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Green diastereoselective synthesis of highly functionalised trifluoromethylated γ-lactone phosphonate esters bearing a thioester or ketothiophene

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Abstract—A facile diastereoselective synthesis of highly functionalised 3-(1-diphenylphosphonylethyl)butyrolactone analogues, **3a**–**c** is achieved from the reaction of dialkyl acetylenedicarboxylates, **2a**,**b**, with thiolated and trifluoromethylated-1,3-diones, CH acids, **1a**,**b**, in the presence of triphenyl phosphite. The resulting products, **3a**–**c**, are obtained in high yields and characterised by $^{1}H/^{13}C$, ^{19}F, ^{31}P NMR and X-ray crystallography.

1. Introduction

Synthetic and natural compounds containing saturated and unsaturated five-membered lactones exhibit biological responses and are used for many medical applications.[1,2] The lactone moiety is an important structural building block for many active drugs and highly substituted and functionalised lactones present synthetic challenges. A wide range of methods are employed in the preparation of lactones and are mainly based on metal-mediated syntheses through to chemoenzymatic approaches.[3] Reports of more traditional multi-component syntheses of γ-lactones are well established starting from α-β-unsaturated esters.[4] Further, new variations employing electrophilic cyclisation of unsaturated carboxylate derivatives are known.[5] Incorporation of phosphonate groups into the lactone ring confers water solubility.[6] Moreover, phosphorus compounds such as phosphonate esters are also biologically active and have been employed for the isolation of certain esterase antibodies amongst other applications.[7,8] In this context, we and others have established synthetic methodology for the preparation of a related class of phosphonate diesters from the condensation of acetylenic diesters with NH or CH acids in the presence of triphenyl phosphite.[9,10]

Perfluorinated compounds have attracted considerable attention and play an important role in the pharmaceutical and agrochemical industries. Their unique biological activity is associated with the presence of fluorine atoms responsible for increased membrane permeability, enhanced hydrophobicity and greater stability against metabolic oxidation.[11,12] Since fluorine is virtually absent in living organisms, fluorinated compounds are of interest for biotechnological applications.[13] Many trifluoromethyl group-containing drugs have been developed including prozac (antidepressant), diflucan (anti-fungal agent), casodex (anticancer agent) and desflurane (inhalation anaesthetic).[14]

The use of water as a reaction medium is gaining prominence in chemical syntheses and offers great potential in green chemical technologies.[15] A green approach is utilised in the present work to access a novel class of highly functionalised lactone phosphonate esters. Lactones containing fluoro and thio moieties may show enhanced biological activity. In

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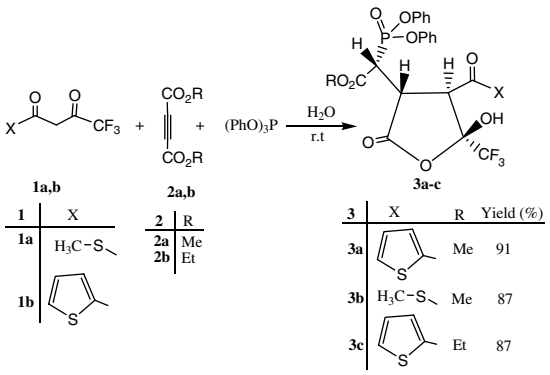
addition, the presence of multiple chiral centres gives rise to stereoisomers, which can have pronounced differences in biological activity and toxicological effects.[16,17]

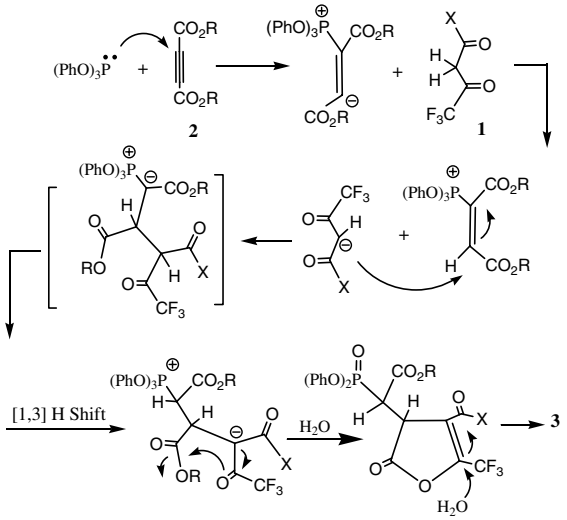
In continuation of our efforts towards the synthesis of new fluorinated phosphonate ester-containing heterocycles, we decided to use trifluoromethylated ketothioester CH acids as precursors for the synthesis of γ-lactones bearing phosphonates and sulfur-containing substituents. Herein, we report the successful preparation of new highly functionalised γ-lactones via a one-pot reaction in an aqueous medium. This synthetic route afforded novel trifluoromethylated γ-lactone phosphonate esters, **3**, via the condensation reaction of dialkyl acetylenic diesters, **2a**,**b** with triphenyl phosphite in the presence of thiolated 4,4,4-trifluoro-1,3-dione CH acids **1a**,**b** (Scheme 1).

The reaction was carried out in water with a small amount of acetone in some cases to achieve homogeneity. The dialkyl acetylenedicarboxylates (DAAD) **2a**,**b** were added in small portions to a mixture of triphenyl phosphite (TPP) and the C–H acids **1a**,**b** and the reaction mixture was stirred for 3 h at room temperature to afford chiefly a single diastereoisomer of **3**. This three-component reaction produces hitherto unknown 3-(diphenylphosphonato)-5-(trifluoromethyl)butyrolactones **3a**–**c** in 87–90% yields. All the products were stable crystalline solids and their structures were assigned by IR, $^{1}H/^{13}C$, ^{19}F and ^{31}P NMR. Unambiguous structural elucidation was accomplished by X-ray diffraction (Fig. 1).

A possible mechanism for the formation of compounds **3a**–**c** involves the initial addition of triphenyl phosphite to the acetylenic ester and then concomitant protonation of the 1:1 adduct by the CH acid, followed by attack of the conjugate base.[18,19] The resulting intermediate undergoes[1,3] proton migration[20] followed by intramolecular attack favouring five-membered ring cyclisation to the unsaturated γ-lactone. The final step involves hydrolysis to form the hydroxylated γ-lactone phosphonate esters **3a**–**c** (Scheme 2).



Scheme 1.



Scheme 2.

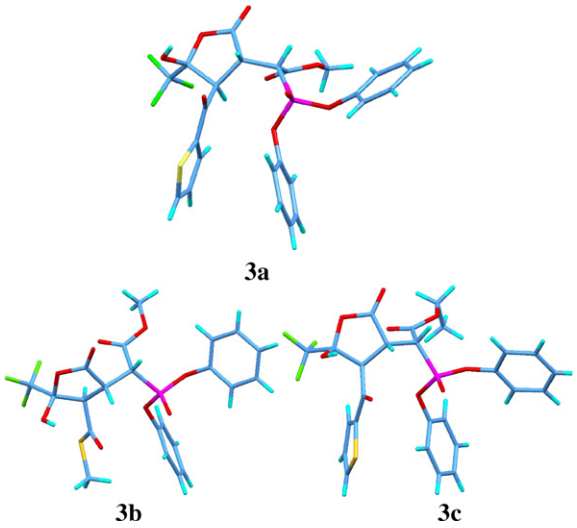


Figure 1. Stick representation of the X-ray structures of compounds **3a**–**c**.

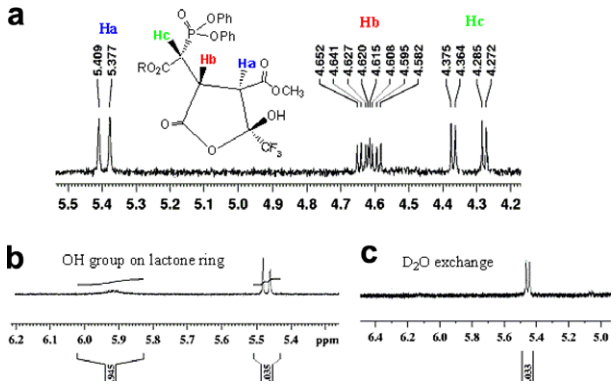


Figure 2. (a) ^{1}H NMR spectrum depicting the chemical shifts of the methine protons H_a, H_b and H_c for product **3a**; (b) chemical shift of the hydroxyl group on the lactone ring in **3a** in $CDCl_3$; and (c) D_2O exchange.

The ^{1}H NMR spectrum of compound **3a** showed three distinct chemical shifts for the methine protons labelled H_a, H_b and H_c (Fig. 2a). The methine proton distant from phosphorus, H_a was observed as a doublet at δ 5.4 ($^3J_{H_aH_b\,(anti)} = 9.6$ Hz). Proton H_b coupled with protons H_a, H_c and with the phosphorus and appeared as an octet at δ 4.6 ($^3J_{PH_b} = 5$ Hz, $^3J_{H_aH_b\,(anti)} = 9.6$ Hz and $^3J_{H_cH_b\,(gauche)} = 3$ Hz). The methine proton proximal to the phosphorus atom, H_c appeared as a doublet of doublets at δ 4.3 accompanied by a large coupling constant with the phosphorus ($^2J_{PH_c} = 27.3$ Hz) and a small coupling with H_b ($^3J_{H_bH_c\,(gauche)} = 4$ Hz). The large coupling constant observed for protons H_a and H_b ($^3J_{H_aH_b} = 9.6$ Hz) is consistent with an *anti* arrangement while the small coupling constant of protons H_b and H_c ($^3J_{H_bH_c\,(gauche)} = 4$ Hz) confirms the gauche arrangement. Confirmation of the presence of a hydroxyl functional group on the lactone ring proved elusive.

The ^{1}H NMR spectrum of compound **3a** in acetone-d_6 showed no signal for the hydroxyl group on the lactone ring because of rapid exchange of the OH group with residual H_2O in the NMR solvent. Performing the NMR experiment in dry $CDCl_3$ with a high concentration of the product revealed the presence of a broad OH signal in the region of δ 5–6 ppm (Fig. 2b).

Moreover, addition of one drop of D_2O to this NMR solution resulted in the disappearance of the hydroxyl signal (Fig. 2c). Similar behaviour was also observed with compounds **3b** and **c**. Compounds **3a**–**c** are very sensitive to protic solvents whereby protons H_a, H_b and H_c undergo epimerisation resulting in 3 or 4 diastereoisomers at different molar ratios upon standing (ca. 1 week).

In contrast, the condensation reaction involving di-*tert*-butyl acetylenedicarboxylate with CH acids **1a**,**b** under the same conditions was unsuccessful. This outcome may be due to the bulky *tert*-butyl groups, which prevent nucleophilic attack of the carbanion of the phosphonium intermediate (Scheme 2).

In conclusion, we have successfully developed a facile diastereoselective synthesis of highly functionalised trifluoromethylated and thiolated γ-lactone phosphonate esters with four contiguous stereogenic centres.

2. Experimental

2.1. Typical procedure for the preparation of compounds 3

To a magnetically stirred acetone/water (1:5) solution of triphenyl phosphite (0.31 g, 1 mmol) and CH acid, **1** (1 mmol) was added dialkyl acetylendicarboxylate, **2** (1 mmol) dropwise over 3 min at rt and the reaction mixture was stirred for 3 h at room temperature. Acetone was removed under reduced pressure and the resultant yellow residue was extracted with ether and crystallised from ether/*n*-hexane (4:1).

2.1.1. Methyl 3-(1-diphenylphosphonato)-5-hydroxy-2-oxo-4-(thiophen-2-yl)ethanone-5-(1,1,1-trifluoromethyl) tetrahydrofuran-4-(2-carboxylate) (3a). Product **3a** was obtained as colourless crystals, 0.53 g, yield 91%, mp 210–212 °C. IR (KBr): 3194 (OH), 1802 (C=O of thiophene), 1736 (C=O of ester), 1659 (C=O of ester), 1588 (C=C) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.7 (s, 3H, OCH_3), 4.3 (dd, 1H, $^2J_{PH_c} =$ 27.3 Hz, $^3J_{H_bH_c\,(gauche)} = 4$ Hz, H_c, P–CH_c), 4.6 (octet, 1H, $^3J_{PH_b} = 5$ Hz, $^3J_{H_aH_b} = 9.6$ Hz, $^3J_{H_cH_b} = 3$ Hz, H_b, P–C–CH_b), 5.4 (d, 1H, $^3J_{H_bH_a} = 9.6$ Hz, H_a, P–CH–CH–CH_a), 5.9 (br, 1H, OH), 7.0–7.9 (m, 13H, 2 × OPh and thiophene ring); ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.9 (d, $^2J_{PC} = 2.5$ Hz, P–CH–^{13}CH), 44.1 (d, $^1J_{PC} =$ 141.9 Hz, P–^{13}CH), 49.5 (s, P–CH–CH–^{13}CH), 53.7 (s, OCH_3), 99 (q, $^2J_{FC} = 35$ Hz ^{13}C–CF_3) (q, $^1J_{FC} = 284$ Hz $^{13}CF_3$), 121.2, 121.7 (2 × s, 2C$_{ortho}$ of 2C_6H_5), 124.8 (s, ^{13}C–CF_3), 126.3, 126.6 (2C$_{para}$ of 2C_6H_5), 129.3, 129.4 (2 × s, 2C$_{meta}$ of 2C_6H_5), 130.6, 134.9, 136.6, 144.6 (4 × s, thiophene ring), 150.4 (d, $^2J_{PC} = 9.6$ Hz, C$_{ipso}$ of C_6H_5), 151.1 (d, $^2J_{PC} = 9.2$ Hz, C$_{ipso}$ of C_6H_5), 167.7 (d, $^2J_{PC} = 3.5$ Hz, C=O proximal ester), 173.2 (d, $^3J_{PC} = 20.9$ Hz, C=O distal ester), 185.1 (s, C=O); ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.60 [–CF_3]; ^{31}P NMR (202 MHz, $CDCl_3$): δ 10.8 [–$(PhO)_2{}^{31}$P=O]; MS *m*/*z* (%), 585 [M^++1] (7), 491 [M^+−OPh] (47), 397 [M^+−2 OPh] (7), 77 [Ph] (18). CHN + S Anal. Calcd for $C_{25}H_{20}F_3O_9PS$ (584): C, 51.37; H, 3.42; S, 5.48. Found: C, 49.83; H, 3.54; S, 5.33.

2.1.2. *S*-Methyl 3-(1-diphenylphosphonato)-5-hydroxy-2-oxo-4-(ethanethioate)-5-(1,1,1-trifluoromethyl) tetrahydrofuran-4-(2-carboxylate) (3b). Product **3b** was obtained as colourless crystals, 0.48 g, yield 87%, mp 158–160 °C. IR (KBr): 3198 (OH), 1800 (C=O of *S*-methyl ethanethioate), 1744 (C=O of ester), 1680 (C=O of ester), 1588 (C=C) cm^{-1}. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 2.2 (s, 3H, S–CH_3), 3.8 (s, 3H, OCH_3), 4.2 (dd, 1H, $^2J_{PH_c} = 28$ Hz, $^3J_{H_bH_c\,(gauche)} =$ 3.5 Hz, H_c, P–CH_c), 4.4 (octet, 1H, $^3J_{PH_b} = 7.8$ Hz, $^3J_{H_aH_b\,(anti)} = 10.5$ Hz, $^3J_{H_cH_b\,(gauche)} = 3.5$ Hz, H_b, P–C–CH_b), 4.7 (d, 1H, $^3J_{H_bH_a} = 10.5$ Hz, H_a), 5.5 (br, 1H, OH), 6.6–7.2 (m, 10H, 2 × OPh); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.2 (s, S–CH_3), 41.7 (d, $^2J_{PC} = 2$ Hz, P–^{13}CH), 42.2 (d, $^1J_{PC} = 142.6$ Hz, P–^{13}CH), 52.8 (s, P–CH–CH–^{13}CH), 53.6 (s, O^{13}CH$_3$), 99.2 (q, $^2J_{FC} = 35.4$ Hz ^{13}C–CF_3), 120.2, 120.4 (2 × s, 2C$_{ortho}$ of 2C_6H_5), 122.5 (q, $^1J_{FC} = 284$ Hz $^{13}CF_3$), 125.8, 125.9 (2 × s, 2C$_{para}$ of 2C_6H_5), 129.8, 129.9 (2C$_{meta}$ of 2C_6H_5), 149.4 (d, $^2J_{PC} = 8.8$ Hz, C$_{ipso}$ of C_6H_5), 149.5 (d, $^2J_{PC} = 10.1$ Hz, C$_{ipso}$ of C_6H_5), 166.0 (d, $^2J_{PC} = 3.9$ Hz, C=O ester), 172.1 (d, $^3J_{PC} = 21.8$ Hz, C=O of lactone), 194.7 (s, C=O); ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.62 [–CF_3]; ^{31}P NMR (202 MHz, $CDCl_3$): δ 11.1 [–$(PhO)_2{}^{31}$P=O]; MS: *m*/*z* (%), 547 [M^+−1] (3), 517 [M^+−OCH_3] (100). CHN + S Anal. Calcd for $C_{22}H_{20}F_3O_9PS$ (548): C, 48.18; H, 3.65; S, 5.84. Found: C, 47.43; H, 3.53; S, 5.78.

2.1.3. Ethyl 3-(1-diphenylphosphonato)-5-hydroxy-2-oxo-4-(thiophen-2-yl)ethanone-5-(1,1,1-trifluoromethyl) tetrahydrofuran-4-(2-carboxylate) (3c). Product **3c** was obtained as white crystals, 0.52 g, yield 87%, mp 191–193 °C. IR (KBr): 3168 (OH), 1805 (C=O of thiophene),

1729 (C=O of ester), 1658 (C=O of ester), 1588 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.3 (t, 3H, $^3J_{HH} = 7$ Hz, CH_3), 4.2 (dd, 1H, $^2J_{PH_c} = 28.5$ Hz, $^3J_{H_bH_c\,(gauche)} = 3$ Hz, H_c, P–CH_c), 4.2 (octet, 1H, $^3J_{PH_b} = 6.0$ Hz, $^3J_{H_aH_b\,(anti)} = 10.5$ Hz, $^3J_{H_cH_b\,(gauche)} = 3.5$ Hz, H_b, P–C–CH_b), 4.3 (t, 2H, $^3J_{HH} = 7.5$ Hz, CH_2), 5.5 (d, 1H, $^3J_{H_bH_a} = 7.5$ Hz, H_a), 5.8 (br, 1H, OH), 6.9–7.8 (m, 13H, 2 × OPh and thiophene ring); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (s, $^{13}CH_3$ of OEt), 42.8 (s, P–CH–^{13}CH), 42.9 (d, $^1J_{PC} = 140.9$ Hz, P–^{13}CH), 46.6 (s, P–CH–CH–^{13}CH), 63.1 (s, O–CH_2), 99 (q, $^2J_{FC} = 36.2$ Hz, ^{13}C–CF_3), 120.0, 120.3 (2 × s, 2C_{ortho} of 2C_6H_5), 122.5 (q, $^1J_{FC} = 284$ Hz $^{13}CF_3$), 125.6, 125.9 (2 × s, 2C_{para} of 2C_6H_5), 129.7, 129.8 (2C_{meta} of 2C_6H_5), 128.7, 135.6, 137.5 and 142.9 (4 × s, thiophene ring), 149.2 (d, $^2J_{PC} = 9.1$ Hz, C_{ipso} of C_6H_5), 149.5 (d, $^2J_{PC} = 9.8$ Hz, C_{ipso} of C_6H_5), 166.1 (d, $^2J_{PC} = 4.2$ Hz, C=O proximal ester), 172.1 (d, $^3J_{PC} = 21.1$ Hz, C=O distal ester), 188.9 (s, C=O); ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.61 [–CF_3]; ^{31}P NMR (202 MHz, $CDCl_3$): δ 10.7 [–$(PhO)_2{}^{31}P$=O]; MS: *m/z* (%), 598 [M^+] (75), 581 [M^+−OH] (20), 554 [M^+−CO_2] (35), 505 [M^+−OPh] (94), 412 [M^+−2 OPh] (28). CHN + S Anal. Calcd for $C_{26}H_{22}F_3O_9PS$ (598): C, 52.2; H, 3.68; S, 5.35. Found: C, 53.73; H, 3.74; S, 5.32.

Data were corrected for Lorentz and polarisation effects and absorption correction was applied using multiple symmetry equivalent reflections. The structures were solved by direct methods and refined on F^2 using the SHELX-97 crystallographic package. All non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were localised from difference Fourier synthesis and their atomic parameters were constrained to the bonded atoms during the refinement. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 656625, 656626 and 656627. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

2.1.4. Crystal/refinement details for compound 3a. $C_{25}H_{20}F_3O_9PS$, $M = 584.44$, $F(000) = 600$ *e*, triclinic, $P\bar{1}$ (No. 2), $Z = 2$, $T = 100(2)$ K, $a = 10.9141(3)$, $b = 11.1823(3)$, $c = 11.9542(5)$ Å, $\alpha = 73.015(3)°$, $\beta = 64.071(3)°$, $\gamma = 84.495(3)°$, V=1254.00(7) Å^3; $D_c = 1.548$ g cm^{-3}; $\mu_{Mo} = 0.269$ mm^{-1}; $\sin\theta/\lambda_{max} = 0.7035$; N(unique) = 7305 (merged from 37318, $R_{int} = 0.0370$, $R_{sig} = 0.0449$), N_o ($I > 2\sigma(I)$) = 5071; $R = 0.0326$, $wR_2 = 0.0774$ (A, B=0.045, 0), GOF = 1.003; $|\Delta\rho_{max}| = 0.43(5)$ e Å^{-3}. CCDC 656627.

2.1.5. Crystal/refinement details for compound 3b. $C_{22}H_{20}F_3O_9PS$, $M = 548.41$, $F(000) = 564$ *e*, triclinic, $P\bar{1}$ (No. 2), $Z = 2$, $T = 100(2)$ K, $a = 10.756(3)$, $b = 11.314(1)$, $c = 11.554(4)$ Å, $\alpha = 71.13(2)°$, $\beta = 62.93(3)°$, $\gamma = 87.89(2)°$, $V = 1174.5(5)$ Å^3; $D_c = 1.551$ g cm^{-3}; $\mu_{Mo} = 0.282$ mm^{-1}; $\sin\theta/\lambda_{max} = 0.7035$; N(unique) = 6847 (merged from 35872, $R_{int} = 0.0285$, $R_{sig} = 0.0357$), N_o ($I > 2\sigma(I)$)=4760; R=0.0383, $wR_2 = 0.0993$ (A, $B = 0.0695$, 0.0), GOF = 1.001; $|\Delta\rho_{max}| = 0.58(7)$ e Å^{-3}. CCDC 656626.

2.1.6. Crystal/refinement details for compound 3c. $C_{26}H_{22}F_3O_9PS$, $M = 598.47$, $F(000) = 4928$ *e*, monoclinic, *Cc* (No. 9), $Z = 16$, $T = 100(2)$ K, $a = 25.5100(5)$, $b = 31.3207(6)$, $c = 18.2700(4)$ Å, $\beta = 134.105(3)°$, $V = 10482.0(4)$ Å^3; $D_c = 1.517$ g cm^{-3}; $\sin\theta/\lambda_{max} = 0.7035$; N(unique) = 15282 (merged from 144564, $R_{int} = 0.0394$, $R_{sig} = 0.0345$), N_o ($I > 2\sigma(I)$) = 11742; $R = 0.0424$, $wR_2 = 0.1085$ (A, $B = 0.084$, 0.0), GOF = 1.004; $|\Delta\rho_{max}| = 0.72(7)$ e Å^{-3}. CCDC 656625.

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