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Characterization of novel isobenzofuranones by DFT calculations and 2D NMR analysis

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Phthalides are frequently found in naturally occurring substances and exhibit a broad spectrum of biological activities. In the search for compounds with insecticidal activity, phthalides have been used as versatile building blocks for the syntheses of novel potential agrochemicals. In our work, the Diels–Alder reaction between furan-2(5*H*)-one and cyclopentadiene was used successfully to obtain (3a*R*,4*S*,7*R*,7a*S*)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one and (3a*S*,4*R*,7*S*,7a*R*)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (2) and (3a*S*,4*S*,7*R*,7a*R*)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one and (3a*R*,4*R*,7*S*,7a*S*)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (3). The *endo* adduct (2) was brominated to afford (3a*R*,4*R*,5*R*,7*R*,7a*S*,8*R*)-5,8-dibromohexahydro-4,7-methanoisobenzofuran-1(3*H*)-one and (3a*S*,4*S*,5*S*,7*S*,7a*R*,8*S*)-5,8-dibromohexahydro-4,7-methanoisobenzofuran-1(3*H*)-one (4) and (3a*S*,4*R*,5*R*,6*S*,7*S*,7a*R*)-5,6-dibromohexahydro-4,7-methanoisobenzofuran-1(3*H*)-one and (3a*R*,4*S*,5*S*,6*R*,7*R*,7a*S*)-5,6-dibromohexahydro-4,7-methanoisobenzofuran-1(3*H*)-one (5). Following the initial analysis of the NMR spectra and the proposed two novel unforeseen products, we have decided to fully analyze the classical and non-classical assay structures with the aid of computational calculations. Computation to predict the ^{13}C and ^{1}H chemical shifts for mean absolute error analyses have been carried out by gauge-including atomic orbital method at M06-2X/6-31+G(d,p) and B3LYP/6-311+G(2d,p) levels of theory for all viable conformers. Characterization of the novel unforeseen compounds (4) and (5) were not possible by employing only the experimental NMR data; however, a more conclusive structural identification was performed by comparing the experimental and theoretical ^{1}H and ^{13}C chemical shifts by mean absolute error and DP4 probability analyses. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: GIAO; DP4; γ-lactones; Diels–Alder; phthalides; MAE

Introduction

Phthalides or isobenzofuranones are well known for their broad range of natural products that display a considerable number of effects such as insecticidal,[1,2] nematicidal,[3] acaricidal,[4] vasodilatation,[5] analgesic,[6] anti-inflammatory,[7,8] protection effect against neuronal impairment induced by deprival of oxygen and glucose,[9] and other biological activities. One method that can be used for the synthesis of isobenzofuran-1(3*H*)-ones derivatives is the Diels–Alder (DA) reaction involving a α,β-unsaturated γ-lactone dienophile.

The DA reaction represents an important and useful strategy in modern organic chemistry.[10–14] This reaction usually requires electron-withdrawing groups in the dienophile and electron-rich dienes, or *vice versa*, to afford acceptable reaction rates. The use of butenolides in DA reactions has been investigated over the last decades.[15–18]

The high applicability of the DA cycloaddition in organic synthesis is due, among other reasons, to build complex molecules where two simple bonds can be formed in a region and stereocontrolled manner, yielding six-membered rings and up to four stereogenic centers in a single step.[19,20]

In general, NMR spectroscopy is one of the most useful tools for the structural determination of new compounds.[21–23] However, even with the aid of 2D NMR, it is not uncommon that molecular elucidation conclusions are erroneous or incomplete.[24] Therefore, many researchers simulate ^{13}C and ^{1}H NMR chemical shifts for many compounds by using quantum chemistry calculations.[25–27] The technique was pioneered by Bifulco[28,29] and has been successfully employed in numerous reports.[30–34] Good matching between the calculated chemical shifts for one of the potential structures with the experimental values constitutes an excellent tool to support structural analysis in organic chemistry.[35]

The gauge-including atomic orbitals method is the most widely used method for achieving the theoretical calculations of NMR chemical shifts; it can provide a better agreement with experimental results when compared with other methods using the same basis set.[36,37]

NMR shift calculation has been used to determine or confirm the stereochemistry and/or structure of products obtained in synthetic chemistry and natural products such as bicyclic peroxides,[38] epoxides of careen,[39] isohasubanan alkaloids,[40] rufoolivacins A and B,[41] gloriosaols A and B,[42] and obtusallenes V, VI, and VII.[43]

Analyses of the discrepancy between calculated and experimental ^{13}C and ^{1}H NMR chemical shifts, mean absolute error (MAE), root mean square, and linear regression methods are frequently described in the literature.[31,44,45]

The CP3 is a parameter used to assign the data of two spectra to two possible structures. This method compares the differences in calculated shifts between two candidate structures with the corresponding differences in experimental shifts. The advantage is that in this method the systematic errors cancel out. A limitation is that it requires two sets of experimental data from both isomers. If only one set of experimental data is available, it can be compared with the calculated data of all candidate structures by using the DP4

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probability method. Therefore, the DP4 method is employed to decide which set of calculated shifts provides the best fit to the data from the experimental spectrum assigning a probability to each candidate structure.

In this paper, we describe a detailed assignment of the NMR data obtained for four phthalide derivatives, including the measurement of most of the homonuclear hydrogen coupling constants. Their stereostructures were thoroughly studied by NMR experiments, such as ^{1}H NMR, ^{13}C NMR, COSY, HETCOR, HSQC, HMBC, NOESY, and NOEDIFF. In some cases, it has not been possible to determine the relative stereochemistry only from the NMR data; therefore, a methodology for the assignment of the relative stereochemistry using MAE analyses in conjunction with DP4 probability has been employed.

Results and discussion

In the search for compounds with insecticidal activity, furan-2(5*H*)-one **1** has been used as starting material for the synthesis of phthalides. DA [4+2] cycloaddition of **1** with cyclopentadiene afforded adducts *endo* **2** and *exo* **3**. These compounds have been used as models for the following structural changes, aimed at increasing the insecticidal activity. Given that halogenated compounds have been the subject of research involving the development of new agrochemicals,[46] we have decided to conduct the bromination and chlorination reactions of adducts obtained from the DA reaction. Some of the halogenated compounds obtained are represented in Fig. 1. These substances have caused the mortality of 84.8 to 96.3% of *Diaphania hyalinata*, a key pest of *Curcubitaceae*, resulting in a patent application.[47]

The pericyclic cycloaddition of a diene and a dienophile where bonds are broken and formed consecutively in a six-membered transition state has been successfully applied for the synthesis of a series of phthalides in our research group.[48] The DA transformation is governed by the $HOMO_{diene}$–$LUMO_{dienophile}$ interaction according to frontier molecular orbital (FMO) theory, but can be alternatively seen as a nucleophilic attack of the diene to the dienophile.[14] The DA reaction of the diene and dienophile may interact in two different orientations, leading to the formation of *endo* and *exo* adducts. Frequently, the *endo* adduct is favored due to a higher orbital overlap in the transition state.[49,50] Consistent with this observation, in our work, the *endo* adduct was the major product obtained from the reaction of furan-2(5*H*)-one **1** with cyclopentadiene. As presented in Scheme 1, the *endo* and *exo* (**2** and **3**) have been formed, and for simplicity, only one enantiomer of each adduct is depicted.

Although these compounds have been previously described in the literature, their NMR spectra have not been fully assigned.[51–58] Therefore, the complete structural elucidations of **2** and **3** have been carried out in the present work. The unequivocal definition of the relative stereochemistry has been performed by the transfer of nuclear spin polarization from one nuclear spin population to another via cross-relaxation (nuclear Overhauser experiments).

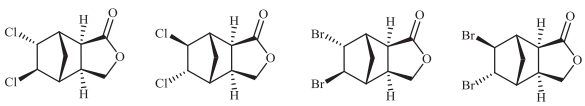
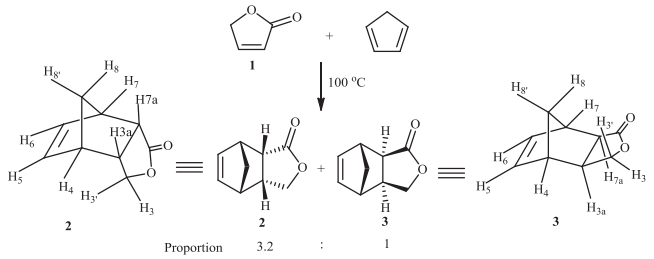


Figure 1. Chemical structures of the halogenated compounds with insecticidal activity.



Scheme 1. Synthesis of adducts **2** and **3** from Diels–Alder reaction.

The most characteristic signals for adduct **2** in the ^{13}C NMR are observed at δ 178.0, 134.3, and 136.7, which are assigned to the carbonyl and the double-bond carbons. The presence of the double bond is confirmed by the multiplet at 6.25–6.33 ppm (H5 and H6) in the ^{1}H NMR spectrum. The correct assignment of C5 (134.3) and C6 (136.7) has been achieved by the long-range C-H correlations observed in the HMBC as can be seen in Fig. 2. Correlations $^{3}J_{H7\text{-}C5}$, $^{3}J_{H3a\text{-}C5}$, $^{3}J_{H7a\text{-}C6}$, and $^{3}J_{H4\text{-}C6}$, which can be seen in this figure, have been used also for the complete assignment of the ^{13}C NMR.

The COSY experiment has been obtained for compound **3** to assign the protons H5 and H6. This was possible because they have presented different chemical shifts and couplings to the neighboring protons. Not less important to say that H5 and H6 have shown correlations with H4 and H7, respectively.

Irradiation of H8 of adduct **2** in the NOEDIFF experiment has enhanced, besides H4 and H7, the spatially close H3a and H7a, which have been essential to establish its relative stereochemistry (Fig. 3). On the other hand for isomer **3**, enhancement of H3′ has been observed when H8 was irradiated in the NOEDIFF experiment. Therefore, the complete assignments of all signals of compounds **2** and **3** have been accomplished using the aforementioned techniques.

Inspired by the insecticide activity of the halogenated products of the *exo* adduct **3** (Fig. 1), we have decided to prepare analogues using the *endo* adduct **2**. Halogenation reactions are mostly stereoselective leading to the *trans*-disubstituted double bond via

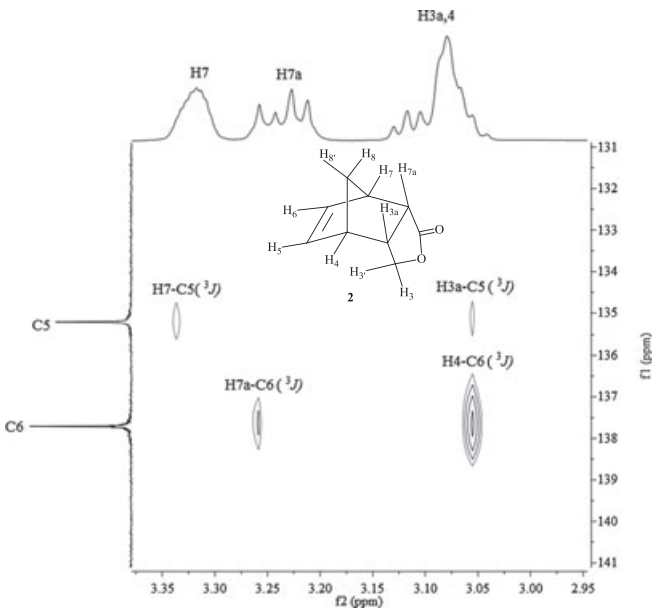


Figure 2. The expanded region of the 2D ^{1}H, ^{13}C HMBC spectrum acquired optimized for a $^{n}J_{CH}$ of 8.0 Hz of compound **2**.

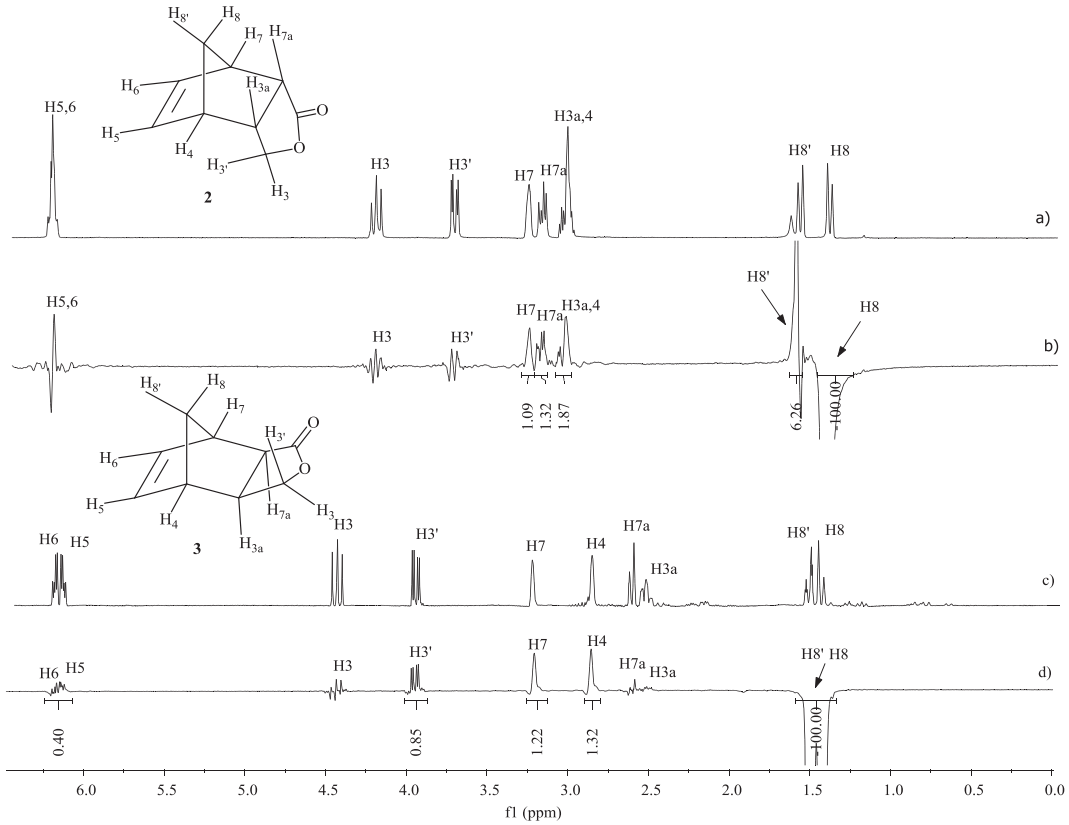
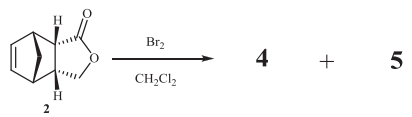


Figure 3. (a) normal ^{1}H NMR spectra of adduct **2** as reference; (b) NOEDIFF experiment (presaturation time of 3.0 s and power of 86 Hz) of adduct **2**, irradiation of H8; (c) normal ^{1}H NMR spectra of adduct **3** as reference; and (d) NOEDIFF experiment (presaturarion time of 3.0 s and power of 86 Hz) of adduct **3**, irradiation of H8 and H8′.

a three-membered intermediate.[59–63] Bromination of the double bond of bicyclic systems, dependent of the reaction conditions, has provided a complex mixture of substituted and rearranged products.[64–66]

Bromination of the *endo* adduct **2**, as shown in Scheme 2, has provided two major products (**4** and **5**), which have been separated and purified by flash column chromatography.

The absence of the signals of the vinyl hydrogens (H5 and H6) in the ^{1}H NMR for both products is a clear indication of the reaction progress. The most deshielded proton of compound **4** has been assigned to H5 (δ 4.74) because of the electrophilic character of the bromine. This assignment has been confirmed after analysis of the COSY and HSQC. This proton appears as a doublet of triplet with coupling constants of 10.7 and 4.2 Hz in the ^{1}H NMR. The formation of the *trans*-disubstituted product may be doubted because the *trans*-vicinal coupling constant is around 3 Hz. Careful inspection of the 2D NMR experiments have suggested C-6 bonded to two hydrogens. Therefore, formation of the *cis*-disubstituted product may be discredited also. Aligned with this observation (C6 with two hydrogens), we have proposed bromine addition to the double bond followed by Wagner–Meerwein rearrangement to give compound **4** as shown in Scheme 3.[67–70]

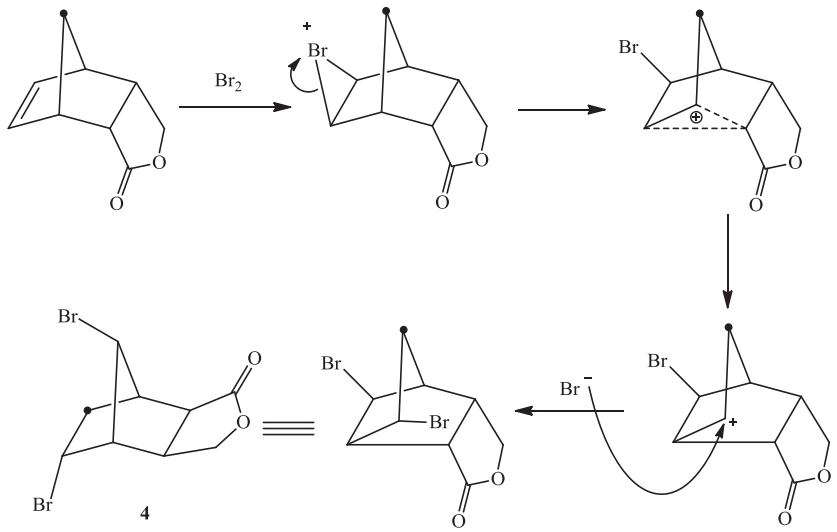


Scheme 2. Bromination reaction of the substance **2**.

At this point, we have started to look at the major product **5** of the bromination reaction (Scheme 2). An important feature observed in the ^{1}H NMR is the broad signal integrated to two hydrogens at δ 4.43, which was assigned to H5 and H6. These protons are the most deshielded due to the withdrawing effect of the bromines attached to C5 and C6. This is the first evidence for the formation of an unexpected *cis*-5,6-disubstituted compound. The chemical shifts of H5 and H6 should be different if the product formed was the most commonly expected *trans*-5,6-disubstituted compound because their chemical environment would be different. Therefore, the *trans* product, after this preliminary analysis, should be considered in a less probable scenario. Although the electrophilic addition of bromine on the double bond has as main characteristic, the formation of *trans*-dibrominated products, *cis*-dibrominated products have been described for norbonenes.[67,68,70–72]

Following the initial analysis of the NMR spectra and the proposal of rearranged product **4** and *cis*-5,6-disubstituted product **5**, we have decided to fully characterize these compounds with the aid of computational calculations. Computation to predict the ^{13}C and ^{1}H chemical shifts for the classical *trans*-brominated (**5b** and **5d**), the *cis*-brominated (**5a** and **5c**), and the rearranged structures (**4a–h**) have been carried out to find the correct products formed in this reaction (Fig. 4).

At first, the DP4 method was applied without assignment of the signals, which gave a probability that a set of experimental chemical shifts matched the computed values of each proposed structure.[73] Furthermore, this methodology is convenient because it can be used at the outset without full assignment of the experimental data.



Scheme 3. Proposed mechanism for the formation of compound **4**.

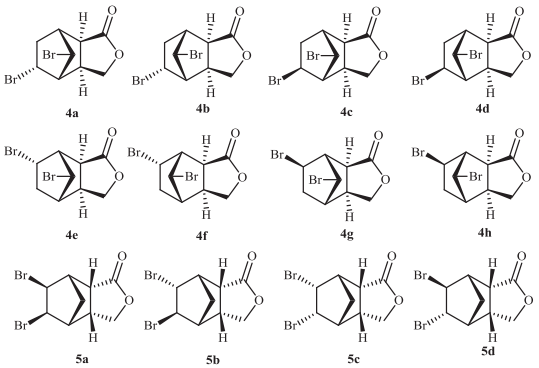


Figure 4. Candidate structures for compounds **4** and **5**.

The first step is to calculate the ^{13}C and ^{1}H shifts for structures **4a–h** and **5a–d** as described in the Experimental section (calculations) and tabulate the numbers (Calcd. δ_H and Calcd. δ_C in Tables 2, 3 and 5). These numbers are now transferred into the Web applet at http://www-jmg.ch.cam.ac.uk/tools/nmr/DP4/, which will automatically calculate DP4 probability. In this stage, the experimental shifts are assigned by matching up in order with the calculated shifts. For example, H5 in **4a** is calculated to have a shift of 4.65 ppm, while H5 in **4b** is calculated to have a shift of 4.07 ppm; so when aligning the experimental data with those calculated for **4a** and **4b**, the 4.74 ppm experimental shift is assigned to H5 in **4a** and to H3′ in **4b**. This is so because the chemical shift of H3′ in **4b** is 4.48 ppm, which is closer to the experimental chemical shift (4.74 ppm) than the chemical shift of H5 in **4b** (4.07 ppm).

The candidate structure **4b** has presented an 86.3% probability of being the compound **4** by comparing the experimental ^{1}H and ^{13}C NMR with the computed data without assignment of the signals (Table 1).

In the case of the candidate structures **5**, DP4 analyses without assignment of the signals has returned a 66.0% probability of being the compound **5a** by comparing the experimental and computed ^{1}H and ^{13}C NMR data (Table 1). Therefore, before making a final decision, we have performed MAE analyses after assignment of the signals by analyzing NMR spectra as presented in Tables 2, 3, and 5. All spectra can be found in the Supporting Information (Figs S1–S13).

Table 1. DP4 analyses of the experimental and computed ^{1}H and ^{13}C NMR data for products **4** and **5** before assignment of the signals

Candidate structures	DP4[a] probability (%)/NMR data		
	^{13}C and ^{1}H	^{13}C	^{1}H
4a	2.5	0.1	35.0
4b	86.3	2.1	61.6
4c	0.0	9.3	0.0
4d	0.0	1.9	0.0
4e	0.2	0.2	1.6
4f	11.0	9.0	1.8
4 g	0.0	75.2	0.0
4 h	0.0	2.3	0.0
5a	66.0	0.1	72.1
5b	31.8	0.1	27.9
5c	2.1	99.7	0.0
5d	0.0	0.1	0.0

[a]Calculations were carried using the B3LYP/6-31G(d,p)//molecular mechanics level of theory.

The MAE is a quantity used to measure how close the calculated chemical shifts are to the experimental chemical shifts. After gaining substantial insight from the first computed data, such analysis should not influence the assignment process, and after all, it turned out to be incorrect, as the correct compound is **4b**, but **4a**.

$$\mathrm{MAE} = \sum\nolimits_n \left|\delta_{calc} - \delta_{exp}\right|$$

The first step is to calculate ^{13}C and ^{1}H shifts for structures **4a–h** and **5a–d** as described in the Experimental (calculations). The next step is to group the calculated ^{13}C and ^{1}H shifts for structures **4a–4d** in Table 2, for structures **4e–h** in Table 3, and for structures **5a–d** in Table 5.

All candidate structures were numbered in the same way starting from the carbonyl carbon as shown for **4a** and **4e** in Fig. 5. The structures **4a–d** were grouped together in one table while structures **4e–h** and **5a–d** were grouped in different tables. Structures **4a–d** were grouped together in one table because they are

Table 2. The assigned and calculated NMR data for candidate structures **4a–d**

Position	Expt.		Calcd. δ_H				Calcd. δ_C				$\lvert\Delta\delta_H\rvert$				$\lvert\Delta\delta_C\rvert$			
	δ_H	δ_C	**4a**	**4b**	**4c**	**4d**	**4a**	**4b**	**4c**	**4d**	**4a**	**4b**	**4c**	**4d**	**4a**	**4b**	**4c**	**4d**
1		177.4					176.7	177.4	176.3	176.9					0.7	0	1.1	0.5
3′	4.05		3.87	4.48	3.84	4.46					0.18	0.43	0.21	0.41				
3	4.59	71.5	4.37	4.44	4.28	4.37	70.1	69.0	69.7	68.8	0.22	0.15	0.31	0.22	1.4	2.5	1.8	2.7
3a	3.44	36.2	3.35	3.39	2.49	2.50	37.5	37.8	43.6	43.0	0.09	0.05	0.95	0.94	1.3	1.6	7.4	6.8
4	2.57	54.3	2.31	2.47	2.43	2.47	56.7	54.9	58.2	57.4	0.26	0.10	0.14	0.10	2.4	0.6	3.9	3.1
5	4.74	47.4	4.65	4.07	3.77	3.77	58.7	57.6	57.9	59.4	0.09	0.67	0.97	0.97	11.3	10.2	10.5	12
6′	2.82		2.82	2.4	2.61	2.00					0.00	0.42	0.21	0.82				
6	1.61	37.3	1.48	1.37	2.25	2.07	38.2	40.5	40.6	42.5	0.13	0.24	0.64	0.46	0.9	3.2	3.3	5.2
7	2.82	46.5	2.53	2.74	2.63	2.83	49.3	49.5	50.7	49.1	0.29	0.08	0.19	0.01	2.8	3	4.2	2.6
7a	2.82	45.7	2.72	2.69	2.56	2.55	47.2	48.5	46.2	48.1	0.10	0.13	0.26	0.27	1.5	2.8	0.5	2.4
8	4.01	50.2	4.13	3.85	4.05	4.46	63.4	62.0	60.4	62.4	0.12	0.16	0.04	0.45	13.2	11.8	10.2	12.2
MAE[a,b]											0.15	0.24	0.39	0.47	3.9	4.0	4.8	5.3

[a] MAE, mean absolute error.

[b] Calculations were carried out using the B3LYP/6-311+G(2d,p)//M06-2X/6-31+G(d,p) level of theory.

Table 3. The assigned and calculated NMR data for candidate structures **4e–h**

Position	Expt.		Calcd. δ_H				Calcd. δ_C				$\lvert\Delta\delta_H\rvert$				$\lvert\Delta\delta_C\rvert$			
	δ_H	δ_C	**4e**	**4f**	**4 g**	**4 h**	**4e**	**4f**	**4 g**	**4 h**	**4e**	**4f**	**4 g**	**4 h**	**4e**	**4f**	**4 g**	**4 h**
1		177.4					177.3	178.0	175.1	176.0					0.1	0.6	2.3	1.4
3′	4.05		3.88	4.43	3.88	4.47					0.17	0.38	0.17	0.42				
3	4.59	71.5	4.34	4.41	4.28	4.34	70.8	69.6	70.7	69.3	0.25	0.18	0.31	0.25	0.7	1.9	0.8	2.2
3a	3.44	36.3	2.63	2.65	2.44	2.46	42.4	43.5	41.2	43.7	0.81	0.79	1.00	0.98	6.2	7.2	5.0	7.4
4	2.82	46.5	2.18	2.33	2.28	2.41	52.0	49.5	53.2	48.8	0.64	0.49	0.54	0.41	5.5	2.9	6.6	2.3
5′	2.82		2.77	2.33	2.54	1.92					0.05	0.49	0.28	0.90				
5	1.61	37.3	1.39	1.34	2.15	2.01	38.3	41.4	40.4	43.3	0.22	0.27	0.54	0.40	1.0	4.1	3.1	6.0
6	4.74	47.4	4.67	4.10	3.85	3.81	58.6	57.0	58.4	59.2	0.07	0.64	0.89	0.93	11.2	9.6	11.0	11.8
7	2.57	54.3	2.71	2.92	2.79	2.87	54.7	55.5	55.4	57.5	0.14	0.35	0.22	0.30	0.4	1.1	1.0	3.1
7a	2.82	45.7	3.44	3.44	2.60	2.61	43.4	44.0	48.0	47.4	0.62	0.62	0.22	0.21	2.3	1.7	2.3	1.7
8	4.01	50.2	4.12	3.83	4.01	4.42	63.5	61.9	60.8	62.0	0.11	0.18	0.00	0.41	13.3	11.7	10.6	11.8
MAE[a,b]											0.31	0.44	0.42	0.52	4.5	4.5	4.8	5.3

[a]MAE, mean absolute error.

[b]Calculations were carried out using the B3LYP/6-311+G(2d,p)//M06-2X/6-31+G(d,p) level of theory.

stereoisomers. Structures **4e–h** and **5a–d** were not grouped in the same table of **4a–d** because these structures are not stereoisomers between themselves. Therefore, the nuclei with the same numbering (for the constitutional isomers) present distinct chemical shifts. For example, H5 in **4a** is calculated to have a shift of 4.65 ppm (Table 2), while H5 in **4e** is calculated to have a shift of 1.39 ppm (Table 3). H5 in **4a** is much more deshielded than H5 in **4e** because of the electron-withdrawing effect of the bromine directly attached to C5 in **4a**.

The candidate structures **4a** (0.15) and **4b** (0.24) presented better MAE values matching than **4e–h** (from 0.31 to 0.52) by comparing the experimental and calculated ^{1}H NMR values. The MAEs observed for hydrogen chemical shift are inherently smaller than carbon and are generally considered to provide better distinction between isomers.[74] After this first MAE analysis, we can exclude tentative structures **4e–h**, because their MAE values have been superseded by **4a–b**.

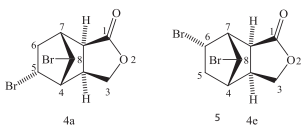


Figure 5. Candidate structures **4a** and **4e**.

Following MAE output for compound **4**, we have excluded tentative structures **4e–h** for DP4 analyses. Therefore, only the candidate structures **4a–d** have been considered in the following DP4 analyses at this time after assignment of the signals (Table 4). The DP4 analysis showed that the calculated data of **4a** were closely matched to the experimental data with a probability of 99.3%, considering ^{1}H and ^{13}C chemical shifts. The conclusion taken from DP4 about the candidate structure was in line with the MAE output (Table 2).

Following MAE and DP4 analyses to characterize compound **4**, we have gone back to the desk for a deeper evaluation of the NMR spectra. The assignment of H6 was carried out by detecting the long-range 'W' coupling with H8 in the COSY. By using this NMR experiment, we have been able to assign H6′ also. By using

Table 4. DP4 analysis of ^{1}H and ^{13}C NMR data for products **4a–d**

Candidate structures	DP4 probability (%)[a]		
	^{13}C and ^{1}H	^{13}C	^{1}H
4a	99.3	1.4	100.0
4b	0.7	28.1	0.0
4c	0.0	57.3	0.0
4d	0.0	13.2	0.0

[a]Calculations were carried using the B3LYP/6-31G(d,p)//molecular mechanics level of theory.

Table 6. DP4 analysis of ^{1}H and ^{13}C NMR data for products **5a** and **5c**

Candidate structures	DP4 probability (%)[a]		
	^{13}C and ^{1}H	^{13}C	^{1}H
5a	100	96.5	100
5b	–	–	–
5c	0.0	3.5	0.0
5d	–	–	–

[a]Calculations were carried using the B3LYP/6-31G(d,p)//molecular mechanics level of theory. **5b** and **5d** were not included in the DP4 analysis. The chemical shifts of carbons C5 and C6 were not included in the analysis.

the NOESY experiment (Fig. 6), we have been able to confirm the identities of H6 and H6′ because the correlation contour between H5/H6′ is stronger than for H5/H6. This is due to the proximity of H5 and H6′. The deeper NMR analyses corroborate with the calculations using both MAE and DP4 methods confirming the candidate structure **4a** for compound **4**.

The analyses of MAE carried out for compound **4** have been done for compound **5** considering the tentative structures **5a–d** (Table 5). Considering all possible candidate structures, **5a** has presented the best-matching in the MAE method (0.16 for ^{1}H NMR and 4.1 for ^{13}C NMR). The MAE result is in line with previous NMR analyses where the 5,6-*trans*-disubstituted candidate structures **5b** and **5d** have been discarded.

The protons H5 and H6 have been spotted by the correlation contours with H8 observed in the COSY experiment. These couplings are due to the long-range 'W' coupling, which are possible only if H5 and H6 are at the endo position. Therefore, the DP4 methodology has been employed for compound **5** considering potential structures **5a** and **5c** after assignment of the signals (Table 6).

There is a significant difference between the experimental and computed shifts for the carbon atoms attached to bromine. This general trend has been noted by Bagno and Saielli[75] who found that the omission of spin-orbit contributions can lead to errors of more than 10 ppm for carbon atoms attached to bromine, but this difference is not a factor for the other assignments. Therefore, the chemical shifts of carbons C5 and C6, which are bonded to bromine, were disregarded in the DP4 analysis for compound **5**.

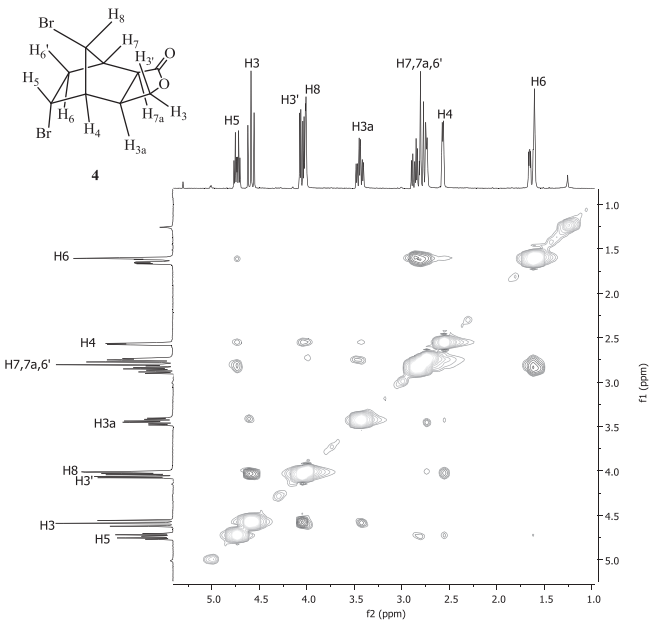


Figure 6. 2D ^{1}H, ^{1}H NOESY spectrum acquired for optimized mixing time of 700 ms of compound **4**.

Table 5. The assigned and calculated NMR data for **5a–d**

Position	Expt.		Calcd. δ_H				Calcd. δ_C				$\lvert\Delta\delta_H\rvert$				$\lvert\Delta\delta_C\rvert$			
	δ_H	δ_C	**5a**	**5b**	**5c**	**5d**	**5a**	**5b**	**5c**	**5d**	**5a**	**5b**	**5c**	**5d**	**5a**	**5b**	**5c**	**5d**
1		176.0					176.1	175.8	176.4	176.0					0.1	0.2	0.4	0.0
3′	4.34		4.13	4.17	4.04	4.07					0.21	0.17	0.30	0.27				
3	4.34	67.5	4.12	4.22	5.50	5.17	66.4	65.2	64.9	65.6	0.22	0.12	1.16	0.83	1.1	2.3	2.6	1.9
3a	2.97	41.6	2.78	2.96	2.94	2.84	43.9	44.2	44.2	43.6	0.19	0.01	0.03	0.13	2.3	2.6	2.6	2.0
4	2.80	52.3	2.44	2.45	2.58	2.48	54.2	52.5	47.6	48.6	0.36	0.35	0.22	0.32	1.9	0.2	4.7	3.7
5	4.43	49.9	4.36	4.02	4.72	4.32	62.8	65.6	64.7	70.0	0.07	0.41	0.29	0.11	12.9	15.7	14.8	20.1
6	4.43	53.2	4.39	4.18	4.54	3.96	66.6	70.3	62.9	67.5	0.04	0.25	0.11	0.47	13.4	17.1	9.7	14.3
7	3.07	51.1	2.79	2.84	2.95	2.72	53.2	51.1	50.0	51.1	0.28	0.23	0.12	0.35	2.1	0.0	1.1	0.0
7a	3.15	46.0	3.03	2.85	2.97	3.23	47.4	43.9	45.2	48.3	0.12	0.30	0.18	0.08	1.4	2.1	0.8	2.3
8′	2.54		2.50	2.15	1.67	2.21					0.04	0.39	0.87	0.33				
8	1.71	37.6	1.60	1.71	1.73	1.71	36.0	39.6	42.5	39.8	0.11	0.00	0.02	0.00	1.6	2.0	4.9	2.2
MAE[a,b]											0.16	0.22	0.33	0.29	4.1	4.7	4.6	5.2

[a]MAE, mean absolute error.
[b]Calculations were carried out using the B3LYP/6-311+G(2d,p)//M06-2X/6-31+G(d,p) level of theory.

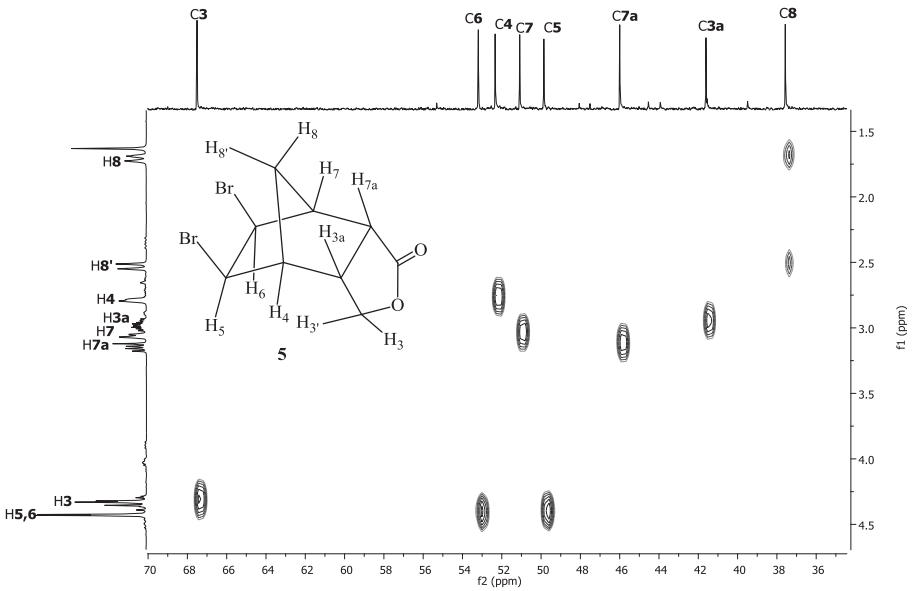


Figure 7. 2D ^{1}H, ^{13}C HETCOR spectrum of compound **5**.

The H8 and H8′ at the methylene bridge (δ_{H8} 1.71 and $\delta_{H8'}$ 2.54) have been easily identified by analysis of the HETCOR (Fig. 7), because they are more shielded than the protons attached to C3 (which is a methylene at the lactone ring).

After the MAE and DP4 analyses we have been able to focus on one of the candidates and characterize compound **5** as molecule **5a**.

Conclusion

The structures and relative stereochemistry of two DA adducts (**2** and **3**) have been established with the aid of 1D/2D NMR spectroscopy. However, the structures of the bromination products (**4** and **5**) of the *endo* adduct (**2**) were determined only by combining NMR spectroscopy data with theoretical calculations.

Experimental

General experimental procedures

Reagents and solvents have been purified according to the procedures described by Perrin and Armarego.[76] The reactions were followed by visualizing the thin-layer chromatography plates coated with silica gel in an ultraviolet chamber at 254 nm.[77] The furan-2(5*H*)-one **1** have been obtained as previously described by Näsman.[78] The cyclopentadiene has been obtained by distillation of dicyclopentadiene, commercially available (Sigma-Aldrich) before use in the DA reaction. Infrared spectra were recorded on a Varian 660-IR, equipped with GladiATR scanning from 4000 to 500 cm^{-1}. Mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument using electron impact (70 eV) for ionization. Melting points are uncorrected and were obtained in MQAPF-301 melting point apparatus (Microquimica, Brazil). Column chromatography was performed over silica gel (60–230 mesh).

NMR spectral methods

The ^{1}H and ^{13}C NMR, COSY, HSQC, HETCOR, HMBC, NOEDIFF, and NOESY spectra were recorded on a Varian Mercury instrument (300 MHz), using deuterated chloroform as solvent. The proton chemical shifts are reported relative to the signal of the residual chloroform in $\delta = 7.27$ ppm. The ^{13}C chemical shifts are reported using the signal in $\delta = 77$ ppm from $CDCl_3$ as reference.

Synthesis

(3aR,4S,7R,7aS)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one and (3aS,4R,7S,7aR)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**2**) and (3aS,4S,7R,7aR)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one and (3aR,4R,7S,7aS)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**3**)

Furan-2(5*H*)-one **1** (1.0012 g, 11.9 mmol) and cyclopentadiene (8.1 g, 0.12 mol) have been added to sealed tube. The resulting reaction mixture has been magnetically stirred and heated at 100 °C for 72 hours. The excess of cyclopentadiene has been evaporated, and the crude product was purified by column chromatography (eluent: hexane:ethyl acetate 2:1 v/v) to give 1.139 g (66% yield) of **2** and 0.363 g (18% yield) of **3**.

(3aR,4R,5R,7R,7aS,8R)-5,8-dibromohexahydro-4,7-methanoisobenzofuran-1(3H)-one and (3aS,4S,5S,7S,7aR,8S)-5,8-dibromohexahydro-4,7-methanoisobenzofuran-1(3H)-one (**4**) and (3aS,4R,5R,6S,7S,7aR)-5,6-dibromohexahydro-4,7-methanoisobenzofuran-1(3H)-one and (3aR,4S,5S,6R,7R,7aS)-5,6-dibromohexahydro-4,7-methanoisobenzofuran-1(3H)-one (**5**)

Phthalide **2** (0.5054 g, 3.37 mmol) has been dissolved in dichloromethane (10 ml) and transferred to a septum sealed round-bottom flask containing a magnetic bar. Then a solution of bromine in dichloromethane has been added dropwise using a syringe. The reaction progress has been followed by thin-layer chromatography and gas chromatography and the substrate was totally consumed after 1 h. The solvent was evaporated under reduced pressure and the residue was flashed in a silica gel column chromatography using hexane:ethyl acetate 3:1 as eluent to afford 0.1180 g (11% yield) of **4** and 0.5021 g (48% yield) of **5**.

Calculations

Geometry optimizations and conformational searches were performed with molecular mechanics in MacroModel.[79] The input

geometry was submitted to a molecular mechanics current-energy calculation to determine the force field best parameterized for the conformer. Each of these conformers was then submitted to geometry optimization and frequency calculation using DFT at M06-2X/6-31+G(d,p) level of theory.[80] Chemical shifts were obtained from the NMR shielding tensor values, which were computed for each conformer at B3LYP/6-311+G(2d,p) level in Gaussian 09.[81] The conformers were subjected to Boltzmann weighting and then converted to empirically scaled chemical shift values for each nucleus of the candidate structure. Regression analysis parameters by Lodewyk[82] were used to scale and reference ^{1}H and ^{13}C chemical shifts. These operations were repeated for each of all diastereoisomers. The NMR and free-energy data were assembled by using the python script created by Willoughby.[83] The experimental data set were compared with the calculated data and mean absolute error values were determined.

A goodness-of-fit probability was determined using the DP4 method described by Goodman.[84] Specifically, a conformational search was performed using the Monte Carlo Multiple Minimum method and the Merck Molecular Force Field. The searches were done in the gas phase with the number of steps large enough to find all low-energy conformers at least ten times. The resulting conformers were subjected to DFT calculations of single-point energy and gauge-including atomic orbitals shielding tensors at the B3LYP/6-31G(d,p) level in the gas phase. The shielding tensors were converted into referenced chemical shifts by subtracting the computed shielding tensors of tetramethylsilane.[84] The resulting chemical shift values have been Boltzmann averaged using the single-point energy obtained from the calculation. The temperature used was 298 K. DP4 analysis was accomplished by inputting computed and experimental chemical shifts into the DP4 analysis tool (located at: http://www-jmg.ch.cam.ac.uk/tools/nmr/DP4/).

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