Crystallisation of C_2-symmetric *endo*,*endo*-bicyclo[3.3.1]nonane-2-6-diols: supramolecular synthons and concomitant degrees of enantiomer separation†‡

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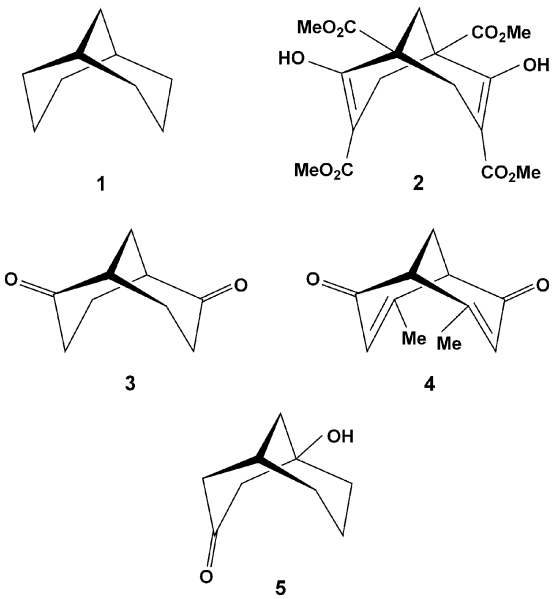
Each of the three racemic C_2-symmetric *endo*,*endo*-bicyclo[3.3.1]nonane-2,6-diols **6–8** shows a dominant, but different, mode of crystallisation across a wide range of solvents. These outcomes depend on the type of supramolecular synthon employed and the resulting degree of enantiomer separation that takes place. Diol **6** utilises the centrosymmetric hydrogen bonded $(O–H)_6$ cycle and forms racemic crystals containing an intimate mix of the two enantiomers. In contrast, diol **7** uses $(O–H)_4$ cycles with concomitant formation of homochiral layers, but racemic crystals still result since adjacent layers have opposite handedness. Diol **8** forms a hydrogen bonded network by using cross-linked $(O–H)_8$ repeat helices and self-resolution yields a mixture of pure (+)- and pure (−)-crystals (a conglomerate). Since conglomerates may be separated into their pure enantiomers, the latter discovery offers a new preparative approach for obtaining chirally pure bicyclo[3.3.1]nonane compounds of value in organic synthesis.

Introduction

The bicyclo[3.3.1]nonane ring skeleton **1** can be regarded as a 1,5-methano-bridged cyclooctane system, or as consisting of two cyclohexane rings joined in Siamese twin-style. Its derivatives have played key roles in the development of many important research areas, such as conformational equilibria,[2] natural products,[3] synthetic organic methodology,[4] host–guest compounds,[5] and bridgehead reactivity.[6] Several review articles have described the chemistry of its compounds in detail.[7–10]

An important characteristic of this ring system is that many of its derivatives may be obtained simply, and in high yield, by means of classical synthetic methods. For example, compounds **2** and **3** are prepared from dimethyl malonate and formaldehyde,[11,12] **4** from acetylacetone and formaldehyde,[13] and **5** from cyclohexenone and ethyl acetoacetate.[14] It should be noted that these preparations of **2–5** commence with achiral reagents but yield handed products.[15] Therefore these compounds can be utilised in further synthetic chemistry in either their racemic or chirally pure forms.

Several methods have been used to resolve the readily available racemic bicyclo[3.3.1]nonane-2,6-dione **3**, thereby making it available for use in the syntheses of enantiopure materials. Chiral HPLC separation on a microcrystalline triacetyl cellulose column gave early and late eluate fractions that were enriched (ee 30–50%). Re-injection of the concentrated eluates then yielded enantiomerically pure **3**, but only on a 10–20 mg scale.[16] Enantioseparation of **3** can also be effected by GC on permethylated α- or β-cyclodextrin columns.[17]



An alternative approach has been to employ enzymatic resolutions. For example, horse liver alcohol dehydrogenase converts **3** to the hydroxyketone and ultimately the diol. Termination of the reaction after 50% of the racemic **3** had been consumed (1.5 g scale), gave 34% of unreacted (−)-**3** (ee 80%). Oxidation of the hydroxyketone afforded (+)-**3** (ee > 50%).[18,19] Alternatively, baker's yeast reduction of

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racemic **3** can be employed. In this case, the slower reacting isomer is (+)-**3**, which can be obtained in 24% yield (93% ee), commencing with 3.0 g of racemic material.[20,21]

Samples of **3** resolved by these methods have been utilised in syntheses of enantiopure methanocycloocta[*b*]indoles,[19] twistbrendanedione,[21] bicyclo[3.3.1]nonane-2,7-dione,[22] 2,6-diaminobicyclo[3.3.1]nonane,[23] and other chiroptically fascinating molecules.

Classical resolution can also be used. Reduction of **3** yields *endo*,*endo*-bicyclo[3.3.1]nonane-2,6-diol **8**,[24] and reaction of the latter with (−)-camphanic chloride affords two diastereomeric diesters that can be separated by crystallisation or by column chromatography. Hydrolysis of each ester, followed by Jones' oxidation, then yields both pure enantiomers of the dione **3**.[25]

The two most suitable resolution procedures on a preparative scale are the baker's yeast and camphanic chloride methods, but both present disadvantages by nature of the significant amount of experimental work and time they involve. Furthermore, the average chemist is unfamiliar with using bioreagents, and (−)-camphanic chloride is expensive (*ca.* \$55 g^{-1}).[26] This paper presents an alternative approach for obtaining resolved samples of the versatile bicyclo[3.3.1]nonane reagents **3** and **8** and many other derivatives accessible from these.

Results and discussion

Alternative crystallisation outcomes

Three common outcomes of crystallising a racemic compound are illustrated in Fig. 1. Most frequently (process A) racemic crystals are produced. These contain an intimate mix of both the (+)- and (−)-enantiomers. Another common result (outcome B) is formation of racemic crystals in which considerable enantiomer separation has taken place, such that the (+)- and (−)-enantiomers now occupy discrete homochiral domains. Relatively little has been written about this type of behaviour, however, despite its inherent interest.[27] Finally, through process C, a complete enantiomer separation (self-resolution) can occur to produce a mixture of pure (+)- and pure (−)-crystals (a conglomerate).[28] These types of behaviour, and their implications, will be explored here in relation to the crystallisation behaviour of the racemic *endo*,*endo*-bicyclo[3.3.1]nonane-2,6-diols **6–8**.

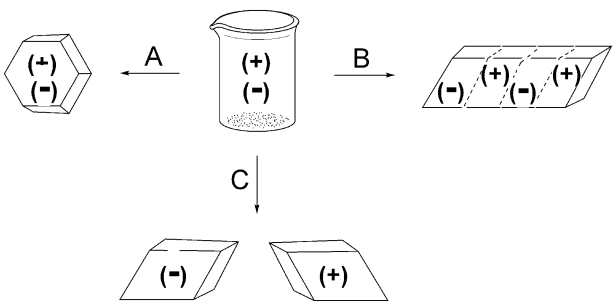
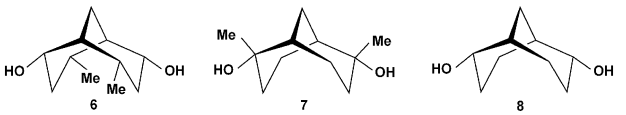


Fig. 1 Three common outcomes observed on crystallisation of a 1 : 1 mixture of enantiomers. A: formation of racemic crystals containing an intimate mix of enantiomers. B: formation of racemic crystals containing enantiomers separated into discrete domains. C: complete separation of the enantiomers into individual homochiral crystals (a conglomerate).



The three compounds **6–8** are very close structural relatives based on *endo*,*endo*-bicyclo[3.3.1]nonane-2,6-diol, but the first two carry additional methyl substituents. All are C_2-symmetric and form hydrogen bonded crystal structures in which each hydroxy group participates in one donor and one acceptor hydrogen bond. However, their differences, especially the varying steric environment around their hydroxy groups, result in their adoption of the different crystallisation outcomes A, B and C, respectively. The dominant attractive forces present in the solids **6–8** are the three hydrogen bonded supramolecular synthons[29] illustrated in Fig. 2.

Crystal structure of diol 6

Compound **6** has yielded inclusion compounds from every crystallisation experiment we have conducted. Nearly all of these are isostructural in the cubic space group $Ia\bar{3}$ and involve $(O–H)_6$ hydrogen bonded cycles that lead to the three-dimensional network lattice.[30] The $(O–H)_6$ cycle is well known in inclusion chemistry since it is central to the formation of the classical clathrate structures formed by β-hydroquinone and Dianin's compound.[31] Indeed, the close familial relationship of these three different crystal types is revealed when their lattices are analysed using nodal points.[30,32] The $(O–H)_6$ cycle present in the cubic crystals is formed by alternating (+)- and (−)-enantiomers of diol **6**, and therefore is an example of outcome A in Fig. 1.

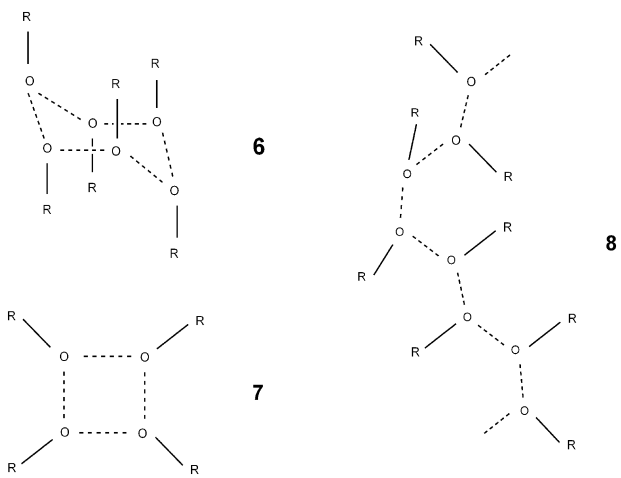


Fig. 2 The hydrogen bonded supramolecular synthons present in the crystal structures of compounds **6–8**; namely the $(O–H)_6$ cycle, the $(O–H)_4$ cycle, and the cross-linked $(O–H)_8$-repeat helix. R represents the remainder of the diol molecule and includes the second hydroxy group that takes part in another identical supramolecular synthon in each structure. The hydroxy hydrogen atoms are omitted and hydrogen bonds are indicated by dashed lines.

Crystal structure of diol 7

The diol **7**[33,34] crystallises as a hydrogen bonded layer structure in the monoclinic space group *Pc* from all twelve solvents tested (see Experimental). Individual molecules are linked by means of $(O–H)_4$ cycles. This supramolecular synthon is another commonly encountered arrangement for alicyclic diol molecules.[34] In this instance, all four molecules forming the cycle have the same handedness, thus leading to the formation of homochiral layers of diol **7**. Adjacent layers have the opposite handedness (Fig. 3). Hence, in this example, outcome B has resulted in substantial enantiomer ordering within the racemic crystal.

Crystal structure of diol 8

The crystal structure of *endo*,*endo*-bicyclo[3.3.1]nonane-2,6-diol **8**[24] has not been previously reported. Racemic **8** undergoes self-resolution, outcome C in Fig. 1, and crystallises from all twelve solvents tested (see Experimental) as a guest free conglomerate. This result is notable since Jacques *et al*. have estimated that conglomerate formation only occurs for about 5–10% of neutral organic molecules.[28] Furthermore, its behaviour is consistent across a disparate range of recrystallisation solvents.

Each enantiomerically pure crystal occupies the tetragonal space group $P4_12_12$, or its enantiomorph $P4_32_12$. Numerical details of the solution and refinement of the crystal structure are presented in Table 1. The hydrogen bonded network structure is constructed from cross-linked $(O–H)_8$-repeat helices.

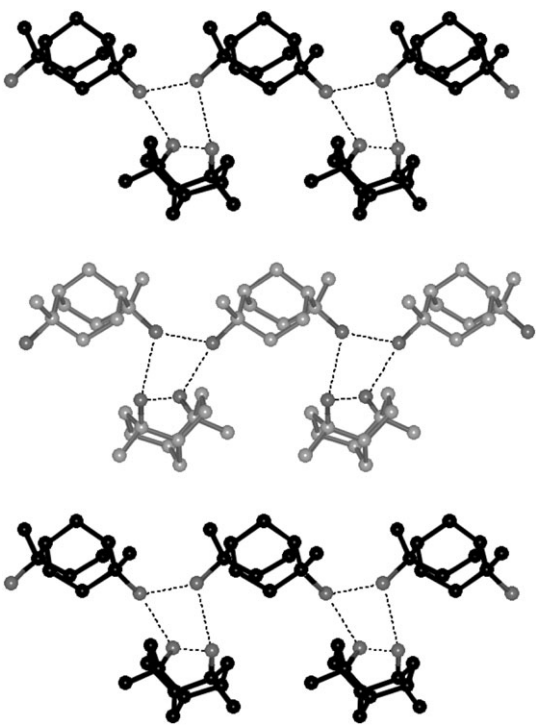


Fig. 3 Part of the crystal structure of compound **7**,[34] showing an edge-on view of the alternating homochiral layers of the diol molecules. Colour code: carbon atoms of opposite enantiomers black or grey. Hydrogen atoms are omitted for clarity, and the hydroxy group hydrogen bonds represented by dashed lines.

Table 1 Numerical values of the solution and refinement of the crystal structure of **8**

Formula	$C_9H_{16}O_2$
Formula mass	156.2
Space group	$P4_12_12$
a/Å	9.891(1)
c/Å	17.167(5)
V/Å^3	1679.5(5)
T/K	294(1)
Z	8
$D_{calc.}$/g cm^{-3}	1.24
Radiation, λ/Å	CuKα, 1.54184
μ/mm^{-1}	0.645
Scan mode	$\theta/2\theta$
$2\theta_{max}$/°	120
No. of intensity meas.	1246
Criterion for obs. ref.	$I/\sigma(I) > 2$
No. of indep. obs. ref.	967
No. of reflections (m),	967
Variables (n) in final ref.	100
$R = \Sigma^m\|\Delta F\|/\Sigma^m\|F_o\|$	0.040
$R_w = [\Sigma^m{}_w\|\Delta F\|^2/\Sigma^m{}_w\|F_o\|^2]^{1/2}$	0.056
$s = [\Sigma^m{}_w\|\Delta F\|^2/(m-n)]^{1/2}$	1.41
Crystal decay	None
Min., max. trans. coeff.	—
R for mult. meas.	0.018
Largest peak in final diff. map/e Å^{-3}	0.24

The crystal structure of diol **8** is illustrated in Fig. 4 as two representations each projected in the *ab* plane. Each oxygen atom takes part in two hydrogen bonds, one as donor and one as acceptor, and this results in a fully hydrogen bonded three-dimensional array.

Hydrogen bonds link molecules along *c* into helical chains which surround 4_1 axes at (1/2, 0) [and (0, 1/2)]. Eight molecules of **8** constitute one turn of the helix, with O···O distances of 2.765(2) and 2.803(2) Å alternating along the chain (Fig. 5). Diol molecules are oriented alternately up and down along the helix. The second hydroxy group of each molecule takes part in an identical helix. Fig. 4 shows this arrangement viewed along the helices, with a comparable side view presented in Fig. 5.

Implications of the crystallisation processes

In an earlier survey of the Cambridge Structural Database,[35] we found that the $(OH)_6$ motif is invariably centrosymmetric in crystal structures.[36] Molecules, such as **6**, with steric packing requirements favouring the use of this centrogenic supramolecular synthon will therefore crystallise by process A. If the molecules are handed, then a racemic crystal containing an intimate mix of the two enantiomers will result.

The $(O–H)_4$ cycle can accommodate either both enantiomers, or just one, depending on the specific case. In our experience, diols with steric packing requirements in favour of adopting this motif tend to yield racemic compounds *via* the crystallisation outcomes A or B.[34] The latter process was preferred in the case of diol **7**. Since only dispersion forces operate between the homochiral layers, we tried to encourage **7** to switch to conglomerate behaviour by using alternative crystallisation solvents. The intended target structure would

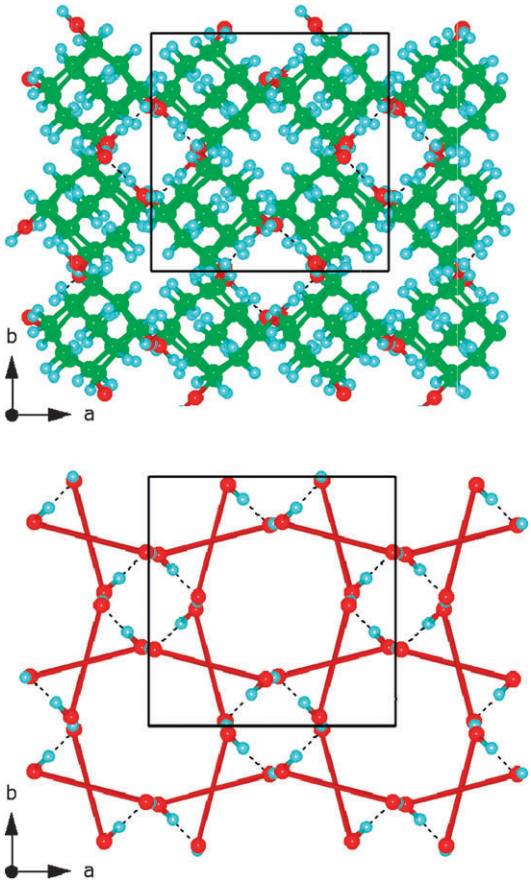


Fig. 4 The crystal structure of diol **8** projected onto the *ab* plane, and shown in both ball and stick and diagrammatic representations. In the latter, the diol molecules are reduced to solid rods with two spheres (O–H groups) at each end. The dashed lines indicate the hydroxy group hydrogen bonding.

have had only (+)-layers in one type of crystal, and only (−)-layers in the second type. However, this result has not yet been achieved despite considerable effort.

Supramolecular synthons resulting in helical arrangements of molecules are likely to result in crystals containing either considerable enantiomer ordering (outcome B) or complete self-resolution (outcome C). In the case of diol **8**, the cross-linked $(O–H)_8$ helical repeat is a chirogenic supramolecular synthon and leads to the formation of a conglomerate (process C).

The different crystallisation outcomes A, B and C determine the degree to which enantiomers become separated in the crystallisation process[37] and whether racemic or conglomerate material will be formed.[38] At our current level of understanding it is difficult to predict which of these processes will be followed for a entirely new compound. However, predictions based on a known example are possible in some cases : a striking example being development of the family of helical tubuland diols that form conglomerate crystals in space groups $P3_121$ and $P3_221$.[39] The lattice adopted by this family is related to that formed by **8** in that both form conglomerates with helical hydrogen bonded arrangements—the former surround threefold screw axes and the latter, fourfold. The threefold arrangement usually results in the formation of

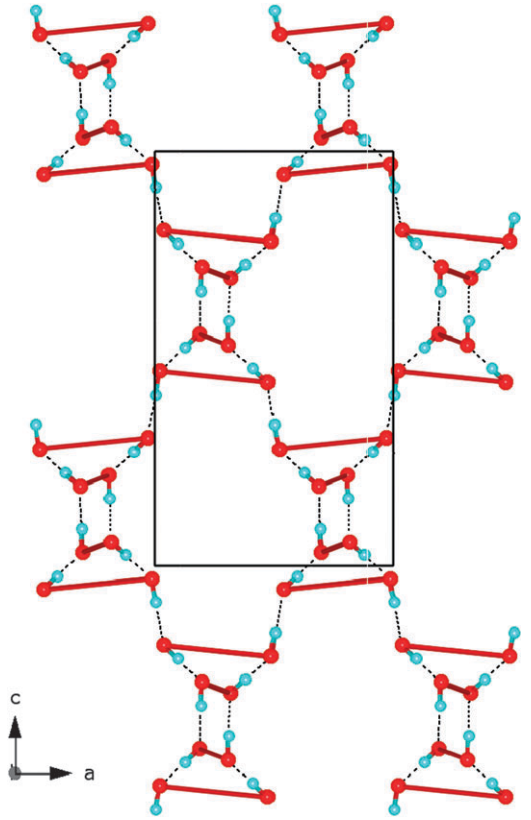


Fig. 5 Diagrammatic representation of the hydrogen bonded crystal structure of **8** projected onto the *ac* plane.

solvent-containing channels, but the tighter packing in **8** precludes this.

Our results show that there is little likelihood of using crystallisation methodology for direct resolution of the diols **6** and **7**, but every opportunity to do so for diol **8**.

Conclusions

Complete resolution of the (+)- and (−)-crystals present in a conglomerate may be effected by mechanical separation, the most famous example being Pasteur's resolution of sodium ammonium tartrate tetrahydrate. This case is atypical, however, in that these crystals exhibit enantiomorphic hemihedral facets and both types could be distinguished using a microscope. In cases where large crystals can be grown, the solution optical rotation of each may be recorded, before combining all the (+)-solutions and all the (−)-solutions.[28,40]

A method more suited for obtaining substantial amounts of material is seeding (resolution by entrainment). Highly preferential precipitation of the seed enantiomer can be achieved directly but, in cases where enantioselectivity is incomplete, then repetition of the process leads to the pure enantiomer. This methodology has been applied successfully on an industrial scale for compounds including L-α-methyldopa, chloroamphenicol, and L-glutamic acid.[40]

Hence, discovery of conglomerate crystal formation represents a formal method of enantiomer resolution for that particular compound. Since we have demonstrated that diol **8** crystallises as a conglomerate from a range of twelve test solvents

(see Experimental), our observation represents a new approach for obtaining chirally pure **8**, its oxidation product **3**, and many other bicyclo[3.3.1]nonane derivatives known to be readily available from these.[7–10] This approach should be simpler than the enzymatic methods, cheaper than the classical resolution procedure, and be more applicable to the larger quantities of material required in organic synthesis.

Experimental section

All crystallisations discussed here used achiral or racemic solvents, and were conducted by allowing slow concentration of the test solution to occur at the laboratory temperature and pressure.

endo,*endo*-Bicyclo[3.3.1]nonane-2,6-diol (8)

Compound **8** was prepared by reduction of a tetrahydrofuran solution of the diketone **3** using lithium aluminium hydride and following the procedure of Stetter and Schwartz. One recrystallisation from acetonitrile gave pure racemic **8** (88% yield) of mp 224–226 °C (lit.[24] 219 °C). ^{13}C NMR (d_6-DMSO) δ 71.6 (CH), 34.0 (CH), 32.7 (CH_2), 31.7 (CH_2), 23.0 (CH_2).

Crystal screening of diol 6

Racemic *endo*-4,*endo*-8-dimethylbicyclo[3.3.1]nonane-*endo*-2,*endo*-6-diol **6** was crystallised from eighteen solvents and the resulting inclusion compounds were shown (using X-ray diffractometry) to be isostructural in the cubic space group $Ia\bar{3}$.[30]

Crystal screening of diol 7

Racemic 2,6-dimethylbicyclo[3.3.1]nonane-*endo*-2,*endo*-6-diol **7**[33] was crystallised from acetone, acetonitrile, cyclohexane, diethyl ether, 1,2-dimethoxyethane, dimethyl formamide, d_6-dimethyl sulfoxide, ethanol, ethyl acetate, methanol, tetrahydrofuran, and trifluoromethylbenzene. X-Ray diffractometry of single crystals showed that all of these had the same racemic structure in *Pc* as reported originally.[34]

Crystal screening of diol 8

The crystallisation properties of racemic *endo*,*endo*-bicyclo-[3.3.1]nonane-2,6-diol **8**[24] were tested using a range of different solvent types. It was found to be insoluble in carbon tetrachloride, cyclohexane, mesitylene, and trifluoromethylbenzene. No crystals were obtained from acetic acid and dimethyl sulfoxide, and crystals of poor quality were obtained from acetone, benzene, bromobenzene, pyridine, *m*-xylene, and xylene mixture. X-Ray quality crystals were formed from acetonitrile, 2-butanol, chloroform, 1,2-dimethoxyethane, 1,4-dioxane, dimethyl formamide, ethanol, ethyl acetate, methanol, tetrahydrofuran, trimethyl acetonitrile, and water. A single crystal from each of these twelve latter experiments was examined by X-ray diffractometry and found to have the same resolved structure in space group $P4_12_12$ (or its enantiomorph). These alternatives could not be distinguished since only light atoms are present in structure **8**.

Determination of the crystal structure of 8

Racemic diol **8** was recrystallised from acetonitrile to give a conglomerate. An irregular chip (average radius of 0.1 mm) was used for diffractometry. Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer at 294 K. The positions of all atoms in the asymmetric unit were determined by direct phasing (SIR92)[41] with hydrogen atoms included in calculated positions with thermal motion equivalent to that for the bonded atom. All non-hydrogen atoms were refined anisotropically. Full details of refinement[42] can be found in the ESI‡.

Acknowledgements

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