APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2003; **17**: 453–457
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.456

Synthesis, characterization, X-ray crystal structure and *in vitro* antitumour activity of bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)di-*n*-butyltin†

Vladimir I. Bregadze[1]*, Sergey A. Glazun[1], Pavel V. Petrovskii[1], Zoya A. Starikova[1], Valery Ya. Rochev[2], Hassan Dalil[3], Monique Biesemans[3,4], Rudolph Willem[3,4], Marcel Gielen[3] and Dick de Vos[5]**

[1]A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Vavilov Str. 28, Moscow 119991, Russia
[2]N.N. Semenov Institute of Chemical Physics of Russian Academy of Sciences, Kosygin Str. 4, Moscow 119977, Russia
[3]Vrije Universiteit Brussel, Department of General and Organic Chemistry (AOSC), Faculty of Applied Sciences, Pleinlaan 2, B-1050 Brussels, Belgium
[4]Vrije Universiteit Brussel, High Resolution NMR Centre, Pleinlaan 2, B-1050 Brussels, Belgium
[5]Medical Department, PCH Nederland, Pharmachemie B.V., NL-2003 RN Haarlem, The Netherlands

Received 24 October 2002; Revised 22 November 2002; Accepted 6 February 2003

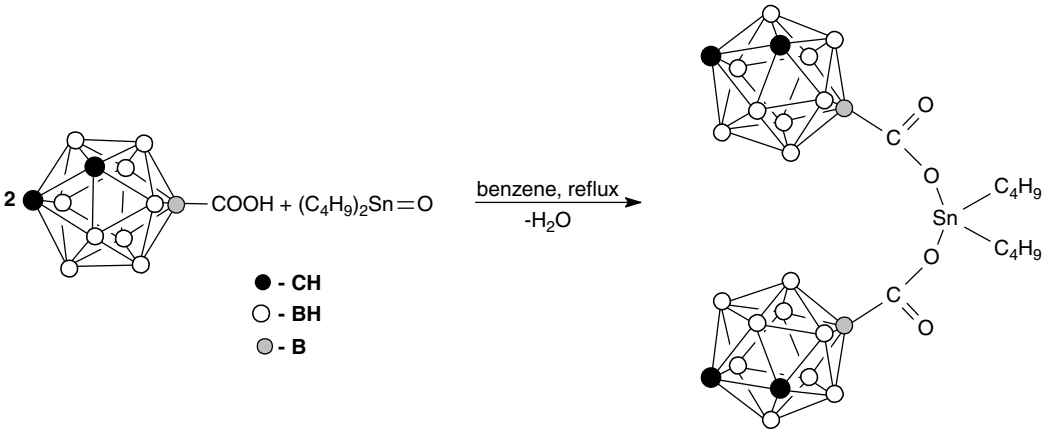
The 1 : 2 condensation of dibutyltin(IV) oxide with 1,2-carborane-9-carboxylic acid resulted in bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)di-*n*-butyltin (1), the first carborane-based organotin compound where the carborane cage is linked to the carboxylic moiety via a boron atom. The structure of 1, characterized by ^{1}H, ^{11}B, ^{13}C, ^{119}Sn NMR spectroscopy and X-ray diffraction, was shown to correspond to bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)di-*n*-butyltin. Compound 1 was screened *in vitro* against seven tumour cell lines of human origin and was found to be significantly more active than 5-fluorouracil, *cis*-platin and carboplatin but less active than methotrexate and doxorubicin. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: organotin carboranecarboxylate; synthesis; crystal structure; antitumour activity

INTRODUCTION

The *in vitro* antitumour activities against a panel of human cancer cell lines of many organotin derivatives have been determined.[1] Several of these appear as quite promising active compounds. On the other hand, boron derivatives are potentially interesting in the anticancer therapy by neutron capture, provided these compounds exhibit a sufficiently selective affinity towards certain tumour cells. Carborane (1,2- or 1,7-dicarba-*closo*-dodecaborane) derivatives of tin have been described.[2] Recently, we reported the synthesis, characterization and *in vitro* antitumour screening of several such compounds. Some of them contain a carborane cage linked to the tin atom via a B–Sn σ-bond.[3] We also examined organotin carboranecarboxylates where the carborane cage is linked to the carboxylic moiety via a carbon atom.[4,5] All carborane-based organotin compounds previously tested revealed *in vitro* antitumour activities less than those of the clinically used methotrexate and doxorubicin, but greater than those of 5-fluorouracil, *cis*-platin and carboplatin.[3–5] In this paper, we report the synthesis, characterization and *in vitro* antitumour activity of bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)di-*n*-butyltin, $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (**1**), the first carborane-based organotin compound where the carborane cage is linked to the carboxylic moiety via a boron atom.

*Correspondence to: Vladimir I. Bregadze, A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Vavilov Str. 28, Moscow 119991, Russia.
E-mail: bre@ineos.ac.ru
**Correspondence to: Marcel Gielen, Vrije Universiteit Brussel, Department of General and Organic Chemistry (AOSC), Faculty of Applied Sciences, Pleinlaan 2, B-1050 Brussels, Belgium.
E-mail: mgielen@vub.ac.be
†Dedicated to Professor Thomas P. Fehlner on the occasion of his 65th birthday, in recognition of his outstanding contributions to organometallic and inorganic chemistry.
Contract/grant sponsor: INTAS; Contract/grant number: 99-00806.
Contract/grant sponsor: Fonds voor Wetenschappelijk Onderzoek–Vlaanderen (FWO); Contract/grant number: G.0074.00NatLot 1999.
Contract/grant sponsor: Russian Foundation for Basic Research; Contract/grant numbers: 02-03-32192; 02-07-90322; 00-03-32807.



Scheme 1.

RESULTS AND DISCUSSION

Synthesis and characterization

The novel bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)-di-*n*-butyltin (**1**) was obtained by the 1 : 2 condensation of di-*n*-butyltin(IV) oxide with 1,2-carborane-9-carboxylic acid (Scheme 1). Its structure was determined by spectroscopy and X-ray diffraction. ^{1}H, ^{11}B, ^{13}C and ^{119}Sn NMR spectra of **1** display the usual resonances for B(9)-substituted carboranes and diorganotin dicarboxylates.

Crystal and molecular structure of bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)di-*n*-butyltin (1)

Figure 1 shows an ORTEP view of the $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (**1**) molecule. Table 1 lists selected interatomic distances and angles.

The analysis of 22 carboxylate complexes of tin deposited in the Cambridge Structural Database (2002 release) have revealed that the geometry of **1** is characterized by typical values for $R_2Sn(O_2CR')$ complexes.

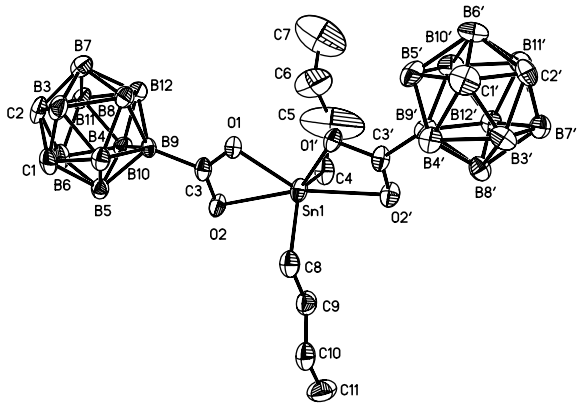


Figure 1. Perspective view of $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (**1**) showing the atom numbering scheme. Hydrogen atoms are omitted for clarity.

Table 1. Selected bond lengths (Å) and angles (°) for $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (**1**)

Sn(1)–O(1′)	2.115(4)
Sn(1)–O(1)	2.115(4)
Sn(1)–O(2)	2.503(3)
Sn(1)–O(2′)	2.489(4)
Sn(1)–C(4)	2.138(7)
Sn(1)–C(8)	2.154(7)
O(1)–C(3)	1.286(7)
O(2)–C(3)	1.242(7)
O(1′)–C(3′)	1.317(6)
O(2′)–C(3′)	1.223(7)
C(3)–B(9)	1.593(8)
C(3′)–B(9′)	1.597(9)
O(1′)–Sn(1)–O(1)	83.17(15)
O(1′)–Sn(1)–C(4)	108.5(2)
O(1)–Sn(1)–C(4)	107.9(2)
O(1′)–Sn(1)–C(8)	107.7(2)
O(1)–Sn(1)–C(8)	108.0(2)
C(4)–Sn(1)–C(8)	131.1(3)
O(1′)–Sn(1)–O(2′)	56.18(14)
O(1)–Sn(1)–O(2′)	139.35(15)
C(4)–Sn(1)–O(2′)	87.0(2)
C(8)–Sn(1)–O(2′)	86.7(2)
C(4)–Sn(1)–O(2)	87.9(3)
C(8)–Sn(1)–O(2)	85.9(2)
O(2′)–Sn(1)–O(2)	164.96(14)
C(3)–O(1)–Sn(1)	100.9(4)
O(1′)–Sn(1)–C(8)	107.7(2)
O(1)–Sn(1)–C(8)	108.0(2)
C(4)–Sn(1)–C(8)	131.1(3)
O(1′)–Sn(1)–O(2′)	56.18(14)
O(1)–Sn(1)–O(2′)	139.35(15)
O(1′)–Sn(1)–O(2)	138.78(15)
O(1)–Sn(1)–O(2)	55.65(15)

The structure of the $[SnC_2O_4]$ coordination polyhedron in **1** is close to the so-called skew-trapezoidal bipyramid.[6,7] The

Sn–O bond lengths vary to a great extent (0.4 Å), the average Sn(1)–O(1) and Sn(1)–O(2) distances being significantly different, 2.115 Å and 2.491 Å respectively. The C–Sn–C bond angle is 131.1(3)°. It should be noted that the base of the $\{SnO_4\}$ bipyramid in **1**, and other complexes containing four-atom SnO_2C chelates, is distorted to a much greater extent than compounds containing four-atom SnS_2C cycles, as well as six-atom cycles. The difference arises first of all with the values of the O(2)–Sn–O(2′) angles of 165.0(1)°, 170.5(2)°, 167.1(2)° and 165.3(3)° in **1**, $Bu_2Sn(OCOCH_2–SPh)_2$,[8] $Bu_2Sn(OCOCR^1R^2)_2$,[9] and $Me_2Sn(OCOCPh)_2$,[10] respectively, and of 176.3(4)° in $Me_2Sn(NO_3)_2$.[11] In almost all the other complexes having a skew-trapezoidal bipyramidal coordination polyhedron, this angle is significantly smaller (140–150°).[7]

The structure of the coordination polyhedron **1** (Fig. 2) is characterized by a significant displacement of the tin atom from the centre of the trapezium. The O(1)···O(1′) (2.807 Å) and O(2)···O(2′) (4.950 Å) distances differ by more than 2 Å. The increase of the O(2)–Sn–O(2′) angle results from the appearance of a 'hole' at tin in the base of the bipyramid. The axial substituents do not 'cover' this 'hole' because the C(4)···C(8) distance (3.910 Å) is greater then the sum of the van der Waals radii for these atoms (3.42 Å).[12]

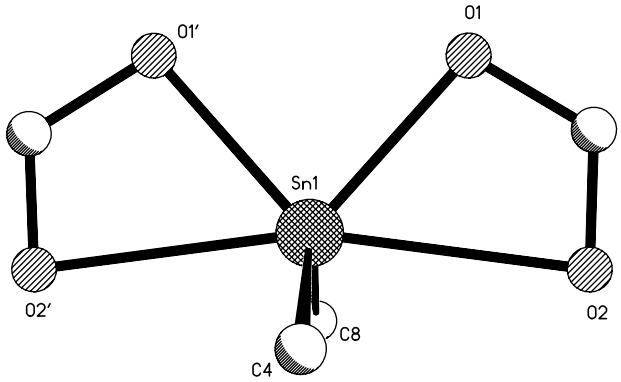


Figure 2. Coordination polyhedron observed for **1**.

Carborane units have different orientations relative to the coordination plane [CO_2–Sn–O_2C], with the pseudo-torsional angles O(1)C(3)B(9)C(1) and O(1′)C(3′)B(9′)C(1′) being 112.4(1)° and 45.7(1)° respectively.

In the chelate cycle [SnO_2C], the C–O bond lengths are different: C(3)–O(1) is 1.302 Å and C(3)–O(2) is 1.232 Å (on average). The delocalization of C–O π-bonds, which is typical for η^2-metallacarboxylate cycles (C–O 1.254–1.257 Å[13]), is low in this case. The length of the B–COO bond (C3–B9 and C3′–B9′, 1.59 Å) is standard for exocyclic B–C sp^2 bonds in carboranes.

Antitumour activities

Compound **1** was screened *in vitro* against seven tumour cell lines of human origin. The ID_{50} values (ng ml^{-1}) obtained are given in Table 2. Compound **1** is significantly more active than 5-fluorouracil, *cis*-platin and carboplatin, is less active than methotrexate and doxorubicin, and is comparable to related compounds reported earlier:[4,5] $\{[(1,7\text{-}C_2B_{10}H_{11}\text{-}1\text{-}COO)_2Bu_2Sn]_2\}_2$ (**2**), $\{[(2\text{-Ph-}1,2\text{-}C_2B_{10}H_{10}\text{-}1\text{-}COO)_2Bu_2Sn]_2\}_2$ (**3**), $\{[(2\text{-Me-}1,2\text{-}C_2B_{10}H_{10}\text{-}1\text{-}CH_2COO)_2Bu_2Sn]_2\}_2$ (**4**).

EXPERIMENTAL

Synthesis

o-Carborane-9-carboxylic acid was prepared following Zakharkin *et al*.[14] by oxidation of 9-ethyl-*o*-carborane by CrO_3 in acetic acid in the presence of H_2SO_4.

Bis(1,2-dicarba-*closo*-dodecaborane-9-carboxylato)di-*n*-butyltin, $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (1)

This was synthesized in benzene (150 ml) from di-*n*-butyltin oxide (623 mg, 2.5 mmol) and *o*-carborane-9-carboxylic acid (940 mg, 5 mmol). After 20 min of reflux, a clear solution was obtained; this was then refluxed for a further 5 h. The binary azeotrope water–benzene was distilled off with a Dean–Stark funnel. The benzene solution obtained was distilled to 50% of its initial volume and the remaining solvent was evaporated

Table 2. *In vitro* antitumour activities (ng ml^{-1}) of $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (**1**) against MCF-7 and EVSA-T (two breast cancers), IGROV (an ovarian cancer), M19 MEL (a melanoma), A498 (a renal cancer) and H226 (a non-small cell lung cancer), together those of some reference compounds used clinically and those of some carborane-based organotin compounds described previously: bis(1,7-dicarba-*closo*-dodecaborane-1-carboxylato)-di-*n*-butyltin oxide (**2**),[4] bis(2-phenyl-1,2-dicarba-*closo*-dodecaborane-1-carboxylato)-di-*n*-butyltin oxide (**3**),[5] and bis(2-methyl-1,2-dicarba-*closo*-dodecaboranylacetato)-di-*n*-butyltin oxide (**4**)[5]

Compound	MCF-7	EVSA-T	WiDr	IGROV	M19MEL	A498	H226
1	146	142	439	139	174	195	291
2	45	38	290	110	110	140	
3	138	164	514	169	220	301	338
4	74	140	283	102	172	182	246
5-Fluorouracil	350	720	440	850	310	340	5300
Methotrexate	15	26	7	20	18	16	70
Doxorubicin	25	13	18	150	21	55	180

in vacuo. The solid obtained was purified by recrystallization from methylene chloride–*n*-hexane to give 1.24 g of colourless crystals. Yield: 82%; m.p.: 247–249 °C. Anal. Found: C, 27.77; H, 6.58; B, 35.71. Calc. for $C_{14}H_{40}B_{20}O_4Sn$: C, 27.69; H, 6.64; B, 35.6%.

^{1}H NMR ($CDCl_3$) [chemical shift in ppm (multiplicity, coupling constants in hertz)]: CH_{Carb}, 3.71 (s) and 3.67 (s); α- and β-CH_2, 1.44–1.54 (m); γ-CH_2, 1.29 (tq, 7, 7); CH_3, 0.85 (t, 7). ^{11}B{^{1}H} NMR ($CDCl_3/CD_2Cl_2$): B(9), −0.047 (s); B(12), −2.639 (d, 152); B(8,10), −9.259 (d, 153); B(4,5,7,11), −14.259 (broad d, 137); B(3,6), −15.222 (d, 161). ^{13}C NMR ($CDCl_3$): C=O, 171.67; C_{Carb}, 53.43 and 52.28; α-C, 26.52; β-C, 26.0; γ-C, 24.92; CH_3, 13.54. ^{119}Sn NMR (CD_2Cl_2): 126.5 ppm. IR (Nujol): ν(BH) = 2603 (s), ν(CO) = 1344, 1544. QS: 3.21, IS: 1.495, Γ_1: 0.98, Γ_2: 1.01.

Structure determination of $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2$ (1)

A crystal suitable for X-ray diffraction study was obtained by a slow evaporation of a methylene chloride–*n*-heptane solution.

Single-crystal X-ray diffraction experiments were carried out with a Bruker SMART 1000 CCD area detector, using graphite monochromated Mo Kα radiation (λ = 0.710 73 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, 2θ < 60°) at 110 K. The crystals were maintained at low temperature with a Cryostream (Oxford Cryosystems) open-flow nitrogen gas cryostat. Reflection intensities were integrated using the SAINT software[15] and the semi-empirical method SADABS.[16]

The structures were solved by direct methods and refined by full-matrix least squares against F^2 in anisotropic (for non-hydrogen atoms) and isotropic (for hydrogen atoms) approximation. All hydrogen atoms of dodecaborane fragments were located from the difference Fourier syntheses. The hydrogen atoms of the butyl moieties and benzene molecule were placed in the geometrically calculated positions and included in the refinement using the riding model approximation with $U_{iso}(H) = 1.2U_{eq}(C)$ for the methyne and $U_{iso(H)} = 1.5U_{eq}(C)$ for methyl and methylene groups, where $U_{eq}(C)$ is the equivalent isotropic temperature factor of the carbon atom bonded to the corresponding hydrogen atom.

All calculations were performed on an IBM PC/AT using the SHELXTL software.[17]

A summary of the crystal data, experimental details and refinement results is presented in Table 3.

Crystallographic data for the structure determination have been deposited with the Cambridge Crystallographic Data Centre as CCDC no. 195927. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk; or www: http://www.ccdc.cam.ac.uk).

Table 3. Crystal data and structure refinement for $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2SnBu_2\cdot 0.5(C_6H_6)$

Formula	$C_{14}H_{40}B_{20}O_4Sn\cdot 0.5(C_6H_6)$
Formula weight	646.40
Crystal colour, habit	colourless, needle
Crystal size (mm^3)	0.50 × 0.20 × 0.15
Crystal system	Orthorhombic
Space group	*Pnn2*
a (Å)	21.809(4)
b (Å)	22.440(4)
c (Å)	6.8954(12)
V (Å^3)	3374.5(10)
Z	4
D_{calc} (g cm^{-3})	1.272
Diffractometer	Bruker SMART 1000 CCD area detector
Temperature (K)	163
Radiation	Mo Kα (λ = 0.710 73 Å)
$2\theta_{max}$ (°)	60.18
Abs. coeff. μ(Mo Kα) (mm^{-1})	0.782
Abs. structure parameter Flack	0.00(4)
Absorption correction	Empirical
T_{max} and T_{min}	0.911 and 0.680
No. reflections collected	27 269
No. independent reflections	9629 (R_{int} = 0.0953)
No. observed reflections ($I > 2\sigma(I)$)	3640
No. of parameters	379
R_1 (on *F* for obs. refls)	0.052
wR_2 (on F^2 for all refls)	0.136
Weighting scheme	$w^{-1} = \sigma^2(F_o^2) + (aP)^2$, $P = 1/3(F_o^2 + 2F_c^2)$, $a = 0.063$
F(000)	1308
Goodness of fit	0.71
Largest diff. peak and hole (e^{-1} Å^{-3})	1.33 and −0.67

NMR experiments

^{1}H, ^{11}B and ^{13}C NMR spectra were obtained on a Bruker AMX-400 spectrometer at 400.13 MHz, 128.38 MHz and 100.61 MHz respectively. ^{119}Sn NMR data were obtained on a Bruker WP 200-SY spectrometer at 74.63 MHz.

IR measurements

IR measurements were performed on a 'Specord M82' spectrophotometer (Carl Zeiss Jena) with a resolution of 2 cm^{-1}. The spectra were recorded for Nujol mulls in the range 400–4000 cm^{-1}.

Mössbauer spectra

The Mössbauer spectrum (MS) was measured on a home-made standard constant acceleration spectrometer at 80 K with a $Ca^{119m}SnO_3$ source at room temperature. The MS

was fitted with Lorentzian line-shapes using a standard program.

In vitro screening

The protocol followed for the antitumour screenings has been reported elsewhere.[18,19]

Acknowledgements

We thank INTAS (project 99-00806), the Fonds voor Wetenschappelijk Onderzoek—Vlaanderen (FWO) (G.0074.00NatLot1999) and the Russian Foundation for Basic Research (projects 02-03-32192, 02-07-90322, 00-03-32807) for the grants that allowed us to perform this research.

We are grateful to I. Verbruggen for recording the NMR spectra and to H. J. Kolker, J. Verweij, G. Stoter, J. H. M. Schellens, Laboratory of Experimental Chemotherapy and Pharmacology, Department of Medical Oncology, Rotterdam Cancer Institute, NL-3008 AE, Rotterdam, The Netherlands, for performing the *in vitro* tests.

REFERENCES

1. Gielen M. *Appl. Organometal Chem.* 2002; **16**: 481.
2. Bregadze VI. *Chem. Rev.* 1992; **92**: 209.
3. Gielen M, Kayser F, Zhidkova OB, Kampel VTs, Bregadze VI, de Vos D, Biesemans M, Mahieu B, Willem R. *Metal-Based Drugs* 1995; **2**: 37.
4. Gielen M, Bouhdid A, Willem R, Bregadze VI, Ermanson LV, Tiekink ERT. *J. Organometal Chem.* 1995; **501**: 277.
5. Tiekink ERT, Gielen M, Bouhdid A, Willem R, Bregadze VI, Ermanson LV, Glazun SA. *Metal-Based Drugs* 1997; **4**: 75.
6. Howard Jr WF, Crecely RW, Nelson WH. *Inorg. Chem.* 1985; **24**: 2204.
7. Ng SW, Wei C, Das VGK, Mak TCW. *J. Organometal Chem.* 1987; **334**: 295.
8. Sandhu GK, Sharma N, Tiekink ERT. *J. Organometal Chem.* 1989; **371**: C1.
9. Sandhu GK, Hundal R, Tiekink ERT. *J. Organometal Chem.* 1991; **412**: 31.
10. Tiekink ERT. *J. Organometal Chem.* 1991; **408**: 323.
11. Hilton J, Nunn EK, Wallwork SC. *J. Chem. Soc. Dalton Trans.* 1973; 173.
12. Zefirov YuV, Zorkii PM. *Russ. Chem. Rev.* 1995; **64**: 415.
13. Burgi Y-D, Dunitz JD (eds). *Structure Correlation*, vol. 2. VCH: Weinheim, 1994; 785.
14. Zakharkin LI, Kovredov AI, Ol'shevskaya VA, Antonovich VA. *J. Organometal Chem.* 1984; **267**: 81.
15. SMART V5.051 and SAINT V5.00, Area detector control and integration software, 1998, Bruker AXS Inc., Madison, WI-53719, USA.
16. Sheldrick GM. SADABS, 1997, Bruker AXS Inc., Madison, WI-53719, USA.
17. Sheldrick GM. SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI-53719, USA.
18. DeVita VT Jr, Hellman S, Rosenberg SA (eds). *Cancer: Principles and Practice of Oncology*, 5th edn. Lippincott-Raven: Philadelphia, 1997.
19. Kepers YP, Peters GJ, Van Ark-Otte J, Winograd B, Pinedo HM. *Eur. J. Cancer* 1991; **27**: 897.

