Crystal Engineering of Hydroxy Group Hydrogen Bonding: Design and Synthesis of New Diol Lattice Inclusion Hosts

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The diols **7**−**11** have been synthesized, and their X-ray crystal structures determined, to learn how to influence and control lattice hydroxy group hydrogen bonding using crystal engineering ideas. To obtain new lattice inclusion hosts precise structural rules can be defined which enable the necessary supramolecular interactions to be duplicated. In this manner the helical tubuland **10** and ellipsoidal clathrate **11** hosts were obtained for the first time and their chloroform inclusion compounds characterized. New synthetic routes were utilized to obtain the bicyclo[3.3.2]decane and 9-thiatricyclo[4.3.1.1^{3,8}]undecane frameworks present in these compounds. The solid-state conformations of bicyclo[3.3.2]decane derivatives **9** and **10** are compared with prior predictions and studies made on this uncommon ring system.

Introduction

Crystal engineering seeks to uncover the roles played by noncovalent interactions in self-assembly and packing and then to apply this information in obtaining solids with designed properties and characteristics.[1,2] For some time we have been developing the helical tubuland family of alicyclic diols (currently comprising 12 examples and typified by **1**−**4**), all of which crystallize in the same crystal space group $P3_121$ (or its enantiomorph $P3_221$).[3] Each crystal consists of chirally pure material despite commencing with a racemic mixture. Hydroxy group hydrogen bonding results in formation of a network of helical arrays of diol molecules which enclose parallel tubes whose contours and dimensions vary considerably from case to case (Figure 1). These large tubes[4] make these diols potent inclusion hosts capable of trapping a wide range of guest species which only interact with the host molecules through van der Waals forces.

We are interested in the design and synthesis of new members of the helical tubuland family, the investigation of their inclusion properties, and understanding the supramolecular chemistry underpinning their unusual behavior.[5,6] Since the hydroxy group is a particularly versatile hydrogen-bonding group,[7] it is unsurprising that many other alicyclic diols closely related in structure,

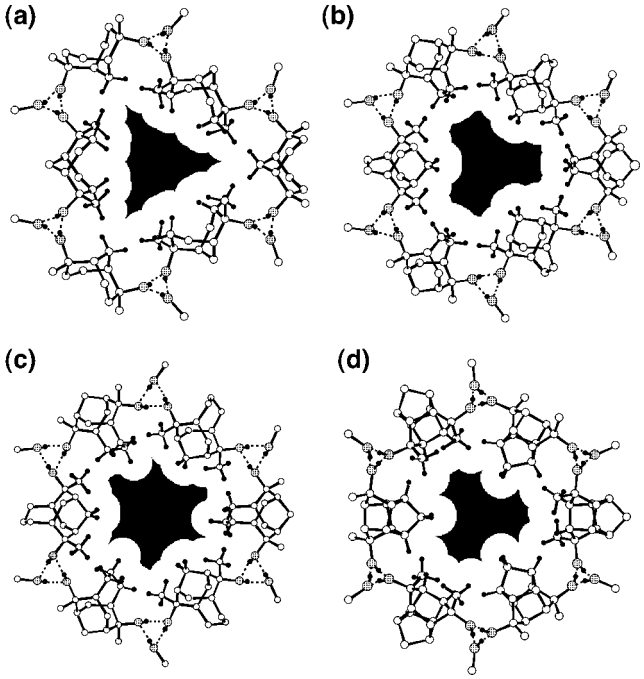

Figure 1. Diagrams a−d represent partial lattice structures of the typical helical tubuland diols **1**−**4**, respectively. For each, a slice is shown through one empty tube projected in the *ab* plane. Oxygen atoms are stippled, and the van der Waals radii of selected hydrogen atoms (shown in black) define the empty tube cross-sectional areas (also colored black).

(1) (a) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: Amsterdam, 1989. (b) *The Crystal as a Supramolecular Entity*; Desiraju, G. R., Ed.; Wiley: New York, 1996. (c) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon, Oxford, U.K., 1996; Vols. 1−11. (d) Nangia, A.; Desiraju, G. R. *Top. Curr. Chem.* **1998**, *198*, 58.

(2) (a) Aakeröy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, *22*, 397. (b) Mascal, M. *Contemp. Org. Synth.* **1994**, *1*, 31. (c) Aakeröy, C. B. *Acta Crystallogr., Sect. B* **1997**, *53*, 569. (d) Fuhrhop, J.-H.; Rosengarten, B. *Synlett* **1997**, 1015. (e) Zaworotko, M. J. *Chem. Commun.* **2001**, 1.

(3) (a) Bishop, R.; Dance, I. G. *Top. Curr. Chem.* **1988**, *149*, 137. (b) Bishop, R. In *Comprehensive Supramolecular Chemistry, Vol. 6: Solid-state Supramolecular Chemistry: Crystal Engineering*; MacNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: Oxford, U.K., 1996; Chapter 4, pp 85−115.

(4) For other tubular assemblies formed using weak forces between small molecules, see, for example: (a) Allcock, H. R. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 1, Chapter 8, pp 351−374. (b) Hollingsworth, M. D.; Harris, K. D. M. In *Comprehensive Supramolecular Chemistry, Vol. 6: Solid-state Supramolecular Chemistry: Crystal Engineering*; MacNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: Oxford, U.K., 1996; Chapter 7, pp 177−237. (c) Pérez, C.; Espinola, C. G.; Foces-Foces, C.; Nuñez-Coello, P.; Carrasco, H.; Martin, J. D. *Org. Lett.* **2000**, 1185.

(5) (a) Dance, I. G.; Bishop, R.; Hawkins, S. C.; Lipari, T.; Scudder, M. L.; Craig, D. C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1299. (b) Dance, I. G.; Bishop, R.; Scudder, M. L. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1309. (c) Bishop, R.; Craig, D. C.; Dance, I. G.; Scudder, M. L.; Marchand, A. P.; Wang, Y. *J. Chem. Soc., Perkin Trans. 2* **1993**, 937.

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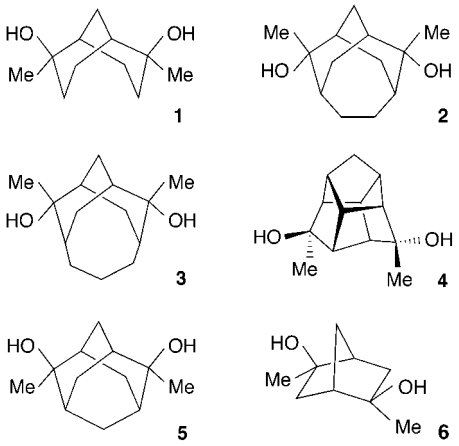


such as **5**[8] and **6**,[9] behave quite differently. For a given diol to form the helical tubuland lattice precise supramolecular requirements must be met. To allow prediction we have identified those structural features which are essential to diols forming this lattice and also those optional features which might be modified or omitted in designing new examples:[10]

(i) The diol molecules must have C_2 rotational symmetry or be capable of achieving this in the solid state through crystallographic disorder.

(ii) The alicyclic structure should have a small degree of twist.

(iii) Substituent groups around the periphery are usually deleterious, but small substituents protruding into the canal may be permitted.

(iv) A bridge on the opposite side of the hydroxy groups is optional.

(v) The two hydroxy groups must be syn and be separated by a molecular bridge.

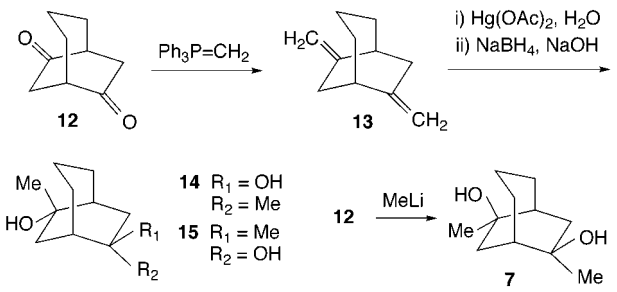
(vi) The tertiary alcohol groups must have methyl substituents.

Molecules satisfying all six of these structural requirements have a high probability of crystallizing with the helical tubuland lattice, subject to its formation being sterically reasonable. If just one rule is broken, then different lattice packing will occur.

Results

In this paper we present some of the experimental evidence which was used to determine and validate the above rules. Each of the diols **7**−**11**, whose syntheses and crystal structures are described here, were chosen carefully to probe specific structural aspects. It should be emphasized that the targeted inclusion properties depend on the entire lattice arrangement of diol molecules, not simply on a molecule interacting with a single guest receptor (as for familiar host types such as crown ethers, calixarenes, or cyclodextrins).[11] Hence, while this work involves conventional organic synthesis, it extends beyond this to duplicate the precise intermolecular contacts necessary for formation of a specific crystal space group.

Scheme 1



Synthesis and Structure of Diol 7. The alicyclic skeleton of all helical tubulands exhibits a small degree of twisting about the C_2 axis in the solid state. This is believed to encourage development of hydrogen bonding in a helical manner. Twist can be attained by conformational means (e.g. **1**−**3**) or built into the ring skeleton itself (e.g. **4**). In marked contrast, the rigid adamantane diol **5** forms a layer structure without inclusion properties.[8] The rigid norbornane diol **6** does form a few unstable inclusion compounds whose structures remain unknown due to crystal twinning difficulties, but we do not believe that these are helical tubulates on the basis of their appearance and behavior.[9] Target **7** was selected since its degree of ring twisting lies between **1** and **6**, and thus, its crystal structure should help define the limits of rule ii.

The synthesis of diol **7** (Scheme 1) commenced with the diketone **12**.[12] Mercuric acetate hydration[13] of diene **13** yielded the unsymmetrical diol **14** and the C_2-symmetric isomer **15**, whose crystals suffered from twinning disorder and were unsuitable for X-ray structure determination. The required C_2-symmetric diol **7** was obtained instead by reacting **12** with methyllithium. Wood and Woo have proposed a solution equilibrium between two conformers of **12**, both of which contain a twist-boat cyclohexane-1,4-dione ring.[12] Their favored major conformation had a particularly exposed face opposite to the propano bridge. Our results are in accord since steric blocking by the propano bridge favored reagent attack from the opposite side in both the above reactions.

Diol **7** failed to include any of the standard test solvents (see Experimental Section) and also butanone and ethyl propionate. From the latter solvent it gave needlelike crystals in the tetragonal space group $I4_1cd$.[14] Each hydroxy group forms hydrogen bonds with two neighbors forming continuous O−H···O−H···O−H spiral chains surrounding 4_1 (or 4_3) axes along c [Etter graph set[15] C(2)]. Eight molecules comprise one helical turn (Figure

(6) (a) Ung, A. T.; Bishop, R.; Craig, D. C.; Dance, I. G.; Rae, A. D.; Scudder, M. L. *J. Inclusion Phenom.* **1993**, *15*, 385. (b) Ung, A. T.; Gizachew, D.; Bishop, R.; Scudder, M. L.; Dance, I. G.; Craig, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 8745. (c) Yue, W.; Bishop, R.; Scudder, M. L.; Craig, D. C. *Chem. Lett.* **1998**, 803. (d) Yue, W.; Bishop, R.; Craig, D. C.; Scudder, M. L. *Tetrahedron* **2000**, *56*, 6667.

(7) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Systems*; Springer-Verlag: Berlin, 1994.

(8) Hawkins, S. C.; Scudder, M. L.; Craig, D. C.; Rae, A. D.; Abdul Raof, R. B.; Bishop, R.; Dance, I. G. *J. Chem. Soc., Perkin Trans. 2* **1990**, 855.

(9) Bishop, R. Unpublished results.

(10) (a) Bishop, R.; Dance, I. G.; Hawkins, S. C.; Scudder, M. L. *J. Inclusion Phenom.* **1987**, *5*, 229. (b) Bishop, R.; Craig, D. C.; Scudder, M. L.; Marchand, A. P.; Liu, Z. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1295.

(11) *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vols. 1−3. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: Oxford, U.K., 1991; Vols. 4 and 5.

(12) Wood, G.; Woo, E. P. *Can. J. Chem.* **1968**, *46*, 3713.

(13) Brown, H. C.; Geohegan, P. J. *J. Org. Chem.* **1970**, *35*, 1844.

(14) Crystal structure of **7**: $C_{11}H_{20}O_2$ (M_r = 184.3); $I4_1cd$; a, b 15.054(3), c 18.240(4) Å; V 4134(1) Å^3; Z 16; R 0.039; R_w 0.038 for 413 observed reflections.

(15) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (b) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601.

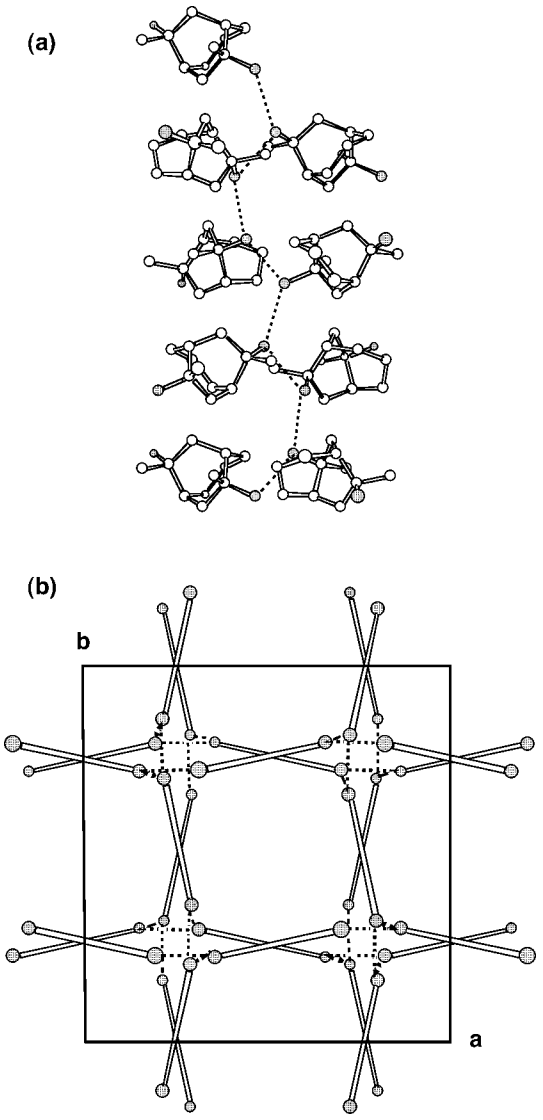


Figure 2. 8-fold repeat helical hydroxy group hydrogen-bonding arrangement present in solid diol **7**, showing hydrogen bonds as dashed lines: (a) drawn with the *c* axis vertical, with hydrogen atoms omitted for clarity; (b) unit cell viewed down *c* showing the recurved nature of the hydrogen bonding motif. Here the diol molecules are abbreviated to hollow spacer rods attached to two oxygen atoms (stippled).

2a). The second diol hydroxy groups contribute to further helices giving a three-dimensional network lattice where each hydrogen bonded helix is surrounded by four equivalent helices of the opposite handedness. Diols which are involved in four neighboring helices abut and interact through hydrocarbon dispersion forces. Unlike the helical tubulands, however, there is insufficient interhelical space for guest inclusion.

The view down *c* (Figure 2b) shows the hydrogen-bonded helices to have a complex recurved projection. We have previously reported recurved helices in the structures of diols **16** and **17**.[16] The former has a 4-fold diol repeat, while **17** has an 8-fold repeat unit. In both instances pairs of diols of one handedness (A) alternate

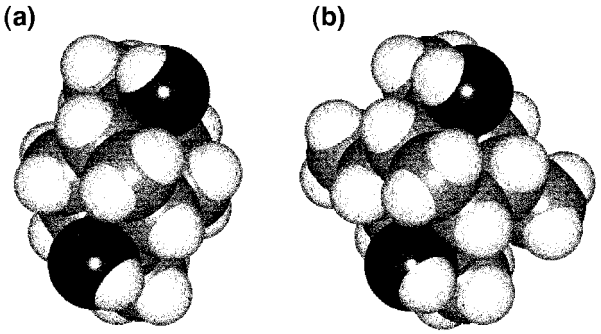
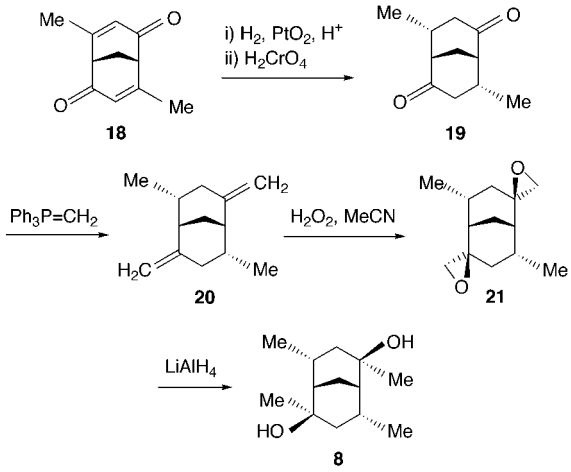
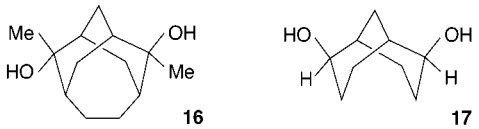


Figure 3. Space-filling representations of (a) diol **1** and (b) diol **8**. Note the similar environments around their hydroxy groups but the large difference in their central regions.

Scheme 2



with pairs of opposite handedness (B) in the sequence −A−A−B−B−A−A−B−B−. In crystalline **7** the enantiomers simply alternate −A−B−A−B− along the helix.



Synthesis and Structure of Diol 8. Space-filling models of diol **1** indicated that additional methyl substitution at most ring positions would result in unacceptable steric bulk around the hydroxy groups. The one exception, preserving C_2 symmetry, was the *endo*-4,*endo*-8-dimethyl derivative **8** (Figure 3), which therefore was synthesized (Scheme 2) to test the substitution rule iii.

Reduction of dione **18**[17,18] (hydrogenation followed by Jones' oxidation)[19] gave *endo*-4,*endo*-8-dimethylbicyclo-[3.3.1]nonane-2,6-dione (**19**).[20] Since the exo faces of the bicyclo[3.3.1]nonane ring system are more exposed than its endo faces, hydrogenation of **18** occurs stereoselectively. Wittig reaction gave diene **20**, which was then epoxidized. Although Payne oxidation[21] of the diene was

(16) Hawkins, S. C.; Bishop, R.; Craig, D. C.; Dance, I. G.; Rae, A. D.; Scudder, M. L. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1737.
(17) Knoevenagel, E.; Bialon, K.; Ruschhaupt, W.; Schneider, G.; Croner, Fr.; Sänger, W. *Chem. Ber.* **1903**, *36*, 2136.
(18) Knott, P. A.; Mellor, J. M. *J. Chem. Soc. C* **1971**, 670.
(19) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.
(20) Hydrogenation of **18** to **19** has been carried out previously: Doerner, T.; Gleiter, R.; Robbins, T. A.; Chayangkoon, P.; Lightner, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 3235. The product was tentatively assigned the opposite stereochemistry on ^{1}H NMR grounds but the present endo, endo interpretation is now agreed.
(21) (a) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Payne, G. B. *Tetrahedron* **1962**, *18*, 763.

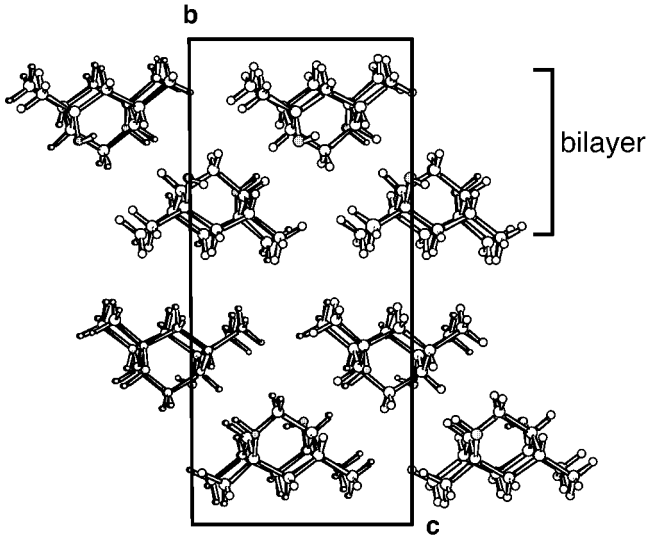


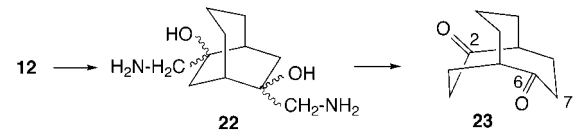
Figure 4. Edge-on view of two hydrogen-bonded bilayers formed by diol **8** showing for each the interior where the hydrogen bonds are located and the outer hydrocarbon surfaces. Oxygen atoms are stippled.

a slow reaction, we found this to be cleaner and higher yielding than use of *m*-CPBA. Reaction again took place mainly on the more exposed exo faces to yield the bis(epoxide) **21**. Reductive ring opening then afforded the target compound **8**.

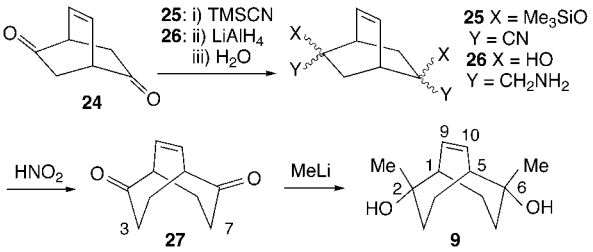
Diol **8** showed no inclusion behavior with any of the test solvents and crystallized from chloroform in the monoclinic space group $P2_1/c$. The X-ray determination[22] confirmed the molecular structure and the proposed stereochemistry and showed that the molecules were in the usually favored twin-chair conformation with both *endo*-methyl groups equatorial. As usual, each hydroxy group participates in one donor and one acceptor hydrogen bond. The diol molecules assemble in the *ac* plane as bilayers with hydrocarbon exterior surfaces as illustrated in Figure 4. The hydroxy groups form parallel hydrogen-bonded helical chains along *c* [graph set[15] C(2)] with the enantiomer ordering sequence −A−A−B−B−A−A−B−B−. These chains also exhibit a recurved helical projection.

Synthesis and Structure of Diol 9. Compound **9** is an excellent probe for rule v, the requirement (or otherwise) for a molecular bridge syn to the hydroxy substituents. The bicyclo[3.3.2]decane ring system, with its two conjoined seven-membered rings, has received sparse attention compared to its common bicyclo[3.3.1]nonane homologue, and no published synthetic routes provided suitably functionalized C2 and C6 positions. In other work, however, Borden had doubly ring-expanded the diketone **12** into bicyclo[3.3.3]undecane-2,6-dione (**23**) (Scheme 3).[23] In this process the bis(amino alcohol) **22** was subjected to double Tiffeneau−Demjanov ring expansion during which the least-substituted carbons migrated preferentially.[24] A smaller amount of a second

Scheme 3



Scheme 4



dione, presumably the 2,7-isomer, was also formed. There is evidence that *exo*-aminomethyl isomers show much greater selectivity in such ring expansions than the corresponding endo isomers.[25]

We therefore applied this concept to making **9** (Scheme 4). Bicyclo[2.2.2]oct-7-ene-2,5-dione (**24**)[26] was reacted with trimethylsilyl cyanide (TMSCN) to yield the bis(silyl cyanohydrin) **25**, which was then converted into the key bis(amino alcohol) intermediate **26**. The Momose[27] TMSCN addition conditions were used here (whereby the process is catalyzed by KCN−crown ether) rather than the earlier Evans zinc iodide procedure.[28] Double ring expansion of **26** (using $NaNO_2$−AcOH−H_2O) afforded bicyclo[3.3.2]dec-9-ene-2,6-dione (**27**), plus a small amount of the 2,7-dione isomer. Finally, reaction of methyllithium on the more exposed exo faces of **27** provided the target **9**.

This compound showed no inclusion using the standard test solvents but underwent self-resolution from chloroform solution yielding enantiomerically pure crystals in tetragonal space group $P4_12_12$ (and its enantiomorph).[29] Figure 5a shows the molecular structure and conformation of **9** in the solid state. This ORTEP diagram, and all others in this paper, are drawn at the 10% probability level. The diol molecules once again form bilayers where each −O−H takes part in one donor and one acceptor hydrogen bond. In this case, however, the molecules forming the bilayers are linked by $(O-H)_4$ cycles (Figure 5b). This motif [graph set[15] $R_4^4(8)$] has been found to be commonplace in other solid diol structures.[30] The unit cell contains parts of four stacked bilayers, with only hydrocarbon contacts between these, related by a 4_1 (or 4_3) axis.

Synthesis and Structure of Diol 10. A similar ring-expansion sequence led from the saturated dione **28**[31] to

(22) Crystal structure of **8**: $C_{13}H_{24}O_2$ (M_r = 212.3); $P2_1/c$; *a* 7.3920(4), *b* 18.8029(6), *c* 9.7706(5) Å; *β* 119.469(2)°; *V* 1182.3(1) Å^3; *Z* 4; *R* 0.041; R_w 0.074 for 1959 observed reflections.

(23) (a) Greenhouse, R.; Borden, W. T.; Ravindranathan, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 6955. (b) Greenhouse, R.; Ravindranathan, R.; Borden, W. T. *J. Am. Chem. Soc.* **1976**, *98*, 6738.

(24) For an overview of one carbon ring expansions of bicyclic ketones, see: Krow, G. R. *Tetrahedron* **1987**, *43*, 3.

(25) This appears to be general; see for example: (a) Miyashita, M.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1974**, *86*, 1917. (b) Momose, T.; Muraoka, O.; Shimada, N.; Tsujimoto, C.; Minematsu, T. *Chem. Pharm. Bull.* **1989**, *37*, 1909.

(26) Jefford, C. W.; Wallace, T. W.; Acar, M. *J. Org. Chem.* **1977**, *42*, 1654.

(27) Momose, T.; Yoshizawa, E.; Muraoka, O. *Synth. Commun.* **1985**, *15*, 17.

(28) (a) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914. (b) Groutas, W. C.; Felker, D. *Synthesis* **1980**, 861.

(29) Crystal structure of **9**: $C_{12}H_{20}O_2$ (M_r = 196.3); $P4_12_12$; *a*, *b* 7.3548(3), *c* 41.500(3) Å; *V* 2244.9(2) Å^3; *Z* 8; *R* 0.038; R_w 0.052 for 1123 observed reflections.

(30) Hawkins, S. C.; Scudder, M. L.; Craig, D. C.; Rae, A. D.; Abdul Raof, R. B.; Bishop, R.; Dance, I. G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 855.

(31) Grob, C. A.; Weiss, A. *Helv. Chim. Acta* **1960**, *43*, 1390.

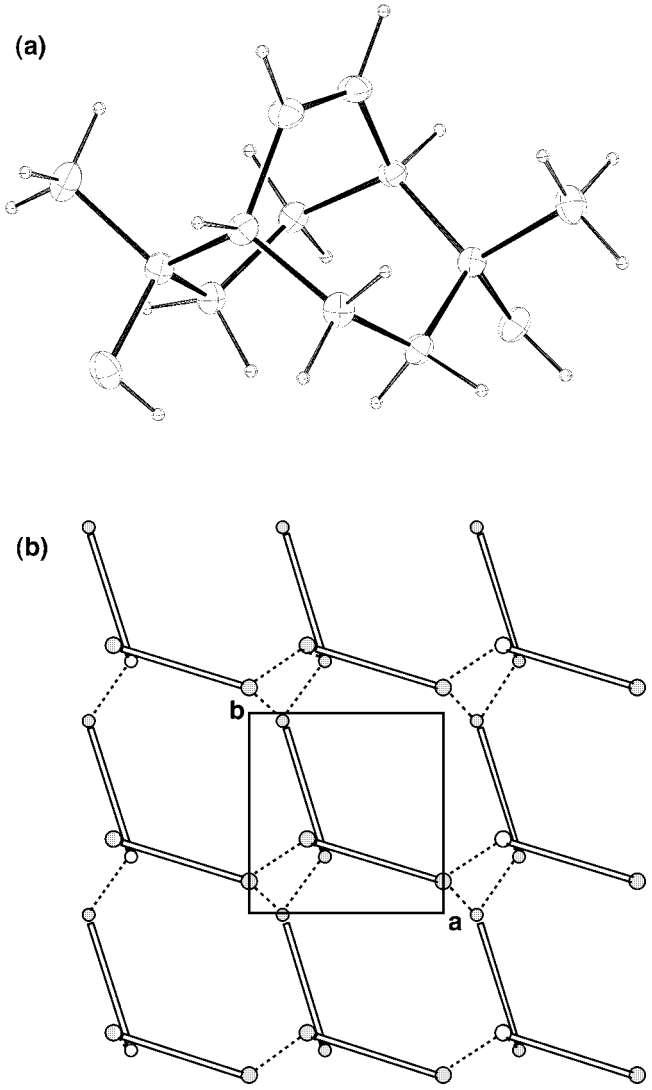
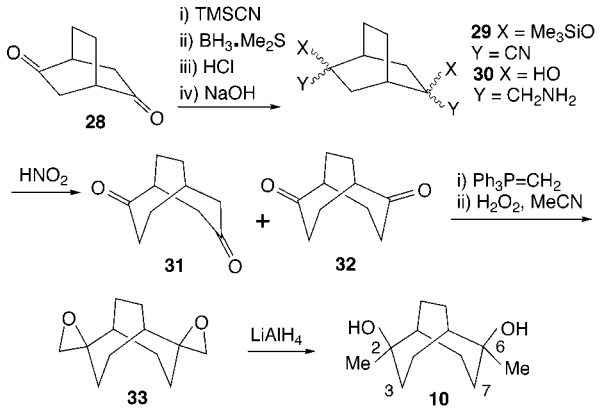


Figure 5. (a) ORTEP diagram of the molecular structure of 2,6-dimethylbicyclo[3.3.2]dec-9-ene-*endo*-2,*endo*-6-diol (**9**), showing its eclipsed twin-chair conformation in the solid state. (b) Hydrogen-bonded lattice present in solid **9** viewed down *c* and showing the $(O-H)_4$ cycles. For clarity, the diol molecules are drawn as hollow spacer rods connecting two oxygen atoms (stippled). Hydrogen bonds are indicated by dashed lines.

Scheme 5



bicyclo[3.3.2]decane-2,6-dione (**32**) (Scheme 5). Some difficulty was encountered removing the silyl groups of intermediate **29**, and the use of borane−dimethyl sulfide[32] proved the most effective route to **30**. The double

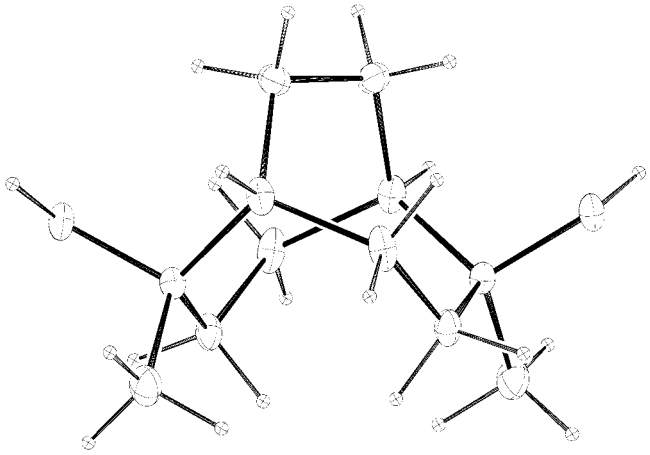


Figure 6. ORTEP diagram of the molecular structure of 2,6-dimethylbicyclo[3.3.2]decane-*exo*-2,*exo*-6-diol (**10**), showing its twin twist-chair conformation in the solid state.

ring expansion afforded a crude product whose ^{13}C NMR data indicated formation of the diones **31**:**32** in a ratio of 1:4. Because of their different symmetry these compounds exhibit 10 or 5 carbon peaks, respectively.

Wittig reaction on pure **32** gave the corresponding diene which underwent Payne oxidation[21] on its more exposed exo faces to yield bis(epoxide) **33**. Once again, the use of *m*-CPBA was less satisfactory. Reductive ring opening finally afforded the target diol **10**. In this case, the diene failed to react completely with mercuric acetate so this method could not be used to generate **10** directly. Steric retardation of $Hg(OAc)_2$ addition reactions is well documented.[13]

Crystals were grown by concentration of a chloroform solution of **10.** These were found to have the composition $(\mathbf{10})_3 \cdot 1.5CHCl_3$ and belong to trigonal space group $P3_1$-21.[33] Figure 6 shows the molecular structure and conformation of diol **10** in this material. Host **10** is a new member of the helical tubuland family, with lattice symmetry identical to the examples **1**−**4** described briefly in the Introduction and more fully in the literature.[3] Once again the hydrogen bonding graph set[15] is C(2). Prior to the synthesis of **10**, we predicted the host canal topology which it might assume. This model, based on the crystal structure of **1** with homologation of the ring skeleton, indicated a wide canal with nearly circular cross section. The experimental result proved to be remarkably similar. Its unobstructed canal cross-sectional area (Figure 7a) is the largest so far observed (36.7 Å^2) for the helical tubuland family and has a maximum canal diameter of 9.13 Å. The chloroform guests are located near the canal walls, with three guests every two unit cell lengths, hence the 2:1 host−guest stoichiometry. Figure 7b shows a projection view of a slice through four parallel canals formed by helical tubuland **10**.

Synthesis and Structure of Diol 11. Our earlier work on thiaadamantane diols had shown that the sulfur atom did not intervene in the hydrogen-bonding network if the hydroxy groups were anti but that intramolecular −O−H···S hydrogen bonds were produced in the syn case.[16] Hence, the stereochemistry of diol **11** was specif-

(32) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

(33) Crystal structure of **10**: $(C_{12}H_{22}O_2)_3 \cdot 1.5CHCl_3$ ($M_r = 774.0$); $P3_1$-21; *a*, *b* 13.3834(6), *c* 7.0257(5) Å; *V* 1089.8(1) Å^3; *Z* 1; *R* 0.066; R_w 0.078 for 1088 observed reflections.

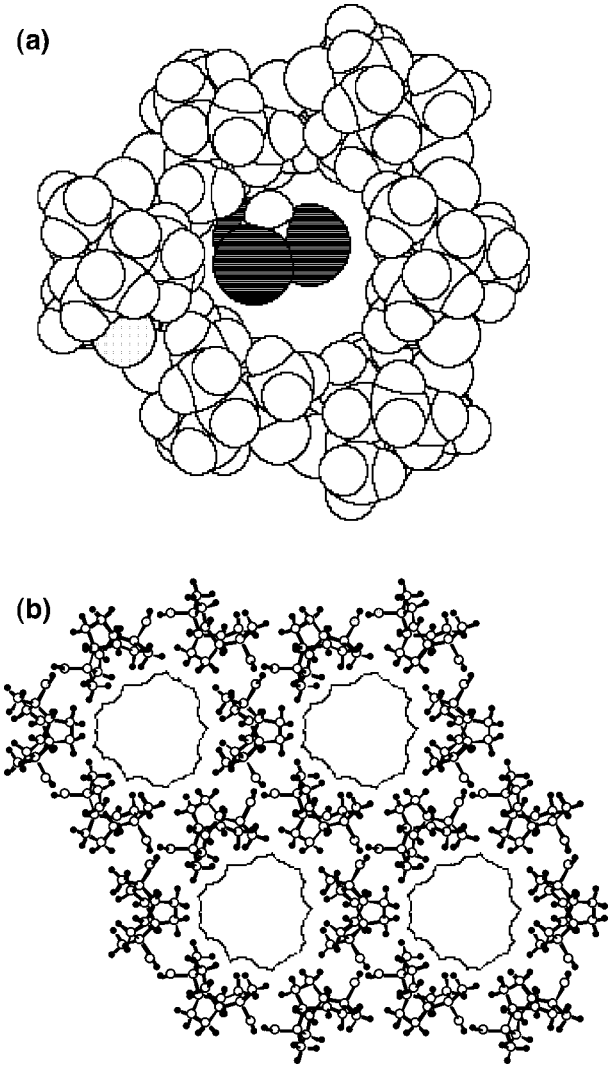


Figure 7. (a) Projection view in the *ab* plane of just one of the parallel tubes present in $(\mathbf{10})_3 \cdot 1.5CHCl_3$ showing a typical orientation of the chloroform guest. The following atom coding is used: oxygen (heavy stippling); chlorine (horizontal hatching); chloroform hydrogen (light stippling). (b) Section through the helical tubuland lattice showing a projection in the *ab* plane of four parallel host tubes with the guest molecules omitted. Hydrogen atoms are colored black, and oxygens are stippled. The van der Waals radii of the host atoms delineate the tube walls producing a nearly circular cross section.

ically targeted to take advantage of this knowledge. This compound extends the substituent rule iii since a heteroatom is incorporated within its ring skeleton.

Bicyclo[3.3.2]decane-2,6-dione (**32**) was converted into its bis(pyrrolidino enamine) **34** and then reacted with sulfur dichloride to give a modest yield of the tricyclic dione **35** (Scheme 6). Attack by methylmagnesium chloride in THF took place from the side of the sulfur atom to produce mainly the required diol **11**. Selective alkylation from this direction would be expected on steric grounds alone (as for the carbocyclic analogue **2**) but could be assisted further by coordination of the sulfur and the organometallic reagent. Methyllithium was a less satisfactory methylating reagent in this case. Compounds **11** and **35** are the first reported examples of the 9-thiatricyclo[4.3.1.1^{3,8}]undecane ring system.

Crystals were grown by evaporation of a chloroform solution of **11** and found to occupy the tetragonal space

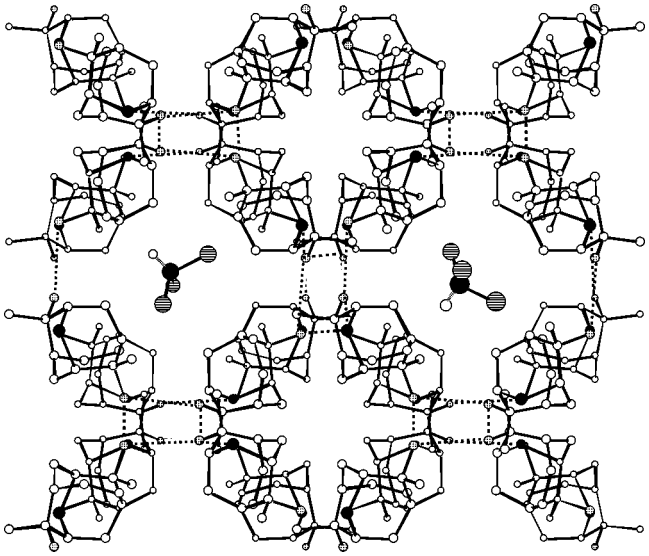
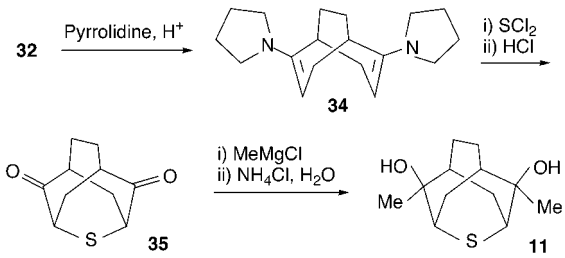


Figure 8. Lattice structure of the ellipsoidal clathrate $(\mathbf{11})_4 \cdot CHCl_3$ viewed down the canal axis *c* and showing the chloroform guest molecules. Hydrogen bonds are indicated by dashed linkages, and host hydrogens are omitted for clarity. The following atom coding is used: sulfur (black); oxygen (stippling); chlorine (hatching); guest carbon (black); guest hydrogen (stippling).

Scheme 6



group $I4_1/acd$ and have the composition $(\mathbf{11})_4 \cdot CHCl_3$.[34] This new inclusion system is isostructural[35] with that of the ellipsoidal clathrate structure formed by diol **2** with small guest molecules [graph set[15] $R_4^4(8)$]. The host lattice is the outcome of two interpenetrating, but unconnected, sublattices of hydrogen-bonded diol molecules. Guest molecules occupy ellipsoidal cavities situated between the two intertwined sublattices (Figure 8). Adjacent guests are separated by *c*/2 along crystallographic 2-fold axes parallel to *c*. In this structure the sulfur atoms simply mimic the corresponding methylene groups present in the compounds $(\mathbf{2})_4 \cdot$guest. They are located away from the center of the cavity and thus avoid any contact with the enclosed guest molecules.

Discussion

Conformations of the Bicyclo[3.3.2]decane Compounds 9 and 10. Parker,[36] Engler,[37] and Osawa[38] have

(34) Crystal structure of **11**: $(C_{12}H_{20}O_2S)_4 \cdot CHCl_3$ (M_r = 1032.8); $I4_1/acd$; *a*, *b* = 23.042(3), *c* 19.022(3) Å; *V* 10099(2) Å^3; *Z* 8; *R* 0.037; R_w 0.036 for 912 observed reflections.

(35) Hawkins, S. C.; Bishop, R.; Dance, I. G.; Lipari, T.; Craig, D. C.; Scudder, M. L. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1729.

(36) Doyle, M.; Hafter, R.; Parker, W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 364.

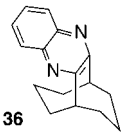
(37) Engler, E. M.; Chang, L.; Schleyer, P. v. R. *Tetrahedron Lett.* **1972**, 2525.

(38) Osawa, E.; Aigami, K.; Inamoto, Y. *J. Chem. Soc., Perkin Trans. 2* **1979**, 172.

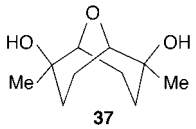
independently discussed the various conformers likely to exist in bicyclo[3.3.2]decane ring compounds. The twist twin-chair with a staggered ethano bridge and the boat-chair with an eclipsed ethano bridge were determined to be the lowest energy arrangements. For the parent compound and simple derivatives these would probably be in equilibrium in solution. As pointed out by Parker,[36] introduction of a double bond in the two-carbon bridge would markedly restrict the flexibility of the molecule (by fixing the coplanarity of carbons 1, 5, 9, and 10) and this would favor the boat-chair. Support for this is available from the crystal structure of the quinoxaline derivative **36**.[39] This is the only bicyclo[3.3.2]decane derivative for which X-ray structural data have been available up until now, so the new data on compounds **9** and **10** are of considerable interest.

In contradiction of the above, **9** adopts the classical twin-chair conformation in the solid state (Figure 5). The transannular C3···C7 separation of 3.06 Å is identical to that recorded for the flattened twin-chair conformation adopted by 1-*p*-bromophenylsulfonyloxymethyl-5-methylbicyclo[3.3.1]nonan-9-ol.[40] Engler,[37] however, has already remarked that the conformation observed will depend very much on the precise substitution pattern, because the various conformers of the bicyclo[3.3.2]-decane ring system are very close in energy. In both **9** and **10** the hydroxy group hydrogen bonding may also play a role in conformational control. Compound **10** adopts the twist twin-chair arrangement with a staggered ethano bridge (Figure 6) in its helical tubuland lattice. The cross-ring C3···C7 separation is 3.04 Å in this structure.

The apparent transannular C3−H···H−C7 hydrogen separations in **9** and **10** are only 1.83 and 1.86 Å, respectively. These short contact distances between the two *endo*-hydrogen atoms will be inaccurate, however, since we used only calculated hydrogen positions in our X-ray determinations. The true separations are almost certainly larger, and a value of 2.05 Å has been calculated by Osawa for the parent hydrocarbon.[37]



36



37

Helical Tubuland Structural Rules

Formation of the helical tubuland lattice requires formation of a helical hydrogen-bonded structure and also self-resolution of the diol molecules to give a crystalline conglomerate.[41] Very special supramolecular conditions are required to bring about these ends, but the structural membership rules allow us to design molecules close to, or within, this window of opportunity. Hence prediction and control of the hydrogen-bonding and lattice packing can be achieved.

Solid diol **7** is unresolved and the net lattice structure is achiral, but its molecules do hydrogen bond in a helical manner. In structural terms the bridged cyclohexane ring cannot quite twist sufficiently to satisfy rule ii, which encourages 3-fold hydrogen-bonding helicity to develop.

The unexpected behavior of **8** was entirely different from that of diol **1**. Figure 3 shows space-filling models from which two observations can be made. First, the immediate steric environment around the hydroxy groups of both molecules is extremely similar so their minor differences are unlikely to have caused this dramatic change. However, the two additional methyl groups of **8** make the latter diol considerably wider and bulkier. Since the diol molecules have to stack in eclipsed columns in the helical tubuland lattice, this volume increase in the alicyclic spacer molecule is critical. Hence substituent groups should be avoided leading to rule iii.

If the *syn*-diol hydroxy groups are not separated by a bridge, as in diol **9**, then they can hydrogen bond easily to give layer structures through use of $(O-H)_4$ cycles. This supramolecular motif is a very favorable one among alicyclic diols,[30] but the presence of a molecular bridge can suppress its formation in favor of helical hydrogen-bonded arrangements. Hence adherence to rule v is crucial. During crystallization of diol **9** self-resolution did take place to yield a conglomerate,[41] where each crystal is chirally pure. In this instance bilayers are produced, and helicity is also present with four stacked bilayers being related by a 4_1 axis (space group $P4_12_12$) or a 4_3 axis ($P4_32_12$), respectively.

Self-resolution of racemic **10** took place on its crystallization, chloroform was included, the space group was $P3_121$, and its crystal structure proved this diol to be a further example of the helical tubuland family. The molecular structure of **10** satisfied all five of the molecular rules, and molecular modeling enabled a sound prediction of its tubular dimensions to be made in advance of its preparation.[42]

Similarly, diol **11** satisfied all the molecular rules and proved to be a further example of the diol inclusion family. It should be noted that diol **2** forms ellipsoidal clathrates (containing both diol enantiomers in space group $I4_1/acd$) with small guests and helical tubulates (containing one enantiomer only in space group $P3_121$) with large guests.[35] This dual nature has not been observed for the other helical tubuland diols.[3] From a solution of **11** in chloroform, the ellipsoidal clathrate structure $(\mathbf{11})_4 \cdot CHCl_3$ results where the sulfur atom effectively mimics a methylene group in **2**. It is probable that **11** will show similar structural duality, and further investigation is in progress. Furthermore, we expect diol **11** to exhibit distinctive inclusion behavior when confronted by guests potentially able to coordinate with sulfur.

It should also be noted that **11** is the first heterocyclic example of these diol inclusion hosts. An earlier approach to such a compound had failed, since the ether oxygen atom of diol **37** was found to participate in the hydroxy hydrogen-bonding network, and therefore, a totally different structure without inclusion properties resulted.[43] The key conclusion here is that a heteroatom can be placed within a molecular bridge, provided that C_2 symmetry is retained and that it cannot interfere with the hydrogen-bonding network. The validity of the struc-

(39) (a) Hafter, R.; Murray-Rust, J.; Murray-Rust, P.; Parker, W. *J. Chem. Soc., Chem. Commun.* **1972**, 1127. (b) Murray-Rust, J.; Murray-Rust, P. *Acta Crystallogr., Sect. B* **1975**, *31*, 310.

(40) Brown, W. A. C.; Martin, J.; Sim, G. A. *J. Chem. Soc.* **1965**, 1844.

(41) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981.

(42) Bishop, R.; Craig, D. C.; Dance, I. G.; Kim, S.; Mallick, M. A. I.; Pich, K. C.; Scudder, M. L. *Supramol. Chem.* **1993**, *1*, 171.

(43) Pich, K. C.; Bishop, R.; Craig, D. C.; Dance, I. G.; Rae, A. D.; Scudder, M. L. *Struct. Chem.* **1993**, *4*, 41.

tural rules has been considerably strengthened by these results. They confirm the value of using defined structural requirements as part of synthetic strategy toward a required supramolecular outcome, and two improvements can be made.

First, substitution can be tolerated *within* the carbocyclic framework provided the heteroatom does not interfere with the hydrogen-bonding network. A series of heteroatom helical tubuland hosts now must be considered as being potentially possible.

Second, increasing the width of the alicyclic moiety may result in a diol which simply cannot pack properly in the 3-fold hydrogen-bonded spine structure of the helical tubuland lattice. Hence, steric problems may override the other structural factors.

Experimental Section

General procedures have been described.[16] Elemental analyses were carried out at UNSW by Dr. H. P. Pham. Petroleum ether refers to bp 60−80 °C material. Dry THF and DME solvents were freshly distilled from $LiAlH_4$, and dry DMSO was freshly distilled under reduced pressure from CaH_2.

6,8-Bis(methylidene)bicyclo[3.2.2]nonane (13). Diketone **12**[12] (6.08 g, 0.04 mol) was added to a stirred solution of methylidenetriphenylphosphorane (0.082 mol) in dry DMSO under N_2, following the Corey procedure and workup.[44] Microdistillation gave the diene **13** (2.98 g, 50%), bp 195−198 °C: IR (neat) 3070 m, 1645 m, 890 s, 870 s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50−1.56 (m, 2H), 1.66−1.70 (m, 4H), 2.43−2.45 (m, 4H) 2.61−2.63 (m, 2H), 4.71−4.72 (m, 2H), 4.77−4.79 (m, 2H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 21.1 (CH_2), 34.7 (CH_2), 35.6 (CH_2), 39.4 (CH), 108.0 (CH_2), 150.8 (C). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.53; H, 11.08.

6,8-Dimethylbicyclo[3.2.2]nonane-*endo*-6,*exo*-8-diol (14). A solution of **13** (2.87 g, 29.4 mmol) in dry THF (20 mL) was reacted with a solution of mercuric acetate (12.5 g, 38.8 mmol) in water (250 mL) and dry THF (250 mL) following Brown's procedure.[13] Evaporation of ethyl acetate solvent gave a gum which was heated with EtOAc and filtered, and the solvent was evaporated from the filtrate. ^{13}C NMR indicated two diol products. The mixture was chromatographed on activated alumina using petroleum ether, followed by increasing amounts of diethyl ether and then increasing amounts of chloroform. The endo, exo isomer **14** was obtained (95:5 $Et_2O/CHCl_3$) (0.57 g, 16%), mp 94−96 °C: IR (paraffin mull) 3330 s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.52 (s, 3H), 1.38−1.82 (m, 11H, reduced to 9H on D_2O exchange), 1.94−2.01 (m, 1H), 2.09−2.20 (m, 1H), 2.27−2.35 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1 (CH_2), 28.7 (CH_2), 30.7 (CH_3), 30.9 (CH_2), 32.7 (CH_3), 40.6 (CH_2), 40.9 (CH_2), 42.5 (CH), 44.5 (CH), 71.9 (C), 72.2 (C). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.42; H, 11.04.

6,8-Dimethylbicyclo[3.2.2]nonane-*endo*-6,*endo*-8-diol (15). Further elution of the above column ($Et_2O/CHCl_3$ 80:20) gave the *endo*,*endo*-diol **15** (0.49 g, 14%), mp 98−100 °C: IR (paraffin mull) 3270 s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H), 1.45−1.69 (m, 8H), 1.86−1.89 (m, 2H), 2.15−2.22 (dd, 2H, *J* 15.4, 7.5), 3.76 (br s, 2H, exchd with D_2O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.4 (CH_2), 28.4 (CH_3), 29.8 (CH_2), 39.6 (CH_2), 41.6 (CH), 72.1 (C). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.85; H, 11.16.

6,8-Dimethylbicyclo[3.2.2]nonane-*exo*-6,*exo*-8-diol (7). Diketone **12** (0.61 g, 4.0 mmol) was dissolved in dry THF (25 mL) and stirred under N_2. MeLi solution in diethyl ether (1.4 M; 7.1 mL, 0.01 mol) was added by syringe, and then the reaction was refluxed overnight. Wet Et_2O was added, followed by H_2O, and the ether layer separated. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were dried (Na_2SO_4). Evaporation of solvent from the filtrate yielded a yellow oil from which solid formed. Filtration, followed by recrystallization from $CHCl_3$, gave the *exo*,*exo*-diol **7** as fine needles (0.33 g, 46%), mp 126−129 °C: IR (paraffin mull) 3350 s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.44−1.51 (m, 4H), 1.70−1.81 (m, 6H), 1.91−1.96 (m, 2H), 2.14−2.21 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7 (CH_2), 29.6 (CH_2), 33.1 (CH_3), 42.0 (CH_2), 44.0 (CH), 71.7 (C). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.53; H, 11.17.

***endo*-4,*endo*-8-Dimethylbicyclo[3.3.1]nonane-2,6-dione (19).** Diketone **18**[17,18] (1.00 g, 5.7 mmol) was dissolved in methanol (20 mL). Adams catalyst (20 mg) and perchloric acid (70%; 3 drops) were added, and the mixture was hydrogenated at room temperature and 1 atm. After filtration and removal of solvent, the residual mixture was subjected to the standard Jones' oxidation procedure.[19] The final $CHCl_3$ extract was evaporated to give the diketone **19**[20] as a colorless oil (0.78 g, 76%), bp ca. 250 °C: IR (neat) 1715 s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.74−0.83 (m, 6H), 1.71−1.86 (m, 2H), 1.99−2.16 (m, 4H), 2.35−2.49 (m, 2H), 2.51−2.57 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.6 (CH_3), 32.9 (CH_2), 34.3 (CH), 47.6 (CH_2), 49.9 (CH), 210.2 (C). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 9.21.

***endo*-2,*endo*-4,*endo*-6,*endo*-8-Tetramethylbicyclo[3.3.1]nonane-*exo*-2,*exo*-6- diol (8).** Dione **19** (1.50 g, 8.33 mmol) was reacted with methylidenetriphenylphosphorane (18.3 mmol) in dry DMSO by following the Corey procedure.[44] After 4 h of stirring at room temperature, the reaction was worked up in the usual manner. Microdistillation gave diene **20** as a colorless oil (0.72 g, 49%), bp 200−203 °C: IR (neat) 3080 m, 2980 s, 2950 s, 2920 s, 2900 s, 1640 s, 1475 m, 1460 s, 1455 s, 1380 m, 1110 s, 1010 m, 895 s cm^{-1}; ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.3 (CH_3), 35.9 (CH), 38.3 (CH_2), 40.6 (CH_2), 43.9 (CH), 109.9 (CH_2), 148.9 (C).

The diene (0.70 g, 4.0 mmol) was added to a mixture of methanol (30 mL), acetonitrile (0.60 g), and $KHCO_3$ (0.14 g), which was stirred at 0 °C. Hydrogen peroxide (27.5% w/w, 1.04 g) was added dropwise. After addition was complete, the mixture was refluxed for 90 h. After cooling, brine was added and organic material extracted using CH_2Cl_2. The combined extracts were washed with water, then dried (Na_2SO_4). Evaporation of solvent from the filtrate gave bis(epoxide) **21** as an oil (0.50 g, 60%): IR (neat) 3050 w, 2980 s, 2950 s, 2920 s, 2890 s, 1470 s, 1380 w, 1115 m, 935 s, 925 s, 780 m, 760 m cm^{-1}.

Crude **21** (0.50 g) was dissolved in dry THF (10 mL), and the solution was added dropwise to a suspension of $LiAlH_4$ (0.76 g, 20 mmol) in dry THF (30 mL) at 0 °C. After stirring at room temperature overnight, wet Et_2O and then aqueous Na_2SO_4 solution were added. The ethereal solution was decanted, the aqueous phase was extracted with further Et_2O, and the extracts were dried (Na_2SO_4). Evaporation of solvent from the filtrate gave dialcohol **8** as a white solid (0.43 g, 84%), mp 205−206 °C (from Et_2O): IR (paraffin mull) 3430 s cm^{-1}; MS *m*/*z* 194 [(M − 18), 7%]; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 0.94 (d, 6H, *J* 6.81), 1.13 (s, 6H), 1.34−1.39 (m, 6H), 1.92 (t, 2H, *J* 3.14), 2.07−2.16 (m, 2H), 3.91 (s, 2H, exchd with D_2O); ^{13}C NMR [126 MHz, $(CD_3)_2SO$] δ 22.5 (CH_3), 31.7 (CH_2), 31.8 (CH), 31.9 (CH_3), 44.8 (CH_2), 45.6 (CH), 71.6 (C). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.82; H, 11.74.

2,5-Bis(trimethylsilyloxy)bicyclo[2.2.2]oct-7-ene-2,5-dicarbonitrile (25). Bicyclo[2.2.2]oct-7-ene-2,5-dione (**24**)[26,45] (3.00 g, 22.0 mmol), dicyclohexyl-18-crown-6 (0.50 g), and KCN (0.25 g) were mixed in dry DME (30 mL), and trimethylsilyl cyanide (TMSCN; 5.0 g, 50.5 mmol) was added. After the initial warming had subsided, the mixture was stirred at room temperature for 4 h and then solvent evaporated to give an oil. After washing several times with petroleum ether, the silyl cyanohydrin **25** was obtained as a pale red-orange oil (6.93 g, 94%): IR (neat) 3080 w, 2240 w, 860 vs cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (mixture of all three epimers) δ 0.21 (s), 0.28 (s), 1.56−1.60 (dd, *J* 14.3, 3.4), 1.71−1.74 (dd, *J* 15.1, 3.6),

(44) Greenwald, B. R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(45) Cookson, R. C.; Wariyar, N. S. *J. Chem. Soc.* **1957**, 327.

2.03−2.07 (dd, *J* 14.8, 2.0), 2.18−2.22 (dd, *J* 14.8, 3.9), 2.62−2.66 (dd, *J* 15.1, 2.3), 2.73−2.76 (dd, *J* 14.3, 2.5), 2.90−2.93 (m), 2.98−3.00 (m), 6.18−6.26 (m), 6.37−6.40 (m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 1.07 (CH_3), 1.13 (CH_3), 1.16 (CH_3), 1.3 (CH_3), 34.5 (CH_2), 37.5 (CH_2), 39.2 (CH_2), 40.2 (CH_2), 41.4 (CH), 41.8 (CH), 42.0 (CH), 68.2 (C), 69.3 (C), 69.7 (C), 69.8 (C), 121.6 (C), 121.8 (C), 122.4 (C), 122.6 (C), 130.0 (CH), 131.1 (CH), 132.4 (CH), 133.2 (C), one bridgehead CH obscured, probably two signals at δ 41.4. Anal. Calcd for $C_{16}H_{26}N_2O_2Si_2$: C, 57.44; H, 7.83; N, 8.37. Found: C, 57.35; H, 8.06; N, 8.46.

Bicyclo[3.3.2]dec-9-ene-2,6-dione (27). Crude **25** (2.02 g, 6.0 mmol) dissolved in dry Et_2O (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.28 g, 7.4 mmol) in Et_2O. After stirring of the mixture for 2 h at room temperature, water (5 mL) and then NaOH solution (2 M; 5 mL) and more water (15 mL) were added. The reaction was extracted using $CHCl_3$, and the combined extracts were dried (Na_2SO_4). Evaporation of solvent from the filtrate gave a viscous yellow oil (1.59 g). A sample (0.29 g) was dissolved in ethanol (18 mL) and NaOH solution (3.75 M; 2 mL) added. The mixture was refluxed and stirred overnight. Water was added and organic material extracted using Et_2O. After drying (Na_2SO_4), solvent was evaporated from the filtrate to give amino alcohol **26** as a colorless syrup (0.11 g, 66%): IR (neat) 3370 s, 3060 m, 1595 s cm^{-1}.

Crude **26** (0.10 g, 0.51 mmol) was dissolved in acetic acid (1 mL) and water (10 mL) and then cooled in ice. Sodium nitrite (0.5 g) was added and the reaction stirred at 0 °C for 2 h. Saturated $NaHCO_3$ solution (20 mL) was added, organic material extracted with Et_2O, and the extract dried (Na_2SO_4). Evaporation of solvent from the filtrate gave an oil which was purified by preparative TLC to afford diketone **27** (0.045 g, 54%), mp 129−130 °C (from petroleum ether): IR (paraffin mull) 3050 w, 1695 s cm^{-1}; MS *m*/*z* 164 (M, 52%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08−2.15 (m, 2H), 2.38−2.44 (m, 2H), 2.46−2.51 (m, 2H), 2.88−2.94 (m, 2H), 3.02−3.06 (m, 2H), 6.24−6.28 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.4 (CH_2), 40.0 (CH_2), 49.4 (CH), 130.7 (CH), 212.7 (C). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.15; H, 7.60.

2,6-Dimethylbicyclo[3.3.2]dec-9-ene-*endo*-2,*endo*-6-diol (9). Diketone **27** (0.29 g, 1.76 mmol) was dissolved in dry THF (10 mL) and stirred under N_2. MeLi in diethyl ether (1.4 M; 5 mL, 7.0 mmol) was added by syringe. The mixture was stirred at room temperature for 30 min and then refluxed for 2 h. Wet Et_2O (20 mL) was added, followed by water (30 mL). Organic material was extracted using $CHCl_3$, and the extracts were dried (Na_2SO_4). Evaporation of solvent from the filtrate gave a pale orange semisolid material which, on addition of a small amount of Et_2O, gave dialcohol **9** as a white solid (0.20 g, 58%), mp 152−155 °C (from petroleum ether): IR (paraffin mull) 3335 s, 3040 m cm^{-1}; MS *m*/*z* 178 [(M − 18), 5%]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 6H), 1.48 (br s, 2H, exchd. with D_2O), 1.58−1.70 (m, 2H), 1.74−1.82 (m, 2H), 1.98−2.08 (m, 2H), 2.19−2.24 (m, 2H), 2.29−2.39 (m, 2H), 5.83−5.86 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.4 (CH_2), 30.9 (CH_3), 39.9 (CH_2), 46.7 (CH), 72.8 (C), 132.8 (CH). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.32.

Bicyclo[3.3.2]decane-2,6-dione (32). Bicyclo[2.2.2]octane-2,5-dione (**28**)[31,46] (3.40 g, 0.025 mol), KCN (0.25 g), and dicyclohexyl-18-crown-6 (0.40 g) were dissolved in dry DME (50 mL). TMSCN (5.00 g, 0.05 mol) was added, and the mixture was stirred for 4 h. The dark orange colored oil obtained on evaporation of the solvent was washed with petroleum ether several times and then eluted through a column of alumina using petroleum ether/Et_2O (1:1). The silyl cyanohydrin **29** was obtained as a colorless oil (7.53 g, 91%) containing all three epimers: IR (neat) 2230 w, 850 vs cm^{-1}; ^{13}C NMR (126 MHz, $CDCl_3$) δ 1.06 (CH_3), 1.11 (CH_3), 1.18 (CH_3), 1.4 (CH_3), 16.7 (CH_2), 16.9 (CH_2), 19.8 (CH_2), 35.9 (CH), 36.2 (CH), 36.3 (CH), 36.5 (CH), 36.8 (CH_2), 37.2 (CH_2), 39.6 (CH_2), 40.8 (CH_2), 67.8 (C), 68.0 (C), 68.2 (C), 68.4 (C), 121.87 (C), 121.92 (C), 122.1 (C), 122.6 (C), one CH_2 signal obscured.

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Method A. The silyl cyanohydrin **29** (7.25 g, 21.54 mmol) was dissolved in dry Et_2O and added dropwise to a stirred suspension of $LiAlH_4$ (1.70 g, 44.85 mmol) in dry Et_2O (60 mL). After stirring of the mixture at room temperature overnight, water was added carefully, followed by aqueous NaOH. The ether solution was decanted and dried (Na_2SO_4), and solvent was evaporated from the filtrate to give the silylamine as a colorless oil (6.68 g, 90%): IR (neat) 3450 s, 2950 s, 1440 m, 1365 m, 1245 s, 1175 m, 1115 m, 1080 m, 1040 s, 835 s, 750 m cm^{-1}. This material (6.34 g, 18 mmol) was dissolved in ethanol (30 mL), NaOH solution (3.75 M, 3 mL) was added, and the mixture was refluxed overnight. Solvent was evaporated, organic material was extracted with Et_2O, and the extracts were dried (Na_2SO_4). Evaporation of solvent from the filtrate gave the amino alcohol **30** (2.58 g, 70%) as a viscous syrup: IR (neat) 3350 s, 3280 s, 1645 m, 1595 m, 1440 m, 1360 m, 1080 m, 1025 s, 960 m cm^{-1}. Alternatively, the silylamine (2.10 g, 6.1 mmol) was dissolved in THF (60 mL), HCl (6.0 M, 20 mL) was added, and the mixture was refluxed for 2 h. Sodium hydroxide (6.00 g in 10 mL water) was added, and the reaction was saturated with K_2CO_3. Extraction using ethyl acetate gave **30** (0.56 g, 46%) as a colorless oil.

Method B. 29 (2.0 g, 6.0 mmol) was dissolved in dry THF (15 mL) and brought to reflux under N_2. Borane−dimethyl sulfide in CH_2Cl_2 (1.0 M, 13.1 mL, 0.013 mol) was added and the Me_2S distilled off. Hydrochloric acid (6.0 M, 10 mL) was added and the mixture refluxed for a further 30 min. After cooling of the mixture to 0 °C, NaOH (2.0 g) was added followed by excess K_2CO_3 to saturate the aqueous phase. The water-soluble organic product was best extracted from a hot aqueous solution saturated with NaCl using EtOAc. The combined extracts were dried (Na_2SO_4), and solvent was evaporated from the filtrate to give the amino alcohol **30** (0.97 g, 82%).

30 (4.35 g, 20.3 mmol) was dissolved in methanol (90 mL), and the solution was then cooled in ice. Concentrated HCl (45 mL) was added slowly with stirring. After the initial vigorous reaction had subsided, the mixture was refluxed for 90 min and then evaporated to dryness under reduced pressure. The resulting frothy brown hydrochloride salt was pumped under vacuum for 12 h to remove excess HCl. It was then dissolved in water (50 mL) and acetic acid (5.5 mL), after which NaOAc (4.6 g) and benzene (90 mL) were added. The solution was cooled in ice, and a solution of sodium nitrite (6.30 g) in water (24 mL) was added in portions with vigorous stirring over 30 min. It was then stirred for a further 18 h. The organic layer was separated, the aqueous phase was extracted with C_6H_6, and the combined extracts were dried (Na_2SO_4). Evaporation of solvent from the filtrate gave an orange oil, which was chromatographed on alumina to separate diketone **31** (0.32 g, 8%) [^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1 (CH_2), 23.3 (CH_2), 25.8 (CH_2), 29.7 (CH_2), 38.1 (CH_2), 40.3 (CH_2), 45.1 (CH), 45.8 (CH), 208.9 (C), 213.3 (C)] from the required isomeric diketone **32** (1.30 g, 32%), mp 143−145 °C: IR (paraffin mull) 1690 s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77−2.04 (m, 4H), 2.18−2.45 (m, 6H), 2.69−2.80 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4 (CH_2), 27.1 (CH_2), 39.1 (CH_2), 47.8 (CH), 215.9 (C). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.76.

2,6-Dimethylbicyclo[3.3.2]decane-*exo*-2,*exo*-6-diol (10). Diketone **32** (1.00 g, 6.0 mmol) was added to a stirred solution of methylidenetriphenylphosphorane (12.6 mmol) in dry DMSO under N_2 using the Corey procedure.[44] After heating for 2 h at 60 °C, the cooled product was worked up in the usual manner with water and petroleum ether. The crude product was eluted through a short column of alumina using petroleum ether to remove traces of triphenylphosphine oxide and keto olefin. Solvent was removed by distillation to give 2,6-bis-(methylidene)bicyclo[3.3.2]decane (0.44 g, 45%) as an oil, bp 177−180 °C: IR (neat) 3070 m, 2930 s, 2860 s, 1635 m, 1440 m, 880 s cm^{-1}; ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.4 (CH_2), 32.5 (CH_2), 33.7 (CH_2), 42.0 (CH), 109.8 (CH_2), 155.3 (C).

The diene (1.70 g, 10.5 mmol) was stirred with methanol (30 mL), acetonitrile (1.57 g), and $KHCO_3$ (0.37 g) at 0 °C. Hydrogen peroxide solution (27.5% w/w; 2.72 g) was added dropwise. After addition the reaction was refluxed for 40 h. Brine was added and then CH_2Cl_2 used to extract organic

material. The combined extracts were washed and then dried (Na_2SO_4). Evaporation of solvent from the filtrate gave the crude bis(epoxide) **33** (1.50 g, 74%) as a pale yellow oil: IR (neat) 3020 m, 2930 s, 2850 s, 1450 m, 1280 m, 880 s, 800 m, 730 m cm^{-1}. This product was dissolved in dry THF (20 mL), and the solution was added to a suspension of $LiAlH_4$ (1.18 g, 31 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred overnight at room temperature, and then excess $LiAlH_4$ was destroyed by addition of aqueous Na_2SO_4 solution. The THF layer was separated, and then organic material was extracted using EtOAc. The combined extracts were dried (Na_2SO_4), and solvent was evaporated from the filtrate to yield a viscous colorless oil (1.52 g), which was dissolved in a small volume of Et_2O/petroleum ether (3:1) and cooled to yield the solid diol **10** (0.83 g, 40%). Recrystallization from chloroform gave the inclusion compound, mp 156−158 °C: IR (paraffin mull) 3375 s, 1110 s, 1080 s, 770 s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H), 1.43 (br s, 2H, exchanged with D_2O), 1.44−1.54 (m, 2H), 1.61−1.91 (m, 10H), 2.19−2.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.5 (CH_2), 24.8 (CH_2), 30.9 (CH_3), 38.1 (CH_2), 46.2 (CH), 75.6 (C). Sublimation under reduced pressure (ca. 120 °C, 15 mmHg) yielded solvent-free **10**, mp 156−157 °C: IR (paraffin mull) 770 cm^{-1}, absorption due to $CHCl_3$ now absent. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 73.03; H, 11.50.

9-Thiatricyclo[4.3.1.1^{3,8}]undecane-2,7-dione (35). Dione **32** (3.47 g, 0.021 mol), pyrrolidine (5.3 mL, 0.064 mol), and *p*-toluenesulfonic acid (20 mg) were mixed with C_6H_6 (100 mL) and heated under reflux using a Dean−Stark trap. After water separation was complete, solvent was evaporated to give the crude bis(enamine) **34** as a dark brown oil, which was dissolved in CH_2Cl_2 (40 mL). Freshly distilled triethylamine (10 mL) was added and the mixture brought to reflux. A solution of freshly purified sulfur dichloride[47] (1.5 mL, 0.023 mol) in CH_2Cl_2 (10 mL) was added in portions over 15 min. The reaction was refluxed for a further 1 h and then stirred overnight at room temperature. Excess HCl (2.5 M) was added with stirring and then the CH_2Cl_2 solution separated. The aqueous phase was extracted several times with $CHCl_3$. The combined organic extracts were washed several times with water and then dried (Na_2SO_4). Evaporation of solvent from the filtrate gave a dark orange oil which partly crystallized on standing. This solid was filtered off and recrystallized from acetone to give the diketone **35** (0.51 g, 12.5%), mp 143−148 °C: IR (neat) 1700 s cm^{-1}; ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.3 (CH_2), 36.3 (CH_2), 43.9 (CH), 46.1 (CH), 206.5 (C). Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.10; H, 6.42.

2,7-Dimethyl-9-thiatricyclo[4.3.1.1^{3,8}]undecane-*anti*-2,*anti*-7-diol (11). A solution of methylmagnesium chloride (3.0 M in THF, 1.8 mL, 5.4 mmol) was added by syringe to a stirred solution of diketone **35** (0.35 g, 1.8 mmol) in dry THF (10 mL) at 0 °C. After 4 h of reflux a saturated solution of NH_4Cl was added and the organic layer separated. The aqueous phase was extracted further using Et_2O. The combined extracts were dried (Na_2SO_4), and evaporation of solvent from the filtrate gave a yellow solid. Recrystallization from chloroform gave fine needles of the diol **11** as an inclusion compound (0.26 g, 64%), mp 153−155 °C: IR (paraffin mull, cm^{-1}) 3405 s; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 6H), 1.52−1.65 (m, 2H), 2.08−2.48 (m, 10H), 4.78 (br s, 2H, exchanged with D_2O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.3 (CH_2), 31.3 (CH_3), 35.7 (CH_2), 43.6 (CH), 43.7 (CH), 74.8 (C). Anal. Calcd for $(C_{12}H_{20}O_2S)_4 \cdot CHCl_3$: C, 56.99; H, 7.91. Found: C, 57.28; H, 8.35.

Inclusion Behavior and Crystal Structures of the Diols 7−11. Compounds **7**−**9** were screened for potential inclusion properties by recrystallization from a standard set of solvents (acetone, acetonitrile, benzene, dichloromethane, diethyl ether, chloroform, ethyl acetate, and chloroform) followed by examination of their IR (paraffin mull) spectra. All cases tested negative. In contrast, both **10** and **11** showed inclusion properties.

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Supporting Information Available: Listings of IR and MS peaks, figures showing the X-ray molecular structures and conformations of diols **7**, **8**, and **11**, details of the solution and refinement of the five crystal structures, including numerical data, and tables listing fractional coordinates, thermal parameters, interatomic distances and angles, and dimensions associated with the hydrogen bonding. This material is available free of charge via Internet at http://pubs.acs.org.

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