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Stereo-specific synthesis of hydroanthracene-dicarboximides

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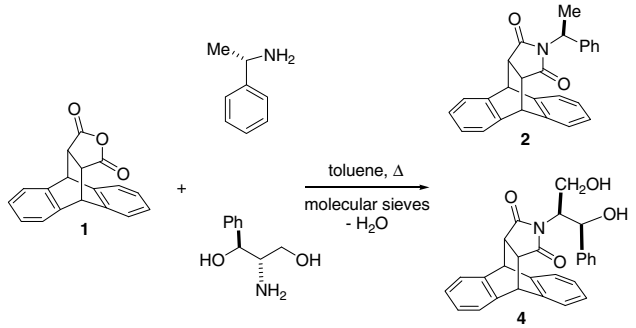
ABSTRACT

Compound **3**, *N*-((1*S*)-1-cyclohexylethyl)-9,10-dihydro-9,10-ethanoanthracene-(11*S*,12*S*)-dicarboximide-1,2,3,4-octahydro, was obtained by ruthenium-assisted hydrogenation of the hydroanthracene-dicarboximide **2** under mild conditions (3 bar H_2 and room temperature). In contrast to other related compounds, dicarboximides **2** and **3** were stereo-selectively obtained, confirmed by both solid state (X-ray diffraction) and solution (NMR). This selectivity denoted a hindered rotation around the N–CH axis together with the aromatic hydrogen bond acceptor behaviour of the hydroanthracene skeleton towards a methylene of the cyclohexyl group of the imide moiety. In addition, the nature of the metallic species involved in the hydrogenation process was also investigated.

Hydroanthracene-dicarboximides are applied in different fields, due to their easy modulation and their chemical stability. Therefore, they have been employed in anticancer chemotherapy[1,2] and also as precursors of pharmacophores such as α,β-unsaturated lactam or lactone compounds.[3,4] Recently, these compounds have also found applications in catalysis, in particular in asymmetric processes such as enantioselective three-component Mannich reaction[5] and enantioselective addition of diethylzinc to arylaldehydes.[6]

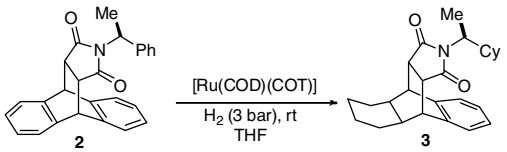
These hydroanthracene derivatives can be readily prepared giving quantitative yields by Diels–Alder cycloadditions from anthracene and maleimides reagents or from anhydride **1** (Scheme 1) and primary amines.[4,7] Concerning their reactivity, it is important to note that these compounds are quite stable towards hydrogenation processes. For instance, the hydrogenation of maleic anhydride-anthracene Diels–Alder cycloaddition product **1** requires harsh conditions.[8] Because of the non-planarity of the dihydroanthracene skeleton and the presence of the bulky anhydride group, only the less hindered aromatic group could be hydrogenated. The interest of this kind of reduced compounds is illustrated by the use of imino-bridged dibenzocycloalkene derivatives, synthesized by hydrogenation of hydroanthracene-dicarboximides, for medical purposes.[9]



Scheme 1.

From a structural point of view, hydroanthracene-dicarboximides can give different conformers because of the rotation around the N–C bond.[10] The ratio of different conformations depends not only on the spatial arrangements and electrostatic interactions, but also on weak interactions such as hydrogen bonds and CH/π interactions.[11] To the best of our knowledge, no reports have been described showing a perfect stereo-control, obtaining in all the cases a mixture of isomers.

In our research concerning the ligand design for catalytic applications, we are interested in the functionalisation of Diels–Alder adducts of anthracene, keeping a rigid backbone and a modular part coming from the anhydride moiety. Here, we describe the hydrogenation of *N*-((1*S*)-1-phenylethyl)-9,10-dihydro-9,10-ethanoanthracene-(11*S*,12*S*)-dicarboximide, compound **2**, under mild conditions. This Ru-promoted selective process leads to the stereo-controlled formation of **3** (Scheme 2).



Scheme 2.

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Hydroanthracene-dicarboximides **2** and **4** were obtained by condensation of anhydride **1** and the corresponding primary amine, (*S*)-α-methylbenzylamine and (*1S,3S*)-2-amino-1-phenyl-1,3-propandiol, respectively, (Scheme 1), based on the methodology previously described.[4,7d] The Diels–Alder adduct **1** was in turn prepared starting from anthracene and maleic anhydride following the reported synthesis with minor modifications (see below).[12]

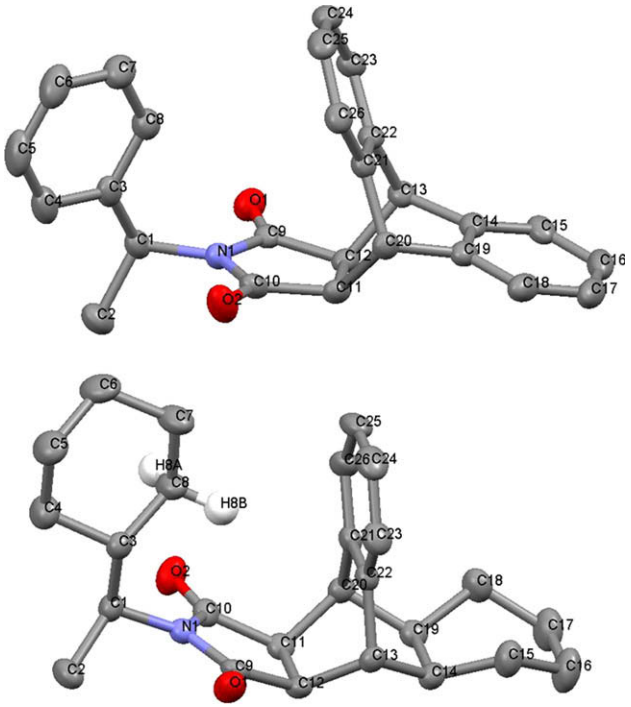

Figure 1. ORTEP drawings of **2** (top) and **3** (bottom). Hydrogen atoms are omitted for clarity except H8 for compound **3** in order to show the π-interaction with the phenyl group.

Further ruthenium-assisted hydrogenation of **2** led quantitatively to the formation of **3** under mild conditions (room temperature and low hydrogen pressure) (Scheme 2). The selective hydrogenation of the aromatic groups could probably be related to steric reasons. Actually, hydrogenation of both aromatic groups of the 9,10-dihydroanthracene fragment for **2** should be avoided by steric hindrance with the imide group, taking into account the syn relative arrangement of both fragments. The hydrogenation of the phenyl group coming from the amine also took place. This partial hydrogenation was also reported for the starting compound **1** using ruthenium on the alumina as catalyst,[8] but under harsher conditions than those here described.

Single crystals of **2** were obtained from a diethylether solution. A search of Cambridge Structural Database (CSD, Version 5.28 of November 2006 and three updates) reveals 32 related structures non-substituted at C13 and C20 positions (Fig. 1), with 14 different N-substituent groups. Compound **2** shows similar structural features than those described, but in contrast to many of them no solvates or co-crystals of the same compound are found. The X-ray crystal structure of **3** evidences the close proximity of the cyclohexyl group to that of the aromatic ring (Fig. 1). The non-bonded distance between C8 to the centre of the aromatic ring is 3.5 Å, appropriated distance for CH/π interaction showing the hydrogen bond acceptor behaviour of the aromatic group.[11c]

^{1}H NMR analyses at variable temperature (193–343 K) of **3** in polar (DMSO-d_6 and THF-d_8) and non-polar (CD_2Cl_2 and $CDCl_3$) solvents showed the presence of only one species, although two isomers could be expected due to the rotational isomerism around N–CH bond: the cyclohexyl group can be in close proximity to the aromatic group of the backbone or on the contrary, the methyl group can be placed near to this fragment. The protons of the C8 methylene group appear upfield shifted (0.25 and 0.35 ppm) compared to the other methylene groups (0.64–1.64 ppm) (Fig. 2). At low temperature in CD_2Cl_2, these two protons appear upfield

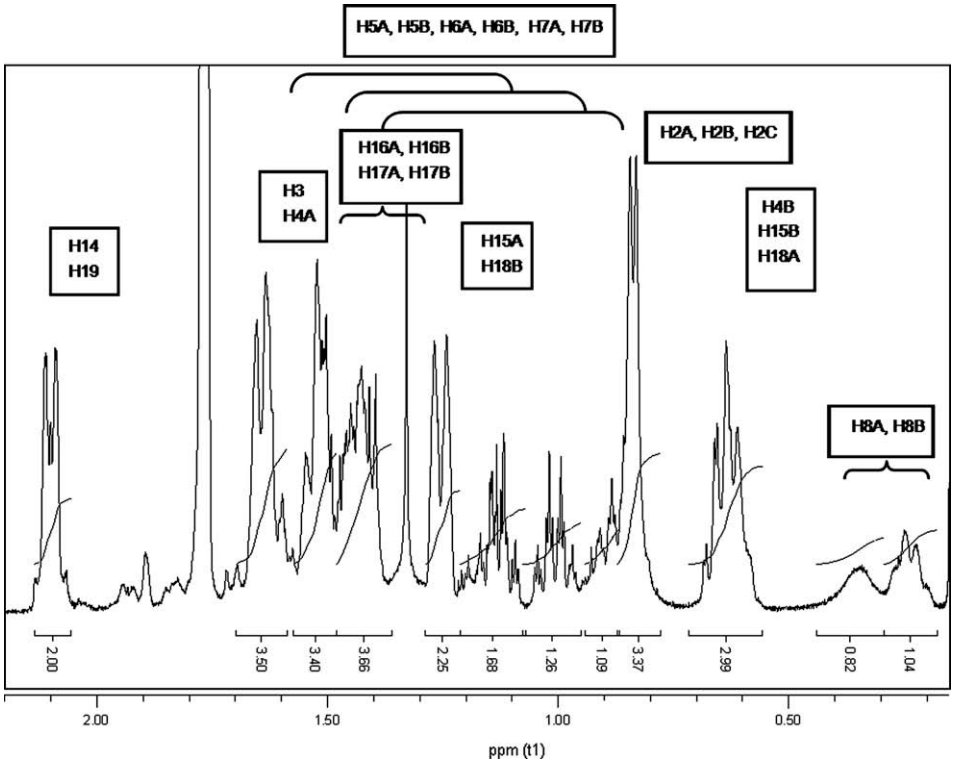

Figure 2. Aliphatic region (0–2.5 ppm) of ^{1}H NMR (500 MHz) spectrum of **3** in THF-d_8 at 298 K.

shifted: −0.2 and −1.0 ppm (see Fig. S1 in Supplementary data). This fact can be justified by the spatial proximity to the aromatic group. This kind of interaction was also reported for non-chiral related compounds,[10] but in contrast to **3**, two isomers were obtained in solution due to the rotation around the N–C bond.

Analogously, the VT ^{1}H NMR study for **2** showed the presence of only one isomer even at 203 K in CD_2Cl_2 (Fig. 3 and Fig. S2 in Supplementary data).

In order to check the relationship between the substituent hindrance on N atom and the rotation around the N–CH bond, dicarboximide **4** containing a less sterically demanding group was also prepared (Scheme 1). Actually, VT ^{1}H NMR spectra (193–293 K) showed two isomers below 223 K with a ratio 1/3, proving the absence of strong intramolecular hydrogen bonds (see Fig. S4 in the Supplementary data).

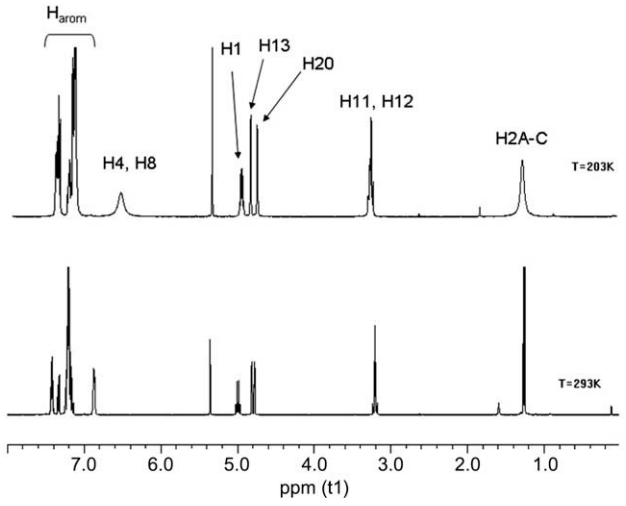

Figure 3. ^{1}H NMR (500 MHz) spectrum of **2** in CD_2Cl_2 at 203 K (top) and at 293 K (bottom).

In order to rationalize the stereo-specificity observed for **2** and **3**, we have modelled their equilibrium geometries and the corresponding energies for both conformers, depending on the relative position of N-substituent group and the aromatic ring of the skeleton, *anti* and *syn* (Fig. 4). Their structures and formation enthalpies were calculated at DFT level. The energy difference between both isomers for **2**, *syn*-**2** and *anti*-**2**, is ca. 0.6 kcal/mol, which corresponds to a ratio *anti*-**2**:*syn*-**2** = 3/1; while for **3**, this difference is ca. 0.4 kcal/mol, corresponding to a ratio *anti*-**3**:*syn*-**3** = 2/1 at 298 K. In both cases, the less hindered conformer, the *anti*-isomer, shows a lower energy. This calculation confirms that the observation of only one stereoisomer (*syn*) in solid state and in solution should be necessarily associated to a high-rotation barrier around the N–CH-axis.

With the aim of shedding some light on the nature of the ruthenium species involved in the hydrogenation, we analyzed by transmission electronic microscopy (TEM) the reaction mixture after the hydrogenation was completed. This analysis evidenced the formation of well-defined ruthenium nanoparticles showing a mean diameter of 1.4 ± 0.4 nm (see Fig. S3 in Supplementary data). Therefore, hydrogenation could be carried out at the metallic surface of the ruthenium nanoparticles in agreement with the reported results concerning the hydrogenation of anthracene.[13]

In summary, we have stereo-selectively prepared the hydroanthracene-dicarboximides *syn*-**2** and *syn*-**3**, as proved by ^{1}H NMR and X-ray diffraction studies. Compound **3** was obtained, under mild conditions, by Ru-promoted hydrogenation of the 9,10-ethanoanthracene-(11*S*,12*S*)-dicarboximide skeleton together with the reduction of the phenyl group of the amide moiety. This

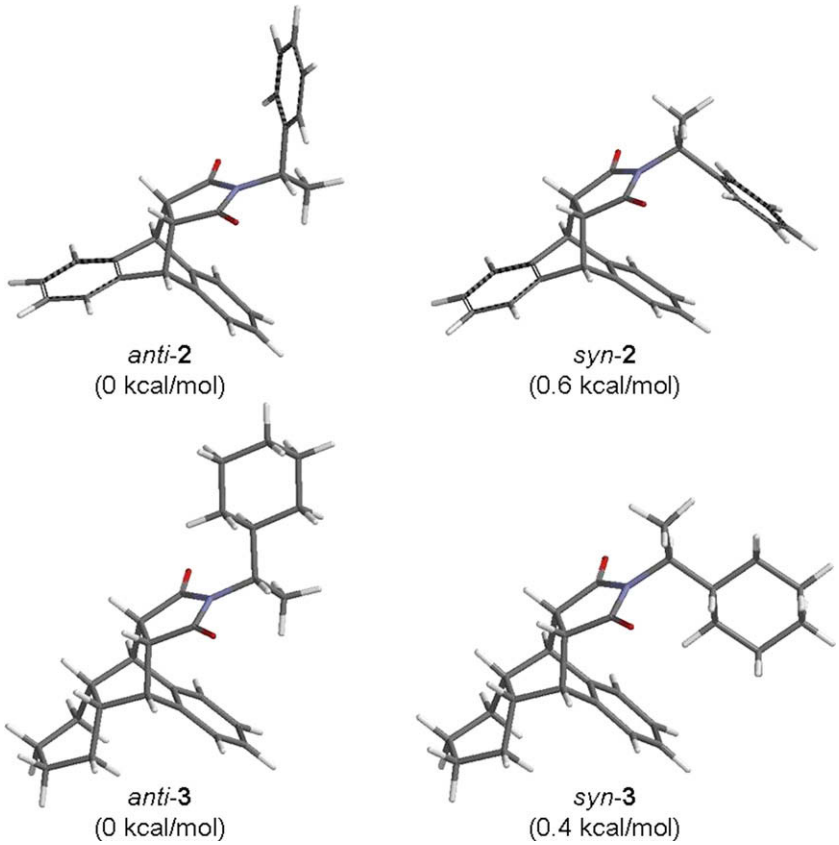

Figure 4. Calculated structures (DFT) for *syn* and *anti* isomers for **2** (top) and **3** (bottom) compounds (in parentheses their relative formation enthalpies).

methodology could open a useful access to prepare 1,2,3,4-tetrahydroanthracenes by retro Diels–Alder reaction from the corresponding dicarboximides.[14,15]

The isomeric purity of **2** should be related to the high barrier associated to the rotation around the N–CH bond. For **3**, this fact is even more evident due to the more sterically demanding cyclohexyl group in comparison with the phenyl group for **2**. In addition, a strong CH/π interaction between a methylene group of the cyclohexyl fragment with the aromatic moiety of the backbone avoids the formation of the corresponding *anti*-isomer. Consequently, for less sterically demanding groups the rotation is favoured as observed for **4**.[15]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.083.

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15. Procedures and characterization data for compounds **1**–**4**:
Synthesis of the compound **1**: A solution of anthracene (5.00 g, 28.1 mmol) and maleic anhydride (3.30 g, 33.7 mmol) in toluene (100 mL) was refluxed for 72 h. The reaction mixture was then cooled, filtered and the solid obtained washed with diethylether and dried under reduced pressure. Crystallisation from ethyl acetate gave a white powder (6.94 g, 89%).
Synthesis of the compound **2:** A solution of **1** (2.00 g, 7.3 mmol) and (*S*)-α-methylbenzylamine (1.85 mL, 14.5 mmol) in toluene (90 mL) was refluxed for 72 h in presence of molecular sieves 4 Å. The reaction mixture was then cooled, filtered, and the solvent removed under reduced pressure. The yellow residue obtained was dissolved in dichloromethane (20 mL) and washed with ammonium chloride saturated aqueous solution (3 × 20 mL). The combined organic layers were dried on anhydrous Na_2SO_4, filtered, and the solvent evaporated under vacuum leading to a white powder. After purification by column chromatography on silica gel with dichloromethane, **2** was obtained as a white powder (1.96 g, 71%). Melting point: 163 °C. ^{1}H NMR (400 MHz, DMSO-d_6: δ 7.40 (m, 2H, H_{arom}), 7.30 (m, 1H, H_{arom}), 7.20 (m, 1H, H_{arom}), 7.16 (m, 7H, H_{arom}), 6.70 (m, 2H, H4 and H8), 4.87 (q, ^3J = 7.2 Hz, 1H, H1), 4.79 (d, ^3J = 2.8 Hz, 1H, H13), 4.77 (d, ^3J = 3.0 Hz, 1H, H20), 3.28 (dd, ^3J = 8.6 Hz, ^3J = 3.0 Hz, 1H, H11), 3.25 (dd, ^3J = 8.6 Hz, ^3J = 3.0 Hz, 1H, H12), 1.16 (d, ^3J = 7.2 Hz, 3H, H2); ^{13}C NMR (100.6 MHz, DMSO-d_6: δ 176.7 (C9), 176.6 (C10), 142.6, 139.9, 139.8, 139.7, 128.5, 127.1, 127.0, 126.9, 126.7, 126.5, 125.2, 124.6, 124.5, 49.2, 46.6, 46.5, 45.2, 16.6 (C2). Mass spectrometry (ES, *m*/*z*): 379. Anal. Calcd for $C_{26}H_{21}NO_2$ (*M* = 379.45): C, 82.30; H, 5.58, N, 3.69. Found: C, 82.17; H, 5.29, N, 3.66. Single crystals were obtained from diethylether solution of **2**.
Synthesis of compound **3**: A solution of **2** (30 mg, 0.08 mmol) and [Ru(COD)(COT)] (28 mg, 0.08 mmol) in dry tetrahydrofuran (10 mL) was exposed under 3 bar H_2 pressure during 4 h at room temperature. The solvent was then removed under vacuum and the residue obtained was dissolved in diethylether (10 mL) and washed with water (3 × 10 mL). The combined organic layers were dried on anhydrous Na_2SO_4 and the solvent evaporated under vacuum, leading to a white powder. Crystallisation from dichloromethane/pentane (1:1 v/v) gave colourless crystals suitable for single-crystal X-ray diffraction (32 mg, 99%). ^{1}H NMR (500 MHz, THF-d_8: δ 7.16 (m, 2H, H_{arom}, H23 and H26), 7.07 (m, 2H, $H_{arom,}$ H24 and H25); 3.40 (m, 1H, H1); 3.22 (s, 2H, H13 and H20), 3.09 (m, 2H, H11 and H12), 2.11 (m, 2H, H14 and H19), 1.64 (m, 2H, H3, H4), 0.64 (m, 1H, H4), 0.35 and 0.25 (m, 2H, H8), 1.35 and 0.64 (m, 4H, H15 and H18), 1.52 and 1.44 (m, 4H, H16 and H17), 1.52 and 1.00, 1.42 and 0.88, 1.64 and 1.14 (m, 6H, H5, H6 and H7), 0.83 (d, 6.5 Hz, 3H2); ^{13}C NMR (125 MHz, THF-d_8: δ 177.27 (C9 or C10), 177.17 (C9 or C10), 137.51 (C21 or C22), 137.45 (C21 or C22), 126.78, 126.60, 126.56, 126.53 (C23, C24, C25, C26), 51.96 (C1), 44.49 (C13 or C20), 44.43 (C13 or C20), 42.22 (C11 and C12), 38.45 (C3), 37.69 (C14 or C19), 37.68 (C14 or C19), 30.17 (C4), 28.80 (C8), 26.09 (C5 or C6 or C7), 25.92 (C5 or C6 or C7), 25.78 (C5 or C6 or C7), 23.70 (C15 or C18), 23.69 (C15 or C18), 19.24 (C16 and C17), 14.29 (C2). HRMS (ES+): *m*/*z* (100%) calcd for $C_{26}H_{33}NO_2$ 391.5522, found 392.2605.
Synthesis of the compound **4**: A solution of **1** (1.00 g, 3.6 mmol) and (1*S*,3*S*)-2-amino-1-phenyl-1,3-propandiol (1.21 g, 7.2 mmol) in toluene (120 mL) was refluxed for 12 h in the presence of molecular sieves 4 Å. The reaction mixture was monitored by TLC (hexane/ethyl acetate = 3/2), then cooled, filtered, and the solvent removed under reduced pressure. The residue obtained was dissolved in dichloromethane (20 mL) and washed with ammonium chloride saturated aqueous solution (3 × 20 mL). The combined organic layers were dried on anhydrous Na_2SO_4, filtered and the solvent evaporated under vacuum leading to a white powder recrystallised from in ethyl acetate (1.34 g, 87%). Melting point: 200 °C. ^{1}H NMR (300 MHz, $CDCl_3$: δ 7.39–7.15 (m, 13H), 5.03 (d, ^3J = 7 Hz, 1H), 4.78 (m, 2H), 4.10 (q, ^3J = 7 Hz, 1H), 3.15 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 179.9 (C), 176.4 (C), 141.1 (C), 141.0 (C), 139.0 (C), 138.9 (C), 129.1 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.8 (CH), 125.7 (CH), 125.3 (CH), 125.2 (CH), 125.1 (CH), 124.3 (CH), 70.7 (CH), 59.8 (CH_2), 59.6 (CH), 46.8 (CH), 46.1 (CH), 45.5 (CH), 45.4 (CH). Mass spectrometry (ESI, *m*/*z*): 448.4 [M+Na], 426.4 [M+H]. Anal. Calcd for $C_{27}H_{23}NO_4$ (*M* = 425.48): C, 76.22, H, 5.45, N, 3.29. Found: C, 76.20, H, 5.24, N, 3.32.
CCDC 690719 for **2** and CCDC 690720 for **3** contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].