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Upper rim substituted thiacalix[4]arenes

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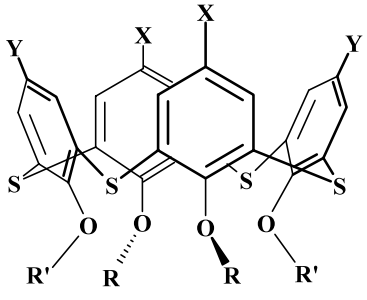
Abstract—The synthesis and structure of new tetrahydroxythiacalix[4]arenes, existing in the *cone* conformation and possessing reactive bromide, chloromethyl or diorganylphosphoryl groups on the upper rim of the macrocycle are described. The molecular structure of tetrakis(diisopropoxyphosphorylmethyl)thiacalix[4]arene was examined by X-ray crystallography.

Thiacalix[4]arenes, new members of the well-known class of calix[4]arenes,[1–4] have been intensively studied over the last seven years.[5–9] The presence of four bridging sulfur atoms in the macrocyclic skeleton of the thiacalixarenes, instead of four methylene groups in the classical calix[4]arenes, opens new prospects for the design of host-molecules. The introduction of the sulfur atoms increases the size of the molecular cavity[7] and enables supplementary modification of the macrocyclic skeleton by oxidation of the sulfide bridges to sulfoxides or sulfones.[10–12] These changes in the framework of the macrocycle, together with the potential, that all calixarenes can be functionalized on the upper and (or) lower rim, make thiacalix[4]arenes attractive as molecular bases for obtaining high-performance receptors of molecules and ions.

However, the use of thiacalix[4]arenes in supramolecular chemistry has been limited by the absence of reasonable methods for the functionalization of the macrocycle upper rim.

At the present time there are just a few examples of *cone*-shaped upper rim functionalized thiacalix[4]arenes (Scheme 1). De-*tert*-butylation of the parent *tert*-butylthiacalix[4]arene **1** with $AlCl_3$ results in formation of thiacalix[4]arene **2**, possessing hydrogen atoms in the *para*-positions of the benzene rings.[7] *ipso*-Sulfonation of *tert*-butylthiacalix[4]arene **1** in concentrated sulfuric acid leads to the water soluble thiacalix[4]arenetetrasulfonate **3**.[13,14] Regioselective bromination of 25,27-dipropoxythiacalix[4]arene with bromine results in formation of the dipropoxy-dibromothiacalix[4]arene **4**.[15]



1-5

Structure	X	Y	R	R'
1	*t*-Bu	*t*-Bu	H	H
2	H	H	H	H
3	SO_3H	SO_3H	H	H
4	Br	H	H	*n*-Pr
5	Br	Br	H	*n*-Pr

Scheme 1.

Keywords: thiacalixarenes; Arbuzov reaction; organophosphorus compounds; X-ray analysis.
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Further bromination of **4** gives dipropoxy-tetrabromothiacalix[4]arene **5**.[15] Compounds **1**–**5** exist in the *cone* conformation, where the benzene rings of the macrocycle skeleton are oriented to one side with respect to the main plane of the macrocycle, formed by the four sulfur atoms. Tetrapropoxy-tetrabromothiacalix[4]arene was obtained by the *O*-propylation of **5**.[15] However, during the propylation, the *cone* conformation was disturbed and the *1,3-alternate* conformer was obtained, where the benzene rings are alternatively oriented upward and downward from the main plane.

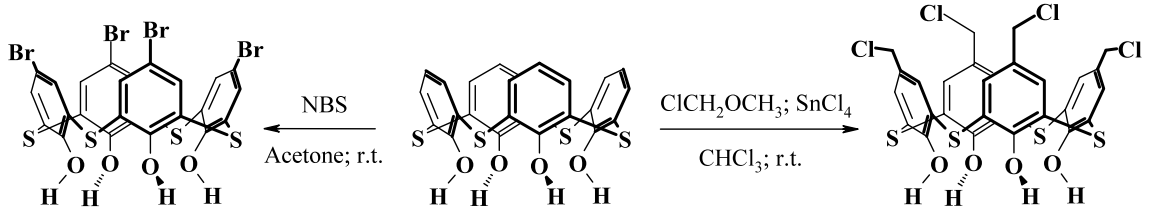
In this article we present a series of new tetrahydroxythiacalix[4]arenes existing in the rational (from the point of view of the Host–Guest chemistry) *cone* conformation, and possessing reactive bromide, chloromethyl or diorganylphosphoryl groups at the upper rim of the macrocycle. An improved method for the synthesis of tetrahydroxythiacalix[4]arene **2** is also reported.[16]

The main method of stabilization of thiacalix[4]arenes in the *cone* conformation consists of the formation of a system of intramolecular hydrogen bonds at the lower rim of the macrocycle as in tetrahydroxythiacalixarenes **1**–**3**[7,14] and 25,27-dihydroxy-26,28-dialkoxythiacalix[4]-arenes **4**–**5**.[15] In our work, tetrahydroxythiacalix-[4]arene **2** was chosen as the platform for the synthesis of *cone*-shaped, upper rim substituted derivatives.

The bromination of tetrahydroxythiacalix[4]arene **2** (Scheme 2) with NBS (acetone, 4 h, rt) gave tetrahydroxy-tetrabromothiacalix[4]arene **6** in 90% yield (colorless crystals, mp>400°C, decomp.).[17–19] The bromine functionality allows further functionalization of the upper rim of the macrocycle by replacement with different nucleophilic groups in the presence of metal catalysts.[20]

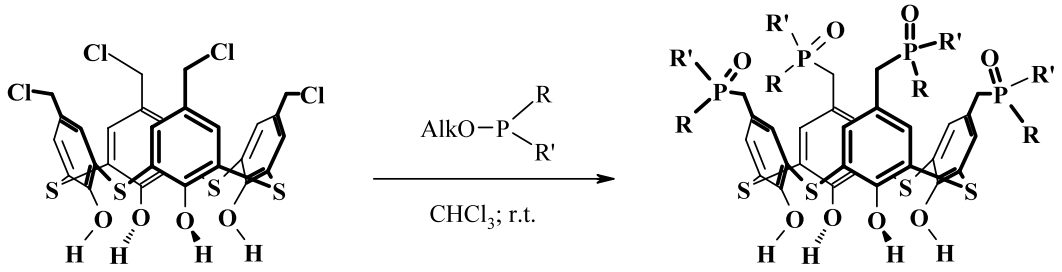
Chloromethyl groups at the calixarene upper rim possess higher reactivity in reactions with nucleophilic reagents.[21–23] These groups were introduced on the upper rim by reaction of the thiacalix[4]arene **2** (Scheme 2) with an excess of methyl chloromethyl ether and tin tetrachloride (chloroform, 4.5 h, rt). Tetrahydroxy tetrakis(chloromethyl)thiacalix[4]arene **7** was obtained in 72% yield as a colorless crystalline substance.[24]

The synthetic potential of chloromethylthiacalixarene **7** was demonstrated by an Arbuzov reaction with esters of P(III) phosphorus acids ($CHCl_3$, 4 h, rt, double excess of the phosphorylating agent). Tetraphosphorylated derivatives **8a**–**f** (Scheme 3) were obtained in good yields.[25] The difference in the reactivities of thiacalixarene **7** ($CHCl_3$, 4 h, rt) and tetrakis(chloromethyl)calix[4]arene,[21,22] which reacts with trialkylphosphites only under harsh conditions (long heating in solution with trialkylphosphite at 160–180°C) should be noted.



6 **2** **7**

Scheme 2.



7 **8a-f**

R=R'=OEt(**a**), O*i*-Pr(**b**), OBu(**c**), Bu(**d**), Ph(**e**); R=O*i*-Pr, R'=Ph(**f**)

Scheme 3.

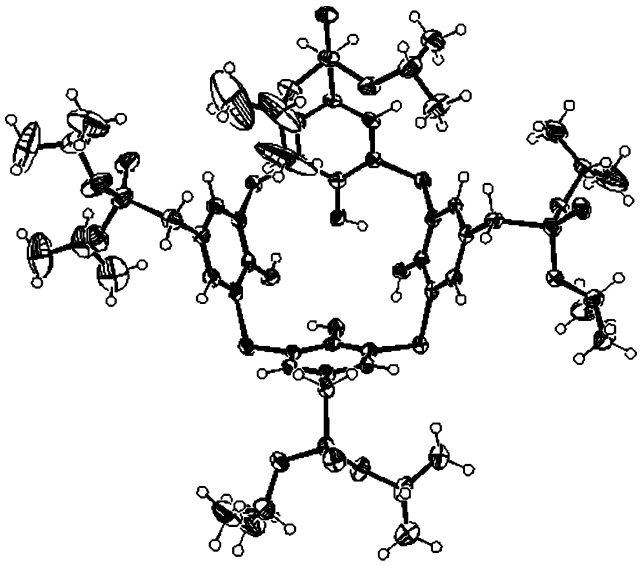


Figure 1. Top view of the X-ray crystal structure of tetrakis(diisopropoxyphosphorylmethyl)tetrahydroxy - thiacalix[4]arene **8b**.

The ^{1}H NMR spectra of the *para*-substituted calixarenes **6–8** showed a singlet for the aromatic protons (7.28–7.77 ppm), a singlet for the *OH* groups (9.21–9.45 ppm), a singlet for the CH_2Cl groups (2.88 ppm) and a doublet for the CH_2P groups (2.80–3.42 ppm, J_{PH} 12.2–21.3 Hz). The low field position of the signals of the hydroxyl groups indicates the presence of an intramolecular hydrogen bonded network, typical for the *cone* conformation. The *cone* conformation of tetrakis(diisopropoxy)phosphorylmethylthiacalix[4]arene **8b** was confirmed by an X-ray crystallographic analysis (Fig. 1).[26]

A suitable monocrystal of **8b** was obtained by crystallization from *n*-pentane. The average C–S distances are 1.786 Å, and the average C–S–C angles are 102.0°; C–P, 1.790 Å; C–C(P), 1.515 Å; P=O, 1.467 Å; P–O, 1.570 Å; O–C, 1.467 Å.

In conclusion, the first efficient synthesis of tetrakis(chloromethyl)tetrahydroxythiacalix[4]arene stabilized in the *cone* conformation by a network of intramolecular hydrogen bonds at the macrocylic lower rim, has been devised. The utility of the compound was demonstrated by the synthesis of *cone*-shaped tetraphosphoryl derivatives—promising receptors for metal cations or organic molecules.

Acknowledgements

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References

1. Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; RSC: Cambridge, 1998.
2. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745.
3. For a review on thiacalixarenes, see: Hosseini, M. W. In *Calixarenes* 2001; Asfari, Z.; Boehmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer Academic Publishers: Dodrecht, 2001.
4. Iki, N.; Miyano, S. J. *Inclusion Phenom. Macrocyclic Chem.* **2001**, *41*, 99–105.
5. Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971–3972.
6. Sone, T.; Ohba, Y.; Moriya, K.; Kumada, H.; Ito, K. *Tetrahedron* **1997**, *53*, 10689–10698.
7. Akdas, H.; Bringel, L.; Graf, E.; Hosseini, M. W.; Mislin, G.; Pansanel, J.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 2311–2314.
8. Antipin, I. S.; Stoikov, I. I.; Gubaidullin, A. T.; Litvinov, I. A.; Weber, D.; Habicher, W. D.; Konovalov, A. I. *Tetrahedron Lett.* **1999**, *40*, 8461–8464.
9. Lhotak, P.; Himl, M.; Pakhomova, S.; Stibor, I. *Tetrahedron Lett.* **1998**, *39*, 8915–8918.
10. Iki, N.; Kumagai, H.; Morohashi, N.; Ejima, K.; Hasegawa, M.; Miyanari, S.; Miyano, S. *Tetrahedron Lett.* **1998**, *39*, 7559–7562.
11. Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Chem. Commun.* **1998**, 1345–1346.
12. Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1999**, *40*, 1129–1132.
13. Iki, N.; Suzuki, T.; Koyama, K.; Kabuto, C.; Miyano, S. *Org. Lett.* **2002**, *4*, 509–512.
14. Iki, N.; Fujimoto, T.; Miyano, S. *Chem. Lett.* **1998**, 625–626.
15. Lhotak, P.; Himl, M.; Stibor, I.; Sykora, J.; Cisarova, I. *Tetrahedron Lett.* **2001**, *42*, 7107–7110.
16. The following method was used for the synthesis of thiacalix[4]arene **2**. *tert*-Butylthiacalix[4]arene **1** (30.0 g, 41.67 mmol) was dissolved in toluene (900 ml) with heating. After cooling down to rt, phenol (40.0 g, 422.53 mmol) was added. Then, $AlCl_3$ (200.0 g, 1500.00 mmol) was added over 3 min. The mixture was refluxed for 5 h (lit. 7 days).[7] The reaction mixture was cooled, and poured into 2N HCl (2.5 L) with additional stirring for 24 h. The precipitate was filtered, washed with chloroform (3×50 ml) and acetone (2×50 ml). The filtered product was dried under vacuum (0.01 mmHg) at 220°C until sublimation of the volatile aluminium salts was complete. Compound **2** (18.0 g, 87%), (lit. 51%)[7] was obtained as a beige crystalline product. Mp 300–305°C (lit. 298–300°C).[7] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (t, 4H, J=7.7 Hz, H-arom.), 7.60 (d, 8H, J=7.7 Hz, H-arom.), 9.45 (s, 4H, OH). Anal. calcd for $C_{24}H_{16}O_4S_4$, %: C, 58.10; H, 3.20; S, 25.80. Found, %: C, 58.00; H, 3.40; S, 25.50.
17. Wong, M. S.; Li, Z. H.; Kwok, C. C. *Tetrahedron Lett.* **2000**, *41*, 5719–5724.
18. Larsen, M.; Jorgensen, M. *J. Org. Chem.* **1996**, *61*, 6651–6655.
19. NBS (2.9 g, 16.13 mmol) was added to a suspension of **2** (1.0 g, 2.02 mmol) in dry acetone (200 ml). The reaction

mixture was stirred for 4 h at rt. The residue was filtered, washed twice with acetone and dried for 1 h under vacuum (0.01 mmHg) at 150°C. Compound **6** (1.5 g, 90%) was obtained as a colorless crystalline product. (The use of methyl ethyl ketone as solvent resulted in a lower yield, 51%). Mp>400°C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.77 (s, 8H, H-arom.). Anal. calcd for $C_{24}H_{12}Br_4O_4S_4$, %: C, 35.49; H, 1.49; Br, 39.35; S, 15.79. Found, %: C, 35.26; H, 1.41; Br, 39.26; S, 15.79.

20. Kalchenko, V.; Atamas, L.; Pirozhenko, V.; Markovsky, L. *Zh. Obshch. Khim.* **1992**, *62*, 2623.
21. Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177.
22. Arimura, T.; Nagasaki, T.; Shinkai, S.; Matsuda, T. *J. Org. Chem.* **1989**, *54*, 3766.
23. Lian-Min, Y.; Yan-Song, Z.; Zhi-Tang, H. *Synth. Commun.* **1999**, *29*, 4451–4460.
24. $SnCl_4$ (42.0 g, 161.29 mmol) and methyl chloromethyl ether (25.9 g, 322.58 mmol) were added to a suspension of **2** (4.0 g, 8.07 mmol) in dry chloroform (160 ml). The reaction mixture was stirred for 5 h at rt and filtered. Distilled water (200 ml) was added to the filtrate and the separated aqueous layer was washed with chloroform (4×75 ml). The combined organic fractions were washed with 4N HCl (3×100 ml), dried over Na_2SO_4 and evaporated. Chloroform (20 ml) was added and the crystalline residue was filtered, washed with chloroform (2×10 ml) and dried for an hour under vacuum (0.01 mmHg) at 100°C. Compound **7** (5.0 g, 90%) was obtained as a colorless crystalline product. Mp>240°C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.44 (s, 8H, CH_2), 7.67 (s, 8H, H-arom.), 9.44 (s, 4H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.65 (s, CH_2), 120.88 (s, C-arom.), 131.26 (s, C-arom.), 139.54 (s, C-arom.), 157.94 (s, C-arom.). Anal. calcd for $C_{28}H_{20}Cl_4O_4S_4$, %: C, 48.70; H, 2.92; Cl, 20.54; S, 18.57. Found, %: C, 48.63; H, 3.00; Cl, 20.13; S, 18.63.
25. **General procedure**. The phosphorylating agent (triethyl phosphite, triisopropyl phosphite, tributyl phosphite, dibutyl-isopropyl phosphinite, diphenyl-isopropyl phosphinite or diisopropyl-phenyl phosphonite, accordingly) (5.80 mmol) was added to a solution of chloromethylthiacalix[4]arene **7** (0.5 g, 0.73 mmol) in dry chloroform (50 ml) with stirring. The reaction mixture was stirred at rt for 4 h. The solvent was removed under vacuum (10 mmHg) at rt. Hexane (20 ml) was added to the residue and the precipitate was (quickly) filtered and washed twice with hexane (2×10 ml) and water (2×10 ml). The obtained product was dried for 2 h under vacuum (0.01 mmHg) at 50°C. **8a**. (0.56 g, 71%). Mp 117–120°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 24H, J=7.0 Hz, CH_3), 2.92 (d, 8H, J=21.3 Hz, CH_2-P), 4.01 (m, 16H, CH_2-O), 7.55 (s, 8H, H-arom.), 9.38 (s, 4H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.39 (d, J=5.0 Hz, P-O-CH_2-CH_3), 32.30 (d, J=140 Hz, P-CH_2), 62.29 (d, J=6.4 Hz, P-O-CH_2), 120.86 (s, C-arom.), 125.21 (d, J=8.9 Hz, C-arom.), 140.35 (d, J=5.6 Hz, C-arom.), 156.86 (s, C-arom.); ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.7. Anal. calcd for $C_{44}H_{60}O_{16}P_4S_4$, %: C, 48.17; H, 5.51; P, 11.29; S, 11.69. Found, %: C, 47.90; H, 5.31; P, 11.26; S, 11.48. **8b**. (0.72 g, 82%). Mp 107–110°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 and 1.25 (two d, 48H, J=6.3 Hz, diastereotopic CH_3 groups), 2.88 (d, 8H, J=21.3 Hz, CH_2-P), 4.55 (m, 8H, CH-O), 7.55 (d, 8H, J=2.6 Hz, H-arom.), 9.30 (s, 4H, OH); ^{31}P NMR (121 MHz, $CDCl_3$): δ 23.7. Anal. calcd for $C_{52}H_{76}O_{16}P_4S_4$, %: C, 51.65; H, 6.33; P, 10.25; S, 10.61. Found, %: C, 51.40; H, 6.17; P, 10.06; S, 10.50. **8c**. (0.48 g, 50%). Mp 101–105°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (t, 24H, J=6.8 Hz, CH_3), 1.30 (m, 16H, CH_2-CH_3), 1.54 (m, 16H, CH_2-CH_2-CH_3), 2.95 (d, 8H, J=21.3 Hz, CH_2-P), 3.95 (m, 16H, CH_2-O), 7.56 (s, 8H, H-arom.), 9.41 (s, 4H, OH). ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.9. Anal. calcd for $C_{60}H_{92}O_{16}P_4S_4$, %: C, 54.53; H, 7.02; P, 9.38; S, 9.71. Found, %: C, 54.23; H, 6.97; P, 9.26; S, 9.70. **8d**. (0.78 g, 90%). Mp 154–157°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 24H, J=7.0 Hz, CH_3), 1.10–1.80 (m, 48H, CH_2-CH_2-CH_2-CH_3), 2.88 (d, 8H, J=12.2 Hz, CH_2-P), 7.57 (s, 8H, H-arom.), 9.41 (s, 4H, OH). ^{31}P NMR (121 MHz, $CDCl_3$): δ 46.4. Anal. calcd for $C_{60}H_{92}O_8P_4S_4$, %: C, 60.38; H, 7.77; P, 10.38; S, 10.75. Found: C, 60.47; H, 7.97; P, 10.12; S, 10.37. **8e**. (0.88 g, 90%). Mp 182–185°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (d, 8H, J=13.4 Hz, CH_2-P), 7.38 (m, 32H, H-arom.), 7.62 (m, 16H, H-arom.), 9.21 (s, 4H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.38 (d, J=66.3 Hz, P-CH_2), 120.61 (s, C-arom.), 124.66 (d, J=5.1 Hz, C-arom.), 128.52 (d, J=10.3 Hz, C-arom.), 130.92 (d, J=7.6 Hz, C-arom.), 131.93 (s, C-arom.), 132.33 (s, C-arom.), 140.50 (s, C-arom.), 156.50 (s, C-arom.); ^{31}P NMR (121 MHz, $CDCl_3$): δ 29.4. Anal. calcd for $C_{76}H_{60}O_8P_4S_4$, %: C, 67.44; H, 4.47; P, 9.15; S, 9.48. Found, %: C, 67.48; H, 4.48; P, 9.10; S, 9.37. MS (FAB) m/z 1353 ([M$^+$]). **8f**. (0.79 g, 85%). Mp 128–130°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 and 1.28 (2 d, 24H, J=6.0 Hz, diastereotopic CH_3 groups), 3.01 (d, 8H, J=17.2 Hz, CH_2-P), 4.50 (m, 4H, CH-O), 7.28–7.63 (m, 28H, H-arom.), 9.30 (s, 4H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.94 and 24.40 (2 s, diastereotopic CH_3 groups), 36.96 (d, J=96.0 Hz, P-CH_2), 70.30 (s, CH-O), 120.50 (s, C-arom.), 125.05 (s, C-arom.), 128.33 (d, J=11.4 Hz, C-arom.), 129.85 (s, C-arom.), 131.71 (d, J=8.4 Hz, C-arom.), 132.29 (s, C-arom.), 140.41 (s, C-arom.), 156.48 (s, C-arom.); ^{31}P NMR (121 MHz, $CDCl_3$): δ 37.9. Anal. calcd for $C_{64}H_{68}O_{12}P_4S_4$, %: C, 59.99; H, 5.35; P, 9.67; S, 10.01. Found, %: C, 59.30; H, 4.98; P, 9.56; S, 9.93.
26. Crystal data for compound **8b**: $C_{52}H_{76}O_{16}P_4S_4$, M=1209.25, monoclinic space group P-1, a=10.6680(4), b=15.7287(6), c=20.3154(9) Å, α=93.376(1), β=103.361(1), γ=106.842(1)°, V (Å^3)=3145.2(2), Z=2, D_x (mg m^{-3})=1.277, μ (mm^{-1})=0.314, radiation type: MoKα; wavelength=0.71073 Å, temperature=120(2) K, F(000)=1280. Diffractometer Nonius Kappa CCD, crystal form: plate; crystal size: 0.20×0.15×0.05 mm; crystal color: colorless; No. of measured reflections=12915, θ range=1.018–20.79°. Refinement method: full-matrix least-squares on F^2; structure solution: SHELXS-97 (Sheldrick, 1990); structure refinement: SHELXL-97 (Sheldrick, 1997), R(F), R$_w$(F^2) [I>2σ(I)]–0.0513, 0.1077, R(F), R$_w$(F^2) all data –0.0774, 0.1152. The crystallographic data for the crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 203909.