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STEREOCHEMISTRY OF TETRAHYDROFUROFURAN DERIVATIVES—CIRCULAR DICHROISM AND ABSOLUTE CONFORMATION

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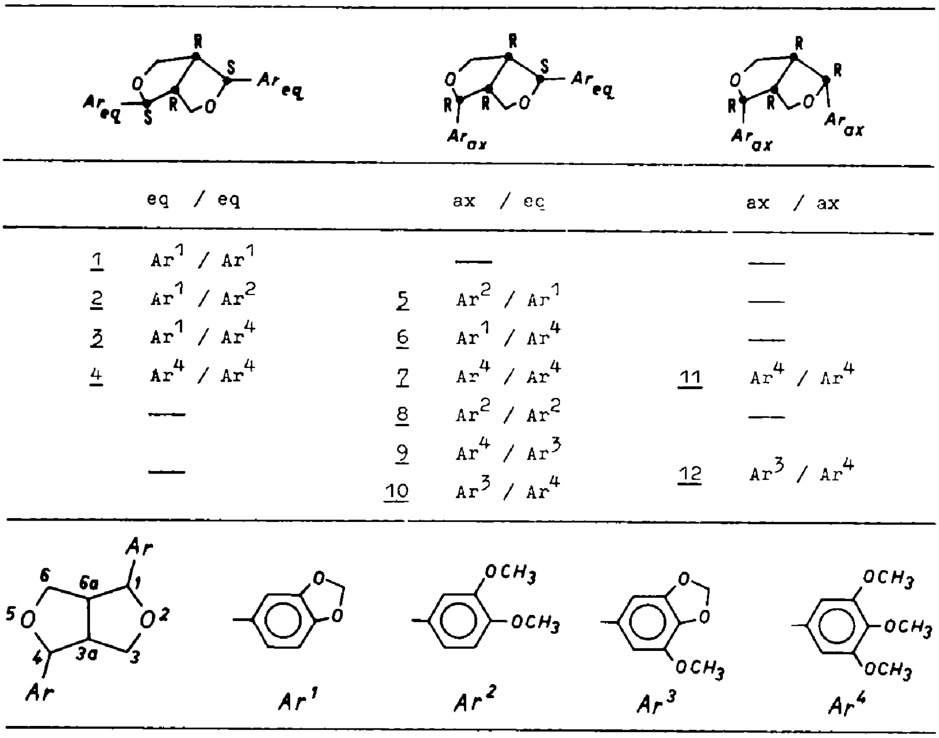
Abstract—The CD spectra of 12 different lignans of the sesamin type were recorded. In several cases the spectra can be interpreted quantitatively in terms of a coupled oscillator model allowing to deduce absolute configurations and conformations. To this end several computer programs were used which reflect the successive steps of the procedure: (i) curve fit for the CD bands in the ^1B_b region giving reliable values for the band splittings of the experimental couplets; (ii) search for possible solutions to simulate these CD splittings, giving geometrical parameters for the transition moments; (iii) PPP SCF-MO-CI calculations of the UV spectra to determine the orientation of the transition moments within the aromatic moieties; (iv) a COORD type program to link these geometrical parameters derived from (ii) and (iii) with the absolute stereochemistry of the total 1,4-diaryl-tetrahydrofurofuran molecule.

A preceding paper[1] reports the isolation of several new tetrahydrofurofuran lignans from *Artemisia absinthium*. The absolute configurations were assigned preliminarily by comparison of the observed optical rotations with the corresponding values of the closely related compounds whose absolute configurations have been determined via chemical degradation of the natural products.[2]

However, some of the compounds are well suited for theoretical calculation of the CD thus furnishing independent evidence for the absolute configurations of the compounds on a non-empirical basis.

1,4-Substituted tetrahydrofurofurans contain four asymmetric carbons. The number of possible enantiomeric pairs is restricted by the cis arrangement of the fused tetrahydrofuran rings.[2,3] A consequence of this restriction is that the configurations of the bridge atoms 3a and 6a are either (*R*)(*R*) or (*S*)(*S*) [(*R*)(*S*) or (*S*)(*R*) would mean a trans fusion of the tetrahydrofuran rings]. This, in turn, allows only three pairs of enantiomers when the aromatic moieties at C-1 and C-4 are identical and four when the C-1 and C-4 rests are different C-3a, -6a, -1, -4: a. (*R*)(*R*)(*R*)(*R*), b. (*R*)(*R*)(*R*)(*S*), c (*R*)(*R*)(*S*)(*R*), d. (*R*)(*R*)(*S*)(*S*), with the corresponding enantiomers a. (*S*)(*S*)(*S*)(*S*), b. (*S*)(*S*)(*S*)(*R*), c. (*S*)(*S*)(*R*)(*S*), d. (*S*)(*S*)(*R*)(*R*); b is identical with c. if both arylic rests at C-1 and C-4 are the same.



	eq / eq		ax / eq		ax / ax
1	Ar^1 / Ar^1		—		—
2	Ar^1 / Ar^2	5	Ar^2 / Ar^1		—
3	Ar^1 / Ar^4	6	Ar^1 / Ar^4		—
4	Ar^4 / Ar^4	7	Ar^4 / Ar^4	11	Ar^4 / Ar^4
	—	8	Ar^2 / Ar^2		—
	—	9	Ar^4 / Ar^3	12	Ar^3 / Ar^4
		10	Ar^3 / Ar^4		

Scheme 1

Usually the relative configurations of the C-1 and C-4 substituents of lignans in the sesamin series are termed "axial" or "equatorial". The folded structure of the tetrahydrofurofuran ring system (Scheme 1) results in a conformation allowing the substituents to stand either quasi-axial or quasi-equatorial.

"Axial" substitution of either C-1 or C-4 in the 3a, 6a/(*R*)(*R*) series means that the corresponding carbon is (*R*)-configurated ["eq" for (*S*)]; in the 3a, 6a/(*S*)(*S*) series "ax" for (*S*) and "eq" for (*R*) at C-1 or C-4 (Scheme 1).

Based on chemical evidence most naturally occuring tetrahydrofurofurans (sesamin type) belong to the series with the bridge atoms 3a, 6a in (*R*) (*R*) configuration.[2]

In this paper we report the CD spectra of 12 lignans; theoretical considerations reveal the absolute stereochemistry for some of the compounds.

RESULTS AND DISCUSSION

Ultraviolet spectra

The UV spectra of the sesamin derivatives under consideration are characterized by bands at 270 287 nm ($\varepsilon = 1500$ 10000) and 228 238 nm ($\varepsilon = 13000$- 21000) and a dominating band at 203 209 nm ($\varepsilon = 100000$). The exact values are listed in Ref. 1.

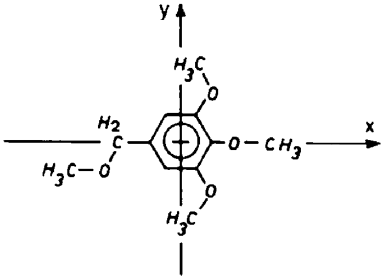
The bands correspond to the transitions ^1L_b, ^1L_a and ^1B_b following the Platt classification or α, p and β in the nomenclature of Clar.

Since the orientations of the excitation dipoles within the aromatic chromophors are of essential importance in the calculation of the theoretical CD spectra we performed suitable PPP–SCF–MO–CI calculations[4] which will be discussed in detail for the arylic moiety of **11**.

The isolated aromatic system is treated as 3,4,5-trimethoxy-benzylalcohol methyl ether. The parameters chosen for the calculation are based on literature data:[5,6] H_{CC} (and γ_{CC}) for aromatic C varies in Lit. between 8.75 (8.25) and 12.4 (12.2), our value of H_{CC} (and γ_{CC}) is well within these limits.[4] [6] The parameters for the substituents are taken mainly from.[5] Special features of the benzyl ether function are the methylene group (treated in analogy to a Me group) and the non-aromatic ether function (note that β_{C-O} is different for the aromatic or aliphatic type; Table 1a).

In Table 1b the results for Ar[4] (**11**) are summarized. The strong band at 201 nm (exp. 207) corresponds to a transition dipole oriented along the rotation axis of the arylic substituent (longitudinal transition), with a deviation from the $C_{tetrahydrofurofuran}$-C_{aryl}axis of 10–15° (depending slightly on the parameters chosen in the calculation). The transition at 230 (exp. 231) nm exhibits a very small displacement from the longitudinal direction (deviation ~4°), the transition at

Table 1 PPP SCF MO-CI calculation for substituent Ar[4] in compound **11**



a. Parameters

Atom X	Bond C—X	H_{XX}	γ_{XX}	β_{C-X}	Z_X
C(arom.)	C(arom.)—C(arom.)	10.2	9.8	-2.4	1
C (in CH_3, CH_2)	C—CH_3 , C—CH_2	10.7	8.6	-1.7	1
H_3, H_2 (in CH_3, CH_2)	C—H_3 , C—H_2	13.6	12.8	-4.8	1
O (aryl ether)	C(arom.)—O	35.8	18.1	-2.3	2
O (aliphat.eth.)	C(aliph.)—O	35.8	18.1	-1.3	2

b. Results

Trans-ition	$\lambda_{exp.}$ [nm]	$\lambda_{calc.}$ [nm]	$\varepsilon_{exp.}$	Osc.Str. calc. [μ_D]	Transition Moment Components along axes x	y	z
^1L_b	273	266	2300	0.01	0.26	-0.85	0.02
^1L_a	235	230	13500	0.28	-1.15	-0.06	-0.06
^1B_b	207	201	96500	0.70	-0.87	-0.20	0.00

266 (270) nm is polarized perpendicular to the C_{tetr}–C_{aryl} axis. All transition moments are calculated to be within the benzene plane (deviations not higher than 4°).

The positions of the maxima and the relative oscillator strengths are reproduced very well by the calculation (Table 1b).

CD spectra

^1B_b and ^1L_a Cotton effects of sesamins **1**–**12** are found in the same wave length region as the corresponding UV transitions.[1] ^1L_b bands of di-ax isomers **11** and **12** do not show any remarkable intensity in the region of 280 nm and there will be a very weak chiral contribution to this transition.

Three types of spectra can be distinguished: Eq–eq (type 1, **1**–**4**) and ax-eq (type 2, **5**–**10**) isomers in general exhibit Cotton effects of aromatic ^1B_b, ^1L_a and ^1L_b transitions with $\Delta\varepsilon_{max}$ values from 0.5 to 21. There are no great differences in the spectra of di-eq sesamin and higher substituted derivatives, only small differences of absolute $\Delta\varepsilon$ values can be detected. Therefore, CD spectra of type 1 are very similar to each other.

^1B_b bands are split into couplets with low $\Delta\bar{\nu}$ values exhibiting weak dipole–dipole coupling of aromatic moieties which contribute to the ^1B_b Cotton effect. Experimental CD parameters are summarized in Table 2.

Spectra of tri-substituted ax-eq isomers (type 2) are also similar to each other representing three well separated Cotton effects with equal signs while spectra of disubstituted derivatives with lower symmetry are more complicated which may be effected by numerous optically active transitions and coupling phenomena. The CD of unsymmetrically substituted **6** is dominated by negative Cotton effects with relatively low rotational strengths. Assignments of absolute configurations for ax–eq derivatives from CD data is a rather complex problem.

Strong dipole–dipole coupling of the aromatic chromophors in ax–ax sesamins (type 3, **11** and **12**) is pedominantly responsible for the origin of high optical activity in the ^1B_b electronic transition because there is a strong interaction etween the aromatic nuclei.[7–10] The short wave length ^1B_b Cotton effect is characterized by a positive couplet with $\Delta\varepsilon_{max}$ values up to 78. In general the $\Delta\varepsilon$ values for the ^1L_a band are in the region of 25.

Selected CD spectra for the different types are shown in Fig. 1.

Ax ax as well as eq–eq sesamins with point group C_2 should be suitable for treatment of short wave length Cotton effects with the "exciton theory" for coupled oscillators.[7–10]

Therefore the splitting of the ^1B_b band can be calculated:

$$\Delta\bar{\nu} = \frac{2\mu_1^2}{h\,c.d^3}(\cos^2\gamma - \cos^2\beta + 2\cos^2\alpha). \tag{1}$$

Rotational strengths of bands with A and B symmetry[7] are expressed by the following equation:

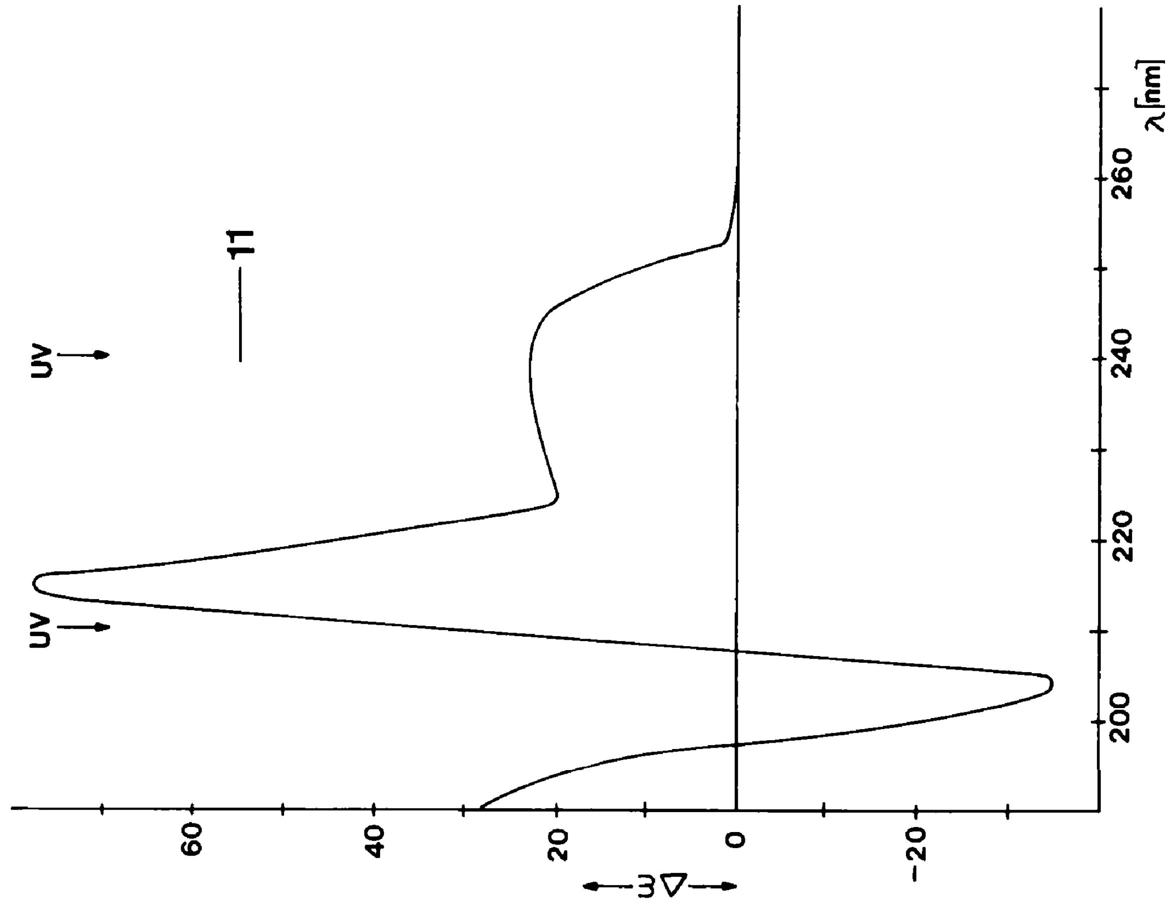
$$R^A = -R^B = \pi\bar{\nu}_0 d\mu^2 \cos\beta . \cos\gamma \tag{2}$$

α, β, γ and d represent the direction and position of the electric transition moment vector μ in a local Kartesian coordinate system according to Ref. 7 (Fig. 2). Therefore, if the direction of μ in an aromatic chromophor is known, the absolute configuration, resp. conformation, can be determined. The "exciton treatment" was mainly used for the determination of the absolute configuration of rigid molecules with symmetry C_2.[7,8]

If a molecule exists in several possible conformations each form will be described by a set of stereochemical parameters for the electric transition moment vector. A special computer program was used to calculate parameter sets for physically meaningful conformations. For each set the calculated $\Delta\bar{\nu}$ values were compared with experimental results. Since this variation process yields numerous solutions with good agreement of experimental and calculated $\Delta\bar{\nu}$ values a

Table 2. CD Spectra of sesamin derivatives 1 12

No.	^1B_b λ[nm] (Δε)			^1L_a λ[nm](Δε)	^1L_b λ[nm] (Δε)		
1	~197(−1)	~198(0)	205(18)	~235(4.8)		280(1.2)	
2	200(−)		207(18)	230(2.2)		280(1)	
3	~197(−1)	200(0)	210(11.7)	235(2.8)		280(1.6)	
4			208(10.5)	~235(2.4)		275(0.8)	
5		210(−)	216(0)	237(3.3)	270(0.2)	280(0)	290(−0.6)
6	200(1.8)	205(0)	216(−5)	247(−1.2)		275(−1)	
7	197(4.4)	207(14)		235(3.4)		275(0.6)	
8	198(21) 215(0)	205(0) 217(2)	208(−4)	235(6.8)	272(0.4)	283(0)	286(−0.3)
9	195(7)	200(3.8)	208(11.4)	235(4)	255(−0.5)	270(0)	285(0.4)
10		200(10)	210(12.8)	235(3.5)		280(0.8)	
11	204(−35)	207(0)	215(78)	240(22)		——	
12	205(−23)	208(0)	215(63)	240(14)		——	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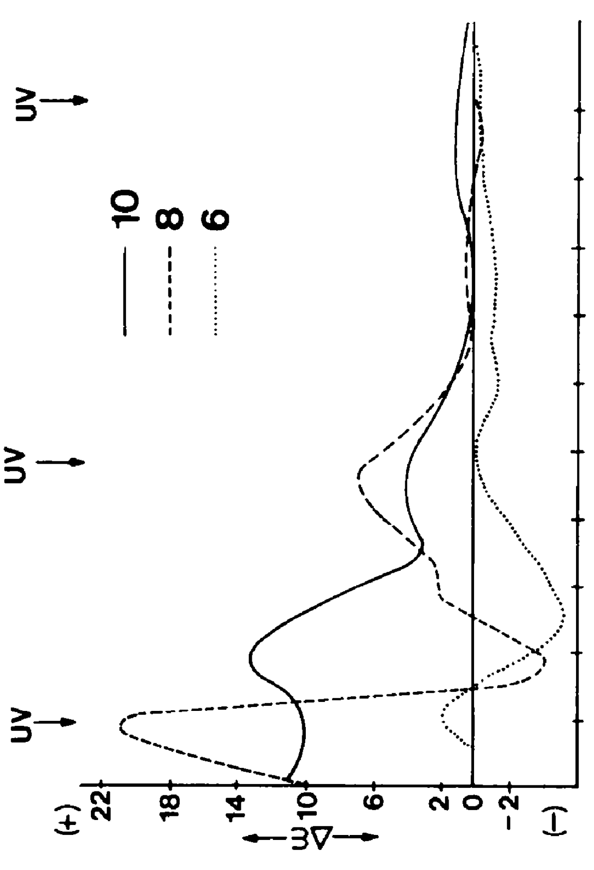
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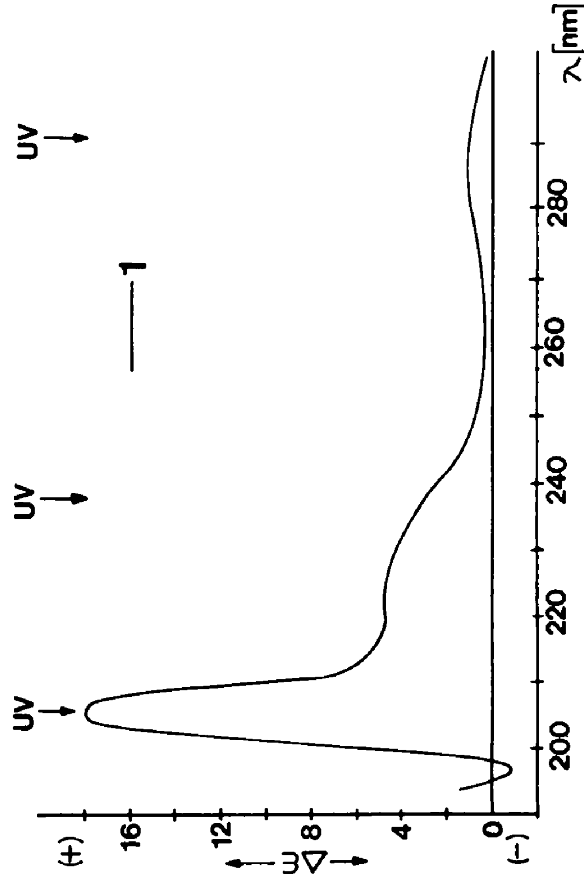
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further selection can be made by comparison of experimental and theoretical rotational strengths.

Quantitatively the two CD bands of opposite signs associated with a given absorption band system do not have equal areas (Fig. 1) and in general the experimental rotational strengths are smaller in magnitude than the corresponding theoretical values. The calculated and the observed succession of rotational strengths shows that a given CD band is flanked on either side by dichroism bands of opposite sign and where the bands overlap there is a mutual cancellation of band area.

Curve-fit with a computer program afforded the parameters $\Delta\bar{\nu}$ as well as $\Delta\varepsilon$ values and rotational strengths for ax-ax and eq eq sesamins which are summarized in Table 3.

Magnitude and direction of the electric transition moment of the ^1B_b transition were obtained from UV measurements and/or PPP calculations. The stereochemical parameters of μ based on eqns (1) and (2) are given in Table 4.

These values can be correlated to a particular molecule geometry by use of a COORD type program[11] comparing calculated sets of parameters with theoretical sets obtained from model considerations (variation of ring puckering and torsion about the C_{THF}–$C_{arom.}$ bond). (Table 5).

However, in the case of ax–ax and eq eq sesamins the qualitative form of the theoretical CD spectrum depends upon the configuration as well as conformation. For the particular absolute configuration (*R*)(*R*)(*R*)(*R*) considered for the compounds ax–ax **11** and **12** the set of stereochemical parameters d, α, β and γ for a given conformation associated with the ^1B_b transition indicates, that the signs of the two CD bands of the ^1B_b transition should run, from larger to shorter wave lengths, positive and then negative. This agrees with the observed CD spectrum confirming the absolute configuration determined by Freudenberg[2] with chemical methods. The absolute conformation of the ax ax derivatives is shown in Fig. 2:

The furofuran system forms a rooflike structure with both oxolane components showing a ring puckering of about 40°. (corresponding to a torsional angle of 25° for C-3a/C-6a/C-1/O-2). The favored conformation of the aromatic substituents at C-1 and

Table 3. CD Parameters for the ^1B_b bands of **11**, **12** and **1**, before (exp. data) and after the curve fit procedure (calc.)

Comp.	Experimental Data			Calculated Parameters			
	$\Delta\bar{\nu}$ [cm^{-1}]	$\Delta\varepsilon_{min}$	$\Delta\varepsilon_{max}$	$\Delta\bar{\nu}$ [cm^{-1}]	$\Delta\varepsilon_{min}$	$\Delta\varepsilon_{max}$	R [cgs]
11 (ax-ax)	2000	-35	+78	1024	-140	+140	$2.6\text{-}3\cdot10^{-38}$
12 (ax-ax)	1800	-23	+63	1024	-115	+115	$2.5\cdot10^{-38}$
1 (eq-eq)	600	-1	+18	250-400	-9	+9	$0.2\cdot10^{-38}$

Table 4. Parameters derived from eqns (1) and (2) (Fig 2) on the basis of the CD parameters obtained in the curve fit (Table 3)

Comp.	Absol. Config. at Carbon 3a 6a 1 4	d [A]	α [°]	β [°]	γ [°]	R [cgs]
11 (ax-ax)	(R) (R) (R) (R)	4-4.5	60-70	60-70	20-30	$1\text{-}2\cdot10^{-38}$
12 (ax-ax)	(R) (R) (R) (R)	4-4.5	60-70	60-70	20-30	$1\text{-}2\cdot10^{-38}$
1 (eq-eq)	(R) (R) (S) (S)	7-8	20-30	70-80	70-80	$2.5\cdot10^{-39}$

Table 5. Parameters d, α, β and γ for favored conformations of **11**, **12** and **1** calculated by means of a modified COORD program under consideration of the transition moment parameters (Table 1b); the most favored conformations are characterized by maximum agreement with the corresponding parameters derived from CD data (Table 4)

Comp.	Absol. Config. at Carbon 3a 6a 1 4	d [A]	α [°]	β [°]	γ [°]
11 (ax-ax)	(R) (R) (R) (R)	4-4.2	65-75	60-70	30-35
12 (ax-ax)	(R) (R) (R) (R)	4-4.2	60-70	60-70	25-35
1 (eq-eq)	(R) (R) (S) (S)	8-9	25-35	60-70	65-75

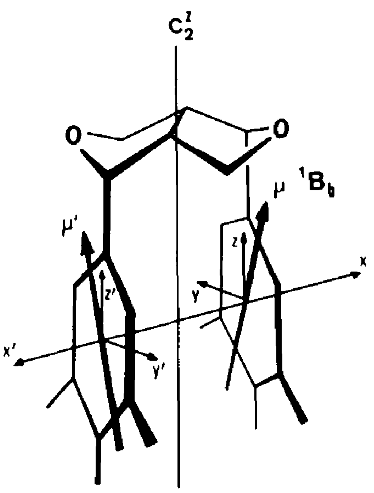

Fig. 2. Favored conformation for **11** and **12**. α, β and γ [used in eqns (1) and (2)] correspond to the angles of the ^1B_b transition with the axes of the local Kartesian coordinate systems, d is the distance between the centers of the two aromatic moieties along the x axis (which is perpendicular to the C_2^z axis).

C-4 is characterized by a torsional angle near to zero for atoms O-2/C-1/C-1(aromat.)/C-2(aromat.) and O-5/C-4/C-1(aromat.)/C-2(aromat.); in other words, the benzene ring is approximately in plane with the adjacent oxygen. The distance of both rings is about 4 Å.

For **1** and **11** the temperature dependance of the CD was checked between −45° and +60°; no effect could be detected thus indicating that the conformation does not change. A change of solvent from EtOH to the less polar C_6H_{12} did not have any effect on the measured CD either.

For eq eq sesamin **1** the absolute configuration $(R)(R)(S)(S)^2$ is conform with the observed weak positive couplet in the CD spectrum. The conformation of the furofuran rings should be very similar to that of the di–ax isomers. No evidence for a favoured conformation of the aromatic rings relative to the furofuran system could be derived from the calculations concerning equatorial aromatic substituents.

EXPERIMENTAL

All compounds investigated are natural products isolated from the roots of *Artemisia absinthium* and other closely related species.[1]

Absorption spectra were measured with a spectrometer Cary 15 (in EtOH) and CD with a dichrograph Mark III (Jobin Yvon). In general the CD spectra were obtained in EtOH at 20°C; **1** and **11** in cyclohexane at 20° and in EtOH at +60, +40, +20, 0, −10, −30 and −45° as well.

The experimental rotational strength R and the dipole strength D were obtained in c.g.s. units from appropriate band areas.[7]

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