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Stable pseudotetrahedral supermolecules based on an oxoporphyrinogen

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ABSTRACT

Topologically asymmetric compounds, important as chiral nanoscale building blocks, were synthesized using stepwise N-alkylation on *tetrakis*(3,5-di-*t*-butyl-4-oxocyclohexadien-2,5-yl) porphyrinogen as revealed by X-ray crystallographic studies on a porphyrinogen molecule bearing four different N-substituents.

Asymmetry is one of the most important subjects of modern chemistry.[1] Its symptoms are evident in fields as diverse as catalysis,[2] supramolecular science[3] and terrestrial biogenesis.[4] Often the source of asymmetry lies at a single tetrahedral carbon atom bearing four non-identical groups, or a collection of these atoms, but can also be found in other structures with non-superimposable mirror images, such as helices,[5] propellers and other twisted molecules,[6] and molecules with axial or planar chirality.[7] Few other structures present stereochemical possibilities[8] and, in the event of a single asymmetric centre, multiplicity of structural isomers is limited to two: right- and left-handed enantiomers. An asymmetric centre might also be replaced by a suitable tecton in which molecular vertices coincide (or approximately coincide) with those of a tetrahedron. A few molecular tectons have been used for such purposes including the cubanes[9] and adamantanes[10] and they have the distinct advantage over the simpler substituted methanes of being resistant to enantiomerization and are consequently tolerant of enantioseparation. There is also increasing interest in nanoscale chirality and therefore in appropriately-sized asymmetric nanostructures.[11] From a geometric point-of-view, a tetrahedron persubstituted at its vertices with non-identical groups is representative.

The tetrapyrrole core of 5,10,15,20-*tetrakis*(3,5-di-*t*-butyl-4-oxocyclohexadien-2,5-yl) porphyrinogen **1**, derived from the base-catalyzed oxidation of the porphyrin *tetrakis*(3,5-di-*t*-butyl-4-hydroxyphenyl) porphyrin[12] (Scheme 1) represents a unique opportunity for the preparation of asymmetrically substituted derivatives since we possess the means to control synthetically the identity of substituents at its core amine groups.[13] In this case, and to demonstrate the utility of the oxoporphyrinogen for design and preparation of asymmetric supermolecular units, we chose different substituents at random and introduced them at the nitrogen atoms of **1** in a stepwise fashion. We had previously observed regioselectivity in the N-alkylation reactions of **1** permitting us to attempt the preparation of the compounds.[13,14]

Preparation of the asymmetrically substituted porphyrinogens (see ESI) is by a simple iterative procedure. The stepwise introduction of alkyl groups at N_{21} and N_{23} proceeds to yield individual structural isomers of N_{21},N_{23}-dialkyl-Ox[T(DtBHP)P] (Scheme 1). Substitution reactions of N_{21},N_{23}-dialkyl-Ox[T(DtBHP)P] compounds give very low yields of the corresponding N_{21},N_{22},N_{23}-trialkyl derivative under the conditions usually employed because the relative reactivity of the N_{21},N_{22},N_{23}-tri-alkyl compounds towards further N-alkylation greatly exceeds that of the starting di-*N*-alkyl compound. This is thought to relate to binding of carbonate anions[15] by the pyrrolic group and can be alleviated by use of stoichiometric amounts of a strong base rather than an excess of potassium carbonate. In any case, there is no advantage apparent in performing the final two alkylations in a stepwise manner and we used a 50:50 mixture of two different benzyl bromides in a one-pot final step to the compound bearing four non-identical groups so that a corresponding isomeric mixture would be obtained.

Racemic mixture *rac*-**2** could be crystallized by diffusion of methanol into a dichloromethane solution and its crystal structure is shown in Figure 1.[16] The most notable feature in the structure of this compound is that substitution of the pyrrole nitrogen atoms occurs without altering the conformation of the porphyrinogen macrocycle so that stepwise substitution results only in the specified substitutional isomer. The unit cell contains one each of the respective *R*- and *S*-enantiomers of compound **2**. The *n*-dodecyl chain has an unusual irregular conformation containing both staggered gauche (C_2–C_3, C_7–C_8) and nearly eclipsed (C_6–C_7) conformations with the remainder all being staggered anti. Similar irregularity has been previously observed in the structure of a symmetrically persubstituted Ox[T(DtBHP)P].[17]

Figure 2 depicts the energy-minimized structures of all possible isomers of compound **3**. Figure 3 shows the partial proton NMR spectra of compounds *rac*-**2** and *rac*-**3**, which indicate their

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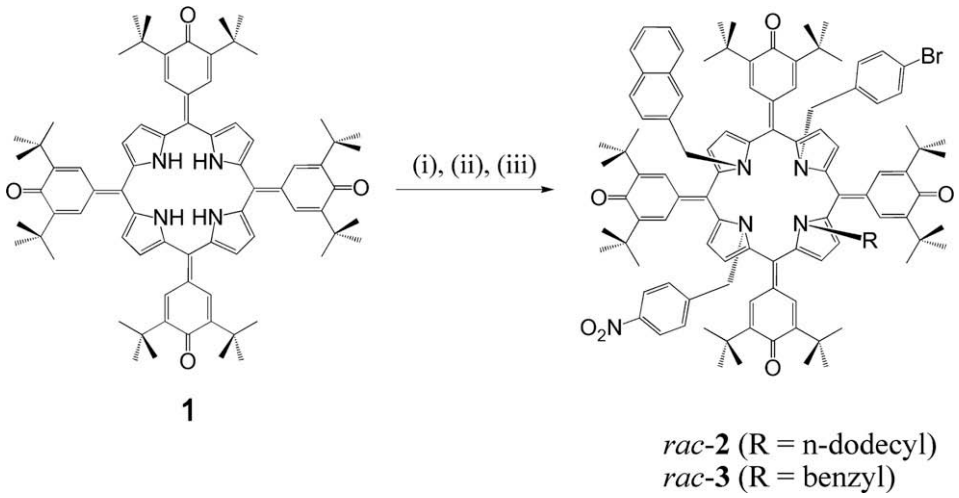

Scheme 1. Preparation of *rac*-**2** and *rac*-**3** from **1**, Ox[T(DtBHP)P]. Reagents: (i) 2-bromomethyl naphthalene/K_2CO_3/EtOH/reflux; (see Ref. 13d); (ii) *n*-dodecyl bromide (or benzyl bromide)/K_2CO_3/EtOH/reflux; (iii) 4-nitrobenzyl bromide:4-bromobenzyl bromide 1:1/K_2CO_3/EtOH/reflux.

substitutional isomeric purities. Weak coupling of the benzylic protons, especially notable in *rac*-**2**, is expected from the *non-symmetry* of the molecule and is not related to enantiomerism but to the differing shielding environments provided by *N*-alkyl and *N*-benzyl pyrrole groups.[18]

What is remarkable about the preparation of these compounds is that they can be isolated at all even as racemic mixtures. In fact, the key to their preparation lies in the regioselective N-alkylation of the N_{21}-monoalkyl-OxTDtBHPP, which occurs exclusively at

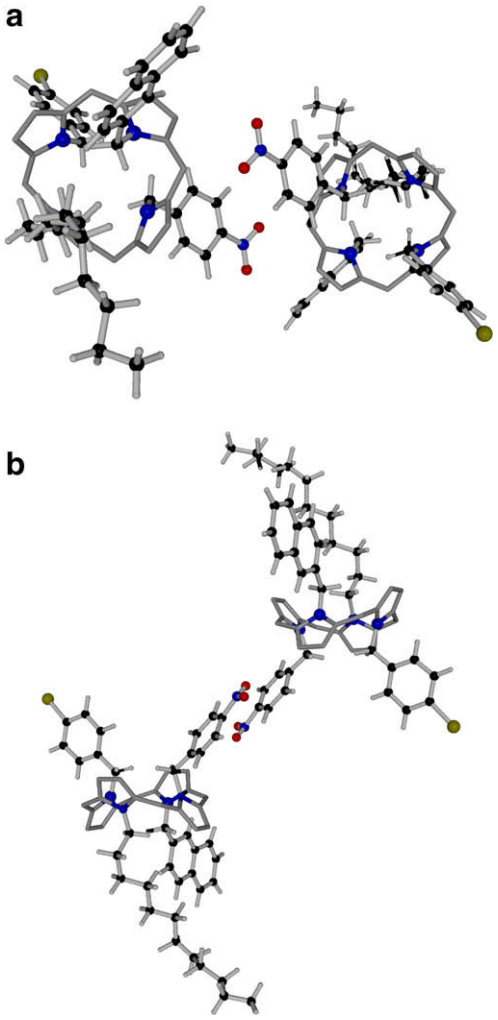

Figure 1. X-ray crystal structure of *rac*-**2**[16] depicting the two enantiomers contained in the unit cell. (a) Viewed down the *a* axis. (b) Viewed at an angle slightly oblique to the *b* axis. Note the non-superimposability of the two molecules in the unit cell. Ox[T(DtBHP)P] unit meso-substituents removed for clarity.

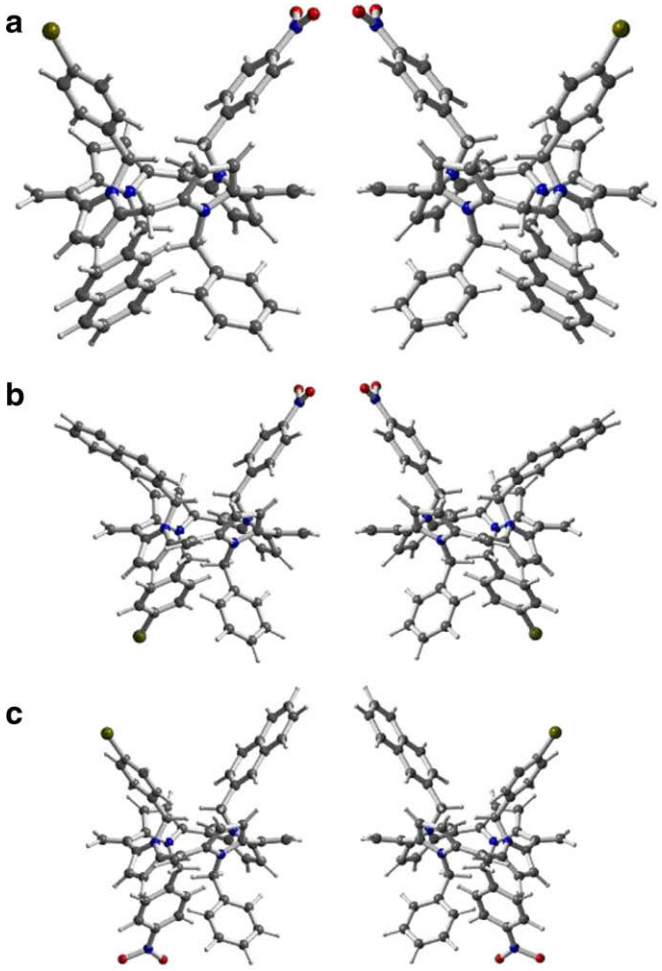

Figure 2. Energy-minimized structures of all possible isomers of compound **3**. (a), (b) and (c) are pairs of enantiomers.

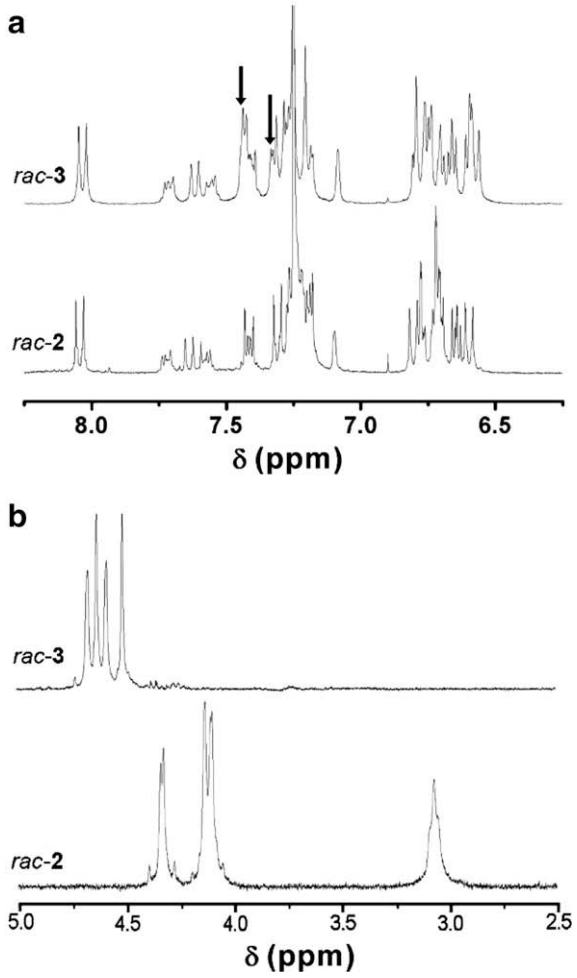

Figure 3. ^{1}H NMR spectra of *rac*-**3** and *rac*-**2** showing (a) aromatic and (b) benzylic regions. (Arrows in (a) indicate the position of resonances due to the benzyl group, which are absent in *rac*-**2**.)

N_{23}. Were this feature not available, then isolation of these compounds with a predetermined disposition of the four substituents would be extremely laborious. Related to this is the further complication of isomerism of the molecules caused by substitution about the tetrapyrrole molecular plane. Thus, when specifying a structural isomer it is useful to define which groups are substituted at which face of the molecule although this is evident from the systematic name since substitution occurs without altering the conformation of the tetrapyrrole. In the cases highlighted here we chose to vary a single substituent although it would be a simple matter to introduce the 4-nitrobenzyl group at the face of the molecule opposing the 4-bromobenzyl group. This substitutional isomerism has the effect of increasing the number of possible isomers, relative to a compound containing one chiral carbon atom, from two (i.e., *R* and *S* forms) to six (i.e., *R* and *S*-enantiomers of all three possible substitutional isomers; see Fig. 2).

Figure 4a shows the MALDI-TOF-MS spectra of *rac*-**2** and *rac*-**3**. Also, in this work we have prepared and isolated racemic mixtures of **2** and **3**. Compounds **2** were prepared containing a long alkyl chain for the purpose of improving solubility for our subsequent attempts at the separation of the two enantiomers. However, separation of the enantiomers was not possible using a chiral stationary phase (Chiralpak 1A or 1B) and under elution with a variety of solvents. Chromatograms contained a single peak except for the case of **2** on Chiralpak 1B eluting with a hexane/chloroform mixture of ratio 97:3. The latter indicates the presence of the two

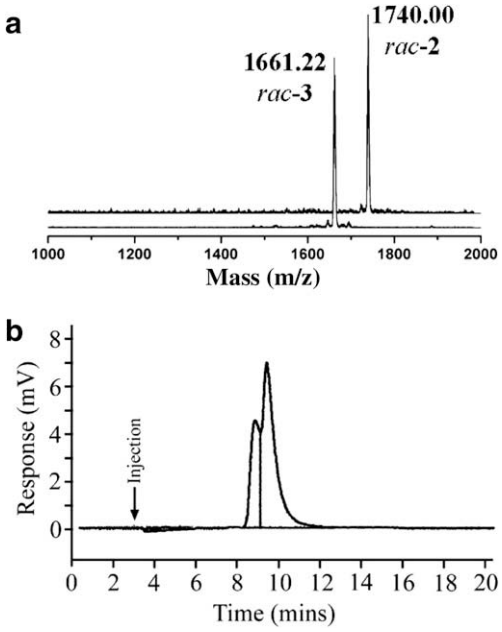

Figure 4. (a) MALDI-TOF mass spectra of *rac*-**2** and *rac*-**3**. (b) HPLC chromatogram for compound *rac*-**2** on Chiralpak 1B eluting with 97:3 hexane/chloroform.

enantiomers but differentiation was not sufficient for the separation (Fig. 4b).

An interesting aside presented by the form of compounds **2** and **3** is found when considering some geometric solids. In particular, amongst the Johnson Solids[18] there exists the gyrobifastigium, designated J_{26}, whose vertices can be considered as consisting of a square plane bisecting a tetrahedron. Analogously, persubstitution of Ox[T(DtBHP)P] gives a molecule where N-substituents occupy similar tetrahedral vertices above and below the plane of the tetrapyrrole macrocycle whose *meso*-substituents occur at the corners of the bisecting square plane. Thus, the structures of **2** and **3** (in fact any tetra-N-alkylated derivative of **1**) can be considered molecular analogues of J_{26}. It is intriguing to speculate on the possibility of attempting 'retrosyntheses' of other more complex solids. In this case, J_{26} is important since it is the only space-filling Johnson Solid.

In summary, we have prepared porphyrinogen derivatives bearing four non-identical groups substituted at their nitrogen atoms in a nearly regioselective manner as chiral nanoscale building blocks. Furthermore, substitutional isomerism provides six possible isomers of a porphyrinogen substituted at its nitrogen atoms with four non-identical groups and possessing an alternating conformation of pyrrole groups. Initially, we were interested in investigating the potential of this system as a scaffold for covalent connection of up to four non-identical functional chromophores within a structurally rigid asymmetric motif and this work proves that it is possible. We are currently undertaking synthesis and separation of chiral multichromophoric molecules based on the unique substitution patterns provided by the *tetrakis*(3,5-di-*t*-butyl-4-oxocyclohexadien-2,5-yl)porphyryinogen system.

Acknowledgements

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14. *General procedure for the N-alkylation reaction of **1** and its derivatives.* Excess potassium carbonate was added to **1** or its N-alkylated derivative (10^{-2} M) and the appropriate alkyl bromide (1–2 equiv) in dry ethanol and the mixture heated at reflux. Reactions were monitored using thin layer chromatography until no starting material remained then the reaction was partitioned between chloroform and water. The organic phase was dried (anhydrous $MgSO_4$) and solvent was evaporated and the residue was subjected to column chromatography over silica gel eluting with dichloromethane or dichloromethane/hexane mixtures. In the step leading to derivatives with four non-identical groups an equimolar mixture of two different benzyl bromides (4-nitrobenzyl bromide/4-bromobenzyl bromide) was used. *N_{21}-(1-n-Dodecyl),N_{23}-(naphth-2-ylmethyl)-5,10,15,20-(3,5-di-tert-butyl-4-oxo cyclohexadien-2,5-yl)porphyrinogen*. Direct precursor to ***rac*-2**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.06, 1.30, 1.34, 1.38 (4 × singlets, 72H, *t*Bu), 3.42 (t, ^2J = 6.89 Hz, 2H, $C_{11}H_{23}CH_2$–N), 4.56 (s, 2H, benzylic CH_2), 6.51, 6.54 (two singlets, 4H, cyclohexadienyl H), 6.84 (d, J = 8.44 Hz, naphthyl Ar-H), 6.93 (m, 6H, cyclohexadienyl H), 7.30 (d, ^3J = 2.20 Hz , 2H, pyrrolic beta-H), 7.38 (m, 2H, naphthyl Ar-H), 7.50–7.69 (m, 8H, naphthyl ABX system, pyrrolic beta-H), 9.44 (s, 2H, NH) ppm. MALDI-TOF-MS (dithranol): calcd for $C_{99}H_{126}N_4O_4$ $[M+2H]^+$ 1435.98; found, 1435.94. *N_{21}-(Benzyl),N_{23}-(naphth-2-ylmethyl)-5,10,15,20-(3,5-di-tert-butyl-4-oxocyclohexadien -2,5-yl)porphyrinogen*. Direct precursor to ***rac*-3**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.08, 1.22, 1.35, 136 (4 × singlets, 72H, *t*Bu), 4.57 (s, 2H, benzylic CH_2), 4.68 (s, 2H, benzylic CH_2), 6.54, 6.56 (2 × singlets, 4H, cyclohexadienyl H), 6.79–6.83 (m, 2H, benzyl Ar-H), 6.85, 6.88 (dd, $^3J_1$ = 8.45 Hz, $^3J_2$ = 1.65 Hz, 1H, naphthyl Ar-H), 6.97 (m, 6H, benzyl Ar-H), 7.04 (d, ^4J = 2.57 Hz, 2H, cyclohexadienyl H), 7.16 (m, 3H), 7.25 (peak obscured by $CHCl_3$, pyrrolic beta H), 7.39 (m, 2H), 7.53–7.72 (m, 8H, naphthyl ABX system, pyrrolic beta-H), 9.81 (s, 2H, pyrrolic NH) ppm. MALDI-TOF-MS (dithranol): calcd for $C_{94}H_{108}N_4O_4$ $[M+2H]^+$ 1357.84; found, 1357.83.
***rac*-2**. UV–vis(CH_2Cl_2): λ = 271, 329, 352(sh), 501(max), 565(sh) nm. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.85 (t, ^2J = 6.79 Hz, 3H, terminal CH_3), 1.12, 1.14, 1.24, 1.28, 1.30, 1.32 (singlets, 90H, *t*Bu and $(CH_2)_9$), 1.43 (m, 2H, CH_2CH_2–N), 3.38 (t, ^2J = 6.15 Hz, 2H, –CH_2–N), 4.43 (s, 2H, 4-bromobenzyl-CH_2), 4.56 (s, 2H, naphth-2-yl-CH_2), 4.62 (m, 2H, 4-nitrobenzyl-CH_2), 6.56–6.81 (m, 14H), 7.09 (s, 1H, naphthyl Ar-H), 7.18–7.33 (m, includes residual $CHCl_3$), 7.44 (m, 5H), 7.55–7.73 (m, 4H, naphthyl Ar-H), 8.03 (d, ^3J = 8.81 Hz, 4-nitrobenzyl *ortho*-H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.04, 20.59, 22.64, 26.48, 29.26, 29.41, 29.52, 29.79, 31.47, 31.86, 35.41, 35.53, 35.62, 45.59, 47.79, 48.01, 49.06, 119.76, 119.82, 119.86, 120.39, 120.48, 120.53, 120.55, 120.63, 120.86, 120.91, 121.02, 122.190, 123.72, 123.74, 124.03, 125.15, 126.61, 126.65, 126.76, 126.81, 126.86, 126.92, 127.54, 127.63, 127.78, 127.84, 127.90, 127.98, 128.82, 129.39, 129.85, 129.91, 130.38, 130.42, 130.54, 130.58, 130.62, 130.79, 130.84, 130.91, 130.99, 131.03, 132.04, 132.82, 133.04, 133.83, 133.86, 134.19, 134.24, 134.28, 134.59, 136.34, 136.37, 137.17, 137.18, 137.62, 137.64, 137.83, 137.85, 137.92, 137.98, 138.01, 138.04, 138.15, 138.39, 138.43, 144.67, 147.68, 148.51, 148.57, 148.59, 148.72, 148.77, 148.82, 148.87, 148.90, 185.77, 185.87, 185.89, 185.99 ppm. MALDI-TOF-MS (dithranol): calcd for $C_{113}H_{137}BrN_5O_6$ $[M+3H]^+$ 1739.98; found, 1740.00. ***rac*-3**. UV–vis(CH_2Cl_2): λ = 272, 328, 355(sh), 499(max), 565(sh) nm. ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 1.05, 1.07, 1.14, 1.16, 1.18 (singlets, 72H, *t*Bu), 4.44, 4.52, 4.55, 4.61 (4 singlets, 8H, benzylic CH_2), 6.57 (d, ^3J = 8.45 Hz, 2H, 4-bromophenyl *ortho*-H), 6.60–6.77 (m, 14H), 7.06 (s, 1H, naphthyl Ar-H), 7.10–7.26 (m, 15H), 7.34 (sex., 2H, naphthyl Ar-H), 7.51–7.64 (m, 4H, naphthyl Ar-H), 7.95 (d, ^3J = 8.81 Hz, 2H, 4-nitrophenyl *ortho*-H) ppm. Not enough material available for ^{13}C NMR spectroscopy. MALDI-TOF-MS (dithranol): calcd for $C_{108}H_{119}BrN_5O_6$ $[M+3H]^+$ 1661.83; found, 1661.22.
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16. *X-ray crystallography*. Samples suitable for single crystal X-ray analysis were grown by vapour diffusion of methanol into a dichloromethane solution of *rac*-**2**. X-ray diffraction data for *rac*-**2** were collected at 150 K using a Bruker APEX 2 diffractometer at SRS Station 9.8 at Daresbury. $C_{114.50}H_{139}BrN_5O_7$, M = 1812.67 g/mol, crystal size 0.22 × 0.06 × 0.03 mm^3, orange plate, space group $\bar{P}$, a = 14.7037(15) Å, b = 15.0252(15) Å, c = 24.932(3) Å, α = 100.7168(12)°, β = 90.0592(12)°, γ = 100.3919(12)°, V = 5319.9(9) Å^3, Z = 2, ρ_{calcd} = 1.132 mg/m^3, μ = 0.466 mm^{-1}, 37950 reflections were measured (2θ <45°) of which 16,440 were unique (R_{int} = 0.0585). Structure solution was by direct methods and refinement with SHELXTL.[19,20] Refinement against F^2 to wR_2: 0.3328 (all data), R_1 (7531 reflections with $F^2 > 2\sigma(F^2)$): 0.1288, 1200 parameters, 679 restraints; all non-H atoms were anisotropically refined. H atoms were constrained in a riding model. A badly disordered DCM and two methanol molecules per unit cell were modelled with the Platon 'squeeze' procedure.[21] Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 747040. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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