Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Vinyl sulfones

Jessica H. Wong, Marilyn M. Olmstead,* James C. Fettinger and Jacquelyn Gervay-Hague

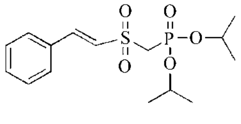
Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, USA
Correspondence e-mail: olmstead@chem.ucdavis.edu

Received 23 January 2008
Accepted 24 January 2008
Online 9 February 2008

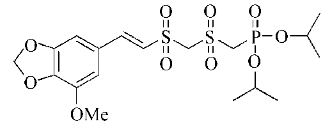
Four neutral vinyl sulfones, two of which are paired with phosphonate groups, are described. The compounds are diisopropyl (2-phenylethenylsulfonylmethyl)phosphonate, $C_{15}H_{23}O_5PS$, (I), diisopropyl {[2-(7-methoxy-1,3-benzodioxol-5-yl)ethenylsulfonyl]methylsulfonylmethyl}phosphonate, $C_{18}H_{27}O_{10}PS_2$, (II), bis(*trans*-2-phenylethenyl) sulfone, $C_{16}H_{14}O_2S$, (III), and bis(*trans*-2-phenylethenylsulfonyl) methane, $C_{17}H_{16}O_4S_2$, (IV). Their structures can be considered as highly functionalized mimics of mono-, di- and triphosphates. These phosphate isosteres are currently of interest as agents for enzyme inhibition in both cancer and HIV therapy. All except one of the compounds has $Z' > 1$. The lone exception is (IV), a disulfone with twofold crystallographic symmetry. Geometrically, the sulfone functionality is found to be a good mimic for phosphate. The principal effect of the vinyl group is to shorten the S—C(vinyl) distance relative to the S—CH_2 distance by *ca* 0.05 Å. The S—C—S and S—C—P backbones resemble the P—O—P backbone but are not identical because the S—C and P—C distances are longer than the P—O distance and the S—C—S and S—C—P angles are more acute than the P—O—P angle. No prior crystal structures of comparable compounds have been published.

Comment

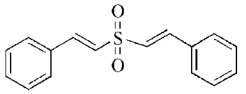
Recent investigations have focused on the replacement of phosphate backbones with phosphate mimics that possess several desirable characteristics. For example, when the bridging O atom of the phosphate is replaced with a methylene unit, greater stability towards hydrolysis is achieved. Replacement of the P atom with sulfur and oxidation to the sulfone maintains metallophilicity, which is of potential importance in inhibition that involves metalloenzymes. The noncharged nature of the sulfone improves cellular penetration over ionizable mimics such as L-chicoric acid (Hadd *et al.*, 2001; Meadows *et al.*, 2005; Meadows & Gervay-Hague, 2006*a*). The vinyl sulfone groups in the compounds reported in this study, (I)–(IV), have been shown to be an important class of antivirals, with the possibility for covalent attachment (Meadows & Gervay-Hague, 2006*b*; Meadows *et al.*, 2007). As part of these ongoing inhibition studies, we previously reported the structures of the saturated phosphonate monosulfone diisopropyl (diisopropoxyphosphorylmethylsulfonylmethyl)phosphonate (Wong, Olmstead & Gervay-Hague, 2007) and the disulfone diisopropyl (diisopropoxyphosphorylmethylsulfonylmethylsulfonylmethyl)phosphonate (Wong, Olmstead, Fettinger & Gervay-Hague, 2007) reagents, which are the starting materials for the title compounds.



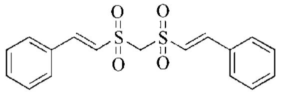
(I)



(II)



(III)



(IV)

Selected bond lengths for (I)–(IV) are given in Tables 1–4, and a summary of selected bond distances and angles in (I)–(IV) is presented in Table 5. The bonds between the S and the vinyl C atoms are systematically shorter [average 1.741 (4) Å] than those between the S atom and a methylene bridging C

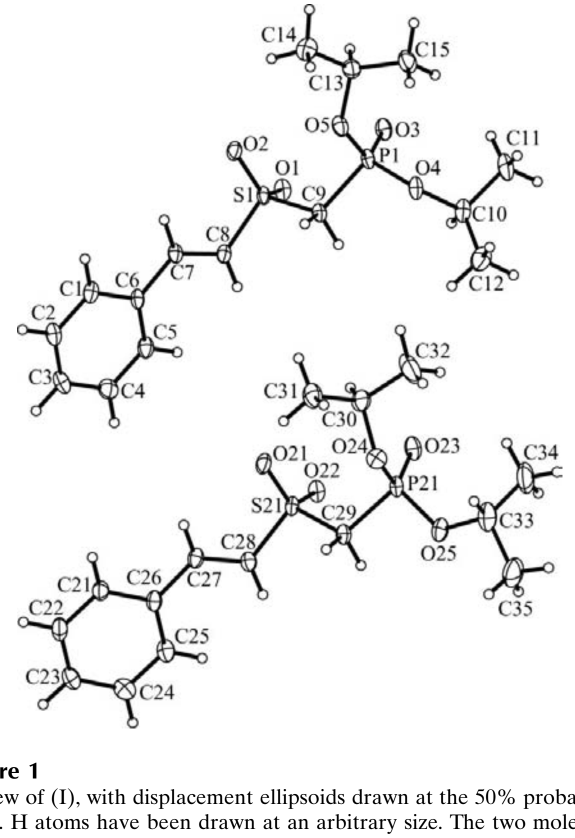


Figure 1
A view of (I), with displacement ellipsoids drawn at the 50% probability level. H atoms have been drawn at an arbitrary size. The two molecules are shown in projection down the vinyl group.

doi:10.1107/S0108270108002692

atom [average 1.780 (7) Å]. Compound (I) has two molecules in the asymmetric unit, shown in Fig. 1 perpendicular to the vinyl group plane in order to demonstrate the flexibility in the backbone of the molecule. The S1···P1 and S21···P21 distances are 3.0262 (10) and 3.0065 (10) Å, respectively. Compound (II) (Fig. 2) also has $Z' = 2$. The intermolecular S···P distances are 3.0274 (5) and 3.0304 (5) Å; the S···S distances are slightly longer at 3.0472 (5) and 3.0470 (5) Å. Compound (III) has $Z' = 3$ (Fig. 3). One of the molecules is disordered in the orientation of the set of atoms C49–C56. Fig. 3 shows the three molecules in their relative orientations in the structure. Again, there are obvious conformational differences among the three molecules. In Table 5 the metric data for the disordered molecule of (III) has been omitted. Compound (IV) (Fig. 4) has a crystallographic twofold axis passing through atom C9. The S1···S1^{i} separation is 3.0549 (6) Å.

In order to compare (I)–(IV) with polyphosphates, average values for P—O(bridging) distances, P—O—P angles and P···P distances can be compared with the P—C, S—C, S—C—S and S—C—P distances and angles, as well as the S···P and S···S distances in di- and triphosphates in the CSD (Allen, 2002; *ConQuest*; Cambridge Structural Database, 2007). We selected 21 acyclic structures with $R < 0.075$. The average P—O distance is 1.603 (18) Å, the P—O—P angle is 133 (2)°, the P···P distance is 2.94 (3) Å and the O···O distance is 2.48 (4) Å. As would be expected, the P—C and S—C distances are longer than the P—O distance, and the S—C—S and S—C—P angles are more acute than the P—O—P angle. Additionally, although the tetrahedral geometry at S and P is similar, the fact that S—C bonds are longer than P—O bonds means that the repeat distance between bridging C atoms is greater than the C···O and O···O distances. Thus, we found that the vinyl sulfone or vinyl sulfone/phosphonate backbone is lengthened relative to the polyphosphate backbone by *ca* 0.40 Å per repeat. None of the structures (I)–(IV) contains solvent molecules or possesses any strong intermolecular interactions. Since all of the crystals were obtained from non-aqueous solvents, the corresponding structures in hydrophillic environments may significantly differ. However, it is clear that the backbones of these vinyl sulfones and mixed sulfone/phosphonate compounds resemble those of polyphosphates, and replacement of the bridging O atom by a CH_2

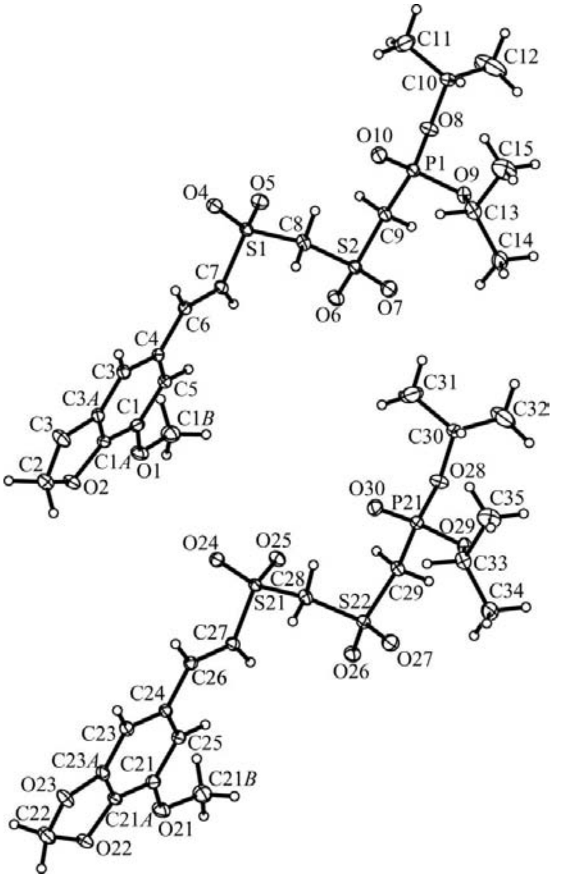


Figure 2
A view of the two molecules of (II) in the asymmetric unit, showing displacement ellipsoids at the 50% probability level. H atoms have been drawn at an arbitrary size. The projection of the two molecules is arbitrarily chosen to show the relationship between the two molecules

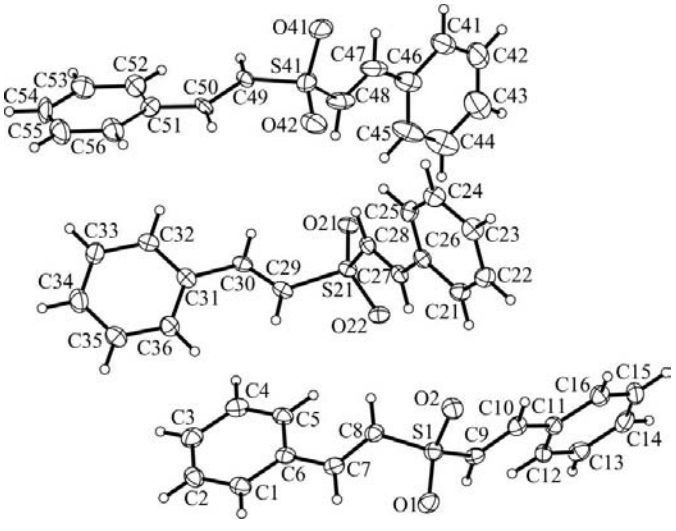


Figure 3
A view of the three molecules of (III), showing displacement ellipsoids at the 50% probability level. The disorder in one of the molecules has been omitted for clarity. H atoms have been drawn at an arbitrary size. The three molecules are shown in the relationship in which they exist in the asymmetric unit.

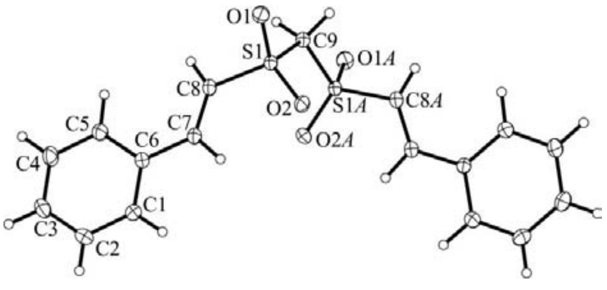


Figure 4
A view of (IV), showing displacement ellipsoids at the 50% probability level. H atoms have been drawn at an arbitrary size. [Symmetry code: (*A*) $-x + 1, y, -z + \frac{1}{2}$.]

group preserves the rotational flexibility of the polyphosphate structure.

Experimental

For the preparation of compound (I), the monosulfone reagent diisopropyl (diisopropoxyphosphorylmethylsulfonylmethyl)phosphonate (Wong, Olmstead & Gervay-Hague, 2007) (600 mg, 1.42 mmol) was dissolved in dry tetrahydrofuran (THF; 1.8 ml) at room temperature under argon in a flame-dried flask. LiBr (180 mg, 2.13 mmol) was added with stirring until dissolved. At this point, sodium hydride (51 mg, 2.13 mmol) was added until all bubbles disappeared, and then benzaldehyde (75 mg, 0.71 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and then quenched with a 1:1 solution of acetic acid and water (2 ml). The solution was partitioned between ethyl acetate and water, and extracted three times with ethyl acetate. The organic phase was collected and dried over sodium sulfate. The solvent was evaporated to yield a crude oil that was subjected to column chromatography (80% hexane:20% ethyl acetate) and eventually crystallized in a test tube to give compound (I) in 39% yield. ^{1}H (400 MHz, $CDCl_3$): δ 7.63 (*d*, J = 15.2 Hz, 1H), 7.56–7.54 (*m*, 2H), 7.45–7.41 (*m*, 3H), 7.28 (*d*, J = 15.2 Hz, 1H), 4.87–4.82 (*m*, 2H), 3.67 (*d*, J = 16.8 Hz, 2H), 1.36 (*d*, J = 6.4 Hz, 12H). ^{13}C (100 MHz, $CDCl_3$): δ 144.5, 132.3, 131.5, 129.2, 128.9, 126.2, 73.0, 72.9, 54.3 (*d*, J = 139.7 Hz), 24.3, 24.2, 24.0, 23.9. LRMS (ESI): *m*/*z* calculated for $C_{15}H_{23}O_5PS$ $(M + Na)^+$ 369.1, found 369.1.

For the preparation of compound (II), the disulfone reagent diisopropyl (diisopropoxyphosphorylmethylsulfonylmethylsulfonylmethyl)phosphonate (Wong, Olmstead, Fettinger & Gervay-Hague, 2007) (224 mg, 0.44 mmol), 7-methoxy-1,3-benzodioxole-5-carbaldehyde (169 mg, 0.94 mmol) and LiBr (115 mg, 1.32 mmol) were dissolved in 3–4 ml of dry THF in a flame-dried flask, and then Hunig's base (230 µl, 1.32 mmol) was added to the solution. After stirring overnight, the reaction mixture was quenched by the addition of 5% HCl until the pH was 3–4. The solution was partitioned between ethyl acetate and water, and extracted three times. The organic phase was collected and dried over sodium sulfate. The solvent was evaporated to yield a crude solid material that was subjected to column chromatography (30% ethyl acetate:70% hexanes, $R_F = 0.21$) to yield crystals of the mono-coupled product as a minor component in a test tube.

Compound (III) was the second product eluted from the column in the preparation of (I). It also crystallized in a test tube in 33% yield.

For the preparation of compound (IV), the disulfone reagent (Wong, Olmstead, Fettinger & Gervay-Hague, 2007) (103 mg, 0.21 mmol), benzaldehyde (0.07 ml, 0.68 mmol) and LiBr (60 mg, 0.069 mmol) were dissolved in 3–4 ml of dry THF, and then Hunig's base (91 µl, 0.069 mmol) was added to the solution. The reaction mixture was stirred overnight before being quenched by the addition of 5% HCl until pH 3–4 was attained. The solution was partitioned between ethyl acetate (80 ml) and water (50 ml), and extracted three times (50 ml). The organic phase was collected and dried over sodium sulfate. After removal of the solvent, the crude material was subjected to column chromatography (40% ethyl acetate:60% hexanes, R_F = 0.43) to yield 65 mg (88%) of (IV). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.68 (*s*, 2H), 7.21 (*d*, 2H, J = 15.6 Hz), 7.38–7.54 (*m*, 10H), 7.67 (*d*, 2H, J = 15.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 74.11, 124.38, 129.18, 129.31, 131.77, 132.09, 147.02. FT–IR (film): ν 3060, 1612, 1448 (C=C), 1323, 1124 (SO_2 str), 976 (*trans* C=C str). Analysis calculated for $C_{17}H_{16}O_4S_2$: C 58.60, H 4.63%; found: C 58.21, H 4.63%.

Table 1
Selected bond lengths (Å) for (I).

P1—O3	1.4794 (19)	P21—O23	1.442 (2)
P1—O5	1.5614 (19)	P21—O25	1.5673 (19)
P1—O4	1.5901 (19)	P21—O24	1.5792 (19)
P1—C9	1.805 (3)	P21—C29	1.813 (3)
S1—O2	1.4324 (18)	S21—O22	1.4368 (19)
S1—O1	1.4480 (19)	S21—O21	1.4539 (19)
S1—C8	1.741 (3)	S21—C28	1.750 (3)
S1—C9	1.790 (2)	S21—C29	1.765 (3)

Table 2
Selected bond lengths (Å) for (II).

P1—O10	1.4734 (10)	P21—O30	1.4736 (10)
P1—O8	1.5623 (10)	P21—O28	1.5623 (10)
P1—O9	1.5736 (10)	P21—O29	1.5739 (10)
P1—C9	1.8156 (14)	P21—C29	1.8167 (14)
S1—O4	1.4430 (10)	S21—O24	1.4424 (10)
S1—O5	1.4431 (10)	S21—O25	1.4452 (10)
S1—C7	1.7356 (13)	S21—C27	1.7330 (13)
S1—C8	1.7877 (14)	S21—C28	1.7891 (14)
S2—O7	1.4389 (11)	S22—O27	1.4376 (11)
S2—O6	1.4420 (10)	S22—O26	1.4420 (10)
S2—C9	1.7698 (13)	S22—C29	1.7707 (13)
S2—C8	1.7816 (14)	S22—C28	1.7795 (14)

Compound (I)

Crystal data

$C_{15}H_{23}O_5PS$
$M_r = 346.36$
Triclinic, $P\bar{1}$
$a = 8.933$ (3) Å
$b = 10.014$ (3) Å
$c = 22.059$ (7) Å
$\alpha = 79.769$ (4)°
$\beta = 89.938$ (4)°
$\gamma = 63.533$ (4)°
$V = 1731.5$ (10) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.30$ mm^{-1}
$T = 90$ (2) K
0.55 × 0.53 × 0.38 mm

Data collection

Bruker SMART 1000 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2006)
$T_{min} = 0.853$, $T_{max} = 0.895$
15459 measured reflections
7911 independent reflections
7462 reflections with $I > 2\sigma(I)$
$R_{int} = 0.032$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.104$
$S = 1.06$
7911 reflections
406 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.71$ e Å^{-3}
$\Delta\rho_{min} = -0.43$ e Å^{-3}

Compound (II)

Crystal data

$C_{18}H_{27}O_{10}PS_2$
$M_r = 498.49$
Triclinic, $P\bar{1}$
$a = 9.8656$ (3) Å
$b = 15.1481$ (5) Å
$c = 15.9024$ (5) Å
$\alpha = 86.929$ (3)°
$\beta = 89.893$ (3)°
$\gamma = 72.267$ (3)°
$V = 2260.11$ (12) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.36$ mm^{-1}
$T = 90$ (2) K
0.49 × 0.08 × 0.07 mm

Table 3
Selected bond lengths (Å) for (III).

S1—O2	1.4422 (17)	S21—O22	1.4415 (16)
S1—O1	1.4432 (16)	S21—O21	1.4428 (15)
S1—C8	1.738 (2)	S21—C28	1.739 (2)
S1—C9	1.751 (2)	S21—C29	1.742 (2)

Table 4
Selected bond lengths (Å) for (IV).

S1—O2	1.4369 (9)	S1—C8	1.7422 (12)
S1—O1	1.4502 (9)	S1—C9	1.7896 (9)

Data collection

Bruker SMART APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2006)
$T_{min} = 0.845$, $T_{max} = 0.976$
25647 measured reflections
13151 independent reflections
11227 reflections with $I > 2\sigma(I)$
$R_{int} = 0.017$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.092$
$S = 1.03$
13151 reflections
623 parameters
Only H-atom displacement parameters refined
$\Delta\rho_{max} = 0.50$ e Å^{-3}
$\Delta\rho_{min} = -0.35$ e Å^{-3}

Compound (III)

Crystal data

$C_{16}H_{14}O_2S$
$M_r = 270.33$
Orthorhombic, *Pbca*
$a = 10.1632$ (7) Å
$b = 23.6753$ (16) Å
$c = 34.339$ (2) Å
$V = 8262.5$ (9) Å^3
$Z = 24$
Mo $K\alpha$ radiation
$\mu = 0.23$ mm^{-1}
$T = 90$ (2) K
0.51 × 0.09 × 0.06 mm

Data collection

Bruker SMART 1000 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2006)
$T_{min} = 0.892$, $T_{max} = 0.987$
60803 measured reflections
9492 independent reflections
5497 reflections with $I > 2\sigma(I)$
$R_{int} = 0.085$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.051$
$wR(F^2) = 0.135$
$S = 1.09$
9492 reflections
562 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.61$ e Å^{-3}
$\Delta\rho_{min} = -1.01$ e Å^{-3}

Compound (IV)

Crystal data

$C_{17}H_{16}O_4S_2$
$M_r = 348.42$
Monoclinic, *C*2/*c*
$a = 15.7551$ (6) Å
$b = 11.9609$ (5) Å
$c = 8.6212$ (3) Å
$\beta = 103.728$ (1)°
$V = 1578.21$ (10) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.35$ mm^{-1}
$T = 90$ (2) K
0.29 × 0.24 × 0.20 mm

Table 5
Summary of structural parameters for (I)–(IV) (Å, °).

In square brackets, the average deviation from the mean value is followed by the number of observations.

S—C(=C)	S—C	S=O	P=O	P—O	P—C	S—C—S	S—C—P
1.741 [4,9]	1.780 [7,9]	1.443 [4,20]	1.467 [10,4]	1.571 [7,8]	1.813 [3,4]	117.23 [17,3]	114.9 [3,4]

Data collection

Bruker SMART 1000 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2006)
$T_{min} = 0.865$, $T_{max} = 0.928$
8747 measured reflections
2302 independent reflections
1978 reflections with $I > 2\sigma(I)$
$R_{int} = 0.022$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.032$
$wR(F^2) = 0.092$
$S = 1.11$
2302 reflections
137 parameters
All H-atom parameters refined
$\Delta\rho_{max} = 0.42$ e Å^{-3}
$\Delta\rho_{min} = -0.31$ e Å^{-3}

In (I), all H atoms were treated as riding, with C—H distances in the range 0.95–1.00 Å and U_{iso}(H) values of 1.2 (for primary and secondary) or 1.5 (for tertiary) times the U_{eq} of the bonded C atom. The structure was refined as a pseudo-merohedral twin. The twin law was $(100/1\bar{1}0/00\bar{1})$ and the twin parameter 0.4822 (10). In (II), H-atom positional parameters were treated as for (I) and the displacement parameters were refined. In (III), one of the three molecules in the asymmetric unit is disordered in one-half of the molecule. Occupancies for these two components were originally refined and subsequently fixed at values of 0.57 and 0.43 for the major and minor parts, respectively. H atoms were treated as in (I). In (IV), all atoms were fully refined [C—H = 0.92 (2)–0.989 (19) Å].

For all compounds, data collection: *SMART* (Bruker, 2002) for (I), (III) and (IV), and *APEX2* (Bruker, 2006) for (II); cell refinement: *SAINT* (Version 7.23; Bruker, 2005) for (I), and *SAINT* (Version 7.16b; Bruker, 2004) for (II), (III) and (IV); data reduction: *SAINT* (Version 7.23) for (I), and *SAINT* (Version 7.16b) for (II), (III) and (IV); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXL97*.

We thank the University AIDS Research Program (grant No. D02-D-400) and the Tobacco-Related Disease Research Program (grant No. 12RT-0254H) for partial support of this research. The Bruker SMART 1000 diffractometer was funded in part by NSF instrumentation grant No. CHE-9808259.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3201). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Bruker (2002). *SMART*. Version 5.054. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2004). *SAINT*. Version 7.16b. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (2005). *SAINT*. Version 7.23. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (2006). *APEX2*. Version 2.0-2. Bruker AXS Inc., Madison, Wisconsin, USA.

Cambridge Structural Database (2007). *ConQuest*. Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, England.

Hadd, M. J., Smith, M. A. & Gervay-Hague, J. (2001). *Tetrahedron Lett.* **42**, 5137–5140.

Meadows, D. C. & Gervay-Hague, J. (2006*a*). *ChemMedChem*, **1**, 16–29.

Meadows, D. C. & Gervay-Hague, J. (2006*b*). *Med. Res. Rev.* **26**, 793–814.

Meadows, D. C., Mathews, T. B., North, T. W., Hadd, M. J., Kuo, C. L., Neamati, N. & Gervay-Hague, J. (2005). *J. Med. Chem.* **48**, 4526–4534.

Meadows, D. C., Sanchez, T., Neamati, N., North, T. W. & Gervay-Hague, J. (2007). *Bioorg. Med. Chem.* **15**, 1127–1137.

Sheldrick, G. M. (2006). *SADABS*. University of Göttingen, Germany.

Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Wong, J. H., Olmstead, M. M., Fettinger, J. C. & Gervay-Hague, J. (2007). *Acta Cryst.* E**63**, o3046.

Wong, J. H., Olmstead, M. M. & Gervay-Hague, J. (2007). *Acta Cryst.* E**63**, o3045.