Acta Crystallographica Section C
**Crystal Structure Communications**
ISSN 0108-2701

# Simvastatin

**Jan Čejka,[a] Bohumil Kratochvíl,[a] Ivana Císařová[b] and Alexandr Jegorov[c]***

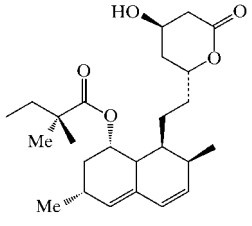
[a]Department of Solid State Chemistry, Prague Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic, [b]Department of Inorganic Chemistry, Charles University, 128 43 Prague 2, Czech Republic, and [c]IVAX Pharmaceuticals sro, Research Unit, Branišovská 31, 370 05 České Budějovice, Czech Republic
Correspondence e-mail: alexandr_jegorov@ivax-cr.com

Received 10 April 2003
Accepted 5 June 2003
Online 12 July 2003

Simvastatin, or (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-hydroxy-6-oxo-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate, $C_{25}H_{38}O_5$, is almost isostructural with lovastatin, and the general conformational features are closely related to those of other reported crystal structures of statins. The only hydrogen bond present facilitates the formation of infinite chains of molecules along the *b* axis.

## Comment

Hypercholesteromia is known to be a primary risk factor for coronary artery disease. In humans, 50% or more of the total body cholesterol is derived from *de novo* synthesis and so the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (EC 1.1.1.34) catalysing a rate-limiting step in cholesterol biosynthesis is a prime target for pharmacological intervention. Originally, the potent competitive inhibitors of HMG-CoA reductase were isolated from various fungi, for example, lovastatin (mevinolin or monacolin K) or mevastatin (ML 236B or compactin), but now a number of semisynthetic or synthetic derivatives are also available (Endo & Hasumi, 1993). The aim of the present work is to compare the structure




(I)

of the novel semisynthetic derivative simvastatin, (I), with the structures of three related HMG-CoA reductase inhibitors, namely lovastatin, (II) (Sato *et al.*, 1984), mevastatin, (III) (Brown *et al.*, 1976), and mevastatin metabolite, (IV) (which corresponds to pravastatin in its lactone form; Haruyama *et al.*, 1986). Besides these compounds, the structures of 6(*S*)-epimevinolin-4-*p*-nitrobenzoate (Stokker *et al.*, 1986) and dihydromevinolin (Albers-Schönberg *et al.*, 1981) have also been reported.

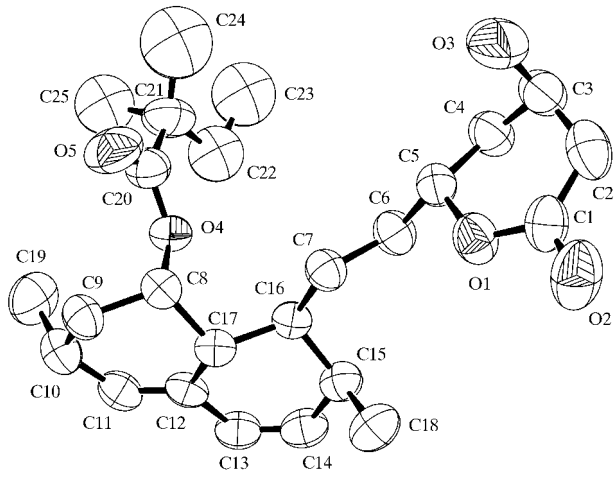



**Figure 1**
An *ORTEP*-3 (Farrugia, 1997) drawing of (I), showing the atom-numbering scheme for non-H atoms and displacement ellipsoids at the 50% probability level. H atoms have been omitted for clarity.

A view of (I), with the atomic numbering scheme, is shown in Fig. 1. The molecular packing (Fig. 2) is based on only one hydrogen bond, *viz*. O3—H531···O5($1-x$, $y+\frac{1}{2}$, $\frac{1}{2}-z$),

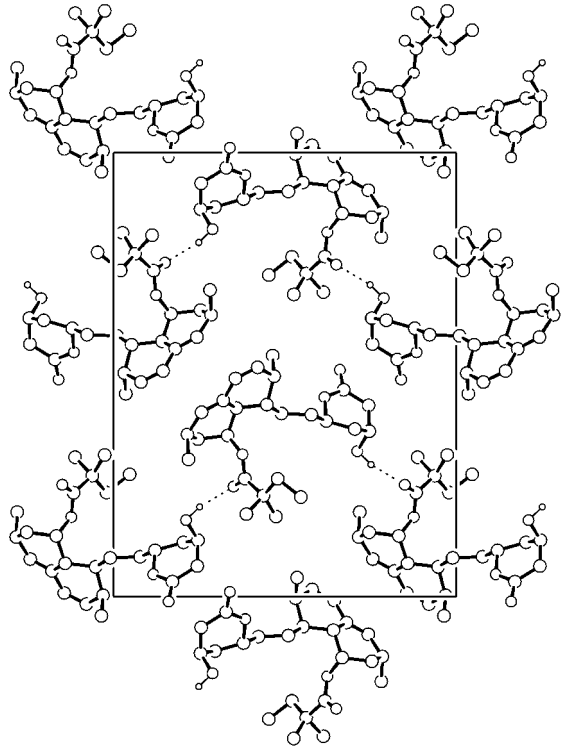


**Figure 2**
The packing diagram of (I) (*ORTEP*-3; Farrugia, 1997), viewed along the *a* axis. The *b* axis is to the right and the *c* axis points upwards.

  DOI: 10.1107/S0108270103012514 

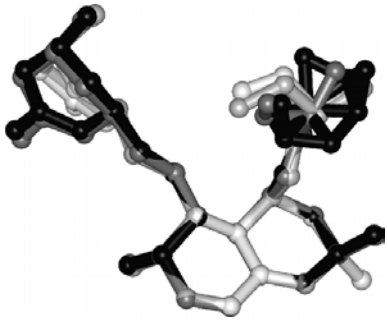


**Figure 3**
A superposition of molecules of (I)–(IV) (fit based on fused rings to reveal differences in side chains). Key: (I) is black, (II) is dark grey, (III) is grey and (IV) is light grey.

which facilitates the formation of infinite chains along the *b* axis.

In order to investigate the chemical relationship of compounds (I)–(IV), we have compared (I) with the three previously known related structures. Despite the expected effect of an additional methyl group on the side chain, (I) and (II) are isostructural. Surprisingly, (III) is not isostructural with (I) and (II) but is isostructural with (IV). Conformational analysis of the fused rings revealed that there are only subtle differences in conformation. The C8–C12/C17 rings adopt approximate $^{1}H_{2}$ half-chair conformations and the C12–C17 rings adopt approximate $^{5}H_{6}$ half-chair conformations (Table 1). Another interesting part of the analysis concerns the flexible chains. Despite the expected differences in the directions of the side chains, the molecules are very similar to one another (Fig. 3). The values of the C17—C8—O4—C20 and C17—C16—C7—C6 torsion angles characterizing the directions of the chains vary in the ranges 141.4–159.2 and −173.5–178.4°, respectively (Table 2).

## Experimental

To a solution of simvastatin (1.1 g) in acetone (3.5 ml) was added *n*-heptane (6.5 ml). The mixture was allowed to stand overnight and the resulting crystals were washed with *n*-heptane.

*Crystal data*

$C_{25}H_{38}O_5$
$M_r$ = 418.57
Orthorhombic, $P2_12_12_1$
$a$ = 6.1283 (3) Å
$b$ = 17.2964 (7) Å
$c$ = 22.4659 (6) Å
$V$ = 2381.33 (16) Å$^3$
$Z$ = 4
$D_x$ = 1.167 Mg m$^{-3}$
Mo $K\alpha$ radiation
Cell parameters from 10 477 reflections
$\theta$ = 1–25°
$\mu$ = 0.08 mm$^{-1}$
$T$ = 293 K
Needle, white
0.36 × 0.14 × 0.08 mm

*Data collection*

Enraf–Nonius KappaCCD diffractometer
$\varphi$ and $\omega$ scans
4673 measured reflections
2692 independent reflections
2281 reflections with $I > 1.96\sigma(I)$
$R_{int}$ = 0.03
$\theta_{max}$ = 26.0°
$h = -7 \rightarrow 7$
$k = -21 \rightarrow 21$
$l = -27 \rightarrow 27$

*Refinement*

Refinement on $F$
$R$ = 0.072
$wR$ = 0.084
$S$ = 1.12
2281 reflections
267 parameters
H-atom parameters constrained
Weighting method: Prince modified Chebychev polynomial (Prince, 1982; Watkin, 1994)
$W$ = weight × $\{1 - [(\delta F/6)\sigma F]^2\}$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.44 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.28 e Å$^{-3}$

**Table 1**
Cremer & Pople (1975) puckering parameters (Å, °) for rings *A* (C8–C12/C17) and *B* (C12–C17).

| Compound† | Ring *A* | | | Ring *B* | | |
|---|---|---|---|---|---|---|
| | $\varphi$ | $\theta$ | $Q$ | $\varphi$ | $\theta$ | $Q$ |
| (I) | 19.4 (5) | 48.7 (4) | 0.440 (3) | −103.3 (4) | 52.9 (3) | 0.468 (3) |
| (II) | 18.9 | 49.0 | 0.447 | −108.0 | 51.5 | 0.475 |
| (III) | 22.4 | 48.3 | 0.468 | 111.3 | 51.6 | 0.473 |
| (IV) | 19.9 | 47.2 | 0.443 | −109.1 | 53.1 | 0.480 |

† (I): this work; (II): Sato *et al.* (1984); (III): Brown *et al.* (1976); (IV): Haruyama *et al.* (1986).

**Table 2**
Torsion angles (°) of flexible residues.

| Compound† | C17—C8—O4—C20 | C17—C16—C7—C6 |
|---|---|---|
| (I) | −159.2 | −170.3 |
| (II) | −154.4 | −173.5 |
| (III) | −141.4 | 178.8 |
| (IV) | −141.8 | 178.4 |

† (I): this work; (II): Sato *et al.* (1984); (III): Brown *et al.* (1976); (IV): Haruyama *et al.* (1986).

The flexible acid residue was disordered and was modelled as two optional rotated parts, namely C22/C23/C24/C25 (occupancy $\frac{2}{3}$) and C32/C33/C34/C35 (occupancy $\frac{1}{3}$). Restraints of 1.550 (5) Å were applied to the interatomic distances of the minor disordered form. Atom H531, which is involved in the hydrogen-bond network, was located from Fourier maps and was refined with a fixed position. The remaining H atoms were placed in calculated positions and refined as riding on their attached C atoms, with C—H distances of 1.0 Å.

Data collection: *COLLECT* (Nonius, 1997–2001); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 2001); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *CRYSTALS*.

This work was partially supported by the Ministry of Education, Youth and Sports of the Czech Republic (research project CEZ:MSM 223100002) and the Grant Agency of the Czech Republic (projects No. 203/02/0436 and No. 203/99/M037).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1633). Services for accessing these data are described at the back of the journal.

## References


Albers-Schönberg, G., Joshua, H., Lopez, M. B., Hensens, O. D., Springer, J. P., Chen, J., Ostrove, S., Hoffman, C. H., Alberts, A. W. & Patchett, A. A. (1981). *J. Antibiot.* **34**, 507–512.

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Brown, A. G., Smale, T. C., King, T. J., Hasenkamp, R. & Thompson, R. H. (1976). *J. Chem. Soc. Perkin Trans.* 1, pp. 1165–1170.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Endo, A. & Hasumi, K. (1993). *Nat. Prod. Rep.* pp. 541–550.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Haruyama, H., Kuwano, H., Kinoshita, T., Terahara, A., Nishigaki, T. & Tamura, C. (1986). *Chem. Pharm. Bull.* **34**, 1459–1467.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Prince, E. (1982). In *Mathematical Techniques in Crystallography and Materials Science*. New York: Springer-Verlag.

Sato, S., Hata, T., Tsujita, Y., Terahara, A. & Tamura, C. (1984). *Cryst. Struct. Commun.* **40**, 195–198.

Stokker, G. E., Rooney, C. S., Wiggins, J. M. & Hirshfield, J. (1986). *J. Org. Chem.* **51**, 4931–4934.

Watkin, D. J. (1994). *Acta Cryst.* A**50**, 411–437.

Watkin, D. J., Prout, C. K., Carruthers, J. R., Betteridge, P. W. & Cooper, R. I. (2001). *CRYSTALS*. Issue 11. Chemical Crystallography Laboratory, Oxford, England.