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An extensive study of bromination of *cis*,*trans*,*trans*-1,5,9-cyclododecatriene: product structures and conformations

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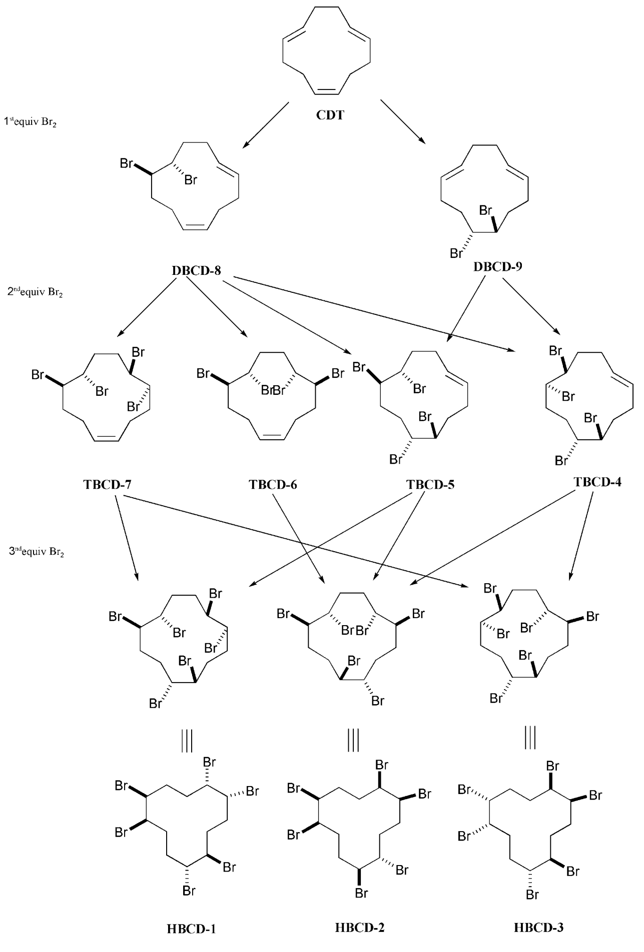
Bromine has been added to *cis*,*trans*,*trans*-1,5,9-cyclododecatriene under various reaction conditions. All expected direct addition products have been isolated, and their structures have been determined by microanalysis, NMR and X-ray crystallography. Advanced NMR techniques were used to determine solution conformations of several of the compounds, enabling comparison with the solid-state conformations obtained by crystallography.

Introduction

1,2,5,6,9,10-Hexabromocyclododecane (HBCD) is a commercially important bromine-containing cycloaliphatic flame retardant containing 74.7% bromine.[1] This important material is suitable for incorporation into various plastics, especially expanded polystyrene resins, and is also used in textiles, adhesives and coatings.[1–3] In general, HBCD is manufactured by the bromination of *cis*,*trans*,*trans*-1,5,9-cyclododecatriene (CDT). Simple *anti*-addition of Br_2 across each of the three double bonds can lead to a mixture of three diastereoisomers: **HBCD-1**, **HBCD-2** and **HBCD-3** (Scheme 1). In practice, the commercial material has a melting range that varies typically from 172–184 °C for a crude product to 201–205 °C for the highest-melting version following crystallisation. The melting range of HBCD is important for its use as a flame retardant for technical reasons associated with the blending process.[4,5] It is therefore highly desirable to develop methods for the selective synthesis of the high-melting isomer.

Although the commercial procedures in use do lead to a significant predominance of the high-melting isomer,[6] relatively few academic studies of the processes or products have been carried out. In the preliminary stages of this study we showed that the structure of the high-melting isomer (HBCD-γ, 207–209 °C) is identical to **HBCD-1** in Scheme 1.[7] Also HBCD-β and HBCD-α have been shown to be identical to **HBCD-2** and **HBCD-3**.[7] However, little is known about any of the intermediates in the process and even less about the factors that influence the course of the reaction. It was felt that an understanding of the structures and solution conformations of the intermediates and products might help in the design of more suitable processes for synthesis of specific products. The aim of this study was therefore to isolate and characterise all nine products shown in Scheme 1, to study their solution and solid phase conformations, and to gain insight into the processes interconnecting them. We also provide details of the preliminary work.



Scheme 1 Possible products resulting from sequential *anti*-addition of bromine to the double bonds of *cis*,*trans*,*trans*-1,5,9-cyclododecatriene (**CDT**). The prefixes refer to dibromocyclododecadienes (**DBCD**), tetrabromocyclododecenes (**TBCD**) and hexabromocyclododecanes (**HBCD**).

Results and discussion

At the outset of the work only the major component of the commercial product (*i.e.* **HBCD-1**) was easily available in pure form, following recrystallisation. In order to monitor reactions, HPLC was used and conditions were found (Spherisorb ODS2 or Zorbax ODS, acetonitrile–water 89 : 11, 1 $cm^3 min^{-1}$) which allowed separation of most of the compounds observed. Initially, it was possible to record only the peak areas of components

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relative to that of the **HBCD-1** peak. Subsequently, however, when other products had been isolated and characterised, it became possible to determine relative response factors for those components. The relative peak areas previously recorded could then be converted into actual proportions of products. Proportions determined in this way are recorded throughout this work unless otherwise indicated. A response factor equal to that of **HBCD-1** was assumed for calculation of the proportion of all unknown products.

Addition of three equivalents of Br$_2$ to CDT

The synthesis of HBCD by addition of three molar equivalents of Br$_2$ to CDT has been studied before.[8,9] The mechanism of addition of bromine to alkenes has been long established and involves *anti*-addition *via* a cyclic bromonium ion.[10–13] This leads to the three potential products **HBCD-1**, **HBCD-2**, and **HBCD-3**. Indeed, the commercial materials generally contain three products, termed α, β and γ. Furthermore, commercial processes for the synthesis of HBCD typically involve the use of a solvent mixture containing polar and non-polar components. It was felt that variations in the proportions of such solvents might have a significant influence on the conformations of the various reaction components, which might lead in consequence to differences in the product proportions. Therefore, in our initial work we prepared solutions of bromine in a variety of solvent mixtures, estimated the bromine concentration by iodometric titration, and added a small excess of such a solution to a solution of CDT in the same solvent. After reaction the solvent was removed entirely and an aliquot of the solid obtained was analysed by HPLC. The reaction was carried out using a large variety of solvents, temperatures and concentrations, the results of a few of which are given in Table 1.

As indicated in Table 1, over a wide range of conditions the amount of **HBCD-3** was never very great. No conditions could be found which gave this isomer in sufficient quantity to allow its isolation by a technique (like crystallisation) that could be used on a manufacturing scale. By contrast, under appropriate conditions either **HBCD-1** or **HBCD-2** could be produced in a yield of over 80%, thereby confirming the importance of the solvent composition on the outcome of the reaction. In the case of **HBCD-1**, it was possible to isolate the pure product in 85% yield by simple washing of the best crude product with ethanol. Pure **HBCD-2** could be obtained by repeated recrystallisation of the appropriate crude product, although an alternative method was achieved by bromination of a TBCD isomer (see later). Meanwhile, in order to provide a sample of pure **HBCD-3**, the thermal rearrangement of **HBCD-1** was investigated.

Synthesis of HBCD-3 by thermal rearrangement of HBCD-1

In previous work it has been reported that at 190 °C **HBCD-1** rearranges to yield a mixture of **HBCD-3** (78%), **HBCD-2** (13%) and **HBCD-1** (9%).[14] It is evident that **HBCD-3** must be the thermodynamically more stable isomer. It is believed that the intermediate transition state involves a cyclic bromonium ion.[15–18]

A reaction was carried out under conditions similar to those reported in the literature, with similar results. After washing and treatment with activated charcoal pure **HBCD-3** was obtained in 74% yield. With conditions established for preparation of pure samples of any of the three HBCD isomers, attention was turned to the production of tetrabromocyclododecenes (TBCD).

Addition of two equivalents of Br$_2$ to CDT

The synthesis of TBCD isomers by addition of two molar equivalents of Br$_2$ to CDT was attempted under conditions similar to those used in the synthesis of HBCD. The results of selected experiments are shown in Table 2.

As can be seen from Table 2, only two of the four isomeric TBCDs are formed in significant quantities under any of the conditions tried. The proportions of the two isomers, later shown to be **TBCD-5** and **TBCD-7**, could be varied greatly merely by changing the amount of ethanol in a dichloromethane–ethanol solvent mixture. With very little ethanol and at low temperature the reaction produced almost entirely **TBCD-5**,

Table 1 Use of various solvents for reaction of **CDT** with three equivalents of bromine[a]

	Product proportions (%)				
Solvent (ratio)	**HBCD-1**	**HBCD-2**	**HBCD-3**	**TBCD-5**	Unknown[b]
EtOH–CH$_2$Cl$_2$ (60 : 40)[c]	91	8	0	1	0
EtOH–CH$_2$Cl$_2$ (5 : 95)	44	45	11	0	0
EtOH–CH$_2$Cl$_2$ (1 : 99)	39	50	11	0	0
EtOH–CHCl$_3$ (1 : 99)	33	56	11	0	0
MeCN–CH$_2$Cl$_2$ (1 : 99)	14	80	13	0	0
n-PrOH–CH$_2$Cl$_2$ (1 : 99)	26	61	11	0	2

[a] The bromine solution added was at 20 °C and the alkene solution at 2 °C; both the Br$_2$ and **CDT** solutions were *ca.* 0.5 M. [b] A response factor equal to that of **HBCD-1** was assumed for calculation of the proportion of this unknown. [c] Triene solution at −78 °C.

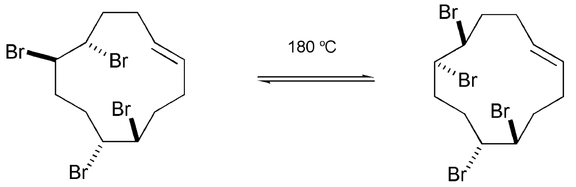
Table 2 Use of various solvents and temperatures for reactions of **CDT** with two equivalents of bromine[a]

		Product proportions (%)			
Temp./°C	Solvent (ratio)	**TBCD-5**	**TBCD-7**	**DBCD-8**	Others[b]
−78	EtOH–CH$_2$Cl$_2$ (1 : 99)	93	6	1	0
−78	EtOH–CH$_2$Cl$_2$ (3 : 97)	82	17	1	0
−78	EtOH–CH$_2$Cl$_2$ (5 : 95)	67	26	7	0
18	EtOH–CH$_2$Cl$_2$ (80 : 20)	0	85	7	8
0	EtOH–CH$_2$Cl$_2$ (80 : 20)	4	73	11	12
−78	*n*-PrOH–CH$_2$Cl$_2$ (1 : 99)	90	7	0	3
−78	*n*-PrOH–CH$_2$Cl$_2$ (3 : 97)	83	17	0	0
−78	*n*-PrOH–CH$_2$Cl$_2$ (5 : 95)	74	20	1	5

[a] The concentration of both solutions was *ca.* 0.5 M. During the addition the bromine solution was at 18–19 °C. [b] Assuming a response factor equivalent to that of **HBCD-1**.

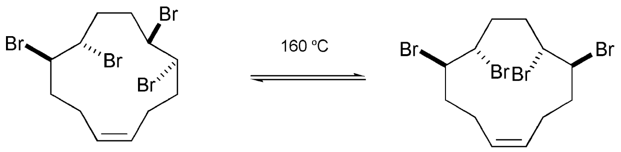
and this product could be isolated pure in 80% yield following washing with ethanol and recrystallisation. In 80% ethanol–CH_2Cl_2 at ambient temperature the major component was **TBCD-7** (85%). A large scale reaction carried out at low temperature gave a crude product which was washed with ethanol and recrystallised to give pure **TBCD-7** in 48% isolated yield.

If the proposed mechanism of isomerisation of the HBCD isomers at high temperature[14–18] is correct, it should be possible to isomerise **TBCD-5** into **TBCD-4** (eqn. (1)) and **TBCD-7** into **TBCD-6** (eqn. (2)) *via* the corresponding bromonium ions. Attention was therefore turned to these possibilities.



TBCD-5 **TBCD-4**

Thermal isomerisation of **TBCD-5** (1)



TBCD-7 **TBCD-6**

Thermal isomerisation of **TBCD-7** (2)

Synthesis of TBCD-4 by thermal isomerisation of TBCD-5

Thermal rearrangement of **TBCD-5** was investigated by heating this compound at elevated temperatures similar to those used for the thermal rearrangement of **HBCD-1**. The optimum temperature appeared to be about 180 °C, and a time study was therefore conducted at this temperature. Table 3 shows the results.

Several features emerge from the results in Table 3. A period of 1–1.5 h at 180 °C is sufficient to establish the equilibrium mixture of **TBCD-4** and **TBCD-5**, and **TBCD-4** (*ca.* 76%) predominates over **TBCD-5** (*ca.* 24%) by a factor of about 3 in that mixture. With prolonged heating some kind of autocatalysed decomposition seems to take place, since a rapid weight loss ensues and a range of additional, mostly unidentified peaks appears in the HPLC trace.

A preparative-scale reaction was carried out for 1 h at 180 °C and a mixture rich in **TBCD-4** was obtained, as described above. The product was washed and repeatedly recrystallised, because the two isomers are not easily separated by a single crystallisation. Eventually, pure **TBCD-4** was obtained in an isolated yield of 21%.

Table 3 Experimental results for thermal rearrangement of **TBCD-5** at 180 °C for various reaction times

		Product proportions (%)		
Time/min	Weight loss (%)	**TBCD-4**	**TBCD-5**	Unknown[a]
45	0.8	69	31	0
60	1.2	73	27	0
75	4.4	77	23	0
90	6.5	76	24	0
105	47.7	71	21	8
120	54.6	Many products obtained		

[a] A response factor equal to that of **HBCD-1** was assumed for this unknown.

Synthesis of TBCD-6 by thermal isomerisation of TBCD-7

The thermal rearrangement of **TBCD-7** was attempted at various temperatures and the optimum appeared to be about 160 °C. A time study was conducted at this temperature and the results are given in Table 4.

The results in Table 4 reveal that the equilibrium mixture contains almost equal amounts of **TBCD-6** and **TBCD-7**, and is established after about 40 minutes at 160 °C. Prolonged heating beyond about 100 minutes causes autocatalysed decomposition, resulting in substantial weight loss and the production of a more diverse product mixture.

Following a larger scale reaction carried out under the optimum conditions the crude product was subjected to repeated washing, partial extraction and recrystallisation processes until a sample of pure **TBCD-6** was obtained in 15% isolated yield.

At this point pure samples of all four TBCD isomers were available in reasonable quantity. It was therefore possible to undertake studies of the addition of bromine to these compounds. Such studies would help in confirmation of the structures of the TBCD isomers because of the pattern of HBCD isomers produced (Scheme 1) and might lead to more efficient means of producing specific HBCD isomers.

Addition of one equivalent of Br_2 to TBCD-4

Addition of one equivalent of bromine to **TBCD-4** gave a mixture of **HBCD-3** and **HBCD-2** in a ratio of *ca.* 50 : 50. Various solvent mixtures, such as ethanol–dichloromethane (60 : 40 to 1 : 99) and dichloromethane–acetonitrile (90 : 10 to 10 : 90), gave very little change in the proportion of the isomers. Therefore, further bromination of **TBCD-4** is not a useful procedure for selective formation of any particular HBCD isomer.

Addition of one equivalent of Br_2 to TBCD-5

Addition of one equivalent of bromine to **TBCD-5** produced a mixture of **HBCD-2** and **HBCD-1** under a variety of conditions and in various solvent mixtures. Table 5 shows a selection of the results obtained.

The results in Table 5 reveal that the proportions of the two products depend greatly on the nature of the solvent. In the presence of a significant amount of a polar solvent the major component is **HBCD-1**. Solubility problems sometimes prevented study of conditions involving a very ethanol-rich solvent, but optimum production of **HBCD-1** appeared to occur in a solvent mixture comprising *ca.* 40% ethanol and 60% of a

Table 4 Experimental results for thermal rearrangement of **TBCD-7** at 160 °C for various reaction times

		Product proportions (%)		
Time/min	Weight loss (%)	**TBCD-6**	**TBCD-7**	Unknowns[a]
10	0	23	63	14
15	0.7	36	64	0
20	0	38	56	6
40	0.1	47	49	5
45	1.4	45	44	8
60	0.9	49	47	4
75	4.0	48	48	4
90	0.8	49	48	3
105	4.6	43	40	17
120	39.3	41	37	22

[a] A response factor equal to that of **HBCD-1** was assumed for the unknowns.

Table 5 Reaction of **TBCD-5** with one equivalent of bromine

		Product proportions (%)		
Temp./°C[a]	Solvent (ratio)	**HBCD-1**	**HBCD-2**	Others[b]
2	EtOH–CH_2Cl_2 (60 : 40)	86	14	0
2	EtOH–CH_2Cl_2 (40 : 60)	89	11	0
2	EtOH–CH_2Cl_2 (10 : 90)	70	30	0
2	EtOH–CH_2Cl_2 (5 : 95)	45	55	0
2	EtOH–CH_2Cl_2 (1 : 99)	23	77	0
2	*n*-PrOH–CH_2Cl_2 (60 : 40)	78	22	0
2	*n*-PrOH–CH_2Cl_2 (40 : 60)	76	23	0
2	*n*-PrOH–CH_2Cl_2 (10 : 90)	53	46	0
2	*n*-PrOH–CH_2Cl_2 (5 : 95)	38	62	0
2	*n*-PrOH–CH_2Cl_2 (3 : 97)	25	75	0
2	*n*-PrOH–CH_2Cl_2 (1 : 99)	10	90	0
40	EtOH–$CHCl_3$ (90 : 10)	68	25	7
40	EtOH–$CHCl_3$ (20 : 80)	65	35	0
40	EtOH–$CHCl_3$ (5 : 95)	28	69	3
40	EtOH–$CHCl_3$ (1 : 99)	11	80	9
35	EtOH–dioxane (60 : 40)	82	18	0
35	EtOH–dioxane (40 : 60)	87	13	0
35	EtOH–dioxane (10 : 90)	61	39	0
35	EtOH–1,2-dichloroethane (30 : 70)	77	23	0
35	EtOH–1,2-dichlorobenzene (70 : 30)	75	25	0
50	EtOH–cyclopentane (60 : 40)	85	15	0
35	EtOH–chlorobenzene (30 : 70)	73	27	0
2	MeCN–CH_2Cl_2 (5 : 95)	6	91	3
2	MeCN–CH_2Cl_2 (1 : 99)	3	94	3

[a] The bromine solution added was at 20 °C in all cases; the temperature refers to the reaction vessel. [b] Assuming a response factor equivalent to that of **HBCD-1**.

non-polar solvent. Under such conditions the proportion of **HBCD-1** produced could be as high as 89%.

When the solvent contained very little of the polar component the major product was **HBCD-2**. The proportion of this component reached 94% in MeCN–CH_2Cl_2 = 1 : 99. The small amount of polar solvent is useful, because without it the product mixture becomes messy and more deeply coloured. Since a low concentration of polar solvent favours the production of **TBCD-5** from CDT and also favours conversion of **TBCD-5** into **HBCD-2**, there is little advantage in carrying out the stepwise reaction sequence if **HBCD-2** is the desired product.

In principle, use of conditions for reaction of CDT with bromine that favour **TBCD-5** production, then replacement of the solvent by one favouring **HBCD-1** production for addition of the final equivalent of bromine, could be used for selective production of **HBCD-1**. However, the yield of **HBCD-1** obtained in such a reaction sequence was not significantly better than that obtained using the optimum solvent for the single step process from CDT and three equivalents of bromine.

Addition of one equivalent of Br_2 to TBCD-6

Addition of one equivalent of bromine to **TBCD-6** should produce **HBCD-2** only (Scheme 1). Indeed, a reaction carried out in 1-propanol–dichloromethane (60 : 40) gave almost 100% of **HBCD-2**. Unfortunately, the relative difficulty of obtaining **TBCD-6** means that this route to **HBCD-2** is not as attractive as the less selective but more direct synthesis of this compound from CDT and three equivalents of bromine.

Addition of one equivalent of Br_2 to TBCD-7

Addition of one equivalent of bromine to **TBCD-7** produced a mixture of **HBCD-1** and **HBCD-3**. The reaction was conducted in a variety of solvent mixtures, the results of a selection of which are recorded in Table 6.

The results in Table 6 demonstrate that the addition of bromine to **TBCD-7** gives mainly **HBCD-1** under a whole range of conditions. Although the reaction can be used for selective synthesis of **HBCD-1**, it cannot be used for selective synthesis of **HBCD-3**. Since the conditions for selective synthesis of **TBCD-7** are also appropriate for its conversion into **HBCD-1**, there is little advantage in carrying out the reaction stepwise *via* **TBCD-7**.

At this point it was appropriate to investigate the production and reaction of the dibromocyclododecadiene isomers, **DBCD-8** and **DBCD-9**. Therefore, the addition of one equivalent of bromine to CDT was studied.

Addition of one equivalent of Br_2 to CDT

One equivalent of bromine was added to CDT under various conditions involving variation of temperature and solvent, but the reaction led to a single DBCD isomer, **DBCD-8**, under all conditions tried. In ethanol–dichloromethane (60 : 40) **DBCD-8** was obtained in 85–91% yield with minimum production of TBCD isomers or residual CDT. Pure **DBCD-8** could be isolated in 74% yield following washing and recrystallisation.

Clearly, the reaction of bromine with CDT could not be used to provide a sample of **DBCD-9**. Also, since isomerisation processes such as those used for interconverting **TBCD-5** and **TBCD-4** involve a common bromonium ion intermediate, **DBCD-9** cannot be produced by isomerisation of **DBCD-8**. Therefore, an alternative approach was necessary. It was hoped that partial debromination of **TBCD-5** might produce a mixture containing sufficient **DBCD-9** to allow its isolation. Reaction of **TBCD-5** with zinc was therefore attempted.

Debromination of TBCD-5 for synthesis of DBCD-9

Previous studies have shown that the debromination of vicinal dibromides by metals such as magnesium and zinc involves exclusively *trans* elimination of bromine.[19–26] Therefore, a sample of **TBCD-5** was dissolved in hot ethanol and added to one equivalent of zinc powder. The mixture was allowed to cool and stirred for two days. The product was shown by HPLC to be a mixture of several components but did contain the product later shown to be **DBCD-9**. The mixture was extracted into pentane and evaporated to give an oil, which was dissolved in ethanol and allowed to crystallise to give pure **DBCD-9** in about 6%

Table 6 Reaction of **TBCD-7** with one equivalent of bromine

Temp. (°C)[a]	Solvent (ratio)	Product proportions (%)			
		HBCD-1	**HBCD-3**	**TBCD-7**	Others[b]
2	EtOH–CH_2Cl_2 (70 : 30)	83	17	0	0
2	EtOH–CH_2Cl_2 (60 : 40)	90	10	0	0
2	EtOH–CH_2Cl_2 (40 : 60)	92	8	0	0
2	EtOH–CH_2Cl_2 (30 : 70)	88	12	0	0
2	*n*-PrOH–CH_2Cl_2 (70 : 30)	85	13	2	0
2	*n*-PrOH–CH_2Cl_2 (30 : 70)	84	16	0	0
2	$CHCl_3$–CH_2Cl_2 (40 : 60)	64	19	9	8
2	$CHCl_3$–CH_2Cl_2 (20 : 80)	41	43	8	8
2	MeCN–CH_2Cl_2 (90 : 10)	77	23	0	0
40	EtOH–$CHCl_3$ (70 : 30)	87	13	0	0
40	EtOH–$CHCl_3$ (30 : 70)	70	13	11	0
40	EtOH–cyclopentane (60 : 40)	82	18	0	0
40	EtOH–cyclopentane (30 : 70)	87	13	0	0
35	EtOH–dioxane (90 : 10)	80	20	0	0
35	EtOH–dioxane (10 : 90)	78	22	0	0
35	EtOH–1,2-dichlorobenzene (90 : 10)	93	7	0	0
35	EtOH–1,2-dichlorobenzene (10 : 90)	73	27	0	0
20	EtOH–MeCN (70 : 30)	78	16	0	0
20	EtOH–MeCN (30 : 70)	78	16	0	0
35	EtOH–1,2-dichloroethane (70 : 30)	79	21	0	0
20	EtOH–chlorobenzene (70 : 30)	69	31	0	0
20	EtOH–chlorobenzene (30 : 70)	83	17	0	0
20	EtOH–$CHCl_3$ (70 : 30)	73	27	0	0

[a] The bromine solution added was at 20 °C in all cases; the temperature refers to the reaction vessel. [b] Assuming a response factor equivalent to that of **HBCD-1**.

yield. Although the recovery was poor, this process provided enough of the product for studies of its structure and reactions. Attention was then turned to the reactions of the DBCD isomers with one equivalent of bromine.

Addition of one equivalent of Br_2 to DBCD-8

One equivalent of bromine was added to **DBCD-8** under various conditions. In principle, it should be possible to produce all four isomers of TBCD by this approach (see Scheme 1). However, the reaction led to **TBCD-5** and **TBCD-7** with little evidence for **TBCD-4** or **TBCD-6** under all conditions tried (Table 7).

The results in Table 7 indicate that it is possible to produce **TBCD-5** cleanly in a solvent comprising dichloromethane–chloroform (20 : 80). By use of CH_2Cl_2–ethanol mixtures it is possible to increase the proportion of **TBCD-7** substantially, and in ethanol–CH_2Cl_2 (20 : 80) at −78 °C for 1 h then overnight at room temperature it is formed in 76% yield, thus explaining the high yield of **TBCD-7** from CDT and two equivalents of bromine under such conditions (Table 2).

Addition of one equivalent of Br_2 to DBCD-9

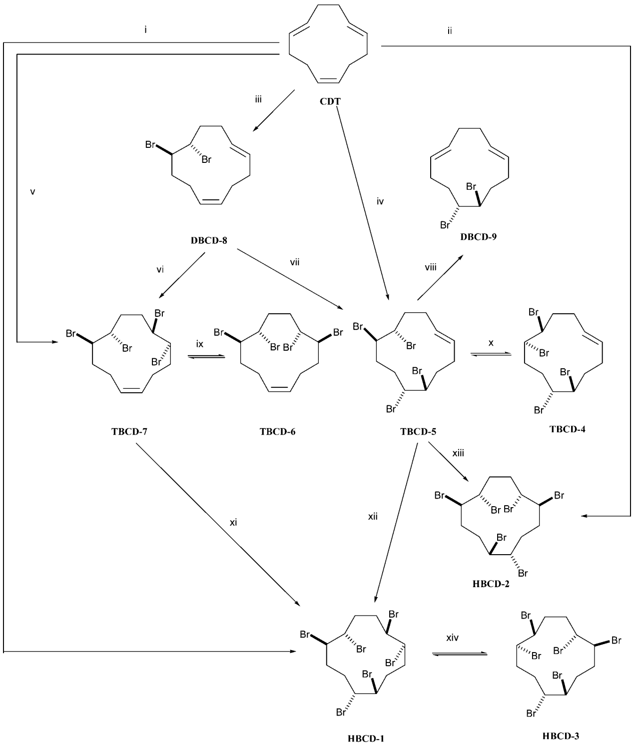
Addition of one equivalent of bromine to **DBCD-9** under a variety of conditions gave rise to both **TBCD-4** and **TBCD-5**, and also to several by-products. Therefore, further bromination of **DBCD-9** does not appear to be a useful procedure for selective formation of any particular TBCD isomer, especially since **DBCD-9** is itself difficult to obtain.

Table 7 Reaction of **DBCD-8** with one equivalent of bromine in different solvents at various temperatures

Temp./°C[a]	Solvent (ratio)	Product proportions (%)			
Temp./°C[a]	Solvent (ratio)	**TBCD-5**	**TBCD-7**	**DBCD-8**	Others[b]
−78	EtOH–CH_2Cl_2 (90 : 10)	25	63	12	0
0	EtOH–CH_2Cl_2 (90 : 10)	33	61	6	0
19	EtOH–CH_2Cl_2 (90 : 10)	37	49	14	0
−78	EtOH–CH_2Cl_2 (80 : 20)	53	45	2	0
0	EtOH–CH_2Cl_2 (80 : 20)	45	51	4	0
19	EtOH–CH_2Cl_2 (80 : 20)	36	62	2	0
−78	EtOH–CH_2Cl_2 (60 : 40)	19	74	7	0
0	EtOH–CH_2Cl_2 (60 : 40)	32	66	2	0
19	EtOH–CH_2Cl_2 (60 : 40)	35	60	5	0
−78	EtOH–CH_2Cl_2 (20 : 80)	18	76	6	0
0	EtOH–CH_2Cl_2 (20 : 80)	21	73	6	0
19	EtOH–CH_2Cl_2 (20 : 80)	31	59	10	0
−78	EtOH–CH_2Cl_2 (10 : 90)	41	58	1	0
0	EtOH–CH_2Cl_2 (10 : 90)	38	59	3	0
19	EtOH–CH_2Cl_2 (10 : 90)	50	45	5	0
−78	EtOH–cyclopentane (90 : 10)	68	30	2	0
−78	EtOH–cyclopentane (40 : 60)	66	27	7	0
−78	$CHCl_3$–CH_2Cl_2 (80 : 20)	90	0	0	10
−78	$CHCl_3$–CH_2Cl_2 (60 : 40)	64	0	0	26

[a] The bromine solution added was at 20 °C in all cases; the temperature refers to the reaction vessel. [b] **HBCD-1** and **HBCD-2**.

At this point the study of the syntheses and interconversions of all nine compounds listed in Scheme 1 was complete. Scheme 2 summarises the approaches developed here for the syntheses of these compounds. Detailed procedures are given in the experimental section for the favoured route to each compound.



Scheme 2 Procedures for preparation of bromination products of CDT. *Reagents and conditions*: i) $3Br_2$, $EtOH–CH_2Cl_2$ (60 : 40), −78 °C; ii) $3Br_2$, $MeCN–CH_2Cl_2$ (1 : 99), 2 °C; iii) Br_2, $EtOH–CH_2Cl_2$ (60 : 40), −78 °C; iv) $2Br_2$, $EtOH–CH_2Cl_2$ (1 : 99), −78 °C; v) $2Br_2$, $EtOH–CH_2Cl_2$ (80 : 20), 18 °C; vi) Br_2, $EtOH–CH_2Cl_2$ (80 : 20), 20 °C; vii) Br_2, $MeCN–CH_2Cl_2$ (1 : 99), 2 °C; viii) Zn, EtOH, 90° → 20 °C; ix) 160 °C; x) 180 °C; xi) Br_2, $EtOH–CH_2Cl_2$ (40 : 60), 2 °C; xii) Br_2, $EtOH–CH_2Cl_2$ (40 : 60), 2 °C; xiii) Br_2, $MeCN–CH_2Cl_2$ (1 : 99), 2 °C; xiv) 190 °C.

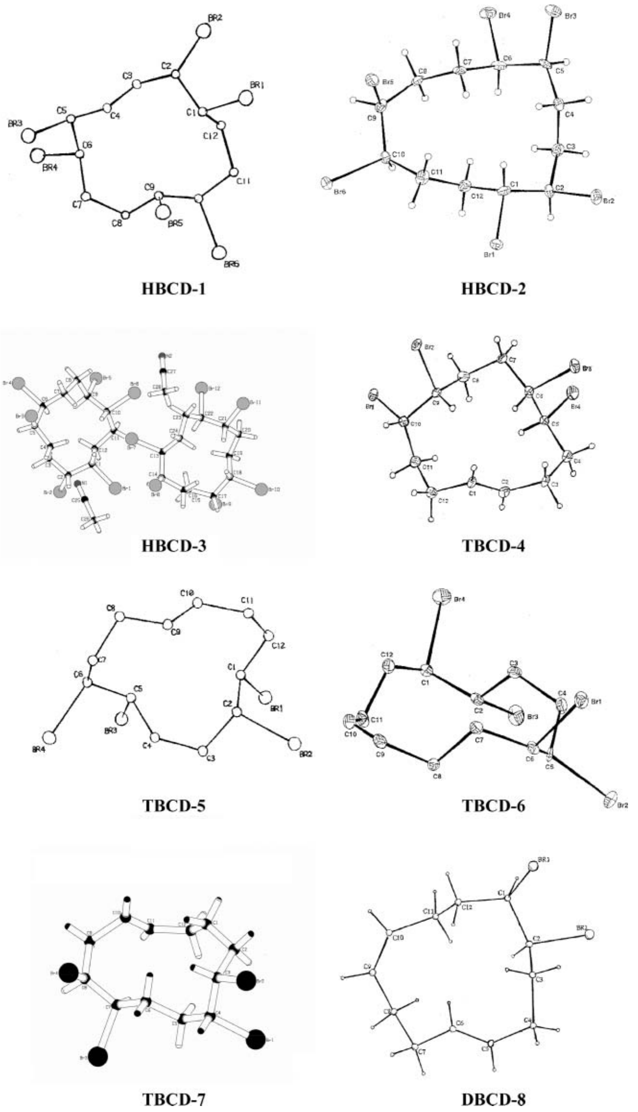
Thus far the identity of each product has been recorded as if known, but many of the products have never previously been characterised. Characterisation was carried out by X-ray crystallography, NMR spectroscopy and by correlation of interconnecting structures as indicated in Tables 1–7, in addition to microanalysis and mass spectrometry.

X-Ray crystallography of products

Crystals of all compounds produced in this study were subjected to X-ray crystallographic analysis, but it proved impossible to obtain a structure from **DBCD-9**. The results for the others confirmed the gross structures of the compounds and also revealed their solid-state conformations. Fig. 1 shows drawings of the structures determined, and Table 8 gives the crystal data and structure refinement information. The CCDC reference numbers are as follows: **HBCD-1**: 261488; **HBCD-2**: 217888; **HBCD-3**: 261191; **TBCD-4**: 217896; **TBCD-5**: 261487; **TBCD-6**: 217898; **TBCD-7**: 217897; **DBCD-8**: 260841. See http://www.rsc.org/suppdata/ob/b4/b417156j/ for crystallographic data in CIF or other electronic format.

NMR spectroscopy

NMR spectroscopy was used with the intention not only of providing confirmation of the gross structures of the compounds described here, but also of providing insight into their solution conformations. However, relatively little information about the NMR properties of such compounds is available in the literature.[7,27] Therefore, the NMR properties of the various compounds were investigated using a combination of simple ^1H and ^{13}C measurements, solvent shifts, NOE and variable temperature measurements, and 2D spectra (H–H COSY and C–H COSY).



HBCD-1

HBCD-2

HBCD-3

TBCD-4

TBCD-5

TBCD-6

TBCD-7

DBCD-8

Fig. 1 X-Ray structures of the 8 compounds determined. Note that for **HBCD-3** there were two different molecules in the unit cell, along with two molecules of acetonitrile.

(a) HBCD-1. The structure of **HBCD-1** was verified by measurement of its NMR spectra at various temperatures and with the help of solvent-induced shifts. **HBCD-1** has a C_2 axis of symmetry. Therefore, the ^1H NMR spectrum should show nine signals. By addition of d_8-toluene to a $CDCl_3$ solution of **HBCD-1**, a best mixture was found ($CDCl_3$–d_8-toluene 45 : 55) which showed all nine signals (labelled a–i) individually. There were also signals due to other conformations, which were largely eliminated at −50 °C (Fig. 2). Further information was derived from the C–H COSY spectrum (Fig. 3). The ^{13}C and ^1H shifts of the nuclei bonded to one another showed up clearly in the contour plot. For example, the protons with shifts at 1.85 ppm (H_d) and 1.36 ppm (H_g) are bonded to the C atom at 35.4 ppm, and all other protons could be similarly assigned to specific carbon atoms. The H–H COSY spectrum (Fig. 4 and Table 9) allowed all proton connectivities to be established. For example, the proton H_i was found as a coupling partner of the proton H_a. Therefore, it became possible to deduce the sequence of atoms

Table 8 Crystal data and structure refinement information for the eight compounds shown in Fig. 1

	HBCD-1	**HBCD-2**	**HBCD-3**	**TBCD-4**	**TBCD-5**	**TBCD-6**	**TBCD-7**	**DBCD-8**
Empirical formula	$C_{12}H_{18}Br_6$	$C_{12}H_{18}Br_6$	$C_{12}H_{18}Br_6 \cdot CH_3CN$	$C_{12}H_{18}Br_4$	$C_{12}H_{18}Br_4$	$C_{12}H_{18}Br_4$	$C_{12}H_{18}Br_4$	$C_{12}H_{18}Br_2$
Formula weight	641.73	641.73	682.78	481.89	481.89	481.89	481.89	322.08
Temp./K	219	150	120	120	219	140	120	293
Crystal system	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Space group	*Pbca*	$P2_1/n$	$P\bar{1}$	*Cc*	*Pbca*	$P2_1/n$	$P2_1/a$	$P2_1/a$
a/Å	11.670(2)	15.676(4)	10.2529(7)	6.5740(2)	17.163(2)	11.4559(14)	9.9321(10)	7.733(3)
b/Å	28.998(6)	6.4009(4)	13.9866(17)	31.5300(6)	12.517(1)	7.4771(13)	13.1468(5)	15.842(2)
c/Å	10.483(3)	18.702(3)	14.4984(13)	7.6670(4)	14.250(1)	17.7504(8)	11.9463(5)	10.620(3)
α/°	90	90	75.851(7)	90	90	90	90	90
β/°	90	112.578(8)	79.144(7)	108.030(6)	90	91.342(7)	109.373(8)	102.83(2)
γ/°	90	90	83.639(8)	90	90	90	90	90
Volume/Å^3	3547.52(6)	1732.744(6)	1975.4(3)	1511.16(10)	3061.32(7)	1520.0(3)	1471.6(2)	1268.53(5)
Z	8	4	4	4	8	4	4	4
Density (calc.) Mg m^{-3})	1.207	2.46	2.296	2.118	2.09	2.106	2.175	1.68
μ/mm^{-1}	13.301	13.886	12.189	10.627	10.395	10.565	10.913	6.294
Independent reflections	1740	2684	9016	1531	3112	2240	2243	2475
R(int)		0.0862	0.0828	0.0579		0.0717	0.0529	0.050
Final R indices ($R1 = F^2 > 2\sigma F^2$; $wR2$ = All data)	$R1 = 0.054$ $wR2 = 0.072$	$R1 = 0.0451$ $wR2 = 0.1166$	$R1 = 0.0484$ $wR2 = 0.1201$	$R1 = 0.0396$ $wR2 = 0.1050$	$R1 = 0.068$ $wR2 = 0.087$	$R1 = 0.0442$ $wR2 = 0.1089$	$R1 = 0.0496$ $wR2 = 0.1349$	$R1 = 0.079$ $wR2 = 0.076$

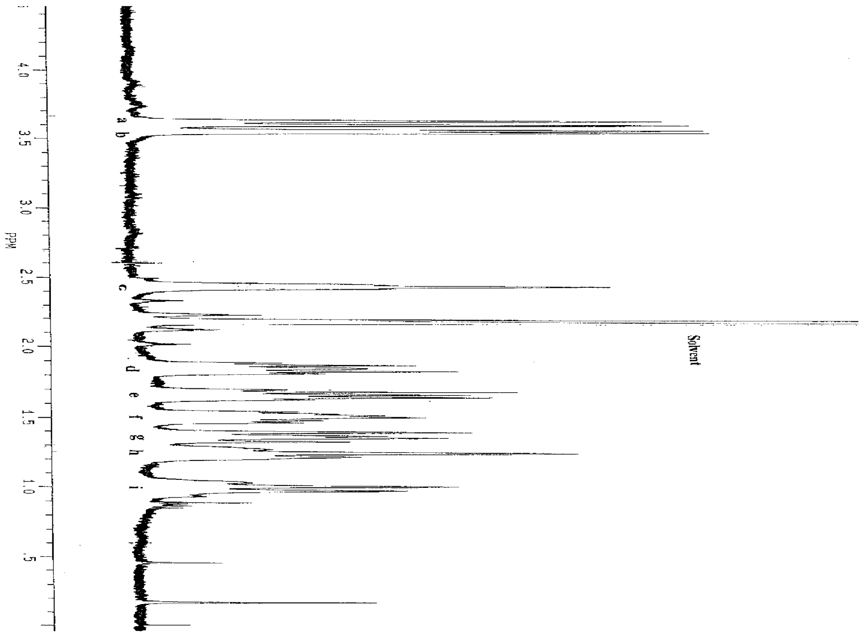


Fig. 2 400 MHz ^{1}H NMR spectrum of **HBCD-1** in $CDCl_3$–d_8-toluene (45 : 55) at −50 °C.

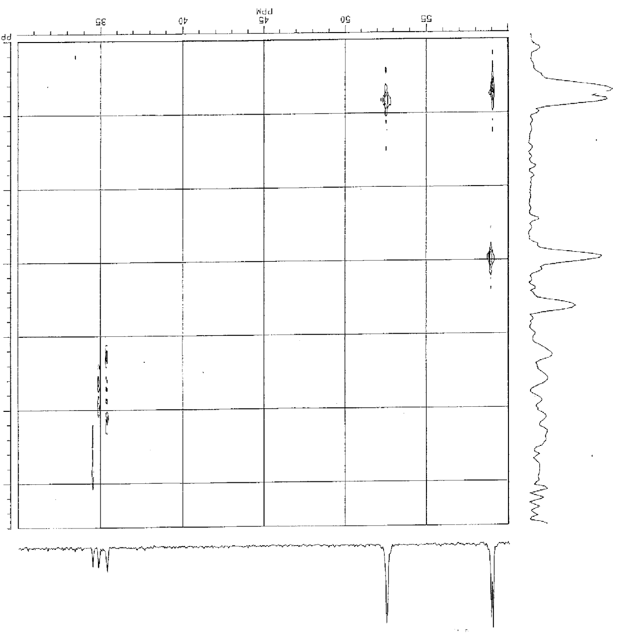


Fig. 3 C–H COSY spectrum of **HBCD-1** in $CDCl_3$–d_8-toluene (45 : 55) at −50 °C.

around the ring. Proton H_c was identified as that associated with the CHBr groups of the *trans*-dibromo unit by the lack of any coupling with either of the other CHBr protons, H_a and H_b. This enabled the construction of a fully assigned structure (Fig. 5).

By reference to the normal spectrum, H_a and H_i could be identified as having the common coupling constant $^3J_{ai}$ = 12 Hz. Similarly H_i and H_h, $H_{i'}$ and $H_{h'}$ could be seen to have $^2J_{ih}$ = $^3J_{ih'}$ = 12 Hz. Protons H_b and H_g couple to H_d with a vicinal coupling constant $^3J_{bd}$ = 7 Hz and a geminal coupling

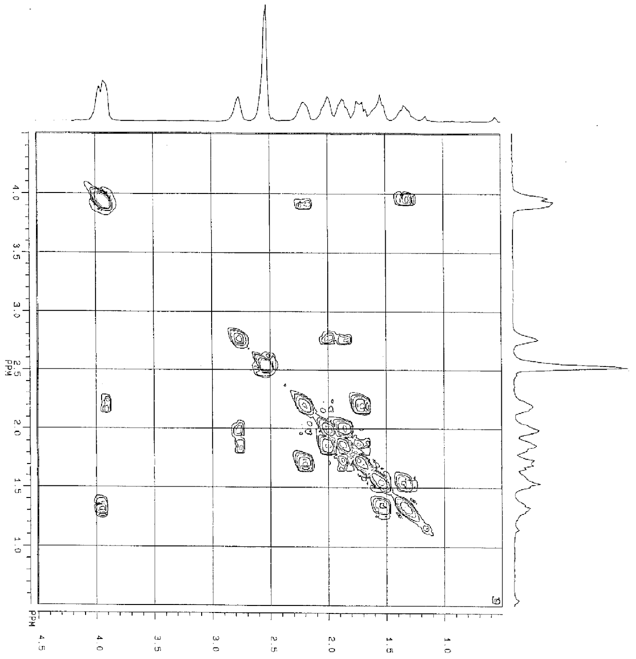


Fig. 4 H–H COSY spectrum of **HBCD-1** in $CDCl_3$–d_8-toluene (45 : 55) at −50 °C.

$^2J_{dg} = 16$ Hz. Proton H_g shows a further coupling to H_f, with vicinal coupling $^3J_{gf} = 11$ Hz. The following additional coupling constants can also be identified: $^3J_{cf} = 6$ Hz, $^3J_{ce} = 6$ Hz, $^3J_{de} = 7$ Hz and $^2J_{ef} = 15$ Hz (Table 9). From the vicinal HH coupling constants the dihedral angles between vicinal hydrogens could be assessed.

The NOE difference spectra (Table 10) provided yet more detailed information regarding the structure. Particularly significant were the long-range NOE effects seen between protons H_b, H_c, H_g and H_i, which indicated the spatial proximity of these protons. When all of the NOEs, connectivities and H–H coupling constants were considered together, a space-filling model could be constructed which satisfied all of the data. The model showed, for example, that this conformation of **HBCD-1** places H_a and H_i at a dihedral angle of *ca.* 180° whilst H_a and H_h have a dihedral angle of *ca.* 90°, so that no coupling is detected. The similarity of the coupling constants J_{ce} and J_{cf} likewise indicates that the C–H_c bond approximately bisects the H_e–C–H_f angle.

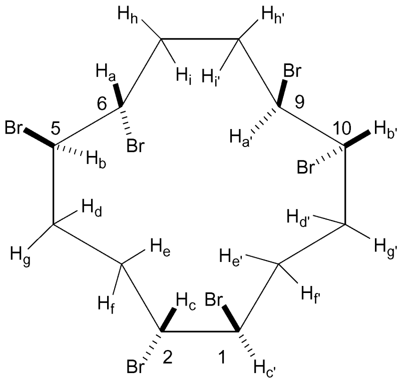


Fig. 5 Assigned structure for **HBCD-1**.

The conformational structure is shown in Fig. 6. This structure of **HBCD-1** was found to be very similar to the X-ray crystal structure.[4,7b] Therefore, it seems that the major solution conformation and the solid-state conformation are almost identical.

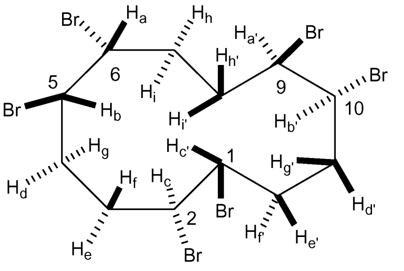


Fig. 6 Conformational structure of **HBCD-1** as determined by NMR.

(b) HBCD-2. **HBCD-2** has no C_2 axis of symmetry. The ^{1}H NMR spectrum should therefore show eighteen signals. At −50 °C the spectum showed only one major conformation. Mixtures of solvents were found ($CDCl_3$–d_8-toluene 10 : 90 and 90 : 10) which showed twelve or thirteen separate signals. Furthermore, C–H COSY spectra in the two mixtures allowed the identification of all geminal pairs of hydrogens. The H–H COSY spectra allowed connectivities to be established. Therefore, a structure showing the locations of all carbon atoms and attached hydrogens could be drawn (Fig. 7). Unfortunately, NOE difference spectra were not very clear, and it was difficult to get estimates of coupling constants for a number of protons

Table 9 Interpretation of H–H/C–H COSY and H–H coupling assignments of **HBCD-1** recorded in $CDCl_3$–d_8-toluene (45 : 55) at −50 °C

δ_C/ppm	Associated proton(s)	δ_H/ppm	H–H multiplicities	J/Hz
59.0	H_a	3.61	d	$J_{ai} = 12$
52.5	H_b	3.55	d	$J_{bd} = 7$
58.9	H_c	2.43	t	$J_{ce} = 6$, $J_{cf} = 6$
35.4	H_d, H_g	1.85, 1.36	dt, dd	$J_{de} = 7$, $J_{db} = 7$, $J_{dg} = 16$, $J_{gf} = 11$
34.9	H_e, H_f	1.66, 1.50	m, m	$J_{ec} = 6$, $J_{ed} = 7$, $J_{ef} = 15$, $J_{fc} = 6$, $J_{fg} = 11$
34.5	H_h, H_i	1.23, 0.99	t, q	$J_{ia} = 12$, $J_{ih} = 12$, $J_{ih'} = 12$

Table 10 Interpretation of the NOE difference spectra for **HBCD-1** in $CDCl_3$–d_8-toluene (45 : 55) at −50 °C

Proton	Irradiation/ppm	Protons exhibiting NOE	NOE increase (%)
H_a	3.61	c, h, i	1.2, 4.1, 1.7
H_b	3.55	c, f, g, h, i	2.7, 1.7, 1.5, 1.4, 3.3
H_c	2.43	b, e, f, g, i	8.4, 3.2, 3.2, 1.9, 1.6
H_d	1.85	b, g	1.8, 7.3
H_e	1.66	b, c, f	2.5, 1.8, 6.1
H_f	1.50	b, c, e	2.6, 3.0, 2.5
H_g	1.36	a/b, c, d	2.7, 3.2, 6.3
H_h	1.23	a, i	7.4, 7.9
H_i	0.99	a/b, c, h	10.1, 4.3, 4.6

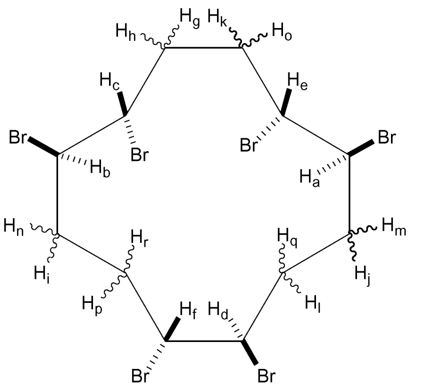


Fig. 7 Labelled structure of **HBCD-2** (for explanation of the subscript letters, see experimental section).

from the simple spectra. Therefore, it was not possible to deduce a proper conformation from the spectral data provided.

(c) HBCD-3. HBCD-3 has a C_2 axis of symmetry. Therefore, the ^{1}H NMR spectrum should show only nine signals. It was found that all nine protons were observed separately when the spectrum was recorded in a mixture of $CDCl_3$–d_8-toluene (75 : 25) at −25 °C. H–H COSY and C–H COSYspectra allowed all connectivities to be established. Further information was derived from the NOE difference spectra and the coupling constants, which provided more detailed information about the conformation, as indicated for **HBCD-1**. The conformational structure deduced is shown in Fig. 8. This conformational structure was found to be very similar to the X-ray crystal structure of **HBCD-3**.

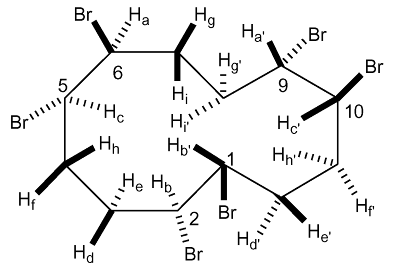


Fig. 8 Conformation of **HBCD-3** (for explanation of the subscript letters, see experimental section).

(d) TBCD-4. TBCD-4 has no C_2 axis of symmetry. Therefore, the ^{1}H NMR spectrum should show eighteen signals. By recording ^{1}H NMR spectra at temperatures between 50 °C and −50 °C in $CDCl_3$, the best temperature was found to be 25 °C, which provided an NMR spectrum with two distinct signals for CH=CH and 4 distinct signals for CHBr, but the 12 signals for the CH_2 groups were not well separated, because of signal overcrowding in the aliphatic range between 1.8 and 2.6 ppm. These results are similar to those obtained by Matsuba *et al.*[27]

Solvent-induced shifts were also investigated by addition of d_8-toluene to a $CDCl_3$ solution of **TBCD-4**, but did not provide good separation. H–H and C–H COSY spectra could not be fully analysed. It was not possible to deduce a solution conformation.

(e) TBCD-5. TBCD-5 has no C_2 axis of symmetry. Therefore, each carbon atom in the molecule is different. In order to clarify the structure of **TBCD-5**, ^{13}C NMR spectra were recorded at various temperatures from 50 °C to −50 °C in $CDCl_3$. The best temperature (−50 °C) showed eleven distinct and major resonance lines. Signals due to other conformations were largely eliminated at this temperature. The ^{1}H NMR spectrum should show eighteen signals, but only the low field signals were separated in $CDCl_3$ at −50 °C. Addition of d_8-toluene to a $CDCl_3$ solution of **TBCD-5** at −50 °C suggested that **TBCD-5** contained a significant amount of a second conformer. The COSY spectrum was very complex and could not be fully analysed. Mixtures of C_2D_5OD and CD_2Cl_2 were also tried, but the results were similar to those with $CDCl_3$–d_8-toluene solvent mixtures and did not help. Therefore the NMR data were not capable of providing the conformation in solution.

(f) TBCD-6. TBCD-6 has a plane of symmetry. Therefore, the ^{1}H NMR spectrum should show nine signals. By addition of d_8-toluene to a $CDCl_3$ solution of **TBCD-6**, mixtures were found ($CDCl_3$–d_8-toluene 50 : 50 and 25 : 75) at −25 °C which showed seven or eight separate signals. Furthermore, the pair which were not separated in the latter mixture were separated in the former mixture, even though other pairs were not. Therefore, by use of two solvent mixtures, all nine protons could be acceptably resolved. C–H and H–H COSY spectra allowed all connectivities to be established (Fig. 9).

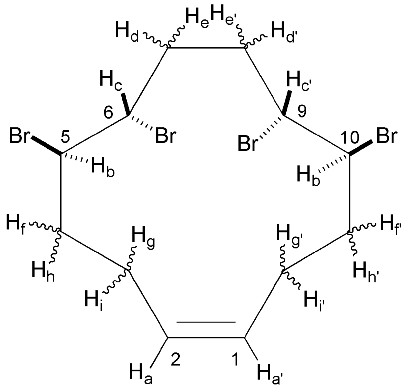


Fig. 9 Labelled structure of **TBCD-6** (for explanation of the subscript letters, see experimental section).

It was hoped that information concerning the conformation of **TBCD-6** in solution could be obtained by measuring coupling constants and NOE difference spectra. However, the spectra did not provide the more detailed information expected, possibly due to the presence of minor conformers or because peaks were overlapping. X-Ray diffraction methods alone were therefore used for the characterisation of **TBCD-6**.

(g) TBCD-7. TBCD-7 has a C_2 axis of symmetry. The NMR spectra of its $CDCl_3$ solutions show that it is a mixture of conformers between 0 °C and −50 °C. Therefore, the H–H COSY spectrum is very complex and could not be fully analysed. The conformers are in rapid equilibrium at 50 °C, but the aliphatic hydrogen signals are not well separated. On addition of d_8-toluene to the $CDCl_3$ solution, the results confirmed the rapid equilibration and also showed two equivalent protons associated with the double bond and two distinct signals each corresponding to protons associated with CHBr groups. The signals corresponding to the six aliphatic hydrogens, however, were still not well separated. X-Ray diffraction methods were therefore used for the full characterisation of **TBCD-7** and the solution conformation could not be determined.

(h) DBCD-8. DBCD-8 has no C_2 axis of symmetry. Therefore, each carbon atom in the molecule is different. In order to clarify the structure of **DBCD-8**, ^{13}C NMR DEPT spectra were recorded at various temperatures from 50 °C to −50 °C in $CDCl_3$. The best temperatures (−10 °C to −30 °C) showed thirteen distinct resonance lines, one extra one appearing in the CH_2 region. At other temperatures, there were also signals due to other conformations. At 50 °C the signals had coalesced but the lines were broad and not all could be seen. The ^{1}H NMR spectrum should show eighteen signals. However, even on addition of d_8-toluene to a $CDCl_3$ solution of **DBCD-8**, it was not possible to see well-separated signals because of signal overcrowding in the aliphatic and double bond regions.

The COSY spectra were very complex and could not be fully analysed. The full structure was therefore confirmed by X-ray crystallography, and the solution conformation could not be determined.

(i) DBCD-9. DBCD-9 has a C_2 axis of symmetry. At −70 °C its ^{1}H NMR spectra were well-resolved and showed only one major conformation. Solvents were found ($CDCl_3$–d_8-toluene 50 : 50 and d_8-toluene) which showed seven separate signals. Furthermore, the pairs that were not separated in the latter solvent were separated in the former mixture, even though other pairs were not. Therefore, by use of two solvent mixtures, all nine protons could be acceptably resolved. C–H and H–H COSY spectra allowed all connectivities to be established (Fig. 10).

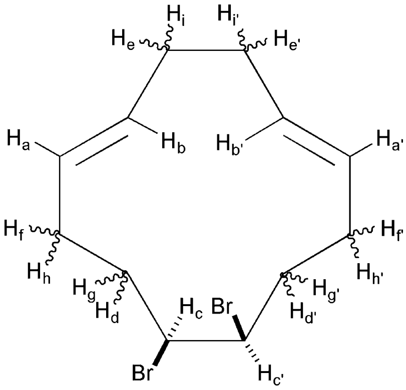


Fig. 10 Labelled structure of **DBCD-9** (for explanation of the subscript letters, see experimental section).

Various NOE difference spectra (Tables 11 and 12) were recorded at −60 °C in $CDCl_3$–d_8-toluene (50 : 50) and in d_8-toluene, because at −70 °C the NOE effects observed were not very clear. Although the NOEs allowed identification of closely proximate protons, it was still not possible to confirm this conformation by use of coupling constants to calculate torsional angles because some of the peaks were overlapping.

Conclusion

The bromination products **HBCD-1** to **HBCD-3, TBCD-4** to **TBCD-7**, and **DBCD-8** and **DBCD-9** have all been successfully synthesised, isolated and characterised. Their NMR spectra and X-ray crystallography have allowed their structures to be identified. For **HBCD-1**, **HBCD-3** and **DBCD-9** the NMR spectra provide evidence of the closely proximate protons (NOE) and approximate torsional angles (from coupling constants), but for **DBCD-8**, all TBCD isomers and **HBCD-2**, such evidence was not so conclusive. For the two compounds for which both solution and solid-state conformations were available, the conformations in solution were very similar to those in the solid state. If this pattern prevails for the other compounds, it may allow better understanding of the reasons for production of particular products on further bromination of such compounds.

Table 11 Interpretation of the NOE difference spectra of **DBCD-9** in $CDCl_3$–d_8-toluene (50 : 50) at −60 °C

Proton irradiated	δ/ppm	Protons exhibiting significant NOE
$H_{a/b}$	4.66	c, f/g, i
H_c	3.90	a/b, f/g, h
H_d	2.20	f/g
H_e	2.03	a/b, i
$H_{f/g}$	1.95	a/b, c, i
H_h	1.83	c
H_i	1.65	a/b, e

Table 12 Interpretation of the NOE difference spectra of **DBCD-9** in d_8-toluene at −60 °C

Proton irradiated	δ/ppm	Protons exhibiting significant NOE
H_a	4.53	c, e/g, f/h, i
H_b	4.44	c, e/g, f/h, i
H_c	3.98	a, b, e/g, f/h
H_d	2.49	e/g, f/h
$H_{e/g}$	2.02–2.06	b, c, d, i
$H_{f/h}$	1.95	a, b, c, d
H_i	1.63	a,b, e/g

Experimental

General

Cis,*trans*,*trans*-1,5,9-cyclododecatriene (98%) was obtained from Aldrich or Fluka and used without further purification. Where necessary, solvents were purified by standard procedures.[28] All glassware was dried in an oven at 150 °C and cooled to room temperature under a flow of nitrogen.

X-Ray analyses were obtained from the EPSRC National Crystallography Service. Elemental analyses were obtained from the laboratories of the University of Wales Cardiff. Ultra-violet spectra were recorded on a Philips PU 8720 UV/vis scanning spectrometer. Melting points were recorded on an electrothermal digital melting point apparatus and are uncorrected. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a VG 12/253 J mass spectrometer. Accurate mass data were obtained on a VG ZAB-E instrument. The data are presented with the molecular ion peak (the most intense one of the cluster) first, followed by several of the most abundant ion peaks with their % relative intensity given in brackets. High performance liquid chromatography (HPLC) involved a 25 cm × 4.6 mm column of 5 μ Spherisorb ODS2 bonded phase or 5 μ Zorbax ODS bonded phase. Spherisorb ODS2 separated all but two of the possible components (**TBCD-4** and **TBCD-5**), while Zorbax ODS was capable of separating these two. Mobile phase 89 : 11 acetonitrile–water; flow rate 1 cm^3 min^{-1}; detection by UV absorption at 210 nm; pump: LDC/Milton Roy constaMetric III; detector: LDC SpectroMONITOR III; recorder: Hewlett Packard 3390A integrator. ^{1}H and ^{13}C NMR spectra and NOE measurements were recorded on a Bruker AC 400 spectrometer at 400 MHz for ^{1}H and NOE and 100 MHz for ^{13}C measurements. The internal reference used in all spectra was tetramethylsilane. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants J are in Hz. DEPT spectra were recorded using the same machine. 2D spectra were not always referenced to TMS for practical reasons, but signals could nevertheless be correlated with those in the normal NMR spectra.

Typical reaction procedures

HBCD-1 by bromination of CDT. A solution of CDT (0.893 g, 5.50 mmol) in a mixture of ethanol (6 ml) and dichloromethane (4 ml) was cooled to −78 °C in a dry-ice/acetone bath and vigorously stirred. Meanwhile, bromine (*ca.* 2.6 ml) was made up to a concentration of *ca.* 0.50 M in ethanol (60 ml) and dichloromethane (40 ml) and standardised by iodometric titration. The bromine solution (51.0 ml, 25.5 mmol) was then transferred dropwise by nitrogen pressure through a plastic double-ended needle into the well-stirred CDT solution. The temperature was kept at −78 °C during the transfer. After the addition was completed, the reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature and then stirred for a further 2 h to give an orange solution. The solvent was evaporated *in vacuo* at 40 °C, to give a crude cream-coloured solid (3.53 g). Quantitative HPLC analysis showed the presence of **HBCD-1** (91%), **HBCD-2** (8%) and **TBCD-5** (1%). The crude solid was purified by washing with ethanol to give pure white solid **HBCD-1** in 85%

isolated yield. Crystallisation from a mixture of acetonitrile and dichloromethane (60 : 40) provided pure white crystals of **HBCD-1**. Mp 207–209 °C, δ_H(−50 °C, CDCl$_3$–d$_8$-toluene 45 : 55) 3.61 (d, 2 H, H$_a$), 3.55 (d, 2 H, H$_b$), 2.43 (t, 2 H, H$_c$), 1.85 (dt, 2 H, H$_d$), 1.66 (m, 2 H, H$_e$), 1.50 (m, 2 H, H$_f$), 1.36 (dd, 2 H, H$_g$), 1.23 (t, 2 H, H$_h$) and 0.99 (q, 2 H, H$_i$); δ_C (−50 °C, CDCl$_3$–d$_8$-toluene 45 : 55) 59.0 (C-6), 52.5 (C-5), 58.9 (C-2), 35.4 (C-4), 34.9 (C-3) and 34.5 (C-7); *m/z* (EI) 563 (M$^+$ − ^{79}Br, <1%), 561 (M$^+$ − ^{81}Br, <1), 482 (M$^+$ − ^{79}Br − ^{81}Br, <1), 403 (<1), 401 (<1), 321 (2), 319 (2), 241 (4), 239 (7), 159 (26), 131 (13), 105 (28), 91 (63), 79 (100), 67 (57), 65 (38), 53 (55), 41 (74) and 39 (75) (Found: C, 22.46; H, 2.96; Br, 74.58. Calc. for $C_{12}H_{18}Br_6$: C, 22.46; H, 2.83; Br, 74.71%).

HBCD-2 by bromination of TBCD-5. **TBCD-5** (7.225 g, 15.0 mmol) was dissolved in dichloromethane (97 ml) and acetonitrile (3 ml) and cooled to 2 °C (ice/water bath) and kept well-stirred. Meanwhile, a solution of bromine (*ca.* 2.6 ml) was made up to a concentration of 0.47 M in dichloromethane (97 ml) and acetonitrile (3 ml) and standardised by iodometric titration. The bromine solution (50.0 ml, 23.5 mmol) was then transferred dropwise by nitrogen pressure through a plastic double-ended needle into the well stirred **TBCD-5** solution. The temperature was kept at 2 °C during the transfer. After the addition was complete, the ice/water bath was removed, and the reaction mixture was allowed to warm to room temperature and then stirred overnight to give an orange solution. The solvent was evaporated in vaccuo at 40 °C to give a crude orange product (9.60 g). Quantitative HPLC analysis showed the presence of **HBCD-2** (94%) and **HBCD-1** (6%). The crude product was triturated with dichloromethane to give a cream-coloured solid which was then washed with ethanol to give **HBCD-2** (8.50 g, 85% yield, 95% purity). Crystallisation from acetonitrile provided pure white crystals of **HBCD-2** (7.24 g, 75%). Mp 170–172 °C, δ_H(−50 °C, CDCl$_3$–d$_8$-toluene 10 : 90) 3.55–4.11 (m, 4 H, H$_a$, H$_b$, H$_c$, H$_d$), 3.19 (d, 1 H, H$_e$), 2.76 (t, 1 H, H$_f$), 2.15–2.32 (m, 2 H, H$_g$, H$_h$), 1.85–1.97 (m, 2 H, H$_i$, H$_j$), 1.53 (m, 1 H, H$_k$), 1.00 (m, 1 H, H$_l$), 0.88 (m, 1 H, H$_m$), 0.65–0.81 (m, 2 H, H$_n$, H$_o$), 0.47 (m, 1 H, H$_p$), 0.33 (td, 1 H, H$_q$) and 0.18 (t, 1 H, H$_r$); δ_H(−50 °C, CDCl$_3$–d$_8$-toluene 90 : 10) 4.35 (m, 1 H, H$_b$), 4.30 (m, 1 H, H$_a$), 4.13 (d, 1 H, H$_c$), 4.08–4.10 (m, 2 H, H$_d$, H$_e$), 3.60 (t, 1 H, H$_f$), 2.64 (m, 1 H, H$_g$), 2.53 (m, 1 H, H$_i$), 2.45 (m, 1 H, H$_j$), 2.36 (m, 1 H, H$_h$), 2.12 (m, 1 H, H$_l$), 2.10 (m, 1 H, H$_k$), 1.74 (m, 1 H, H$_q$), 1.67 (m, 1 H, H$_n$), 1.54–1.60 (m, 2 H, H$_m$, H$_o$) and 1.38–1.43 (m, 2 H, H$_p$, H$_r$); δ_C(− 50 °C, CDCl$_3$–d$_8$-toluene 10 : 90) 61.3 (C-5 or C-10), 59.6 (C-10 or C-5), 57.5 (C-1 or C-2), 57.2 (C-2 or C-1), 52.6 (C-9 or C-6), 49.3 (C-6 or C-9), 37.6 (C-4 or C-11), 32.9 (C-7 or C-8), 32.6 (C-3 or C-12), 31.7 (C-12 or C-3), 31.6 (C-8 or C-7) and 29.5 (C-11 or C-4); δ_C (− 50 °C, CDCl$_3$–d$_8$-toluene 90 : 10) 60.8 (C-5 or C-10), 59.1 (C-10 or C-5), 56.8 (C-1 or C-2), 56.8 (C-2 or C-1), 52.1 (C-9 or C-6), 48.9 (C-6 or C-9), 38.0 (C-4 or C-11), 33.1 (C-7 or C-8), 32.8 (C-3 or C-12), 32.3 (C-12 or C-3), 31.8 (C-8 or C-7) and 29.9 (C-11 or C-4); *m/z* (EI) 563 (M$^+$ − ^{79}Br, <1%), 561 (M$^+$ − ^{81}Br, <1), 482 (M$^+$ − ^{79}Br − ^{81}Br, <1), 403 (<1), 401 (<1), 321 (2), 241 (5), 239 (8), 159 (32), 131 (12), 105 (28), 91 (62), 79 (100), 67 (58), 65 (36), 53 (54), 41 (63) and 39 (62) (Found: C, 22.42; H, 2.80; Br, 74.79. Calc. for $C_{12}H_{18}Br_6$: C, 22.46; H, 2.83; Br, 74.71%).

HBCD-3 by thermal rearrangement of HBCD-1. **HBCD-1** (11.475 g, 17.88 mmol) in a dry 100 ml round-bottomed flask equipped with a condenser, a magnetic stirrer and a rubber septum was flushed with nitrogen and maintained under a positive nitrogen pressure. The flask was placed in a silicone oil bath regulated with a contact thermometer to ±1 °C. The mixture was heated for 45 min at 190 °C, then the flask was removed from the oil bath and allowed to cool to room temperature to give a hard black crude product (11.07 g). Quantitative HPLC analysis showed the presence of **HBCD-3** (81%), **HBCD-2** (12%) and **HBCD-1** (7%). The crude product was triturated with a mixture of ethanol and acetonitrile (60 : 40) overnight and filtered to give a grey solid (9.75 g, 85% yield). The solid was dissolved in acetonitrile and stirred with activated charcoal then filtered and concentrated to give white crystals (8.50 g, 74%). Mp 179–181 °C, δ_H(−25 °C, CDCl$_3$–d$_8$-toluene 75 : 25) 3.78 (d, 2 H, H$_a$), 3.63 (dd, 2 H, H$_b$), 3.59 (d, 2 H, H$_c$), 2.20 (td, 2 H, H$_d$), 2.07 (t, 2 H, H$_e$), 1.75 (m, 2 H, H$_f$), 1.59 (m, 2 H, H$_g$), 1.40 (t, 2 H, H$_h$) and 1.09 (q, 2 H, H$_i$); δ_C(−25 °C, CDCl$_3$–d$_8$-toluene 75 : 25) 57.8 (C-6), 52.1 (C-2), 50.4 (C-5), 34.6 (C-7), 33.5 (C-3) and 32.2 (C-4), *m/z* (EI) 563 (M$^+$ − ^{79}Br, <1%), 561 (M$^+$ − ^{81}Br, <1), 482 (M$^+$ − ^{79}Br − ^{81}Br, <1), 403 (<1), 401 (<1), 321 (3), 319 (2), 241 (8), 239 (10), 159 (35), 131 (12), 105 (22), 91 (52), 79 (86), 67 (65), 65 (31), 53 (48), 41 (100) and 39 (69) (Found: C, 24.35; H, 2.99; Br, 72.66. Calc. for $C_{12}H_{18}Br_6$ + 0.65 MeCN: C, 23.87; H, 2.98; Br, 71.79%).

TBCD-4 by thermal rearrangement of TBCD-5. **TBCD-5** (11.75 g, 22.00 mmol) in a dry 100 ml round-bottomed flask equipped with a condenser, a magnetic stirrer and a rubber septum was flushed with nitrogen and maintained under a positive nitrogen pressure. The flask was placed in a silicone oil bath regulated with a contact thermometer to ±1 °C. The mixture was heated for 60 min at 180 °C, then the flask was removed from the oil bath and allowed to cool to room temperature to give a dark, transparent, crude product (11.64 g). The HPLC peak area analysis showed the presence of **TBCD-4** (~68%) and **TBCD-5** (~32%). The crude product was triturated with a mixture of ethanol and acetonitrile (60 : 40) overnight to give a brown solid. The solid was dissolved in acetonitrile and then stirred with activated charcoal, filtered and concentrated to give a light brown solid, **TBCD-4** (10.81 g, 92% yield, 52% purity). Consecutive recrystallisation from a mixture of ethanol and dichloromethane (60 : 40) provided pure white crystals of **TBCD-4** (2.5 g, 21%). Mp 125–127 °C, δ_H(25 °C, CDCl$_3$) 5.63 (m, 1 H, CH=CH), 5.46 (m, 1 H, CH=CH), 4.51 (m, 1 H, CH–Br), 4.43 (m, 1 H, CH–Br), 4.18 (m, 1 H, CH–Br), 4.18 (m, 1 H, CH–Br) and 1.89–2.52 (br m, 12 H, 6 × CH$_2$); δ_C(25 °C, CDCl$_3$) 132.9, 131.2 (2 × CH=C), 61.4, 52.8 (double intensity), 51.0 (4 × CHBr) and 36.8, 35.5, 33.8, 31.4, 30.4, 30.1 (6 × CH$_2$); *m/z* (EI) 482 (M$^+$(^{79}Br$_2$^{81}Br$_2$), <1%), 403 (M$^+$ − ^{79}Br, <1), 401 (M$^+$ − ^{81}Br, <1), 321 (M$^+$ − H − ^{79}Br − ^{81}Br, 3), 241 (11), 239 (11), 160 (10), 159 (52), 131 (14), 119 (18), 105 (25), 93 (29), 91 (52), 81 (46), 79 (92), 77 (35), 67 (100), 65 (38), 53 (63) and 41 (85) (Found: C, 29.97; H, 3.79; Br, 66.24. Calc. for $C_{12}H_{18}Br_4$: C, 29.91; H, 3.76; Br, 66.33%).

TBCD-5 by bromination of CDT. A solution of CDT (4.47 g, 27.5 mmol) in a mixture of ethanol (0.5 ml) and dichloromethane (49.5 ml) was cooled to −78 °C in a dry-ice/acetone bath and kept well-stirred. Meanwhile, a solution of bromine (*ca.* 5.2 ml) was made up to a concentration of 0.50 M in ethanol (2 ml) and dichloromethane (198 ml), and standardised by iodometric titration. The bromine solution (106 ml, 53 mmol) was then transferred dropwise by nitrogen pressure through a plastic double-ended needle into the well-stirred CDT solution. The temperature was kept at −78 °C during the transfer. After the addition was complete, the reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature and then stirred for a further 2 h to give an orange solution. The solvent was then evaporated *in vacuo* at 40 °C to give a crude cream-coloured solid (13.27 g). The HPLC peak area analysis showed the presence of **TBCD-5** (94%) and an unknown (6%). The crude solid was then washed with ethanol to give **TBCD-5** (11.28 g, 85% yield, 99% purity) as a white solid; crystallisation from dichloromethane provided pure white crystals of **TBCD-5** (10.8 g, 80%). Mp 167–169 °C, δ_H(−50 °C, CDCl$_3$) major conformation: 4.99 (s, 2 H), 4.58 (m, 1 H), 4.10 (m, 1 H), 3.69 (d, 1 H), 3.56 (m, 1 H) and 1.48–2.13 (m, 12 H); minor conformation: 5.16 (s, 2 H), 4.58 (m, 1 H, 4.10 (m, 1 H), 3.56 (m, 1 H), 3.43 (d, 1 H) and 1.50–2.10 (m, 12 H); δ_C(−50 °C, CDCl$_3$) 132.9, 129.3 (2 × CH=C), 63.0, 58.5, 54.0, 53.5 (4 × CHBr), 2 × 35.0, 33.8, 33.7, 32.2, 30.3 (6 ×

$\mathrm{CH_2}$); m/z (EI) 482 ($\mathrm{M^+(^{79}Br_2{}^{81}Br_2)}$, <1%), 403 ($\mathrm{M^+ - {}^{79}Br}$, <1), 401 ($\mathrm{M^+ - {}^{81}Br}$, <1), 321 ($\mathrm{M^+ - H - {}^{79}Br - {}^{81}Br}$, 5), 241 (18), 239 (18), 160 (14), 159 (63), 131 (15), 119 (18), 105 (22), 93 (26), 91 (45), 81 (37), 79 (67), 77 (25), 67 (100), 65 (31), 53 (41) and 41 (48) (Found: C, 29.79; H, 3.74; Br, 66.48. Calc. for $\mathrm{C_{12}H_{18}Br_4}$: C, 29.91; H, 3.76; Br, 66.33%).

TBCD-6 by thermal rearrangement of TBCD-7. **TBCD-7** (13.767 g, 28.58 mmol) in a dry 100 ml round-bottomed flask equipped with a condenser, a magnetic stirrer and a rubber septum was flushed with nitrogen and maintained under a positive nitrogen pressure. The flask was placed in a silicone oil bath regulated with a contact thermometer to ±1 °C. The mixture was heated for 40 min at 160 °C, then the flask was removed from the oil bath and allowed to cool to room temperature to give a light yellow, transparent, crude product (13.76 g). The HPLC peak area analysis showed the presence of **TBCD-6** (46%), **TBCD-7** (48%), and two unknowns (5%). The crude product was triturated with a mixture of ethanol and acetonitrile (60 : 40) overnight and filtered to give a white solid (12.10 g, 88% yield) with composition similar to the crude material. The TBCD mixture was washed with ethanol, which removed the unknowns to leave a mixture of **TBCD-6** and **TBCD-7** (9.706 g, 71% yield). This material was extracted with a mixture of ethanol and dichloromethane (80 : 20), so as to leave a little undissolved solid, which was mainly **TBCD-7**. The mixture was filtered and the filtrate was concentrated to give a solid richer in **TBCD-6**. The extraction process was repeated several times until the solid obtained by evaporation showed a peak area ratio of *ca.* 66 : 34 (**TBCD-6** : **TBCD-7**). The solid (5.82 g) was then repeatedly recrystallised from acetonitrile until the solid obtained was pure **TBCD-6** (2.11 g). Mp 118–121 °C, δ_H(−25 °C, $\mathrm{CDCl_3}$–$\mathrm{d_8}$-toluene 25 : 75) 5.23 (m, 2 H, $\mathrm{H_a}$), 4.11 (m, 2 H, $\mathrm{H_b}$), 4.05 (m, 2 H, $\mathrm{H_c}$), 1.98 (m, 4 H, $\mathrm{H_d}$, $\mathrm{H_e}$), 1.75 (m, 2 H, $\mathrm{H_f}$), 1.20 (m, 2 H, $\mathrm{H_g}$), 1.05 (m, 2 H, $\mathrm{H_h}$) and 1.00 (m, 2 H, $\mathrm{H_i}$); δ_C(−25 °C, $\mathrm{CDCl_3}$–$\mathrm{d_8}$-toluene 25 : 75) 128.7, 61.5, 51.0, 33.7, 39.2 and 24.8; m/z (EI) 482 ($\mathrm{M^+(^{79}Br_2{}^{81}Br_2)}$, <1%), 403 ($\mathrm{M^+ - {}^{79}Br}$, 3.5), 401 ($\mathrm{M^+ - {}^{81}Br}$, 3.5), 321 ($\mathrm{M^+ - H - {}^{79}Br - {}^{81}Br}$, 5), 241 (10), 239 (10), 160 (12), 159 (49), 131 (15), 119 (20), 105 (25), 93 (30), 91 (55), 81 (40), 79 (95), 77 (40), 67 (90), 65 (40), 53 (65) and 41 (100) (Found C, 29.80; H, 3.85; Br, 66.36. Calc. for $\mathrm{C_{12}H_{18}Br_4}$: C, 29.91; H, 3.76; Br, 66.33%).

TBCD-7 by bromination of CDT. A solution of CDT (10.71 g, 66.0 mmol) in ethanol (96 ml) and dichloromethane (24 ml) was cooled to −78 °C in an dry-ice/acetone bath while maintaining vigorous stirring. Meanwhile, a solution of bromine (*ca.* 12.9 ml) was made up to a concentration of 0.44 M in ethanol (400 ml) and dichloromethane (100 ml), and standardised by iodometric titration. The bromine solution (431 ml, 190 mmol) was then transferred dropwise by use of nitrogen pressure through a plastic double-ended needle into the well-stirred CDT solution. The temperature was kept at −78 °C during this transfer. After the addition was complete, the reaction mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature. The mixture was then stirred for a further 2 h to give an orange solution. The solvent was evaporated *in vacuo* at 40 °C to give a crude cream-coloured solid (31.78 g). Quantitative HPLC analysis showed the presence of **TBCD-7** (72%), **TBCD-5** (10%) and CDT (18%). The crude solid was then washed with ethanol to give **TBCD-7** (20.34 g, 64% yield, 91% purity) as a white solid. Recrystallisation from a mixture of ethanol and dichloromethane (60 : 40) provided pure white crystals of **TBCD-7** (15.16 g, 48%). Mp 129–131 °C, δ_H(50 °C, $\mathrm{CDCl_3}$) 5.53 (m, 2 H, CH=CH), 4.49 (br s, 2 H, CHBr), 4.32 (br s, 2 H, CHBr) and 2.13–2.41 (br m, 12 H, $\mathrm{CH_2}$); δ_C(50 °C, $\mathrm{CDCl_3}$) 129.2 (CH=CH), 55.5 (2 × CHBr), 36.2, 33.6 and 25.0 (3 × $\mathrm{CH_2}$); m/z (EI) 482 ($\mathrm{M^+(^{79}Br_2{}^{81}Br_2)}$, 1%), 403 ($\mathrm{M^+ - {}^{79}Br}$, 2), 401 ($\mathrm{M^+ - {}^{81}Br}$, 2), 323 ($\mathrm{M^+ - H - 2 \times {}^{79}Br}$, 3), 321 ($\mathrm{M^+ - H - {}^{79}Br - {}^{81}Br}$, 6), 319 ($\mathrm{M^+ - H - 2 \times {}^{81}Br}$, 3), 241 (12), 239 (12), 160 (12), 159 (53), 131 (10), 119 (18), 105 (22), 93 (28), 91 (51), 81 (40), 79 (79), 77 (31), 67 (100), 65 (33), 53 (52) and 41 (74) (Found: C, 29.98; H, 3.81; Br, 66.22. Calc. for $\mathrm{C_{12}H_{18}Br_4}$: C, 29.91; H, 3.76; Br, 66.33%).

DBCD-8 by bromination of CDT. A solution of CDT (1.785 g, 11.00 mmol) in ethanol (12 ml) and dichloromethane (8 ml) was cooled to −78 °C in a dry-ice/acetone bath whilst maintaining vigorous stirring. Meanwhile, a solution of bromine (*ca.* 1.3 ml) was made up to a concentration of 0.46 M in ethanol (30 ml) and dichloromethane (20 ml) and standardised by iodometric titration. The bromine solution (26 ml, 11.96 mmol) was then transferred dropwise by use of nitrogen pressure through a plastic double-ended needle into the well-stirred CDT solution. The temperature was kept at −78 °C during this transfer. After the addition was complete, the reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature and then stirred for a further 2 h to give an orange solution. The solvent was then evaporated *in vacuo* at 40 °C to give crude **DBCD-8** as an oil. The HPLC peak area analysis showed the presence of **DBCD-8** (87%), **TBCD-5** (3%) and CDT (10%). The crude product was triturated with acetonitrile, filtered and washed with acetonitrile to give **DBCD-8** (2.76 g, 78% yield) as a brown solid, which was substantially pure by HPLC. Crystallisation from acetonitrile provided pure white crystals of **DBCD-8** in 74% yield. Mp 58–59 °C; δ_H(−20 °C, $\mathrm{CDCl_3}$) 5.39–5.56 (m, 4 H, CH=CH), 4.53–4.5 (m, 2 H, CHBr) and 1.83–2.48 (m, 12 H, $\mathrm{CH_2}$); δ_C(−20 °C, $\mathrm{CDCl_3}$) 128.2, 128.4, 129.1, 131.1 (4 × *C*H=C), 53.6, 60.7 (2 × CHBr), 36.3, 32.9, 31.1, 30.3, 27.9 and 26.6 (6 × $\mathrm{CH_2}$); m/z (EI) 324 ($\mathrm{M^+(^{81}Br^{81}Br)}$, 0.5), 322 ($\mathrm{M^{+79}Br^{81}Br}$, 1), 320 ($\mathrm{M^+(^{79}Br^{79}Br)}$, 0.5), 243 ($\mathrm{M^+ - {}^{79}Br}$, 5), 241 ($\mathrm{M^+ - {}^{81}Br}$, 5), 162 (14), 161 (100), 133 (31), 119 (32), 107 (42), 105 (25), 93 (33), 91 (51), 81 (6) and 79 (14) (Found: C, 44.66; H, 5.80; Br, 49.55. Calc. for $\mathrm{C_{12}H_{18}Br_2}$: C, 44.75; H, 5.63; Br, 49.62%).

DBCD-9 by debromination of TBCD-5 with zinc. **TBCD-5** (7.32 g, 15.20 mmol) was dissolved in ethanol (600 ml) at 90 °C. The **TBCD-5** solution was transferred dropwise by nitrogen pressure through a double-ended needle into a vigorously stirred mixture of zinc powder (0.995 g, 15.22 mmol) in ethanol (100 ml) over a period of 10 min. The TBCD solution was kept at 90 °C during this transfer. After the addition was complete, the reaction mixture was allowed to cool to room temperature, stirred for an additional 48 h, filtered and concentrated. The concentrate was diluted with water and extracted twice with pentane to give an oil which was dissolved in hot ethanol and allowed to crystallise to provide pure white crystals of **DBCD-9** (0.3 g). Mp 55 °C; δ_H(−70 °C, $\mathrm{CDCl_3}$–$\mathrm{d_8}$-toluene 50 : 50) 4.66 (m, 4 H, $\mathrm{H_a}$ and $\mathrm{H_b}$), 3.90 (dd, 2 H, $\mathrm{H_c}$), 2.20 (m, 2 H, $\mathrm{H_d}$), 2.03 (m, 2 H, $\mathrm{H_e}$), 1.95 (m, 4 H, $\mathrm{H_f}$ and $\mathrm{H_g}$), 1.83 (m, 2 H, $\mathrm{H_h}$) and 1.65 (m, 2 H, $\mathrm{H_i}$); δ_H(−70 °C, $\mathrm{d_8}$-toluene) 4.53 (m, 2 H, $\mathrm{H_a}$), 4.44 (m, 2 H, $\mathrm{H_b}$), 3.98 (dd, 2 H, $\mathrm{H_c}$), 2.49 (t, 2 H, $\mathrm{H_d}$), 2.1–2.0 (m, 4 H, $\mathrm{H_e}$ and $\mathrm{H_g}$), 2.0–1.9 (br, 4 H, $\mathrm{H_f}$ and $\mathrm{H_h}$) and 1.63 (m, 2 H, $\mathrm{H_i}$); δ_C(−70 °C, $\mathrm{d_8}$-toluene) 128.8, 134.0, 55.4, 38.0, 32.2 and 30.7; m/z (EI) 322 ($\mathrm{M^+(^{79}Br^{81}Br)}$, <1), 243 ($\mathrm{M^+ - {}^{79}Br}$, 2), 241 ($\mathrm{M^+ - {}^{81}Br}$, 2), 162 (7), 161 (50), 133 (14), 119 (16), 107 (24), 105 (14), 93 (18), 91 (34), 79 (78), 77 (27), 67 (83), 65 (27), 54 (100), 53 (46), 41 (69) and 39 (65) (Found: C, 44.57; H, 5.78; Br, 49.66. Calc. for $\mathrm{C_{12}H_{18}Br_2}$: C, 44.75; H, 5.63; Br, 49.62%).

General procedure for analytical scale reactions

To the stirred substrate in the appropriate solvent at the temperature given was added a standardised solution of bromine in the appropriate solvent which was also at a set temperature before the addition, though not necessarily at the same temperature. After the appropriate time at the desired temperature the solvent was removed, the crude product was weighed and the sample was analysed by HPLC. The analytical results are given in the appropriate tables.

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