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Enantioselective catalysis. Part 142: Carbohydrate-derived oxime ethers from functionalised aldehydes and *O*-β-D-glucopyranosylhydroxylamine—new C=N ligands stable towards hydrolysis†

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Abstract—A new way of linking carbohydrates to phosphorus- or nitrogen-containing aldehydes via oxime ethers is described resulting in novel C=N ligands which are stable towards hydrolysis. Reaction of *O*-β-D-glucopyranosylhydroxylamine **2** with 2-diphenylphosphanylbenzaldehyde **3** or pyridine-2-carbaldehyde **4** afforded the oxime ethers *O*-(β-D-glucopyranosyl)-2-diphenylphosphanylbenzaldoxime **5** and *O*-(β-D-glucopyranosyl)pyridine-2-carbaldoxime **6**. After peracetylation of the hydroxyl groups in **5** and **6**, the protected sugar derivatives *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-diphenylphosphanylbenzaldoxime **7** and *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)pyridine-2-carbaldoxime **8** were obtained. The molecular structure of **7** was established by X-ray diffraction studies.

1. Introduction

The most effective non-enzymatic approach towards asymmetric catalysis is the use of chiral metal complexes as catalysts.[1] This approach requires chiral ligands that bind to the metal during the catalytic cycle, multiplying their chiral information throughout the reaction by transfer to the substrate. The availability of chiral building blocks for ligand synthesis is an important factor. Compounds from the chiral pool such as carbohydrates and amino acids meet these requirements and have been successfully implemented in different ligand concepts, e.g. imines from the condensation of primary amines with carbonyl compounds have been successfully used in transition-metal catalysed reactions.[2] A limiting factor for these products is their susceptibility to hydrolysis which often prevents chromatographic purification, further derivatisation or the use of aqueous solvents. The tendency for hydrolysis is high for imines, it is reduced for hydrazones and much lower for oximes. In fact, oxime ethers are very stable towards hydrolytic conditions (Fig. 1).

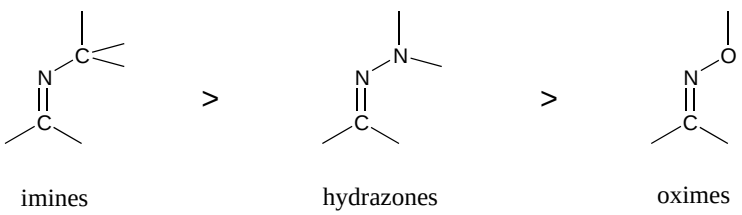

Figure 1. Carbonyl derivatives and their tendency towards hydrolysis.

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‡ X-Ray structure analysis.

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Our new approach is the connection of carbohydrate derivatives and phosphorus- or nitrogen-ligands via oxime ethers. The acid-catalysed condensation of aldehydes and hydroxylaminoglycosides can be carried out in the presence of water, yielding products resistant to hydrolysis over a wide pH range. Herein, an enantiopure building block from the chiral pool is introduced into the ligand which, due to its many functional groups, may bind additives and orient substrates prior to the actual catalysis. Another aspect is the ready protection of the sugar's hydrophilic hydroxyl groups by acetylation or benzoylation resulting in lypophilic esters soluble in organic solvents.

2. Results and discussion

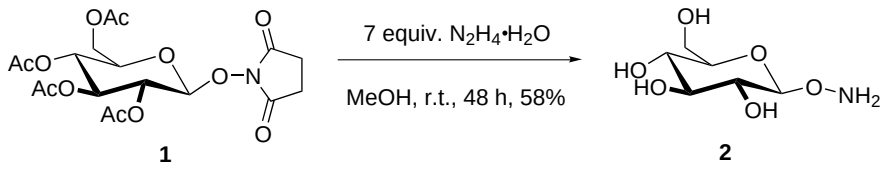
O-β-D-Glucopyranosylhydroxylamine **2** was prepared by a modification of the method published for the synthesis of its galactose analogue.[3] When *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*-hydroxysuccinimide **1** was treated with an excess of hydrazine hydrate in methanol, *O*-β-D-glucopyranosylhydroxylamine **2** was obtained after recrystallisation from methanol in 58% yield (Scheme 1).

Condensation of **2** with 2-diphenylphosphanylbenzaldehyde **3** under acidic conditions using 0.1 equiv. HCl and a mixture of water/THF as the solvent gave *O*-(β-D-glucopyranosyl)-2-diphenylphosphanylbenzaldoxime **5** (Scheme 2). THF as a co-solvent was needed to dissolve the phosphine **3**. The progress of the condensation was monitored by TLC and the reaction was found to be complete after 24 h. Removal of the solvent and subsequent chromatography on silica gel afforded pure **5** as a white solid in almost quantitative yield. **5** is soluble in most organic solvents but not in water. The $^{31}P\{^{1}H\}$ NMR spectrum showed only one signal at −14.98 ppm indicating that no phosphine oxide was formed during the reaction or the work-up.

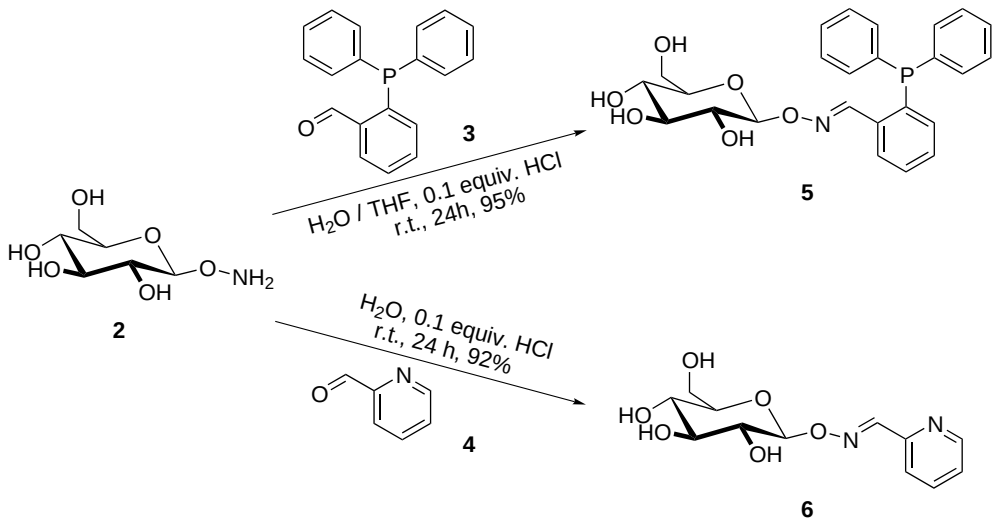
In a similar reaction, pyridine-2-carbaldehyde **4** gave *O*-(β-D-glucopyranosyl)pyridine-2-carbaldoxime **6** in very good yield (Scheme 2). Since aldehyde **4** is soluble in water, THF was not needed as a co-solvent. Work-up as for **5** yielded **6** as a white hygroscopic powder soluble in water and methanol.

Both oxime ethers **5** and **6** were esterified with acetic anhydride in pyridine, resulting in the peracetylated oxime ethers **7** and **8** (Scheme 3). After aqueous work-up and recrystallisation from hexanes/ethyl acetate, **8** was obtained as white needles, while **7** formed colourless crystals suitable for X-ray diffraction analysis. The ^{1}H NMR spectra of **7** and **8** exhibited almost identical chemical shifts and multiplet structures of the hydrogen atoms in the sugar moiety. The imine analogue of **8** is reported in the literature.[4]

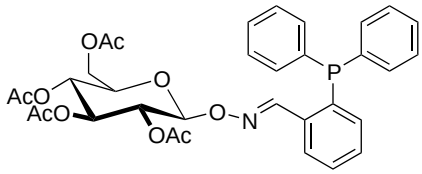
Fig. 2 shows the molecular structure of **7**. The C=N double bond has *trans*-configuration with a torsion



Scheme 1.



Scheme 2.



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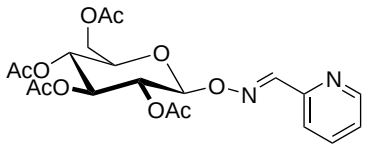

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Scheme 3.

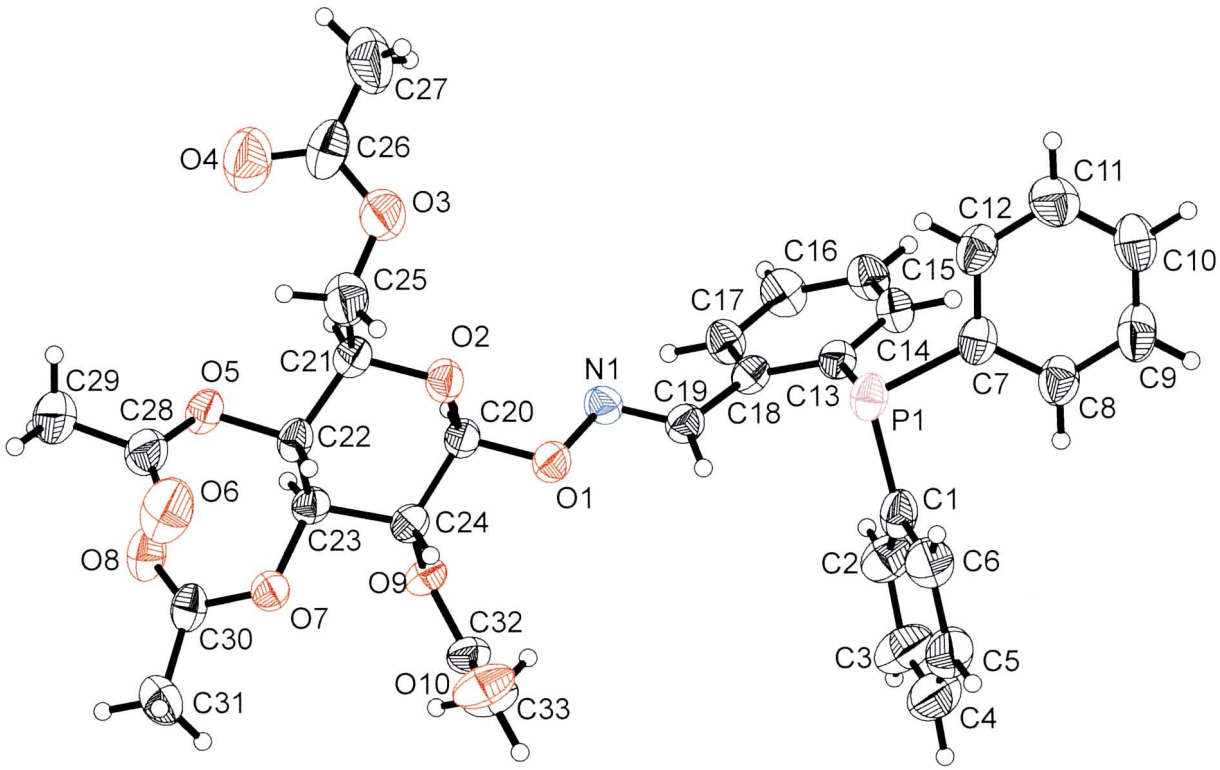

Figure 2. Molecular structure of **7**.

angle O(1)–N(1)–C(19)–C(18) of 177.11(1)°. The torsion angle N(1)–C(19)–C(18)–C(17) is 29,79(1)° indicating that the C=N double bond is inclined with respect to the adjacent phenyl ring. With 1.476(2) Å the bond C(19)–C(18) is a single bond open for rotation to allow bidentate metal-binding through both the phosphorus and the nitrogen atom. The substituents of the pyranose ring are all in equatorial positions confirming the configurational stability of the sugar moiety throughout the reaction sequence.

3. Conclusion

A synthesis of new chiral water-stable C=N ligands has been established by linking hydroxylamino–carbohydrates to aldehydes via oxime ether substructures. By reaction of **5** and **6** with acetic anhydride, the peracetylated oxime ethers **7** and **8** were obtained. Compound **7** could be examined by X-ray diffraction analysis. The method described allows the use of varying aldehydes and a manifold of sugars. Analysis of the efficiency of the new ligands in asymmetric transition-metal catalysis is currently in progress.

4. Experimental

4.1. General remarks

^{1}H NMR (i-TMS): Bruker AC 250 and ARX 400, ^{31}P NMR (ext. 85% H_3PO_4): Bruker ARX 400. Melting points: Büchi SMP-20. Optical rotations: Perkin–Elmer polarimeter 241. Mass spectra: Varian MAT 95. Compound **3** was prepared according to the literature.[5]

4.2. *O*-β-D-Glucopyranosylhydroxylamine 2

To a suspension of *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*-hydroxysuccinimide **1** (10 g, 22.5 mmol) in methanol (400 mL) was added hydrazine hydrate (7 mL, 157 mmol) and the mixture was stirred at room temperature for 48 h. The precipitated butanedioic acid dihydrazide was filtered off and the solution was cooled to −18°C for 10 h affording pure crystalline

2 (2.53 g, 57%). Mp 182°C; $[\alpha]_D^{25}=-40.0$ (*c* 1, H_2O); ^1H NMR (250 MHz, D_2O): $\delta=3.17$ (dd, 1H, $J_{2,1}=8.2$ Hz, $J_{2,3}=9.2$ Hz, H-2), 3.24 (dd, 1H, $J_{4,3}=8.7$ Hz, $J_{4,5}=9.6$ Hz, H-4), 3.35 (ddd, 1H, $J_{5,6a}=2.2$ Hz, $J_{5,6b}=5.7$ Hz, $J_{5,4}=9.6$ Hz, H-5), 3.38 (dd, 1H, $J_{3,4}=8.7$ Hz, $J_{3,2}=9.2$ Hz, H-3), 3.60 (dd, 1H, $J_{6b,5}=5.7$ Hz, $J_{6b,6a}=12.3$ Hz, H-6b), 3.81 (dd, 1H, $J_{6a,5}=2.2$ Hz, $J_{6a,6b}=12.3$ Hz, H-6a), 4.44 (d, 1H, $J_{1,2}=8.2$ Hz, H-1); MS (ESI, MeOH+1% AcOH): $m/z=196.2$ (MH^+, 100); anal. calcd for $C_6H_{13}NO_6$ (195.2): C, 36.92; H, 6.17; N, 7.18. Found: C, 36.86; H, 6.94; N, 7.38%.

4.3. *O*-(β-D-Glucopyranosyl)-2-diphenylphosphanylbenzaldoxime 5

To a solution of **2** (195 mg, 1 mmol) and 2-diphenylphosphanylbenzaldehyde **3** (290 mg, 1 mmol) in H_2O (20 mL) and THF (20 mL) was added 0.1 M HCl (1 mL) and the reaction mixture was stirred at room temperature for 24 h. After removal of the solvents under reduced pressure the residue was taken up in CH_2Cl_2 (50 mL), washed with water (2×20 mL) and brine (1×10 mL) and purified by column chromatography on silica gel using CH_2Cl_2/methanol 12:1 to give pure **5** as a white solid in 95% yield. Mp 145°C; $[\alpha]_D^{25}=-1.8$ (*c* 3, CH_2Cl_2); ^1H NMR (400 MHz, DMSO-d_6): $\delta=3.05$–3.25 (m, 4H, H_{gluc}), 3.40–3.48 (m, 1H, H_{gluc}), 3.57–3.65 (m, 1H, H_{gluc}), 4.50–4.44 (m, 1H, H_{gluc}), 4.83 (d, 1H, $^3J=8.3$ Hz, OH), 4.97 (d, 1H, $J=5.0$ Hz, OH), 5.06 (d, 1H, $J=4.8$ Hz, OH), 5.32 (d, 1H, $J=5.2$ Hz, OH), 6.81–6.86 (m, 1H, H_{ar}), 7.15–7.22 (m, 4H, H_{ar}), 7.38–7.44 (m, 7H, H_{ar}), 7.44–7.49 (m, 1H, H_{ar}), 7.85–7.89 (m, 1H, H_{ar}), 8.74 (d, 1H, $J_P=4.4$ Hz, CH=N); $^{31}P\{^1H\}$ NMR (400 MHz, $CDCl_3$): $\delta=-14.98$; MS (FAB): $m/z=288.2$ (100), 468.5 (MH^+, 49); anal. calcd for $C_{25}H_{26}NO_6P$ (467.5): C, 64.24; H, 5.61; N, 3.00. Found: C, 64.01; H, 5.82; N, 2.81%.

4.4. *O*-(β-D-Glucopyranosyl)pyridine-2-carbaldoxime 6

Obtained as above from pyridine-2-carbaldehyde **4** and **2** without using THF as a co-solvent and after chromatography on silica gel using EtOAc/methanol 7:3 to give pure **6** as a white hygroscopic powder in 92% yield. Mp 76°C; $[\alpha]_D^{25}=-16.3$ (*c* 2, CH_3OH); ^1H NMR (250 MHz, D_2O): $\delta=3.30$–3.43 (m, 1H, H_{gluc}), 3.44–3.55 (m, 3H, H_{gluc}), 3.63 (dd, 1H, $J_{6a,6b}=12.3$ Hz, $J=5.8$ Hz, H_{gluc}-6a), 3.82 (dd, 1H, $J_{6b,6a}=12.3$ Hz, $J=2.14$, H_{gluc}-6b), 5.07–5.12 (m, 1H, H_{gluc}), 7.39 (ddd, 1H, $J_{2,3}=7.6$ Hz, $J_{2,1}=5.0$ Hz, $J_{2,4}=1.3$ Hz, H_{py}-2), 7.68 (ddd, 1H, $J_{4,3}=7.9$ Hz, $J_{4,2}=1.3$ Hz, $J_{4,1}=0.9$ Hz, H_{py}-4), 7.81 (ddd, 1H, $J_{3,4}=7.9$ Hz, $J_{3,2}=7.6$ Hz, $J_{3,1}=1.7$ Hz, H_{py}-3), 8.29 (s, 1H, CH=N), 8.45 (ddd, 1H, $J_{1,2}=5.0$ Hz, $J_{1,3}=1.7$ Hz, $J_{1,4}=0.9$ Hz, H_{py}-1); MS (CI-MS): $m/z=107.0$ (100), 122.0 (48), 285.2 (MH^+, 4); anal. calcd for $C_{12}H_{16}O_6N_2$ (284.3): C, 50.70; H, 5.67; N, 9.85. Found: C, 50.43; H, 5.78; N, 9.65%.

4.5. *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-diphenylphosphanylbenzaldoxime 7

O-(β-D-Glucopyranosyl)-2-diphenylphosphanylbenzaldoxime **5** (200 mg, 0.43 mmol) was dissolved in pyridine (2 mL). Acetic anhydride (191 μl, 206 mg, 2 mmol) was added and the solution was stirred for 16 h at 60°C. The reaction mixture was poured on ice water (50 mL) and 20% HCl (10 mL), extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent chromatography on silica gel eluting with EtOAc/hexanes 2:1 gave pure **7** as a white solid in 89% yield. Colourless crystals suitable for X-ray diffraction analysis were obtained after recrystallisation from hexanes/EtOAc. Mp 77°C; $[\alpha]_D^{25}=-17.3$ (*c* 3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.97$ (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.74 (ddd, 1H, $J_{5,4}=9.9$ Hz, $J_{5,6a}=4.2$ Hz, $J_{5,6b}=2.2$ Hz, H_{gluc}-5), 4.08 (dd, 1H, $J_{6b,6a}=12.4$ Hz, $J_{6b,5}=2.2$ Hz, H_{gluc}-6b), 4.30 (dd, 1H, $J_{6a,6b}=12.4$ Hz, $J_{6a,5}=4.2$ Hz, H_{gluc}-6a), 5.10–5.27 (m, 4H, H_{gluc}), 6.90–6.95 (m, 1H, H_{ar}), 7.19–7.25 (m, 4H, H_{ar}), 7.27–7.40 (m, 8H, H_{ar}), 7.83–7.88 (m, 1H, H_{ar}), 8.83 (d, 1H, $J_P=4.4$ Hz, CH=N); $^{31}P\{^1H\}$ NMR (400 MHz, $CDCl_3$): $\delta=-13.94$; MS (CI-MS): $m/z=288.2$ (100), 366.3 (12), 636.3 (MH^+, 3); anal. calcd for $C_{33}H_{34}NO_{10}P$ (635.6): C, 62.36; H, 5.39; N, 2.20. Found: C, 62.10; H, 5.62; N, 2.09%.

4.6. *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-pyridine-2-carbaldoxime 8

Reaction procedure as for **7** with *O*-(β-D-glucopyranosyl)pyridine-2-carbaldoxime **6** (107 mg, 0.43 mmol) gave **8** as colourless needles in almost quantitative yield. Mp 117°C; $[\alpha]_D^{25}=-22.0$ (*c* 2, CH_2Cl_2); ^1H NMR (250 MHz): $\delta=2.03$ (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.85 (ddd, 1H, $J_{5,4}=9.8$ Hz, $J_{5,6a}=4.3$ Hz, $J_{5,6b}=2.4$ Hz, H_{gluc}-5), 4.15 (dd, 1H, $J_{6b,6a}=12.4$ Hz, $J_{6b,5}=2.4$ Hz, H_{gluc}-6b), 4.33 (dd, 1H, $J_{6a,6b}=12.4$ Hz, $J_{6a,5}=4.3$ Hz, H_{gluc}-6a), 5.13–5.39 (m, 4H, H_{gluc}), 7.31 (ddd, 1H, $J_{2,3}=6.5$ Hz, $J_{2,1}=4.9$ Hz, $J_{2,4}=2.3$ Hz, H_{py}-2), 7.72 (ddd, 1H, $J_{3,4}=7.9$ Hz, $J_{3,2}=6.7$ Hz, $J_{3,1}=1.7$ Hz, H_{py}-3), 7.76 (ddd, 1H, $J_{4,3}=7.9$ Hz, $J_{4,2}=2.3$ Hz, $J_{4,1}=1.0$ Hz, H_{py}-4), 8.27 (s, 1H, CH=N), 8.65 (ddd, 1H, $J_{1,2}=4.9$, $J_{1,3}=1.7$, $J_{1,4}=1.0$, H_{py}-1); MS (CI-MS): $m/z=107.0$ (100), 246.1 (23), 453.2 (MH^+, 41); anal. calcd for $C_{20}H_{24}N_2O_{10}$ (452.4): C, 53.10; H, 5.35; N, 6.19. Found: C, 53.10; H, 5.39; N, 6.20%.

4.7. Crystal data for compound 7

$C_{33}H_{34}NO_{10}P$ **7**: colourless thin rod from EtOAc/hexanes, Fw=635.58, monoclinic, space group $P2_1$ (no. 4), $a=14.300(1)$, $b=7.6003(5)$, $c=15.008(1)$ Å, $\beta=96.135(9)°$, $V=1621.8(2)$ Å^3, $Z=2$, $D_x=1.301$ Mg m^{-3}, μ(Mo-Kα)=0.142 mm^{-1}, crystal dimensions 0.46×0.20×0.08 mm^3, $\lambda=0.71073$ Å (Mo-Kα radiation, graphite monochromator, STOE Imaging Plate Diffraction System). Data collection at $T=173$ K, $1.87<\theta<25.73°$, h −17→17, k −9→9, l −18→18, 16306 reflections measured, 6134 unique, merging $R_{int}=0.0486$). The structure was solved by direct methods (SIR-97[6]) and refined by full-matrix least-squares based on F^2 (SHELXL-97[7]) with weights $w=1/[\sigma^2(F_o)^2+(0.0723P)^2]$,

where $P=(F_o^2+2F_c^2)/3$. The H atoms were calculated geometrically and a riding model was used during the refinement process. The final consistency indexes for all data were $R_1=0.0693$ and $wR_2=0.1184$, goodness-of-fit = 0.936. The last difference Fourier map showed peaks between 0.678 and −0.210 e Å^{-3}. The correct absolute configuration was confirmed by the Flack parameter −0.08(12). 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 169983. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; email: deposit@ccdc.cam.ac.uk].

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