that these hydrophobic interactions, together with intermolecular hydrogen bonds, stabilize the crystal structure of the methylphosphonate (1).

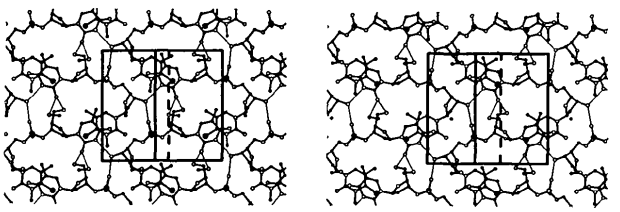


Fig. 3. The crystal structure (H atoms omitted) of the (thymidin-3'-yl) (N^3-methyl-4-thiothymidin-5'-yl) methylphosphonate dimer shown as a stereoview of one layer of molecules viewed perpendicular to the stacking direction. Hydrogen bonds are indicated by thinner lines.

Experimental

The title compound was prepared according to the procedure of Clivio, Fourrey, Szabó & Stawiński (1994) (see *Comment*).

Crystal data

$C_{22}H_{31}N_4O_{10}PS.CH_4O$
M_r = 606.59
Monoclinic
$P2_1$
a = 9.217 (3) Å
b = 13.589 (4) Å
c = 11.237 (3) Å
β = 92.47 (2)°
V = 1406 (1) Å^3
Z = 2
D_x = 1.433 (1) Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 20 reflections
θ = 10.8–23.5°
μ = 0.241 mm^{-1}
T = 173 (1) K
Prismatic
0.49 × 0.22 × 0.05 mm
Yellow

Data collection

Stoe four-circle diffractometer
ω–2θ scans
Absorption correction: none
3003 measured reflections
2480 independent reflections
1164 observed reflections [$I > 5\sigma(I)$]
R_{int} = 0.022
θ_{max} = 25.5°
$h = 0 \rightarrow 11$
$k = -1 \rightarrow 16$
$l = -13 \rightarrow 13$
3 standard reflections
frequency: 360 min
intensity decay: 1.3%

Refinement

Refinement on F
R = 0.044
wR = 0.054
S = 1.76
1164 reflections
275 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F) + 0.0007F^2]$
$(\Delta/\sigma)_{max}$ = 0.1
$\Delta\rho_{max}$ = 0.4 e Å^{-3}
$\Delta\rho_{min}$ = −0.13 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
P	0.3029 (4)	0.2500	0.1781 (3)	0.030 (1)
OP	0.3527 (9)	0.3522 (7)	0.1792 (7)	0.036 (3)
CP	0.1606 (14)	0.2251 (12)	0.0723 (11)	0.044 (4)
O2*T*	−0.0066 (9)	0.0816 (6)	0.6845 (7)	0.032 (3)
C2*T*	−0.0216 (13)	0.1672 (10)	0.7174 (10)	0.023 (3)
N3*T*	−0.1128 (10)	0.1899 (8)	0.8073 (8)	0.024 (4)
C4*T*	−0.1386 (14)	0.2843 (10)	0.8523 (10)	0.031 (3)
O4*T*	−0.2351 (8)	0.2939 (7)	0.9249 (6)	0.034 (3)
C5*T*	−0.0537 (13)	0.3592 (9)	0.8051 (10)	0.028 (3)
C6*T*	0.0375 (13)	0.3387 (10)	0.7166 (10)	0.025 (3)
N1*T*	0.0509 (9)	0.2451 (8)	0.6735 (7)	0.022 (2)
C7*T*	−0.0685 (14)	0.4637 (10)	0.8542 (11)	0.034 (3)
C1'*T*	0.1438 (12)	0.2251 (10)	0.5722 (9)	0.022 (3)
O4'*T*	0.2594 (8)	0.2921 (7)	0.5755 (6)	0.026 (3)
C2'*T*	0.0631 (12)	0.2333 (11)	0.4512 (9)	0.031 (3)
C3'*T*	0.1696 (13)	0.2870 (10)	0.3725 (10)	0.029 (3)
O3'*T*	0.2518 (8)	0.2146 (7)	0.3038 (6)	0.035 (3)
C4'*T*	0.2741 (13)	0.3402 (10)	0.4595 (9)	0.024 (3)
C5'*T*	0.2468 (14)	0.4481 (10)	0.4710 (12)	0.036 (4)
O5'*T*	0.0970 (9)	0.4635 (7)	0.4973 (8)	0.039 (3)

C1′*msT*	0.6094 (13)	−0.0564 (9)	0.1308 (10)	0.024 (3)
O4′*msT*	0.6676 (9)	0.0306 (7)	0.1862 (7)	0.030 (3)
C2′*msT*	0.5101 (14)	−0.0187 (9)	0.0246 (10)	0.028 (3)
C3′*msT*	0.6005 (11)	0.0690 (9)	−0.0143 (9)	0.020 (3)
O3′*msT*	0.7185 (8)	0.0375 (6)	−0.0832 (7)	0.028 (3)
C4′*msT*	0.6592 (12)	0.1099 (9)	0.1031 (9)	0.019 (3)
C5′*msT*	0.5773 (12)	0.1949 (9)	0.1508 (10)	0.027 (3)
O5′*msT*	0.4218 (8)	0.1701 (6)	0.1509 (6)	0.025 (3)
N1*msT*	0.5303 (10)	−0.1103 (8)	0.2200 (8)	0.018 (2)
C2*msT*	0.5427 (14)	−0.2107 (10)	0.2206 (10)	0.029 (3)
O2*msT*	0.6188 (8)	−0.2559 (7)	0.1534 (6)	0.031 (3)
N3*msT*	0.4687 (9)	−0.2572 (8)	0.3109 (7)	0.021 (2)
C3*msT*	0.4963 (14)	−0.3653 (10)	0.3211 (11)	0.031 (3)
C4*msT*	0.3856 (13)	−0.2110 (11)	0.3927 (10)	0.029 (3)
S4*msT*	0.3100 (4)	−0.2740 (4)	0.5018 (3)	0.039 (1)
C5*msT*	0.3713 (13)	−0.1055 (9)	0.3797 (10)	0.024 (3)
C6*msT*	0.4433 (11)	−0.0602 (10)	0.2945 (9)	0.020 (3)
C7*msT*	0.2815 (14)	−0.0483 (10)	0.4641 (11)	0.033 (4)
O*M*	0.0374 (15)	−0.0792 (10)	0.8292 (11)	0.094 (6)
C*M*′	0.1975 (26)	−0.0869 (19)	0.8060 (19)	0.046 (6)
C*M*″	0.1512 (51)	−0.1445 (47)	0.8250 (40)	0.046 (6)

Table 2. *Selected geometric parameters* (Å, °)

C1′*T*—N1*T*	1.479 (13)	N1*T*—C2*T*	1.356 (16)
C2*T*—O2*T*	1.230 (16)	C2*T*—N3*T*	1.377 (15)
N3*T*—C4*T*	1.403 (17)	C4*T*—O4*T*	1.240 (14)
C4*T*—C5*T*	1.401 (18)	C5*T*—C7*T*	1.532 (18)
C5*T*—C6*T*	1.358 (16)	C6*T*—N1*T*	1.368 (17)
C1′*T*—C2′*T*	1.526 (15)	C2′*T*—C3′*T*	1.534 (17)
C3′*T*—O3′*T*	1.479 (15)	C3′*T*—C4′*T*	1.524 (17)
C4′*T*—O4′*T*	1.470 (13)	O4′*T*—C1′*T*	1.401 (15)
C4′*T*—C5′*T*	1.494 (19)	C5′*T*—O5′*T*	1.440 (15)
O3′*T*—P	1.583 (8)	P—O*P*	1.462 (9)
P—C*P*	1.765 (13)	P—O5′*msT*	1.582 (8)
O5′*msT*—C5′*msT*	1.473 (13)	C5′*msT*—C4′*msT*	1.493 (17)
C4′*msT*—O4′*msT*	1.426 (14)	O4′*msT*—C1′*msT*	1.430 (15)
C1′*msT*—C2′*msT*	1.560 (17)	C2′*msT*—C3′*msT*	1.528 (18)
C3′*msT*—O3′*msT*	1.428 (13)	C3′*msT*—C4′*msT*	1.510 (15)
C1′*msT*—N1*msT*	1.461 (15)	N1*msT*—C2*msT*	1.369 (17)
C2*msT*—O2*msT*	1.218 (15)	C2*msT*—N3*msT*	1.398 (15)
N3*msT*—C3*msT*	1.494 (17)	N3*msT*—C4*msT*	1.373 (15)
C4*msT*—S4*msT*	1.672 (13)	C4*msT*—C5*msT*	1.447 (19)
C5*msT*—C7*msT*	1.502 (17)	C5*msT*—C6*msT*	1.338 (16)
C6*msT*—N1*msT*	1.366 (15)		

N1*T*—C1′*T*—O4′*T*	109.0 (9)
O4′*T*—C1′*T*—C2′*T*	108.5 (9)
C2′*T*—C3′*T*—C4′*T*	104.9 (9)
O3′*T*—C3′*T*—C4′*T*	109.1 (9)
C3′*T*—C4′*T*—C5′*T*	114.7 (10)
C5′*T*—C4′*T*—O4′*T*	109.7 (9)
C3′*T*—O3′*T*—P	116.3 (8)
O3′*T*—P—O*P*	112.7 (5)
C*P*—P—O5′*msT*	103.8 (6)
O9—P—C*P*	114.3 (6)
N1*msT*—C1′*msT*—O4′*msT*	107.7 (9)
O4′*msT*—C1′*msT*—C2′*msT*	105.0 (10)
C2′*msT*—C3′*msT*—C4′*msT*	102.5 (9)
O3′*msT*—C3′*msT*—C4′*msT*	109.4 (8)
C3′*msT*—C4′*msT*—C5′*msT*	115.5 (9)
C5′*msT*—C4′*msT*—O4′*msT*	111.4 (9)
N1*T*—C1′*T*—C2′*T*	113.4 (9)
C1′*T*—C2′*T*—C3′*T*	104.4 (9)
C2′*T*—C3′*T*—O3′*T*	109.8 (10)
C3′*T*—C4′*T*—O4′*T*	106.2 (10)
C4′*T*—O4′*T*—C1′*T*	111.4 (8)
C4′*T*—C5′*T*—O5′*T*	109.1 (10)
O3′*T*—P—C*P*	107.6 (5)
O3′*T*—P—O5′*msT*	101.5 (4)
O*P*—P—O5′*msT*	115.7 (5)
P—O5′*msT*—C5′*msT*	121.7 (7)
N1*msT*—C1′*msT*—C2′*msT*	113.3 (10)
C1′*msT*—C2′*msT*—C3′*msT*	99.5 (9)
C2′*msT*—C3′*msT*—O3′*msT*	111.0 (9)
C3′*msT*—C4′*msT*—O4′*msT*	107.5 (10)
C4′*msT*—O4′*msT*—C1′*msT*	109.3 (8)
C4′*msT*—C5′*msT*—O5′*msT*	109.2 (10)

Table 3. *Endocyclic torsion angles and pseudorotational parameters* (°) *of the deoxyribofuranosyl moieties of* (1), *together with torsion angles of the phosphonate–sugar backbone and the N-glycosidic bonds [corresponding values for* S_P-Tp(Me)sT *are included for comparison]*

Designations of torsion angles follow recommendations of the IUPAC–IUB Joint Commission on Biochemical Nomenclature (1983). Thymidine and N^3-methyl-4-thiothymidine are abbreviated as T and msT, respectively.

	Designation	T	msT
C4′–O4′–C1′–C2′	$\nu 0$	−5.7 (13)	−21.4 (11)
O4′–C1′–C2′–C3′	$\nu 1$	17.1 (13)	36.9 (11)
C1′–C2′–C3′–C4′	$\nu 2$	−21.4 (13)	−37.8 (11)
C2′–C3′–C4′–O4′	$\nu 3$	18.5 (13)	27.4 (11)
C3′–C4′–O4′–C1′	$\nu 4$	−8.3 (13)	−3.6 (11)
Pseudorotational phase angle	P	183.5 (22)	167.0 (10)
Degree of ring puckering	ψ	21.9 (8)	40.0 (7)
		(1)	Tp(Me)sT†
O5′*T*–C5′*T*–C4′*T*–C3′*T*	$\gamma(1)$	52.7 (13)	47
C5′*T*–C4′*T*–C3′*T*–O3′*T*	$\delta(1)$	139.5 (10)	139
C4′*T*–C3′*T*–O3′*T*–P	$\varepsilon(1)$	−95.4 (9)	−94
C3′*T*–O3′*T*–P–O5′*msT*	$\zeta(1)$	163.8 (7)	163
O3′*T*–P–O5′*msT*–C5′*msT*	$\alpha(2)$	−110.6 (8)	−123
P–O5′*msT*–C5′*msT*–C4′*msT*	$\beta(2)$	−170.8 (7)	−169
O5′*msT*–C5′*msT*–C4′*msT*–C3′*msT*	$\gamma(2)$	50.8 (12)	55
C5′*msT*–C4′*msT*–C3′*msT*–O3′*msT*	$\delta(2)$	144.5 (10)	145
O4′*T*–C1′*T*–N1*T*–C2*T*	χT	−150.8 (9)	−144
O4′*msT*–C1′*msT*–N1*msT*–C2*msT*	χmsT	−140.4 (10)	−145

† Data from Szabó, Noréus, Norrestam & Stawiński (1993).

Table 4. *Bond distances* (Å) *for the indicated intermolecular hydrogen bonds in the crystal structure of* (1)

D—H···*A*	H···*A*	*D*···*A*
N3*T*—H···O3′*msT*	1.88	2.90
O5′*T*—H···O2*T*	1.74	2.70
O3′*msT*—H···O*P*	1.91	2.81
O*M*—H···O2*T*		2.74

The origin along the polar y axis was defined by keeping the y coordinate of the P atom constant during the structure refinement. The equivalent isotropic displacement parameters of the anisotropically refined S, P and O atoms were estimated as $1/3 \times \text{trace}(U)$. H atoms other than the methanol H atoms were located from $\Delta\rho$ maps and their positions were refined with the (non-H)—H bond distance constrained to 1.00 Å. Program used for structure determination was *SHELXS*86 (Sheldrick, 1985) and that used for structure refinement *SHELX*76 (Sheldrick, 1976).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and interatomic distances within the dimer have been deposited with the IUCr (Reference: LI1104). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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9,11-Secogorgost-5-en-9-one-3β,11-diol, a Marine Steroid from the Sea Whip *Pseudopterogorgia hummelinkii*

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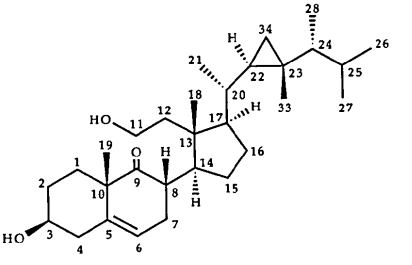
Abstract

The title steroid [(22*R*,23*R*,24*R*)-22,23-methylene-23,24-dimethyl-9,11-secocholest-5-en-9-one-3β,11-diol, $C_{30}H_{50}O_3$], was isolated from *Pseudopterogorgia hummelinkii*, a Caribbean gorgonian. The cyclopropane ring in the side chain of this molecule, a feature very unusual in terrestrial steroids, has been found in several other marine steroids. The molecular structure is potentially very flexible because of the oxidative cleavage of ring *C*, but the two independent molecules in the crystal have quite similar overall conformations. The observed conformational differences correlate with dissimilar participation of the hydroxyl and carbonyl groups of each molecule in hydrogen bonding, which is entirely intermolecular. The crystal structure was solved by direct methods, but only with great difficulty.

Comment

Marine organisms with restricted mobility have evolved a variety of chemical defenses. Novel sterols, with structures having few or no terrestrial counterparts (Djerassi & Silva, 1991), might be among these, although their functions are not well established. As part of a continuing study of bioactive metabolites from marine invertebrates, we investigated the sea whip *Pseudopterogorgia hummelinkii*, a gorgonian octocoral collected in the Caribbean off the coast of Belize. Broadly speaking, the genus *Pseudopterogorgia* is the most highly chemically defended of all Caribbean gorgonians (Pawlik, Burch & Fenical, 1987).

The major polar secondary metabolite of *P. hummelinkii* is 9,11-secogorgost-5-en-9-one-3β,11-diol, (I). Compound (I) was isolated from this gorgonian by homogenization and solvent extraction, followed by chromatography of the crude extract on silica gel. X-ray analysis confirmed the structure proposed on the basis of spectral evidence, primarily NMR.



(I)

Compound (I) was first isolated by Spraggins (1970) from *Pseudopterogorgia americana* (Gmelin). The relationship of (I) to gorgosterol (Hale *et al.*, 1970; Ling, Hale & Djerassi, 1970), which is found in a relatively high proportion in the same species, was unambiguously demonstrated and its absolute configuration determined by an X-ray crystal structure analysis of the prepared 3-(*p*-iodobenzoyl)-11-acetate derivative (Enwall *et al.*, 1972). Our analysis is of the native unsubstituted molecule. The structure is a 9,11-secosteroid (ring *C* opened), and has a cyclopro-