C3A—C10A	1.514 (8)	C3B—C10B	1.530 (8)
C4A—C4aA	1.517 (6)	C4B—C4aB	1.506 (6)
C4A—C11A	1.525 (7)	C4B—C11B	1.517 (7)
C4aA—C5A	1.377 (8)	C4aB—C5B	1.386 (7)
C4aA—C8aA	1.398 (8)	C4aB—C8aB	1.390 (7)
C5A—C6A	1.383 (8)	C5B—C6B	1.389 (8)
C6A—C7A	1.368 (11)	C6B—C7B	1.386 (10)
C7A—C8A	1.386 (11)	C7B—C8B	1.368 (10)
C8A—C8aA	1.384 (8)	C8B—C8aB	1.379 (7)
N2A—C1A—C8aA	122.6 (5)	N2B—C1B—C8aB	121.8 (5)
N2A—C1A—O9A	63.5 (3)	N2B—C1B—O9B	63.8 (4)
C8aA—C1A—O9A	118.7 (5)	C8aB—C1B—O9B	117.2 (5)
C1A—N2A—C3A	114.7 (4)	C1B—N2B—C3B	116.0 (5)
C1A—N2A—O9A	57.2 (3)	C1B—N2B—O9B	58.1 (3)
C3A—N2A—O9A	108.8 (4)	C3B—N2B—O9B	110.3 (4)
N2A—C3A—C4A	115.9 (4)	N2B—C3B—C4B	116.3 (4)
N2A—C3A—C10A	107.2 (4)	N2B—C3B—C10B	107.2 (5)
C4A—C3A—C10A	111.7 (4)	C4B—C3B—C10B	111.4 (5)
C3A—C4A—C4aA	111.6 (4)	C3B—C4B—C4aB	112.9 (4)
C3A—C4A—C11A	111.2 (4)	C3B—C4B—C11B	109.2 (4)
C4aA—C4A—C11A	113.4 (4)	C4aB—C4B—C11B	113.7 (4)
C4A—C4aA—C5A	123.7 (4)	C4B—C4aB—C5B	122.7 (4)
C4A—C4aA—C8aA	118.1 (4)	C4B—C4aB—C8aB	119.0 (4)
C5A—C4aA—C8aA	118.2 (5)	C5B—C4aB—C8aB	118.3 (4)
C4aA—C5A—C6A	120.8 (5)	C4aB—C5B—C6B	120.9 (5)
C5A—C6A—C7A	121.3 (6)	C5B—C6B—C7B	119.5 (6)
C6A—C7A—C8A	118.6 (6)	C6B—C7B—C8B	120.0 (6)
C7A—C8A—C8aA	120.7 (6)	C7B—C8B—C8aB	120.4 (6)
C1A—C8aA—C4aA	119.2 (5)	C1B—C8aB—C4aB	119.4 (5)
C1A—C8aA—C8A	120.3 (5)	C1B—C8aB—C8B	119.6 (5)
C4aA—C8aA—C8A	120.4 (5)	C4aB—C8aB—C8B	120.9 (5)
C1A—O9A—N2A	59.3 (3)	C1B—O9B—N2B	58.2 (3)
C4A—C11A—C12A	120.3 (4)	C4B—C11B—C12B	121.1 (4)
C4A—C11A—C16A	122.0 (4)	C4B—C11B—C16B	120.6 (4)

C8aA—C1A—N2A—C3A	11.4 (5)
C1A—N2A—C3A—C4A	23.2 (4)
N2A—C3A—C4A—C4aA	−46.8 (4)
C3A—C4A—C4aA—C8aA	37.1 (4)
C4A—C4aA—C8aA—C1A	−4.6 (5)
C4aA—C8aA—C1A—N2A	−22.0 (5)
C4aA—C8aA—C1A—O9A	53.3 (5)
C8A—C8aA—C1A—O9A	−129.2 (7)
C4A—C3A—N2A—O9A	−38.5 (4)
C10A—C3A—N2A—O9A	86.9 (5)
C1A—N2A—C3A—C10A	148.7 (6)
C3A—C4A—C11A—C12A	−126.4 (5)
C4aA—C4A—C11A—C16A	−71.9 (5)
C8aB—C1B—N2B—C3B	8.4 (5)
C1B—N2B—C3B—C4B	23.7 (5)
N2B—C3B—C4B—C4aB	−42.8 (4)
C3B—C4B—C4aB—C8aB	30.5 (4)
C4B—C4aB—C8aB—C1B	0.1 (5)
C4aB—C8aB—C1B—N2B	−21.6 (5)
C4aB—C8aB—C1B—O9B	53.0 (5)
C8B—C8aB—C1B—O9B	−124.1 (7)
C4B—C3B—N2B—O9B	−39.8 (4)
C10B—C3B—N2B—O9B	85.6 (5)
C1B—N2B—C3B—C10B	149.0 (6)
C3B—C4B—C11B—C12B	−115.6 (5)
C4aB—C4B—C11B—C16B	−63.5 (5)

For (1), very high thermal motion was observed for the BF$_4$ anion. Isotropic displacement parameters of H atoms were set equal to $1.30 \times U_{eq}$ of the bonded atom. For (2), two large blocks were used in the refinement; thus, the origin of the space group was fixed. Isotropic displacement parameters of H atoms were set equal to $1.10 \times U_{eq}$ of the bonded atom.

For both compounds, data collection: CAD-4 Software (Enraf–Nonius, 1989); data reduction: NONIUS (Riche, 1989); program(s) used to solve structures: SHELXS86 (Sheldrick, 1985); program(s) used to refine structures: SHELX76 (Sheldrick, 1976); molecular graphics: R3M (Riche, 1983), ORTEP (Johnson, 1965); software used to prepare material for publication: ACTACIF (Riche, 1992).

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A 10-Deacetylbaccatin III Derivative: 11,12-Dihydro-7-triethylsilyl-10-deacetylbaccatin III

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Abstract

The title compound (systematic name: 2a,3,4,4a,5,6,7,-8,9,10,11,12,12a,12b-tetradecahydro-6,9,11-trihydroxy-4a,8,13,13-tetramethyl-4-triethylsiloxy-7,11-methano-1H-cyclodeca[3,4]benz[1,2b]oxete-12,12b-diyl 12b-acetate 12-benzoate), $C_{35}H_{52}O_{10}Si$, was obtained from 10-deacetylbaccatin III by the reduction of the C11=C12 double bond of the 13-keto derivative. The saturation of the C11=C12 bond results in a large change in the orientation of the C13—OH hydroxy group. The

distance between this group and the C4 acetyl group decreases leading to a strong hindrance of the hydroxy group, which explains the non-esterification at this position.

Comment

Taxol (paclitaxel) (1*a*), extracted from the bark of the yew tree (*Taxus brevifolia*) (Wani, Taylor, Wall, Coggon & McPhail, 1971), is now available for cancer chemotherapy. This compound and another related derivative, taxotere (docetaxel) (1*b*) (Guéritte-Voegelein *et al.*, 1990), can be obtained by hemisynthesis from a natural molecule, 10-deacetylbaccatin III, (2).
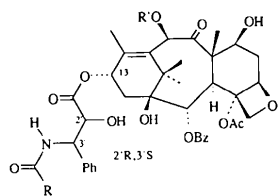
(1*a*) Paclitaxel *R* = Ph, *R'* = Ac
(1*b*) Docetaxel *T* = O^{t}Bu, *R'* = H
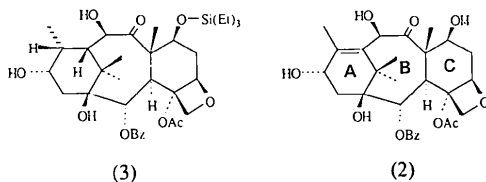
(3) (2)

Study of structure–activity relationships within the taxoid family (Guéritte-Voegelein *et al.*, 1991) provides no information about the influence of the C11═C12 double bond present in the taxane skeleton. In order to verify the importance of this bond on the conformation of the molecule and, by extension, on the biological activity with respect to its receptor, the tubulin-microtubule system (Schiff, Fant & Horwitz, 1979), we prepared 11,12-dihydro-7-triethylsilyl-10-deacetyl-baccatin III, (3), from 10-deacetylbaccatin III in four steps (Marder, Dubois, Guénard, Guéritte-Voegelein & Potier, 1995). The dihydro derivative must be esterified at C13 with a suitable side-chain for a useful evaluation of its binding to tubulin.

The X-ray structure of compound (3) is shown in Fig. 1 with the known absolute configuration and conventional atomic labelling. As expected, the main effect of the saturation of the C11═C12 bond concerns ring *A*, which adopts a chair conformation flattened at C14 [atoms C11 and C14 deviate from the mean plane of the other four atoms by −0.685 (3) and 0.435 (3) Å, respectively], and the hydroxy group at C13, which becomes axial. In taxotere (Guéritte-Voegelein *et al.*, 1990), ring *A* is boat-shaped and the O atom fixing the side-chain

to ring *A* is in an equatorial position. Fig. 2 shows the superimposition of the two molecules according to the *BMFIT* routine (Nyburg, 1974). Fitting of rings *B* and *C* leads to a mean standard deviation of 0.24 Å with large deviations for atoms C10, C11 and C15 (0.37, 0.58 and 0.22 Å, respectively). The best fit is obtained by selecting atoms C1–C9 and adding atoms C20 and O5 of the oxetane ring (mean e.s.d. = 0.09 Å). In this case, atoms
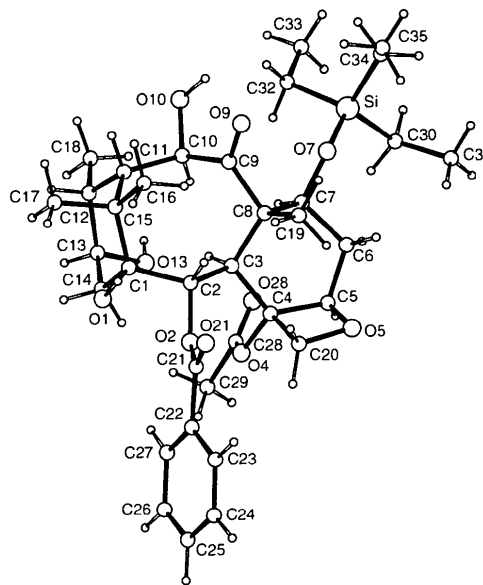

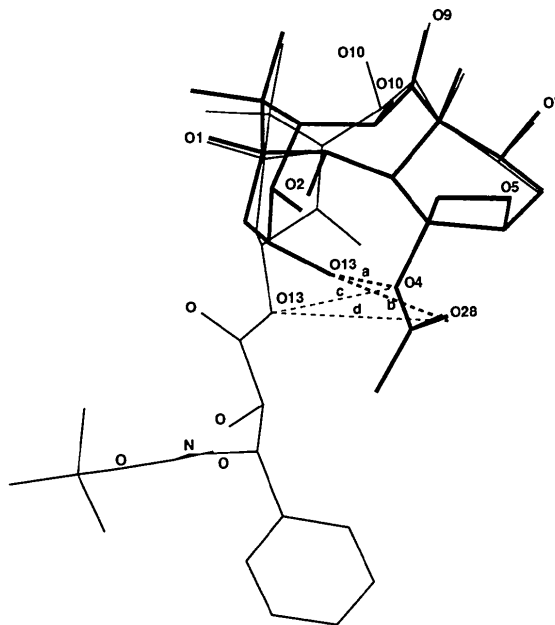Fig. 1. Perspective view of (3) showing the atom labelling.

Fig. 2. Superimposition of (3) (bold) and taxotere showing the differences in the orientation of O13. Selected contacts: in (3) *a* = 3.445 (3), *b* = 2.879 (4); in taxotere *c* = 4.457, *d* = 3.898 Å.

of ring A are more or less separated: C13 0.169, C14 0.328, C15 0.372 Å, with maximum deviations of 0.676 for C11 and 1.094 Å for C12. Consequently, as can be seen clearly in Fig. 2, the distances between atom O13 and the atoms of the acetyl group at C4 are decreased [O13···O28 2.879 (4), O13···O4 3.445 (4) Å] compared with the analogous distances in taxotere [3.898 (7) and 4.457 (9) Å, respectively]. However, the O13—H group does not form any hydrogen bonds, either intramolecularly or with neighbouring molecules in the crystal. The only hydrogen bonds present involve the O1—H group linking the nearest molecule [O1—H···O28($x-1$, y, z) 2.879 (5), H···O 2.01 Å, O—H···O 144°] and the O10—H group establishing an intramolecular hydrogen bond with atom O9 [O10—H···O9 2.618 (5), H···O 2.05 Å, O—H···O 114°]. The large steric hindrance around the O13—H hydroxy group explains the absence of esterification at this position, which eventually could be performed by removing the 4-acetyl group.

Experimental

Crystallization of the compound was performed by dissolving the crude material in methanol and adding 30% water.

Crystal data

$C_{35}H_{52}O_{10}Si$
$M_r = 660.88$
Orthorhombic
$P2_12_12_1$
$a = 8.517 (6)$ Å
$b = 15.512 (9)$ Å
$c = 25.925 (14)$ Å
$V = 3425 (4)$ Å^3
$Z = 4$
$D_x = 1.28$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 25 reflections
$\theta = 12.0–21.1°$
$\mu = 1.04$ mm^{-1}
$T = 293$ K
Prism
$0.56 \times 0.16 \times 0.10$ mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
3862 measured reflections
3749 independent reflections
3206 observed reflections
$[I > 3\sigma(I)]$

$R_{int} = 0.023$
$\theta_{max} = 64.91°$
$h = -5 \rightarrow 10$
$k = 0 \rightarrow 18$
$l = 0 \rightarrow 30$
3 standard reflections
frequency: 60 min
intensity decay: 2.5%

Refinement

Refinement on F
$R = 0.041$
$wR = 0.056$
$S = 0.96$
3193 reflections
181 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F) + 0.0006F^2]$

$(\Delta/\sigma)_{max} = 0.01$
$\Delta\rho_{max} = 0.29$ e Å^{-3}
$\Delta\rho_{min} = -0.36$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from International Tables for X-ray Crystallography (1974, Vol. IV, Table 2.2B)

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

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

	x	y	z	U_{eq}/U_{iso}
C1	0.2608 (3)	0.6456 (2)	0.5862 (1)	0.030 (3)
C2	0.3195 (4)	0.5599 (2)	0.6123 (1)	0.028 (3)
C3	0.4819 (3)	0.5564 (2)	0.6395 (1)	0.025 (3)
C4	0.5703 (4)	0.4720 (2)	0.6253 (1)	0.029 (3)
C5	0.6927 (4)	0.4325 (2)	0.6621 (1)	0.038 (3)
C6	0.7260 (4)	0.4764 (2)	0.7130 (1)	0.044 (3)
C7	0.6519 (4)	0.5650 (2)	0.7188 (1)	0.031 (3)
C8	0.4763 (4)	0.5684 (2)	0.6997 (1)	0.028 (3)
C9	0.4229 (4)	0.6594 (2)	0.7159 (1)	0.033 (3)
C10	0.4734 (4)	0.7371 (2)	0.6845 (1)	0.038 (3)
C11	0.3557 (4)	0.7731 (2)	0.6429 (1)	0.038 (3)
C12	0.4448 (5)	0.8132 (2)	0.5968 (2)	0.045 (4)
C13	0.4959 (4)	0.7478 (2)	0.5565 (1)	0.042 (3)
C14	0.3715 (4)	0.6795 (2)	0.5433 (1)	0.038 (3)
C15	0.2127 (4)	0.7191 (2)	0.6236 (1)	0.036 (3)
C16	0.1096 (4)	0.6867 (3)	0.6680 (1)	0.048 (4)
C17	0.1031 (5)	0.7820 (2)	0.5940 (2)	0.054 (4)
C18	0.5783 (6)	0.8745 (3)	0.6119 (2)	0.071 (5)
C19	0.3784 (4)	0.5020 (2)	0.7293 (1)	0.037 (3)
C20	0.4857 (4)	0.3857 (2)	0.6303 (1)	0.038 (3)
O1	0.1239 (3)	0.6199 (1)	0.5571 (1)	0.039 (2)
O2	0.3237 (2)	0.4983 (1)	0.5701 (1)	0.030 (2)
O4	0.6304 (3)	0.4797 (2)	0.5729 (1)	0.033 (2)
O5	0.5951 (3)	0.3551 (1)	0.6685 (1)	0.048 (3)
O7	0.6569 (3)	0.5880 (2)	0.7717 (1)	0.043 (2)
O9	0.3560 (3)	0.6708 (2)	0.7564 (1)	0.050 (3)
O10	0.5037 (4)	0.8055 (2)	0.7197 (1)	0.061 (3)
O13	0.6367 (3)	0.7018 (2)	0.5711 (1)	0.055 (3)
C21	0.2037 (4)	0.4413 (2)	0.5662 (1)	0.037 (3)
O21	0.1008 (3)	0.4338 (2)	0.5974 (1)	0.049 (3)
C22	0.2213 (4)	0.3864 (2)	0.5198 (1)	0.041 (3)
C23	0.1491 (6)	0.3073 (3)	0.5190 (2)	0.067 (5)
C24	0.1653 (8)	0.2523 (3)	0.4779 (2)	0.095 (7)
C25	0.2521 (7)	0.2771 (4)	0.4362 (2)	0.097 (7)
C26	0.3243 (7)	0.3539 (4)	0.4361 (2)	0.100 (7)
C27	0.3143 (6)	0.4098 (3)	0.4783 (2)	0.070 (5)
C28	0.7646 (4)	0.5248 (2)	0.5664 (1)	0.038 (3)
O28	0.8337 (3)	0.5596 (2)	0.6011 (1)	0.043 (2)
C29	0.8138 (5)	0.5235 (3)	0.5113 (2)	0.060 (4)
Si	0.7999 (1)	0.6346 (1)	0.8046 (1)	0.056 (1)
C30	0.9897 (5)	0.5745 (3)	0.7982 (2)	0.069 (5)
C31	0.9997 (7)	0.4865 (4)	0.8230 (2)	0.101 (7)
C32	0.8320 (6)	0.7469 (3)	0.7791 (2)	0.082 (6)
C33	0.9720 (7)	0.7933 (4)	0.8019 (3)	0.102 (7)
C34	0.7235 (7)	0.6339 (7)	0.8709 (2)	0.164 (13)
C35	0.5914 (12)	0.6147 (8)	0.8867 (3)	0.208 (18)
HO1	0.04988	0.60408	0.58549	0.042
HO10	0.46778	0.78781	0.75485	0.067
HO13	0.72151	0.74441	0.57887	0.061

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

C1—C2	1.573 (4)	C12—C18	1.532 (6)
C1—C14	1.550 (4)	C13—C14	1.537 (5)
C1—C15	1.550 (4)	C13—O13	1.445 (4)
C1—O1	1.446 (4)	C15—C16	1.533 (5)
C2—C3	1.554 (4)	C15—C17	1.553 (5)
C2—O2	1.454 (3)	C20—O5	1.441 (4)
C3—C4	1.556 (4)	O2—C21	1.356 (4)
C3—C8	1.572 (4)	O4—C28	1.350 (4)
C4—C5	1.540 (4)	O7—Si	1.652 (3)
C4—C20	1.525 (4)	C21—O21	1.198 (4)
C4—O4	1.458 (4)	C21—C22	1.480 (5)
C5—C6	1.511 (5)	C22—C23	1.374 (6)
C5—O5	1.469 (4)	C22—C27	1.384 (6)
C6—C7	1.520 (4)	C23—C24	1.372 (7)
C7—C8	1.576 (4)	C24—C25	1.366 (9)
C7—O7	1.420 (4)	C25—C26	1.341 (9)
C8—C9	1.541 (4)	C26—C27	1.400 (7)

C8—C19	1.531 (4)	C28—O28	1.203 (4)
C9—C10	1.518 (4)	C28—C29	1.489 (5)
C9—O9	1.209 (4)	Si—C30	1.873 (5)
C10—C11	1.574 (5)	Si—C32	1.882 (5)
C10—O10	1.423 (4)	Si—C34	1.839 (6)
C11—C12	1.546 (5)	C30—C31	1.512 (7)
C11—C15	1.560 (5)	C32—C33	1.513 (8)
C12—C13	1.520 (5)	C34—C35	1.234 (12)

C2—C1—C14	113.7 (2)	C11—C12—C18	114.7 (3)
C2—C1—C15	115.9 (2)	C13—C12—C18	112.1 (3)
C2—C1—O1	104.4 (2)	C12—C13—C14	114.6 (3)
C14—C1—C15	111.1 (2)	C12—C13—O13	112.8 (3)
C14—C1—O1	102.1 (2)	C14—C13—O13	106.9 (3)
C15—C1—O1	108.4 (2)	C1—C14—C13	119.5 (3)
C1—C2—C3	120.5 (2)	C1—C15—C11	112.9 (3)
C1—C2—O2	103.8 (2)	C1—C15—C16	112.3 (3)
C3—C2—O2	107.3 (2)	C1—C15—C17	108.2 (3)
C2—C3—C4	110.7 (2)	C11—C15—C16	112.5 (3)
C2—C3—C8	114.8 (2)	C11—C15—C17	106.9 (3)
C4—C3—C8	110.4 (2)	C16—C15—C17	103.4 (3)
C3—C4—C5	121.1 (2)	C4—C20—O5	92.4 (2)
C3—C4—C20	119.3 (2)	C2—O2—C21	117.8 (2)
C3—C4—O4	108.7 (2)	C4—O4—C28	117.2 (2)
C5—C4—C20	85.4 (2)	C5—O5—C20	91.1 (2)
C5—C4—O4	111.9 (2)	C7—O7—Si	129.1 (2)
C20—C4—O4	108.5 (2)	O2—C21—O21	124.3 (3)
C4—C5—C6	119.2 (3)	O2—C21—C22	111.1 (3)
C4—C5—O5	90.7 (2)	O21—C21—C22	124.5 (3)
C6—C5—O5	112.1 (3)	C21—C22—C23	118.8 (3)
C5—C6—C7	114.6 (3)	C21—C22—C27	122.6 (3)
C6—C7—C8	113.2 (2)	C23—C22—C27	118.6 (4)
C6—C7—O7	108.1 (2)	C22—C23—C24	121.5 (4)
C8—C7—O7	108.9 (2)	C23—C24—C25	119.7 (5)
C3—C8—C7	106.2 (2)	C24—C25—C26	120.0 (6)
C3—C8—C9	112.7 (2)	C25—C26—C27	121.4 (5)
C3—C8—C19	115.8 (2)	C22—C27—C26	118.8 (4)
C7—C8—C9	103.0 (2)	O4—C28—O28	123.5 (3)
C7—C8—C19	109.7 (2)	O4—C28—C29	110.6 (3)
C9—C8—C19	108.6 (2)	O28—C28—C29	125.9 (3)
C8—C9—C10	119.9 (3)	O7—Si—C30	111.9 (2)
C8—C9—O9	120.6 (3)	O7—Si—C32	109.4 (2)
C10—C9—O9	118.9 (3)	O7—Si—C34	102.6 (3)
C9—C10—C11	117.9 (3)	C30—Si—C32	107.7 (2)
C9—C10—O10	107.4 (3)	C30—Si—C34	112.6 (3)
C11—C10—O10	107.0 (3)	C32—Si—C34	112.6 (3)
C10—C11—C12	111.1 (3)	Si—C30—C31	117.5 (3)
C10—C11—C15	121.8 (3)	Si—C32—C33	114.7 (4)
C12—C11—C15	110.6 (3)	Si—C34—C35	129.4 (7)
C11—C12—C13	113.7 (3)		

C15—C1—C2—C3	−71.6 (3)	C12—C13—C14—C1	−35.3 (3)
C1—C2—C3—C8	97.7 (3)	C13—C14—C1—C15	37.9 (3)
C2—C3—C8—C9	−66.5 (3)	C8—C3—C4—C5	−25.0 (2)
C3—C8—C9—C10	−36.8 (3)	C3—C4—C5—C6	0.5 (3)
C8—C9—C10—C11	96.9 (3)	C4—C5—C6—C7	−9.5 (3)
C9—C10—C11—C15	−15.9 (3)	C5—C6—C7—C8	44.1 (3)
C10—C11—C15—C1	−74.8 (3)	C6—C7—C8—C3	−68.3 (3)
C11—C15—C1—C2	82.9 (3)	C7—C8—C3—C4	55.4 (3)
C14—C1—C15—C11	−48.8 (3)	C20—C4—C5—O5	−5.2 (3)
C1—C15—C11—C12	58.4 (3)	C4—C5—O5—C20	5.5 (3)
C15—C11—C12—C13	−54.6 (3)	C5—O5—C20—C4	−5.6 (3)
C11—C12—C13—C14	42.8 (3)	O5—C20—C4—C5	5.3 (3)

The H atoms of methyl group C29 are disordered: two positions with occupancy factors of 0.5 were found. In each position one H atom eclipses O28 or O4, respectively. The isotropic displacement parameters of the H atoms are equal to $1.10U_{eq}$ of the bonded atom.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Data reduction: *NONIUS* (Riche, 1989). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1976). Program(s) used to refine structure: *SHELX*76 (Sheldrick, 1985). Molecular graphics: *R3M* (Riche,1983); *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *ACTACIF* (Riche, 1992).

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O-Methyl-4,5,6,7-tetrahydroisoxazolo-[4,5-*c*]pyridin-3-ol Hydrochloride, *O*-Me-THPO.HCl

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Abstract

In the title compound (3-methoxy-4,5,6,7-tetrahydro-isoxazolo[4,5-*c*]pyridinium chloride, $C_7H_{11}N_2O_2^+.Cl^-$) the isoxazole ring is planar and the methoxy group