

X-Ray Structural Analysis of Tetrahydrofurofuran Lignans

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The crystal structures of two diastereomeric tetrahydrofurofuran lignans, diasesartemin (**1**) and episesartemin-B (**2**), were determined. The former one is of the classical "axial-axial" substitution type (the two aryl moieties of the 1,4-diaryl-tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan in "ax"- "ax" position), the latter one belongs to the "axial-equatorial" type. Analysis of the X-ray results revealed that in both cases the substituents are attached in pseudo-equatorial positions due to a flip of the (slightly twisted) envelope conformation of the oxolane five-rings. In **1** the oxygen atoms of the two five rings point against each other (overall boat conformation of the tetrahydrofurofuran system or *endo-endo* topology), in **2** one ring is folded towards and the other one is folded away from the second ring (overall "boat-chair" conformation of the tetrahydrofurofuran system or *endo-exo* topology): as a consequence, *all* aryl substituents adopt a pseudo-equatorial position. The terms "ax-ax", "ax-eq", and "eq-eq" used throughout in the literature are therefore misleading as far as the true conformations are concerned. Analysis of the aromatic short wavelength CD couplet of **1** by means of the coupled oscillator model shows that the X-ray derived geometry is compatible with the CD data in solution.

(Keywords: Crystal structure; Circular dichroism; Oxolane ring, envelope; Conformational analysis)

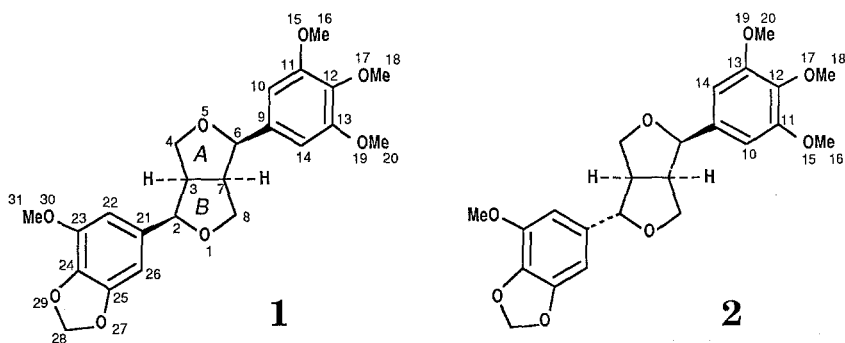
Röntgenstrukturanalyse von Tetrahydrofurofuran-Lignanen

Es wurde die Kristallstruktur von zwei diastereomeren Tetrahydrofurofuran-Lignanen, Diasesartemin (**1**) und Episesartemin-B (**2**), bestimmt. Ersteres gehört dem klassischen „axial-axial“-substituierten Typ an (dabei sind die zwei Arylsubstituenten des 1,4-Diaryl-tetrahydro-1*H*,3*H*-furo[3,4-*c*]furans in „ax“- „ax“-Position), das zweite gehört zum „axial-equatorial“-Typ. Die Röntgenstrukturanalyse zeigte, daß die Aryl-Substituenten immer in pseudo-equatorialen Positionen stehen, da die Oxolan-Fünfringe eine entsprechende (leicht getwistete) Briefumschlag-Konformation einnehmen. In **1** zeigen die Sauerstoffatome der beiden Ringe zueinander (insgesamt eine Boot-Konformation des Tetrahydrofurofuransystems bzw. *endo-endo*-Topologie), in **2**

ist ein Ring in Richtung zum, der andere Ring jedoch weg vom jeweils zweiten gegenüberliegenden gefaltet (insgesamt eine „Boot-Sessel“-Anordnung in der Tetrahydrofurofuran-Einheit bzw. *endo-exo*-Topologie): Eine Folge davon ist, daß alle Arylsubstituenten eine pseudo-equatoriale Position einnehmen. Die in der Literatur durchgehend verwendete Bezeichnung „ax-ax“, „ax-eq“ oder „eq-eq“ ist daher bezüglich der tatsächlichen Konformation mißverständlich. Die Analyse der kurzwelligen aromatischen CD-Banden von **1** mittels des Modells der gekoppelten Oszillatoren zeigte, daß die Konformation aus der Röntgenstrukturanalyse mit den CD-Daten in Lösung in Übereinstimmung ist.

Introduction

Diaryl-tetrahydrofurofurans comprise an interesting group of naturally occurring lignan derivatives [1]. They have attracted much attention due to their interesting stereochemistry [2–7], their chemosystematic significance [8, 9], and their medicinal [10, 11] as well as insecticidal properties [12].



From the roots of *Artemisia absinthium* L. we have previously isolated a series of 1,4-diaryl substituted tetrahydrofurofurans [6]. Of special interest was one group of diastereomeric 1-[(3,4-methylenedioxy-5-methoxy)phenyl]-4-(3,4,5-trimethoxyphenyl)-tetrahydro-1*H*,3*H*-furo[3,4-*c*]furans, because all four possible stereoisomers were obtained: the so-called “ax-ax”, “ax-eq”, “eq-ax”, and “eq-eq” isomeric structures. “Axial” aromatic substituents may be easily identified by the characteristic chemical shift of the proton opposite to the “axial” aromatic ring (position 3 ax or 6 ax); this proton is within the shielding field of the ring current since the phenyl rest is restricted in its free rotation [2]. However, with two different “axial” aromatic moieties it cannot be decided, whether Ar^1 or Ar^2 is “axial” or “equatorial”; for this special

problem the lanthanide induced shift method was used successfully [6]. So the relative stereochemistries of the above mentioned group of unsymmetrically substituted tetrahydrofurofuran could be determined. The crystals of two of the compounds, diasartemin (**1**, the “ax-ax” stereoisomer) and episesartemin B (**2**, the “ax-eq” isomer with trimethoxyphenyl “axial” and methylenedioxy-methoxyphenyl “equatorial”) were well suited for a crystal structure analysis.

Experimental

The compounds **1** and **2** were isolated from the roots of *A. absinthium* according to Ref. [6]. Slow crystallisation from ether at -20°C yielded crystals for X-ray analysis on a locally modified STOE 4-circle diffractometer (MoK α -radiation, graphite monochromator, $\lambda = 0.71069 \text{ \AA}$) equipped with a Nonius low temperature attachment and an Eurotherm temperature controller. The whole diffractometer was placed inside a glove box to minimize the formation of ice on the crystal. Relevant experimental conditions and a summary of the results of structure refinement are given in Table 1.

Table 1. *Experimental parameters for the X-ray analysis of compounds 1 and 2*

	1	2
Chemical formula	C ₂₃ H ₂₆ O ₈	C ₂₃ H ₂₆ O ₈
Molecular weight	430.1628	430.1628
Space group	P 2 ₁	P 2 ₁
Number of molecules / unit cell	4	2
a [Å]	7.661 (5)	8.627 (2)
b [Å]	30.754 (35)	7.810 (2)
c [Å]	8.829 (7)	15.754 (8)
β [°]	88.97 (4)	91.37 (3)
V [Å ³]	2079.9 (1.0)	1066.9 (0.5)
Temperature [°C]	-173.6	-171.7
Calculated density [g cm ⁻³]	1.375	1.303
Limits of data collection	3.5° ≤ 2 θ ≤ 50° -9 ≤ h ≤ 9 0 ≤ k ≤ 36 0 ≤ l ≤ 10	3° ≤ 2 θ ≤ 60° -12 ≤ h ≤ 12 0 ≤ k ≤ 10 0 ≤ l ≤ 22
Observed reflections	5893	3534
Independent reflections	3783	3359
Significant reflections $ F_{\text{obs}} > 4\sigma(F_{\text{obs}})$	2644	2940
R / R _w - factors [%]	9.4 / 9.61	4.51
Number of parameters	498	591
Number of observations	2696	2966
Weighting system	a / [$\sigma^2(F) + b(F^2)$]	unit weights
a / b	4.01 / 0.003	
Highest peak in final ΔF -Fouriersynthesis [eÅ ⁻³]	0.28	0.32

Data processing involved Lp-correction and for structure **1** extinction correction. The structures were solved by direct methods and refined by least-squares techniques. In the final cycles computer limitations forced a blocking of the least-squares matrix.

In structure **1** only atoms O1-C8, O15-C20, O27-C31, O1'-C8', O15'-C20' and O27'-C31' were refined with anisotropic temperature coefficients. The positions of the hydrogens were calculated. All non-hydrogen atoms were refined anisotropically in structure **2**. H-atoms were included at observed positions and C—H bonding distances were constrained to 1.08 Å in the last cycles of refinement.

The computer programs used (some in locally modified versions) are summarized in Ref. [13].

Results and Discussion

Crystallographic data and fractional coordinates are collected in Tables 1 and 2. For compound **1** two independent molecules were found in the asymmetric unit (**1 a** and **1 b**). Selected bond distances, bond angles, and torsional angles are listed in Table 3. A presentation of the X-ray structures of **1 (a, b)** and **2** in a directly comparable view is shown in Fig. 1.

Conformations of the Oxolane Rings

The most important result is that the individual oxolane five-membered rings in **1** and **2** adopt a slightly twisted envelope conformation with all aromatic moieties in pseudo-equatorial positions. The torsional angles C6-C7-C3-C4 for ring *A* and C2-C3-C7-C8 for ring *B* were found to be -7.4° (**1 a**, ring *A*), -3.0° (**1 a**, *B*), -2.8° (**1 b**, *A*), -3.9° (**1 b**, *B*), -6.3° (**2**, *A*), and -7.3° (**2**, *B*) (Table 3, numbering of the X-ray measurement). These values indicate a rather small deviation from the pure envelope conformation. The slight twist of the envelope is in such a direction to decrease some non-bonded interaction between the aromatic rings and the close methylene proton of the opposite ring [for instance $Ar(OMe)_3$ at C6 and H_{ps-ax} at C8]. The ring puckering was found to be $42 \pm 1^\circ$ for all oxolane rings in **1** and **2**. As a measure for the puckering the folding angles lying in the bisecting plane of the approximately symmetric bicyclic tetrahydrofurofuran system (passing through O1 and O5) were taken; puckering angle of ring *A*: center C3/C7—center C4/C6—O5; puckering of ring *B*: center C3/C7—center C2/C8—O1 (X ray numbering, Table 3).

In compound **1** (the so-called “ax-ax” diastereomer) the folding of both five-rings is directed towards the opposite five-ring: both aromatic substituents are then positioned equatorially and both oxygen atoms are in *endo* (or *syn*) positions relative to the second ring.

Table 2. Fractional atomic coordinates and equivalent isotropic tensor components ($\times 10^4$, U values in \AA^2) for the non-hydrogen atoms of both molecules of **1** and of **2**

Atom	1a				1b				2			
	X/a	Y/b	Z/c	Ueq	X/a	Y/b	Z/c	Ueq	X/a	Y/b	Z/c	Ueq
O-1	-6970(7)	800(2)	3331(7)	397(38)	-4205(7)	-4824(2)	-6360(7)	331(34)	13753(2)	-200(3)	87(1)	203(10)
C-2	-8105(11)	1076(3)	4171(11)	378(53)	-5307(13)	-5115(3)	-9184(11)	371(54)	12947(3)	793(4)	-662(2)	185(12)
C-3	-9496(11)	773(3)	4944(11)	368(52)	-6705(12)	-4823(3)	-6967(11)	362(53)	12677(3)	2591(4)	-152(2)	184(13)
C-4	-11007(11)	629(3)	3941(12)	368(55)	-8306(11)	-4695(3)	-8990(12)	393(57)	10996(4)	3253(5)	-240(2)	234(15)
O-5	-10542(7)	247(2)	3210(7)	342(35)	-7844(8)	-4289(2)	-9228(7)	391(37)	10247(2)	2708(3)	529(1)	212(10)
C-6	-9611(12)	0(3)	4374(11)	310(50)	-6897(12)	-4046(3)	-9335(11)	378(54)	11399(3)	2966(4)	1198(2)	192(13)
C-7	-8419(11)	332(3)	5099(10)	342(51)	-5697(12)	-4379(3)	-10158(13)	412(56)	12897(3)	2261(4)	822(2)	179(13)
C-8	-6657(11)	425(3)	933(11)	380(55)	-3922(11)	-4470(3)	-9354(13)	411(56)	13048(3)	298(4)	672(2)	196(13)
C-9	-8750(11)	-401(3)	3612(10)	315(22)	-6032(11)	-3657(3)	-8616(10)	324(21)	10890(3)	2117(4)	2018(2)	183(13)
C-10	-8707(12)	-447(3)	2014(11)	386(23)	-6002(11)	-3611(3)	-7024(11)	359(22)	11948(3)	2694(5)	2708(2)	213(14)
C-11	-7931(11)	-815(3)	1401(10)	327(21)	-6142(11)	-3280(3)	-6407(11)	332(21)	11518(3)	1236(4)	3468(2)	203(13)
C-12	-7120(11)	-1128(3)	2325(11)	312(21)	-4336(11)	-2936(3)	-7298(11)	350(22)	10032(3)	515(4)	3534(2)	203(13)
C-13	-7207(12)	-1076(3)	3996(11)	396(24)	-4412(11)	-2989(3)	-6834(10)	393(21)	8996(3)	644(4)	2944(2)	200(13)
C-14	-7998(11)	-708(3)	4504(11)	357(22)	-5259(11)	-3344(3)	-6562(11)	341(22)	9397(3)	1447(4)	2086(2)	198(13)
O-15	-7908(8)	-697(2)	-165(7)	392(38)	-5086(8)	-3167(2)	-4669(7)	388(37)	12437(3)	1064(4)	4177(1)	262(11)
C-16	-9905(11)	-605(3)	-1119(10)	329(51)	-6169(13)	-3456(3)	-3921(11)	402(57)	13949(4)	1813(6)	4172(2)	336(20)
O-17	-6207(8)	-1467(2)	1663(7)	373(37)	-3352(8)	-2610(2)	-6711(7)	389(37)	8638(4)	444(6)	4822(2)	234(11)
C-18	-7262(13)	-1814(3)	1037(12)	425(60)	-4330(15)	-2272(3)	-6010(13)	465(63)	9679(3)	-421(3)	4254(1)	312(17)
O-19	-6439(8)	-1403(2)	4696(7)	378(37)	-3686(8)	-2664(2)	-6755(7)	405(39)	7566(2)	-105(3)	2974(1)	254(11)
C-20	-6854(14)	-1416(3)	6367(12)	464(64)	-4123(12)	-2624(4)	-11369(11)	463(63)	6429(4)	87(5)	2310(2)	258(15)
C-21	-9614(11)	1431(3)	3172(11)	358(22)	-6025(11)	-5468(3)	-6110(10)	311(21)	13920(3)	840(4)	-1355(2)	190(13)
C-22	-9382(12)	1626(3)	3777(12)	422(25)	-6801(11)	-6859(3)	-6740(11)	347(22)	13245(3)	412(5)	-2146(2)	213(13)
C-23	-10113(14)	2158(4)	2935(13)	464(28)	-7366(12)	-6190(3)	-7625(11)	380(24)	14091(3)	515(4)	-2904(2)	219(14)
C-24	-10230(13)	2072(3)	1334(12)	412(25)	-7469(13)	-6100(3)	-6255(12)	416(25)	15617(3)	1023(4)	-2620(2)	221(14)
C-25	-9631(13)	1687(3)	723(12)	456(27)	-6853(12)	-6720(3)	-6650(11)	397(24)	16275(3)	1442(4)	-2037(2)	199(13)
C-26	-9908(12)	1358(3)	1545(11)	427(26)	-6156(12)	-5384(3)	-6526(11)	394(24)	15475(3)	1366(4)	-1283(2)	200(13)
O-27	-9862(9)	1693(2)	-841(8)	490(44)	-7115(9)	-6715(2)	-4061(7)	481(43)	17781(3)	2005(3)	-2147(1)	262(11)
C-28	-10495(14)	2121(4)	-1211(14)	508(69)	-7749(14)	-6141(3)	-3709(13)	474(67)	18112(4)	1605(5)	-3023(2)	268(16)
O-29	-10658(9)	2349(3)	253(8)	542(47)	-8155(8)	-6366(2)	-6135(6)	456(42)	16656(3)	1309(4)	-3465(1)	290(12)
O-30	-10793(9)	2550(2)	3390(8)	514(45)	-7994(9)	-6577(2)	-6277(7)	444(41)	13551(3)	136(4)	-3707(1)	306(13)
C-31	-10696(14)	2622(4)	5026(12)	509(69)	-8018(12)	-6637(3)	-6878(11)	401(59)	11891(4)	63(6)	-3622(2)	304(17)

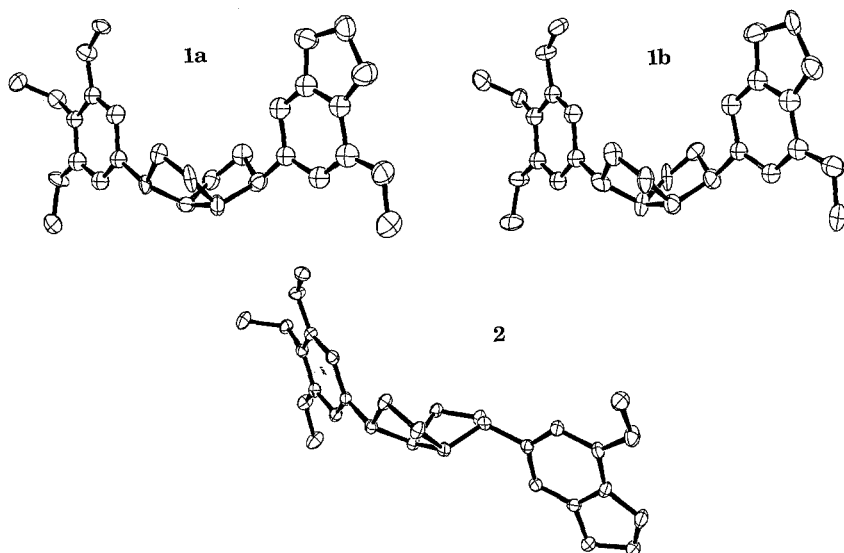


Fig. 1. Comparable ORTEP drawings of **1** (**a** and **b** are the two independent molecules in the asymmetric unit) and **2** (temperature ellipsoids show 50% probability)

This geometry cannot be characterized by the hitherto used term “ax-ax” (referring to the aromatic substituents), the terms “*endo-endo*” (based on the relative geometries of the five-ring envelopes) or “boat-boat” (related to the bridged overall dioxacyclooctane integrating both oxolane rings) may be more appropriate (compare Fig. 1, compound **1**). The most simple and still correct expression for the characterization of the relative positions of the aromatic substituents in **1** may be to call it the “*cis-cis* isomer”, referring to the *cis* arrangement of *Ar* relative to the second five-ring.

In compound **2** (the so-called “ax-eq” diastereomer) the folding of the oxolane envelope is directed towards the opposite ring only in the case of ring *A* (with the “ax” substituent), in ring *B* (“eq” substituent) the envelope is folded away from the opposite ring (the approximate puckering angles are 42° *endo* and 41° *exo*; cf. the projection shown in Fig. 2a). Again both aromatic substituents adopt pseudo-equatorial positions.

The term “ax-eq” is therefore misleading and wrong and should be substituted by the relative denotations “*cis-trans*” if the relative configurations of the aromatic moieties should be characterized. The conformation of the tetrahydrofuran system may be described as “*endo-exo*” (referring to the two heteroatoms in the fused five-ring systems) or as a “boat-chair” conformation of the bridged dioxacyclooctane system (s. Fig. 2a).

Table 3. Selected bond distances, bond angles and torsional angles for compounds **1** and **2**; the formulas show the numbering used in the X-ray analysis (note that in **1** C10 is *syn* to the oxygen O5, in **2** C14 is in *syn* conformation relative to O5)

Dist. (Å)	1a	1b	2	Angle (°)	1a	1b	2
O1—C2	1.415	1.435	1.449	C2—O1—C8	105.0	104.5	104.9
O1—C8	1.474	1.413	1.443	C4—O5—C6	103.7	104.8	104.7
O5—C4	1.384	1.465	1.452	O1—C2—C3	105.8	106.3	105.2
O5—C6	1.473	1.421	1.443	O1—C8—C7	105.2	107.1	104.9
C2—C3	1.548	1.565	1.566	O5—C6—C7	104.4	105.5	104.0
C7—C8	1.526	1.570	1.548	O5—C4—C3	108.4	106.2	105.4
C3—C4	1.552	1.537	1.550	C2—C3—C7	102.5	101.9	104.0
C6—C7	1.519	1.548	1.549	C3—C7—C8	104.2	102.8	102.8
C3—C7	1.583	1.578	1.562	C4—C3—C7	101.4	102.8	103.6
C6—C9	1.546	1.513	1.525	C6—C7—C3	103.3	103.7	103.4
C2—C21	1.511	1.538	1.524	C2—C3—C4	115.7	116.4	114.3
				C6—C7—C8	118.3	114.7	114.0

Derived standard deviations are as follows: **1**: C-C, $\sigma \sim 0.012\text{--}0.015$ Å; C-O, $\sigma \sim 0.011\text{--}0.014$ Å; X-Y-Z, $\sigma \sim 0.6\text{--}1.0^\circ$. **2**: C-C, $\sigma \sim 0.004\text{--}0.005$ Å; C-O, $\sigma \sim 0.004$ Å; X-Y-Z, $\sigma \sim 0.2\text{--}0.3^\circ$ (X,Y,Z = C,O)

Torsional angle (°)	1a	1b	2	
Oxolane ring A	O5—C6—C7—C3	30.4	26.7	30.3
	C6—C7—C3—C4	- 7.4	- 2.8	- 6.3
	C7—C3—C4—O5	-19.7	-21.2	-19.5
	C3—C4—O5—C6	39.8	39.6	40.1
Oxolane ring B	C4—O5—C6—C7	-44.2	-41.1	-44.2
	O1—C2—C3—C7	27.3	27.5	-18.1
	C2—C3—C7—C8	- 3.0	- 3.9	- 7.3
	C3—C7—C8—O1	-21.0	-21.1	30.7
Linking A—B	C7—C8—O1—C2	39.7	39.6	-43.9
	C8—O1—C2—C3	-42.0	-42.4	38.6
	C2—C3—C7—C6	-127.2	-123.7	-126.2
	C4—C3—C7—C8	116.8	117.0	112.5
Trimethoxyphenyl	C10—C11—O15—C16	- 6.8	- 5.2	2.7
	C11—C12—O17—C18	-75.7	- 76.7	107.6
	C14—C13—O19—C20	15.7	12.3	- 5.1
Methylenedioxy	C24—C25—O27—C28	5.3	6.6	-10.5
	C25—C24—O29—C28	- 4.1	- 6.0	11.2
	O27—C25—C24—O29	- 0.6	- 0.3	- 0.5
	O27—C28—O29—C24	7.2	10.1	-17.5
Linking Ar—ring A	C25—O27—C28—O29	- 7.6	-10.1	17.3
	O5—C6—C9—C10	9.3	9.6	171.4
Linking Ar—ring B	O5—C6—C9—C14	-172.5	-170.6	- 9.3
	O1—C2—C21—C22	-155.1	-158.0	129.4
	O1—C2—C21—C26	25.1	24.7	- 52.5

Aromatic Moieties and ^1H NMR

Details on the conformations of the aromatic alkyloxy substituents (3,4,5-trimethoxy and 3,4-methylenedioxy-5-methoxy) may be seen directly from Table 4 and need therefore no further comments. However, the torsional angles of the *Ar*-oxolane links characterizing the orientation of the aromatic planes in relation to the corresponding oxolane rings

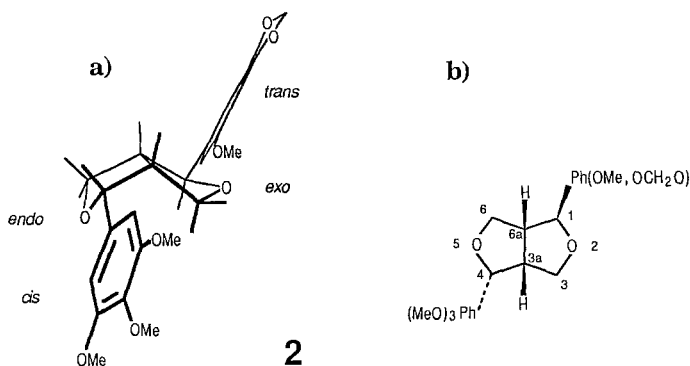


Fig. 2. *a* View of compound **2** showing clearly the *endo-exo* geometry of the tetrahydrofuran moiety and the *cis-trans* position of the aryl substituents (projection of the X-ray coordinates including the proton positions). *b* Systematic (IUPAC) numbering of the tetrahydrofuran system

deserve some attention: A closer inspection of these angles show that all “*cis*” orientated aryl groups (the previously called “*ax*” substituents) are arranged in a way that the torsional angles O5-C6-C9-C10 in **1** (-C14 in **2**, numbering Table 3) and O1-C2-C21-C26 (in **1**) are relatively small (**1 a/b**: 9.3°/9.6 and 25.1°/24.7°; **2**: -9.3°; s. Table 3); in other words, the phenyl rings are approximately in plane with the adjacent oxygens. As a consequence, the opposite “*cis*” (previously called “*ax*”) proton of the second oxolane ring is facing the aromatic plane. This hindered rotation seems to prevail in solution as well, since the chemical shifts of *cis*-protons at C-3 or C-6 (systematic numbering, Fig. 2b) show always downfield displacements due to the ring current effect of aromatic C-4 or C-1 substituents [e.g. 4-*Ph* (OMe)₃ ... 3-H_{ps,ax} in Fig. 2, systematic numbering]. This practical criterion for the determination of relative configurations in tetrahydrofuran compounds was originally formulated for “axial” aryl rings [2, 3]; however, a pseudo-equatorial aryl substituent at an *endo*-oxolane envelope gives an equivalent and more realistic explanation for the observed ring current shifts. It should be emphasized that the aryl substituents are always equatorially positioned, the close methylene proton at the opposite ring, suffering the ring current upfield shift may be axial (as in **2**) or equatorial (as in **1**), depending on the relative configuration at the second ring. Not an “*ax*” *Ar*—“*ax*” H relationship as originally formulated is decisive, but a “*cis*” *Ar*—“*cis*” H relationship (whether the *cis* H is axial or equatorial is another, independent question).

Circular Dichroism of **1**

Further evidence concerning the conformations of the oxolane rings in solution may be derived from CD data of compound **1** [6]. The aromatic short wavelength 1B_b transition appears in the CD spectrum as a very strong couplet (split band) with an intense positive peak at 214 nm and a somewhat less intense negative peak at 205 nm [6] (corresponding UV band at 207 nm [5]). With respect to the almost identical aromatic chromophors, compound **1** may be treated as an essentially C_2 symmetric molecule and the coupled oscillator model may be used to prove the absolute configuration if the conformation is known or vice versa [14]. In our case the absolute configuration was determined unambiguously by chemical degradation [15, 16]: by means of the coupled oscillator model it should therefore be possible to prove whether the X-ray geometry—especially the conformations of the oxolane rings determining the spatial arrangement of the aromatic rings and in consequence the direction of the electromagnetic transitions in the molecule—is compatible with the conformation in solution. A previous (misinterpreted) calculation of the couplets in this type of compounds was based on incorrect substrate geometries (*exo-exo* tetrahydrofurofuran system and pure axial phenyl

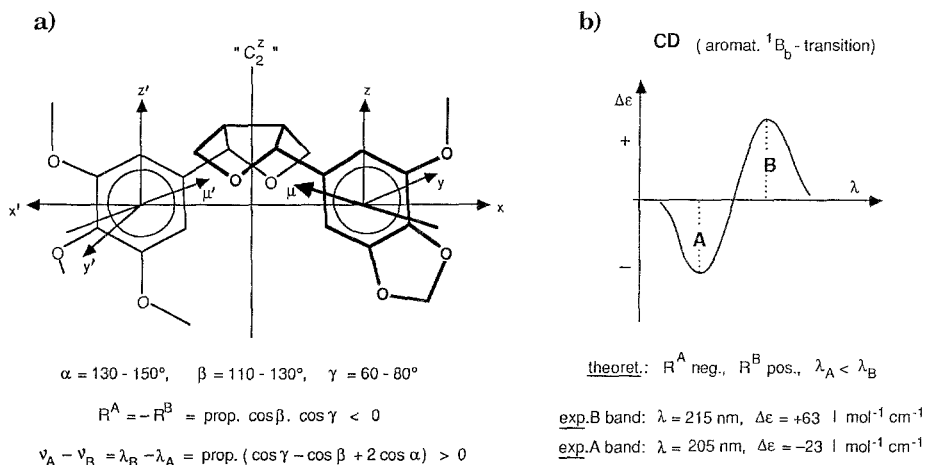


Fig. 3. a Compound **1** and the coordinate systems used in the coupled oscillator model [14]. The angles α , β , and γ correspond to the angles of the 1B_b transition (μ and μ' derived from semiempirical *Pariser-Parr-Pople* calculations [7]) with the axes of the local *Kartesian* coordinate systems. The x axes (x and x') connect the centers of the aromatic transition and are perpendicular to the C_2^z axis of the molecule. The presentation of the structure of **1** is a projection of the experimental coordinates (*not* schematically). b Theoretical CD spectrum showing the expected *A* and *B* bands, and comparison with the experimental data taken from [7].

substituents) and should have led to a disagreement between experimental and calculated CD bands: the so-called *A* band of the coupled [6, 14] using the wrong conformation should be positive and should appear at higher wave number or lower wave length than the negative *B* band, which is contrary to the experimental data. Fig. 3 shows the results of an application of the equations presented in Ref. [14], using the calculations of the UV transitions (direction of the transition moments μ) and the experimental data from Ref. [6]. The agreement between experimental and theoretical couplets demonstrates that the conformation in solution is also *endo-endo* (or boat-boat) for the tetrahydrofurofuran system and pseudo-equatorial for the aromatic substituents.

Conclusion

The X-ray derived geometries show that the generally used terms “axial” or “equatorial” for the 1,4-substituents in tetrahydrofurofuran lignans are actually wrong. Both types of substituents possess almost identical pseudo-equatorial positions at the slightly twisted envelope conformation of the oxolane five ring, the only difference being the direction of the folding of the oxolane envelope, either *endo* (*syn*) or *exo* (*anti*) relative to the second oxolane ring system. Substitution of the term “ax” with “*cis*” and “eq” with “*trans*” (*cis* and *trans* relative to the second fused oxolane ring) is the correct alternative to describe the relative configurations of aromatic substituents at C1 and C4 positions of naturally occurring tetrahydrofurofurans (compare Fig. 2).

In the light of these results, the conformation derived for “ax-ax” tetrahydrofurofuran lignans and the interpretation of the circular dichroism data given in Ref. [7] had to be revised. Presentations of stereoforulas for these compounds with axially styled aromatic substituents [5–7, 9] should be avoided since they are based on wrong conformations of the oxolane five ring. However, the ^1H NMR criterion for the discrimination of lignans with “axial” phenyl rings still holds, even when the assumption of a true axial position of the aromatic system is not correct [2]: the closer one of the protons at C3 or C6 is within the shielding cone of the actually equatorial aromatic substituent, independent on the oxolane conformation. The X-ray derived geometries are found to be compatible with ^1H NMR data (ring current effects due to hindered rotation of the phenyl substituents) and CD measurements (coupled oscillator model for **1**).

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