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ABSOLUTE CONFIGURATION OF THE BENZOFURANOID NEOLIGNANS*

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Key Word Index—2,3-Dihydrobenzofuranoid neolignans; 2,3,3a,6-tetrahydrobenzofuranoid neolignans; 2,3,5,6-tetrahydrobenzofuranoid neolignans; absolute configurations.

Abstract—The benzofuranoid neolignans, classified into structurally homogeneous groups by constitution and ORD curves, have had their relative configurations established by ^{1}H and ^{13}C NMR, including LIS, as well as by X-ray crystallography. Chemical inter-relations of several compounds, which ultimately gave (2*S*,3*S*)-, (2*R*,3*R*)-, and (2*R*,3*S*)-2,3-dihydrobenzofurans, have shown what the absolute configurations are.

INTRODUCTION

The tentative assignment of configuration to C-5 in the 2,3,5,6-tetrahydrobenzofuran neolignans (types **7–9**) was based solely on biogenetic reasoning [2]. In the present paper, we propose a chemical solution to this problem and report comprehensively on the absolute stereochemistry of the benzofuranoid neolignans of types **1–9**.

RESULTS

Chemical and ORD data

The absolute configurations of the 2*S*, 3*S* (**1a–g**) and the 2*R*, 3*R* (**2a, b**) groups of *trans*-2,3-dihydrobenzofuran neolignans were established by correlation with representatives of established structure [3] by ORD curves. Acid isomerization of **3a** (negative Cotton effect at 290 nm) led to **1d** (positive Cotton effect at 290 nm). Clearly this reaction proceeds by epimerization only of C-2, and defines the absolute configuration of **3a** [4]. Since all natural and synthetic *cis*-dihydrobenzofuran neolignans (**3a–f**) show negative Cotton effects, they must all possess the 2*R*,3*S*-configuration.

For the 2,3,3a,6-tetrahydrobenzofuran neolignans **4a–d**, **5b**, **6a–c** ^{13}C NMR data [5], confirmed for **5b** and **6b** by X-ray crystallography (see below), indicate the relative stereochemistry of the 2,3,3a-bonds. Hydrogenolytic (**4a** → **1h**) [3], pyrolytic (**4a** → **1f, h** [2]; **5b** → **1l** [6]; **6b** → **3a, c, d**; **6c** → **3e, f** [2]) and photolytic (**5b** → **1l** [6]) conversions to 2,3-dihydrobenzofurans of established stereochemistry allow, consequently, assignment of absolute configuration to **4a, 5b, 6b** and **6c**. The Cotton effects related to the aryl (295 nm) and the dienone (260 nm) chromophores of these compounds were analysed and found to be positive in the cases, respectively, of 2*S* (**4a, 5b**) and 3a*S* (**5b, 6b, 6c**) configurations; and negative in the cases, respectively, of 2*R* (**6b, 6c**) and 3a*R* (**4a**)-configurations. Proof of the correctness of UV/ORD correlations was seen in the fact that acid isomerization of **5b** to **6d** was accompanied solely by inversion of the Cotton effect around 312 nm [6]. The ORD data were used subsequently in the assignment of absolute stereochemistry to the remaining compounds of types **4–6**.

The absolute configuration of the heterocycles of compounds **8c** and **8d** were again deduced by pyrolytic conversion, respectively to **1g, i** and **1e, j, k, l**, 2,3-dihydrobenzofurans of established stereochemistry [2]. The negative Cotton effect related to the aryl chromophore (280 nm) of **8c, d**, and of the other compounds of type **7** and **8**, thus signals a 2*S*-configuration, and the positive Cotton effect at 280 nm of compounds of type **9** signals a 2*R*-configuration. The stage was thus set for the solution of the problem concerning the chirality at C-5. Indeed, the absolute stereochemistry of **4a** and **6b** being known, their thermal Cope rearrangement products, which must originate by suprafacial allyl migration, can only be represented respectively by **7a** [7] and **9b** [4]. Thus, again, the positive Cotton effect related to the dienone chromophore (315 nm) of **7a**, and of the other compound of this type **7b**, signals a 5*S*-configuration, and the negative Cotton effect at 315 nm of **9b**, and the other compounds of type **8** and **9**, signals a 5*R*-configuration. The relative stereochemistry of **8d** was confirmed by X-ray crystallography (see below).

LIS data

The NMR shift reagent Pr(fod)$_3$ associates strongly with carbonyls. It was hoped, therefore, that the relative geometry of the substituents around the CO-group of the oxo-tetrahydrobenzofuran neolignans (types **4–9**) might

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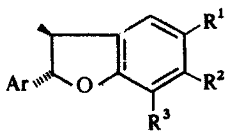
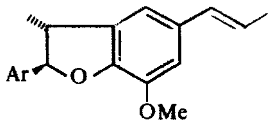
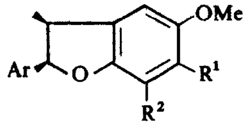


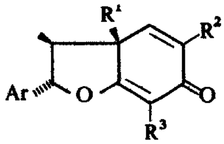
	Ar	R^1	R^2	R^3	
1a*	Gu	(E)-Pr	H	OMe	[9]
1b*	Pi	(E)-Pr	H	OMe	[9]
1c*	Pi	OMe	OAl	H	[10]
1d*	Mp	OMe	OAl	H	[4]
1e*	Tp	OMe	OAl	H	[2]
1f*	Pi	OMe	OH	Al	[10]
1g*	Mp	OMe	OH	Al	[2]
1h	Pi	OMe	OH	H	[3]
1i	Mp	OMe	OH	H	[2]
1j	Tp	OMe	OH	H	[2]
1k	Tp	OMe	OH	Al	[2]
1l	Tp	Al	OH	H	[2]



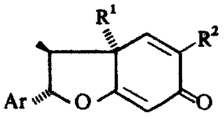
	Ar	
2a*	Ve	[11]
2b*	Tp	[6]



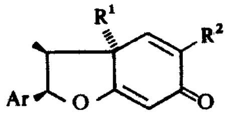
	Ar	R^1	R^2	
3a*	Mp	OAl	H	[2]
3b*	Pi	OH	Al	[10]
3c*	Mp	OH	Al	[2]
3d	Mp	OH	H	[2]
3e	Tp	OH	H	[2]
3f	Tp	OH	Al	[2]



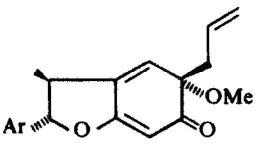
	Ar	R^1	R^2	R^3	
4a*	Pi	Al	OMe	H	[3]
4b*	Ve	Al	OMe	H	[11]
4c*	Ve	Al	OMe	OMe	[11]
4d*	Tp	OMe	Al	H	[6]



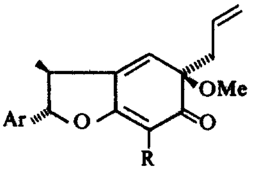
	Ar	R^1	R^2	
5a*	Tp	Al	OMe	[2]
5b*	Tp	OMe	Al	[6]



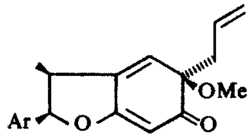
	Ar	R^1	R^2	
6a*	Pi	Al	OMe	[10]
6b*	Mp	Al	OMe	[2]
6c*	Tp	Al	OMe	[2]
6d*	Tp	OMe	Al	[6]



	Ar	
7a*	Pi	[7]
7b*	Ve	[7]



	Ar	R	
8a*	Pi	H	[10]
8b*	Ve	H	[11]
8c*	Mp	H	[2]
8d*	Tp	H	[2]
8e*	Tp	OMe	[4]



	Ar	
9a*	Pi	†
9b*	Mp	[4]

Gu = Guaiacyl
Pi = Piperonyl
Mp = *O*-Methyl-*O*,*O*-methylenylpyrogallyl
Tp = Tri-*O*-methylpyrogallyl
Ve = Veratryl
Pr = Propenyl
Al = Allyl

* Natural products. † Compound **9a**, originally detected only by spectral means as an impurity of **8a** [10], was now obtained pure and will be described in full in a forthcoming publication.

Table 1. Wavelength (nm) of ORD extrema and of UV maxima of neolignans of structural types 1–9

	C-2	C-3	C-3a	C-5	ORD pk	ORD tr	ORD 0	UV enone obs.	UV band calc.	benzenoid band
1a, b	*S*	*S*			249 ± 1	297 ± 3	274 ± 6			
1c–l	*S*	*S*			291 ± 6	316 ± 8	302 ± 5			
2a, b	*R*	*R*			301 ± 6	250 ± 5	280 ± 0			
3a–f	*R*	*S*			314 ± 7	282 ± 6	295 ± 10			
4a–c	*S*	*S*	*R*		316 ± 13	288 ± 8	303 ± 10	264 ± 7	262	294 ± 9
4d	*S*	*S*	*R*		335	290	312	280		300
5a	*S*	*S*	*S*		282	320	301	257	262	285
5b	*S*	*S*	*S*		335	275	312	280		300
6a–c	*R*	*S*	*S*		284 ± 9	319 ± 2	302 ± 3	258 ± 2	262	293 ± 8
6d	*R*	*S*	*S*		291	335	312	280		300
7a, b	*S*	*S*		*S*	342 ± 1	290 ± 2	312 ± 0	315 ± 0	320	260 ± 10
8a–e	*S*	*S*		*R*	281 ± 11	347 ± 6	317 ± 5	315 ± 2	320	283 ± 5
9a, b	*R*	*S*		*R*	295 ± 0	344 ± 1	316 ± 1	316 ± 1	320	290 ± 0

be amenable to confirmation by a LIS study. Indeed, relatively strong Δ values were observed for the $\mathrm{OC\underline{H}_3}$-5 or $\mathrm{C\underline{H}_2}$-5 signals of compounds of types **4**–**6** in which OMe or CH_2 and CO are coplanar (Table 2). The carbonyl is probably tilted towards the α-face of the molecules, since the Δ values for $\mathrm{C\underline{H}_2CH{=}CH_2}$ and H-2 signals are larger in compounds **6a**–**c**, which have these units on this face, than in compound **4a**, which sustains these units on the β-face. This is clearly also the case for compounds of type **7**–**9** [cf. in Table 2 ΔH-2 for **9a** (Ar-β) vs. **7a**, **8a**, **c**, **d** (Ar-α) and ΔH-6′ for **8a** (Ar-α) vs. **9a** (Ar-β)]. The values of $\mathrm{OC\underline{H}_3}$-5 and $\mathrm{C\underline{H}_2}$-5, however, are of the same order of magnitude and the relative configuration at C-5 is not amenable to analysis by the LIS method.

X-ray crystallographic data

Constitutions and relative stereochemistries of **5b**, **6b** and **8d** were confirmed by direct X-ray crystallographic analyses. Crystals of **5b** are monoclinic, space group $P2_1$ with a = 10.635 (3), b = 10.021 (3), c = 10.708 (3) Å, β = 115.72 (2)° and Z = 2. Crystals of **6b** are orthorhombic, space group $P2_12_12_1$ with a = 7.77, b = 11.36, c = 21.47 Å and Z = 4. Crystals of **8d** are orthorhombic, space group $P2_12_12_1$, with a = 8.532 (4), b = 9.588 (4), c = 25.260 (19) Å and Z = 4. The intensitites of 2222 (**5b**), 1139 (**6b**) and 2432 (**8d**) independent reflections were measured with an automatic four-circle diffractometer using graphite monochromated Cu Kα radiation. The phase problem was solved by direct methods. The E-map of the best set gave the positions of 23 (**5b**), 19 (**6b**) and 25 (**8d**) atoms. A difference Fourier was used to locate 5 (**5b**), 8 (**6b**) and 3 (**8d**) additional atoms. Several cycles of full matrix least square refinement considering anisotropic temperature factors reduced the R factors to 0.079 (**5b**) and 0.81 (**8d**). For **5b** and **8d**, difference Fourier calculations gave positions of some of the hydrogens and a Generation of Atomic Positions program [8] was used to locate all remaining hydrogen atom positions. Refinement of all parameters using isotropic temperature factors for hydrogen gave final R factors of 0.044 (**5b**) and 0.040 (**8d**). For **6b**, the approximate locations of the 24 hydrogen atoms were determined by orbital geometric considerations. Several cycles of full matrix anisotropic

Table 2. LIS Δ values (ppm) recorded for proton signals of oxo-tetrahydrobenzofuranoid neolignans*

	Benzofuran				system			Aromatic				ring		
Compound	OMe	H-7	H-4	$CH_2CH{=}$ CH_2	H-2	H-3	Me-3	H-2′	H-5′	H-6′	O_2CH_2– 3′,4′	OMe-3′	OMe-4′	OMe-5′
4a	27.0	11.7	9.1	4.6	2.4	3.3	2.7	0.7	0.1	0.8	0.2	—	—	—
5b	2.3	8.5	2.8	8.0		2.4	2.0	2.7	—	2.7	—	2.7	5.0	2.7
6a	28.2	14.2	10.4	5.6	3.4	4.4	4.0	2.0	0.8	2.0	0.4	—	—	—
6b	28.4	14.3	11.7		3.5		4.0	2.0	—	2.0	0.4	—	—	0.4
6c	30.0	13.4	10.6		3.5		3.5	1.8	—	1.8	—	0.6	0.8	0.6
7a	10.7	8.9	5.8	10.2	2.2	2.8	1.6	0.6	0.3	0.7	0.1	—	—	—
8a	11.8	11.2	7.0	10.4	1.6	2.8	2.2	0.8	0.8	1.6	0.6	—	—	—
8c	12.0	9.4	6.8	8.4	1.8	3.0	1.8	1.0	—	1.5	0.4	—	—	—
8d	8.0	8.6	5.4		1.8	4.6†	2.0	2.4	—	2.4	—	3.0	5.6	3.0
9a	11.7	9.2	8.7	9.8	3.0	3.0	2.1	0.8	0.8	0.8	0.4	—	—	—

* Shift studies were carried out by stepwise addition of known amounts of $Pr(fod)_3$ to *ca* 0.15 M solutions of substrate in $CDCl_3$. The LIS data were obtained by graphic extrapolation of observed shifts to 1:1 molar shift reagent–substrate ratio.

† Association of reagent with CO and trimethoxyaryl is responsible for, respectively, 2/3 and 1/3 of this value.

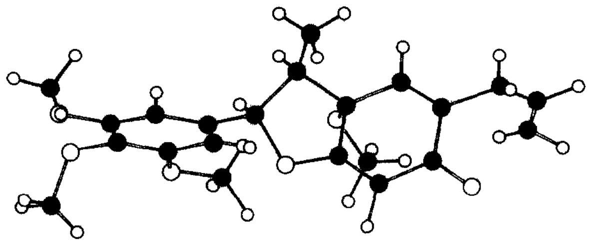


Fig. 1. X-Ray structure of **5b**.

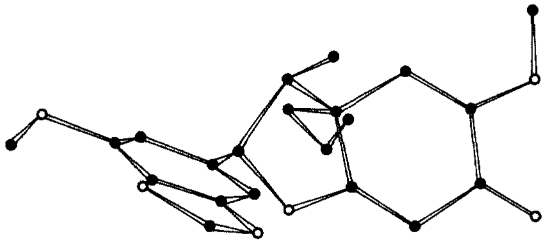


Fig. 2. X-Ray structure of **6b**.

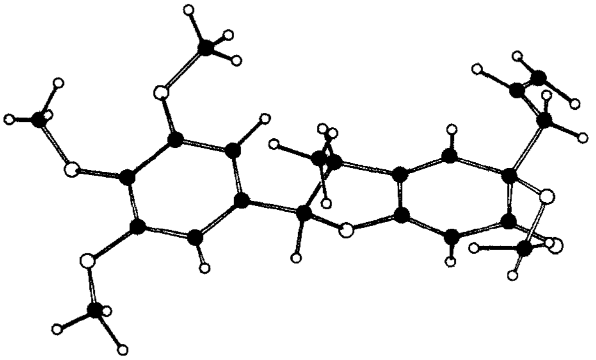


Fig. 3. X-Ray structure of **8d**.

least-squares refinement, with fixed isotropic thermal parameters for the H atoms, reduced the R factor to 0.098. Details of the X-ray structural analyses will be published elsewhere.

The molecular structures found in the crystals of **5b**, **6b** and **8d** are shown respectively in Figures 1, 2 and 3.

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