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Synthesis of enantiomeric menthol derivatives for forming and probing chiral surfaces. X-ray crystal and molecular structures of (+)-(1*S*,2*R*,5*S*)-1-(2-tricyanovinyl-1*H*-pyrrol-1-yl-methoxy)-2-isopropyl-5-methylcyclohexane

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Abstract—Two enantiomeric pairs of menthol derivatives, the menthol ester with 10-undecynoic acid and the 2-tricyanovinyl-pyrrole derivative of the methoxy-menthol, have been synthesized and their pure enantiomers obtained. The X-ray crystal and molecular structure of the (+)-enantiomer of the latter compound is reported.

1. Introduction

To investigate the electrochemical enantioselectivity displayed by chiral surfaces, we decided to synthesize the pure enantiomers of two different enantiomeric pairs, bearing additional functional groups suitable for specific experiments to be carried out. The main enantiomeric pair molecules would be used as probes in solution in order to induce both chiral and electroactive interactions, by analogy to well-known species, tested in asymmetric electrochemistry on various solid chiral surfaces, such as (*S*,*S*)- and (*R*,*R*)-tartaric acid on Au/CuO[1] or D- and L-glucose on Pt[2] or Au.[3] The other pair could be used for inducing chirality on the surfaces of inorganic solids after chemisorption, providing a stable chiral interfacial region potentially useful for many applications, whenever an enantioselective discrimination capability is required.[4–7] To this end, these enantiomers have been functionalized with a terminal HC≡C– group for attaining a covalent anchoring, as reported in the literature, on the surfaces of important materials such as silicon[8] or carbon.[9] In this context, starting from commercial (+)- and (−)-menthols, we attached 2-tricyanovinylpyrrole (TCVP), which is a reversible redox group, thus affording 1-(2-tricyanovinyl-1*H*-pyrrol-1-yl-methoxy)-2-isopropyl-5-methylcyclohexane **1** in both forms, (+)-**1** and (−)-**1**. The same menthols were then esterified with 10-undecynoic acid, and transformed into the derivative 1-(10-undecynoate)-2-isopropyl-5-methylcyclohexane **2**, again in both enantiomeric forms (+)-**2** and (−)-**2**. It should be noted that by following this strategy, the same chiral substrates, for example, (+)- and (−)-menthol, are present in the two pairs and, as a consequence, one may expect to observe a chiral discrimination, when running the proper experiments, for instance, when silicon or carbon electrode surfaces, modified by covalently binding **2**'s, are probed with **1**'s. Herein we report the synthesis and characterization of **1** and **2**. The X-ray crystal and molecular structure of (+)-**1** are also reported.

2. Results and discussion

2.1. Synthesis

All reactions were carried out starting from menthol (Scheme 1). Compound **2** has been prepared following a method reported in the literature for the esterification of carboxylic acids.[10] However, the synthesis of **1** is new and deserves some comments. Compounds similar to **1**, such as 2-tricyanovinyl-*N*-methyl-[11] or -*N*-phenyl-pyrrole,[12] are well-known and have been prepared from pyrrole through

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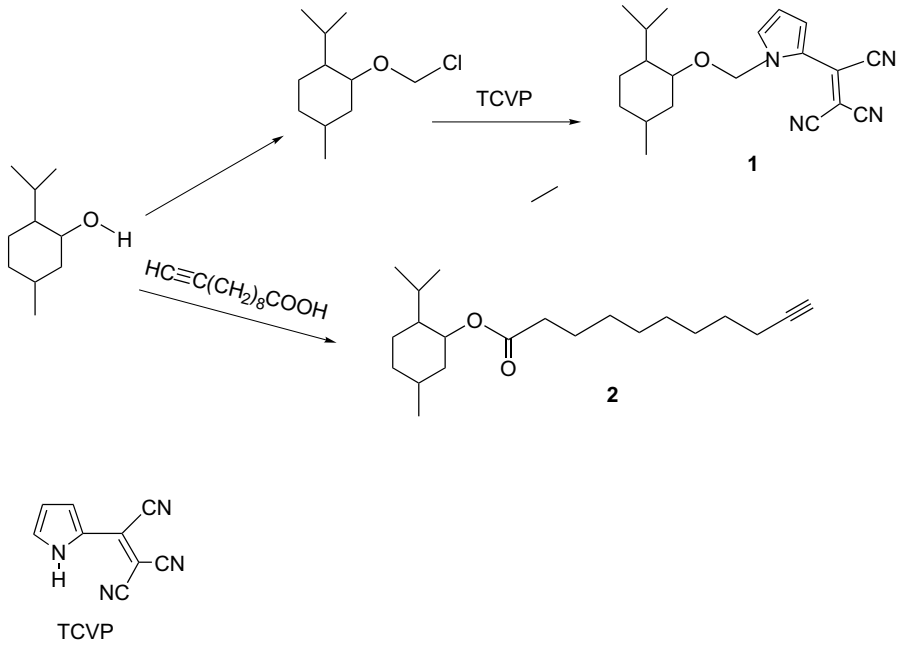

Scheme 1.

a two-step procedure. First, the pyrrole nitrogen is alkylated and the resulting product then reacted with tetracyanoethylene (TCNE) to give 2-tricyanovinyl-derivative in high yield. Here, the well-known chloromethyl-menthyl-ether has been selected as an alkylating agent for joining the menthol to the pyrrole. With this particular reactant however, the order of the steps in the above procedure must be inverted to obtain a satisfactory yield of the desired product. TCVP was first made, as described in the literature,[11] and then alkylated by adopting the reaction conditions we have previously applied in the mono-alkylation, with an ordinary halide, of the primary amino-group of a poorly nucleophilic amine, the anion C_5N_3–$C_4N(CN)_2$–NH_2^-.[13] Interestingly, this reaction proceeds more smoothly on TCVP than on the above substrate, probably due to the electrophilicity of the alkylating halide in the current case being enhanced by the presence of an oxygen atom at the α position.

2.2. X-ray crystal structure analysis of (+)-1-(2-tricyanovinyl-1*H*-pyrrol-1-yl-methoxy)-2-isopropyl-5-methylcyclohexane (+)-1

In order to confirm that the original configuration of the parent (+)-menthol has not been modified during the synthesis of **1**, we have undertaken the X-ray crystal structure of the final product. The (+)-**1** enantiomer crystallizes from a mixture of heptane/CH_2Cl_2 as very thin orange platelets. Crystal data: $C_{20}H_{24}N_4O$, $M = 336.44$, orthorhombic, $a = 7.677(6)$ Å, $b = 35.23(2)$ Å, $c = 7.188(6)$ Å, $V = 1943(2)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $D_c = 1.15$ Mg/m^3, $F(000) = 720$, μ(Cu-Kα) = 0.588 mm^{-1}, $T = 293$ K. A crystal of dimensions $0.95 \times 0.5 \times 0.01$ mm was selected and fixed on a glass fiber. Diffraction data were collected on a Rigaku four-circle diffractometer equipped with a rotating anode (graphite monochromated Cu-Kα radiation) by the θ–2θ scan method in the range $2.5° \leqslant \theta \leqslant 62.4°$. Data were corrected for Lorentz and polarization effects and from absorption by the semiempirical ψ-scan method. The structure was solved by direct methods and refined using the SIR2004 package of crystallographic programs.[14] Non-hydrogen atoms were refined anisotropically, while hydrogens were included at calculated positions and refined in a riding mode.

The refinement of 226 parameters, carried out on F^2, with the molecule in a (1*S*,2*R*,5*S*)-configuration, converged at $R_F = 0.055$ for 1141 reflections with $F_0 > 3\sigma(F_0)$.

Refinement of the absolute structure Flack factor x[15] for such a configuration gave the expected value for the right solution $x = 0.00$, while $x = 0.99$ for the inverted (1*R*,2*S*,5*R*)-configuration. Such values allowed us to unambiguously assign the (1*S*,2*R*,5*S*)-configuration to the (+)-enantiomer of compound **1** (see Fig. 1), thus confirming the fact that the configuration of the starting compound (+)-menthol has been retained.

2.3. Spectroscopic characterization of the new compounds

The IR and ^{1}H NMR spectroscopic data clearly support the given formulae of both **1** and **2** and are directly related to the analogous data of the corresponding starting materials. For **1**, the IR spectrum shows the medium intensity bands in the 3132–3102 and 2951–2846 cm^{-1} regions, due to the C–H stretching vibrations of pyrrole and menthol, respectively, and the strong sharp band with a maximum at 2232 cm^{-1} due to the C≡N stretching vibration. Another significant feature of this spectrum is the absence of absorptions expected from the stretching vibrations of N–H of pyrrole and of C–Cl of chloromethylmenthyl ether, falling at 3357 and 644 cm^{-1}, respectively, in the starting materials. The ^{1}H NMR data are even more diagnostic,

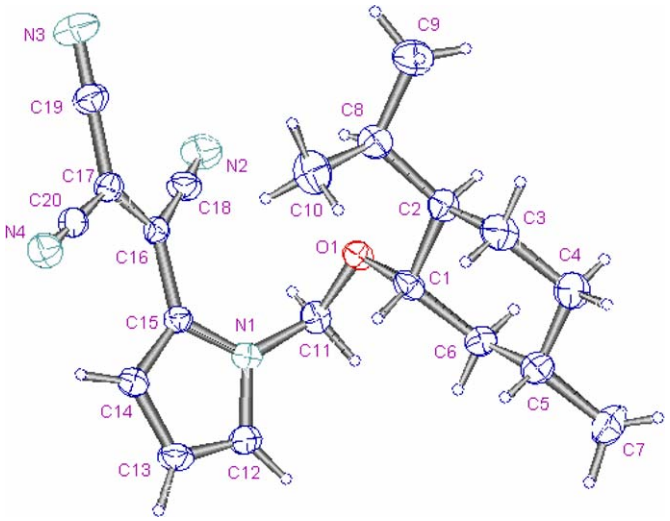

Figure 1. A perspective view of the molecular structure of the (+)-**1** enantiomer in its (1*S*,2*R*,5*S*) configuration showing the labelling of the atoms. Displacements ellipsoids are at 30% probability level. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 602438.

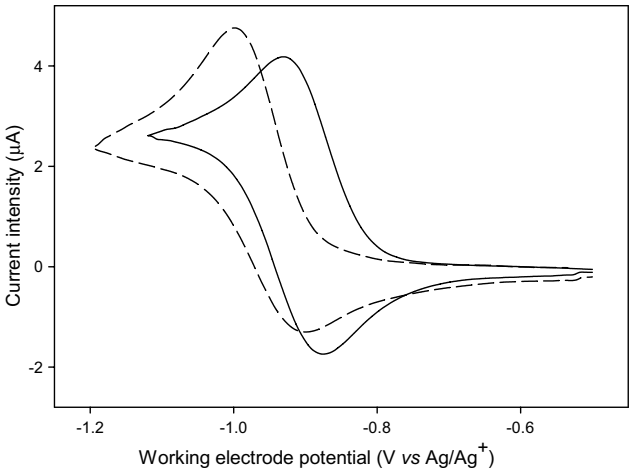

Figure 2. Cyclic voltammogram of TCVP (---) and **1** (—); (0.00166 M) in a 0.1 M TBAP acetonitrile solution. Scan rate 0.1 V s^{-1}, Pt working electrode.

revealing the signals of the pyrrole protons at the 3, 4 and 5 positions and of the protons of the menthyl-methyl-ether residue as well. Incidentally, it should be noted that in **1**, the interaction between the two non-equivalent protons of the group CH_2O (δ 6.03–5.81, $J \sim 11.7$) is larger than that between the protons of the analogous group (CH_2Cl) in the chloromethylmenthyl ether (δ 5.62 5.55, $J \sim 5.4$). Also for compound **2**, the spectroscopic characterization is straightforward. The IR shows the stretching bands of the distinctive groups present: C–H of menthol at 2955–2857, H–C≡ at 3312 and C=O at 1731 cm^{-1}. In the ^{1}H NMR spectra, the typical signals of the undecynoic acid residue are easily assignable: the triplets from –CH_2–CO (δ 2.31, J 7.6), from –CH_2–C≡C (2.21, J 6.8) further split by the interaction with acetylenic proton (J 2.6) and finally the triplet from H–C≡C, which is clearly identifiable (1.96, J 2.8), although it overlaps the menthol proton signals.

2.4. Electrochemical properties of 1

The electrochemical properties of **1** were examined in view of its use as electrochemical probe.

In this context, a comparison between **1** and TCVP is interesting. In Figure 2, the CV's of both compounds are reported. Noticeably, the reduction is easier and more reversible in **1** than in TCVP, as shown by the associated parameter values: the half-wave potential is less negative ($E_{1/2}$ −0.87 and −0.93 V), the peak potential difference is lower (Δ_p 0.08 and 0.10 V) and the charges passed during the cathodic and anodic sweeps are closer to each other (1.95 and 1.17 μC in **1**, 2.66 and 1.27 μC in TCVP). Finally, controlled potential coulometry on **1** was performed. This revealed that an irreversible following reaction occurs involving **1** itself so that the specific Faradaic charge passed is just 0.5 electron/molecule during the coulometry time interval. This could explain the lack of a fully reversible reaction during the CV time interval also, suggesting that the anion radical **1**$^{-\cdot}$, produced during the reduction, reacts with neutral **1** at a rate comparable with that of the electron transfer process.

3. Experimental

3.1. General

Melting points were determined on a Büchi SMP-20 model melting point apparatus. Elemental analyses were carried out by Servizio Microanalisi of CNR, Area della Ricerca di Roma. Solution optical spectra were recorded in $CHCl_3$ on a Cary 5 spectrometer; the wavelength band maximum (λ/nm), the corresponding extinction coefficient (ε/dm^3 mol^{-1} cm^{-1}) and half-height band width (*hhw*/nm) are given. IR measurements were performed with a Perkin–Elmer 16F PC FT spectrometer on KBr pellets (0.75% w/w) or as neat liquid between CsI disks; the stretching frequencies (ν/cm^{-1}) of the absorption maximum are given and the most significant bands assigned. The ^{1}H NMR spectra were obtained in $CDCl_3$ or C_2D_6CO solution with a Bruker AMX-250 spectrometer. The chemical shifts (δ/ppm) are in reference to the residual $CHCl_3$ proton (7.238 ppm, singlet) of $CDCl_3$ or to the residual C_2HD_5CO proton (2.078 ppm, quintuplet) of C_2D_6CO. The J-values are given in hertz. Electrochemical measurements were made under prepurified dinitrogen with an AMEL electrochemistry system (Model 568 function generator, Model 2059 potentiostat, Model 721 integrator) in 0.1 M NBu_4ClO_4 (tetrabutylammonium perchlorate, TBAP, dried under vacuum at 60 °C) in dry CH_3CN; a silver wire immersed in 0.01 M $AgNO_3$/0.1 M TBAP in acetonitrile, separated from the main solution by a porous fritted glass + agar plug, served as a reference electrode. Coulometric experiments were carried out in a two-compartment cell with Pt-wire electrodes. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter.

3.2. Materials

Tetracyanoethylene (TCNE), *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine or proton sponge (PS), (+)-menthol, (−)-menthol, 1,3,5-trioxane, pyrrole, $MgSO_4$, 10-undecynoic acid, *N*,*N*-dimethylaminopyridine (DMAP), Et_3N, $Me_3N{\cdot}HCl$, dimethylsulfamoyl chloride (Me_2NSO_2Cl), TBAP were commercial reagents of Fluka analytical grade. The reaction solvents, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were carefully dried and freshly distilled before use; in particular, they were refluxed and then distilled at atmospheric pressure under dinitrogen over sodium-benzophenone ketyl (THF), or CaH_2 (CH_2Cl_2) and CH_3CN). Tricyanovinylpyrrole ($C_9H_4N_4$, TCVP) was prepared from TCNE and pyrrole in acetone, following the procedure reported in the literature[11] (mp: 212–215 °C dec, lit.: 211–213 °C). Furthermore, it was purified by column chromatography on silica gel (220–440 mesh) eluting with CH_2Cl_2/acetone (97/3) and characterized by optical, IR and ^1H NMR spectroscopy: λ_{max} 422, ε_{max} 24500, *hhw* 53; ν_{max} 3357 (N–H), 3140–3103 (CH pyrrole ring), 2225 (CN), 1156, 1496, 1465, 1421, 1352, 1262, 1145, 1062, 955, 874, 844, 773, 695, 652, 607, 579, 545, 530, 506; δ 7.76–7.75 (1H, dd, *J* 1.4, 1.4, C_3H), 7.61–7.59 (1H, dd, *J* 1.4, 1.4, C_5H), 6.74–6.71 (1H, dd, *J* 2.4, 2.4, C_4H), 5.77 (1H, d, *J* 2.6, NH). Cyclic voltammetry: E_{pc} −0.98 and −0.88 V.

The (1*S*,2*R*,5*S*)- and (1*R*,2*S*,5*R*)-1-(chloromethoxy)-2-isopropyl-5-methylcyclohexane, or (+)- and (−)-chloromethyl-menthyl-ether, enantiomers were prepared from commercial (+)- and (−)-menthol, respectively, according to a recipe reported in the literature.[16] They were purified by distillation under reduced pressure: bp 94 °C (2.0 mm Hg) [lit. bp 82–84 °C (0.8 mm Hg)]; $[\alpha]_D^{20} = +7.7$ and −7.2 (*c* 2.5, $CHCl_3$); ν_{max} 2955–2848 (CH), 1456, 1386, 1369, 1346, 1312, 1286, 1257, 1236, 1180, 1160, 1121, 1034, 992, 980, 952, 905, 879, 841, 644 (CCl); δ 5.62–5.55 (2H, dd, *J* 5.4, 5.4, CH_2Cl), 3.58–3.48 (1H, ddd, *J* 4.2, 4.3, 4.3, C_1H), 2.14 (2H, m, CH), 1.67 (2H, m, CH), 1.27 (2H, m, CH), 0.92 [9H, m, CH+CH_3(isopropyl)], 0.80 [3H, d, *J* 7.0, CH_3 (methyl)].

3.3. Synthesis of 1-(2-tricyanovinyl-1*H*-pyrrol-1-yl-methoxy)-2-isopropyl-5-methylcyclohexane 1

A solution of TCVP (0.150 g, 1.39 mM), PS (0.300 g, 1.40 mM) and chloromethyl-menthyl-ether (0.494 g or 0.5 mL, 2.41 mM) in THF (5 mL) was reacted under nitrogen at 25 °C for 16 h. The solvent was removed under a stream of air. The residue was purified by column chromatography on silica gel (220–440 mesh) eluting with CH_2Cl_2. The first yellow eluted fraction was collected and evaporated to dryness. After crystallization from *n*-heptane, light orange crystals of **1** (0.175 g, 38%) were obtained, mp: 83–85 °C (Found: C, 71.37; H, 7.42; N, 16.74. $C_{20}H_{24}N_4O$ requires C, 71.40; H, 7.19; N, 16.65); λ_{max} 439, ε_{max} 21,200, *hhw* 58; ν_{max} 3132–3102 (CH pyrrole ring), 2951–2846 (CH menthol), 2232–2221 (CN), 1534, 1484, 1449, 1416, 1394, 1330, 1246, 1212, 1174, 1102, 1091, 1072, 1050, 1028, 952, 846, 772, 730, 682, 595, 558, 546, 522; δ 7.86–7.84 (1H, dd, *J* 1.8, 1.6, C_3H pyrrole ring), 7.68–7.65 (1H, dd, *J* 1.6, 1.6, C_5H pyrrole ring), 6.60–6.57 (1H, dd, *J* 2.4, 2.4, C_4H pyrrole ring), 6.03–5.81 (2H, dd, *J* 11.6 11.8, CH_2O), 3.28–3.18 (1H, ddd, *J* 4.4, 4.4, 4.2, C_1H), 1.87 (2H, m, CH), 1.65 (2H, m, CH), 1.64 (2H, m, CH), 0.90 [9H, m, CH+CH_3(isopropyl)], 0.50 [3H, d, *J* 7.0, CH_3 (methyl)]. Cyclic voltammetry: E_{pc} −0.91 and −0.83 V. Potentiostatic coulometry for 16.14 mg in CH_3CN, at −1.05 V (vs $Ag/AgNO_3$): initial current 0.4 mA, Faradic charge passed 2.28 C (required charge for the monoreduction of **1** 4.63 C. The (+)-**1** and (−)-**1** pure enantiomers were prepared starting from the corresponding (+)- and (−)-chloromethyl-menthyl-ether, respectively; $[\alpha]_D^{20} = +4.2$ and −4.05 (*c* 1.5, $CHCl_3$).

3.4. Synthesis of 1-(10-undecynoate)-2-isopropyl-5-methylcyclohexane 2

This ester ($C_{21}H_{36}O_2$) was prepared from menthol and 10-undecynoic acid in CH_3CN and in the presence of DMAP, Et_3N, $Me_3N{\cdot}HCl$ and Me_2NSO_2Cl according to a procedure reported in the literature for the esterification of menthol.[10] This was purified by column chromatography on silica gel (220–440 mesh) eluting with *n*-hexane/ethylacetate (5/1). Colorless liquid (yield 50%); ν_{max} 3312 (H–C≡C), 2955–2857 (CH), 1731 (C=O), 1455, 1370, 1242, 1179, 1099, 1039, 1012, 984, 965, 917, 844, 725, 630; δ 4.76–4.66 (1H, ddd, *J* 4.6, 4.4, 4.4, C_1H menthol), 2.31 (2H, t, *J* 7.6 CH_2–CO), 2.24–2.18 (2H, m, CH_2–C≡), 1.96–1.95 [3H, m, CH(menthol)+≡C–H], 1.55 [16H, m, CH(menthol)+CH_2(undecynoic acid)], 0.93 [9H, m, CH+CH_3-(isopropyl)], 0.79 [3H, d, *J* 7.0, CH_3 (methyl)]. The (+)-**2** and (−)-**2** pure enantiomers were prepared starting from the corresponding (+)- and (−)-menthol, respectively; $[\alpha]_D^{20} = +4.7$ and −4.9 (*c* 1.5, $CHCl_3$).

References

1. Switzer, J. A.; Kothari, H. M.; Polzot, P.; Nakanishi, S.; Bohannan, E. W. *Nature* **2003**, *425*, 490–493.
2. Attard, G. A. *J. Phys. Chem. B* **2001**, *105*, 3158–3167.
3. Martins, A.; Ferreira, V.; Queirós, A.; Aroso, I.; Silva, F.; Feliu, J. *Electrochem. Comm.* **2003**, *5*, 741–746.
4. Pirkle, W. H.; Chang, J. P.; Burke, J. A. *J. Chromatogr.* **1992**, *598*, 1–6.
5. Mariani, R. D.; Abruna, H. D. *J. Electrochem. Soc.* **1989**, *136*, 113–119.
6. Avnir, D.; Wellner, E.; Ottolenghi, M. *J. Chem. Soc., Chem. Comm.* **1984**, 452–453.
7. Blaser, H. U. *Tetrahedron: Asymmetry* **1991**, *2*, 843–866.
8. Sieval, A. B.; Opitz, R.; Maas, H. P. A.; Schoeman, M. G.; Meijer, G.; Vergeldt, F. J.; Zuilhof, H.; Sudhölter, E. J. R. *Langmuir* **2000**, *16*, 10359–10368.
9. Ssenyange, S.; Anariba, F.; Bocian, D. F.; McCreery, R. L. J. *Langmuir* **2005**, *21*, 11105–11112.
10. Wakasugi, K.; Nakamura, A.; Iida, A.; Nishii, Y.; Nakatani, N.; Fukushima, S.; Tanabe, Y. *Tetrahedron* **2003**, *59*, 5337–5345.
11. Sausen, G. N.; Engelhardt, V. A.; Middleton, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 2815–2822.
12. McCormac, T.; Farrell, D. *Electrochimica Acta* **2001**, *46*, 3287–32909.
13. Fares, V.; Flamini, A.; Pasetto, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4520–4525.

14. Burla, M. C.; Calandro, R.; Cavalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381–388.
15. Flack, H. D. *Acta Cryst.* **1983**, 876–881.
16. Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1529–1535.