Disorder *versus* symmetry in the helical tubuland inclusion host lattice—a successful trishomocubyl diol probe

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New examples of the helical tubuland diol host family may be targeted for synthesis by consideration of structural rules which result in formation of the specific hydrogen bonding arrangement required. To test crystal engineering requirements of symmetry and substitution in these diols, the 4,7,11-trimethylpentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-4,7-diol isomer **8a** has been prepared and its X-ray structure determined: [$C_{14}H_{20}O_2$, $P3_121$, a 12.609(2), c 7.209(2) Å, Z 3, R 0.032]. This diol is a further example of the helical tubuland family despite it lacking C_2 symmetry. Instead, overall C_2 symmetry results in the solid state by means of crystallographic disorder. The C11 methyl group which is equally disposed over its two possible positions reduces the canal unobstructed cross-sectional area to only 8.9 Å^2, but demonstrates that disruption of the lattice type can be avoided provided substituents are placed within the parallel canals. These observations now allow prediction of a much wider range of helical tubuland structures. The diol isomer **8b** [$C_{14}H_{20}O_2$, $P2_1/c$, a 12.795(1), b 6.4608(4), c 15.003(1) Å, β 111.846(4)°, Z 4, R 0.043] forms a layer structure involving $(-OH)_4$ cycles in common with other diols of closely related structure.

The alicyclic diols **1–4** are typical examples of the helical tubuland host family. These compounds all crystallise in space group $P3_121$ (or enantiomorph $P3_221$) with each crystal comprising enantiomerically pure material despite being obtained from a racemic solution. The diols are linked through hydroxy hydrogen bonds and assemble in the solid state to produce parallel chiral canals whose cross-sections and contours vary considerably as illustrated in Fig. 1.[1] In all of these examples the large canal cross-sectional areas ensure that these compounds are excellent inclusion hosts capable of trapping a wide range of guest species.[2,3]

We are interested in the deliberate design and synthesis of new members of this novel family of hosts, in thereby obtaining a range of diols with a gradation of canal dimensions, in the study of their inclusion behaviour and in understanding the factors which govern this unusual type of molecular self-assembly.[4]

Since crystal structures cannot be predicted from first principles,[5] in devising syntheses of new members of the helical tubuland family we require to identify the structural features which are mandatory for success and also those non-essential features which might be modified or even eliminated in the molecular design. In doing so we are not just producing a hydrogen bonded structure, or a network structure, or an inclusion host with parallel canals, but *all* of these things in a *specific* crystal space group. To carry out such crystal engineering successfully[6] we require to control the hydrogen bonding motif and transplant it without change in order to produce a new host diol.[7]

As a guide we have drawn up a series of molecular determinants which define the membership rules for formation of the helical tubuland lattice. Briefly, these are:[8] (*i*) the diol molecules must have average C_2 rotational symmetry in solution; (*ii*) the alicyclic structure must have a small degree of twist; (*iii*) substituent groups around the periphery generally are deleterious; (*iv*) a bridge on the opposite side to the hydroxy groups is optional; (*v*) the two hydroxy groups must be separated by a molecular bridge; and (*vi*) the tertiary alcohol groups must have a methyl substituent. Molecules satisfying these requirements are likely to crystallise with the helical tubuland lattice, whereas other diols will behave differently. Hence the molecular determinants allow us to target candidate compounds with a high probability of success and this synthetic approach has worked remarkably well.[3,7]

Since these molecular determinants offer us the means of synthesising new molecules with helical tubuland structures, it is important to determine precisely what limits are attached to these structural requirements. For example, diols **1–3** can attain the degree of skeletal twisting (*ii*) necessary to encourage the helical hydrogen bonding network through conformational motion but, in marked contrast, the rigid adamantane diol **5** cannot and consequently adopts a quite different layer lattice structure.[9] However, in recent work we have demonstrated that another completely rigid diol **4** does adopt the helical tubuland structure, since the necessary degree of twist was already built into its pentacyclic molecular skeleton.[3] Such fine-tuning of the molecular determinants not only widens the range of structures which may belong to the family but also increases the likelihood of targeting and synthesising them.

Results and discussion

In this paper we report the outcome of work aimed at testing the symmetry (*i*) and substitution (*iii*) requirements of the diol. Examples such as **1,2** have exact C_2 symmetry in the crystalline state, however, for molecules such as **3** this is impossible because of the conformational requirements of the propano bridge. This diol exhibits the expected eight carbon signals in its ^{13}C NMR spectrum thus indicating average C_2 symmetry in solution. In the solid state, however, the central methylene group of the propano bridge is equally disordered between the two equivalent conformations on either side of the two-fold axis running through the remainder of the molecule.[10]

This raises the question whether average C_2 symmetry in solution is really necessary as a molecular determinant. Perhaps molecules such as **6,7**, which do not have C_2 symmetry, might achieve this average symmetry in the solid state as a helical tubuland simply by means of disorder similar to **3**.[11] We chose to test this structural requirement of disorder *versus* symmetry using the pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane[12] (D_3-trishomocubane) model compound **8a**.

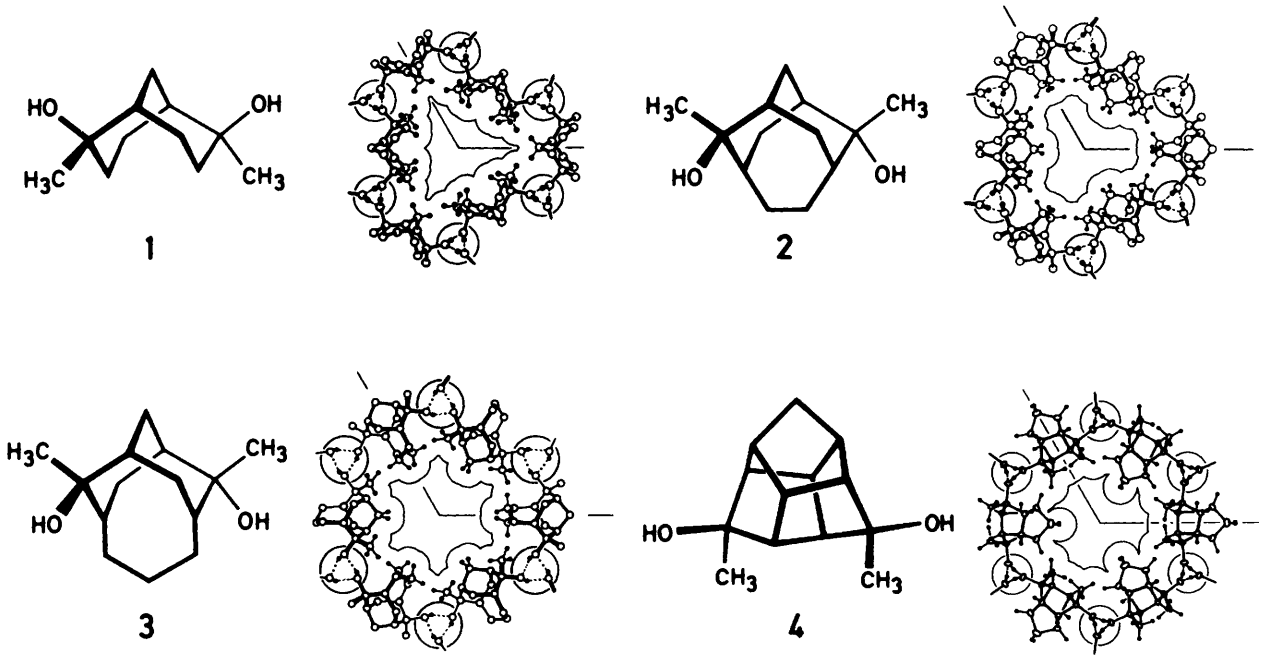
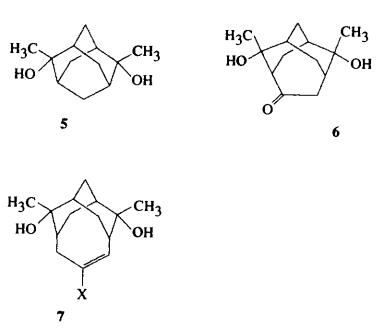


Fig. 1 Projection view in the *ab* plane of one canal only of the helical tubuland lattices of diols **1**–**4**. Key hydrogen atoms defining the van der Waals surface of the host canals are shown as solid black spheres. The hydrogen bonded spines are circled in these diagrams and the hydrogen bonds represented as dashed lines.

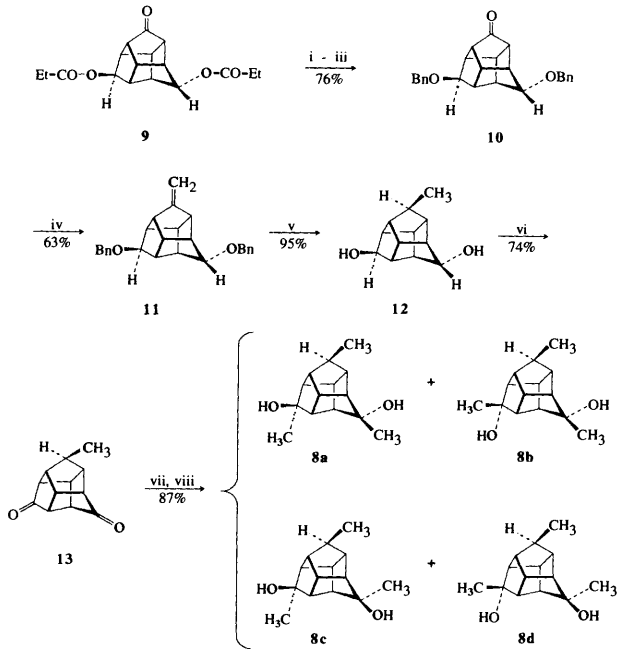


The synthesis of **8a** commenced with the known keto diester **9**[13] and is outlined in the Scheme. First, the ester groups were saponified and the resulting alcohol groups protected as benzyl ether functionalities to give **10**. Next, Wittig reaction produced the methylene derivative **11**. Hydrogenation simultaneously converted the alkene to a methyl group and removed the benzyl groups yielding **12**. Jones oxidation then afforded the key 11-methyltrishomocubanedione intermediate **13**.

Bis(methylation) of **13** using methylmagnesium bromide led, as expected, to a mixture of all four possible trimethyl diol isomers **8a**–**d** (see Scheme). One isomer (mp 211–212 °C) was separated *via* column chromatography on silica gel. Fractional crystallisation of the mixture of three remaining isomers from ethyl acetate yielded a second pure compound (mp 206–207 °C). The structures of these two diol isomers were determined by means of X-ray crystallography as being **8a** (the required *anti,anti*-diol) and **8b** (one of the two possible *syn,anti*-diols) respectively. (The descriptors *anti* and *syn* are used in the same sense as used previously[14] to indicate the relative stereochemistries of structures depicted in the Scheme.)

Numerical details of the solution and refinement of the two crystal structures are shown in Table 1. For both of these the bond lengths and angles obtained for the carbocyclic skeleton are in good agreement with earlier structures carried out on derivatives of pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane.[3,13–16]

Fig. 2 shows the molecular structure of diol **8b** and defines the common crystallographic numbering system adopted for the diol isomers **8a**,**8b**. Bond lengths and angles for these structures



Scheme *Reagents:* i, Na–CH_3OH; ii, oxalic acid; iii, 50% aq. KOH–$PhCH_2Cl$–$(Bu)_4N^+HSO_4^-$, 50 °C; iv, $Ph_3P^+CH_3Br^-$–BuLi–dry THF, −78 °C; v, H_2–10% Pd–C–EtOH; vi, Jones' reagent–acetone; vii, CH_3MgBr–dry diethyl ether; viii, aq. NH_4Cl

are given in Table 2, while Table 3 lists the various dimensions associated with hydrogen bonding for the two crystalline diols.

The hypothetical addition of a methyl group at C11 of the *anti,anti*-diol **4** to form **8a** results in a molecule with no symmetry. However, since this site of substitution is on the former C_2 axis there remains only one such (racemic) *anti,anti*-diol structure. This change in symmetry might force **8a** to adopt a different type of hydrogen bonded lattice. Alternatively, although the model compound **8a** itself lacks C_2 symmetry, it is possible that it could assemble into the helical tubuland lattice with net C_2 symmetry produced through crystallographic disorder.

Table 1 Numerical details of the solution and refinement of compounds **8a** and **8b**

	8a	**8b**
Formula, formula mass	$C_{14}H_{20}O_2$, 220.3	$C_{14}H_{20}O_2$, 220.3
Crystal description	{100}(10–2)(−102)	{100}(001)(−10–4)(−102)(−110)(120)(0–10)
Space group	$P3_121$	$P2_1/c$
a/Å	12.609(2)	12.795(1)
b/Å	12.609(2)	6.4608(4)
c/Å	7.209(2)	15.003(1)
β/°	(90)	111.846(4)
V/Å^3	992.6(3)	1151.1(2)
T/°C	21(1)	21(1)
Z	3	4
D_{calc}/g cm^{-3}	1.11	1.27
Radiation, λ/Å	Cu-Kα, 1.5418	Cu-Kα, 1.5418
μ/cm^{-1}	5.37	6.17
Crystal dimensions/mm	0.35 × 0.35 × 0.15	0.15 × 0.14 × 0.25
Scan mode	$\theta/2\theta$	$\theta/2\theta$
$2\theta_{max.}$/°	140	140
ω scan angle	0.60 + 0.15 tan θ	0.60 + 0.15 tan θ
No. of intensity measurements	3772	2457
Criterion for observed reflection	$I/\sigma(I) > 3$	$I/\sigma(I) > 3$
No. of independent obsd. reflections	1223	1689
No. of reflections (m) and variables (n) in final refinement	1223, 82	1689, 146
$R = \Sigma^m\|\Delta F\|/\Sigma^m\|F_o\|$	0.032	0.043
$R_w = [\Sigma^m{}_w\|\Delta F\|^2/\Sigma^m{}_w\|F_o\|^2]^{\frac{1}{2}}$	0.038	0.069
$s = [\Sigma^m{}_w\|\Delta F\|^2/(m - n)]^{\frac{1}{2}}$	2.06	2.65
Crystal decay	1 to 0.98	None
Max., min. transmission coefficients	0.84, 0.92	0.93, 0.88
Largest peak in final diff. map/e Å^{-3}	0.21	0.23
R for multiple measurements	0.017	0.014
Extinction coefficients	—	3.24 × 10^{-4}

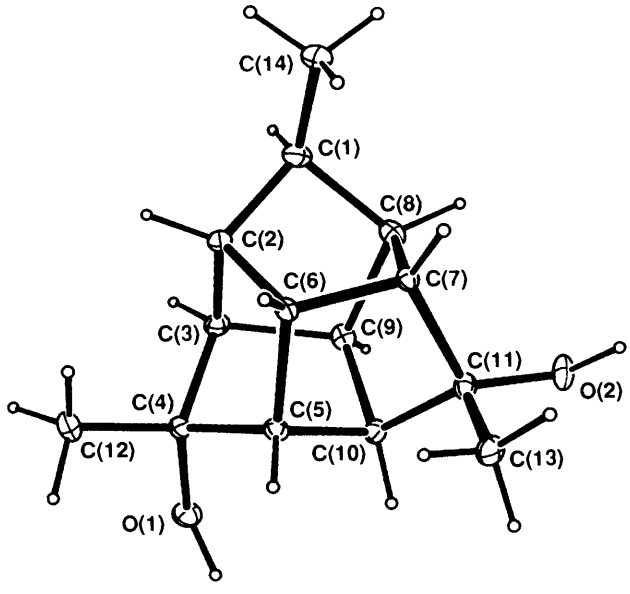


Fig. 2 Molecular structure of **8b** from the X-ray structure determination, showing the common crystallographic numbering system used for the diol isomers **8a,b**

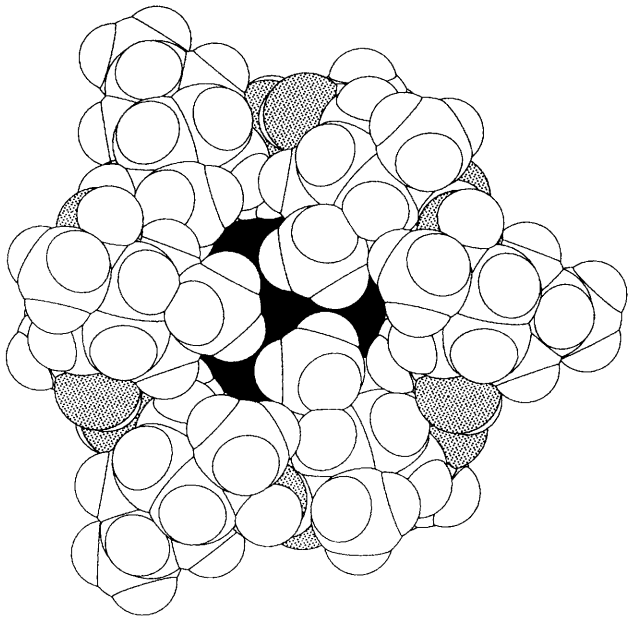


Fig. 3 Projection view in the *ab* plane of the helical tubuland lattice of crystalline **8a** showing one canal only. Oxygen atoms are indicated by stippling and the unobstructed cross-sectional area of the canal by black shading. In this figure the disordered C11 [crystallographic C(14)] methyl groups are arbitrarily orientated upwards within the canal and downwards around its periphery.

This is precisely what was found from the X-ray determination. Molecules of diol **8a** crystallised with the helical tubuland lattice structure in space group $P3_121$ as illustrated in Fig. 3 for one canal of the structure. The C11 [or crystallographic C(14)] methyl groups are disordered, having random orientations up or down the canal z axis thus creating net crystallographic C_2 symmetry. In Fig. 3, for convenience, these methyl groups are all orientated upwards within the canal and downwards at the periphery of the diagram. Compared with the structure of diol **4** there is, as expected, a considerable reduction in the canal unobstructed cross-sectional area from 22.7 to 8.9 Å^2 and this is now insufficient for guest inclusion properties to result.

The *syn,anti*-diol **8b** breaks the symmetry molecular determinant (*i*) and therefore should not have a helical tubuland structure. More specifically, it would be expected to behave in a similar fashion to the trishomocubyl *syn,anti*-diol reported in our earlier work.[3] This nor-C11 methyl compound crystallised

Table 2 Bond lengths (Å) and interbond angles (°) for structures **8a** and **8b**

	8a	**8b**
O(1)–C(4)	1.439(2)	1.439(2)
O(2)–C(11)		1.430(2)
C(1)–C(2)	1.540(2)	1.526(3)
C(1)–C(8)		1.528(3)
C(1)–C(14)	1.545(8)	1.518(3)
C(2)–C(3)	1.516(3)	1.531(3)
C(2)–C(6)	1.573(3)	1.587(3)
C(3)–C(4)	1.512(3)	1.514(3)
C(3)–C(9)	1.585(2)	1.576(3)
C(4)–C(5)	1.519(2)	1.524(2)
C(4)–C(12)	1.511(3)	1.520(3)
C(5)–C(6)	1.564(3)	1.586(2)
C(5)–C(10)	1.530(3)	1.526(3)
C(6)–C(7)		1.571(2)
C(7)–C(8)		1.533(3)
C(7)–C(11)		1.532(3)
C(8)–C(9)		1.573(2)
C(9)–C(10)		1.574(3)
C(10)–C(11)		1.530(2)
C(11)–C(13)		1.521(3)
O(1)–HO(1)	0.90(3)	0.85[a]
O(1)–H'O(1)		0.78[a]
O(2)–HO(2)		0.90[a]
O(2)–H'O(2)		0.83[a]
C(2)–C(1)–C(8)	92.7(2)	94.0(1)
C(2)–C(1)–C(14)	111.1(4)	117.0(2)
C(8)–C(1)–C(14)	119.8(4)	115.7(2)
C(1)–C(2)–C(3)	104.0(2)	103.0(2)
C(1)–C(2)–C(6)	106.3(2)	106.0(2)
C(3)–C(2)–C(6)	98.6(1)	98.3(1)
C(2)–C(3)–C(4)	103.8(1)	104.1(2)
C(2)–C(3)–C(9)	98.9(1)	98.7(1)
C(4)–C(3)–C(9)	105.0(1)	105.3(1)
O(1)–C(4)–C(3)	112.5(1)	109.1(2)
O(1)–C(4)–C(5)	109.5(1)	111.9(1)
O(1)–C(4)–C(12)	108.3(1)	109.3(2)
C(3)–C(4)–C(5)	94.5(1)	94.6(1)
C(3)–C(4)–C(12)	116.0(2)	116.3(2)
C(5)–C(4)–C(12)	115.4(2)	115.0(2)
C(4)–C(5)–C(6)	105.2(1)	105.2(1)
C(4)–C(5)–C(10)	103.2(1)	103.3(1)
C(6)–C(5)–C(10)	98.9(1)	98.8(1)
C(2)–C(6)–C(5)	103.9(1)	103.6(1)
C(2)–C(6)–C(7)	103.1(2)	103.6(1)
C(5)–C(6)–C(7)	103.7(1)	103.7(1)
C(6)–C(7)–C(8)		98.8(1)
C(6)–C(7)–C(11)		105.1(1)
C(8)–C(7)–C(11)		103.6(1)
C(1)–C(8)–C(7)		104.2(2)
C(1)–C(8)–C(9)		105.1(2)
C(7)–C(8)–C(9)		98.6(1)
C(3)–C(9)–C(8)		103.8(1)
C(3)–C(9)–C(10)		103.9(1)
C(8)–C(9)–C(10)		104.3(1)
C(5)–C(10)–C(9)		98.5(1)
C(5)–C(10)–C(11)		103.0(1)
C(9)–C(10)–C(11)		105.5(1)
O(2)–C(11)–C(7)		111.7(2)
O(2)–C(11)–C(10)		109.7(1)
O(2)–C(11)–C(13)		109.4(2)
C(7)–C(11)–C(10)		94.3(1)
C(7)–C(11)–C(13)		114.8(2)
C(10)–C(11)–C(13)		116.2(2)
C(4)–O(1)–HO(1)	106(2)	120[a]
C(4)–O(1)–H'O(1)		124[a]
C(11)–O(2)–HO(2)		113[a]
C(11)–O(2)–H'O(2)		142[a]

[a] Errors not estimated since hydroxy hydrogen positions not refined.

with a layer structure involving hydrogen bonded cycles $(-OH)_4$. We have encountered this type of hydrogen bonding motif frequently during our work on alicyclic diols and have

Table 3 Dimensions (Å and °) associated with hydrogen bonding for structures **8a** and **8b**

8a	
O(1)···O(2)[a]	2.771(3)
O(1)···HO(2)[a]	1.88(2)
C(4)–O(1)···O(2)[a]	126.1(2)
C(4)–O(1)···O(2)[b]	125.0(2)
O(2)[a]···O(1)···O(2)[b]	128.9(1)
O(1)–H···O(2)[b]	176(3)
Symmetry operators	
a $1-y, 1+x-y, \frac{1}{3}+z$	
b $-x+y, 1-x, -\frac{1}{3}+z$	
8b	
O(1)···O(2)[a]	2.724(2)
O(1)···O(2)[b]	2.762(2)
O(1)···H'O(2)[a]	1.91(1)
O(1)···HO(2)[b]	1.87(1)
HO(1)···O(2)[a]	1.91(1)
H'O(1)···O(2)[b]	1.99(1)
C(4)–O(1)···O(2)[a]	128.2(1)
C(4)–O(1)···O(2)[b]	124.9(1)
O(2)[a]···O(1)···O(2)[b]	94.08(6)
O(1)–HO(1)···O(2)[a]	163(2)
O(1)–H'O(1)···O(2)[b]	169(2)
C(11)–O(2)···O(1)[c]	150.2(2)
C(11)–O(2)···O(1)[d]	118.1(1)
O(1)[c]···O(2)···O(1)[d]	85.92(6)
O(1)···H'O(2)[a]–O(2)[a]	169(2)
O(1)···HO(2)[b]–O(2)[b]	172(2)
Symmetry operators	
a $2-x, -\frac{1}{2}+y, \frac{1}{2}-z$	
b $x, \frac{1}{2}-y, -\frac{1}{2}+z$	
c $2-x, \frac{1}{2}+y, \frac{1}{2}-z$	
d $x, \frac{1}{2}-y, \frac{1}{2}+x$	

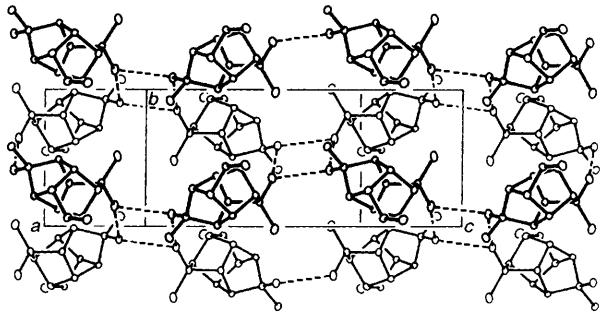


Fig. 4 Crystal structure of **8b** showing how the diol molecules are arranged to produce a layer structure constructed from $(-OH)_4$ hydrogen-bonded cycles. Hydrogen bonds are shown as dashed lines and hydrogen atoms are omitted for clarity.

observed that such layers may be assembled in many different ways resulting in a variety of different space groups.[9] In this case the structure **8b** was isostructural with the earlier compound in space group $P2_1/c$. The hydrogen bonding arrangement results again in a corrugated layer structure (Fig. 4), almost identical to its precursor,[3] but with a slightly larger unit cell dimensions and a slightly reduced value of β.

Conclusions

Our observation that diol **8a** adopts the helical tubuland lattice provides further strong support for the concept of using molecular determinants to predict new members of this fascinating family of materials. The structure of model compound **8a** is significant in two regards. We can now extend

the symmetry molecular determinant (*i*) to diols which are able to achieve net C_2 symmetry in the solid state by means of disorder—even if they lack that exact symmetry themselves. Although substituents on the molecular skeleton normally prevent formation of this lattice type, this molecular determinant (*iii*) clearly does not apply to the 11-methyl substituent of **8a**. This group merely occupies space within the canal and does not interfere with crystal packing arrangements.

These findings therefore indicate that the helical tubuland host family could be much more widespread than suspected previously and therefore molecules like **6,7** and close relatives now must be considered to be strong candidates. Furthermore, the possibility of placing substituent groups directed into the host canals offers the distinct possibility of quite different inclusion behaviour in future cases. Incorporation of polar or semi-polar functionalities has especially intriguing implications and the synthesis of such compounds is currently under active investigation.

Experimental

^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded using a Varian Gemini-200 instrument and are reported as chemical shifts (δ) relative to $SiMe_4$. Coupling constants are measured in Hz. IR spectra were obtained by using a Nicolet 20 SXB FTIR spectrometer. Melting points are uncorrected.

7-*exo*,11-*exo*-Bis(benzyloxy)pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-4-one 10

To a solution of **9**[13] (4.80 g, 14.8 mmol) in methanol (50 cm^3) was added Na (30 mg, 1.3 mmol) and the resulting mixture was stirred for 1 h. The solution was rendered neutral *via* addition of oxalic acid (0.5 g, excess) and the resulting mixture was filtered through a pad of $NaHCO_3$. The filtrate was concentrated under reduced pressure to afford a gummy residue. To this was added 50% aq. KOH (5 cm^3, excess), tetrabutylammonium bisulfate (250 mg, catalytic amount) and benzyl chloride (4 cm^3, excess) and the resulting mixture stirred overnight at *ca.* 50 °C. The reaction was quenched by addition of water (50 cm^3) and the resulting aqueous suspension extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed with water (50 cm^3), brine (30 cm^3) and dried (Na_2SO_4). Evaporation of solvent from the filtrate gave a viscous oil which was purified *via* column chromatography on silica gel by eluting with ethyl acetate–hexane (1:10). The product **10** was obtained as a colourless microcrystalline solid (4.2 g, 76%), mp 108–110 °C. Repeated crystallisation from EtOAc–hexane afforded pure **10** with mp 111–112 °C (Found: C, 80.5, H, 6.6. $C_{25}H_{24}O_3$ requires C, 80.6; H, 6.5%); ν_{max}(KBr)/cm^{-1} 3761m, 3391w, 3281w, 2993s, 2966s, 2863s, 2822m, 2774w, 1754s, 1486m, 1452m, 1349s, 1178s, 1103s, 1069s, 1020s, 918m, 732s and 692s; δ_H($CDCl_3$) 2.29 (4 H, m), 2.63 (4 H, s), 4.08 (2 H, s), 4.42 (2 H, H_{AB} *J* 12.0), 4.50 (2 H, H_{AB} *J* 12.0 and 7.31 (10 H m); δ_C($CDCl_3$) 38.7 (d), 42.3 (d), 46.2 (d), 46.8 (d), 71.2 (t), 84.4 (d), 127.5 (d), 127.7 (d), 128.4 (d), 138.0 (s) and 215.7 (s).

4-*exo*,7-*exo*-Bis(benzyloxy)-11-methylenepentacyclo-[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane 11

A suspension of methyltriphenylphosphonium bromide (4.3 g, 12 mmol) in dry THF (150 cm^3) was cooled to −78 °C *via* application of an external dry ice–acetone bath. To the resulting suspension was added butyllithium (4.8 cm^3 of 2.5 mol dm^{-3} solution in hexane, 12 mmol) and the resulting mixture was stirred at this temperature under argon for 1 h. A solution of **10** (3.0 g, 8.0 mmol) in dry THF (100 cm^3) was added to the reaction mixture. The external cold bath was then removed, and the stirred reaction mixture was allowed to warm gradually to room temperature overnight. The reaction mixture was refluxed for 1 h and then allowed to cool to room temperature. Water (100 cm^3) was added, and the resulting mixture was extracted with hexane (3 × 100 cm^3). The organic layer was washed sequentially with water (50 cm^3) and saturated aq. NH_4Cl (50 cm^3), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure thereby affording an oily yellow residue. This was purified *via* column chromatography on silica gel (200 mesh) by eluting with EtOAc–hexane (1:10). A colourless oil was thereby obtained which solidified upon trituration with EtOH at 0 °C. The resulting crude **11** (1.8 g, 5 mmol, 63%) displayed mp 70–72 °C. Recrystallisation from EtOAc–hexane afforded pure **11**, mp 70–71 °C (Found: C, 84.1; H, 7.2. $C_{26}H_{26}O_2$ requires C, 84.3; H, 7.1%); ν_{max}(KBr)/cm^{-1} 3056m, 3021m, 2987s, 2973s, 2882s, 2831m, 2352w, 2331w, 1683m, 1492m, 1442m, 1394w, 1350s, 1309m, 1281m, 1210m, 1182m, 1093s, 1080s, 985m, 884s, 884m, 752s and 698s; δ_H($CDCl_3$) 2.22 (2 H, s), 2.33 (4 H, s), 2.82 (2 H, m), 3.94 (2 H, s), 4.46 (2 H, H_{AB} *J* 11.8), 4.55 (2 H, H_{AB} *J* 11.8), 4.75 (2 H, s) and 7.31 (10 H, m); δ_C($CDCl_3$) 40.8 (d), 45.6 (d), 47.9 (d), 48.0 (d), 71.1 (t), 84.0 (d), 98.8 (t), 127.5 (d), 127.5 (d), 128.3 (d), 138.7 (s) and 156.2 (s).

4-*exo*,7-*exo*-Dihydroxy-11-methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane 12

To a solution of **11** (1.65 g, 4.2 mmol) in EtOH (100 cm^3) was added 10% Pd/C (300 mg). The resulting mixture was shaken under a H_2 atmosphere (40 psig) at ambient temperature overnight on a Parr hydrogenation apparatus. The reaction mixture was filtered through Celite to remove spent catalyst and the filtrate was concentrated under reduced pressure. Crude **12** (0.77 g, 4.0 mmol, 95%) was thereby obtained as a colourless microcrystalline solid. Fractional recrystallisation from EtOAc afforded pure **12**, mp 207–208 °C (Found: C, 74.7; H, 8.25. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%); ν_{max}(KBr)/cm^{-1} 3239s, 2959s, 2890s, 2342w, 1452m, 1335s, 1280m, 1185m, 1055s and 801m; δ_H[$(CD_3)_2SO$] 0.87 (3 H, d, *J* 6.7), 1.79–2.39 (9 H, m), 3.82 (1 H, br s), 3.88 (1 H, br s) and 4.46 (2 H, m); δ_C[$(CD_3)_2$-SO] 15.1 (q), 38.5 (d), 38.7 (d), 40.9 (d), 47.8 (d), 48.0 (d), 48.1 (d), 48.9 (d), 49.8 (d), 51.4 (d), 74.8 (d) and 75.3 (d).

11-Methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-dione 13

A solution of **12** (600 mg, 3.1 mmol) in acetone was titrated (until the brown colour persisted) by dropwise addition of freshly prepared Jones' reagent[17] while stirring at room temperature. The resulting mixture was filtered through a pad of $NaHCO_3$ and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O and the resulting ethereal solution washed with water (2 × 50 cm^3), dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure gave an oily residue, which subsequently was purified *via* column chromatography on silica gel by eluting with EtOAc–hexane (1:5). The colourless oil (570 mg) thereby obtained solidified on trituration with Et_2O at *ca.* 0 °C. Recrystallisation from EtOAc–hexane afforded pure **13** (423 mg, 2.3 mmol, 74%), mp 52–53 °C (Found: C, 76.8; H, 6.6. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%); ν_{max}(KBr)/cm^{-1} 3281m, 2960s, 2918m, 2870m, 1750s, 1444w, 1151m, 1068m; δ_H($CDCl_3$) 0.83 (3 H, d, *J* 6.7), 1.95–2.26 (5 H, m), 2.31–2.50 (2 H, m) and 2.58–2.78 (2 H, m); δ_C($CDCl_3$) 13.7 (q), 36.1 (d), 37.6 (d), 41.80 (d), 41.83 (d), 44.0 (d), 45.5 (d), 45.5 (d), 46.9 (d), 47.4 (d), 48.2 (d), 211.0 (s) and 211.4 (s).

4,7,11-Trimethylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-diols 8a–8d

A stirred solution of **13** (433 mg, 2.3 mmol) in anhydrous Et_2O and under argon was cooled to *ca.* −5 °C. A solution of methylmagnesium bromide in Et_2O (25 cm^3 of 3.0 mol dm^{-3} solution in Et_2O, 75 mmol) was added dropwise. The resulting solution was stirred at −5 °C for 3 h, allowed to warm to room

temperature and then stirred overnight. After cooling, the reaction was quenched *via* careful addition of saturated aq. NH_4Cl (50 cm^3). The diethyl ether layer was separated, the aqueous layer extracted with Et_2O (3 × 100 cm^3), and the combined organic extracts dried ($MgSO_4$). Evaporation of solvent from the filtrate gave a mixture of the isomeric diols **8a–d** (445 mg, 87%), mp 155–163 °C. This mixture was purified *via* column chromatography on silica gel (250–400 mesh) by eluting with EtOAc.

The first material eluted was diol **8a** (102 mg, 20%), mp 211–212 °C (Found: C, 76.2; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%); ν_{max}(KBr)/cm^{-1} 3314s, 3256s, 2969s, 2928s, 2921s, 1738w, 1453m, 1366m, 1278m and 1109s; δ_H($CDCl_3$) 0.90 (3 H, d, *J* 7.0), 1.30 (3 H, s), 1.35 (3 H, s), 1.55 (2 H, s), 1.79–1.98 (4 H, m), 2.08–2.19 (1 H, m) and 2.28–2.56 (4 H, m); δ_C($CDCl_3$) 14.8 (q), 23.1 (q), 23.5 (q), 39.9 (d), 42.0 (d), 44.4 (d), 50.2 (d), 50.9 (d), 53.1 (d), 53.6 (d), 53.9 (d), 56.2 (d), 82.0 (s) and 82.4 (s). The structure **8a** was established by X-ray crystallography.

The second fraction eluted comprised a mixture of the other three diol isomers **8b–d**. Fractional crystallisation of this mixture from EtOAc yielded diol **8b** (*ca.* 20 mg), mp 206–207 °C (Found: C, 76.2; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%); ν_{max}(KBr)/cm^{-1} 3320s, 2957s, 2892m, 1440w, 1376m, 1298m and 1161w; δ_H($CDCl_3$) 0.82 (3 H, d, *J* 6.6), 1.30 (3 H, s), 1.33 (3 H, s), 1.37–1.48 (2 H, m), 1.76–1.98 (3 H, m), 1.98–2.28 (4 H, m) and 2.41–2.62 (2 H, m); δ_C($CDCl_3$) 14.6 (q), 23.1 (q), 23.5 (q), 40.3 (d), 41.0 (d), 45.4 (d), 49.9 (d), 50.0 (d), 53.2 (d), 53.4 (d), 54.7 (d), 56.7 (d), 82.0 (s) and 82.3 (s). The structure of **8b** was established by X-ray crystallography.

Crystallography.

Crystals of diol **8a** were grown from acetone solution and diol **8b** from ethyl acetate. Data for both structures were recorded using an Enraf-Nonius CAD4 X-ray diffractometer. Data collection and processing procedures have been described.[18] Corrections were made for absorption.[19]

For **8a** there was an unusually low number of unobserved reflections in the data set (33 out of a total of 1232) arousing immediate suspicions that the crystal was twinned. The least squares program RAELS,[20] which has the ability to include twinning was used to calculated structure factors based on the coordinates of the nor-C11 methyl analogue **4**.[3] The methyl carbon atom was readily located in a difference map. The two twin components which were initially set equal were refined, but their sum was maintained at 1. The hydroxy hydrogen atom was included in its map position and was refined. All other hydrogen atoms were included in calculated positions. The hydrogen atoms were assigned isotropic temperature factors equivalent to those of the atoms to which they were bound. The non-hydrogen atoms were refined anisotropically. Refinement converged with $R = 0.032$; the two twin components refining to 0.674(2) and 0.327. The largest peak in the final difference Fourier map was 0.21 e $Å^{-3}$. Crystals of **8a** grown from ethyl acetate had the same cell dimensions as the above structure, thereby indicating the absence of guest molecules in both crystals.

The structure of **8b** was solved by direct methods (MULTAN).[21] The hydroxy hydrogen atoms which were located on a difference map after initial refinement, were disordered, with each disorder component being included in the refinement with an occupancy of 0.5. All other hydrogen atoms were included in calculated positions, with the torsion angle of the methyl hydrogen atoms being initially determined from a difference map. The hydrogen atoms were assigned isotropic temperature factors equivalent to those of the atoms to which they were bound. The non-hydrogen atoms were refined anisotropically. Refinement was carried out using BLOCKLS, a local version of ORFLS.[22] Refinement converged with $R = 0.043$ after the inclusion of an extinction correction. The largest peak in the final difference Fourier map was 0.23 e $Å^{-3}$.

Supplementary structural data consisting of positional parameters, thermal parameters, and structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Instructions for Authors (1995),' *J. Chem. Soc., Perkin Trans. 2*, 1995, issue 1.

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