CONFORMATIONAL AND CONFIGURATIONAL ANALYSIS OF 2-SUBSTITUTED 7-OXABICYCLO[2.2.1]HEPTADIENIC α–TETRALONES

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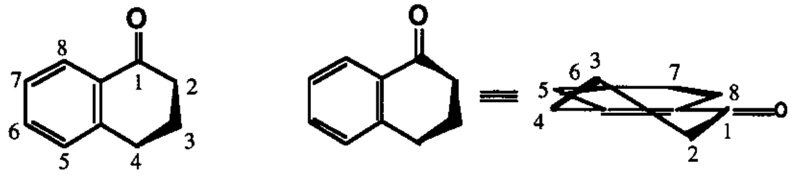
Abstract- The diastereoisomeric pairs of 1-(2-tetralonyl)-2,3-dicarbomethoxy-7-oxa-bicyclo[2.2.1]hepta-2,5-dienes were purified and separated using tlc procedures and their ^{1}H and ^{13}C spectra were recorded and assigned. The respective conformations and configurations of the enantiomeric pairs were determined using a combination of selective homonuclear decoupling techniques, NOE difference spectroscopy and 2D heteronuclear correlation sequences (HETCORR and COLOC).

INTRODUCTION

The conformational behaviour of α-tetralone has been investigated with variable degrees of success using theoretical calculations and uv and nmr spectroscopies.[1] Results, compared with those of cyclohexenone,[2] have been contradictory. Most studies have concentrated on the determination of the torsional angle between the carbonyl group and the aromatic ring to differentiate between the two prefered conformers: the so called *envelope* and the *half chair* forms (Figure 1). This angle has been generally found to be small, indicating that the carbonyl group is essentially coplanar with the aromatic ring in the tetralone.[1]



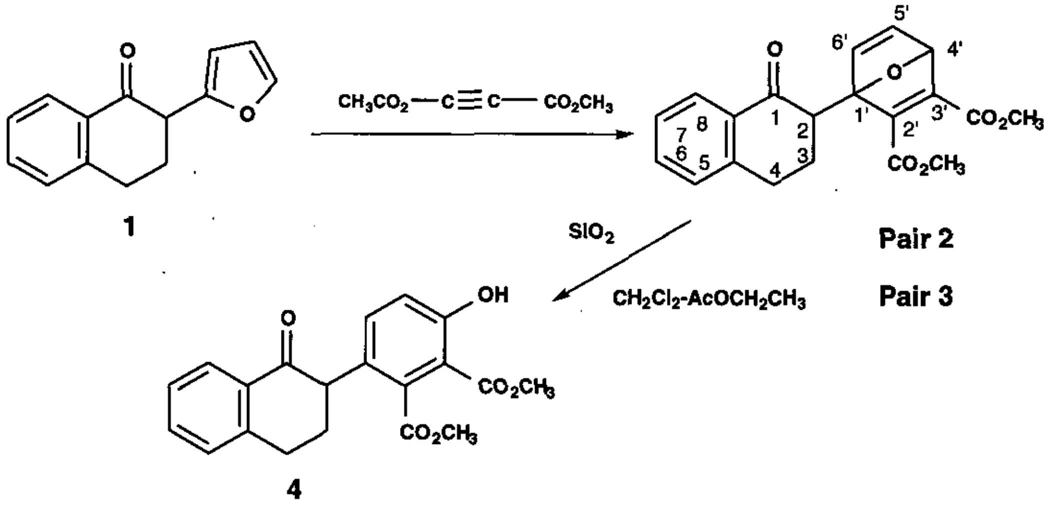
envelope *half chair*

Figure 1 enveloppe (a) and half chair (b) conformations of the α-tetralone

Using Lanthanide-Induced Shift (LIS) nmr techniques, Abraham *et al.* showed that the predominance of one conformer could not be resolved unequivocally.[3] Likewise, in the same paper, theoretical calculations using the semi empirical MNDO technique gave similar energies for the *half chair* and *envelope* conformations, whilst force field MMPI calculations (which were believed to give more realistic energies than the MNDO programme) estimated the *envelope* conformer to be only *ca.* 0.9 kcal mol^{-1} more stable than its *half chair* counterpart.

In connection with our preparation of novel heterocyclic systems with important pharmacological activities, most notably the benzo[*c*]phenanthridine series,[4,5] we wish to report the conformations of substituted α-tetralone derivatives; they present ideal opportunities for the analysis of this motif by a combination of nmr techniques.

In our previously reported synthesis, the Diels-Alder reaction between dimethyl acetylenedicarboxylate and 2-furyl-2-tetralone (**1**) yielded a suspected mixture of diastereoisomers (**2**) and (**3**) (Scheme 1), which was employed in the ensuing step of the reaction sequence without further purification.[5,6] We have since found that the diastereoisomeric components of this [4+2] cycloaddition reaction (and similar cycloaddition reactions employing α-furylated norbornanones and indanones)[7] can be conveniently isolated and have determined that they are present in equal proportions.



Scheme 1 : Synthesis of the diastereoisomeric mixture and ring openning of the enantiomeric pairs

The absence of data pertaining to the physical and chemical properties of these species and an interest in the determination of the conformational arrangements of 2-substituted α-tetralone motivated us to conduct a detailed nmr study of their ^1H- and ^{13}C-nmr spectra and to obtain information leading to the determination of their configurations. With this aim in mind, we undertook a series of spectroscopic analyses, making use of selective homonuclear decoupling techniques, NOE difference spectroscopy and 2D heteronuclear correlation sequences (HETCORR and COLOC).

RESULTS AND DISCUSSION

Following the chromatographic separation of the Diels-Alder reaction products between 2-furyl-2-

tetralone (**1**) and dimethyl acetylenedicarboxylate, evidence consistent with a diastereomeric relationship between the two unstable isolated components (designated as pairs (**2**) and (**3**)) was visible from the routine analysis of their respective ^1H nmr spectra. Further support for the presence of two different enantiomeric pairs was obtained through the inspection of their ^{13}C nmr spectra.

In deuterated chloroform ($CDCl_3$), the ^1H spectra of compounds (**2**) and (**3**) were suitably resolved to allow for the identification and assignment of the different signals in the aromatic region. Although the peaks due to the as yet unattributed alicyclic axial and equatorial α-tetralone protons (H-3a and H-3e) were clearly distinguishable from those of the enantiomeric pair (**2**), the peaks due to the neighbouring H-4a and H-4e protons overlaped even at higher fields. Moreover, the spectrum of enantiomeric pair (**3**) was doubly complicated by the complete overlap of the H-3a and H-3e peaks as well as the overlap of the H-4a and H4-e peaks. To circumvent these problems, and make the full assignment of peaks due to the alicyclic protons, deuterated acetonitrile (CD_3CN) was used as the working solvent. Better peak separation and resolution were offered in this solvent and the signals for the alicyclic H-3a, H-3e, H-4e, H-4a and H-2 protons were readily identified (Table 1).

The least shielded alicyclic protons, at 3.67 and 3.69 ppm, identified as the H-2 α-ketone protons of the tetralone moiety, were used as reference points for the determination of scalar couplings for enantiomeric pairs (**2**) and (**3**) respectively. Selective irradiation of H-2 in pair (**2**) gave rise to significant changes in peak intensities in the 1.9-2.5 ppm region, associating this multiplet with the H-3a and H-3e protons. By elimination, the peaks located between 2.9 and 3.3 ppm were attributed to the two H-4 protons.

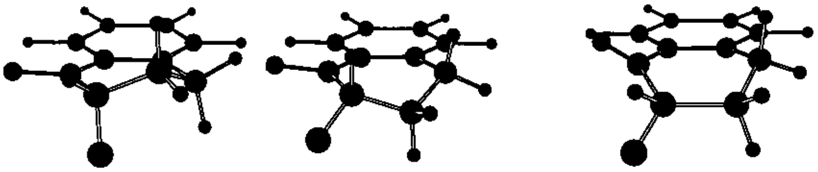
		H-8	H-7	H-6	H-5	H-4a	H-4e	H-3a	H-3e	H-2	H-6'	H-5'	H-4'	OCH3	OCH3
Pair (2)	δ	7.92	7.33	7.54	7.33	3.12	3.03	1.95	2.32	3.67	7.05	7.21	5.59	3.72	3.69
		dd	m	ddd	m	ddd	ddd	m	m	ddd	d	ddd	d	s	s
	J	8.2		7.5		16.5	16.5			13.2	5.3	5.3	2.0		
		1.5		7.5		12.0	4.0			4.7		2.0			
				1.5		4.4	4.0			0.8		0.8			

		H-8	H-7	H-6	H-5	H-4a	H-4e	H-3a	H-3e	H-2	H-6'	H-5'	H-4'	OCH3	OCH3
Pair (3)	δ	7.91	7.33	7.52	7.33	3.09	3.01	2.32	2.15	3.69	7.28	7.23	5.59	3.73	3.64
		dd	m	ddd	m	ddd	ddd	m	m	dd	d	ddd	d	s	s
	J	8.2		7.4		16.5	16.5			12.8	5.2	5.2	1.9		
		1.5		7.4		12.0	4.0			4.7		1.9			
				1.5		4.4	4.0								

Table 1 : ^1H nmr shifts and assignments for pairs (**2**) and (**3**) in CD_3CN (δ in ppm, J in Hz).

Having established the approximate locations of respective peaks in the ^1H spectra, we would like to probe the conformational arrangements of the tetralonic system by the analysis of their coupling constants. This approach had been previously employed in a conformational study of the six-membered alicyclic ring in α-tetralone itself.[8] Based on the assumption of sp^3 hybridisation, the two fragments C(2)-C(3) and C(3)-C(4) were assigned to have dihedral angles of about 55°, consistent with an *envelope* conformation.[8]

In our study, prior to the examination of coupling constants, the conformational spaces of the three extreme conformers of the cyclohexane ring were examined using Dreiding models. These forms are illustrated below for the **2R**-tetralone: the ***a-envelope***, the ***b-envelope***, and the *boat* (Figure 2).



a-envelope *b-envelope* *boat*

Figure 2 a-enveloppe, b-half chair and boat conformations of the 2(R)-substituted α-tetralone

From the nmr experiments, some important facts were established concerning the coupling networks of both pairs of enantiomers.

Two vicinal coupling constants in pair (**2**) were identified for H-2: the larger, $^3J= 13.2$ Hz, was consistent with a *trans* coplanar coupling, associated with a dihedral angle of *ca.* 180° (axial-axial), and the smaller, $^3J= 4.7$ Hz, with a dihedral angle of *ca.* 45° (axial-equatorial). These angles were crosschecked by refering to Dreiding models and were in accord with the placement of H-2 in an axial position, in favour of the ***b-envelope*** conformer (Figure 2). The same findings and conclusions were drawn for pair (**3**). The dihedral angles of tetralonic system in *boat* conformations did not tally with these results: 0°, $^3J = 11.0$ Hz (axial-axial); 135°, $^3J = 8.0$ Hz (axial-equatorial).[9] On the basis of these couplings, we dismissed this conformation as representative of the enantiomeric tetralonic system. Moreover, simple analysis of the Drieding model in the boat conformation shows that the planar sp^2 carbonyl group must be distorted through an angle of *ca.* 38° to allow full overlap for π-conjugation in the plane of the aromatic ring. Subsequent NOE difference studies substantiated this dismissal (cf. NOE results; Figure 5).

The ***a-envelope*** was excluded on similar grounds since the experimental couplings were not consistent with the dihedral angles separating H-2 from H-3a and H-3e. In this model, these angles are identical due to the staggered alignment of the hydrogen atoms as viewed in the Newman projection along the C(2)-C(3) bond. This dismissal was also reinforced through scalar couplings: no long-range coupling (^4J) was observed between the putative equatorial H-2e and H-4e protons, which adopt a planar W-conformation in this model. The same findings and conclusions were also drawn for pair (**3**).

Further evidence in favour of the ***b-envelope*** was found through the application of homonuclear decoupling experiments. When this technique was applied to the upfield H-3 proton of pair (**2**), resonating at 1.95 ppm, (which was now deemed to be in a *trans* axial position with respect to H-2 by its high ^3J value of 13.2 Hz), irradiation resulted in a selective loss of the second largest ^3J (12 Hz) for the downfield H-4 signal. This result is consistent with a *trans* vicinal alignment of one of the H-4 protons with H-3a, separated by a dihedral angle of approximately 180° and entirely consistent with the ***b-envelope*** conformation. In the complementary experiment, selective irradiation of the suspected H-3e proton disclosed the location of the other vicinal H-4 proton.

Having defined the ***b-envelope*** conformer as our working model, we probed its structure in more detail by considering the separations between the aromatic H-5 proton and the aliphatic H-4a,e protons using NOE difference spectroscopy. In Dreiding models, the respective distances separating H-5 from H-4a and H-4e differ significantly in the ***b-envelope***, but are roughly equal in the *half chair* **c** conformation (Figure 3). Presaturation of the respective H-4 lines in (**2**) led to nearly identical enhancements at H-5 (see Figure 5: NOE experiments). This was also the case when the same type of experiment was conducted on pair (**3**). Although the ***b-envelope*** conformation was in accord with the previous experimental findings, it did not fully correlate with these results since the H-4 protons are not equidistant from H-5. We thus conclude that molecules adopt *half chair* conformations **c** (2R) and **d** (2S), in agreement with the conclusions of Abraham for the parent α-tetralone, with substituents in equatorial positions (Figure 3). This conclusion is quite reasonable when one considers the steric repulsion exerted by the spacial proximity of the H-2a and H-4a protons in ***b***.

half chair ***c***, (2R) *half chair* ***d***, (2S)

Figure 3 half chair c and half chair d conformations of the 2(R) and 2(S) substituted α-tetralones H-4a and H-4e approximately equidistant from H-5

Interestingly, the interpretation of the ^{13}C spectrum of α-tetralone has been subject to debate. The resonance lines of carbons C-5 and C-8 have been assigned differently from LIS methods *via* the monoaddition of $Yb(dpm)_3$[10] and by the Chemically Induced Dynamic Nuclear Polarisation technique (CINDP).[11] Our assignment closely matches that reported in reference 9, and that of Abraham (2a), wherein the C-5 carbon resonates slightly further downfield with respect to its *para* counterpart (Table 2). The complete assignment of the respective peaks in the ^{13}C nmr spectra of pairs (**2**) and (**3**) was facilitated by 2D nmr spectroscopy. ^{13}C-^{1}H Correlations were established through the application of the HETCORR and COLOC spectroscopic techniques, which confirmed the skeletal framework of the diastereoisomeric 1-(2-tetralonyl)-2,3-dicarbomethoxy-7-oxabicyclo[2.2.1]hepta-2,5-diene cycloadducts. A pictorial representation of the COLOC results and ^{13}C nmr data are given in Figure 4 and Table 2 respectively.

In completing the conformational analysis of both diastereoisomers, we sought to establish the spacial orientations of the oxabicyclo substituents in both pairs of enantiomers as well as the displacements of the α,ß-unsaturated esters with respect to the tetralone ring system.

The salient proton enhancements from NOE experiments are summarized in Figure 5. Among the most prominant were those recorded following the presaturation of the H-2, H-3 and H-4 protons. Presaturation of the H-2 proton in pair (**2**), caused enhancements of H-6' (4%), H-4a (13%) and H-3e (16%) whereas irradiation of the H-2 proton in pair (**3**) led to NOE on the H-6' (16%), H-4a (18%) and H-3e (18%) protons. Different enhancements of the H-6' signals were observed following the presaturations of H-3a and H-3e: irradiation of H-3a led to 8% signal increase in pair (**2**) and no measurable effect in pair (**3**). On the other hand, presaturation of H-3e led to no measurable effect on H-6' in pair (**2**) compared to a NOE effect of 28% in pair (**3**).

Interestingly, a ^{5}J long range coupling of 0.8 Hz was observed between the H-2 and the H-5' olefinic protons in pair (**2**) (confirmed by selective homonuclear decoupling). This unusual coupling, which is transmitted through sp^2 and sp^3 bonds, indicates that there is a high probability for the adoption of a trans "zig-zag" bond arrangement between these protons, placing them in the same plane.

		C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
Pair 2	δ	196.9	46.5	25.4	28.5	144.0	128.6	133.6	126.5	127.0	132.1
Pair 3	δ	195.8	46.8	25.1	28.7	143.9	128.5	133.5	126.5	127.3	132.1

		C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	CO_2Me	CO_2Me	OCH_3	OCH_3
Pair 2	δ	96.9	157.2	149.6	82.6	143.9	143.3	165.0	162.6	52.2	51.9
Pair 3	δ	97.0	156.0	148.3	83.2	144.3	144.9	165.1	162.7	52.2	51.9

Table 2 : ^{13}C Nmr shifts and subsequent assignments for pairs (**2**) and (**3**) in $CDCl_3$ (δ in ppm)

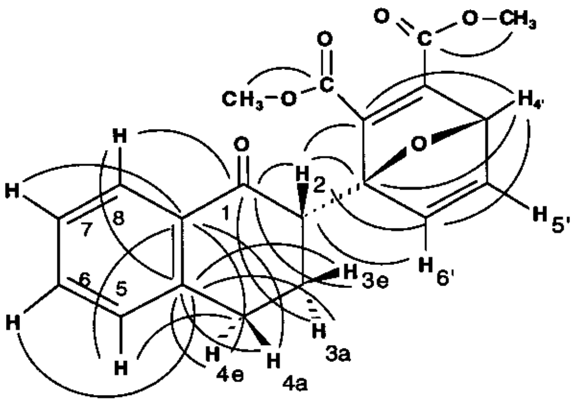
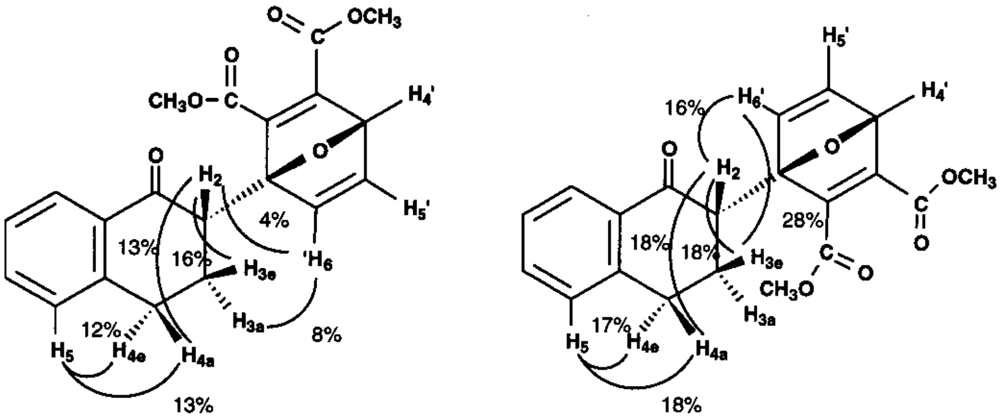


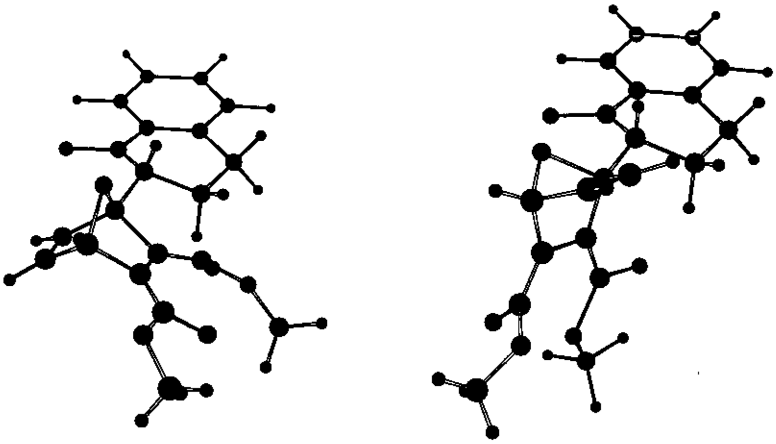
Figure 4 : COLOC results for pairs (**2**) and (**3**) (^{2}J, ^{3}J couplings)

On the basis of these combined nmr results, we propose that in deuteroacetonitrile the enantiomeric pair (**2**) adopts conformation (**2c**) illustrated below, along with its corresponding mirror image (Figure 6). Further evidence for this assertion was obtained through the analysis of their relative chemical shifts. A slight shielding effect was observed for the H-3a and H-6' protons of pair (**2**), in accord with the placement of the ester groups *"trans"* to the tetralone carbonyl. The shielding of the H-3a proton was accredited to a diamagnetic anisotropic effect induced by the close proximity of the ester carbonyl group in this orientation, whilst the minor shielding experienced by the H-6' olefinic proton was attributed to the neighbouring *"cis"* tetralone carbonyl group. These arguments were borne out by models.



Pair (2) **Pair 3**

Figure 5: Most significant NOE results



2c **3c**

Figure 6 3D representation of enantiomeric pairs (**2**) and (**3**)

Furthermore, we propose that pair (**3**) preferably adopts the conformation (**3c**) illustrated below, whereby H-6' sees only H-2 and H-3e. An insignificant NOE effect was recorded between H-6' and H-3a in pair (**3**) (as opposed to an effect of 28% for H-3e), indicating that rotation around the C(2)-C(1') bond was limited.

We thus conclude that the enantiomeric pair (**2**) adopts the (2R,1'S, 4'S) and (2S,1'R, 4'R) configurations, the former illustrated below by **2c**, whilst pair (**3**) adopts the (2R,1'R,4'R) and (2S,1'S,4'S) configurations, with its former being represented by **3c**.

CONCLUSION

In conclusion, the spacial arrangements and configurations of two diastereoisomeric tetralones were examined by extensive nmr studies. Results strongly favoured the adoption of *half chair* conformations, with oxabicyclo substituents placed in equatorial positions. A computational study should confirm the nmr spectroscopic data.

EXPERIMENTAL

^{1}H and ^{13}C spectra of (2) and (3) in $CDCl_3$ and CD_3CN were recorded at 500 MHz and 125 MHz respectively on a Bruker AM-500 spectrometer equipped with an Aspect 3000 system. HETCORR, COLOC and NOE difference experiments were performed and the corresponding data was processed using standard Bruker software. For NOE difference spectroscopy, 0.07 mmol of (2) and (3) were each dissolved in 0.5 ml of CD_3CN, and the resulting solutions were degassed following a freeze-thaw cycle and sealed in nmr tubes. $\{^1H\}$-^1H NOE's were then determined using 10-s low-power presaturation delays. Prior to Fourier transformation, a 2 Hz line broadening function was applied to each FID. High resolution mass spectra were recorded under electronic impact at 70 eV on a Varian MAT 311 instrument.

Preparation of cycloadduct mixture (**2**) and (**3**) :

1-(2-Tetralonyl)-2,3-dicarbomethoxy-7-oxabicyclo[2.2.1]hepta-2,5-diene diastereoisomers : An equimolar mixture of 2-furyl-2-tetralone (**1**) (1 g, 4.7 mmol) and dimethyl acetylenedicarboxylate (0.67 g, 4.7 mmol) was heated for 3 h at 100°C. After cooling, the crude product was obtained as an oil and was recrystallized from ether giving 1.92 g (97%) as a white powder. m p. : 135°C . Ir (KBr): ν(C=O) 1725, 1705, 1680, 1675 cm^{-1}, ν(C=C)1640, 1555 cm^{-1}. Anal. Calcd. for $C_{20}H_6O_6$: C, 67.77; H, 5.12. Found: C, 67.59; H, 5,14.

The separation of the diastereoisomeric mixture was carried out using preparative tlc [SiO_2, cyclohexane / ethyl acetate (4:1)], which yielded two amorphous masses. They were, respectively, introduced into two nmr tubes along with the appropriate deuterated solvent. The tubes were then degassed and immediately sealed. Under these experimental conditions, pairs (**2**) and (**3**) were stable.

The major drawback in these experiments was the instability of pairs (**2**) and (**3**) on exposure to molecular oxygen and the difficulty in avoiding the formation of the phenolic product (**4**) (Scheme 1) through the partial breakage of the oxabridge during and after the chromatographic separation. For these reasons, separate isomers could not be readily recrystallized and kept aside for affirmative X-Ray studies.

The isolated enantiomeric pairs (**2**) and (**3**) shared the same molecular formula $C_{20}H_{18}O_6$, as determined using high resolution mass spectrometry. Only very slight differences in peak ratios could be detected.

Pair (**2**) : HRms found 354.1105, calcd 354.11033; (relative intensity, m/z) 354 (M^+, 2), 322 (6), 323 (7), 294 (69), 118 (100), 90 (62), 28 (58).

Pair **3** : HRms found 354.1108, calcd 354.11033; (relative intensity, m/z) 354 (M^+, 2), 322 (9), 323 (9), 294 (69), 118 (100), 90 (62), 28 (58).

^{1}H- and ^{13}C-nmr, see Tables 1 and 2.

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