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# Generation and reactions of new ether and acetal functionalized tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene derivatives. DSC and NMR studies on the [2+2] retrocycloaddition of several cyclobutane dimers

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**Abstract**—Two new highly pyramidalized tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene derivatives containing ether and acetal functionalities have been generated, trapped as Diels–Alder adducts and dimerized. The initially obtained diene dimers were photochemically converted into cyclobutane derivatives. The thermal reversion of several cyclobutane derivatives to the corresponding dienes has been studied by $^1$H NMR, ab initio calculations and DSC. For the first time, transannular additions of bromine and iodine to a diene dimer of this series have been observed.


## 1. Introduction

The chemistry of highly pyramidalized alkenes attracts attention of many chemists due to their unusual reactivity and possible synthetic applications. Several reviews have been published till present covering different periods of time.[1–4] Highly pyramidalized alkenes, such as 1,2-dehydrocubane,[5] **1**, 4,5-dehydrohomocubane,[6,7] **2**, or tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene and derivatives,[8–10] **3**, are highly reactive toward nucleophiles and dienes (Fig. 1). In the absence of such reagents they usually dimerize through a [2+2]cycloaddition reaction. Much of the work carried out in this field is mainly of interest to physical organic chemists, due to the lack of functionality of the generated pyramidalized alkenes. We have been working for several years on the generation of functionalized highly pyramidalized alkenes[11–17] and in their cross-coupling reactions[11,12,15,16] to increase the synthetic value of this kind of reactive intermediates.


**Figure 1**. Structure of the highly pyramidalized alkenes: 1,2-dehydrocubane (**1**), 4,5-dehydrohomocubane (**2**), and tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene (**3**).

Herein we report the generation, trapping, and dimerization of two functionalized tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene derivatives, 3,7-(oxydimethylene)tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene, **9** (Scheme 1) and 3,7-[isopropylidenebis(oxymethyl)]tricyclo[3.3.0.0$^{3,7}$]oct-1(5)-ene, **16** (Scheme 2), containing ether and acetal functionalities, respectively. The dienes **12** and **19** obtained when these alkenes were generated in the absence of a trapping agent were photochemically converted (partially in the case of **12**) into the corresponding cyclobutane derivatives, **8** and **18**, respectively. Hydrolysis of **18** gave tetrol **20**. The thermal conversion of the cyclobutane derivatives **8**, **18**, and **20** into the corresponding dienes was studied by $^1$H NMR and by theoretical ab initio methods while the last two transformations were also studied by DSC. Moreover, for the first time, a transannular addition of bromine and iodine to a diene dimer of this polycyclic skeleton, **12**, has been observed.

## 2. Results and discussion

The required precursor of alkene **9** would be diiodide **6**, which was readily prepared from the recently described diiodide diester **4**[18] (Scheme 1). $LiAlH_4$ reduction of **4** in diethyl ether afforded diol **5** in 93% yield. Not unexpectedly, reaction of this diol with tosyl chloride (2 equiv) in hot pyridine gave

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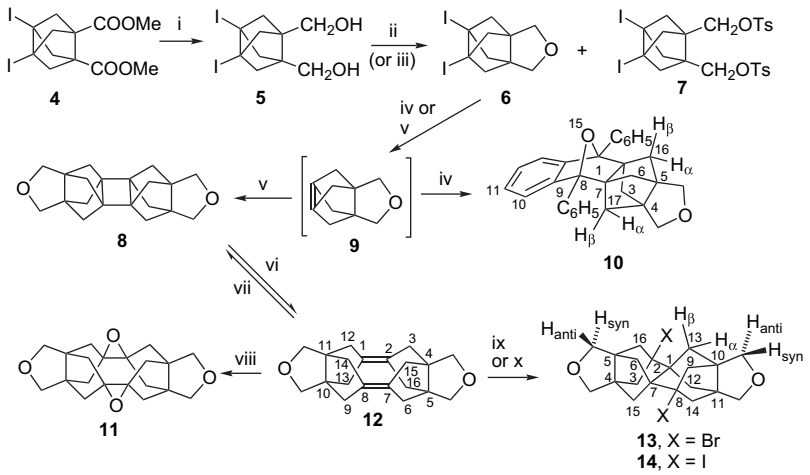
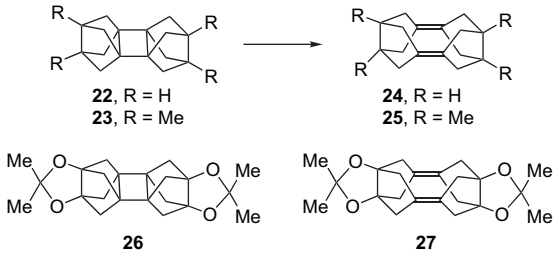
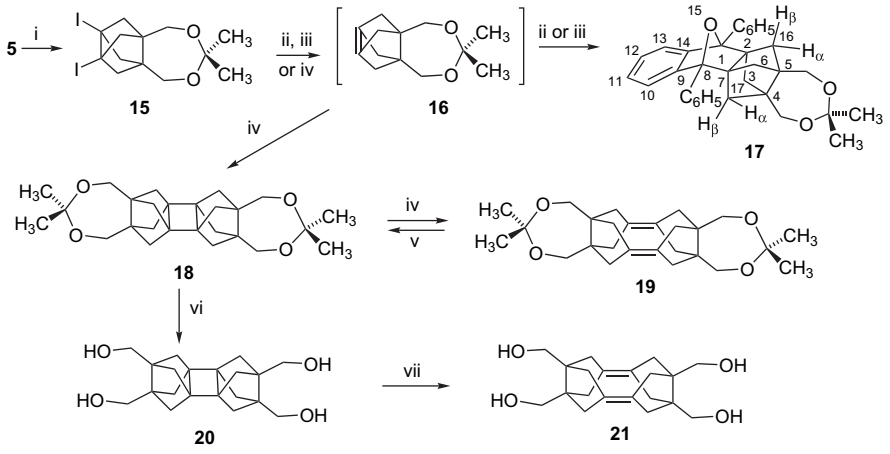


**Scheme 1**. Generation, trapping, and dimerization of pyramidalized alkene **9**: transformations from dimer **12**. (i) $LiAlH_4$, diethyl ether, rt, 1 h, 93% yield. (ii) Tosyl chloride (2 equiv), pyridine, 100 °C, 6 h, 92% yield of **6**. (iii) Tosyl chloride (2 equiv), pyridine, 0 °C, 1 h, 26% yield of **7**. (iv) *t*-BuLi, *n*-pentane/THF, 1,3-diphenylisobenzofuran (DPIBF), −64 °C→rt, 77% yield. (v) Molten sodium, 1,4-dioxane, reflux, 3 h, 56% yield. (vi) $CDCl_3$ solution, rt, overnight, quantitative conversion. (vii) *n*-Pentane, h$\nu$, 6 h, mixture **12**:**8** in the ratio of 1:0.5. (viii) Dimethyldioxirane, acetone, rt, 1 h, quantitative yield. (ix) $Br_2$, *n*-pentane/$CH_2Cl_2$, rt, 13 h, 69% yield of **13**. (x) $I_2$, *n*-pentane/$CH_2Cl_2$, rt, 20 h, 69% yield of **14**.

ether **6** in 92% yield. Reasonably, the initially formed monotosylate undergoes intramolecular nucleophilic substitution to give the obtained cyclic ether. When this reaction was carried out at lower temperature (0 °C), ditosylate **7** was isolated in 26% yield. Generation of the highly pyramidalized alkene was carried out in two ways: (a) by reaction with *t*-BuLi and (b) by reaction with molten sodium in boiling 1,4-dioxane. Thus, reaction of diiodide **6** with *t*-BuLi in anhydrous THF in the presence of 1,3-diphenylisobenzofuran (DPIBF, 1.2 equiv) gave compound **10**, the Diels–Alder adduct derived from the pyramidalized alkene **9** and the used diene, in 77% yield after column chromatography. Moreover, reaction of **6** with molten sodium in boiling 1,4-dioxane in the absence of any trapping agent gave diene dimer **12** in an acceptable 56% isolated yield. Worthy of note and contrary to previous observations with related dienes, such as the parent compound, pentacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$]hexadeca-1,7-diene, **24**, and its 4,5,10,11-tetramethyl derivative **25** (Scheme 3), diene **12** is quite reactive toward the oxygen of the air, giving a mixture of the corresponding mono- and bis-epoxides. In fact, purification of **12** by column chromatography had to be carried out using degassed eluents to avoid this oxidation. Oxidation of diene **12** to the corresponding bis-epoxide **11** was easily carried out by reaction of **12** with an acetone solution of dimethyldioxirane. Also, reaction of **12** with an excess of bromine or iodine in a mixture *n*-pentane/$CH_2Cl_2$ gave products **13** and **14**, respectively, derived from the transannular *anti*-addition of bromine or iodine to



**Scheme 3**. Structures of cyclobutanes **22**, **23**, and **26** and dienes **24**, **25**, and **27**.



**Scheme 2**. Generation, trapping, and dimerization of pyramidalized alkene **16**: transformations from dimer **19**. (i) 2,2-Dimethoxypropane, cat. TsOH·$H_2O$, $CH_2Cl_2$, reflux, 3 h, 96% yield. (ii) *t*-BuLi, *n*-pentane/THF, DPIBF, −64 °C→rt, 55% yield. (iii) 0.45% Na(Hg), 1,4-dioxane, DPIBF, rt, 54% yield. (iv) Molten sodium, 1,4-dioxane, reflux, 2 h, 59% yield. (v) *n*-Pentane, h$\nu$, 86 h, quantitative yield. (vi) TsOH, $CH_2Cl_2$/$H_2O$, ultrasound irradiation, 35 °C, 10 min, 82% yield. (vii) 1,4-Dioxane, reflux, 3 h, quantitative yield.

the diene system. The transannular *anti*-addition of halogens to related dienes had been previously observed,[19,20] but this is the first time this kind of addition is observed with diene dimers containing the polycyclic skeleton of **24**.

Moreover, irradiation of diene **12** with a low-pressure mercury lamp gave a mixture containing variable amounts of the starting diene and the cyclobutane derivative **8**. A solution of one of these mixtures in $CDCl_3$ at room temperature was rapidly transformed into a solution of diene **12**, showing the high thermal instability of cyclobutane **8**. A similar situation had been previously observed for the parent diene and cyclobutane derivatives, **24** and **22**, respectively (Scheme 3).[10]

For the generation of the pyramidalized alkene **16**, we required the diiodide **15**, which was easily obtained from diol **5** by reaction with 2,2-dimethoxypropane in $CH_2Cl_2$ under acidic catalysis (*p*-TsOH). Compound **15** and its derivatives containing the seven-membered acetal function are very labile to acidic conditions and must be carefully handled. As before, reaction of diiodide **15** with *t*-BuLi in THF in the presence of 1,3-diphenylisobenzofuran gave compound **17**, the Diels–Alder adduct derived from pyramidalized alkene **16** and DPIBF, in 55% yield. Also, reaction of **15** with molten sodium in boiling 1,4-dioxane gave diene dimer **19** in 59% isolated yield. Irradiation of diene **19** with a low-pressure mercury lamp gave quantitatively the cyclobutane derivative **18**, which showed to be relatively thermally stable and could be fully characterized. Acidic hydrolysis of this compound gave the corresponding tetrol **20** in good yield. Heating a suspension of cyclobutane tetrol **20** in 1,4-dioxane under reflux for 2 h, diene tetrol **21** was quantitatively obtained.

As we will see later on, compound **19** exists preferentially in two conformations with chair 1,3-dioxepane rings in *anti* or *syn* relative arrangements (see theoretical calculations and Fig. 6). The $^1$H NMR spectrum of compound **19** at 25 °C was deceptively simple, showing a singlet (1.46 ppm) corresponding to the four methyl groups, a broad and nearly collapsed AB system (2.28 ppm) corresponding to the allylic methylene protons and a singlet (3.65 ppm) corresponding to the $CH_2O$ protons. This fact is due to a relatively fast equilibration of the different conformers in the $^1$H NMR time scale. However, at this temperature, the signal of the methyl carbon atoms in the $^{13}$C NMR spectrum was not observed, probably due to a slow equilibration among conformers in the $^{13}$C NMR time scale. In fact, the HSQC NMR spectrum of **19** at 0 °C showed a cross signal between the signal at 1.49 ppm corresponding to the methyl groups and signals at about 20 and 32 ppm, which must correspond to two kinds of methyl carbon atoms in the $^{13}$C NMR spectrum (not registered). At lower temperatures, the $^1$H NMR spectra of **19** showed broad signals, which split and become sharper as the temperature decreases. At −50 °C, the $^1$H NMR spectrum (see Section 5) may be interpreted as the spectrum of a nearly equimolar mixture of the above cited *anti* ($C_{2h}$ symmetric) and *syn* ($C_{2v}$ symmetric) conformers of **19**. For each of these conformers of **19**, two kinds of allylic methylene, only one kind of $CH_2O$ groups, both with diastereotopic protons, and two kinds of methyl groups are to be expected. In fact, the $^1$H NMR spectrum of **19** at −50 °C, shows eight doublets corresponding to the eight possible kinds of allylic protons of both conformers, three doublets (one of them of roughly double intensity) corresponding to the four possible kinds of $CH_2O$ protons of both conformers, and two singlets corresponding to the four possible kinds of methyl groups of both conformers. From the chemical shift difference of the methyl groups at −50 °C (55 Hz), a rate constant $k_c$=122 at the coalescence temperature (0 °C) was calculated. From this value and applying the Eyring equation, a $\Delta G^{\ddagger}$=13.3 kcal/mol was obtained for this process.

### 2.1. Kinetics of [2+2] retrocycloaddition of cyclobutane to diene derivatives by $^1$H NMR

The kinetics of the thermal conversion of cyclobutane derivatives **8**, **18**, and **20** to the corresponding diene derivatives, **12**, **19**, and **21**, respectively, were studied by $^1$H NMR spectroscopy. For compound **8**, the starting material was a mixture with **12** in the ratio of 0.38:1 and the experiments were carried out in $CDCl_3$ solution at 45 and 50 °C. The ratio **8**:**12** was easily obtained every 5.5 min by integration of the clearly resolved signals (s) for the methyleneoxy groups, appearing at $\delta$ 3.60 and 3.65 ppm for **8** and **12**, respectively. The plot of ln[**8**]/ln([**8**]+[**12**]) versus time at both temperatures gave straight lines (first order kinetics) ($r^2$=0.995, $n$=15 for the process at 50 °C and $r^2$=0.998, $n$=15 for the process at 45 °C) with rate constant values of $k_{50}=12.2\times10^3$/min and $k_{45}=9.7\times10^3$/min. From these rate constant values, by using the Arrhenius equation, an activation energy ($E_a$) of 9.3 kcal/mol (Table 1) was obtained. Due to the reduced range of the used temperatures, only an approximate Arrhenius pre-exponential factor (ln $A$=10.3) could be calculated.

A similar study was performed for the conversion of **18** to **19**. In this case, we started with pure **18** and since this compound is more thermally stable than **8**, we carried out the experiments at higher temperatures (60, 70, and 90 °C) in pyridine-$d_5$. As in the previous case, the ratio **18**:**19** was easily obtained by integration of the signals (s) of the methyleneoxy groups, appearing at $\delta$ 3.83 and 3.65 ppm for **18** and **19**, respectively. For the experiments carried out at 60, 70, and 90 °C, $^1$H NMR spectra were recorded every 5, 3, and 2 min, respectively. The plots ln[**18**]/ln([**18**]+[**19**]) versus time at these temperatures gave straight lines (first order kinetics) ($r^2$=0.999, $n$=12 for the process at 60 °C, $r^2$=0.995, $n$=18 for the process at 70 °C, and $r^2$=0.961, $n$=6 for the process at 90 °C) with rate constant values of $k_{60}=9.9\times10^3$/min, $k_{70}=27.3\times10^3$/min, and $k_{90}=150.2\times10^3$/min. From these rate constant values, as before, an $E_a$=21.9±0.4 kcal/mol and a ln $A$=28.6±1.4 (Table 1) were calculated.

Similarly, the conversion of **20** to **21** was studied by $^1$H NMR. As in the precedent case, we started with pure **20**,

**Table 1**. Activation energies ($E_a$, kcal/mol) and Arrhenius pre-exponential factors (ln $A$) for the [2+2] retrocycloadditions of cyclobutanes **8**, **18**, and **20** to dienes **12**, **19**, and **21**, respectively

| | **8**→**12** | **18**→**19** | **20**→**21** |
|---|---|---|---|
| $E_a$ | 9.3 | 21.9±0.4 | 21±2 |
| ln $A$ | 10.3 | 28.6±1.4 | 23.4±3.0 |

whose thermal stability is intermediate between **8** and **18**. The experiments were carried out at similar temperatures than the preceding case (60, 70, 80, and 90 °C) in pyridine-$d_5$. In this case, the ratio **20**:**21** was easily obtained by integration of two different signals of each compound: (a) the signal corresponding to the annular methylene protons, appearing as a singlet at $\delta$ 1.94 ppm for **20** and as a nearly collapsed AB system at $\delta$ 2.62 ppm for **21** and (b) the signal (s) corresponding to the hydroxymethyl groups, appearing at $\delta$ 4.17 and 4.01 ppm for **20** and **21**, respectively. For the experiments carried out at 60, 70, 80, and 90 °C, $^1$H NMR spectra were collected approximately every 6, 3.5, 2, and 2 min, respectively. The plots ln[**20**]/ln([**20**]+[**21**]) versus time at these temperatures gave straight lines (first order kinetics) ($r^2$=0.997, $n$=14 for the process at 60 °C, $r^2$=0.997, $n$=12 for the process at 70 °C, $r^2$=0.992, $n$=17 for the process at 80 °C, and $r^2$=0.981, $n$=9 for the process at 90 °C) with rate constant values of $k_{60}=6\times10^3$/min, $k_{70}=18\times10^3$/min, $k_{80}=42\times10^3$/min, and $k_{90}=90\times10^3$/min. From these rate constant values, as before, an $E_a$=21±2 kcal/mol and a ln $A$=23.4±3.0 (Table 1) were calculated. The $E_a$ values for the conversions of **18** to **19** and **20** to **21** are roughly the same.

### 2.2. Thermal analysis

The solid-state thermal conversion of cyclobutanes **18** and **20** to give dienes **19** and **21** was studied by differential scanning calorimetry. This technique measures the heat flow exchanged by a sample as a function of temperature or as a function of time at a defined temperature. It is thus very useful to monitor solid-state chemical reactions.[21]

Cyclobutane **18** gave on heating the DSC profile shown in Figure 2. For a heating rate of 10 °C/min, a first highly exothermic peak at temperatures between 70 and 120 °C was observed, followed by a sharp endothermic peak at 281 °C. The exothermic phenomenon corresponds to the heat generated by the cyclobutane ring opening reaction to give the corresponding diene **19**. As it would be expected, this reaction exotherm did not appear when a sample of diene **19** was submitted to the same temperature profile. In this case, only an endothermic peak appeared at 281 °C, which most probably corresponded to the melting of diene **19**. Melting of **19** was also observed in the DSC analysis of cyclobutane **18**, indicating that the cyclobutane converted to crystalline diene on heating.

On the other hand, cyclobutane **20** also presented a highly exothermic peak in the temperature range between 65 and 120 °C (Fig. 3) caused by the transformation to diene **21**. For this substrate, the reaction took place consistently at slightly lower temperatures compared to cyclobutane **18**, irrespective of the heating rate used, although the differences were very small (3–5 °C, depending on the heating rate). Melting of the diene was not observed. Instead, a second less exothermic process at 220–260 °C was detected, which probably corresponds to the decomposition of the sample, a fact that is also observed in determining its melting point in a capillary tube.

For both cyclobutane substrates, the NMR analysis of samples that were rapidly cooled after being heated to a temperature just above the reaction peak showed that the process occurring in the DSC, happened in a straightforward manner, giving a clean reaction product. The reaction took place in the solid state, starting and ending in a white powder. The shape of the peak is an indication that the heat flow is due mainly to a single process, and that possible conformational rearrangements during the reaction do not take place or have a very small associated heat.

The heat of reaction was determined from the integration of the heat flow signal over the temperature range where the exothermic phenomena had taken place. The reaction enthalpy for the conversion of **18** to **19** (−39.4±1.7 kcal/mol) is much higher than the enthalpy for the conversion of **20** to **21** (−31.3±0.7 kcal/mol). Nevertheless, both

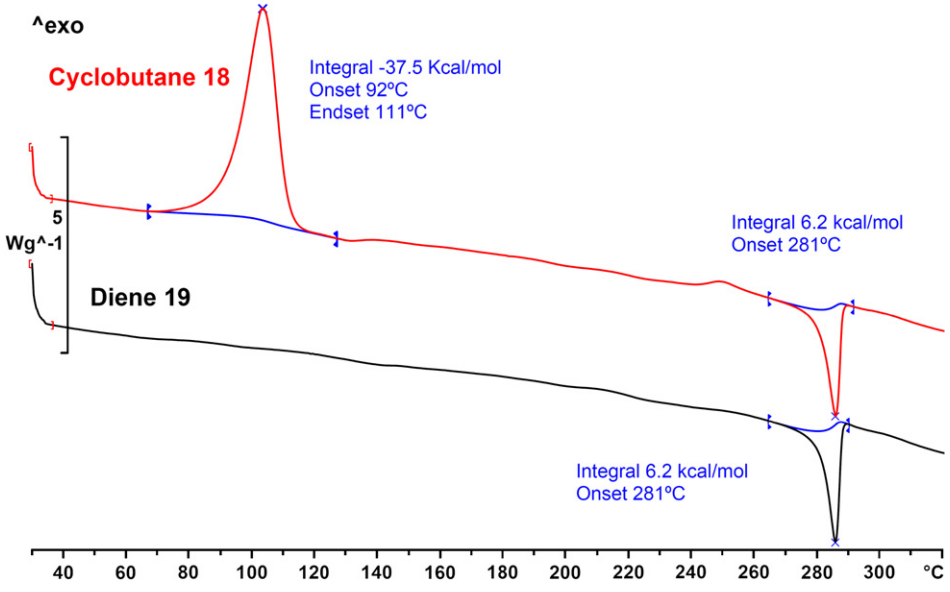



**Figure 2**. DSC curves at 10 °C/min for cyclobutane **18** and diene **19**.

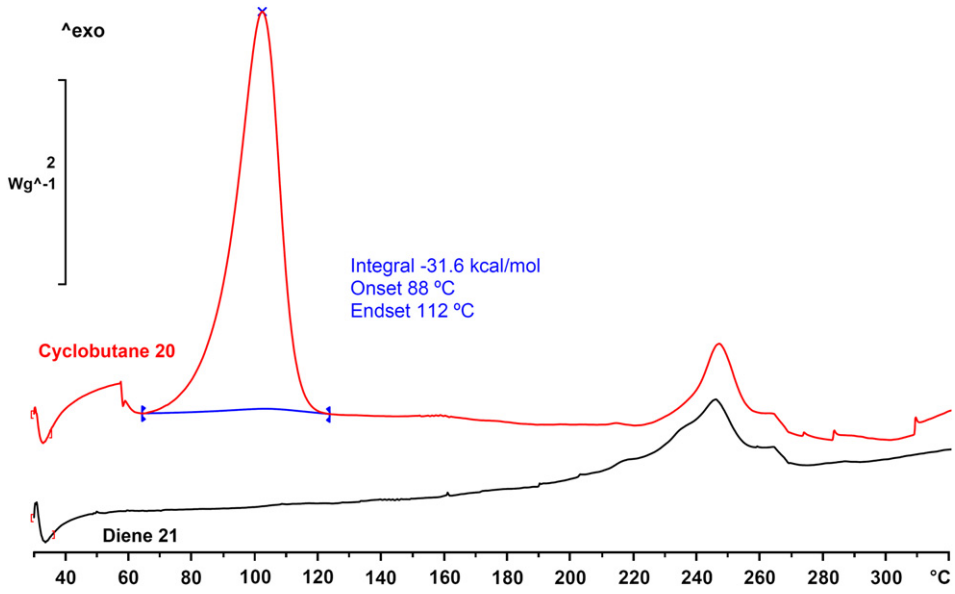



**Figure 3**. DSC curves at 10 °C/min for cyclobutane **20** and diene **21**.

substrates have a smaller heat of reaction compared to the structurally related tetramethyl derivative **23** (−45.6 kcal/mol, Scheme 3).[9]

From the DSC curves at different heating rates, the activation energy of the ring opening processes could be calculated (Fig. 4). Very gratifyingly, similar results were obtained applying the isoconversion method of Vyazovkin[22,23] or the Ozawa's method.[24] This second methodology assumes a first order kinetic model, which is what is reasonably expected for the cyclobutane conversion to the diene. Thus, activation energies of 28−31 and 24−26 kcal/mol were calculated for the thermal rearrangement of cyclobutanes **18** and **20**, respectively.

## 2.3. Theoretical calculations

**2.3.1. [2+2] Retrocycloaddition of cyclobutane to diene derivatives.** We have previously studied the thermal [2+2] retrocycloaddition of cyclobutane derivatives **22** and **23** to the corresponding dienes **24** and **25** (Scheme 3), by different theoretical methods (molecular mechanics, semiempirical, ab initio and DFT). Compound **22** was stable enough to be fully characterized although its half-life in $CDCl_3$ at 20 °C is about 50 h.[9] By way of contrast, compound **23** could never be obtained in pure form after irradiation of diene **25**, because it readily reverts to diene **25**. A mixture of **23** and **25** in the ratio of 8:2 in $CDCl_3$ solution at 20 °C was fully transformed into **25** after 18–20 h.[10] For the conversion of

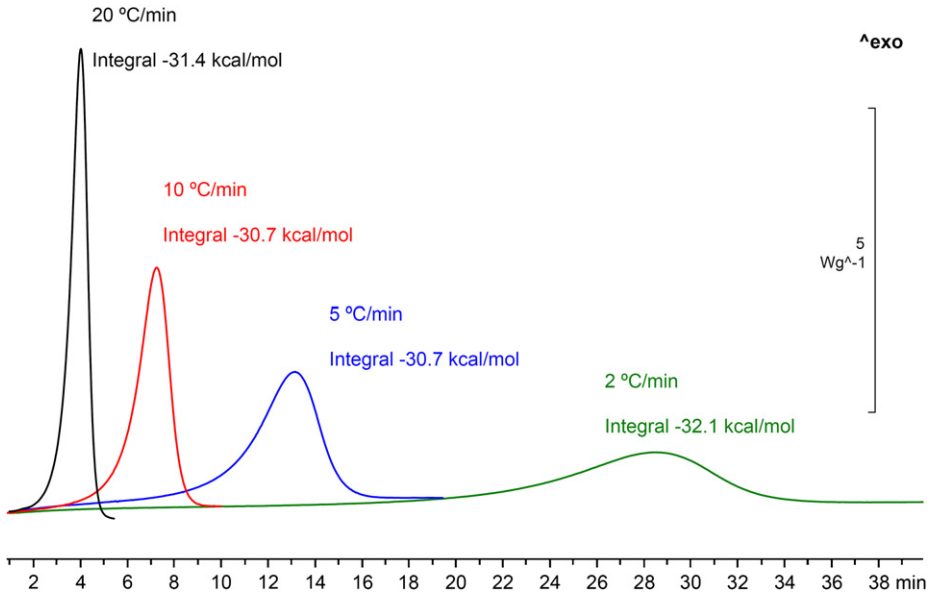



**Figure 4**. Heat flow profiles for the ring opening reaction of cyclobutane **20** to diene **21** at different heating rates.

**22** to **24**, the calculated enthalpies by MM2 (−43.2 kcal/mol) and by MP2/6-31G*//HF/3-21G (−41.7 kcal/mol) were in good agreement with the experimental values obtained by differential scanning calorimetry (DSC) in dynamic (−45.6±1.1 kcal/mol) and isothermic (−44.4 kcal/mol) experiments. For the faster conversion of **23** to **25** the enthalpies of the reaction were slightly higher (−46.1 kcal/mol by MM2 and −45.4 kcal/mol, using the MP2/6-31G*//HF/3-21G method). These results suggest processes with product like transition states (TS).

Although DFT calculations (B3LYP/6-31G*) gave not so accurate results (−59.0 kcal/mol for the conversion of **22** to **24** and −52.3 kcal/mol for the conversion of **23** to **25**), the same trend was observed, i.e., the higher the absolute value of the reaction enthalpy, the faster the process. This trend has also been observed in the case of cyclobutane **26** and diene **27**. In this case, cyclobutane **26** is so unstable that we could never observe it after irradiation of diene **27**.[13] The enthalpy of this process, for the compounds in their lower energy conformations having two envelope dioxolane rings in an *anti* arrangement, was calculated to be −57.1 kcal/mol by MM2[13] and we have calculated a value of −62.0 kcal/mol by B3LYP/6-31G*. These values are higher in absolute value than the corresponding ones calculated for the conversion of **22** to **24**, in accord with the previously observed trend. Since the reactivity trend in the cyclobutane to diene conversion is indistinctly observed with the molecular mechanics, ab initio, and DFT methods, in this paper we have restricted calculations to the B3LYP/6-31G* method.

Two preferred conformations were calculated for cyclobutane **8** and diene **12**, which show the tetrahydrofuran rings in envelope conformations with relative *anti* and *syn* arrangements (Fig. 5). The enthalpy for the conversion of **8** to **12** in the more stable *anti* arrangement was calculated to be −61.7 kcal/mol (−61.4 kcal/mol in the *syn* arrangement). This value is intermediate between those calculated for the conversions of **26** to **27** (−62.0 kcal/mol) and **22** to **24** (−59.0 kcal/mol), roughly in accord with the relative stabilities of these cyclobutanes (**22**>**8**>**26**).

Similarly, two preferred conformations were obtained for compounds **18** and **19**, in which the 1,3-dioxepane rings adopt chair conformations with an *anti* or *syn* relative arrangement (Fig. 6). The enthalpy for the conversion of **18** to **19** in the more stable *anti* arrangement was calculated to be −57.0 kcal/mol (−56.5 kcal/mol in the *syn* arrangement). This value is lower than that calculated for the conversion of **23** to **25** (−59.0 kcal/mol), in accord with the greater relative stability of cyclobutane **18**.

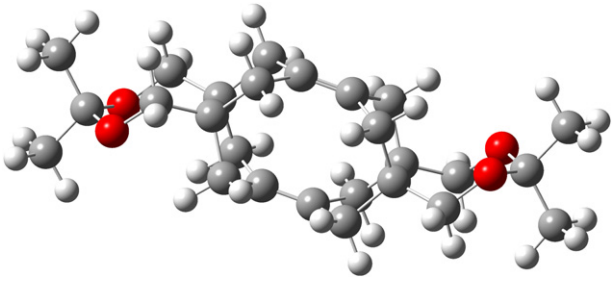


**Figure 6**. Optimized structure of the double chair *anti* conformer of **19**.

Similarly, for tetrols **20** and **21**, two preferred conformations were calculated in which the proximal hydroxyl groups establish intramolecular hydrogen bonds. The seven-membered rings thus formed adopt boat conformations with an *anti* or *syn* relative arrangement, in which the O–H···O angle is close to 180° (Fig. 7). The enthalpy for the conversion of **20** to **21** in the more stable *anti* arrangement was calculated to be −55.0 kcal/mol (−54.5 kcal/mol in the *syn* arrangement). This value is intermediate between those calculated for the conversion of **18** to **19** (−57.0 kcal/mol) and **23** to **25** (−52.3 kcal/mol), roughly in accord with their relative stabilities. Comparison of the relative theoretical and experimental data for the opening of tetrol **20** with those of **18** and **23** is not so clear. This is probably due to the presence of hydrogen bonds in the first case, which may vary depending on the conditions of the experiments [pyridine-$d_5$ solution ($^1$H NMR) and solid state (DSC)] or gas phase (calculations).

**2.3.2. Theoretical calculations on pyramidalized alkenes.** As we and others have previously found that B3LYP/6-31G* calculations are a reliable method for theoretically predicting the geometry and energy of highly pyramidalized alkenes,[25–29] we have also used B3LYP/6-31G* on pyramidalized alkenes **9** and **16**. The geometrical parameters of the pyramidalized alkenes **9** (mean value of the pyramidalization angle $\Phi$: 61.8°, C=C length: 1.383 Å; C3–C7 length: 1.671 Å; $\Delta H_{\mathrm{HOMO-LUMO}}$=3.88 eV) and **16** (mean value of $\Phi$: 61.8°, C=C length: 1.379 Å; C3–C7 length: 1.686 Å; $\Delta H_{\mathrm{HOMO-LUMO}}$=3.98 eV), are very close to the calculated values for the parent compound **3** ($\Phi$: 61.9°, C=C length: 1.380 Å; C3–C7 length: 1.667 Å; $\Delta H_{\mathrm{HOMO-LUMO}}$=4.17 eV).[4]

On the other hand, the geometrical parameters of dienes **12** (mean value of the pyramidalization angle $\Phi$: 14.2°, C=C

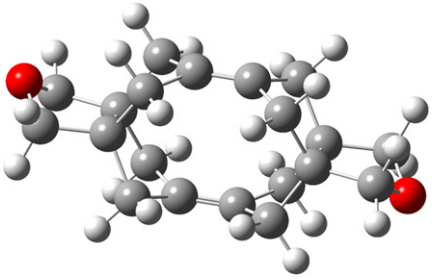


**Figure 5**. Optimized structure of the double envelope *anti* conformer of **12**.

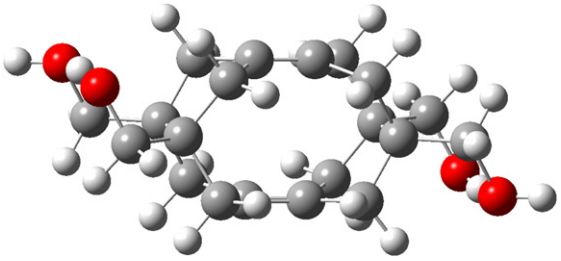


**Figure 7**. Optimized structure of the *anti* conformer of **21**.

length: 1.340 Å; distance among olefinic bonds: 3.042 Å) and **19** (mean value of the pyramidalization angle $\Phi$: 13.7°, C=C length: 1.339 Å; distance among olefinic bonds: 3.014 Å) are very close to the values calculated for the parent compound **24** ($\Phi$: 14.4°, C=C length: 1.339; distance among olefinic bonds: 3.055 Å).

## 3. Conclusions

In conclusion, the generation, trapping, and dimerization of two new highly pyramidalized and functionalized alkenes, **9** and **16**, have been carried out. The thermal [2+2] retrocycloadditions of the cyclobutane compounds **8**, **18**, and **20** to the corresponding diene derivatives **12**, **19**, and **21** have been studied by $^1$H NMR and by theoretical calculations (B3LYP/6-31G*). In the cases of **18** and **20**, the process has also been studied by DSC. From these studies, the previously observed qualitative trend—the higher the absolute value of the enthalpy of the [2+2] retrocycloaddition, the faster the process—may be extended to the new cyclobutanes **8** and **18**. Moreover, for the first time in this series of dienes, a transannular addition of bromine or iodine to diene **12** has been carried out. This kind of transformation had not been previously observed in related dienes containing the same carbocyclic skeleton.

## 4. Computational details

All quantum-mechanical calculations were carried out at Becke's three-parameter hybrid functional with the Lee, Yang, and Parr correlation functional (B3LYP) level,[30,31] using the 6-31G* basis set,[32,33] as implemented in Gaussian 03 on a Compaq HPC320 computer.[34] Geometry optimizations were undertaken using appropriate symmetry constraints and default convergence limits. The minimum energy nature of the optimized structures was verified from vibrational frequency analysis.

## 5. Experimental section

### 5.1. General methods

Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ in the following spectrometers: $^1$H NMR (500 MHz), $^{13}$C NMR (75.4 MHz). Assignments given for the NMR spectra are based on DEPT, COSY $^1$H–$^1$H, HETCOR $^1$H–$^{13}$C (HSQC and HMBC sequences for one bond and long range heterocorrelations, respectively), and NOESY experiments for selected compounds. Diastereotopic methylene protons in tricyclo[3.3.0.0$^{3,7}$]octane derivatives are referred as $H_\alpha$ and $H_\beta$ as shown in the corresponding structures. DSC curves were recorded with a DSC 822e from Mettler Toledo. Samples of approximately 0.5 mg of cyclobutane were weighted into 40-μL aluminum pans and heated at different heating rates (2, 5, 10, 15, and 20 °C/min).

**5.1.1. 3,7-Diiodotricyclo[3.3.0.0$^{3,7}$]octane-1,5-dimethanol (5).** To a suspension of $LiAlH_4$ (730 mg, 95% content, 18.4 mmol) in anhydrous diethyl ether (25 mL), a solution of diester **4** (2.50 g, 5.25 mmol) in anhydrous diethyl ether (170 mL) was added and the mixture was stirred at room temperature for 1 h till disappearance of the starting compound (TLC). Water (125 mL) was carefully added, the organic phase was separated and the aqueous one was extracted with diethyl ether (3×125 mL). The combined organic phases were dried (anhydrous $Na_2SO_4$) and concentrated in vacuo to give diol **5** (2.03 g, 93% yield). The analytical sample was obtained by crystallization from diethyl ether/*n*-pentane. Mp 186.5–188.5 °C; IR (KBr) $\nu$ 3343 and 3267 (O–H st), 2980, 2966, 2887, 1474, 1438, 1348, 1216, 1134, 1030, 1016, 978, 959, 894, 737/cm; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$: 2.13 (br d, $J$=9.9 Hz, 4H) and 2.17 (br d, $J$=9.9 Hz, 4H) [2(4,6,8)-$H_\alpha$ and 2(4,6,8)-$H_\beta$], 3.83 (s, 4H, $OCH_2$), 4.84 (s, mobile H, 2OH); $^{13}$C NMR ($CD_3OD$) $\delta$: 44.7 [C, C3(7)], 56.4 [C, C1(5)], 61.2 ($CH_2$, $CH_2OH$), 62.9 [$CH_2$, C2(4,6,8)]; MS (EI), *m*/*z* (%): 420 ($M^{\bullet+}$, 5), 372 (23), 275 [$(M-H_2O-I)^+$, 31], 261 (22), 257 (25), 245 (42), 148 [$(M-H_2O-2I)^{\bullet+}$, 66], 147 (21), 135 (27), 130 (67), 129 (30), 120 (29), 119 (46), 118 (70), 117 (100), 115 (39), 105 (39), 92 (22), 91 (92), 79 (64), 78 (33), 77 (54), 65 (30), 57 (28), 55 (28), 53 (22), 51 (30). Anal. Calcd for $C_{10}H_{14}O_2I_2$ (420.03): C, 28.60; H, 3.36; I, 60.43. Found: C, 28.52; H, 3.32; I, 60.72.

**5.1.2. 1,5-Diiodo-3,7-oxydimethylenetricyclo[3.3.0.0$^{3,7}$]-octane (6).** A magnetically stirred solution of diol **5** (500 mg, 1.19 mmol) and tosyl chloride (460 mg, 98% content, 2.38 mmol) in pyridine (2.5 mL) was heated at 100 °C for 6 h. The mixture was allowed to cool to room temperature and was acidified with 2 N HCl (13 mL). The acidic aqueous phase was extracted with $CH_2Cl_2$ (3×13 mL) and the combined organic extracts were washed with water (2×13 mL), dried (anhydrous $Na_2SO_4$), and concentrated in vacuo to give a brown residue (480 mg), which was subjected to column chromatography [silica gel (6 g), hexane/AcOEt mixtures]. On elution with a mixture hexane/AcOEt in the ratio 80:20, ether **6** (440 mg, 92% yield) was obtained. The analytical sample was obtained by crystallization from diethyl ether/*n*-pentane in the ratio of 1:1. Mp 176.0–176.5 °C; IR (KBr) $\nu$ 2976, 2938, 2915, 2890, 2852, 1474, 1456, 1348, 1262, 1221, 1160, 1101, 1076, 1024, 947, 924, 902, 890, 793, 615/cm; $^1$H NMR (300 MHz) $\delta$: 2.10 (d, $J$=7.8 Hz, 4H) and 2.36 (br d, $J$=7.8 Hz, 4H) [2(4,6,8)-$H_\alpha$ and 2(4,6,8)-$H_\beta$], 3.74 (s, 4H, $OCH_2$); $^{13}$C NMR $\delta$: 44.3 [C, C1(5)], 60.7 [$CH_2$, C2(4,6,8)], 62.2 [C, C3(7)], 67.6 ($CH_2$, $CH_2O$); MS (EI), *m*/*z* (%): 402 ($M^{\bullet+}$, 2), 275 [$(M-I)^+$, 37], 245 (11), 148 [$(M-2I)^{\bullet+}$, 45], 130 (59), 120 (31), 119 (42), 118 (100), 117 (95), 115 (33), 105 (24), 91 (75), 79 (34), 78 (32), 77 (46), 65 (30), 53 (21), 52 (22), 51 (43). Anal. Calcd for $C_{10}H_{12}OI_2$ (402.01): C, 29.88; H, 3.01; I, 63.13. Found: C, 30.17; H, 2.90; I, 62.97.

**5.1.3. 1,5-Diiodo-3,7-bis(tosyloxymethyl)tricyclo-[3.3.0.0$^{3,7}$]octane (7).** To a cold (0 °C) solution of diol **5** (200 mg, 0.48 mmol) in pyridine (0.5 mL), a solution of tosyl chloride (210 mg, 98% content, 1.08 mmol) was added and the mixture was magnetically stirred at this temperature for 1 h. The mixture was allowed to warm to room temperature during 24 h, acidified with aqueous 2 N HCl (10 mL), and extracted with $CH_2Cl_2$ (3×5 mL). The combined organic extracts were washed with water (2×10 mL), dried (anhydrous $Na_2SO_4$), and concentrated in vacuo to give a solid (230 mg), which was subjected to column

chromatography [silica gel (4.6 g), hexane/AcOEt mixtures]. In order of elution, impure ether **6** (80 mg) and ditosylate **7** (92 mg, 26% yield), as white solids, were obtained. The analytical sample of **7** was obtained by crystallization from $CH_2Cl_2$/diethyl ether in the ratio of 1:1. Mp 153–154 °C; IR (KBr) $\nu$ 3054, 2967, 2923, 2888, 2854, 1598, 1476, 1462, 1364, 1354, 1192, 1178, 1172, 1096, 961, 846, 837, 825, 815, 792, 678, 666, 658/cm; $^1$H NMR (400 MHz) $\delta$: 2.04 (d, $J$=8.0 Hz, 4H) and 2.16 (br d, $J$=8.0 Hz, 4H) [2(4,6,8)-$H_\alpha$ and 2(4,6,8)-$H_\beta$], 2.47 (s, 6H, 2Ar–$CH_3$), 4.22 (s, 4H, $OCH_2$), 7.38 [d, $J$=8.0 Hz, 4H, Ar-3(5)–H], 7.75 [d, $J$=8.0 Hz, 4H, Ar-2(6)–H]; $^{13}$C NMR (100.6 MHz) $\delta$: 21.7 ($CH_3$, Ar–$CH_3$), 41.5 [C, C1(5)], 52.6 [C, C3(7)], 61.3 [$CH_2$, C2(4,6,8)], 67.7 ($CH_2$, $CH_2O$), 127.9 [CH, Ar–C2(6)], 130.1 [CH, Ar–C3(5)], 132.3 (C, Ar–C1), 145.3 (C, Ar–C4); MS (EI), $m/z$ (%): 601 [(M−I)$^+$, 2], 557 [(M−TsO)$^+$, 20], 431 (18), 429 (19), 385 [(M−TsOH−TsO)$^+$, 63], 275 (34), 259 (49), 257 (24), 201 (19), 173 (100), 157 (26), 155 (35), 149 (33), 133 (20), 132 (20), 131 (67), 129 (20), 93 (26), 65 (27); MS (ESI$^+$), $m/z$ (%): 1479 [(2M+Na)$^+$, 12], 1353 [(2M−I+H+Na)$^+$, 12], 767 [(M+K)$^+$, 91], 751 [(M+Na)$^+$, 100], 641 [(M−I+H+K)$^+$, 59], 625 [(M−I+H+Na)$^+$, 60], 307 (45), 295 (53), 245 (100). Accurate mass measurement: calcd for $C_{24}H_{26}I_2NaO_6S_2$ ([M+Na]$^+$): 750.9152; Found: 750.9156.

**5.1.4. 1,8-Diphenyl-4,5-oxydimethylene-15-oxahexacyclo[6.6.1.1$^{2,5}$.1$^{4,7}$.0$^{2,7}$.0$^{9,14}$]heptadeca-9,11,13-triene (10).** To a cold (−64 °C) solution of diiodide **6** (100 mg, 0.25 mmol) and 1,3-diphenylisobenzofuran (81 mg, 0.30 mmol) in anhydrous THF (4 mL), a solution of *t*-BuLi in *n*-pentane (1.5 M, 0.7 mL, 1.05 mmol) was added dropwise. The mixture was magnetically stirred for 30 min at this temperature and then it was allowed to warm to room temperature. Methanol (1 mL) and water (5 mL) were cautiously added and the mixture was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried (anhydrous $Na_2SO_4$) and concentrated in vacuo to give a yellow solid (140 mg), which was subjected to column chromatography [silica gel (14 g), hexane/AcOEt mixtures]. On elution with a mixture hexane/AcOEt in the ratio of 95:5 adduct **10** (80 mg, 77% yield) was obtained as a white solid. The analytical sample of **10** was obtained by crystallization from diethyl ether (8 mL). Mp 221–221.5 °C; IR (KBr) $\nu$ 3059, 3031, 2982, 2962, 2933, 2914, 2883, 2834, 1603, 1499, 1473, 1457, 1449, 1346, 1307, 1284, 1266, 1045, 1021, 980, 897, 754, 746, 729, 699, 638/cm; $^1$H NMR $\delta$: 1.22 [dd, $J$=8.0 Hz, $J'$=3.3 Hz, 2H, 3(16)-$H_\beta$], 1.72 [d, $J$=8.5 Hz, 2H, 6(17)-$H_\alpha$], 1.78 [dd, $J$=8.5 Hz, $J'$=3.3 Hz, 2H, 6(17)-$H_\beta$], 1.85 [d, $J$=8.0 Hz, 2H, 3(16)-$H_\alpha$], 3.52 (s, 2H, 4-$CH_2O$), 3.56 [s, 2H, 5-$CH_2O$), 6.95 [m, 2H, 10(13)-H], 7.09 [m, 2H, 11(12)-H], 7.36 [tt, $J$=7.5 Hz, $J'$=1.5 Hz, 2H, 2H$_{para}$ phenyl], 7.44 [tm, $J$=7.5 Hz, 4H, 2H$_{meta}$ phenyl], 7.62 [dm, $J$=7.5 Hz, 4H, 2H$_{ortho}$ phenyl]; $^{13}$C NMR (100.6 MHz) $\delta$: 49.5 [$CH_2$, C6(17)], 49.7 [$CH_2$, C3(16)], 63.8 (C, C4), 64.2 (C, C5), 68.7 ($CH_2$, 4-$CH_2O$ and 5-$CH_2O$), 69.4 [C, C2(7)], 87.7 [C, C1(8)], 120.0 [CH, C10(13)], 125.7 (CH, C$_{ortho}$ phenyl), 126.7 [CH, C11(12)], 127.5 (CH, C$_{para}$ phenyl), 128.4 (CH, C$_{meta}$ phenyl), 137.8 (C, C$_{ipso}$ phenyl), 147.9 [C, C9(14)]; MS (EI), $m/z$ (%): 418 (M$^{\bullet+}$, 6), 346 (9), 314 (27), 313 (100), 270 (17), 241 (15), 165 (17), 105 (60), 91(27), 77 (51). Anal. Calcd for $C_{30}H_{26}O_2$ (418.54): C, 86.09; H, 6.26. Found: C, 86.03; H, 6.30.

**5.1.5. 4,5:10,11-Bis(oxydimethylene)pentacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$]hexadeca-1,7-diene (12).** Diiodide **6** (700 mg, 1.74 mmol) was added at once onto a mixture of molten sodium (400 mg, 17.4 mmol) in boiling anhydrous 1,4-dioxane (10 mL) and the mixture was heated under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and was filtered through a pad of Celite®, washing the solid with diethyl ether (3×20 mL). The combined filtrates and washings were concentrated in vacuo to dryness to give a residue (282 mg), which when analyzed by GC–MS showed to contain mainly diene **12** [retention time ($t_R$) 26.6 min; 74% relative area (ra)]. The above residue was subjected to column chromatography [neutral aluminum oxide (32 g), heptane/AcOEt mixtures]. On elution with a mixture heptane/AcOEt in the ratio of 96:4, diene **12** (146 mg, 56% yield) was obtained as a white solid. The analytical sample was obtained by crystallization from $CH_2Cl_2$/*n*-pentane in the ratio of 2:1. Mp 192.4–193.8 °C; IR (KBr) $\nu$ 2977, 2964, 2932, 2915, 2891, 2858, 2837, 2825, 1480, 1452, 1246, 1176, 1116, 1083, 1031, 982, 936, 920, 711/cm; $^1$H NMR (300 MHz) $\delta$: 2.12 [d, $J$=12.0 Hz, 8H, 3(6,9,12,13,14,15,16)-$H_\alpha$], 2.63 [d, $J$=12.0 Hz, 8H, 3(6,9,12,13,14,15,16)-$H_\beta$], 3.65 (s, 8H, 4$CH_2O$); $^{13}$C NMR $\delta$: 44.0 [$CH_2$, C3(6,9,12,13,14,15,16)], 55.6 [C, C4(5,10,11)], 80.7 ($CH_2$, 4$CH_2O$), 134.2 [C, C1(2,7,8)]; MS (EI), $m/z$ (%): 297 (21), 296 (M$^{\bullet+}$, 100), 129 (12), 128 (12), 117 (11), 115 (14), 105 (14), 91 (29), 79 (19), 77 (22), 65 (10), 53 (11). Anal. Calcd for $C_{20}H_{24}O_2$ (296.41): C, 81.04; H, 8.16. Found: C, 80.81; H, 8.23.

**5.1.6. 4,5:10,11-Bis(oxydimethylene)heptacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$.0$^{1,8}$.0$^{2,7}$]hexadecane (8).** A suspension of diene **12** (40 mg, 0.13 mmol) in degassed *n*-pentane (60 mL) was placed in a quartz reactor and the magnetically stirred mixture was irradiated under Ar with a 125 W medium pressure mercury lamp for 6 h. The solvent was removed in vacuo at room temperature and the oily residue (40 mg), analyzed by $^1$H NMR showed to be a mixture of starting **12** and product **8** in an approximate ratio of 1:0.5. NMR data of **8** from the spectra of the mixture: $^1$H NMR (300 MHz) $\delta$: 1.64 (d, $J$=7.2 Hz, 8H) and 1.93 (d, $J$=7.2 Hz, 8H) [3(6,9,12,13,14,15,16)-$H_2$], 3.60 (s, 8H, 4$CH_2O$); $^{13}$C NMR $\delta$: 50.6 [$CH_2$, C3(6,9,12,13,14,15,16)], 54.1 [C, C1(2,7,8)], 63.9 [C, C4(5,10,11)], 67.8 ($CH_2$, 4$CH_2O$).

**5.1.7. 1,2:7,8-Diepoxy-4,5:10,11-bis(oxydimethylene)-pentacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$]hexadecane (11).** Diene **12** (5.4 mg, 18 μmol) was added to a solution of dimethyldioxirane in acetone[35] (0.7 mL, 0.07 M, 49 μmol) and the mixture was stirred for 1 h at room temperature. The solution was concentrated in vacuo to dryness to give **11** (6 mg, quantitative yield) as a white solid. An analytical sample of **11** was obtained by crystallization from a mixture of $CH_2Cl_2$/*n*-pentane (1:1). Mp >298 °C (dec); IR (KBr) $\nu$ 2967, 2934, 2855, 1474, 1464, 1431, 1364, 1302, 1291, 1277, 1208, 1195, 1154, 1132, 1085, 1041, 991, 971, 952, 925, 898, 718, 694, 662/cm; $^1$H NMR (300 MHz) $\delta$: 1.85 [d, $J$=13.5 Hz, 8H, 3(6,9,12,13,14,15,16)-$H_\alpha$], 2.15

[d, $J$=13.5 Hz, 8H, 3(6,9,12,13,14,15,16)-$H_\beta$], 3.75 [s, 8H, $4CH_2O$); $^{13}C$ NMR $\delta$: 42.2 [$CH_2$, C3(6,9,12,13,14,15,16)], 56.6 [C, C4(5,10,11)], 74.3 [C, C1(2,7,8)], 82.1 ($CH_2$, $4CH_2O$); MS (EI), $m/z$ (%): 329 (8), 328 ($M^{\bullet+}$, 36), 164 (16), 133 (18), 123 (28), 117 (50), 107 (51), 105 (32), 95 (29), 91 (100), 79 (66), 77 (59), 65 (33), 55 (34), 53 (34). Anal. Calcd for $C_{20}H_{24}O_4\cdot 0.25H_2O$ (332.91): C, 72.16; H, 7.42. Found: C, 71.90; H, 7.29.

**5.1.8. 2,8-Dibromo-4,5:10,11-bis(oxydimethylene)hexacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$.0$^{1,7}$]hexadecane (13).** To a stirred suspension of diene **12** (20 mg, 0.07 mmol) in degassed $n$-pentane (10 mL) under Ar, a solution of bromine (60 μL, 1.19 mmol) in $CH_2Cl_2$ (3 mL) was added dropwise and the mixture protected from light with aluminum foil was stirred at room temperature for 13 h. The brown solution was diluted with $CH_2Cl_2$ and washed with 10% aqueous solution of $Na_2S_2O_3$ (3×10 mL). The organic phase was dried (anhydrous $Na_2SO_4$) and concentrated in vacuo to dryness to give a slightly yellow solid (42 mg), which by crystallization from a mixture AcOEt/$n$-pentane at −30 °C yielded pure **13** (21 mg, 69% yield) as a colorless solid. Mp 313.5–314 °C (dec); IR (KBr) $\nu$ 2958, 2920, 2874, 2841, 1459, 1359, 1306, 1267, 1237, 1176, 1103, 1089, 1028, 979, 951, 924, 910, 857, 739, 723, 659/cm; $^1H$ NMR $\delta$: 1.91 [d, $J$=11.5 Hz, 4H, 3(9,14,16)-$H_\beta$], 2.01 [dd, $J$=11.5 Hz, $J'$=2.0 Hz, 4H, 3(9,14,16)-$H_\alpha$], 2.11 [dd, $J$=11.5 Hz, $J'$=2.0 Hz, 4H, 6(12,13,15)-$H_\alpha$], 2.32 [d, $J$=11.5 Hz, 4H, 6(12,13,15)-$H_\beta$], 3.51 [d, $J$=9.5 Hz, 4H, $OCH_{anti}$), 3.61 [d, $J$=9.5 Hz, 4H, $OCH_{syn}$); $^{13}C$ NMR (100.6 MHz) $\delta$: 44.7 [$CH_2$, C3(9,14,16)], 54.3 [$CH_2$, C6(12,13,15)], 59.9 [C, C4(5,10,11)], 61.5 [C, C1(7)], 70.7 [C, C2(8)], 76.2 ($CH_2$, $4CH_2O$); MS (EI), $m/z$ (%): 378 (21), 377 (98), 376 (22), 375 ([M−Br]$^+$, 100), 295 ([M−HBr−Br]$^+$, 31), 165 (22), 143 (20), 141 (26), 131 (20), 129 (32), 128 (31), 119 (21), 117 (30), 116 (20), 115 (39), 107 (21), 105 (37), 93 (24), 91 (70), 83 (22), 81 (30), 79 (44), 77 (48), 67 (20), 65 (24), 55 (37), 53 (27). Anal. Calcd for $C_{20}H_{24}Br_2O_2\cdot 0.75H_2O$ (469.73): C, 51.14; H, 5.47. Found: C, 51.15; H, 5.32. Accurate mass measurement: calcd for $C_{20}H_{23}O_2{}^{79}Br_2$ ([M−H]$^+$): 453.0065; found: 453.0057; calcd for $C_{20}H_{23}O_2{}^{79}Br^{81}Br$ ([M−H]$^+$): 455.0044; found: 455.0022; calcd for $C_{20}H_{23}O_2{}^{81}Br_2$ ([M−H]$^+$): 457.0024; found: 457.0033.

**5.1.9. 2,8-Diiodo-4,5:10,11-bis(oxydimethylene)hexacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$.0$^{1,7}$]hexadecane (14).** To a stirred suspension of diene **12** (37 mg, 0.13 mmol) in degassed $n$-pentane (13 mL) under Ar, a solution of iodine (203 mg, 0.8 mmol) in $CH_2Cl_2$ (4 mL) was added dropwise and the mixture protected from light with aluminum foil was stirred at room temperature for 20 h. The dark violet solution was diluted with $CH_2Cl_2$ (10 mL) and washed with 10% aqueous solution of $Na_2S_2O_3$ (3×10 mL). The organic phase was dried (anhydrous $Na_2SO_4$) and concentrated in vacuo to dryness to give a slightly yellow solid (59 mg), which by crystallization from toluene yielded pure **14** (47 mg, 69% yield) as a colorless solid. Mp 341–342 °C; IR (KBr) $\nu$ 2971, 2946, 2845, 1466, 1455, 1355, 1304, 1259, 1237, 1189, 1171, 1103, 1081, 1060, 1028, 991, 975, 949, 918, 906, 854, 731, 724, 653/cm; $^1H$ NMR $\delta$: 1.92 [dd, $J$=11.0 Hz, $J'$=2.0 Hz, 4H, 3(9,14,16)-$H_\alpha$], 1.96 [d, $J$=11.0 Hz, 4H, 3(9,14,16)-$H_\beta$], 2.22 [dd, $J$=11.0 Hz, $J'$=2.0 Hz, 4H, 6(12,13,15)-$H_\alpha$], 2.46 [d, $J$=11.0 Hz, 4H, 6(12,13,15)-$H_\beta$], 3.52 (d, $J$=9.5 Hz, 4H, $OCH_{anti}$), 3.61 (d, $J$=9.5 Hz, 4H, $OCH_{syn}$); $^{13}C$ NMR (100.6 MHz) $\delta$: 47.6 [$CH_2$, C3(9,14,16)], 55.6 [C, C2(8)], 57.7 [$CH_2$, C6(12,13,15)], 61.5 [C, C1(7)], 61.6 [C, C4(5,10,11)], 75.9 ($CH_2$, $4CH_2O$); MS (EI), $m/z$ (%): 424 (20), 423 ([M−I]$^+$, 90), 296 ([M−2I]$^{\bullet+}$, 100), 129 (21), 128 (28), 115 (25), 105 (28), 91 (53), 81 (21), 79 (33), 77 (38), 55 (23). Accurate mass measurement: calcd for $C_{20}H_{25}O_2I_2$ ([M+H]$^+$): 550.9944; found: 550.9933.

**5.1.10. 3,7-Diiodo-1,5-[isopropylidenebis(oxymethylene)]tricyclo[3.3.0.0$^{3,7}$]octane (15).** 2,2-Dimethoxypropane (2.2 mL, 17.5 mmol), $p$-TsOH·$H_2O$ (46 mg, 0.24 mmol) and 4 Å molecular sieves (1.0 g) were added to a suspension of diol **5** (1.65 g, 3.97 mmol) in anhydrous $CH_2Cl_2$ (85 mL) and the mixture, protected with a dry $CaCl_2$ tube, was heated under reflux for 3 h. The solution was allowed to cool to room temperature, solid $K_2CO_3$ (≈100 mg) was added, the mixture was filtered and the filtrate was concentrated in vacuo to dryness to give acetal **15** (1.76 g, 96% yield) as a white solid. The analytical sample was obtained by crystallization from diethyl ether at 4 °C. Mp 144–145 °C (diethyl ether); IR (KBr) $\nu$ 2993, 2910, 2859, 1477, 1441, 1380, 1285, 1254, 1219, 1184, 1149, 1134, 1079, 1038, 955, 921, 878, 807, 615/cm; $^1H$ NMR (300 MHz) $\delta$: 1.42 (s, 6H, $CH_3$), 2.17 [m, 8H, 2(4,6,8)-$H_2$], 3.86 (s, 4H, $4CH_2O$); $^{13}C$ NMR $\delta$: 24.3 (broad signal, $CH_3$, $CH_3$), 43.7 [C, C3(7)], 55.5 [C, C1(5)], 61.9 [$CH_2$, C2(4,6,8)], 62.1 ($CH_2$, $4CH_2O$), 101.8 [C, O–$C(CH_3)_2$–O]; MS (EI), $m/z$ (%): 445 ([M−$CH_3$]$^+$, 1), 402 ([M−$C_3H_6O$]$^{\bullet+}$, 2), 372 ([M−$C_4H_8O_2$]$^{\bullet+}$, 15), 303 (19), 275 (36), 245 (35), 148 (42), 130 (46), 120 (26), 119 (33), 118 ([M−$C_4H_8O_2$−$I_2$]$^{\bullet+}$, 100), 117 (70), 115 (25), 105 (20), 91 (54), 79 (23), 78 (22), 77 (25), 58 (22). Anal. Calcd for $C_{13}H_{18}I_2O_2$ 460.09): C, 33.94; H, 3.94; I, 55.16. Found: C, 33.95; H, 3.89; I, 55.11.

**5.1.11. 1,8-Diphenyl-4,5-[isopropylidenebis(oxydimethylene)]-15-oxahexacyclo[6.6.1.1$^{2,5}$.1$^{4,7}$.0$^{2,7}$.0$^{9,14}$]heptadeca-9,11,13-triene (17).**

**5.1.11.1. Procedure (A) by reaction of 15 with sodium amalgam in the presence of 1,3-diphenylisobenzofuran.** Sodium amalgam (0.45%) was prepared by heating with a Bunsen a magnetically stirred mixture of mercury (19.2 g) and sodium (87 mg, 3.8 mmol). The amalgam was allowed to cool to room temperature, anhydrous 1,4-dioxane (2.2 mL) was added and then **15** (134 mg, 0.29 mmol) and 1,3-diphenylisobenzofuran (87 mg, 0.32 mg) were rapidly added and the mixture, protected from light with aluminum foil, was stirred at room temperature for 5 h. The reaction mixture was filtered through a pad of Celite® washing the filter with diethyl ether (3×10 mL) and $CH_2Cl_2$ (10 mL). The combined filtrates and washings were concentrated in vacuo to dryness to give a yellowish residue (167 mg), which was subjected to column chromatography [neutral aluminum oxide (15.6 g), heptane/AcOEt mixtures]. On elution with a mixture heptane/AcOEt in the ratio of 99:1, slightly impure **17** (75 mg, 54% yield) was obtained. The analytical sample of **17** (35 mg, 25% yield) was obtained as a slightly yellow solid by crystallization of the above product from $n$-pentane (5 mL). Mp 191–193 °C; IR (KBr) $\nu$ 3064, 3052, 3030, 2995, 2960, 2930, 2908, 2883, 2860, 1602, 1498, 1475, 1456, 1447, 1382, 1366, 1348, 1307, 1284, 1246, 1215, 1195, 1178, 1156, 1079, 1054, 1039, 1031, 979, 926, 841,

810, 760, 745, 722, 701, 678/cm; $^1$H NMR $\delta$: 0.95 [dd, $J$=9.0 Hz, $J'$=3.5 Hz, 2H, 3(16)-H$_\beta$], 1.38 (s, 6H, 2CH$_3$), 1.54 [dd, $J$=9.0 Hz, $J'$=3.5 Hz, 2H, 6(17)-H$_\beta$], 1.75 [br d, $J$=6.7 Hz, 2H, 6(17)-H$_\alpha$], 1.89 [br d, $J$=6.7 Hz, 2H, 3(16)-H$_\alpha$], 3.69 (s, 2H, 4-CH$_2$O), 3.73 (s, 2H, 5-CH$_2$O), 6.96 [m, 2H, 10(13)-H], 7.09 [m, 2H, 11(12)-H], 7.34 [tt, $J$=7.5 Hz, $J'$=1.5 Hz, 2H, 2H$_{para}$ phenyl], 7.43 [tm, $J$=7.5 Hz, 4H, 2H$_{meta}$ phenyl], 7.60 [dm, $J$=7.5 Hz, 4H, 2H$_{ortho}$ phenyl]; $^{13}$C NMR (100.6 MHz) $\delta$: 24.5 (broad signal, CH$_3$, CH$_3$), 50.1 [CH$_2$, C6(17)], 50.2 [CH$_2$, C3(16)], 57.9 (C, C5), 58.8 (C, C4), 64.1 (CH$_2$, 4-*C*H$_2$O), 64.4 (CH$_2$, 5-*C*H$_2$O), 66.4 [C, C2(7)], 87.8 [C, C1(8)], 101.6 [C, O*C*(CH$_3$)$_2$O], 120.0 [CH, C10(13)], 125.7 (CH, C$_{ortho}$ phenyl), 126.6 [CH, C11(12)], 127.5 (CH, C$_{para}$ phenyl), 128.4 (CH, C$_{meta}$ phenyl), 137.9 (C, C$_{ipso}$ phenyl), 147.9 [C, C9(14)]; MS (EI), *m*/*z* (%): 476 (M$^{\bullet+}$, <1), 371 (14), 271 (23), 270 ([C$_{20}$H$_{14}$O]$^{\bullet+}$, 100), 241 (11), 105 (21), 91 (11), 77 (17). Anal. Calcd for C$_{33}$H$_{32}$O$_3$·0.6H$_2$O (487.42): C, 81.32; H, 6.87. Found: C, 81.02; H, 6.77.

**5.1.11.2. Procedure (B) by reaction of 15 with *t*-BuLi in the presence of 1,3-diphenylisobenzofuran.** To a cold (−64 °C) solution of diiodide **15** (105 mg, 0.23 mmol) and 1,3-diphenylisobenzofuran (68 mg, 0.25 mmol) in anhydrous THF (3.6 mL), a solution of *t*-BuLi in *n*-pentane (0.7 M, 0.6 mL, 0.42 mmol) was added dropwise. The mixture was magnetically stirred for 30 min at this temperature and then it was allowed to heat to room temperature. Methanol (0.5 mL) and water (5 mL) were added and the mixture was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried (anhydrous Na$_2$SO$_4$) and concentrated in vacuo to give a yellow solid (122 mg), which was subjected to column chromatography [neutral aluminum oxide (6.1 g), hexane/AcOEt mixtures]. On elution with a mixture hexane/AcOEt in the ratio of 98:2 adduct **17** (61 mg, 55% yield) was obtained as a slightly yellow solid. An analytical sample of **17** (11 mg) was obtained by crystallization of a fraction (23 mg) of the above product from CH$_2$Cl$_2$/*n*-pentane (1.2 mL).

**5.1.12. 4,5:10,11-Bis[isopropylidenebis(oxymethylene)]-pentacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$]hexadeca-1,7-diene (19).** Diiodide **15** (2.40 g, 5.21 mmol) was added at once onto a mixture of molten sodium (1.20 g, 52.1 mmol) in boiling anhydrous 1,4-dioxane (25 mL) and the mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature and was filtered through a pad of Celite®, washing the solid with diethyl ether (3×30 mL). The remaining sodium was removed and the solid on the filter was washed with CH$_2$Cl$_2$ (3×30 mL). The combined filtrate and washings were concentrated in vacuo to dryness to give an orange colored residue (1.19 g). The above residue was crystallized three times from CH$_2$Cl$_2$/*n*-pentane mixtures to give pure **19** (634 mg, 59% yield) as a white solid. Mp 228–231 °C; IR (KBr) $\nu$ 2986, 2968, 2941, 2914, 2864, 2833, 1448, 1378, 1370, 1364, 1296, 1259, 1239, 1192, 1151, 1081, 1069, 1033, 924, 847, 668/cm; $^1$H NMR $\delta$: 1.46 (s, 12H, 4CH$_3$), 2.28 [nearly collapsed AB system, 16H, 3(6,9,12,13,14,15,16)-H$_2$], 3.65 [br s, 8H, 4CH$_2$O); $^1$H NMR (−50 °C) $\delta$: 1.48 (s), 1.59 (s), 1.88 (d, $J$=12.5 Hz), 1.93 (d, $J$=12.5 Hz), 2.26 (d, $J$=12.5 Hz), 2.30 (d, $J$=12.5 Hz), 2.35 (d, $J$=12.5 Hz), 2.41 (d, $J$=12.5 Hz), 2.75 (d, $J$=15.0 Hz), 2.78 (d, $J$=15.0 Hz), 3.52 (d, $J$=13.5 Hz), 3.91 (d, $J$=13.5 Hz), 3.92 (d, $J$=13.5 Hz); $^{13}$C NMR $\delta$: 42.6 [broad CH$_2$, C3(6,9,12,13,14,15,16)], 48.8 [C, C4(5,10,11)], 67.8 (CH$_2$, 4CH$_2$O), 101.1 (C, O*C*-(CH$_3$)$_2$O], 131.3 [C, C1(2,7,8)]. (At this temperature the signal corresponding to the methyl groups is not observed due to slow conformational changes); gHSQC (0 °C): Cross signal between 1.49 ppm (broad CH$_3$) and two carbon atoms at about 20 and 32 ppm; MS (EI), *m*/*z* (%): 412 (M$^{\bullet+}$, 5), 354 ([M−C$_3$H$_6$O]$^{\bullet+}$, 9), 297 (21), 296 ([M−2C$_3$H$_6$O]$^{\bullet+}$, 100), 91 (16), 58 (20). Anal. Calcd for C$_{26}$H$_{36}$O$_4$·0.05CH$_2$Cl$_2$ (416.82): C, 75.11; H, 8.73. Found: C, 75.11; H, 8.73.

**5.1.13. Bis[isopropylidenebis(oxymethylene)]heptacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$.0$^{1,8}$.0$^{2,7}$]hexadecane (18).** A suspension of diene **19** (200 mg, 0.45 mmol) in degassed *n*-pentane (150 mL) was placed in a quartz reactor and the magnetically stirred mixture was irradiated under Ar with a 125 W medium pressure mercury lamp for 8 h. The solvent was removed in vacuo at room temperature to give **18** as a white solid. The analytical sample was obtained by crystallization from CH$_2$Cl$_2$/*n*-pentane. Mp 227–229 °C; IR (KBr) $\nu$ 2986, 2967, 2924, 2878, 1473, 1443, 1379, 1366, 1290, 1275, 1248, 1215, 1178, 1156, 1080, 1072, 1035, 843, 806, 668/cm; $^1$H NMR (300 MHz) $\delta$: 1.43 (s, 12H, 4CH$_3$), 1.69 [s, 16H, 3(6,9,12,13,14,15,16)-H$_2$], 3.83 (br s, 8H, 4CH$_2$O); $^{13}$C NMR $\delta$: 24.7 (broad signal, CH$_3$, 4CH$_3$), 50.8 [C, C1(2,7,8)], 51.1 [broad CH$_2$, C3(6,9,12,13,14,15,16)], 58.2 [C, C4(5,10,11)], 64.2 (CH$_2$, 4CH$_2$O), 101.4 (C, O*C*-(CH$_3$)$_2$O]; MS (EI), *m*/*z* (%): 412 (M$^{\bullet+}$, 11), 354 ([M−C$_3$H$_6$O]$^{\bullet+}$, 19), 297 (22), 296 ([M−2C$_3$H$_6$O]$^{\bullet+}$, 100), 265 (14), 207 (24), 91 (22), 58 (16). Accurate mass measurement: calcd for C$_{26}$H$_{36}$NaO$_4$ ([M+Na]$^+$): 435.2511; found: 435.2524.

**5.1.14. 4,5:10,11-Tetrakis(hydroxymethyl)heptacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$.0$^{1,8}$.0$^{2,7}$]hexadecane (20).** A mixture of acetal **18** (38 mg, 0.09 mmol) in CH$_2$Cl$_2$ (10 mL) and *p*-TsOH (1 mg) in water (50 μL) was placed in an ultrasound bath at 35 °C for 10 min. The precipitated solid was filtered and the solid was washed with water and dried under reduced pressure in the presence of P$_2$O$_5$, to give tetrol **20** as a white solid (25 mg, 82% yield). Mp ≈240 °C (dec); IR (KBr) $\nu$ 3261, 2957, 2930, 2881, 1474, 1306, 1276, 1220, 1178, 1119, 1078, 1030, 748, 684/cm; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.47 (d, $J$=7.7 Hz, 8H) and 1.67 (d, $J$=7.7 Hz, 8H) [3(6,9,12,13,14,15,16)-H$_\alpha$ and 3(6,9,12,13,14,15,16)-H$_\beta$], 3.61 (d, $J$=4.7 Hz, 8H, 4CH$_2$O), 4.78 (t, $J$=4.7 Hz, 4H, 4OH); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 50.4 [CH$_2$, C3(6,9,12,13,14,15,16)], 49.6 [C, C1(2,7,8)], 57.8 (CH$_2$, 4CH$_2$O), 61.6 [C, C4(5,10,11)]; MS (EI), *m*/*z* (%): 333 (22), 332 (M$^{\bullet+}$, 100), 283 (11), 265 (17), 253 (18), 181 (16), 165 (15), 157 (15), 155 (16), 143 (16), 141 (17), 129 (24), 128 (21), 115 (22), 105 (29), 91 (56), 79 (41), 77 (33), 55 (32). Accurate mass measurement: calcd for C$_{20}$H$_{28}$NaO$_4$ ([M+Na]$^+$): 355.1885; found: 355.1898.

**5.1.15. 4,5,10,11-Tetrakis(hydroxymethyl)pentacyclo[8.2.1.1$^{2,5}$.1$^{4,7}$.1$^{8,11}$]hexadeca-1,7-diene (21).** A suspension of tetrol **20** (15 mg, 0.045 mmol) in 1,4-dioxane (10 mL) was heated under reflux for 2 h. The mixture was concentrated in vacuo to dryness to give tetrol **21** as a white solid (15 mg, quantitative yield). Mp >245 °C (dec); IR (KBr) $\nu$ 3270, 2979, 2960, 2897, 2852, 2834, 1451, 1330,

1313, 1299, 1269, 1240, 1200, 1173, 1134, 1071, 1040, 1023, 962, 864, 727, 693/cm; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.10 (d, $J$=12.2 Hz, 8H) and 2.29 (d, $J$=12.2 Hz, 8H) [3(6,9,12,13,14,15,16)-$H_\alpha$ and 3(6,9,12,13,14,15,16)-$H_\beta$], 3.48 (d, $J$=5.1 Hz, 8H, 4$CH_2$O), 5.08 (t, $J$=5.1 Hz, 4H, 4OH); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 42.9 [$CH_2$, C3(6,9,12,13,14,15,16)], 47.7 [C, C4(5,10,11)], 65.3 ($CH_2$, 4$CH_2$O), 130.3 [C, C1(2,7,8)]; MS (EI), $m/z$ (%): 333 (25), 332 ($M^{\bullet+}$, 91), 283 (10), 265 (17), 253 (18), 193 (15), 181 (21), 165 (20), 157 (21), 155 (24), 143 (25), 141 (26), 129 (39), 128 (34), 119 (27), 117 (34), 115 (40), 107 (25), 105 (52), 91 (100), 79 (75), 77 (66), 55 (47). Anal. Calcd for $C_{20}H_{28}O_4\cdot 0.75H_2O$ (345.95): C, 69.44; H, 8.59. Found: C, 69.26; H, 8.33.

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