evaporated in vacuo from the filtrate to afford the air-sensitive, analytically pure **4** (4.48 g, 66%). Colorless, single crystals suitable for X-ray structure analysis were obtained from hexane. Elemental analysis $C_{72}H_{168}N_{32}Si_{16}Tl_8$ (%): calcd: C 24.25, H 4.75, N 12.6; found: C 25.9, H 4.80, N 12.4; ^{1}H NMR (500.13 MHz, $C_6D_5CD_3$, 293 K): $\delta = 9.72$ (s, 2H), 8.45 (s, 1H), 0.21 (s, 18H, $SiMe_3$); $^{13}C\{^1H\}$ NMR (125.76 MHz): $\delta = 175.5$, 167.45, 0.6.

Crystal data for **3**: $C_{27}H_{63}Na_3N_{12}Si_6(C_6H_{12})_{1/2}$, $M_r = 835.5$, triclinic, space group $P\bar{1}$ (no. 2), $a = 10.372(8)$, $b = 22.57(2)$, $c = 23.50(2)$ Å, $\alpha = 92.76(6)$, $\beta = 102.75(5)$, $\gamma = 103.25(6)^\circ$, $V = 5194(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.07$ g cm^{-3}, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $\mu(Mo_{K\alpha}) = 2.2$ cm^{-1}. Data for a specimen of dimensions $0.4 \times 0.4 \times 0.4$ mm^3 were collected at 173(2) K on an Enraf-Nonius CAD-4 diffractometer, 14448 unique reflections for $2^\circ < \theta < 23^\circ$, $R1 = 0.078$ (for 9400 reflections with $I > 2\sigma(I)$), w$R2 = 0.235$ (all data). In **3** there are two independent molecules of the trimer and one poorly defined cyclohexane solvent molecule. For **4**: $C_{72}H_{168}N_{32}Si_{16}Tl_8$, $M_r = 3566.8$, monoclinic, space group $C2/c$, $a = 15.6556(4)$, $b = 30.3470(9)$, $c = 30.2663(3)$ Å, $\beta = 96.195(1)^\circ$, $V = 14295.6(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.657$ g cm^{-3}, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $\mu(Mo_{K\alpha}) = 0.9159$ cm^{-1}. Data for a specimen of dimensions $0.33 \times 0.21 \times 0.12$ mm^3 were collected at 193 K in the hemisphere mode on a Siemens P4 instrument fitted with a CCD area detector, 8557 unique reflections for $4.6^\circ < \theta < 54^\circ$, $R1 = 0.0565$ (for 6019 reflections with $I > 2\sigma(I)$), w$R2 = 0.1443$ (all data). Each of the structures **3** and **4** was solved by using the heavy atom method and refined with full-matrix least-squares on all F^2 (SHELXL-93 and 97, respectively) with non-hydrogen atoms anisotropic.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133067 and -133068. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Genetic Engineering of *Streptomyces coelicolor* A3(2) for the Enantioselective Reduction of Unnatural β-Keto-Ester Substrates**

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The use of whole cells for the biotransformation of organic substrates is a well-documented technique[1] which has a number of benefits over conventional, reagent-based methods. For example, bakers' yeast is routinely used for the reduction of β-keto-esters, and the resulting β-hydroxy-esters are obtained with predictably high chemo- and enantioselectivities, under mild and neutral conditions.[2] With the huge advances made in molecular biology over the last 20 years it has become possible to manipulate microbial biosynthetic pathways at the genetic level.

For a number of years Hopwood et al.[3] and others[4] have been studying the genetics of *Streptomyces coelicolor* A3(2), a soil bacterium that produces the dimeric benzoisochromanequinone antibiotic actinorhodin (**1**). The biosynthesis of **1** proceeds by the polyketide pathway outlined in Scheme 1,[5] where key features involve a type II minimal *act* polyketide synthase (PKS)—consisting of β-ketoacyl synthase (KS), chain length factor (CLF), and acyl carrier protein (ACP)—and associated aromatase and cyclase enzymes to assemble the naphthol **2**, which undergoes selective reduction to **3** and cyclization to the yellow pigment (*S*)-DNPA (**4**). Recently we have provided definitive proof that the *act*VI genetic region of *S. coelicolor* A3(2) is involved in the stereospecific construction of the pyran ring of **1**.[6] More specifically it was found that the engineered strain CH999/pIJ5660 (a pRM5-based plasmid[4b] containing the *act* minimal PKS, aromatase (ARO), and cyclase (CYC) genes as well as the *act*VI-

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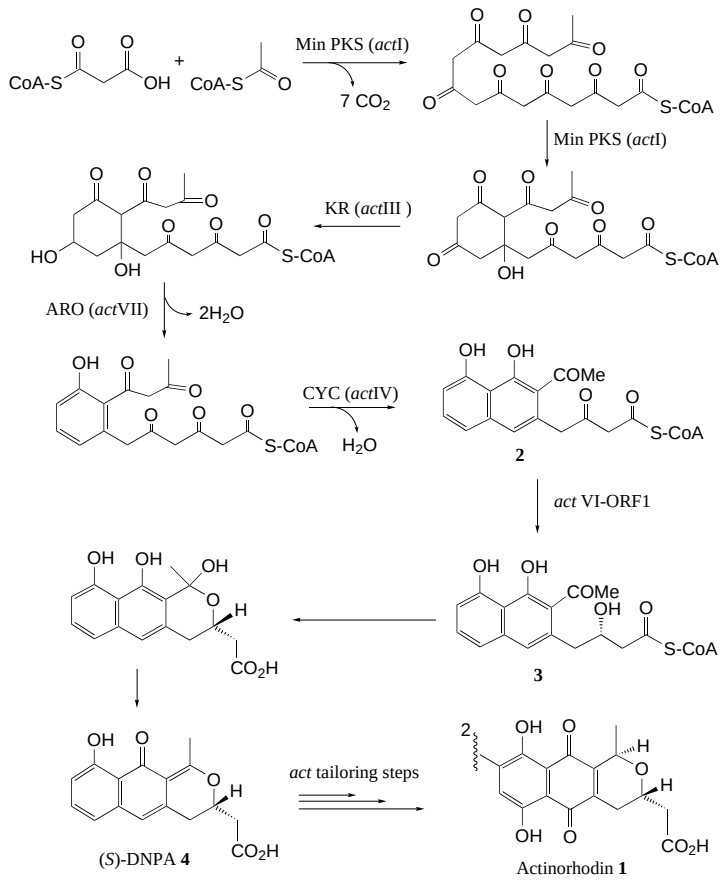
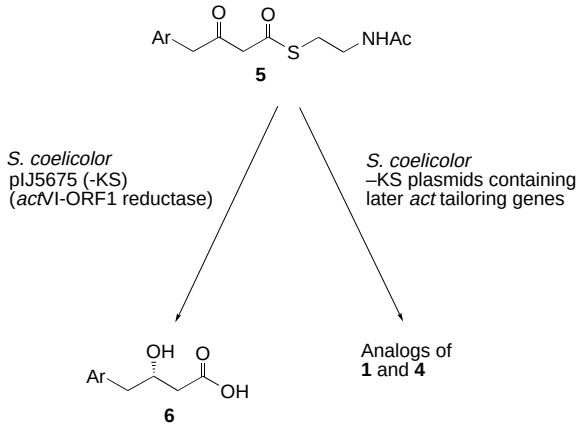


Scheme 1. Biosynthesis of actinorhodin (**1**). CoA = coenzyme A.

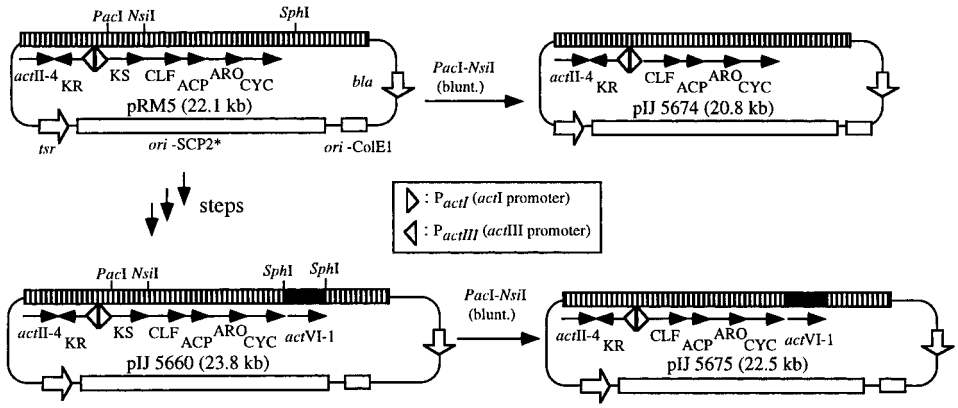
ORF1 gene) produced **4** with complete selectivity. This clearly indicates that the *act*VI-ORF1 gene encodes the reductase that selectively reduces C-3 in the β-keto-ester **2**, thus ultimately creating one of the corresponding stereocentres in the pyran ring of **1** (Scheme 1).

Here we describe the construction of pIJ5675, a pRM5-based recombinant plasmid containing the *act*VI-ORF1 gene, like pIJ5660, but in which a gene (*act*I-ORF1) for the ketosynthase (KS) has been deleted from the minimal *act* PKS gene cluster (Scheme 2). This was carried out with the express aim of feeding unnatural β-keto-ester substrates such as **5** (Scheme 3) so that the action of the *act*VI-ORF1 reductase would lead to the stereospecific formation of analogues of **3** (e.g. **6**).[7] Since pIJ5675 lacks the KS gene involved in the formation of the early polyketide products by the natural pathway shown in Scheme 1 the natural substrate **2** would not be formed and therefore there would be no competition between **2** and unnatural substrates such as **5**. The results reported herein prepare the way for the initiation of a larger, more ambitious program involving the construction of KS-deficient plasmids to which the feeding of unnatural substrates may allow the biosynthesis of functionalized analogues of **4** and eventually **1**.



Scheme 3. Feeding of the unnatural β-keto-ester substrates **5**.

The *N*-acetylcysteamine (NAC) thioesters were chosen as they are known to be good analogues of SCoA.[8] The substrates **8**–**10** were prepared from the corresponding arylacetic acid chlorides using the methodology developed by Gilbert et al.[9] Thus, treatment of the Meldrum's acid derivatives **7** with *N*-acetylcysteamine leads to the NAC thioesters in reasonable overall yield from the starting acids (Scheme 4). We also sought to prepare the more complex NAC thioester **13**, closely resembled the natural substrate **2** in the actinorhodin pathway. The basic naphthalene core of **13** was easily assembled using the elegant methodology developed by Yamaguchi et al.[10] and furnished multigram quantities of the diester **11** in an operationally simple, though low yielding step. Protection of the phenolic units followed by selective ester hydrolysis gave the acid ester **12** in excellent yield. Attempts to form **13** by the above



Scheme 2. Scheme for the construction of the recombinant plasmids. The starting plasmid, pRM5, is bifunctional for replication in both *E. coli* (ColE1 replicon: *ori*-ColE1) and *Streptomyces* (SCP2* replicon: *ori*-SCP2*). Selection marker genes used: *bla* (β-lactamase) for *E. coli*, *tsr* (thiostrepton resistance) for *Streptomyces*. The *act* genes to be expressed: *act*II-4 (pathway-specific activator), KR (ketoreductase), KS (β-ketoacyl synthase), CLF (chain length factor), ACP (acyl carrier protein), ARO (aromatase), CYC (cyclase). pIJ5660 was constructed by introducing *act*VI-ORF1 gene at the *Sph*I site downstream of the CYC as described previously.[5] KS (–) derivatives of pRM5 and pIJ5660 were constructed in *E. coli* as follows: 1) restriction digests with the unique sites, *Pac*I and *Nsi*I, to remove the 1.3-kb KS gene; 2) treatment with T4 DNA polymerase to generate blunt ended fragments; 3) blunt-end ligation to afford pIJ5674 and pIJ5675.

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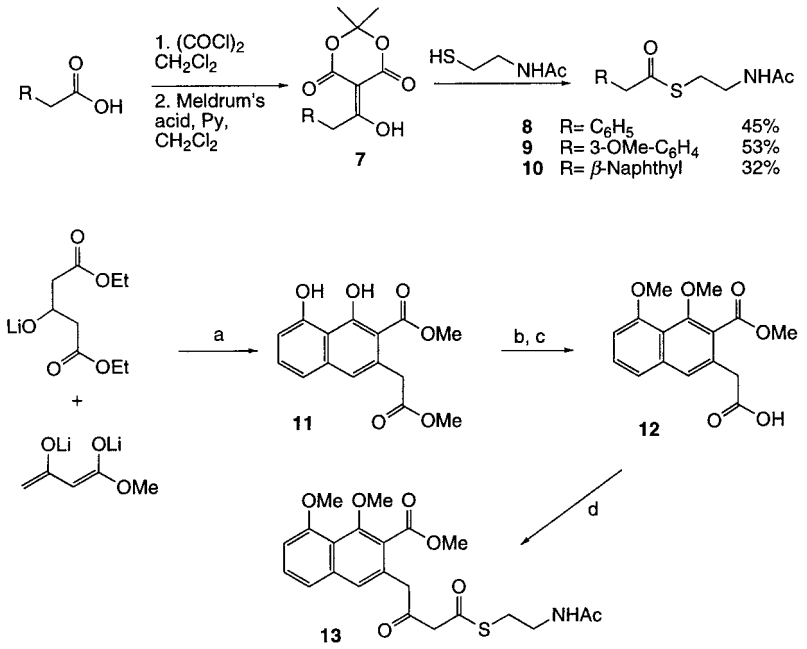


Scheme 4. Synthesis of substrates **8**–**10** and **13**. a) Ref. [10]; b) MeI, K_2CO_3, acetone, reflux, 88%; c) KOH, MeOH, H_2O, 93%; d) carbonyl diimidazole, THF, 6 h, then 5 equiv of $Mg(O_2CCH_2COSCH_2CH_2NHAc)_2$ (**14**), THF, room temperature, 8 h, 70% overall.

methodology failed with this more advanced intermediate due to the instability of the acid chloride. An alternative procedure was developed by which the required NAC thioester **13** could be synthesized in high yield by conversion of **12** into the corresponding acyl imidazole[11] followed by reaction with an excess of the magnesium half thioester salt **14** of *N*-acetylcysteamine (Scheme 4).

The four substrates **8**, **9**, **10**, and **13** were then incubated with mycelium of CH999/pIJ5675 (CH999 is *S. coelicolor* with the natural *act* gene cluster deleted[4b]) in a liquid YEME medium[3a] under sterile conditions at 30 °C for two days. After centrifugation and extraction the crude β-hydroxy acids were esterified to aid purification, and the resulting methyl esters (**15**–**18**) were purified by column chromatography. The results are summarized in Table 1. The enantioselectivity in each case was determined by NMR spectroscopy using a combination of chiral shift reagents and Mosher ester derivatives.[12] In all four cases the reduced β-hydroxy esters were obtained with good to excellent enantioselectivity (55–99% *ee*). Particularly noteworthy in that respect is the lactone **18**, which was formed as essentially a single enantiomer by cyclization of the initially formed β-hydroxy acid. This high selectivity is attributed to the close structural similarity between the NAC thioester **13** and the natural substrate of the *act*VI-ORF1 reductase (i.e., **2**).

The molecular structure of **18** was confirmed by X-ray crystallography (Figure 1).[13] It was also found that *N*-acetylcysteamine thioesters were essential because simple Me or *t*Bu esters were not reduced by CH999/pIJ5675. This indicates that NAC thioesters are required for recognition by the *act*VI-ORF1 reductase and/or they are required for successful transport across the cell membrane. Finally, as a control,

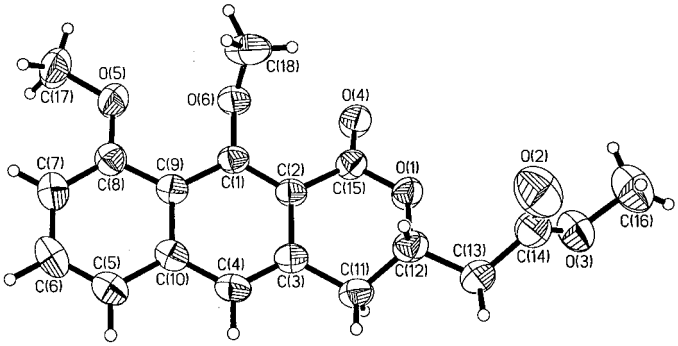
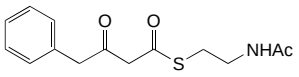
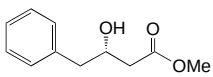
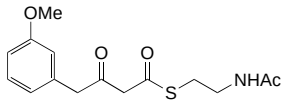
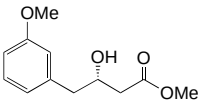
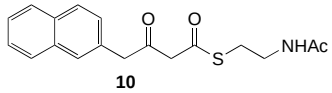
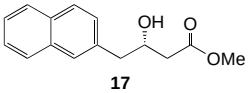
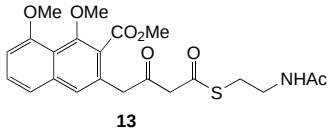
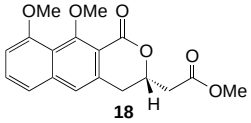


Figure 1. Molecular structure of tricyclic lactone **18** with 50% probability thermal elipsoids.

Table 1. Enantioselective reduction of NAC thioesters by the recombinant *S. coelicolor* A3(2) strain CH999/pIJ5675.

NAC substrate	Product	Yield [%]	*ee* [%][a]	$[\alpha]_D$[b]
 **8**	 **15**	18	85	+1.2 (c = 0.9)
 **9**	 **16**	27	74	+1.1 (c = 0.8)
 **10**	 **17**	55	55	+1.0 (c = 1.77)
 **13**	 **18**	42	99	−39.2 (c = 1.0)

[a] Determined by ^{1}H NMR spectroscopy using Mosher ester derivatives and confirmed with a chiral shift reagent (1 mg of substrate per 0.5 ml of $CDCl_3$; 1 equiv of $[Eu(hfc)_3]$ (hfc = 3-(heptafluoropropyl-hydroxymethylene)-D-camphorate). [b] Concentration in grams per 100 ml of CH_2Cl_2.

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the plasmid CH999/pIJ5674 was prepared which lacks both the KS and *act*VI-ORF1 genes (Scheme 2). Feeding of all four substrates (**8**–**10**, **13**) to this strain gave no reduction products. These results are highly significant in that they prove that the *act*VI-ORF1 gene is indeed the source of the reductase responsible for the formation of **15**–**18** and it is the same reductase that plays a role in the biosynthesis of actinorhodin.

In summary, these results establish, for the first time, the feasibility of novel biotransformations based on KS-deficient strains of *S. coelicolor*. We believe that this study has provided the groundwork for the engineering of more elaborate multienzyme constructs that will hopefully allow the biotransformation of simple NAC thioesters into complex, enantiopure, analogues of (*S*)-DNPA (**4**) and actinorhodin (**1**).

Experimental Section

Under sterile conditions a 250-ml conical flask was charged with 50 ml of YEME media, and a suspension of CH999/pIJ5675 spores in glycerol (0.2 ml) was added. In a separate flask the same procedure was repeated with CH999/pIJ5660 as an indicator of secondary metabolite production. The cultures were incubated on an orbital shaker at 30 °C until the indicator had turned dark brown (approx. 2 d). A solution of the NAC thioester **13** (0.15 g, 0.336 mmol) was dissolved in methanol (1 ml) and added to the CH999/pIJ5675 culture, which was shaken for a further 2 d at 30 °C. After centrifugation the supernatant was decanted and acidified to pH 1 with 2 M HCl, saturated with sodium chloride, and extracted with ethyl acetate (2 × 100 ml). The solvent was removed in vacuo to give a brown residue, which was dissolved in anhydrous methanol (1 ml) and then added to a premixed solution of acetyl chloride (0.2 g, 2.54 mmol) in anhydrous methanol (10 ml). The resulting solution was stirred for 15 min, and then the solvent removed in vacuo to give a brown residue. Purification by flash chromatography over silica gel (EtOAc/petroleum ether 30/70) gave the lactone **17** as white solid (46 mg, 42 %). M.p. 210–211 °C (from EtOAc/petroleum ether 40/60); $[\alpha]_D = -39.2$ ($c = 1.0$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} =$ 2956, 2840, 1734, 1624, 1564, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.7$ (dd, $^2J(H,H) = 16$, $^3J(H,H) = 7$ Hz, 1H; CH_2CO_2Me), 2.9 (dd, $^2J(H,H) = 16$, $^3J(H,H) = 6$ Hz, 1H; CH_2CO_2Me), 3.1 (ddd, $^2J(H,H) =$ 16, $^3J(H,H) = 10$, $^4J(H,H) = 1$ Hz, 1H; aryl−CH_2), 3.15 (ddd, $^2J(H,H) = 16$, $^3J(H,H) = 3.5$, $^4J(H,H) = 0.5$ Hz, 1H; aryl−CH_2), 3.68 (s, 3H; CO_2Me), 4.0 (s, 6H; 2 × aryl−OMe), 5.9 (m, 1H, CH_2CHOCH_2), 6.9 (dd, $^3J(H,H) = 8$, $^4J(H,H) = 0.5$ Hz, 1H; aryl−H), 7.3 (dd, $^3J(H,H) = 8$, $^4J(H,H) = 1$ Hz, 1H; aryl−H), 7.36 (s, 1H, aryl−H), 7.5 (approx. t, $^3J(H,H) = 8$ Hz; aryl−H); ^{13}C NMR (67.5 MHz, $CDCl_3$, 25 °C, $CHCl_3$): $\delta = 34.2$ (CH_2), 39.3 (CH_2), 52.0 and 56.3 (2 × aryl−OMe), 63.5 (CO_2CH_3), 73.7 (CH_2CHOCH_2), 106.6 (aryl−CH), 120.1 (aryl−CH), 121.5 (aryl−CH), 129.7 (aryl−CH), 134.8 (aryl−C), 139.1 (aryl−C), 157.9 (C=O, lactone), 161.7 (aryl−C), 162.0 (aryl−C), 170.1 (C=O, ester); HR-MS: calcd for $C_{18}H_{18}O_6$ (M^+): 330.1103, found: 330.1098.

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[12] Racemates of all four examples were prepared for comparison by $NaBH_4$ reduction of the methyl β-keto-esters corresponding to **8**–**10** and **13**. The absolute configuration of **15** was assigned by comparing the $[\alpha]_D$ value of (3*S*)-4-phenylbutanoic acid obtained from the feeding study (+2.6, $c = 1$) with that of the known (3*R*)-enantiomer (−5.3, $c = 1$): G. Capozzi, S. Roelens, S. Talami, *J. Org. Chem.* **1993**, *58*, 7932.

[13] Data were collected at 293 K on a Rigaku AFC7R diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å) and ω scans, and corrected for Lorentz polarization effects and absorption effects (ψ scans). The structure was solved by direct methods, and refined (isotropic U for all hydrogen atoms, anisotropic for all other atoms) by full-matrix least squares on F^2 (all data). Crystal data for **18** ($C_{18}H_{18}O_6$): colorless block, 0.45 × 0.25 × 0.15 mm, orthorhombic, space group $P2_12_12_1$, $a = 14.624(2)$, $b = 16.821(1)$, $c = 6.501(1)$ Å, $V = 1599.3(4)$ Å^3, $\rho_{calcd} = 1.372$ Mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.103$ mm^{-1}, $3.5 < 2\theta < 50°$; of 9946 reflections measured, 2396 were unique; $R_{int} =$ 0.0450, wR_2 (all data) = 0.0742, R_1 ($I > 2\sigma(I)$) = 0.0283, $S = 1.022$, Flack $\chi = 0.0(11)$, largest diff. peak/hole = 0.93/−0.86 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication no. CCDC-127928. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.uk.ac).