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General Method of Assignment of Relative Stereochemistry in C-1-Substituted 2,4-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one by ^{1}H and ^{13}C NMR Correlations

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ABSTRACT: The ^{1}H and ^{13}C NMR spectra of *cis-endo* (a) and *cis-exo* (b) diastereoisomeric pairs of five differently C-1-functionalized 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ones were completely assigned. Several trends regarding the variation of chemical shifts and coupling constants of hydrogen and carbon atoms, on changing the configuration at C-2 and C-4 in both diastereoisomers, were observed by correlation of spectral data: methyl groups attached at C-2 and C-4 in (**a**) appear in ^{1}H NMR at higher field than in diastereoisomer (**b**). Simultaneously, H-2 and H-4 result in a lower field in **a** than in **b**. Both effects are due to the different interactions of hydrogens H-2, H-4, H-9 and H-10 with the bridging oxygen. In ^{13}C NMR spectra it is possible to observe an upfield shift of C-9, C-10 and C-3 in **b** *versus* **a**. The difference observed in chemical shifts of the aforementioned hydrogens and carbons, between both diastereoisomers, allows one to assign the configuration at C-2 and C-4 in such structures. This phenomenon has wide scope and validity and could be applied to the stereochemical determination of any pair of diastereoisomers (**a** and **b**), independently of the function attached to C-1 of the oxabicyclic system.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; 8-oxabicyclo-[3.2.1]-oct-6-en-3-one; assignment of relative stereochemistry; spectral data correlation

INTRODUCTION

The structure of 8-oxabicyclo-[3.2.1]-oct-6-en-3-one is of interest in chemistry owing to its usefulness as a valuable building block in the synthesis of bioactive naturally occurring organic molecules.[1] Also, this type of molecule and structurally related compounds have been the object of study[2] because of their importance from the structural and stereochemical point of view.

As part of our research on the transformation of such oxabicyclic structures into polyfunctionalized seven-membered synthons, with up to five stereocenters, we have prepared a series of differently C-1-functionalized 2,4-dimethyl-8-oxabicyclo-[3.2.1]-oct-6-en-3-ones. This was carried out by [4 + 3] cycloaddition reactions of C-2-substituted furans with 1,3-dimethyl-2-oxyallyl cation, generated *in situ* by reaction of 2,4-dibromopentan-3-one with Cu–NaI in acetonitrile at 60 °C.[3] Under these conditions, the reaction mechanism passes through an oxyallyl cation as intermediate, which has a W configuration.[4] This cation interacts, in a concerted way, with the furan diene affording two racemic diastereoisomers, **a** (major) and **b** (minor), in a ratio ranging from 60:40 up to 98:2. These diastereoisomers have opposite configurations at C-2 and C-4.

We present here the complete assignment of the ^{1}H and ^{13}C NMR spectra of the five diastereoisomeric pairs (**a**–**b**) shown. We made correlations of clearly identified ^{1}H and ^{13}C NMR data and we analyzed the effects responsible for the upfield or downfield shifts in signals within each pair of diastereoisomers and among the pairs of the series of cycloadducts studied. The observed effects depend on both the kind of function attached to C-1 of the bicyclic skeleton and the relative position of methyl groups H_3C-9 and H_3C-10 with respect to the bridging oxygen, following certain trends which allowed us to establish a general method of assignment of relative stereochemistry in this type of oxabicyclo structure.

We exemplified the observed phenomena for the pair of diasteroisomers **1a** and **1b** where R = OMe, confirming our structural assignment by x-ray diffraction analyses on single crystals of these particular molecules. Subsequently, we extended our observations to the remaining pairs of cycloadducts of the studied series.

RESULTS AND DISCUSSION

For the aforementioned objectives, a complete assignment of ^{1}H and ^{13}C NMR spectral data was required.

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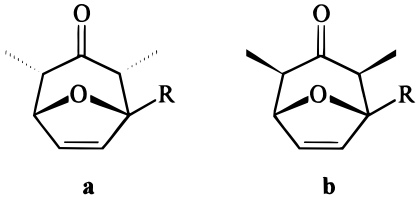

a **b**

1: R= OMe
2: R= Me
3: R= SMe
4: R= $OSiMe_3$
5: R= H

In some cases, the signals of H-2 and H-4 appeared very close to each other or overlapped, so to distinguish them we pursued one of the following approaches: (a) to run the spectra at 500 MHz to increase resolution; (b) to carry out selective 1D double-irradiation experiments on methyl groups H_3C-9 and H_3C-10 to observe the chemical shifts and multiplicities of H-2 and H-4; (c) to run the spectra in C_6D_6 in order to resolve the overlapped signals by aromatic solvent-induced shifts (ASIS).[5] The final assignment of signals to the corresponding hydrogens was achieved by COSY-90 experiments.

The ^{13}C signals from the 1D totally decoupled spectra were analyzed by DEPT experiments (in order to establish multiplicities) and 2D heterocorrelated spectroscopy (HETCOR). In the minor diastereoisomer (**b**), the assignment of ^1H and ^{13}C signals corresponding to positions C-2, C-4, C-9 and C-10 was initially not clear owing to H-4 appearing as a quartet without coupling to H-5. To obviate this difficulty, HMQC and HMBC experiments were carried out, varying the parameter τ_{MB} from 0.06 to 0.11 in order to elucidate the H–C long-distance couplings. From these experiments we observed the couplings of: H_3C-10 with C-3, C-4 and C-5 and of H_3C-9 with C-1, C-2 and C-3. This information allowed us to assign clearly all the above-mentioned signals and to corroborate previous assigments made for the remaining carbons and hydrogens of the molecule, and also to confirm the C–C connectivities of the carbon skeleton. Hence, as C-1 and C-5 are clearly identified by the HETCOR experiment, and based on the previous observations, it was possible to assign the signals corresponding to H-2, H-4, H-9, H-10, C-2, C-4, C-9 and C-10, which have an interesting stereochemical diagnostic value, as will be discussed below.

By performing NOESY experiments for both diastereoisomers (**a** and **b**), it was possible to establish the relative stereochemistry for both of them. The stereochemistry of the molecule in both cases was confirmed by a careful correlation and comparative study of ^1H and ^{13}C spectra (δ, multiplicity and J), as will be analyzed later. From the NOESY spectra we observed the NOE effects[6] shown in Fig. 1 (exemplified for **1a** and **1b**). It is worth noting that the optimum mixing-time parameter for the NOESY pulse sequence was 750 ms; lower values did not give NOE signals and higher values gave COSY signals and artifacts.

The NOE observations allowed us to establish a working model of the relative stereochemistry for both diastereoisomers. Thus, we assigned to **a**, the major isomer, a 1,3-*cis*-diequatorial disposition of methyl groups H_3C-9 and H_3C-10, attached to C-2 and C-4,

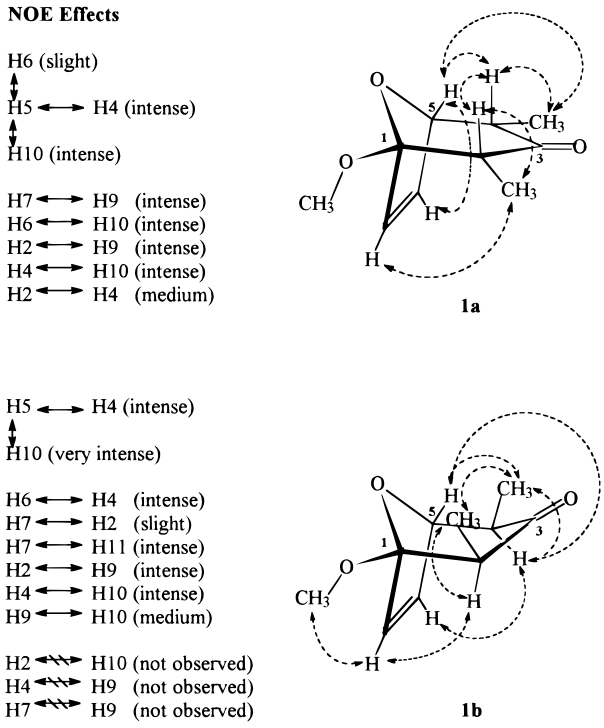

Figure 1. NOE effects observed in the NOESY Spectra of **1a** and **1b**.

respectively, and a chair-like conformation to the 1-oxan-4-one ring. For the minor diastereoisomer, **b**, in the light of NOE effects a quasi-1,3-*cis*-diequatorial disposition for methyl groups and a boat-like conformation for the 1-oxan-4-one ring, were considered. Additionally, it was deduced that the configurations of C-2 and C-4 stereocenters in **a** were simultaneously opposite to those of **b**.

Comparative analysis of ^1H NMR spectra for 1a and 1b

The chemicals shifts, δ, multiplicities and coupling constants, J, of signals corresponding to the ^1H spectra of **1a** and **1b** are given for comparative purposes in Table 1. The main differences observed in both spectra are commented upon below; some of them give considerable structural information.

The multiplicity of H-4 varies from **1a** to **1b**, observing in **1a** $J_{4,5} = 4.8$ Hz and in **1b** $J_{4,5} = 0$ Hz. Also in **1b** $J_{4,10} = J_{2,9} = 7.5$ Hz whereas in **1a** $J_{4,10} = J_{2,9} = 7.0$ Hz. This phenomenon is observed with all pairs of diastereoisomers of the studied series, independently of the function attached to C-1 in the cycloadduct. From Table 1 we can observe that the most significant differences in δ, multiplicity and J between the two diastereoisomers are at H-2, H-4, H_3C-9 and H_3C-10. In **1b** $J_{4,5} = 0$ Hz is only possible for a dihedral angle (H-4)—(C-4)—(C-5)—(H-5) of *ca.* 90°, which is consistent with a major population of conformers having a 1,3-*cis*-quasi-diequatorial disposition for methyl groups H_3C-9

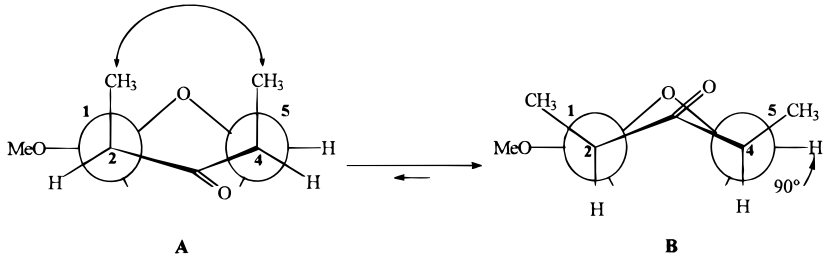

Figure 2. Inverse reflex effect in **1b**: (A) Destabilization by steric compression for 1,3-cis-diaxial orientation for H_3C-9 and H_3C-10; (b) 1,3-cis-quasi-equatorial orientation for methyl groups on C-2 and C-4.

and H_3C-10, as previously observed in NOESY experiments. Also, according to this J value, the 1-oxan-4-one ring would necessarily adopt a boat-like conformation, which is logical from the thermodynamic point of view in order to decrease the destabilizing steric repulsions existing in a typical 1,3-*cis*-diaxial disposition for methyl groups attached to C-2 and C-4. This phenomenon is known as inverse reflex effect[7] (see Fig. 2).

An effect with high stereochemical diagnostic value is that H_3C-9 and H_3C-10 in **1b** isomers are deshielded with respect to their homologous methyl groups in **1a** (see Table 1). This behavior is due to a deshielding 1,3-dipolar interaction, (electric field effect)[8] of the methyl groups in **1b** with the bridging oxygen, an interaction which is not possible in **1a**. At the same time, H-2 and H-4 are deshielded in **1a** compared with **1b**, because of the same aforementioned interaction with the bridging oxygen (see Fig. 3 and Table 1). These observations are consistent with a simultaneous opposite configuration at C-2 and C-4 stereocenters of diastereoisomers **1a** and **1b**.

Another effect contributing to the upfield shift of H_3C-9 and H_3C-10 in **1a** *versus* **1b** is the shielding influence of the anisotropy cone of carbonyl group[9] of C-3, which could affect to a certain extent these methyl groups in **1a**.

The molecules under study, owing to their bicyclic structure, have a low degree of conformational freedom, as can be judged from molecular models. There is a major conformation with an energy minimum, as calculated by molecular modeling (MM2), so the weighted contribution of this preferred conformation to the chemical shifts and coupling constants should be very important. On the basis of this consideration, for the value of $J_{4,5} = 4.8$ Hz in **1a** we made an estimate of the dihedral angle (H-4)—(C-4)—(C-5)—(H-5) with the Karplus equation,[10] obtaining an approximate value of 44°. This indicates that the 1-oxan-4-one ring has a half-boat-like conformation in which C-1, C-2, C-3, C-4 and C-5 are almost on the same plane (see Fig. 4).

Another observation consistent with the previous stereochemical assignment is that in **1b** H-5 appears at higher field than its homologous hydrogen in **1a**. The origin of this phenomenon may lie in the shielding 1,2-

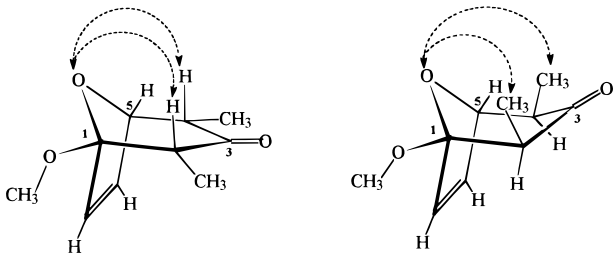

Figure 3. Electrostatic deshielding interactions exerted by the bridging oxygen.

Table 1. ^{1}H NMR data for **1a** and **1b** in $CDCl_3$.

	1a			**1b**				
	δ (ppm)	M[a]	J (Hz)	δ (ppm)	M[a]	J (Hz)	$\Delta\delta_{1a-1b}$	ΔJ
H_3-10	0.84	d	$J_{10,4} = 7.0$	1.36	d	$J_{10,4} = 7.5$	−0.52	$\Delta J_{10,4} = -0.5$
H_3-9	0.91	d	$J_{9,2} = 7.0$	1.27	d	$J_{9,2} = 7.5$	−0.36	$\Delta J_{9,2} = -0.5$
H-2	2.62	q	$J_{2,9} = 7.0$	2.54	q	$J_{2,9} = 7.5$	0.08	$\Delta J_{2,9} = -0.5$
H-4	2.60	dq	$J_{4,10} = 7.0$	2.23	q	$J_{4,10} = 7.5$	0.37	$\Delta J_{4,10} = -0.5$
			$J_{4,5} = 4.8$			$J_{4,5} = 0$		$\Delta J_{4,5} = 4.8$
H-11	3.28	s	0	3.42	s	0	−0.14	0
H-5	4.73	dd	$J_{5,6} = 1.9$	4.67	d	$J_{5,6} = 1.9$	0.06	$\Delta J_{5,6} = 0$
			$J_{5,4} = 4.8$			$J_{5,4} = 0$		$\Delta J_{5,4} = 4.8$
H-7	6.06	d	$J_{7,6} = 6.1$	6.09	d	$J_{7,6} = 6.0$	−0.03	$\Delta J_{7,6} = 0.1$
H-6	6.28	dd	$J_{6,5} = 1.9$	6.36	dd	$J_{6,5} = 1.9$	−0.08	$\Delta J_{6,5} = 0$
			$J_{6,7} = 6.1$			$J_{6,7} = 6.0$		$\Delta J_{6,7} = 0.1$

[a] Multiplicity.

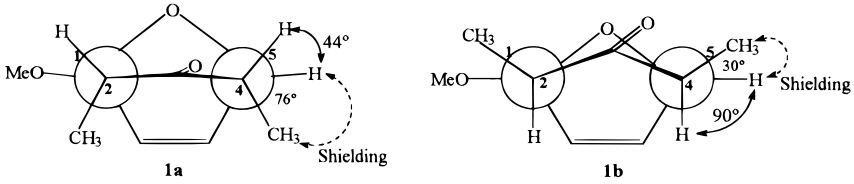

Figure 4. Different intensity of shielding effects H_3C-9 ↔ H-5 in **1a** and **1b**: approximate values of dihedral angles obtained from $J_{4,5}$ coupling constants.

interaction between methyl group H_3C-10 and H-5, which is more intense in **1b** than in **1a** because of the close proximity of both kinds of interacting hydrogens in the former stereoisomer. This can be seen in Fig. 4, where the estimated values for the dihedral angle (H-5)—(C-5)—(C-4)—(C-10) are shown: as 30° for **1b** and 76° for **1a**.

The protons H-6 and H-7 do not have stereochemical diagnostic value because δ(H-6) ⩾ or ⩽ δ(H-7) and/or δ(H-6, H-7)[**1a**] ⩾ or ⩽ δ(H-6, H-7)[**1b**], depending on the stereoelectronic effects exerted by the organic function attached to C-1 of the cycloadduct (see Table 1).

Table 2. ^{13}C NMR data for **1a** and **1b** in $CDCl_3$.

	δ_{1a} (ppm)	δ_{1b} (ppm)	$\Delta\delta_{1a-1b}$
C-1	112.16	110.27	1.89
C-2	54.68	54.05	0.63
C-3	208.11	213.74	−5.63
C-4	48.01	47.82	0.19
C-5	79.00	79.72	−0.72
C-6	136.10	137.01	−0.91
C-7	132.42	133.39	−0.97
C-9	10.18	13.14	−2.96
C-10	8.64	17.83	−9.19
C-11	51.14	51.39	−0.25

Correlation of ^{13}C spectra of 1a and 1b

The correlation of the ^{13}C NMR spectra of diastereoisomers **a** and **b** affords interesting information for the establishment of the configuration at the C-2 and C-4 stereocenters. The main differences between the spectra of the two stereoisomers are the δ values for C-1, C-3, C-9 and C-10 (see Table 2).

First, we can observe an upfield shift for C-6, C-7, C-9 and C-10 in **a** with respect to the homologous carbons in its diastereoisomer **b** (see Table 2). This shielding effect could be due to a *γ-gauche* interaction[11] between C-7 and C-9 and also between C-6 and C-10 in **a**. However, this interaction is not possible in the stereoisomer **b** (see Fig. 5).

The important $\Delta\delta$(C-3) observed between stereoisomers **a** and **b** could be interpreted on the basis of the different intensities of destabilizing repulsive interactions between the non-shared electron pairs of the

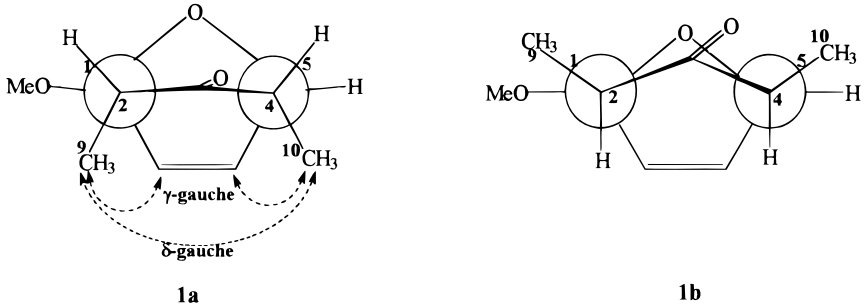

Figure 5. γ-Gauche and δ-Gauche interactions in **1a**.

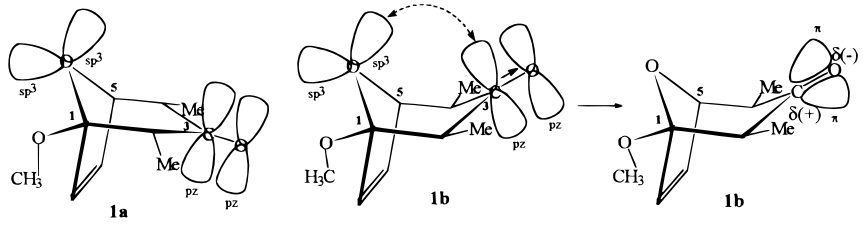

Figure 6. Downfield shift of C-3 in **1b**.

bridging oxygen and the π-electrons of the carbonyl group. In structure **b**, owing to the close proximity of orbitals, the electron density of the π orbital in the carbonyl group is disymmetrically pushed towards its oxygen atom, leaving the carbonyl carbon deshielded. This effect would not be observed or it would be produced to a lesser extent in isomer **a**, where the 1-oxan-4-one ring adopts a half-chair-like-conformation (Fig. 6).

CONCLUSIONS

We have found complete internal consistency between the relative stereochemistry assigned to diastereoisomers **a** and **b** and the differences in the δ and J values of diagnostic signals. The stereochemical assignments made based on NMR data correlation were confirmed by x-ray diffraction analysis of single crystals in the case of **1a** and **1b**.[12]

The ^{1}H and ^{13}C chemical shifts of pairs of diastereomeric cycloadducts synthesized in our laboratory are given in Tables 3 and 4, respectively. The identification of each individual signal was carried out unequivocally by the general methodology already considered here. From the data in Tables 3 and 4, it is possible to draw the same conclusions and observations as those based on **1a**–**1b** system. This is an indication of the wide scope and applicability of our method of stereochemical assignment for the C-1-functionalized oxabicyclic structures under study.

The general trends in the correlation of the ^{1}H and ^{13}C NMR spectra of diastereomeric pairs (**a**–**b**) of cycloadducts can be summarized as follows:

1. The most significant differences in chemical shifts (δ), multiplicity and coupling constants between the two diastereoisomers are at the level of H-2, H-4, H-9 and H-10.
2. δ(H-9) and δ(H-10) of the major diastereoisomer **a** are smaller than the homologous signals of the minor stereoisomer **b**; this is caused by the different interaction of methyl groups with the bridging oxygen.
3. $J_{2,9}$ (**a**) $< J_{2,9}$ (**b**); $J_{4,10}$ (**a**) $< J_{4,10}$ (**b**); $J_{4,5}$ (**a**) $\neq 0$, normally $4 < J_{4,5} < 5$ Hz; $J_{4,5}$ (**b**) ≈ 0.
4. δ(H-2) and δ(H-4) of **a** are higher than δ(H-2) and δ(H-4) of **b**, because of the different interactions of these hydrogens with the bridging oxygen.
5. δ(H-5) (**a**) $>$ δ(H-5) (**b**) owing to 1,2-shielding effects with H_3C-4.
6. The main differences in $\delta(^{13}C)$ are observed for carbons C-1, C-3, C-9 and C-10.
7. δ(C-9) (**a**) $<$ δ(C-9) (**b**) and δ(C-10) (**a**) $<$ δ(C-10) (**b**), owing to the *γ-gauche* interactions in diastereoisomer (**a**).
8. δ(C-3) (**a**) $<$ δ(C-3) (**b**), caused by electron compression between an sp^3 orbital of the bridging oxygen and a p_z orbital of the C-3 atom.

Table 3. ^{1}H chemical shifts, δ(ppm), in $CDCl_3$ of diastereoisomeric pairs in the cycloadduct series.

	Compound									
	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**	**5a**	**5b**
H-2	2.60	2.54	2.57	2.26	2.81	2.52	2.65	2.18	2.81	2.28
H-4	2.62	2.23	2.77	2.26	2.79	2.28	2.70	2.51	2.81	2.28
H-5	4.73	4.67	4.84	4.65	4.89	4.72	4.80	4.63	4.85	4.65
H-6	6.28	6.33	6.25	6.19	6.33	6.29	6.23	6.06	6.34	6.27
H-7	6.06	6.09	6.12	6.04	6.15	6.08	6.10	6.22	6.34	6.27
H-9	0.91	1.27	0.96	1.26	1.11	1.34	0.91	1.25	0.97	1.36
H-10	0.84	1.36	1.01	1.33	0.98	1.31	1.03	1.34	0.97	1.36

Table 4. ^{13}C chemical shifts, δ (ppm), in $CDCl_3$ of diastereoisomeric pairs in the cycloadduct series.

	Compound									
	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**	**5a**	**5b**
C-1	112.16	110.27	87.54	87.84	115.60	115.60	109.80	107.70	82.66	81.95
C-2	54.68	54.05	49.27	48.93	54.03	54.03	57.42	55.39	50.30	49.78
C-3	208.11	213.74	208.79	209.00	209.10	214.40	208.75	214.31	208.95	213.68
C-4	48.01	47.82	55.36	53.35	49.65	49.08	48.11	47.73	50.30	49.78
C-5	79.00	79.72	82.24	82.24	82.65	82.97	79.36	79.91	82.66	81.95
C-6	136.10	137.01	136.31	137.75	135.30	136.57	135.83	136.74	133.47	133.63
C-7	132.42	133.39	132.89	133.29	134.78	135.18	133.67	134.36	133.47	133.63
C-9	10.18	13.14	9.75	14.54	10.62	14.87	8.97	17.89	10.05	17.75
C-10	8.64	17.83	10.11	17.53	10.33	17.68	10.28	13.23	10.05	17.75

EXPERIMENTAL

Preparation and purification of cycloadducts

All the oxabicyclic compounds were synthesized by reaction of the appropriately C-2-functionalized furans (commercially available or prepared *ad hoc* according to known procedures) with 2,4-dibromopentan-3-one in acetonitrile at 60 °C for 20 h in the presence of Cu–NaI under an argon atmosphere.[3] By gas-liquid chromatography, two diastereoisomers (**a** and **b**) were detected in ratios from 6:4 to 98:2. After the appropriate work-up, the products were isolated and purified by column chromatography on silica gel. Once pure samples of both diastereoisomers for each cycloadduct had been isolated, all compounds were characterized physically and spectroscopically, obtaining their melting points (when solids), FT-IR, ^{1}H and ^{13}C NMR spectra, mass spectra and elemental analyses.[13]

NMR Spectra

^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.4 MHz, respectively, on a Varian Unity-300 apparatus, at room temperature. Deuterated solvents were dried over 4 Å molecular sieves. Chemical shifts are reported in ppm relative to tetramethylsilane. ^{1}H NMR spectra were obtained from a 10 mg of sample dissolved in 0.7 ml of $CDCl_3$. ^{13}C NMR spectra were measured by using 40 mg of pure analyte in 0.7 ml of $CDCl_3$. Resonance multiplicities for ^{13}C were established via acquisition of DEPT spectra. For the DEPT sequence,[14] the width of a ^{13}C 90° pulse was 4.5 μs, that of a ^{1}H 90° pulse was 10 μs and the $(2J)^{-1}$ delay was set at 3.1 ms

Homodecoupling experiments and two-dimensional COSY, NOESY, HETCOR, HMBC and HMQC experiments,[13] were performed by using standard Varian software under typical conditions as follows.

For the COSY experiment,[15] data were collected at room temperature in 4 K t_2 data points with 16 scans and 256 t_1 increments. The pulse angle was 90° with a relaxation delay of 1.0 s. Data were pseudo-echo shaped before Fourier transformation.

NOESY data[16] were collected in 4 K t_2 data points with 16 scans and 256 t_1 increments. A mixing time of 1.0 s was randomly modulated by $\pm 10\%$ in order to eliminate coherent magnetization transfer. Data were filtered by Gaussian filtering and doubly transformed in a 4 × 0.5 K data matrix. Samples were degassed prior to the experiment.

For HETCOR[17] experiments, data were obtained at room temperature in 4 K t_2 data points with 32 scans and 256 t_1 increments. The pulse width was 90° and the relaxation delay 1.5 s in the gated decoupling mode. Data were pseudo-echo shaped before Fourier transformation. The FT size was 4 K × 256.

The ^{1}H-detected one-bond heteronuclear multiple quantum coherence (HMQC)[18] spectra were obtained in a 500 MHz Varian Unity-500 apparatus by using a pulse sequence which included the bilinear rotational decoupling (BIRD)[19] pulse to invert the magnetization of the points not coupled to ^{13}C. These spectra were collected with 2 K × 256 data points and a data acquisition of 32 scans × 256 in the t_1 domain. Spectral widths of 2 and 5 kHz were employed in the $F_2(^1\text{H})$ and $F_1(^{13}\text{C})$ dimensions, respectively. Data were processed using sine-bell functions for weighting in both domains. The delay D_1 was set to 3.1 ms and D_2 was empirically optimized as 400 ms.

The long-range heteronuclear multiple quantum bond connectivity (HMBC) spectra were obtained by using the standard pulse sequence.[20] The spectral widths were 2 kHz (F_2) and 10 kHz (F_1) and the delays D_1 and D_2 were set to 3.1 and 60 ms, respectively.

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