EFFICIENT SYNTHESIS OF FUNCTIONALIZED DIAZACYCLOPENTA[*C*]PENTALENE WITH MULTIPLE INTERMOLECULAR INTERACTIONS IN CRYSTAL

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Dedicated to Professor Nikolay S. Zefirov with recognition of his contributions to organic chemistry and on the occasion of 75th birthday

Abstract − Atom economic synthesis of functionalized polysubstituted racemic diazacyclopenta[*c*]pentalene **7** has been developed using sequential organocatalytic 1,3-dipolar cycloaddition of azomethine ylide with maleic anhydride and three successive amide bonds formation induced by interaction of 4-fluorobenzylamine with heterocyclic anhydride **5**. Enantiomers of **7** are connected by *Cl-π, H⋯F* and *C=O⋯H* intermolecular interactions in crystal.

INTRODUCTION

Different classes of natural compounds are characterized by polycyclic molecular skeletons. Attaching of functional groups at definite positions of polycyclic scaffold could be responsible for specific biological activities of natural products and their derivatives through formation of selected ligand-target interactions.[1] Non-aromatic complex carbon- and heteropolycyclic compounds are objects of diversity-oriented synthesis (DOS) since the possibility to regulate scaffold appendages along the spherical surface of ligand exists.[2] Introduction of different functional groups and/or substituents in three-dimensional space of polycyclic molecular skeleton allows to generate additional diversity and to optimize discovered biological activity. The fusion of several non-aromatic rings provides geometrically well-defined structures that are important for both receptor fitting and covering of pharmaceutically relevant chemical space.[3] Several synthetic strategies including cascade reactions[1] and aza-annulations[4] are utilized for effective construction of polycyclic skeleton of natural compounds. In this communication we report a three-step synthetic procedure toward the well-defined functionalized diazatricyclic scaffold **1**, heterocyclic analog of angular triquinane **2**,[5] that is a constituent of a wide family of sesquiterpene natural

products (Figure 1). The only published method of synthesis of heterocycles **3** possessing molecular scaffold **1** is based on interaction of *N*-allyl-*N*-phenylprolinamides with benzaldehydes.[6]
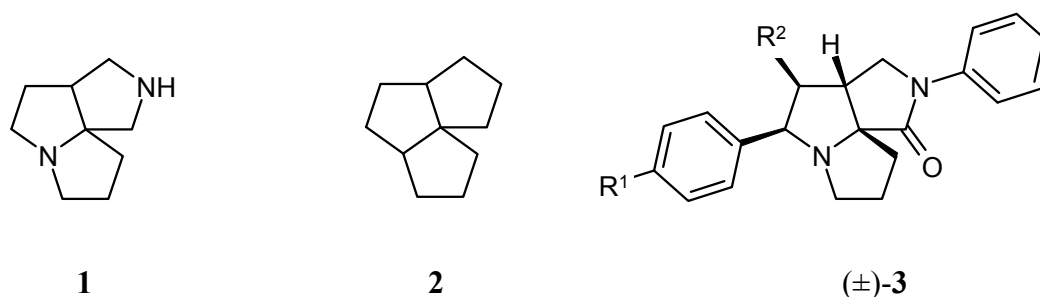

Figure 1. Structural formulae of octahydro-2,5a-diazacyclopenta[*c*]pentalene (**1**), decahydrocyclopenta-[*c*]pentalene (**2**), and known compounds **3** with molecular skeleton **1**.

RESULTS AND DISCUSSION

Our approach to functionalized diazacyclopenta[*c*]pentalene scaffold included three operational steps (Scheme 1). At the first stage iminoester **4** was synthesized from 4-chlorobenzaldehyde and glutamate dimethyl ester hydrochloride. Cycloaddition of azomethine ylides generated from iminoesters and dipolarophiles is a widely used method of synthesis of functionalized pyrrolidines derivatives.[7] Typically interaction of 1,3-dipoles with olefins occurs under Lewis or Bronsted acids catalysis or requires elevated temperatures.[7]
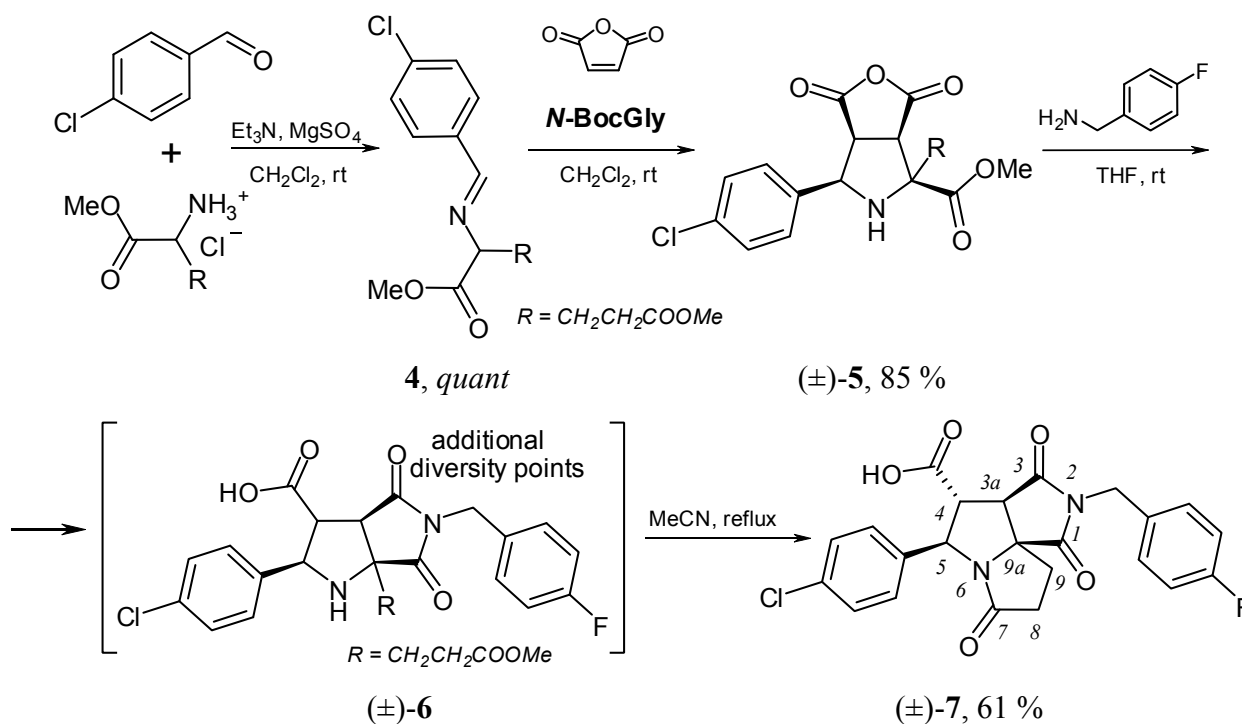
Scheme 1. Synthesis of functionalized diazacyclopenta[*c*]pentalene **7** by sequential 1,3-dipolar cycloaddition – intramolecular amide bond formation.

Recently we reported an amino acid catalyzed cycloaddition of activated dipolarophiles (maleimides, maleic anhydride) to azomethine ylides under mild conditions.[8] Cycloadditions of 1,3-azadipoles with maleic anhydride are insufficiently studied because of the last reagent reactivity towards nucleophilic species and reagents. Our method[8] overcomes these limitations and provides approach to heterocyclic anhydrides but in case of iminoester **4** leads to pyrrolidine tricarboxylic acid anhydride **5** contaminated with an amino acid catalyst. To perform reaction homogeneously we have used soluble in non-polar solvents *N-tert*-butoxycarbonyl glycine (*N*-BocGly) as a Bronsted acid catalyst of cycloaddition process[9] and succeeded in good yield of functionalized pyrrolidine **5** (Scheme 1). Presumably *N*-BocGly protonates iminoester **4** at the first step and subsequent deprotonation of α-position leads to ylide **A** formation (Scheme 2). *endo*-Cycloaddition of maleic anhydride to the reactive species **A** gives rise to the stereoselective formation of four stereogenic centers in molecule **5**. Relative *cis*-stereochemistry of protons at *6-*, *6a-* and *3a*-positions of pyrrolidine ring of heterocyclic anhydride **5** is deduced from the 9.1 Hz value of $^3J(\text{H}^6\text{-H}^{6a})$ constant in compound **5** ^{1}H NMR spectrum[10] and corresponds to our previous results on cycloaddition of maleic anhydride to other types of azomethines catalyzed by amino acids.[8]
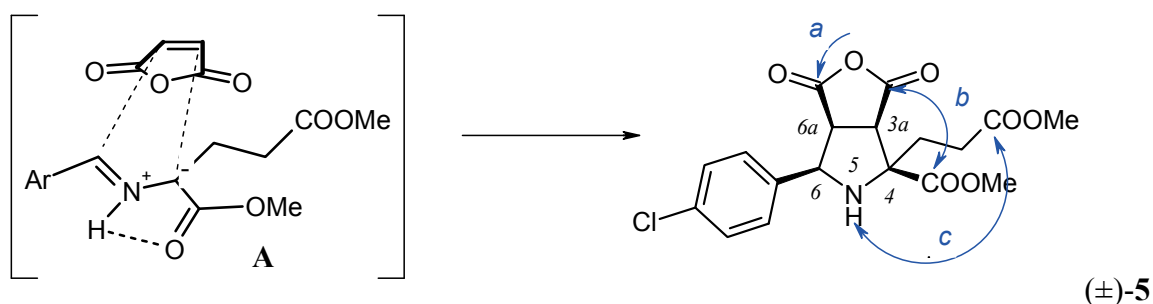
Scheme 2. *endo*-Transition state for heterocyclic anhydride **5** formation and possible nucleophilic attack directions in **5**.

Polyfunctional nature of bicyclic anhydride **5** prompted us to study it's reactivity toward nitrogen nucleophiles. There are four possible positions for nucleophilic attack in **5** according to number of carbonyl functions (Scheme 2). The most reactive functionalities should be anhydride carbonyls (Scheme 2, routes *a* and *b*) and in case *b* primary nucleophilic interaction with anhydride could be followed by cyclization at *4*-carboxymethyl group leading to annulation at *3a,4*-bond of starting heterocycle **5**. Inramolecular interaction of *5*-nitrogen and distal carboxymethyl group (Scheme 2, route *c*) could provide annulation at *4,5*-bond of starting heterocycle **5**. Considered lactamization may take place spontaneously[11a] or under elevated temperatures[11b] and has been used by us for construction of pyrrolizidin-3-one scaffold.[11]

Treatment of THF solution of anhydride **5** with equimolar amount of 4-fluorobenzylamine led to expected consumption of starting materials (Scheme 1). The progress of the reaction was monitored by ^{1}H NMR of concentrated at room temperature probes. After the changes in the reaction mixture ceased we observed a predominant product in ^{1}H NMR. Thorough analysis of obtained ^{1}H NMR data let us to assign structural formula **6** to the major product (Scheme 1). Formation of substituted octahydropyrrolo[3,4-*b*]pyrrole **6** corresponds to the discussed above tandem *3a,4*-annulation of anhydride **5** induced by 4-fluorobenzylamine (Scheme 2, route *b*). The second step of this process occurred spontaneously at remarkably mild conditions: formation of the imide bridge in our recent approach towards 3,6-diazabicyclo[3.2.1]octane scaffold took place at elevated temperatures and in the presence of copper salt catalyst.[12] Subsequent heating of the mixture contained predominantly compound **6** in acetonitrile led to the isolation after purification of a major component – functionalized diazacyclopenta[*c*]pentalene **7** (Scheme 1).
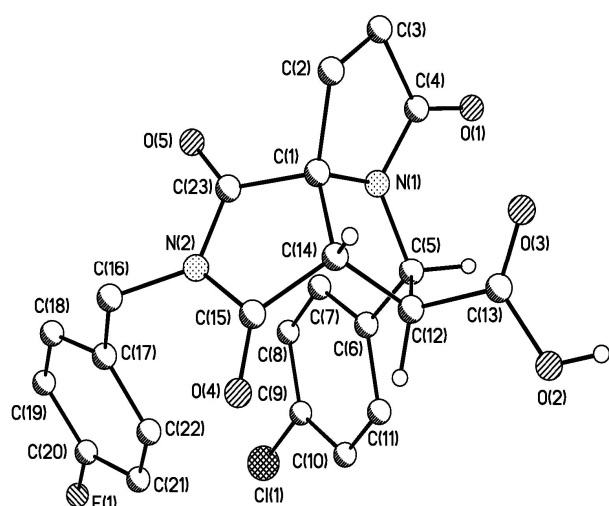

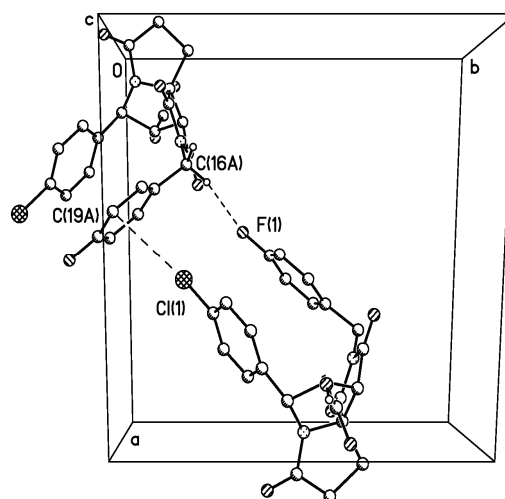**Figure 2.** General view of molecule **7** (only 3a*S*,4*S*,5*S*,9a*R*-enantiomer is shown).

Figure 3. Fragment of crystalline structure of **7** along the *c* crystallographic axis. Intermolecular contacts Cl(1)-π and F(1)···H(16AB) are shown.

Structure of the novel polysubstituted diazatricycle **7** was unambiguously determined by X-ray analysis (Figure 2).[13] Epimerization of β-carboxylic function took place apparently during the lactamization step at elevated temperature, all other stereochemical outcomes accord with considered reactions pathways. Detailed examination of solid state structure of **7** revealed two types of interesting intermolecular interactions in crystal (Figures 3, 4). The first type of intermolecular contacts comprises rarely observed C^{Ar}–F···H–C_α–N contact[14] and more frequent Cl–π interaction[15] with both halogen atoms belonging to one enantiomeric molecule **7** and connecting to the benzylic part of another (Figure 3). The distance between F(1) and H(16AB) atoms is significantly below the sum of the van der Waals radii (2.67Å) and

amounts to 2.20 Å (Figure 3). The chlorine atom Cl(1) is located 3.50 Å from aromatic carbon C(19A) (Figure 3). This distance practically coincides with 3.45 Å sum of chlorine-carbon van der Waals radii and appropriate interaction could provide up to 2 kcal/mol energetic benefit.[15a] Both types of observed in **7** non-covalent bonding exampled in complexes of thrombin with small-molecule inhibitors. C^{Ar}–F···H–C_α–C=O contact has been observed in inhibitor-enzyme complex for 4-fluorobenzyl fragment of an inhibitor and Asn98 in the S3-pocket of the thrombin active site.[14] Chlorine–π contacts are characteristic for chloroaryl fragments of small-molecule inhibitors interacting with Tyr228 in the S1-pocket of the thrombin active site.[15] We have tested diazacyclopenta[c]pentalene **7** on thrombin inhibition activity and unfortunately found only poor enzyme inactivation.[16] Another type of intermolecular interactions in crystal of **7** represents canonical hydrogen bonds between carbonyl oxygen atoms and carboxylic protons (Figure 4). Two mirror enantiomers of fused diazatricycle **7** are connected by two practically linear O···H–O interactions forming 16-membered circular chain (Figure 4).
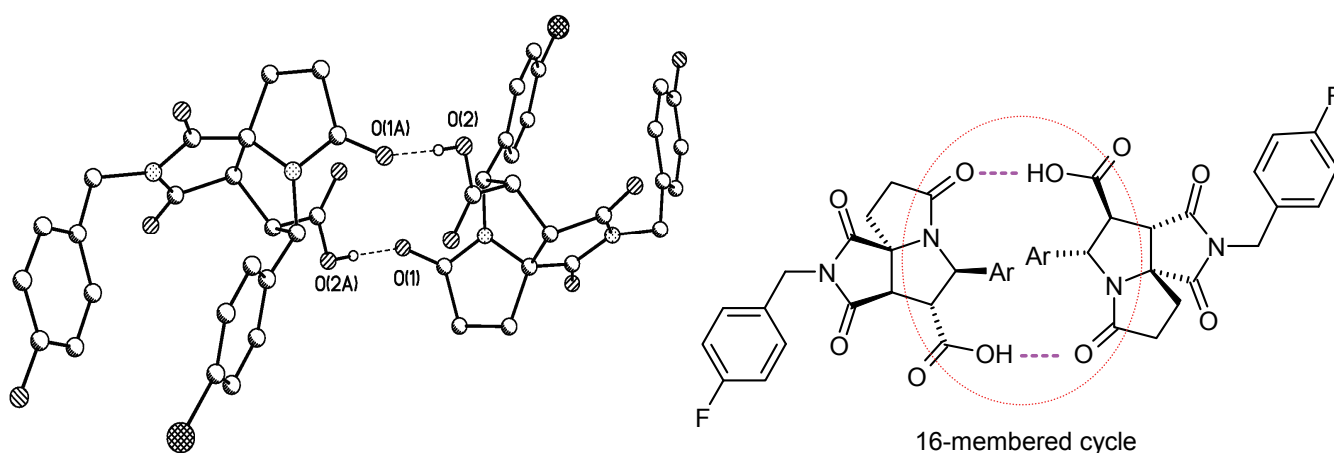

Figure 4. H-bonded dimer of **7**: O^2-H^{O2} 0.82, H^{O2}-O^{1A} 1.85, O^2-O^{1A} 2.667(3) Å; angle O^2-H^{O2}-O^{1A} 173°.

In conclusion we have developed short and convenient synthetic approach towards functionalized octahydro-2,5a-diazacyclopenta[c]pentalene (**1**) scaffold. It was demonstrated the effectiveness of application of *N-tert*-butoxycarbonyl α-amino acid as a homogeneous organocatalyst of 1,3-dipolar cycloaddition of activated dipolarophile to azomethine. The method is characterized by good atom economy with only one molecule of water and two molecules of methanol excreted during the whole synthetic cycle. Different intermolecular interactions in functionalized diazacyclopenta[c]pentalene **7** monocrystal could be used in crystal engineering and structure-based design of enzymes inhibitors.

EXPERIMENTAL

Reagents were obtained from Alfa Aesar and used without further purification unless otherwise stated.

Solvents were dried using standard procedures. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (Sorbfil) with a UV indicator. Melting points were determined in open capillary and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer. The chemical shifts (δ) are reported in parts per million upfield using residual signals of solvents as internal standards. Coupling constants (J values) were measured in hertz (Hz). Combustion analyses were performed with a Carlo Erba CHN analyzer.

Dimethyl 2-(4-chlorobenzylideneamino)pentanedioate (4)

Under argon atmosphere 5.02 ml (3.643 g, 36 mmol) of NEt$_3$ were added to a suspension of 7.620 g (36 mmol) of glutamic acid dimethyl ester hydrochloride and 7.222 g (60 mmol) of MgSO$_4$ in 100 mL of CH$_2$Cl$_2$. After 1 h stirring at rt 4-chlorobenzaldehyde (4.217 g, 30 mmol) was added and the resulted mixture was stirred at rt overnight. The solid was removed by filtration and the filtrate was washed once with H$_2$O. The aqueous phase was extracted once with 30 mL of CH$_2$Cl$_2$ and the combined organic layers were washed with brine. The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The product was isolated as yellowish oil, 8.900 g (100%), and used in the next step without additional purification. ^{1}H NMR (400 MHz; CDCl$_3$): δ 8.26 (s, 1H, CH=), 7.72 (d, J = 8.4, 2H, Ar), 7.40 (d, J = 8.4, 2H, Ar), 4.06 (dd, J = 8.0, 5.0, 1H, CHN), 3.76 (s, 3H, OCH$_3$), 3.66 (s, 3H, OCH$_3$), 2.43-2.21 (m, 4H, CH$_2$CH$_2$).

Methyl (3aR*,4S*,6R*,6aS*)-6-(4-chlorophenyl)-4-(3-methoxy-3-oxopropyl)-1,3-dioxohexahydro-1H-furo[3,4-c]pyrrole-4-carboxylate (5)

Iminoester **4** (4.500 g, 15.1 mmol) was dissolved in 20 mL of CH$_2$Cl$_2$ under air atmosphere and CH$_2$Cl$_2$ solutions of 1.480 g of maleic anhydride (15.1 mmol) and 0.264 g N-BocGly (1.5 mmol) were added sequentially. The mixture was stirred for 24 h at rt. The solution was concentrated under reduced pressure, and the residue was recrystallized from hexane/CH$_2$Cl$_2$. 5.083 g (85%), colorless crystals, mp 96-99 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.42-7.37 (m, 4H, Ar), 4.70 (d, J = 9.1, 1H, H^6), 3.98 (dd, J = 9.1, 7.8, 1H, H^{6a}), 3.75 (d, J = 7.8, 1H, H^{3a}), 3.72 (s, 3H, OCH$_3$), 3.58 (s, 3H, OCH$_3$), 2.58-2.52 (m, 1H, CH$_2$), 2.18-2.14 (m, 2H, CH$_2$), 2.10-2.02 (m, 1H, CH$_2$). ^{13}C NMR (100 MHz; DMSO-d_6): δ 173.07, 171.89, 171.23, 170.31, 137.99, 132.61, 129.44 (2C), 128.54 (2C), 70.40, 59.87, 55.64, 52.61, 51.92, 50.38, 29.60, 28.54. Anal. Calcd for C$_{18}$H$_{18}$ClNO$_7$: C, 54.62; H, 4.58; N, 3.54. Found: C, 54.79; H, 4.55; N, 3.81.

(3aR*,4R*,5R*,9aS*)-5-(4-Chlorophenyl)-2-(4-fluorobenzyl)-1,3,7-trioxooctahydro-7H-pyrrolo[3,4-g]pyrrolizine-4-carboxylic acid (7)

Anhydride **5** (1.000 g, 2.53 mmol) was dissolved in 25 mL of dry THF and 0.300 mL (0.320 g, 2.53 mmol) of 4-fluorobenzylamine were added to the solution. The mixture was stirred for 72 h at rt, concentrated under reduced pressure, and the residue was redissolved in 25 mL of MeCN. The solution

was heated at 82 °C for 24 h, concentrated and the residue was recrystallized from CH_2Cl_2/MeOH. 0.703 g (61%), colorless crystals, mp 282-283 °C. ^{1}H NMR (400 MHz; DMSO-d_6): δ 13.36 (br.s, 1H, COOH), 7.15 (d, J = 8.6, 2H, Ar), 7.04-7.02 (m, 2H, Ar), 7.01-6.94 (m, 4H, Ar), 5.42 (s, 1H, H^5), 4.27-4.16 (m, 2H, CH$_2$Ar), 3.76 (s, 1H, H^4), 3.67 (s, 1H, H^{3a}), 2.99 (ddd, J = 16.4, 11.2, 9.2, 1H, H^8), 2.58 (dd, J = 12.8, 9.2, 1H, H^8), 2.45-2.39 (m, 1H, H^9), 2.30 (dd, J = 12.8, 11.2, 1H, H^9). ^{13}C NMR (100 MHz; DMSO-d_6): δ 178.06, 177.69, 175.66, 173.24, 161.94 (J 243.7), 137.34, 132.90, 131.23, 130.72, 130.64, 128.94 (2C), 127.04 (2C), 115.68, 115.47, 73.10, 61.57, 53.93, 52.41, 41.88, 32.89, 29.73. Anal. Calcd for $C_{23}H_{18}ClFN_2O_5$: C, 60.47; H, 3.97; N, 6.13. Found: C, 60.69; H, 4.05; N, 6.01.

Crystal structure determination of compound 7.

The single crystal of **7** of approximate dimensions 0.40 x 0.20 x 0.20 mm was mounted in inert oil on the top of glass fibre and transferred on the Bruker SMART APEX II diffractometer. Crystal data: $C_{23}H_{18}ClFN_2O_5$, M = 456.84, monoclinic, a = 13.6113(18), b = 12.5729(18), c = 12.4174(16) Å, β = 108.234(4)°, V = 2018.3(5) Å^3, space group $P2_1$/c, Z = 4, D_c = 1.503 g/cm^3, F(000) = 944, μ(Mo-Kα) = 0.239 mm^{-1}. Total of 18287 reflections (4187 unique, R_{int} = 0.0457) were measured using graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å) at 100 K.   Data were collected in the range $1.58 < \theta < 26.54$ (-17 ≤ h ≤ 17, -15 ≤ k ≤ 15, -15 ≤ l ≤ 15). The structure was solved by direct methods[17] and refined by full matrix least-squares on F^2. All H atoms (except H^{O2}) were placed in calculated positions and refined using a riding model. The final residuals were: R_1 = 0.0527, wR_2 = 0.0981 for 3076 reflections with $I > 2\sigma(I)$ and 0.0784, 0.1079 for all data and 289 parameters. Goof = 1.108, maximum Δρ = 0.487 e/Å^3.

ACKNOWLEDGEMENTS

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13. Crystallographic data (excluding structure factors) for the compound **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-761400. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int.code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

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