Selective formation of the *rctt* chair stereoisomers of octa-*O*-alkyl resorcin[4]arenes using Brønsted acid catalysis†

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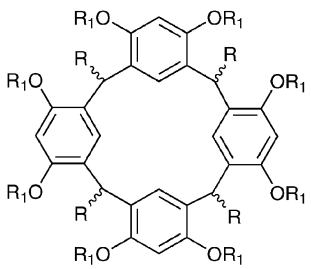
New synthetic conditions are described for the fully selective formation of the *rctt* chair stereoisomers of octa-*O*-alkyl resorcin[4]arenes; these offer a clean route into the chair conformer of these interesting receptor molecules. Brønsted acid catalysis in acetic acid solutions results in the formation of the single isomer when 1,3-dimethoxybenzene is heated at 80 °C with a range of aldehydes, straight- and branched-chain or aromatic, and with an aldehyde synthon. An investigation of reaction conditions indicated that, in this case, the *rctt* chair stereoisomer was the thermodynamic product, a result confirmed by molecular modelling studies that show that this stereoisomer is of lower energy than the expected *rccc* boat stereoisomer.

Introduction

The field of supramolecular chemistry has generated many elegant examples of macrocyclic structures capable of functioning as hosts for molecular recognition and sensing.[1] Of such structures, the resorcin[*n*]arene **1**[2] (the general structure for $n = 4$ is depicted in Fig. 1) are particularly attractive building blocks for supramolecular chemists, as they possess highly symmetrical 'bowl' shape cavities, can be tailored to different sizes (by changing the number of aryl units),[3,4] can readily be functionalised[5,6] and consequently can be employed in the formation of larger self-assembled structures.[7] It is, therefore, somewhat surprising that octa-*O*-alkyl resorcin[4]arenes, in which the hydroxy groups are masked, such as **2**, are a relatively unexplored variation on the resorcin[4]arene system. To date, only a few studies on their applications have been reported; however, these have shown them to be useful new host molecules with a wide range of applications. Hence, they are able to complex alkali-metal,[8] transition-metal[9] and organic cations,[8] can be used to bind neutral electron-acceptors,[8,10] have been used for chiral recognition (when carrying chiral substituents)[11] and have the potential for the development of more complex structures through selective functionalisation of the methylene bridges.[12]



1 R_1 =H, R = alkyl, aryl
2 R_1 = Me, Bn, Allyl, R = alkyl, aryl

Fig. 1 Resorcin[4]arenes and octa-*O*-alkyl resorcin[4]arenes.

Resorcin[4]arenes can readily be prepared from resorcinol and a large range of aldehydes using Brønsted-acid catalysis.[13,14] To date, derivatives featuring methoxy substituents have only been prepared by Lewis-acid catalysis of 1,3-dimethoxybenzene–aldehyde mixtures in chloroform or diethyl ether ($SnCl_4$)[15] or of 2,4-dimethoxycinnamates ($BF_3 \cdot Et_2O$).[16] Similar approaches have also been used for the preparation of hybrid alkoxy/hydroxy analogues,[17–19] the parent resorcin[4]arene[20–23] which is unavailable through acid-catalysed condensation of resorcinol with formaldehyde, ring expanded derivatives featuring between five and nine aromatic units,[24] and confused cyclotetramers[25] in which an aromatic ring is connected through the 2–6 positions. Interestingly, it has been reported that mineral-acid catalysed reactions fail to yield the cyclic tetramers (<1% yield) under standard conditions with 1,3-dimethoxybenzene.[14]

As part of a synthetic programme focussed on selective derivatisation of the methylene bridge residues of resorcin[4]arenes,[26] we investigated the synthesis of octa-*O*-alkyl resorcin[4]arenes bearing hydroxy-containing residues at the methylene bridges. In this paper, we report the first example of selective formation of the *rctt* chair stereoisomer in acetic acid–H_2SO_4 or acetic acid–HCl mixtures and propose that this isomer is the thermodynamic product under Brønsted-acid-catalysis, an unprecedented observation in resorcinarene chemistry.

Results and discussion

Our initial studies focussed on the reaction of 4-hydroxybenzaldehyde with 1,3-dimethoxybenzene to prepare octa-*O*-alkyl

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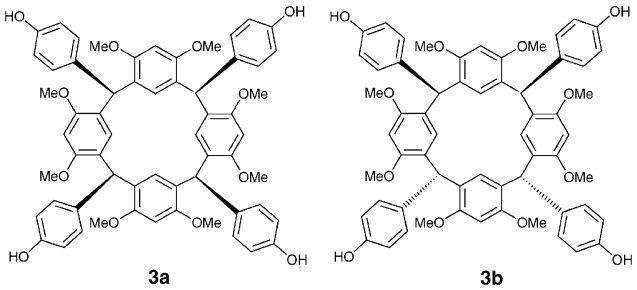


Fig. 2

resorcin[4]arenes **3** bearing aromatic hydroxy groups on the methylene bridge positions as both the *rccc* boat **3a** and *rctt* chair **3b** stereoisomers (Fig. 2).

Stereoisomers of octa-*O*-alkyl resorcin[4]arenes

The condensation reaction of resorcinol or dialkoxybenzenes with aldehydes, other than formaldehyde, results in cyclic tetramers which may exist as a number of different stereoisomers.[1] These stereoisomers can be categorised through (i) the configuration at each methylene bridge position, (ii) the conformation adopted by the aromatic residues and (iii) the relative position, axial or equatorial, of each residue at the methylene bridge position. Of the many possible stereoisomers three; the *rccc* boat (crown), the *rctt* chair and *rcct* diamond (Fig. 3), have been isolated in the case of reactions between resorcinol and aldehydes with the additional *rccc* saddle, a conformational isomer of the *rccc* boat, having been reported for octa-*O*-alkyl derivatives where rotation of the aromatic residues is restricted. In addition, the *rccc* boat is often observed as the C_{2v} flattened boat conformational isomer in ^{1}H NMR and X-ray crystal structure studies.

Lewis acid-catalysed reactions

Iwanek and Syzdól[15] have described the selective formation of the *rccc* boat stereoisomer of octa-*O*-methylresorcin[4]arenes from branched-chain aldehydes when using $SnCl_4$, a Lewis acid catalyst, in chloroform. Other Lewis acids resulted in more complex mixtures in which the *rcct* diamond was the major contaminating isomer (43–62%), while trace amounts of the chair compound could also be isolated in most cases.

Following these experimental conditions we were unable to isolate a single conformer. Instead a mixture of two isomers was observed, not only the expected boat but also the *rctt* chair stereoisomer (*vide infra*) (Table 1). Changing the solvent to diethyl ether, a solvent reported to be more suited to reactions with straight-chain aldehydes,[15b] indicated that lengthening the reaction time could significantly alter the product distribution in favour of the boat isomer but it was still not the sole product. In all cases, there was no evidence for the formation of the diamond stereoisomer.

Brønsted acid-catalysed reactions

Following from these results, we decided to re-investigate the use of Brønsted-acid catalysts in the formation of octa-*O*-alkyl resorcin[4]arenes. While this has been reported previously to give exceptionally low yields (<1%)[14] of the cyclic tetramer, it has proved successful in forming the parent resorcin[4]arene using paraformaldehyde in 2-ethoxyethanol.[22]

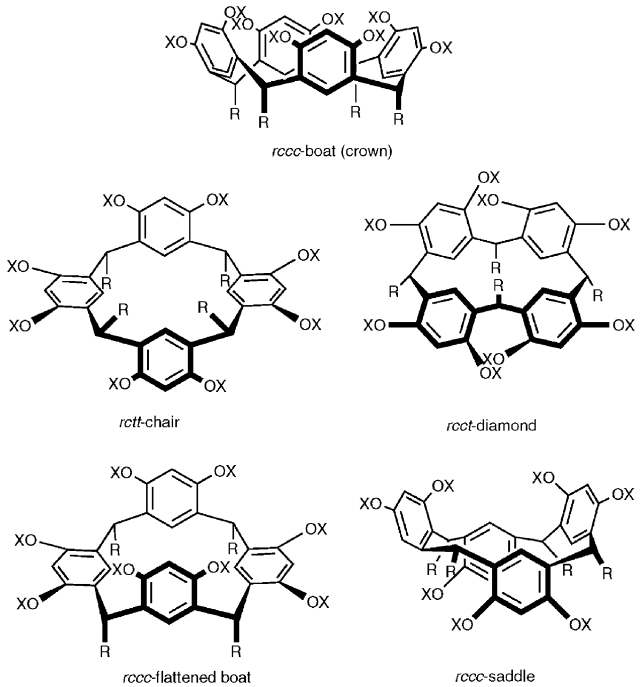


Fig. 3 Common diastereoisomers and conformers of resorcin[4]-arenas.

The condensation was initially investigated using the standard conditions for the formation of resorcin[4]arenes, catalytic HCl in boiling ethanol (Table 2). Short reaction times resulted in the formation of a mixture of both boat and chair isomers, whereas increasing the reaction time, led to a slight increase in the formation of the *rctt* chair but did not give complete selectivity. Equally using a high pressure reaction at 150 °C did not significantly alter the ratio of the products and reducing the temperature to decrease the reaction rate resulted in failure to condense.

It has been noted that the parent resorcin[4]arene can be prepared from 1,3-dimethoxybenzene and paraformaldehyde using a sulfuric acid–acetic acid mixture at room temperature.[27] Using similar conditions with 4-hydroxybenzaldehyde again gave a mixture of two isomers.

The ^{1}H NMR (DMSO-d_6) for this mixture clearly shows the presence of the two isomers through the appearance of two non-equivalent singlets in the characteristic peak range (δ 4.9–5.5) for the methylene bridge hydrogen (Fig. 4(a)). Additionally, two series of peaks, with integrals corresponding

Table 1 Distribution of conformers of **3** formed using $SnCl_4$ catalysis[a]

Solvent	*t*/h	Ratio boat : chair conformers	Overall yield (%)
$CHCl_3$	16	28 : 72	61
$CHCl_3$	72	37 : 63	69
Et_2O	16	4 : 6	70
Et_2O	72	3 : 1	76
Et_2O	334	3 : 1	75

[a] $SnCl_4$, 25 °C.

Table 2 Distribution of conformers of **3** formed using HCl in ethanol

T/°C	t/h	Ratio boat : chair conformers	Overall yield (%)
−20	16	—	0[a]
0	16	—	0[a]
75	5	25 : 75	70
75	16	21 : 79	68
75	72	21 : 79	73

[a] Unreacted starting material isolated.

to the two individual bridge signals, can be identified, leading to the conclusion that the mixture contains both boat and chair isomers (*vide infra*).

However, when the reaction was carried out at 80 °C the chair isomer was formed exclusively (Fig. 4(b)). This assignment was confirmed by ^{1}H NMR analysis of **2b** which was in agreement with spectra of previously describe *rctt* chair configurations.[28,29] A single resonance for the bridging H_a proton is observed but the presence of four signals for the ring aromatic groups (H_b and H_c) indicates two different types of resorcinol units and an *rctt* configuration of the methylene bridge substituents. The spectra showed no changes upon heating to 60 °C, indicating that the conformation was rigid and thus confirming the presence of a chair, rather than a C_{2v} temperature-dependent flattened boat. The spectrum was additionally assigned using comparisons with NOE experiments on the acylated derivative **20**. It is worth noting that, in the case of the derivatives **20** and **21**, the purified *rccc*-boat conformer was seen as the C_{2v} flattened boat on the ^{1}H NMR time scale (Fig. S1, ESI†).

Consideration of the reaction conditions showed that the addition of a stronger acid catalyst was essential, as no condensation was observed in acetic acid alone, and that the catalysis could also be achieved with HCl but not by TFA or HNO_3 (Table 3). With the two latter acids, only the original starting materials were isolated, even after longer reaction times. Thus the catalytic activity of the Brønsted acids cannot

Table 3 Distribution of conformers of **3** formed using protic acid catalysis[a]

Catalyst	T/K	Boat (%)	Chair (%)	Overall yield (%)
None	25	0	0	0
HCl	80	0	100	54
H_2SO_4	80	0	100	50
HNO_3	80	0	0	0
CF_3COOH	80	0	0	0
HCl	25	33.3	66.6	55
H_2SO_4	25	67	33	50
HNO_3	25	0	0	0
CF_3COOH	25	0	0	0

[a] 20 ml acetic acid, *ca.* 10 meq. H^+ 18 h.

be directly related to their strength. The lack of condensation with TFA is particularly interesting, as Urbaniak and Iwanek[30] have noted that halogenoacetic acids can cause isomerisation of octa-*O*-alkyl resorcin[4]arenes. In that case, addition of the acid to a $CHCl_3$ solution of an *rccc* boat octa-*O*-methyl resorcin[4]arene, which had been prepared by Lewis-acid condensation, resulted, after 48 h, in a product which was a mixture of the *rcct* diamond and *rccc* boat isomers with the chair being an additional minor component (~10%).

While we have shown that the *rctt* chair conformer could readily be prepared selectively at high temperature, it can also be obtained by separation from the isomeric mixture formed at low temperature, by hot filtration from a methanolic solution. However, isolation of the pure boat form from the mixture is more problematic, with the hot filtration method resulting in ~10% contamination by the chair conformer. Esterification of the phenolic hydroxy group leads to compounds with enhanced solubility which can be separated by flash column chromatography. Reaction with butanoic anhydride and chromatography ($CHCl_3$–EtOAc 95 : 5) of the product **21** proved more successful than separation of the acetates **20**. Hydrolysis with ethanolic potassium hydroxide then yielded the pure boat stereoisomer (Fig. 4(c)). The ^{1}H NMR (DMSO-d_6) gives clear

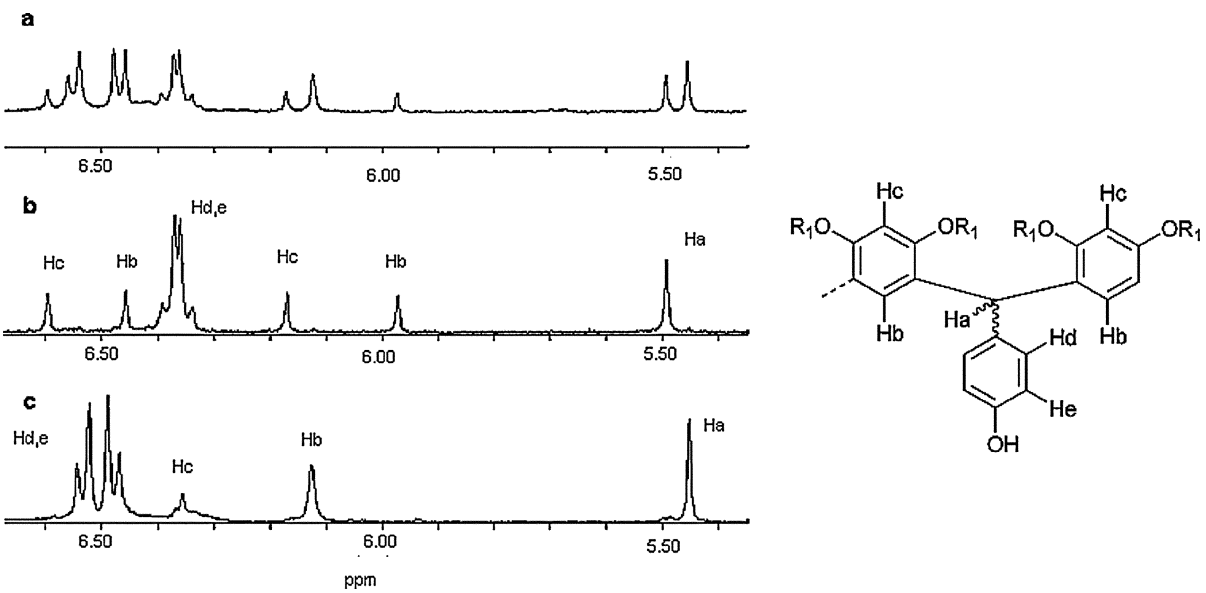


Fig. 4 Expansion of the aromatic region of the ^{1}H NMR (400 MHz) in DMSO-d_6 spectra of **3**. (a) Products isolated from reaction at 25 °C in acetic acid using H_2SO_4 catalysis, showing the presence of **3a** and **3b**, (b) purified chair conformer **3b**, (c) purified boat conformer **3a**.

identification of the *rccc* boat configuration,[28,29] in which all resorcinol units and substituents are identical, featuring single peaks for the bridging proton (H_a) and for each of the aromatic peaks (H_b and H_c) and a pair of doublets for the 4-hydroxybenzyl substituents (H_d and H_e). Comparison of the mass spectrometric data for the two stereoisomers provides a preliminary indication of different binding abilities for group 1 metals, with the *rccc* boat showing the presence of both sodium and potassium complexes while the *rctt* chair shows minimal complexation of potassium and diminished complexation of sodium (Fig. 2 and 3, ESI†).

Generality of reaction

With this important result in hand, the generality of this stereoisomerically selective reaction for synthesis of other octa-*O*-alkyl resorcin[4]arenes was explored (Table 4, Scheme 1). Condensation reactions under these new synthetic conditions with a series of aldehydes and masked aldehydes were investigated to determine the role of hydrogen bonding interactions and steric bulk in directing the formation of products.

Reaction with a long chain *O*-alkyl derivative of 4-hydroxybenzaldehyde, where there is no possibility of intra or intermolecular hydrogen bonding, yielded **13**. This reaction gave consistent results at 80 °C (100% *rctt* chair formation) and showed further selectivity for the chair conformer under low-temperature (25 °C) conditions, indicating that the results obtained for **3** are not solely a result of hydrogen bonding.

Equally, when using a simple straight-chain aliphatic aldehyde such as acetaldehyde, full selectivity for the *rctt* chair was again achieved at high temperature. This leads to the conclusion that the previously observed selectivity is not only a consequence of steric interactions between the large aryl units. The reaction of acetaldehyde with 1,3-dimethoxybenzene has been reported[14] to yield the boat stereoisomer, in very low yield, when the condensation is performed in methanolic HCl for 1 h. Comparison of the ^{1}H NMR spectroscopic data for **14** with those reported (Table 5) confirms the formation of a different stereoisomer under our high-temperature conditions and the formation of a mixture of the previously reported and new isomer at room temperature. This is clearly shown by the appearance of four separate signals for the aromatic ring protons, two for the acetyl protons and a quartet for the CH bridging proton.

Additionally, when using the branched-chain aliphatic isovaleraldehyde the condensation at high temperature again results in exclusive formation of the *rctt* chair isomer (Table 5, **15**). This isomer has previously been reported only as a minor component (maximum 10% with $AlCl_3$) in Lewis-acid catalysed condensation reactions[15] which tend to favour the formation of the boat and diamond.

Octa-*O*-methyl resorcin[4]arenes featuring ω-hydroxyalkyl substituents at the methylene bridge have been prepared previously through post-condensation reduction of CH_2CO_2R esters of the corresponding octa-*O*-methylresorcin[4]arenes, which in turn had been prepared by the reaction of 2,4-dimethoxycinnamates with $BF_3{\cdot}Et_2O$.[31] In that case, while three separate isomers could be characterised from the initial condensation [an *rccc*-boat, a *rcct* diamond-like structure and a *rccc* 1,3-alternate (or saddle) conformation], treatment with $LiAlH_4$ resulted in only the boat and diamond ω-hydroxyalkyl derivatives being isolated.

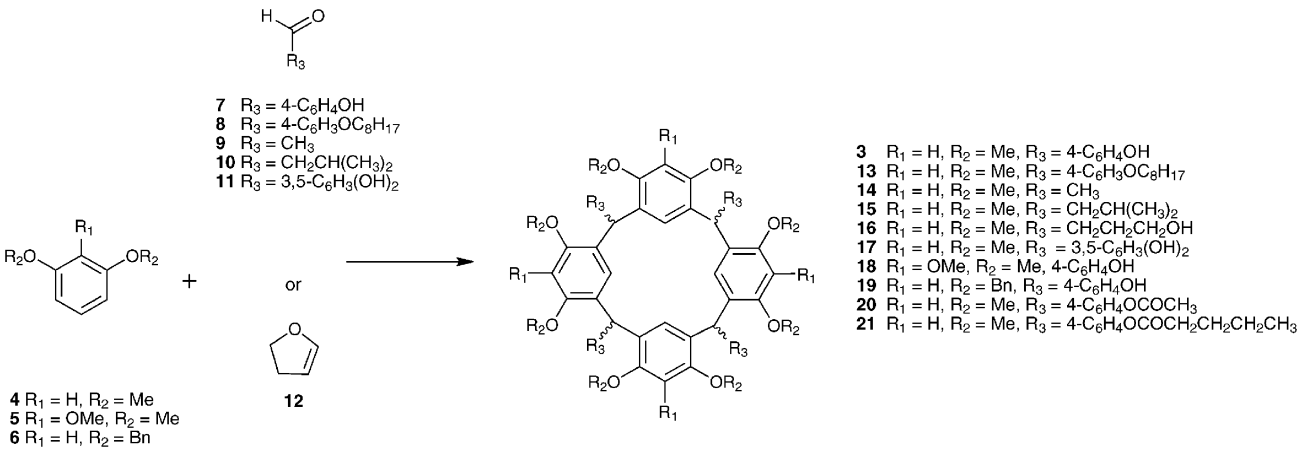
This makes the results obtained for the reaction of 1,3- dimethoxybenzene and 2,3-dihydrofuran, an enol–ether masked aldehyde, particularly interesting. While Lewis-acid catalysis ($SnCl_4/CHCl_3$) failed to yield any cyclic tetramer, a single isomer was isolated both at room temperature (albeit in low 17% yield) and on heating to 60 °C using HCl catalysis in acetic acid. Comparison of the spectroscopic data for **16** (Fig. 5) with the published data for the similar boat and diamond shows this to be a previously unobtainable conformer, which can be formed in a single-step reaction. This was identified as a C_2-symmetrical structure on the basis of its ^{1}H NMR spectrum. In this spectrum, there is a doubling of all aromatic proton signals, while the bridging proton gives a single triplet, confirming that it is the *rctt* isomer in the chair conformation.

Thus the selective formation of *rctt* chair stereoisomers of octa-*O*-methyl resorcin[4]arenes proceeds in excellent yield for a wide range of aldehydes under these newly developed synthetic conditions, opening up the chemistry of these molecules for further development for diverse applications. However, it should be noted that the use of the highly sterically demanding and less reactive 3,5-dihydroxybenzaldehyde failed to yield any cyclic product in this reaction.

Table 4 Application of conditions to other substrates[a]

	R_1	R_2	R_3	T/°C	Boat (%)	Chair (%)	Overall yield (%)
13	H	Me	4-$C_6H_4OC_8H_{17}$	25	17	83	21
				80	0	100	54
14	H	Me	CH_3	25	40	60	91
				80	0	100	70
15	H	Me	$CH_2CH(CH_3)_2$	25	48	52	88
				80	0	100	30.5
16	H	Me	$CH_2CH_2CH_2OH$	25	0	100	17.4[b]
				60	0	100	61.4[b]
17	H	Me	3,5-$C_6H_3(OH)_2$	25	—	—	—[c]
				80	—	—	—[c]
18	OMe	Me	4-C_6H_4OH	25	—	—	—[c]
				80	—	—	—[c]
19	H	Bn	4-C_6H_4OH	25	—	—	—[c]
				80	17	83	76

[a] 20 ml acetic acid, 0.0102 mmol H^+, 18 h. [b] HCl catalysis. [c] Starting materials isolated.



Scheme 1 General scheme for the reaction of aldehydes with alkylated resorcinols.

To investigate further that the selective formation of the *rctt* chair was not solely a property of the alkoxybenzene, we first examined the reaction of 1,3-dibenzoxybenzene with 4-hydroxybenzaldehyde. In this case, no condensation was seen at lower temperatures. However, upon heating (80 °C) a mixture of the two isomers was observed which was biased in an ~4 : 1 ratio in favour of the chair. This suggests that similar results could be obtained with a wide range of dialkoxybenzenes, although the actual product distribution may be affected by steric effects with larger *O*-alkyl groups. In contrast, when 1,2,3-trimethoxybenzene, a pyrogallol analogue, is used in the condensation reaction, no product was observed under either set of reaction conditions. This lack of reactivity is in line with the results observed by Iwanek *et al.*[8] using $SnCl_4$ catalysis, where only the parent pyrogallorene could be formed through the reaction of 1,2,3-trimethoxybenzene with trioxane, and reactions with aliphatic aldehydes failed to yield cyclic tetramers.

Selectivity of the reaction

In this study, we have observed selectivity for the formation of the *rctt* chair isomer of octa-*O*-alkyl resorcin[4]arenes for a range of aldehydes and resorcinol derivatives. In the synthesis of resorcin[4]arenes under homogeneous conditions where there is no protection of the phenolic OH groups, the chair is considered to be the kinetic product which is only observed in the early part of the reaction, whereas the *rccc* boat is the thermodynamic product. The situation is more complex in heterogeneous reactions,[1,14] where the solubility of each isomer can affect the distribution of products, but it has still been shown that prolonged treatment of the *rctt* chair isomer with acid results in formation of the boat. This preference for the boat conformer has been related to the ability to form the maximum number of hydrogen bonds between the resorcinol units with the minimum steric interference between the substituents at the methylene-bridge positions.[1,14]

In the case of octa-*O*-alkyl resorcin[4]arenes, the major driving force to the formation of the boat, the presence of an array of hydrogen bonds between the resorcinol units, is no longer an important factor. In the previous synthetic accounts where Lewis acids have been used, stereoisomer mixtures have been observed. In the cases of catalysis by $SOCl_2$, $POCl_3$ and $AlCl_3$ the *rcct* diamond isomer has been the preferentially formed product: selectivity for the boat is only observed when $SnCl_4$ is used, a result that has been ascribed to templation by complexation of the metal ions to the ether oxygens.[15]

In view of these previous reports, the isolation of the *rctt* chair from the reactions of 1,3-dimethoxybenzene with a range of aldehydes is initially somewhat surprising. While in the majority of cases this reaction is heterogeneous, identical results in favour of the *rctt* chair stereoisomer are observed even when the reaction conditions are homogeneous, as in the case of **14**. In this Brønsted-acid catalysed reaction, potentially templating metal and potential hydrogen bonding arrays between the aromatic units are absent. This suggests that, in this case, the thermodynamically more stable isomer may be a result of minimised steric interactions, *i.e.* is one in which the *O*-methylresorcinol units are as far apart as possible both from themselves and, through a *rctt* configuration at the methylene bridge positions, from the side chains.

To investigate whether this chair arrangement was particularly stable in comparison to the boat, which is only formed at

Table 5 Comparison of ^{1}H NMR data for **14** and **15** ($CDCl_3$) with previously reported data for isolated stereoisomers

Compound	Stereoisomer	Spectrum	Ref.
14	*rctt* chair	6.56 (s), 6.44 (s), 6.41 (s), 6.36 (s) 4.59 (q), 3.87 (s), 3.79 (s), 1.45 (d)	This study
	rccc boat	6.50 (s), 6.46 (s), 4.47 (q), 3.61 (s), 1.32 (d)	14
15	*rctt* chair	6.96 (s), 6.51 (s), 6.43 (s), 6.27 (s), 4.69 (m), 3.91 (s), 3.65 (s), 1.62 (m), 1.43 (m), 0.85 (d)	This study
	rctt chair	6.93 (s), 6.59 (s), 6.40 (s), 6.25 (s), 4.66 (m), 3.88 (s), 3.62 (s), 1.60 (m), 1.42 (m), 0.82 (d)	15
	rccc boat	6.60 (s), 6.32 (s), 4.60 (t), 3.60 (s), 1.69 (dd), 1.55 (m), 0.91 (d)	15
	rcct diamond	7.66 (s), 6.52 (s), 6.43 (s), 6.36 (s), 5.23 (t), 4.76 (m), 3.86 (s), 3.83 (s), 3.76 (s), 3.58 (s), 1.82 (m), 1.55 (m), 1.33 (m), 0.89 (m), 0.79 (m), 0.55 (d)	15

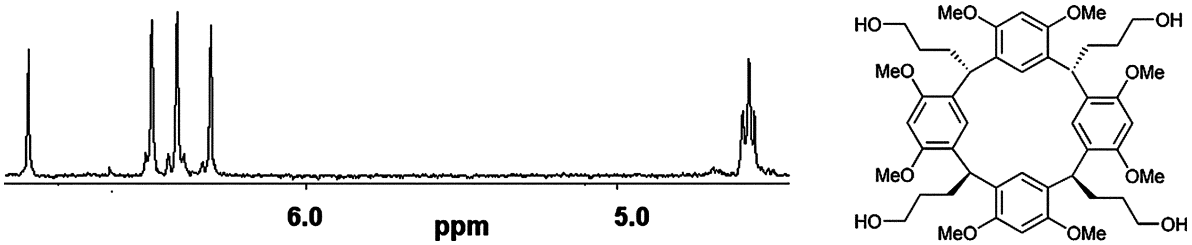


Fig. 5 ^{1}H NMR spectrum of **16** in $CDCl_3$ (side-chain signals not shown).

lower temperatures, we undertook hybrid density functional theory calculations at the B3LYP level with a 6-31G(d) basis set in the Gaussian 03 package.[32] Calculations were performed on a range of starting conformations of the two fixed configurations (*rccc* and *rctt*) of **14**, which features methyl residues at the methylene bridges. The minimised conformations are shown in Fig. 6 with the energies in Table 6. The calculations predict an energy difference of 1.2 kJ mol^{-1}, in favour of the chair conformation, in line with our experimental results. Inspection of the optimised conformer for **14a** shows that the octa-*O*-methyl resorcin[4]arene exists in a flattened boat arrangement. The angles between the flattened aromatic units are 0° with the methyl groups orientated above the plane such that a methyl hydrogen atom interacts with a methoxy oxygen on the adjacent ring. For **14b**, a normal chair conformation is obtained, once again with the methyl groups on the co-planar rings orientated to maximize their interaction with adjacent methoxy groups.

To ensure validation of the results obtained for **14a** and **14b**, calculations were also performed on the known analogous resorcin[4]arenes **22a** and **22b** which have been shown experimentally to exist preferentially in the *rccc* boat stereoisomer.[1,14] The optimised conformations are shown in Fig. 7,

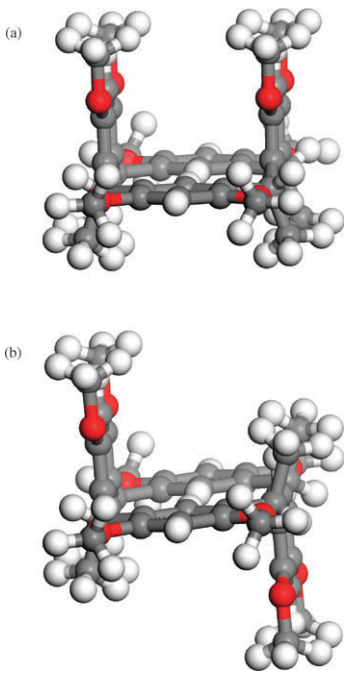
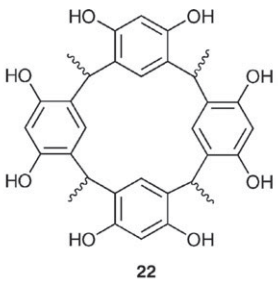


Fig. 6 Predicted structure of (a) **14a** and (b) **14b** using B3LYP/6-31G(d).

Table 6 Comparison of energy of minimised conformations of **14** and **22**

Stereoisomer	**14**	**22**
rccc Boat (Hartrees)	−2154.88076 (**14a**)	−1840.461459 (**22a**)
rctt Chair (Hartrees)	−2154.881482 (**14b**)	−1840.443855 (**22b**)
Chair − Boat (kJ mol^{-1})	−1.2	46.2



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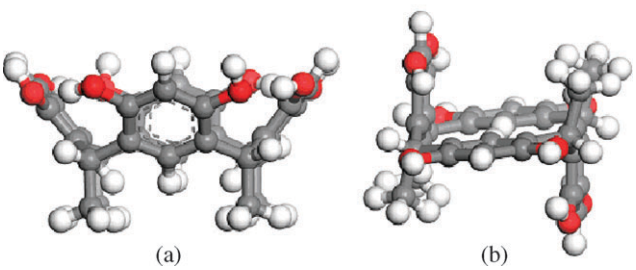

Fig. 7 Predicted structure of (a) **22a** and (b) **22b** using B3LYP/6-31G(d).

with the corresponding energies in Table 6. As expected, the lower energy macrocycle has a *rccc* configuration with adoption of the boat conformation. This achieves maximum hydrogen bonding (1.92 Å), with the angle between opposite aromatic units being 77°. In contrast, the higher energy *rctt* configuration adopts a chair conformation with minimal hydrogen bonding (3.25 Å). To quantify the effect of the hydrogen bonding MM3 calculations were carried out using the Cache Package.[33] These calculations indicate that the hydrogen bonding stabilizes the *rccc* configuration by over 30 kJ mol^{-1}. This confirms that H bonding is a significant driving force in the adoption of the *rccc* conformation for **22**, a factor which is absent for **14**.

Conclusions

Condensation reactions of 1,3-dimethoxybenzene with a diverse series of aldehydes using Brønsted-acid catalysis in acetic

acid at 80 °C lead exclusively to the formation of the *rctt* chair stereoisomer of the octa-*O*-alkyl resorcin[4]arenes. Unlike previously reported methods for the formation of the *rccc* boat stereoisomer,[15] the new reaction conditions are applicable over a wide range of starting aldehydes, including branched- and straight-chain aliphatic aldehydes, aromatic aldehydes and even the masked aldehyde 2,3-dihydrofuran. The presence of the expected competing *rccc* boat stereoisomer in lower-temperature reactions leads to the conclusion that, in the synthesis of octa-*O*-alkyl resorcin[4]arenes in which there is no templating metal or the possibility of positive hydrogen-bonding interactions, the *rctt* chair is the thermodynamic product. This result has been confirmed using quantum chemical calculation studies which indicate that the *rctt* chair stereoisomer is, indeed, the lower energy product.

Experimental

All chemicals were obtained from Sigma-Aldrich, Fluka, Lancaster or Acros Organics and, unless specified, were used without further purification. Deuterated solvents for NMR use were purchased from Apollo. NMR spectra were recorded at 273 K, except when stated otherwise, using a Bruker DPX-400 Avance spectrometer, operating at 400.13 MHz (proton) and 100.6 MHz (carbon), Shifts are referenced relative to the internal solvent signals. Melting points were determined using IA9000 digital melting point apparatus and are uncorrected. (ESI ^{1}H NMR data for *rccc* boat stereoisomers at 25 °C).

General methods for the preparation of octa-*O*-alkyl resorcin[4]arenes

Method 1: Condensation in the presence of $SnCl_4$. 1,3-Dimethoxybenzene (2.00 cm^3, 15.3 mmol) and 4-hydroxybenzaldehyde (1.86 g, 15.3 mmol) were added to $SnCl_4$ (1.78 cm^3, 15.3 mmol) in either Et_2O or $CHCl_3$ (20 cm^3). The reaction mixture was stirred at 25 °C for 16 or 72 h. The product was isolated by filtration and washed with Et_2O to yield the crude mixture of isomers as a purple powder.

Method 2: Condensation with HCl in ethanol. Aq. HCl (9 M, 0.8 cm^3) was added dropwise to a stirred solution of 1,3-dimethoxybenzene (0.5 cm^3, 3.82 mmol) and 4-hydroxybenzaldehyde (0.46 g, 3.82 mmol) in EtOH (6.25 cm^3). The mixture was then allowed to stir at reflux for 16 or 72 h. The mixture was allowed to cool to room temperature and then filtered to yield the crude mixture of isomers as a purple powder.

Method 3: Condensation in acetic acid. 1,3-Dimethoxybenzene (0.528 g, 3.82 mmol) and the aldehyde (3.82 mmol) were stirred together in acetic acid (20 cm^3) in the presence or absence of H^+ (8.36–13.90 meq.) from a catalytic Brønsted acid at 25 or 80 °C for 18 h. The reaction mixture was cooled and the resulting precipitate isolated by filtration. If no precipitation occurred, water (50 ml) was added to the reaction mixture to aid precipitation.

Compound 3

rctt-*Chair*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 4H, O*H*), 6.60 (s, 2H, Ar*H*), 6.46 (s, 2H, Ar*H*), 6.36 (m, 16H, Ar*H*), 6.17 (s, 2H, Ar*H*), 5.97 (s, 2H, Ar*H*), 5.49 (s, 4H, ArC*H*), 3.64 (s, 12H, OCH_3), 3.59 (s, 12H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.5, 178.6, 155.6, 154.8, 132.6, 129.7, 125.1, 123.5, 114.1, 55.7, 55.6; ν_{max} 1609, 1582, 1504, 1452, 1437, 1199, 1093, 1030 cm^{-1}; mp 320 °C (decomp.); MALDI *m*/*z* (relative intensity) 968.4 ((M − H, 92), 991.4 (M + Na, 100), 1007.3 (M + K, 35).

rccc-*Boat*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.4 (s, 4H, O*H*), 6.53 (d, J = 8.5 Hz, 8H, Ar*H*), 6.47 (d, J = 8.5 Hz, 8H, Ar*H*), 6.36 (s, 4H, Ar*H*), 6.13 (s, 4H, Ar*H*), 5.45 (s, 4H, ArC*H*), 3.60 (s, 12H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.9, 154.8, 133.5, 129.5, 129.4, 114.4, 114.3, 114.2, 55.7, 41.6; ν_{max} 1611, 1582, 1509, 1499, 1542, 1438, 1200, 1095 cm^{-1}; mp 280–285 °C; MALDI *m*/*z* (relative intensity) 968.4 (M − H, 100), 991.4 (M + Na, 93).

Compound 13. Method 3 was applied to 1,3-dimethoxybenzene (0.5 cm^3, 3.8 mmol) and 4-octyloxybenzaldehyde (0.89 g, 3.8 mmol) using H_2SO_4 (H^+ 8.36 meq.). The crude products of these reactions were isolated by filtration as pale blue powders.

Method 3 (80 °C): overall yield 54%, chair isomer 100%
Method 3 (25 °C): overall yield 21%, chair : boat 8.3 : 1.7

rctt-*Chair*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, J = 8.0 Hz, 8H, Ar*H*), 6.49 (d, J = 8.0 Hz, 8H, Ar*H*), 6.46 (s, 2H, Ar*H*), 6.41 (s, 2H, Ar*H*), 6.21 (s, 2H, Ar*H*), 5.83 (s, 2H, Ar*H*), 5.69 (s, 4H, ArC*H*), 3.84 (t, J = 6.5 Hz, 8H, OCH_2), 3.71 (s, 12H, OCH_3), 1.75 (m, 8H, OCH$_2$CH_2), 1.2–1.5 (m, 40H, (CH_2)$_5$CH$_3$), 0.91 (t, J = 7 Hz, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 183.0, 156.3, 155.5, 155.1, 134.5, 129.5, 127.8, 125.0, 124.2, 112.9, 96.1, 94.9, 67.3, 55.9, 55.4, 41.5, 31.4, 29.2, 29.1, 28.9, 25.7, 22.4, 13.7; ν_{max} 2929, 2852, 1609, 1584, 1508, 1202, 1038 cm^{-1}; mp 245–250 °C. Anal. Calc. for $C_{92}H_{120}O_{12}$: C: 77.80, H: 8.45. Found: C: 77.93, H: 8.53%.

Compound 14. Method 3 was applied to 1,3-dimethoxybenzene (0.5 cm^3, 3.8 mmol) and acetaldehyde (0.168 g, 3.82 mmol) using H_2SO_4 (H^+ 8.36 meq.). The crude products of these reactions were isolated by filtration as pale blue powders.

Method 3 (80 °C): overall yield 70%, chair isomer 100%
Method 3 (25 °C): overall yield 91%, chair : boat 6 : 4

rctt-*Chair*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 2H, Ar*H*), 6.44 (s, 4H, Ar*H*), 6.41 (s, 4H, Ar*H*), 6.36 (s, 4H, Ar*H*), 4.59 (q, J = 7.0 Hz, J = 7.0 Hz, 4H, ArC*H*), 3.87 (s, 12H, OCH_3), 3.79 (s, 12H, OCH_3), 1.45 (d, J = 7.50 Hz, 12H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 155.5, 127.7, 127.6, 126.9, 123.6, 97.5, 96.4, 56.4, 56.3, 44.3, 33.5, 26.0, 23.8, 22.2; ν_{max} 2946, 2923, 2853, 1465, 1297, 1201, 1037 cm^{-1}; mp 320–322 °C.

Compound 15[10]. Method 3 was applied to 1,3-dimethoxybenzene (0.5 cm^3, 3.8 mmol) and isovaleraldehyde (0.41 ml, 0.329 g, 3.82 mmol) using H_2SO_4 (H^+ 8.36 meq.). The crude products of these reactions were isolated by filtration as off-white powders.

Method 3 (80 °C): overall yield 30.5%, chair isomer 100%
Method 3 (25 °C): overall yield 88.1%, chair : boat 5.2 : 4.8

rctt-*Chair*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H, Ar*H*), 6.51 (s, 2H, Ar*H*), 6.43 (s, 2H, Ar*H*), 6.27 (s, 2H, Ar*H*) 4.69 (m, 4H, ArC*H*), 3.91 (s, 12H, OCH_3), 3.65 (s, 12H, OCH_3), 1.62 (m, 8H, CH_2), 1.43 (m, 4H, C*H*), 0.85 (d, J = 6.0 Hz, 24H, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 154.9, 127.1, 127.0, 126.3, 123.0, 96.9, 95.7, 55.8, 55.7, 43.7, 32.8, 25.4, 23.1, 21.6.

Compound 16. Aq. HCl (9 M, 1 cm^3) was added dropwise to a solution of 1,3-dimethoxybenzene (0.5 cm^3, 3.8 mmol) and 2,3-dihydrofuran (0.289 cm^3, 3.82 mmol) in acetic acid (20 cm^3). The reaction mixture was then heated at 60 °C overnight. After cooling, the product was isolated by filtration and washed with Et_2O to yield a white powder (0.489 g, 61.4%).

rctt-*Chair*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 2H, Ar*H*), 6.50 (s, 2H, Ar*H*), 6.41 (s, 2H, Ar*H*), 6.30 (s, 2H, Ar*H*), 4.57 (t, J = 7.5 Hz, ArC*H*), 4.01 (t, J = 6.5, 8H, CH_2OH), 3.90 (s, 12H, OCH_3), 3.68 (s, 12H, OCH_3), 1.74 (m, 8H, CHCH_2), 1.54 (m, 8H, CH_2CH$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.3, 126.5, 126.3, 125.8, 122.6, 96.2, 95.3, 64.3, 55.6, 55.5, 34.7, 30.5, 30.3, 26.5; ν_{max} 2940, 2837, 1735, 1608, 1578, 1496, 1439, 1243, 1203, 1027, 889 cm^{-1}; mp 236–238 °C.

Compound 20

rccc-*Boat*. A catalytic amount of pyridine (0.5 cm^3) was added to a solution of **3** (0.467 g, 0.48 mmol) in acetic anhydride (20 cm^3). The reaction mixture was heated at reflux for 3 h. After complete cooling, MeOH (20 cm^3) was slowly added to aid precipitation. The precipitate was isolated by filtration and washed with MeOH (50 cm^3) to yield the acylated mixture of conformers as a white powder. This crude product was then purified by column chromatography ($CHCl_3$–EtOAc 4 : 1) to give the boat isomer as a white powder (0.07 g, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, J = 9 Hz, 16H, Ar*H*), 6.43 (s, 2H, Ar*H*), 6.22 (s, 2H, Ar*H*), 6.22 (s, 2H, Ar*H*), 6.07 (s, 2H, Ar*H*), 5.79 (s, 2H, Ar*H*), 5.73 (s, 4H, ArC*H*), 3.66 (s, 12H, OCH_3), 3.52 (s, 12H, OCH_3), 2.33 (s, 12H, OCCH_3).

rctt-*Chair*. A catalytic amount of pyridine (1 cm^3) was added to a solution of **3b** (1.00 g, 1.03 mmol) in acetic anhydride (20 cm^3). The reaction mixture was then heated at reflux for three hours. After complete cooling, MeOH (30 cm^3) was added slowly to aid precipitation. The precipitate was isolated by filtration and washed with MeOH (70 cm^3) to yield the desired product as a white powder (0.98 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J = 8.5 Hz, 8H, Ar*H*), 6.65 (d, J = 8.5 Hz, 8H, Ar*H*), 6.45 (s, 2H, Ar*H*), 6.41 (s, 2H, Ar*H*), 6.18 (s, 2H, Ar*H*), 5.76 (s, 4H, ArC*H*), 5.64 (s, 2H, Ar*H*), 3.72 (s, 12H, OCH_3), 3.69 (s, 12H, OCH_3), 2.29 (s, 12H, OCCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 155.6, 155.4, 147.9, 141.5, 140.2, 131.2, 129.4, 128.0, 123.8, 119.7, 95.5, 94.6, 55.6, 55.4, 41.6, 30.5; ν_{max} 2943, 2837, 1733, 1609, 1583, 1503, 1463, 1291, 1200, 1033 cm^{-1}; mp 351–353 °C. Anal. Calc. for $C_{68}H_{64}O_{16}$·2$CH_3CO_2COCH_3$: C: 68.05, H: 5.71. Found: C: 67.79, H: 5.43%.

Compound 21. Pyridine (0.5 cm^3) was added to **2** (1.00 g, 1.03 mmol) and butanoic anhydride (2.00 cm^3, 11.7 mmol) in $CHCl_3$ (20 cm^3). The reaction mixture was heated at reflux for 18 h. After cooling, MeOH (30 cm^3) was added slowly and the resultant precipitate was collected by filtration and washed with Et_2O (40 cm^3) to give the chair isomer as an off-white powder. The filtrate was evaporated to dryness and the residue stirred in Et_2O. This suspension was filtered off and the isolated powder was further purified by column chromatography ($CHCl_3$–EtOAc 95 : 5) to give the boat isomer as a yellow powder. chair 31%, boat 26%.

rctt-*Chair*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, J = 8.5 Hz, 8H, Ar*H*), 6.65 (d, J = 8.5 Hz, 8H, Ar*H*), 6.44 (s, 2H, Ar*H*), 6.41 (s, 2H, Ar*H*), 6.19 (s, 2H, Ar*H*), 5.76 (s, 4H, ArC*H*), 5.69 (s, 2H, Ar*H*), 3.71 (s, 12H, OCH_3), 3.69 (s, 12H, OCH_3), 2.52 (t, J = 7.0 Hz, 8H, COCH_2), 1.80 (m, 8H, $CH_2CH_2CH_3$), 1.06 (t, J = 7.5 Hz, 12H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.6, 155.4, 147.9, 140.1, 131.1, 129.4, 128.0, 123.9, 123.6, 119.7, 95.5, 94.7, 55.6, 55.4, 41.6, 35.9, 18.0, 13.3; ν_{max} 2966, 2935, 2878, 2832, 1751, 1612, 1586, 1502, 1451 cm^{-1}; mp 334–337 °C. Anal. Calc. for $C_{76}H_{80}O_{16}$: C: 73.06, H: 6.45. Found: C: 73.08, H: 6.47%.

rccc-*Boat*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (m, 16H, Ar*H*), 6.42 (s, 2H, Ar*H*), 6.23 (s, 2H, Ar*H*), 6.10 (s, 2H, Ar*H*), 5.82 (s, 2H, Ar*H*), 5.73 (s, 4H, ArC*H*), 3.62 (s, 12H, OCH_3), 3.51 (s, 12H, OCH_3), 2.55 (t, J = 7.5 Hz, 8H, COCH_2), 1.83 (sextet, 8H, $CH_2CH_2CH_3$), 1.09 (t, J = 7 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.8, 155.5, 148.0, 140.9, 132.3, 129.2, 127.9, 123.9, 123.6, 120.0, 95.9, 95.6, 55.6, 41.9, 35.9, 18.1, 13.3; ν_{max} 2963, 2936, 2877, 2832, 1752, 1502, 1299, 1244, 1165 cm^{-1}; mp 261–263 °C. Anal. Calc. for $C_{76}H_{80}O_{16}$: C: 73.06, H: 6.45. Found: C: 72.56, H: 6.42%.

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