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CONFORMATIONAL ANALYSIS OF SOME 11,12-DIHYDRODIBENZ[B,F][1,5]OXAZOCIN-6-ONE DERIVATIVES BY NMR SPECTROSCOPY

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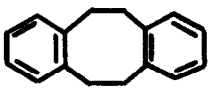
Summary - A variable temperature 200 MHz ^{1}H NMR investigation of some N-acyl substituted 11,12-dihydrodibenz[b,f][1,5]oxazocin-6-ones showed the presence at room temperature of at least two conformationally restricted diastereomers (and their enantiomers) which molecular mechanics calculations strongly suggested to be a boat-like structure (major conformer) and a pseudo-chair and/or twistboat-like structure (minor conformer). The diastereomers interconvert through a bond rotation mechanism just above room temperature (51-54°C, depending upon the nature of the N-acyl substituent), and the boat enantiomers interconvert at higher temperatures (75-95°C, depending upon the nature of the N-acyl substituent and the substitution pattern of the aromatic rings) *via* a ring inversion process. The N-acyl groups exocyclic to the eight-membered ring are shown to wholly exist - probably as a result of severe dipole:dipole interactions - in the sterically disfavoured conformation where the alkyl substituent bonded to the exocyclic carbonyl carbon atom is *trans* to the benzylic methylene group. Corresponding N-unsubstituted derivatives exhibit rapid ring inversion on the NMR time scale at room temperature.

The 11,12-dihydrodibenz[b,f][1,5]oxazocine ring system is of pharmacological interest, because several derivatives having the dibenz[b,f]-[1,5]oxazocine parent structure are effective as antiinflammatories, and neurotropic agents, e.g. antidepressants, analgesics, and sedatives.[1] A deeper knowledge of the conformational behaviour of this tricyclic system could be of help in understanding the basis of the biological activity of these compounds.

The conformational analysis of medium-sized rings, such as dibenzocyclooctadiene **1**, is generally complicated by virtue of the large number of possible interconverting conformations of similar energy. The situation in heterocyclic ring systems is somewhat simplified because of the torsional rigidity conferred upon the molecule by p-p and/or π-p orbital interactions. In a definitive series of papers in the mid-1970's, Ollis and co-workers[2] elegantly described the conformational behaviour of several classes of heterocyclic analogues of dibenzocyclooctatetraene **2** through the interpretation of variable temperature NMR



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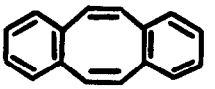

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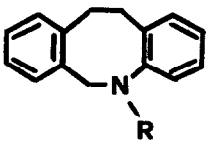
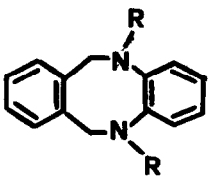
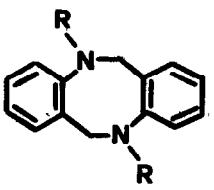


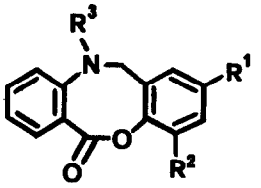
3 R = Ac,Bz,H



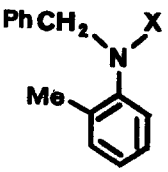
4 R = Ac,Bz,H



5 R = Ac,Bz



	R^1	R^2	R^3
6	Cl	Cl	Ac
7	Cl	Cl	COisoPr
8	Me	H	COisoPr
9	Me	H	H
10	Me	Me	H



11 X = Ac,Bz,Ts

studies with respect to molecular models and empirical molecular mechanics calculations. Of particular interest to us were the tetrahydrodibenzazocine and tetrahydrodibenzodiazocine derivatives **3** - **5** which exhibited an intermediate degree of flexibility with respect to the carbocyclic compounds **1** and **2**. With reference to this work, we now discuss the conformational behaviour of some derivatives of the biologically important 11,12-dihydrodibenz[b,f][1,5]oxazocin-6-one ring system, which contains only one methylene group in the eight-membered ring, and, for the first time, we describe the conformational preference of amide functions with the acyl groups exo- to the heterocyclic ring.

The syntheses of the three 11-acyl-11,12-dihydrodibenz[b,f][1,5]oxazocin-6-ones **6** - **8** have been reported by some of us elsewhere,[3] while the N-unsubstituted analogues **9** and **10** were prepared via the intramolecular esterification of N-(2-hydroxybenzyl)anthranilic acids[4] under mild conditions employing polyphosphate ester (PPE) as the condensing agent.[5]

The non-equivalence of the geminal H_2-12 protons in the ^1H NMR spectra (Table 1) of **6** - **8** pointed to the occurrence of restricted conformational processes in the eight-membered rings, and a variable temperature (VT) ^1H NMR study was undertaken to quantify these phenomena. The VT spectra of each of the N-acyl substituted compounds in $(CD_3)_2SO$ showed the

following key features:

(A) The presence of two sets of AB signals for the H_2-12 protons at room temperature (27°C) (in approximately a 50:1 ratio) which coalesce first to one AB system (51-54°C, Table 2) and then at higher temperatures (75-95°C, Table 2) to a singlet.

(B) A shift to lower field with increasing temperature for the α protons of the amide group.

(C) A change in the chemical shifts and splitting patterns of the aromatic protons.

In addition, the VT ^{1}H NMR spectra of the two isobutanoyl derivatives **7** and **8** showed:

(D) The coalescence (72°C) of the methyl groups of the amide function and an accompanying shift to lower field.

The VT ^{1}H NMR spectrum of **8** is reproduced in Figures 1 and 1a (expansion of the methylene region) since it illustrates well the physical manifestations of the dynamic processes exhibited by these tricyclic systems.

MM-2 calculations[6,7] clearly suggested that the most stable conformations for **8** were of the boat type (Figure 2), although local minimum energy conformations (0.5-1 kcal/mol higher) were also found for twistboat and pseudo-chair structures. Actually the resonance demand for the lactone moiety to be planar is expected to favour boat conformation of the tricyclic system under study.[8] In view of our calculations, the simplest interpretation of the NMR data in (A) is that at room temperature (27°C) a thermodynamically controlled ratio (50:1) of boat and other - either twistboat and/or pseudo-chair - diastereomers exist which interconvert slowly on the NMR time scale (unfortunately, cooling the sample in order to distinguish the possible conformers led to the precipitation of the solute). Line shape analysis via the DNMR technique (DNMR 5 program[9]) gives an energy barrier for this process of 14.9 kcal/mol (compound **8**). Furthermore, inspection of Dreiding molecular models indicates that interconversion of the twistboat and pseudo-chair conformers should be relatively unhindered - consistent with the broad signal observed in the ^{1}H NMR spectrum for the methylene protons of the minor component(s) (Figure 1). The interconversion which causes equivalence of the H_2-12 protons must be an enantiomeric one, therefore boat:boat* (Figure 3). Line shape analysis gives the energy barrier for this process as 17.4 kcal/mol (compound **8**). Changing the substitution pattern of the aromatic rings has little effect upon the energy barrier (**7**: 17.2 kcal/mol), however, changing the acyl group does have a significant impact (**6**: 16.3 kcal/mol), which we attribute to steric interactions between the alkyl chain and the ortho-proton of the aromatic ring.[2c] As expected, the methylene resonance in the ^{1}H NMR spectra of the deamidated compounds (**9** and **10**) appeared as a singlet at

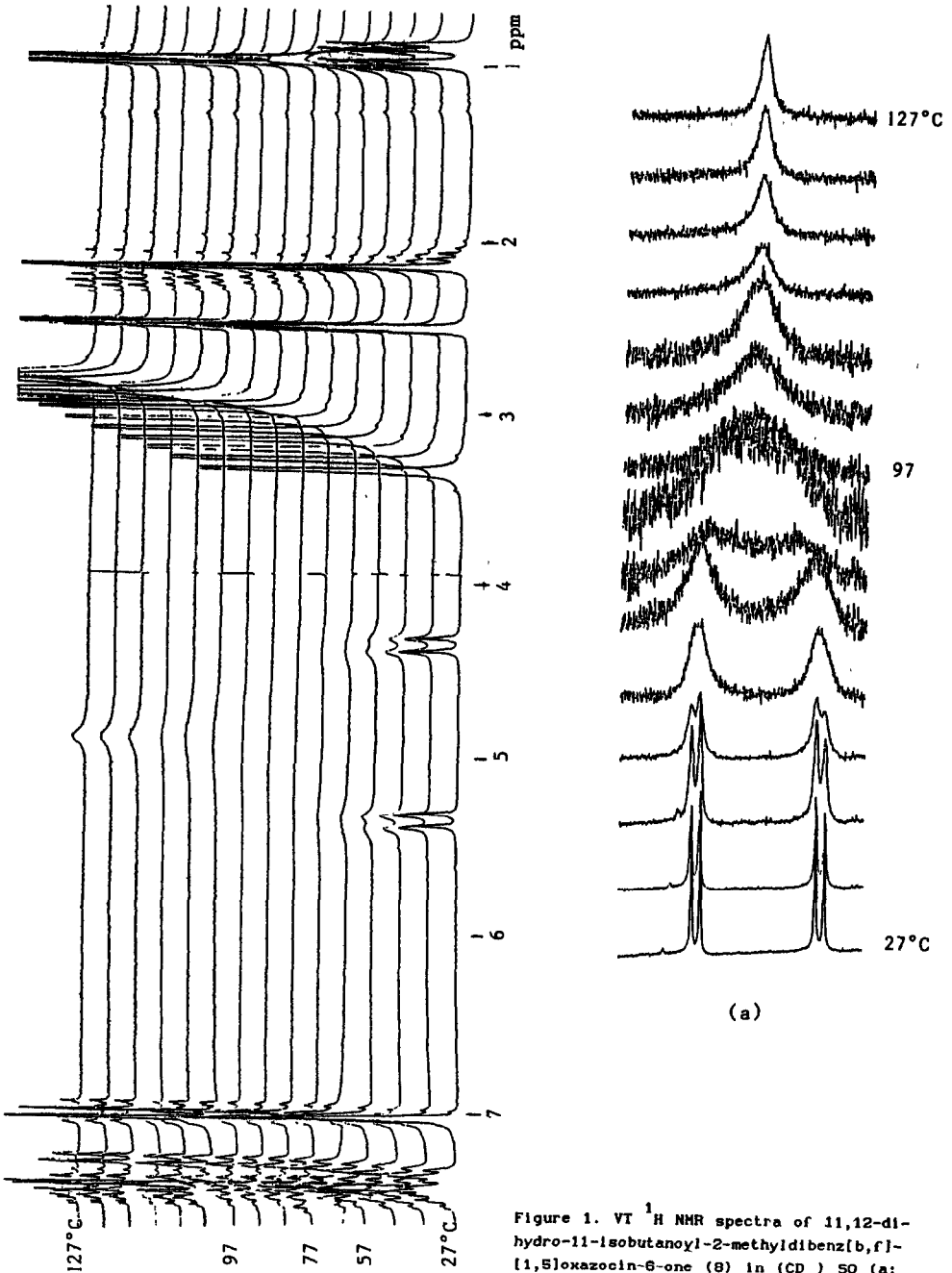


Figure 1. VT ^{1}H NMR spectra of 11,12-dihydro-11-isobutanoyl-2-methyldibenz[b,f]-[1,5]oxazocin-6-one (8) in $(CD_3)_2SO$ (a: methylene region).

Table 1. ^{1}H NMR spectroscopic data of the 11,12-dihydrodibenz[b,f][1,5]oxazocin-6-ones 6-10 (δ,ppm; J,Hz) at room temperature (27°C)[a]

	7	10	8		6	9	
	$(CD_3)_2SO$ 500 MHz	$CDCl_3$ 500 MHz	$CDCl_3$ 500 MHz	$(CD_3)_2SO$ 200 MHz	$(CD_3)_2SO$ 200 MHz	$CDCl_3$ 60 MHz	
Protons							Protons
$-CHMe_2$	0.91,d 1.00,d J_{vic} 6.5		0.98,d 1.03,d J_{vic} 6.5	0.89,d 0.99,d J_{vic} 7.0			$-CHMe_2$
$-CHMe_2$	2.11,m		2.20,m	2.12,m			$-CHMe_2$
H_2-12	4.51,d 5.40,d J_{gem} -15.0	4.27,brs	4.27,d 5.46,d J_{gem} -13.8	4.35,d 5.37,d J_{gem} -14.0	4.49,d 5.42,d J_{gem} -16.0	4.26,brs	H_2-12
ArMe		2.20,s 2.21,s	2.16,s	2.17,s		2.26,s	ArMe
-NH-		4.27,[b] brs				4.26,[b] brs	-NH-
-COMe					1.72,s		-COMe
H-1	7.48,d $J_{1,3}$ 2.0	6.86,brs	6.84,d $J_{1,3}$ 1.5	7.0-7.6,m	7.4-7.7,m	6.2-7.2,m	ArH
H-3	7.71,d	6.86,brs	6.92,dd $J_{3,4}$ 8.1				
H-4			6.86,d				
H-7	7.58,dd $J_{7,8}$ 8.0 $J_{7,9}$ 1.5	7.22,dd $J_{7,8}$ 8.0 $J_{7,9}$ 1.5	7.34,dd $J_{7,8}$ 7.5 $J_{7,9}$ 1.5				
H-8	7.52,dt $J_{8,9}$ 8.0 $J_{8,10}$ 0.5	6.68,dt $J_{8,9}$ 7.1 $J_{8,10}$ 1.1	7.28,dt $J_{8,9}$ 7.5 $J_{8,10}$ 0.8				
H-9	7.65,dt $J_{9,10}$ 8.0	7.07,dt $J_{9,10}$ 8.0	7.36,dt $J_{9,10}$ 8.0				
H-10	7.46,dd	6.43,dd	7.03,dd				

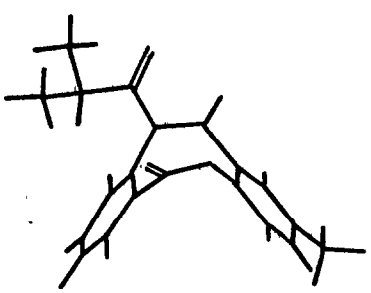


Figure 2. The MM-2 calculated minimum energy conformation for compound 8.

[a] The reported spectral data for compounds 6-8 refer to major conformers (see text) while absorptions of the minor conformations are unequivocally detectable only for H_2-12 protons : the chemical shifts of the minor AB signals in $(CD_3)_2SO$ are δ_A = 5.62, 5.60, 5.56 and δ_B = 4.28, 4.29, 4.18 ppm for compounds 6, 7, and 8, respectively.

[b] This signal exchanges upon D_2O shake.

Table 2. Activation parameters for the conformational changes of 11-acyl-11,12-dihydrodibenz[b,f][1,5]oxazocin-6-ones 6-8[a] in $(CD_3)_2SO$

	Process					
	MinC[b]:Boat		C-CHMe$_2$-Rotation		Boat:Boat*	
Compound	T_c	$\Delta G^{\ddagger}$	T_c	$\Delta G^{\ddagger}$	T_c	$\Delta G^{\ddagger}$
6	51	14.8			75	16.3
7	54	14.9	72	16.6	94	17.2
8	54	14.9	72	16.6	95	17.4

[a] For margin of errors in temperature and energy barrier values, see experimental section.
[b] The abbreviation MinC is not specific and refers to minor conformer(s) (twist-boat and/or pseudo-chair).

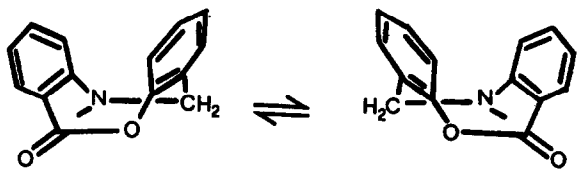


Figure 3. Interconversion of the enantiomeric boat:boat* conformers.

room temperature (Table 1), suggesting rapid ring inversion on the NMR time scale when N-11 is unsubstituted.

The coalescence of the isopropyl methyl groups above 72°C in the ^1H NMR spectrum of **8** (and **7**) was clear evidence of yet another dynamic process involving this class of molecules. Cis-trans amide isomerization - via the restricted rotation of the N-CO bond - did not seem an appealing explanation since this would imply the apparent depopulation of one amide conformation with increasing temperature and also would not explain the shift of the COCH proton to lower field (Figure 1). Furthermore, only one signal is seen for the acetyl methyl group in **6**. Previously, the stereochemistry in amides such as **4** and the ortho-toluidine derivatives **11** has been reported with the R group cis to the benzylic methylene group,[2a,10] on the basis of apparent steric requirements. However, irradiation of the acetyl methyl group of **6** gave nuclear Overhauser enhancements (nOe's) solely in the protons of the non-chlorinated aromatic ring indicating a mutual trans-stereochemistry of the methyl and methylene groups in **6**. Similarly, nOe's were observed from the methyl group at 0.99 ppm and the CH-amide proton of compound **8** to aromatic protons, but not to the methylene protons of the eight-membered ring (the complete unambiguous assignment of all the hydrogen and carbon signals was carried out at 500 MHz using ^{13}C-^1H-correlated two-dimensional spectroscopy[11]). No nOe's were observed upon irradiation of the methyl group at 0.89 ppm of compound **8**. MM-2 calcula-

tions showed, indeed, that the trans-amide of **8** (Figure 2) was stabilised by 2.2 kcal/mol over the cis-amide, sufficient to ensure that the trans-conformer is almost exclusively populated at normal temperatures. Therefore, the explanation for the NMR phenomena reported above in (B) - (D) is that rotation about the C-$CHMe_2$ bond is restricted at room temperature by the close proximity of the aromatic ring and thus one methyl group is shielded far more than the other. When free rotation occurs (above 72°C) on the NMR time scale then the second methyl group also experiences considerable deshielding (hence the downfield shift) as does the CH proton. Moreover, when the enantiomeric ring inversion occurs rapidly on the NMR time scale, the α protons of the amide groups are deshielded, since they get close to the aromatic ring plane during the interconversion of B:B* conformations: for instance, the methyl group of **6** resonates at 1.72 ppm at room temperature and is deshielded to 1.78 ppm when the temperature gets over 75°C (Table 2).

Although the influence of solvent interactions (either hydrogen bonding to the amide or lactam moiety of the heterocycle or dipole:dipole interactions) should not be overlooked, the suggested tendency for the amide group to adopt the trans-stereochemistry despite considerable steric compression is probably caused by a severe unfavourable dipole:dipole interaction between the carbonyl group and the aromatic ring current in the cis-conformation. This kind of electronic conformational control may play an important or, indeed, crucial role in determining the physical and biological properties of not only 6,8,6 ring systems, but also those of a wide variety of heterocyclic compounds and sterically congested peptides and proteins.

Experimental

Melting points are uncorrected. IR spectra were determined with a Perkin Elmer 682 spectrophotometer by using nujol mulls between NaCl plates. The mass spectrum of **10** was obtained (EI, 70 eV) on a CH7 Finnigan Mat instrument. NMR spectra were recorded on Varian EM 360A, Bruker AM-200 and 500 instruments. The variable temperature ^1H NMR spectra were obtained using a Bruker AM-200 spectrometer equipped with a standard variable temperature unit. Calibration using a copper-constantan thermocouple inside a solvent containing NMR tube indicates the reported temperatures are precise within +/- 0.1°C. Line shape analysis was performed using DNMR5 obtained from QCPE:[9] temperature values are accurate to +/- 1°C and energy values to +/- 0.1 kcal/mol. The proton samples were prepared as 0.1M solutions in $(CD_3)_2SO$ or $CDCl_3$, and chemical shifts are reported on the δ

scale referenced to Me_4Si. Molecular mechanics calculations were performed on a Micro-Vax 2 using a modified version of Allinger's MM-2 program[7] also obtained from QCPE and visualised on an IBM 386 using Alchemy. The compounds **6-8** were prepared by the N-acylation and intramolecular esterification of N-(2-hydroxybenzyl)anthranilic acids,[4] as reported.[3]

11,12-Dihydro-2-methyldibenz[b,f][1,5]oxazocin-6-one (**9**): N-(2-hydroxy-5-methylbenzyl)anthranilic acid[4] (772 mg, 3 mmol) was added to PPE[12] (19.5 g, 45 mmol) and the mixture slowly stirred at room temperature for 24 h. A 10% $NaHCO_3$ solution was carefully added under cooling and stirring until an alkaline pH was measured. The reaction mixture was stirred for a further 2 h, then chloroform (30 ml) was added, and the organic phase separated, dried over sodium sulfate, and concentrated. Purification by column chromatography on silica gel using 1:1 diethyl ether/petroleum ether (bp 30-50°C) gave compound **9** in 68% yield: mp 154-156°C; IR 3360 (NH), 1720 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) (126 MHz) δ 20.81 (Me), 43.31 (C-12) 111.72 (C-6a), 117.69 and 118.25 (C-8 and C-10), 119.59 (C-4), 129.60 and 130.25 (C-7 and C-9), 130.25 (C-3), 131.33 (C-1), 132.28 (C-12a), 136.15 (C-10a), 136.58 (C-2), 143.23 (C-4a), 169.20 (C-6).[13] Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.59; H, 5.58; N, 5.88.

11,12-Dihydro-2,4-dimethyldibenz[b,f][1,5]oxazocin-6-one (**10**) was prepared in 70% yield from N-(3,5-dimethyl-2-hydroxybenzyl)anthranilic acid[4] following the above described procedure: mp 158-160°C; IR 3360 (NH), 1710 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) (126 MHz) δ 15.09 (4-Me), 20.75 (2-Me), 43.75 (C-12), 111.30 (C-6a), 117.87 and 118.24 (C-8 and C-10), 127.12 (C-1), 128.49 (C-4), 129.60 and 131.33 (C-7 and C-9), 131.56 (C-3), 132.18 (C-12a), 136.48 (C-2), 136.57 (C-10a), 143.93 (C-4a), 169.62 (C-6);[13] mass spectrum m/z (relative intensity) 253 (M^+, 100), 238 (10), 225 (60), 224 (41), 210 (22), 208 (15), 120 (11), 119 (17), 92 (16), 91 (15), 77 (12). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.10; H, 6.14; N, 5.50.

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6. Molecular mechanics calculations cannot usually give information about the dynamic behaviour of molecules since the "snapshot" minimum energy conformation that they calculate is not unique and, indeed, may be virtually unpopulated at room temperature depending upon the shape of the entire energy hypersurface. However, these calculations can be of great use in determining the relative stabilities of idealised conformations and we have used them as such for the rational interpretation of our experimental data. Although there are special problems in producing accurately parameterised forcefields for systems involving non-coplanar heteroatoms and π-systems, and, as we are grateful to a referee for pointing out, despite the fact that polar solvents such as $(CD_3)_2SO$ can play an influential role in determining conformational stability and flexibility, molecular mechanics has been successfully used to calculate preferred conformations of several 6,8,6 compounds (including **1** and **2**)[2] and other related unsaturated hydrocarbons.[14] We therefore feel confident, given the complete correlation between our theoretical and experimental results, that these forcefields can, in fact, be successfully extrapolated to include a wide range of medium-sized heterocyclic ring systems.

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11. Compound **8**: ^{13}C NMR ($CDCl_3$) (126 MHz) δ 19.63 and 19.65 (-$CHMe_2$), 20.61 (2-Me), 32.40 (-$\underline{C}HMe_2$), 50.20 (C-12), 121.85 (C-4), 127.87 (C-7), 128.02 (C-6a), 128.45 (C-10), 129.17 (C-8), 130.24 (C-3), 131.53 (C-1), 132.17 (C-9), 132.58 (C-12a), 136.73 (C-2), 136.88 (C-10a), 149.68 (C-4a), 168.37 (C-6), 177.31 (-$\underline{C}OCHMe_2$).

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