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SYNTHESIS OF N-CYANOPORPHYRINS AND RELATED COMPOUNDS. CRYSTAL STRUCTURE OF N-CYANO-*MESO*-TETRATOLYLPORPHYRIN.

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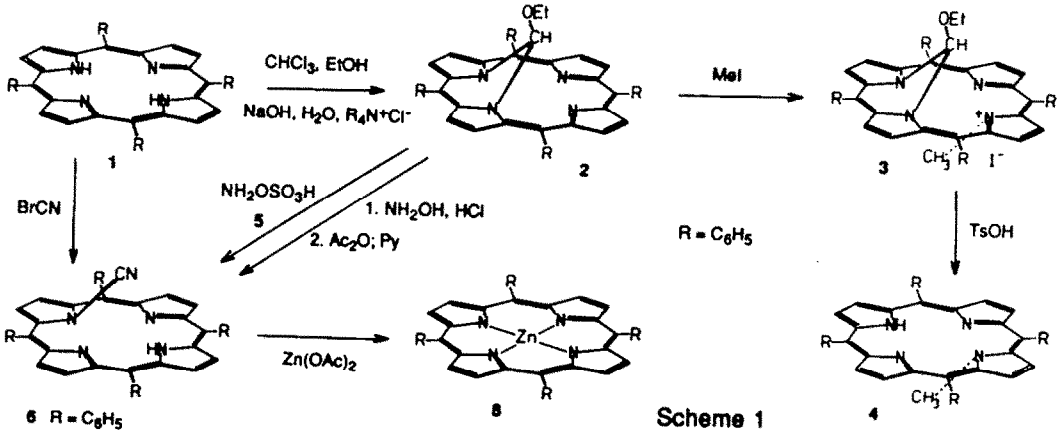
Abstract: N-Cyano-tetraphenylporphyrin was prepared either from N,N'-ethoxymethylene-*meso*-tetraphenylporphyrin and hydroxylamine-O-sulfonic acid or by direct cyanation with cyanogen bromide. Its metallation is rapid and concommitant cleavage of the N-substituent was observed. Such a reactivity can be used for rapid introduction of short-lived radionuclides into porphyrins. The crystal structure of N-cyano-*meso*-tetra-*p*-tolylporphyrin was determined. The macrocycle is ruffled, the pyrrole bearing the cyano group is tipped out of the (4N) plane by 29.3°. The angle of the cyano group with the corresponding pyrrole is 150°.

Not only are N-substituted porphyrins[1] of major biochemical interest as abnormal metabolites of hemes but they also display a versatile chemical reactivity which is a consequence of the distortion of the porphyrinic macrocycle. A variety of methods for preparing N-substituted porphyrins have been published, those involving the direct alkylation of the pyrrolic nitrogen atoms being the most straightforward. However polyalkylation often gives rise to mixtures and only in some cases selective



Scheme 1

or specific monoalkylation was observed.[2-6] One way to overcome this difficulty first involves the formation of a bridge between two pyrrolic nitrogen atoms.[7] Alkylation of a third position, activated by the distortion of the macrocycle induced by the bridge, followed by acid-catalyzed cleavage of the bridge gave pure N-alkylporphyrins (Scheme 1). When we tried to extend this method to the preparation of more unusual compounds like N-amino[8] or N-carbalkoxyporphyrins,[9] the results were quite different from those expected but allowed us to characterize some new N-substituted porphyrins.

RESULTS AND DISCUSSION.

Synthesis and characterization of N-cyanoporphyrins.

N-Amination of heterocyclic compounds has been achieved using hydroxylamine O-sulfonic acid **5**.[10] Accordingly, compound **2** was treated with **5** in dimethylformamide (DMF) (86°C; 40 min). The reaction gave, instead of the expected salt, a neutral porphyrin which was found to be N-cyanoTPP **6** (67 %). This was deduced from the spectroscopic data, in particular the strong IR band at 2250cm^{-1}. In addition **6** was easily prepared, albeit in lower yield (16 %), by heating H_2TPP **1** with BrCN in CH_2Cl_2 / toluene.

The NMR spectra for **6** (and its tetratolyl analog **7**) show the expected signals with the peculiarity that the coupling between the pyrrolic protons and the NH attached to the pyrrole ring opposite to NCN is detectable (1.4 Hz), suggesting a highly localized NH proton (attribution verified by NH decoupling). Also the difference between the various signals for the pyrrolic protons - spread over only 0.4 ppm for **6** (in $CDCl_3$) while this value is in the range of 1.3-1.4 ppm for simple N-alkyl-tetraaryl-porphyrins[1] - is small, the shifts of the protons of the N-substituted pyrrole being close to normal. This indicates either a strong deshielding effect of the electron-withdrawing cyano group or a geometry more similar to that of a non-N-substituted porphyrin.

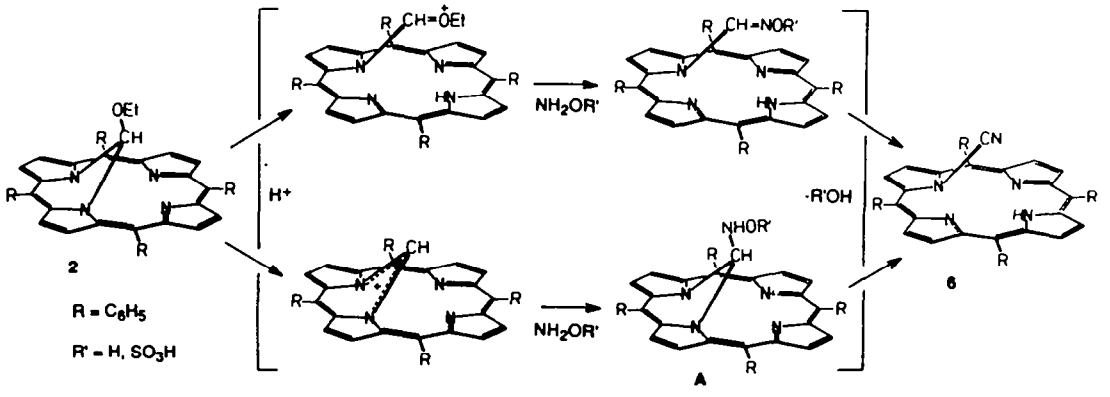
Its UV-visible data are shown in Table 1, together with those of related compounds for comparison.

H_2TPP 1	418 (100)	514 (5.35)	550 (2.5)	592 (1.75)	648 (1.65)
H(NCN)TPP 6	430 (100)	518 (7.4)	558 (4.7)	632 (1.4)	692 (2.3)
H(NCH_3)TPP 4	430 (100)	534 (5.4)	574 (8.3)	620 (sh. 3)	676 (2.9)

Table 1: UV-visible data (λ_{max} and relative intensities in CH_2Cl_2).

The UV-visible data for 6 differ from both those of H_2TPP 1 and the known N-alkyl or N-arylporphyrins, the relative intensities of the 4 smaller absorption bands being closer to those of H_2TPP 1 (band I > other bands) than to those of N-substituted porphyrins (band II > other bands). One expects an effect due to the electron-withdrawing properties of the nitrile group, but little steric perturbation. The best way to test this last contribution and the points discussed in connection with the NMR data was to carry out an X-ray diffraction study. However since 6 did not crystallize in a form suitable for the structural study we duplicated the synthesis using tetratolylporphyrin as starting material to produce 7 which crystallized from toluene-pentane (see second section of this paper).

With regard to the formation of N-cyanoTPP 6, we suggest that the reaction is initiated by the acidic nature of the reagent. Although the order of the various steps (O→N substitution, bridge cleavage) is not known, an intermediate **A** is likely to form (Scheme 2). The elimination of sulfate anion from such structures, when derived from aldehydes, is known to produce nitriles in high



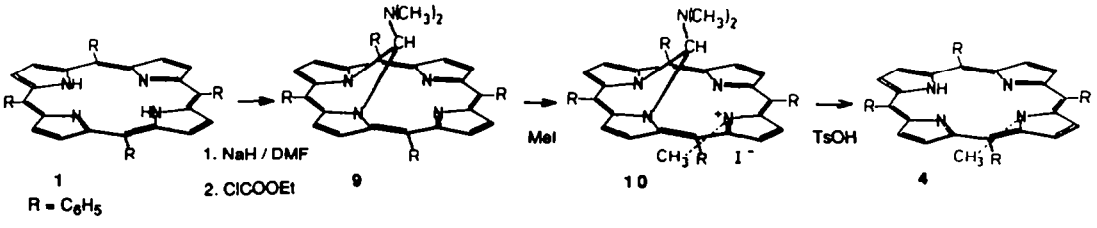
Scheme 2

yields.[11] Analogously the bridged porphyrin **2** was treated first with hydroxylamine hydrochloride, followed by Ac_2O and pyridine, to give **6**.

N-CyanoTPP **6** is a thermally stable compound and does survive for at least 24 h in refluxing toluene. However its metalation with zinc acetate resulted in the quantitative formation of ZnTPP **8**. A similar result was obtained with cobalt(II) acetate. When the metalation by zinc acetate was followed by TLC, an unstable polar green product could be detected, presumably the zinc complex of **6**, but it did not survive any isolation procedure. The cleavage of N-substituent by nucleophiles is an efficient reaction[1,12] and the accessibility and charge deficiency of the cyano group carbon may only accelerate the process. An analogous loss of a cyano group as a formal "CN^+" was observed from N-cyanopyridines, the group being transfered to an imidazole.[13]

A method for the rapid metalation of porphyrins with short-lived radionuclides takes advantage of the high lability of certain N-substituents and has been applied to the labeling of antibodies.[14] Indeed N-substitution dramatically accelerates the incorporation of the metal, while subsequent cleavage of the N-substituent regenerates the normal porphyrin metal complex. In this context we see the N-cyano moiety as an attractive alternative to the previously used *p*-nitrobenzyl group.

Independently we attempted to prepare, directly from H_2TPP **1**, N-carboethoxyTPP[9] by reaction of ethylchloroformate. The use of a variety of conditions did not give any positive result (and usually led to the recovery of the starting material) until we tried to react the dianion of H_2TPP **1** with $ClCO_2Et$ in DMF. A olive-green basic product **9** formed which could be chromatographed but rapidly decomposed even in the solid state into **1**. The formation of **9** can result from a double reaction of the dianion of **1** with a chloroiminium salt (Vilsmeier reagent) generated from $ClCO_2Et$ and DMF. (Scheme 3)



Scheme 3

Although the unstability of **9** precluded its isolation in a pure state, the following reaction sequence confirmed structure **9**, the nitrogen analog of **2**. When crude **9** was treated with MeI a very polar green compound formed which we formulate as salt **10**. Salt **10** is somewhat more stable than base **9** and could be crystallized as its perchlorate. Its NMR spectrum shows the typical high-field signals associated with the presence of a substituent attached to a pyrrolic nitrogen: bridge protons at -2.17 and -3.20 ppm (respectively dimethylamino and methine protons) and N-methyl protons at -3.42 ppm. The corresponding signals in **3**, are located at -3.10 (methine) and -3.45 ppm (N-methyl).[7] The acid-catalyzed cleavage of the bridge in **10** parallels the reaction described above for **3** and N-methylTPP **4** was produced in quantitative yield.

Structure of N-cyano-*meso*-tetra-*p*-tolylporphyrin.

Although a series of structure of metal complexes of N-substituted porphyrins have been determined by X-ray diffraction studies,[1,12,15-17] only two structures of mono-substituted free bases are known: N-methyl–*meso*-tetra(*p*-bromophenyl)porphyrin (NMeTpBrPP)[16] and octaethylporphyrin N-oxide,[17] this last compound being unfortunately partially disordered in the crystalline state. In addition the structure of the iodide of protonated N-ethoxycarbonylmethylene-octaethylporphyrin has been solved.[18]

A drawing of **7** with the numbering scheme is displayed in Figure 1. The atoms of the porphyrin core are nonplanar, while the pyrrole rings (N1), (N2), (N3) and (N4) are individually planar. The four pyrrolic nitrogens N1, N2, N3 and N4 are coplanar (± 0.06 Å), defining the (4N) reference plane.

The cyano substituted pyrrole (N1) is the most highly canted from the (4N) plane (29.3°). The N-protonated pyrrole (N3) is tilted in the same direction by only 4.7°, while the two last pyrroles are tilted by 15.9 and 11.1° in the opposite direction. Thus the porphyrin presents a "ruffled" geometry, similar to that found in NMeTpBrPP[16] which shows corresponding angles of 27.7, 8.1, 10.2 and 11.9° respectively (angles defined with respect to a N1, N2, N4 plane). The N-H proton is attached to N3 in both compounds.

The geometry of the cyano group is significantly different from that of the methyl group in NMeTpBrPP: the angle between the C1A-N1A direction and the (N1) plane is about 150° while the

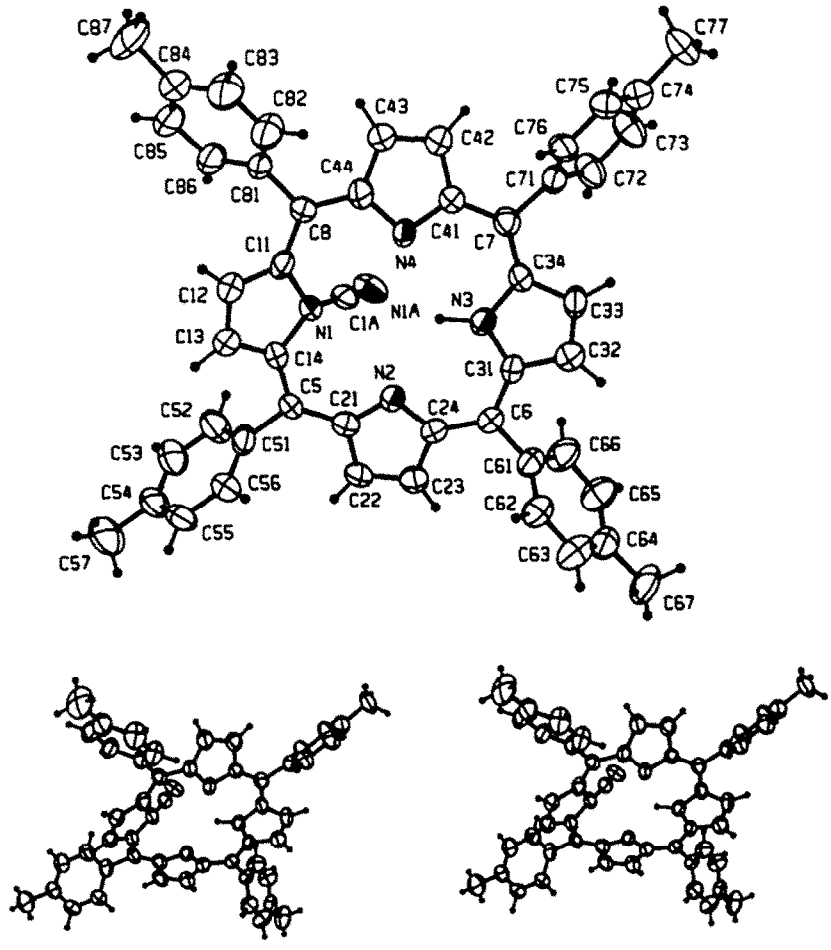


Figure 1: Numbering scheme and stereo pair of molecule Z

corresponding angle is only 120.2° in NMeTpBrPP[16] (149° in octaethylporphyrin N-oxide).[17] The deviations from the (4N) plane of the cyano atoms C1A and N1A are 1.21(1) and 2.17(1)Å, respectively. The N1-C1A-N1A group is linear (177.2(8)°), with normal N1-C1A and C1A-N1A bonding distance values of 1.378(9) and 1.124(9) Å, respectively (cf. cyanamide[19] H_2N-C≡N, 1.31 and 1.15 Å). The reduced angle between the cyano group and (N1) - and by consequence between the cyano group and the whole macrocycle - illustrates, as for the N-oxide, its reduced steric requirements as compared to those of a methyl group. The NMR data for 6 and Z suggest the NH

proton to be firmly bound to N3. This may be a consequence of either a loss of basicity of the remaining nitrogen atoms (vicinity of the CN group) or a hydrogen bond between this group and the NH. The observed distance between N1A and N3 (3.51 Å) excludes the second hypothesis. All other bond lengths and angles are in good agreement with those generally found for this class of compounds.

EXPERIMENTAL SECTION

Nmr spectra were obtained in $CDCl_3$ (unless otherwise stated) at 200 MHz on a Bruker WP-200 SY spectrometer. Chemical shifts (δ) are expressed in ppm from TMS. Coupling constants of pyrrolic and aromatic (phenyl) protons are in the normal 5- or 8 Hz range and will not be specified. Visible spectra were taken in CH_2Cl_2 on a Hewlett-Packard 8451 A spectrophotometer. Elemental analyses were performed by the "Service de Microanalyse de l'Institut de Chimie de Strasbourg". Reactions were run under argon and followed by using Merck Alumina 150 F-254 TLC plates. Chromatographic separations were obtained using Merck alumina 90 columns. Yields are for recrystallized products.

N-Cyano-meso-tetraphenylporphyrin 6.

a) Bridged porphyrin **2** (100 mg)[7] was added to a solution of hydroxylamine-O-sulfonic acid **5** (3 g) in DMF (60 mL) and the mixture heated for 40 min at 86°C. After cooling the solution was diluted with CH_2Cl_2, washed twice with saturated aqueous $NaHCO_3$, then five times with water, dried over Na_2SO_4 and evaporated. Chromatography of the residue (alumina, 100 mL in CH_2Cl_2) gave some H_2TPP **1** followed by **6** (eluted with 5 % AcOEt), which was recrystallized from CH_2Cl_2 - MeOH (58 mg; 67 %).

b) Bridged porphyrin **2** (50 mg) was treated with hydroxylamine hydrochloride (200 mg) in DMF (10 mL) and the mixture heated at 50° for 1 h. To the cooled solution pyridine (5 mL) and acetic anhydride (3 mL) were added. After 24 h the solution was diluted with CH_2Cl_2, washed five times with water, dried (Na_2SO_4) and evaporated. Chromatography as above gave **6** (31 mg; 64 %).

c) A solution of H_2TPP **1** (200 mg) and BrCN (1 g) in CH_2Cl_2 (6 mL) + toluene (15 mL) was heated under reflux for 21 h. The resulting dark solution was diluted with chloroform (100 mL) and washed three times with water, dried (Na_2SO_4) and evaporated. Chromatography of the residue on alumina gave recovered H_2TPP (140 mg) followed by **6** (crystallized from CH_2Cl_2-pentane; 33 mg; 16 %). In order to obtain crystals suitable for the X-ray study we followed the same procedure using tetratolylporphyrin and obtained **7** in 20 % yield.

6 : NMR: 8.81 (2H, d, J = 1.4 Hz, pyrrole opposite to N-CN), 8.51 (4H, s, vicinal pyrroles), 8.45 (2H, s, N-substituted pyrrole), 8.6 and 8.15 (4H, 2 broad signals, *ortho*), 8.31 and 8.18 (4H, 2 m, *ortho*), 7.85-7.7 (12H, m, *meta* + *para*), -1.8 (1H, broad signal, NH); visible spectrum: λ_{max} = 430 nm (ε = 200000), 518 (14800), 558 (9400), 632 (2800), 692 (4600).

7 : NMR: 8.82 (2H, d, J = 1.4 Hz, pyrrole opposite to N-CN), 8.51 (4H, s, vicinal pyrroles), 8.46 (2H, s, N-substituted pyrrole), 8.5 and 8.0 (4H, 2 broad signals, *ortho*), 8.19 and 8.07 (4H, 2 dd, *ortho*), 7.7-7.5 (4H, m, *meta*), 2.71 (12H, s, tolyl CH_3), -1.77 (1H, broad signal, NH); NMR in C_6D_6: 8.89 (2H, d, J = 1.4 Hz, pyrrole opposite to N-CN), 8.76 and 8.73 (4H, 2 d AB, J = 5 Hz, vicinal pyrroles), 8.13 (2H, s, N-substituted pyrrole), 8.2-7.9 (4H, broad signal, *ortho*), 8.03 and 7.86 (4H, 2 broad d, *ortho*), 7.15-

7.35 (8H, m, *meta*), 2.38 (slightly broadened s, tolyl CH_3), -0.76 (1H, broad signal, NH); visible spectrum: λ_{max} = 430 nm (ε = 190000), 521 (12200), 558 (10200), 624 (2800), 692 (5100).

Metallation of 6.

Zinc(II) acetate (200 mg) in MeOH (5 mL) was added to a boiling solution of 6 (40 mg) in CH_2Cl_2 (50 mL). Most of the solvent was boiled off and addition of MeOH precipitated violet crystals of ZnTPP 8 (36 mg).

Preparation of bridged porphyrin 9.

A mixture of H_2TPP 1 (200 mg), NaH (50 mg; 50% dispersion in oil) and DMF (45 mL) was stirred vigorously under argon until a homogeneous bright green solution was obtained (*ca* 4 h). Ethyl chloroformate (0.25 mL) was then added and the stirring continued for 20 min, after which the solution was diluted with water, extracted 4 times with CH_2Cl_2 containing 1% Et_3N. The organic phase was washed twice with water, evaporated and pumped overnight. Chromatography of the residue (alumina in CH_2Cl_2) gave H_2TPP 1 (73 mg) followed by 9 (110 mg; *ca* 50 %; base 9 contained always 1 due to its instability). NMR: -2.33 (s) + complex multiplets between 7.5 and 9 (aromatic protons of 9 and 1 from decomposition); visible spectrum (CH_2Cl_2) λ_{max} = 432 nm (rel. int. 100), 540 (7), 578 (9), 636 (5.5), 676 (5). Analysis ($C_{47}H_{35}N_5$) calcd: C, 84.18; H, 5.22; N, 10.45. Found: C, 82.38; H, 5.30; N, 9.81.

Methylation of base 9 and transformation into N-methylTPP 4.

Base 9 (20 mg) in CH_2Cl_2 (2 mL) was treated with MeI (1 mL) for 4 h. After evaporation of the solvent the residue was chromatographed on alumina. Elution with CH_2Cl_2 gave some 1, while CH_2Cl_2-MeOH (94:6) eluted salt 10. The product crystallized as its perchlorate on dilution of its methanolic solution with aqueous $NaClO_4$ (19 mg; 83 %). NMR: 8.95 (d, 1H, pyrrolic H), 8.65 (d, 1H, pyrrolic H), 8.6-7.4 (m, 24, phenyl + pyrrolic H), -2.17 (s, 6H, NMe_2), -3.20 (s, 1H, methine H), -3.42 (s, 3H, NMe). Analysis ($C_{48}H_{38}N_5ClO_4$) calcd: C, 73.52; H, 4.85; N, 8.93. Found: C, 72.25; H, 5.11; N, 8.39.

When salt 10 was treated overnight with *p*-toluenesulfonic acid (same weight) in CH_2Cl_2-MeOH (90:10) N-methylTPP 4 was obtained quantitatively.

X-ray Data Collection and Structure Solution.[20]

Single crystals of N-cyano-*meso*-tetra-*p*-tolylporphyrin $C_{49}H_{37}N_5.C_7H_8$, 7, were grown by slow diffusion of pentane into a solution of 7 in toluene. A dark blue crystal of approximate dimensions 0.12 x 0.14 x 0.14mm was mounted in a glass capillary. It was accurately aligned on an Enraf-Nonius CAD4 diffractometer equipped with CuKα radiation and a graphite monochromator. Crystallographic study was realized at 18±1°C.

A careful survey of a preliminary data set revealed the systematic extinctions. The space group is C2/c. Final cell parameters and orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 22 reflections in the range 22<θ<26°. Crystal data: $C_{56}H_{45}N_5$, fw = 788.02, monoclinic space group C2/c, a = 29.646(3)Å, b = 16,692(3)Å, c = 17.762(3)Å, β = 91.38(4)°, V = 8787(4)Å^3, Z = 8, Dc = 1.19g cm^{-3}, F(000) = 3328, μ(CuKα) = 5.1cm^{-1}.

A total of 7468 unique reflections was collected in the ω/2θ scan mode up to 2θ = 130°. Lorentz and polarization corrections were applied to the data. No decay was observed and no absorption correction was made in view of the small crystal size. 2523 reflections having $F_o^2 > 3\sigma(F_o^2)$ were con-

sidered observed and used in the subsequent determination and refinement of the structure.[20]

All attempts to solve the structure by Multan direct methods failed. DIRDIF[21] was then employed, using a known porphyrin core as model fragment. The contributions of the atoms from the reoriented and translated model were included in a structure factor calculation. The subsequent Fourier synthesis map revealed the position of the remaining non-hydrogen atoms and the presence of a toluene molecule as solvent. The atomic scattering factors were taken from the usual source,[22] and the effects of anomalous dispersion were included.[23] All hydrogen atoms were located from a series of difference-Fourier syntheses and included as fixed contributions. The non-hydrogen atoms were refined anisotropically using the full-matrix least-squares procedure. The minimized function was $\Sigma w(|F_o|-|F_c|)^2$, with the weights calculated as $w = 4F_o^2/\sigma^2(F_o^2)$ and $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$. $\sigma(I)$ is based on counting statistics and p is an instability factor (value = 0.06) obtained from plots of F_o *vs* weighted error. The last cycle of refinement converged to R and Rw values of 0.069 and 0.080, respectively. A final difference-Fourier map showed no significant features with the highest peak at 0.23 e $Å^{-3}$.[24]

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(24) Supplementary Material Available: a) The atomic coordinates for this structure can be obtained on request from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. Any request should be accompanied by the full literature citation for the communication.
b) Positional and thermal parameters, bond lengths, bond angles, least- squares planes and structure factors. See Notice to Authors, *Tetrahedron* **1984**, ***40*** (2), ii.