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Article

Neolignan Aurein Rearrangement with Trifluoroacetic Acid

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O tratamento da neolignana aureina com ácido trifluoroacético forneceu o produto de rearranjo 2-(2-alil-4-hidroxi-3,5-dimetoxifenil)-1-(3,4,5-trimetoxifenil)-propano previamente descrito na literatura e os seus derivados resultantes da adição de ácido trifluoracético e água à ligação dupla do grupo alila. Os produtos obtidos foram caracterizados com base em dados espectrais e a atribuição inequívoca dos deslocamentos químicos dos átomos de hidrogênio e carbono-13 foi realizada com base na análise de dados fornecidos por espectros uni- e bi-dimensional de RMN. Propostas mecanísticas justificam a formação dos produtos obtidos.

Treatment of the neolignan aurein with trifluoroacetic acid furnished the rearranged product 2-(2-allyl-4-hydroxy-3,5-dimethoxyphenyl)-1-(3,4,5-trimethoxy-phenyl)-propane, previously described in the literature, as well as its derivatives produced by the addition of trifluoroacetic acid and water to the carbon-carbon double bond of the allyl group. The products were characterized on the basis of spectral data, and the complete ^{1}H and ^{13}C chemical shift assignments have been established by one- dimensional (1D) and homonuclear and heteronuclear 2D shift-correlated NMR methods. Mechanisms are proposed to justify the products obtained.

Keywords: *Aurein rearrangement*; *^{1}H and ^{13}C-NMR spectral data*

Introduction

Aurein (**1**), a neolignan isolated from *Licaria* species, was transformed into **2** by acid (H_2SO_4 + HOAc) treatment[1]. On the basis of this result, a sample of **1** was used to investigate its reactivity with trifluoroacetic acid. A mixture was obtained containing **2**, **3**, and **4** as the major products. The characterization of these rearranged products was based on the spectral data, mainly ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR data, including 2D NMR experiments ^{1}Hx^{1}H-COSY and ^{1}Hx^{13}C-COSY-$^nJ_{CH}$ (n = 1; n = 2 and 3, COLOC), and NOE difference spectra (^{1}H {^{1}H}-NOE)[2], which also allowed the complete ^{1}H and ^{13}C chemical shift assignments. The analysis of the ^{1}H and ^{13}C-NMR spectra involved data obtained from mixtures and pure products.

Results and Discussions

Treatment of the neolignan aurein (**1**) with trifluoroacetic acid furnished the rearranged product (**2**), described in the literature[1], its derivative produced by the addition of trifluoroacetic acid (**3**, a mixture of epimers at C-8'), and water (**4**, a mixture of epimers at C-8') to the carbon-carbon double bond of the allyl group. Thin layer chromatography (TLC) revealed a mixture containing **2**, **3** and **4** as the major products. The presence of these rearranged products in this mixture was confirmed by ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR: i) the signals at δ_H 6.23 (s, 2H-2,6), 6.22 (s, 2H-2,6) and 6.16 (s, 2H-2,6), together with the δ_C 106.14 (d, 2C-2,6+2C-2,6) and 106.01 (d, 2C-2,6), allowed the recognition of the unchanged 3,4,5-trimethoxyphenyl moiety; ii) the signals at δ_H 6.61 (s, H-6'), 6.57 (s, H-6') and 6.56 (s, H-6'), together with the δ_C 104.62 (d,C-6') and 104.14 (d, C-6'+C-6'), were consistent with the presence of a 4'-hydroxy-3,5-methoxyphenyl unit with an additional substitution at C-2' [allyl (**2**), 2-trifluoroacetate-*n*-propyl (**3**) and 2-hydroxy-*n*-propyl (**4**)]; iii) the signals at δ_H 6.1-5.8 (m, H-8'), 5.2-4.8

(m, 2H-9') and 2.9-2.7 (m, 2H-7'), and δ_C 138.05 (d, C-8'), 114.63 (t, C-9') and 29.30 (t, C-7') were attributed to an allyl group; iv) the signals at δ_H 5.2-4.8 [m, H-8', superposed on the signals of the 2H-9' which was revealed by homonuclear (^{1}Hx^{1}H-COSY) and heteronuclear (^{1}Hx^{13}C-COSY-$^1J_{CH}$) 2D shift-correlated NMR spectra], 2.80 and 2.65 (m, 2H-7', assigned by ^{1}Hx^{1}H-COSY), and 1.25 and 1.10 (d, each, 3H-9', deduced by ^{1}Hx^{1}H-COSY and ^{1}Hx^{13}C-COSY spectra, consistent with the presence of two epimers at C-8', as anticipated), along with the signals at δ_C 80.85 (d, C-8'), 30.76 (t, C-7') and 18.56 (q, C-9'), were used to characterize the 2-trifluoroacetate-*n*-propyl substituent; v) an analogous procedure described above (iv) was also used in the ^{1}H and ^{13}C chemical shift assignments of the 2-hydroxy-*n*-propyl moiety [δ_H 3.70 (m, H-8'), 3.30 (m, 2H-7'), 1.41 (d, J = 6.2 Hz, 3H-9') and δ_C 69.34 (d, C-8'),

Table 1. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectral data for 2, compared with those of 1 [in $CDCl_3$, chemical shifts in δ (ppm) and coupling constants (J) in Hz].*

	2				**1**			
	^{1}Hx^{13}C-COSY-$^1J_{CH}$		^{1}Hx^{13}C-COSY-$^nJ_{CH}$		^{1}Hx^{13}C-COSY-$^1J_{CH}$		^{1}Hx^{13}C-COSY-$^nJ_{CH}$	
C	δ_H	δ_C	$^2J_{CH}$	$^3J_{CH}$	δ_H	δ_C	$^2J_{CH}$	$^3J_{CH}$
1	-	136.52			-	136.13	2H-2,6;2H-7	
3,5	-	152.65	2H-2,6	2MeO-3,5	-	152.50	2H-2,6	2MeO-3,5
4	-	136.52		2H-2,6;MeO-4	-	135.82		2H-2,6;MeO-4
1'	-	136.75	H-8	2H-7;3H-9	-	142.19	2H-2',6';H-8	2H-7;3H-9
2'	-	123.09		H-6'	-	-		
3'	-	145.07		MeO-3'	-	152.89	H-2'	MeO-3'
4'	-	136.75		H-6'	-	134.69		2H-2',6'
5'	-	146.08	H-6'	MeO-5'	-	152.89	H-6'	MeO-5'
CH								
2,6	6.23(s)	105.92		2H-7	6.19(s)	105.84		2H-7
8	3.3-3.0(m)	36.19	H-7;3H-9	H-6'	3.4-2.9(m)	42.04	2H-7;3H-9	2H-2',6'
2'	-	-			6.31(s)	103.90		H-8
6'	6.57(s)	104.38			6.31(s)	103.90		H-8
8'	6.0-5.7(s)	137.81	2H-7'		6.4-6.0(m)	134.43	2H-7'	
CH_2								
7	2.76(dd,J=6.0,12.0)	45.14		2H-2,6	2.9-2.7(m)	45.34	H-8	2H-2,6;3H-9
	2.58(dd,J=8.1,12.0)	-				-		
7'	3.4-3.2(m)	29.33		H-9'a	4.45(br d,J=5.9)	73.94	H-8'	2H-9'
9'	4.96(dd,J=10.2,1.7)	114.50			5.27(br d,J=16.2)	117.30		
	4.84(dd,J=17.1,1.7)	-			5.14(br d,J=16.2)	-		
CH_3								
9	1.15(d,J=6.8)	21.35		2H-7	1.33(d,J=6.4)	20.96	H-8	2H-7
2MeO-3,5	3.75(s)	55.84			3.73(s)	55.74		
MeO-4	3.77(s)	60.83			3.77(s)	60.60		
MeO-3'	3.77(s)	60.83			3.77(s)	55.87		
MeO-5'	3.87(s)	55.89			3.77(s)	55.87		
OH-4'	5.47(s)	-			-	-		

* The multiplicity of signals of carbon-13 atoms was deduced by comparative analysis of the PND- and DEPT-^{13}C-NMR spectra. Homonuclear ^{1}Hx^{1}H-COSY 2D NMR spectra were also used for these assignments. The chemical shifts and coupling constants (J) of hydrogen atoms were obtained from ^{1}H-NMR (1D).

31.25 (t, C-7'), 18.94 (q, C-9')]. The intensity of the signal corresponding to C-8' (δ_C 69.34) of **4** allowed the minor percentage of this product to be deduced as constituent of the mixture.

Preparative thin layer chromatography (PTLC) was used to isolate **4** and a mixture of **2** and **3**, when the formation of an additional quantity of **4** was observed by the hydrolysis of **3**. The presence of **2** in this mixture was also recognized by ^{1}H and ^{13}C-NMR spectral data involving comparative analysis with literature values[1] (^{1}H-NMR) and direct comparison with the data from the rearranged product **2**, prepared as described in the literature[1]. The comparative analysis of the proton noise decoupled (PND) and DEPT ^{13}C-NMR[2,3] spectra of **2** was used to deduce the multiplicities of the signals corresponding to methine (CH), methylene (CH_2), and methyl (CH_3) groups, and quaternary carbon atoms (Table 1).

The complete ^{1}H and ^{13}C-NMR chemical shift assignment of **2** was also based on ^{1}Hx^{1}H-COSY, ^{1}Hx^{13}C-COSY-$^1J_{CH}$, ^{1}Hx^{13}C-COSY-$^nJ_{CH}$ (n = 2 and 3, COLOC), and ^{1}H {^{1}H}-NOE difference spectra. The ^{1}H and ^{13}C-NMR spectral data are summarized in Table 1. The heteronuclear 2D

Table 2. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectral data for 4-1 and 4-2 (a mixture of epimers at C-8', 4) [$CDCl_3$ as solvent, chemical shifts in δ (ppm) and coupling constants (J) in Hz].*

	4-1				**4-2**			
	^{1}Hx^{13}C-COSY-$^1J_{CH}$		^{1}Hx^{13}C-COSY-$^nJ_{CH}$		^{1}Hx^{13}C-COSY-$^1J_{CH}$		^{1}Hx^{13}C-COSY-$^nJ_{CH}$	
C	δ_H	δ_C	$^2J_{CH}$	$^3J_{CH}$	δ_H	δ_C	$^2J_{CH}$	$^3J_{CH}$
1	-	136.27	2H-7		-	136.27		
3,5	-	152.59	2H-2,6	2MeO-3,5	-	152.59	2H-2,6	2MeO-3,5
4	-	135.98		2H-2,6;MeO-4	-	136.21		2H-2,6;MeO-4
1'	-	136.43	H-6'	3H-9	-	136.43		
2'	-	122.45		H-6'	-	122.75		H-6'
3'	-	145.04		MeO-3'	-	145.10		MeO-3'
4'	-	136.27		H-6'	-	136.27		
5'	-	146.32	H-6'	MeO-5'	-	146.32	H-6'	MeO-5'
CH								
2,6	6.18(s)	105.83		2H-7	6.23(s)	105.83		
8	3.19(qu,J=6.0)	36.43	2H-7	H-6'	3.19(qu,J=6.0)	36.43	2H-7	H-6'
6'	6.57(s)	104.37			6.58(s)	104.37		
8'	**	68.76			**	68.94		
CH_2								
7	2.9-2.5(m)	45.36			2.9-2.5(m)	45.25		
7'	2.9-2.5(m)	34.68		3H-9'	2.9-2.5(m)	34.78		
CH_3								
9	1.20(d,J=6.0)	21.42			1.20(d,J=6.0)	21.42		
9'	1.18(d,J=6.0)	23.09			1.18(d,J=6.0)	23.10		
2MeO-3,5	3.74(s)	55.75			3.73(s)	55.75		
MeO-4	3.77(s)	60.71			3.77(s)	60.66		
MeO-3'	3.80(s)	60.10			3.80(s)	60.05		
MeO-5'	3.87(s)	56.07			3.87(s)	56.07		
HO-4'	5.60(br s)	-			5.60(br s)	-		
HO-8'	2.30(br s)	-			2.30 (br s)	-		

* The multiplicity of signals of carbon-13 atoms was deduced by comparative analysis of the PND- and DEPT-^{13}C-NMR spectra. Homonuclear ^{1}Hx^{1}H-COSY 2D NMR spectra were also used for these assignments. The chemical shifts and coupling constants (J) of hydrogen atoms were obtained from ^{1}H-NMR (1D).

** Superimposed with MeO signals.

NMR experiments ^{1}Hx^{13}C-COSY-$^{1}J_{CH}$ (spin-spin coupling of hydrogen and carbon-13 through one bond) and ^{1}Hx^{13}C-COSY-$^{n}J_{CH}$ (n = 2 and 3, long-range spin-spin interaction of hydrogen and carbon-13, which detects proton resonance correlated with non-directly bound carbon), along with the chemical shift parameters[3] and signal multiplicities, were used in the unambiguous assignments of the ^{13}C-NMR chemical shifts (Table 1). The protonated carbons were assigned with the aid of hydrogen and carbon-13 correlations in the ^{1}Hx^{13}C-COSY-$^{1}J_{CH}$, whereas the quaternary carbon atoms and the methoxyl groups were assigned with the aid of ^{1}Hx^{13}C-COSY-$^{n}J_{CH}$ (n = 2 and 3), as described in Table 1. The superposition of the signals of carbon atoms C-1' and C-4' [δ_C 136.75 (s)] was deduced by couplings of the C-1' via two-bond with H-8 [δ_H 3.3-3.0 (m)] and three-bond with 2H-7 [δ_H 2.76 (dd) and 2.58 (dd)] and 3H-9 [δ_H 1.15 (d)], and of the C-4' three-bond coupling to H-6' [δ_H 6.57 (s)]. Furthermore, the signals at δ_C 152.65 [2C-3,5 two-bond coupling to 2H-2,6 (δ_H 6.23, s) and C-3

Table 3. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectral data for 4a-1 and 4a-2 (a mixture of epimers at C-8', 4a) [$CDCl_3$ as solvent, chemical shifts in δ (ppm) and coupling constants (J) in Hz].*

	4a-1				**4a-2**			
	^{1}Hx^{13}C-COSY-$^{1}J_{CH}$		^{1}Hx^{13}C-COSY-$^{n}J_{CH}$		^{1}Hx^{13}C-COSY-$^{1}J_{CH}$		^{1}Hx^{13}C-COSY-$^{n}J_{CH}$	
C	δ_H	δ_C	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_H	δ_C	$^{2}J_{CH}$	$^{3}J_{CH}$
1	-	135.95	2H-7		-	135.95	2H-7	
3,5	-	152.65	2H-2,6	2MeO-3,5	-	152.56	2H-2,6	2MeO-3,5
4	-	135.95		2H-2,6;MeO-4	-	135.95		2H-2,6;MeO-4
1'	-	144.11		2H-7';3H-9	-	144.11		2H-7';3H-9
2'	-	121.81	2H-7'	H-6'	-	121.46	2H-7'	H-6'
3'	-	151.14		MeO-3'	-	151.14		MeO-3'
4'	-	130.93		H-6'	-	130.93		H-6'
5'	-	150.74	H-6'	MeO-5'	-	150.74	H-6'	MeO-4'
AcO-4'	-	168.56	2.31(AcO-4')		-	168.56	2.31(AcO-4')	
AcO-8'	-	170.54	1.95(AcO-8')		-	170.54	1.95(AcO-8')	
CH								
2,6	6.19(s)	105.80		2H-7	6.24(s)	105.80		2H-7
8	3.44(m)	36.44	2H-7;3H-9		3.40(m)	36.68	2H-7;3;H-9	
6'	6.62(s)	105.04			6.66(s)	105.04		
8'	4.85(m)	71.44			4.71(m)	71.18		
CH_2								
7	2.70(m)	45.83		2H-2,6;3H-9	2.70(m)	45.10		2H-2,6;3H-9
7'	2.55(m)	30.97		3H-9'	2.55(m)	30.97		3H-9'
CH_3								
9	1.30(d)	21.22			1.20(d, 21.97			
9'	1.09(d,J=6.0)	19.10			0.99(d,J=5.9)	18.88		
2MeO-3,5	3.74(s)	55.79			3.74(s)	55.79		
MeO-4	3.74(s)	60.70			3.74(s)	60.70		
MeO-3'	3.66(s)	60.80			3.66(s)	60.80		
MeO-5'	3.81(s)	55.93			3.81(s)	55.93		
AcO-4'	2.31(s)	20.48			2.31(s)	20.48		
AcO-8'	1.95(s)	21.22			1.95(s)	21.22		

* The multiplicity of signals of carbon-13 atoms was deduced by comparative analysis of the PND- and DEPT-^{13}C-NMR spectra. Homonuclear ^{1}Hx^{1}H-COSY 2D NMR spectra were also used for these assignments. The chemical shifts and coupling constants (J) of hydrogen atoms were obtained from ^{1}H-NMR (1D).

and C-5 three-bond interaction with hydrogens of MeO-3 (δ$_H$ 3.75, s) and MeO-5 (δ$_H$ 3.75, s) respectively], 136.75 (C-1' and C-4'), and 136.52 [C-1 and C-4, this latter three-bond coupled to 2H-2,6 (δ$_H$ 6.23, s)] and to hydrogens of the MeO-4 (δ$_H$ 3.77, s) showed practically the same intensity. The chemical shifts for carbon C-3' [δ$_C$ 145.07 (s)] was assigned through its three-bond coupling to hydrogens of MeO-3' [δ$_H$ 3.77 (s)], whereas C-5' [δ$_C$ 146.08 (s)] was characterized by its two-bond interaction with H-6' [δ$_H$ 6.57 (s)] and three-bond coupling to the hydrogens of the MeO-5' [δ$_H$ 3.87 (s)]. Additionally, the quaternary carbon atom C-2' [δ$_C$ 123.09 (s)] showed a coupling through three-bonds to H-6' [δ$_H$ 6.57 (s)]. Other analogous correlations are described in Table 1.

Homonuclear ^{1}H {^{1}H}-NOE difference spectra were performed for compound **2**. Irradiation at δ$_H$ 3.87 (MeO-5') showed 4% NOE at δ$_H$ 6.57 (H-6') and irradiation at δ$_H$ 3.75 (2 MeO-3,5) revealed 16% NOE at δ$_H$ 6.23 (2H-2,6). These data were used to confirm the attribution of the

Table 4. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectral data for **2**, in CDCl$_3$, benzene-d$_6$ and acetone-d$_6$ as solvents [chemical shifts in δ (ppm) and coupling constants (J) in Hz].*

	CDCl$_3$		Benzene-d$_6$		Δδ		Acetone-d$_6$		Δδ	
C	δ$_C$	δ$_H$	δ$_C$	δ$_H$	Δδ$_C$	Δδ$_H$	δ$_C$	δ$_H$	Δδ$_C$	Δδ$_H$
1	136.52	-	136.39	-	-0.13	-	137.50	-	0.98	-
3,5	152.65	-	153.87	-	1.22	-	153.75	-	1.10	-
4	136.52	-	137.46	-	0.94	-	136.81	-	0.29	-
1'	137.75	-	136.82	-	-0.93	-	136.81	-	-0.94	-
2'	123.09	-	123.69	-	0.60	-	123.79	-	0.70	-
3'	145.07	-	145.85	-	0.78	-	146.44	-	1.37	-
4'	136.75	-	137.46	-	0.71	-	137.50	-	0.75	-
5'	146.08	-	146.71	-	0.63	-	147.90	-	1.82	-
CH										
2,6	105.92	6.23(s)	107.10	6.33(s)	1.18	0.10	107.16	6.36(s)	1.24	0.13
8	36.19	3.3-3.0(m)	36.61	3.4-3.2(m)	0.42	0.10	37.01	3.15(m)	0.82	0.00
6'	104.38	6.57(s)	104.40	6.51(s)	0.02	-0.07	105.88	6.75(s)	1.50	0.18
8'	137.81	6.0-5.7(m)	138.55	6.1-6.8(m)	0.74	0.10	139.31	5.86(m)	1.30	0.01
CH$_2$										
7	45.14	2.76(dd,J=6.0,12.0)	45.55	2.90(dd,J=5.8,13.5)	0.41	0.14	45.45	2.8-2.7	0.31	-0.01
	-	2.58(dd,J=8.1,12.0)	-	2.64(dd,J=8.2,13.5)	0.00	0.06	-	2.8-2.7	-	-0.17
7'	29.33	3.4-3.2(m)	29.94	3.5-3.3(m)	0.61	0.01	30.07	3.26(m)	0.74	-0.04
	-	3.4-3.2(m)	-	3.4-3.2(m)	-	0.00	-	3.26(m)	-	-0.04
9'	114.50	4.96(dd,J=10.2,1.7)	114.50	4.97(dd,J=9.4,1.9)	0.00	0.01	114.54	4.97(dd,J=17.1,1.7)	0.04	0.01
	-	4.84(dd,J=17.1,1.7)	-	4.95(dd,J=14.3,1.9)	-	0.11	-	4.86(dd,J=17.1,1.7)	-	0.02
CH$_3$										
9	21.35	1.15(d,J=6.8)	21.63	1.2(d,J=6.8)	0.28	0.09	21.89	1.15(d,J=6.8)	0.54	0.00
2MeO-3,5	55.84	3.75(s)	55.78	3.43(s)	-0.06	-0.32	56.15	3.72(s)	0.31	-0.03
MeO-4	60.83	3.77(s)	60.50	3.85(s)	-0.33	0.08	60.46	3.64(s)	-0.37	-0.13
MeO-3'	60.83	3.77(s)	60.36	3.73(s)	-0.47	-0.04	60.54	3.74(s)	-0.29	-0.03
MeO-5'	55.89	3.87(s)	55.61	3.30(s)	-0.28	-0.47	56.48	3.84(s)	0.59	-0.03
HO-4'	-	5.47(s)	-		-		-	8.00(s)	-	-2.53

* The mMultiplicity of signals of carbon-13 atoms was deduced by comparative analysis of the PND- and DEPT-^{13}C-NMR spectra. Homonuclear ^{1}Hx^{1}H-COSY and heteronuclear ^{1}Hx^{13}C-COSY-^{n}J$_{CH}$[n=1; n=2 and 3, COLOC (Table 5)] 2D NMR spectra were also used for these assignments. The chemical shifts and coupling constant (J) of hydrogen atoms were obtained from ^{1}H-NMR (1D).

signals corresponding to methoxyl groups located at C-5' and 2C-3,5, respectively.

Thus, the unambiguous ^{1}H and ^{13}C chemical shifts of **2** were established. Similarly, the ^{1}H and ^{13}C chemical shifts of **1** were also assigned (Table 1), and may be used for the confirmation of the values described in the literature[1,4,5].

An analogous procedure described for **2** was used in the analysis of the ^{1}H and ^{13}C-NMR spectra of **4** (Table 2) and its diacetyl derivative **4a** (Table 3). Extensive 1D and 2D NMR experiments, not detailed here because they involve a procedure analogous to that reported for **2** (*vide supra*), were used to elaborate Tables 2 and 3, which summarize the ^{1}H and ^{13}C-NMR assignments for **4**, a mixture of epimers at C-8' [8'-(S)- and 8'-(R)-], and their diacetyl derivatives [**4a**: 8'-(S) and 8'-(R)-] obtained by the treatment of **4** (**4-1** and **4-2**) with acetic anhydride (Ac_2O) in the presence of pyridine.

The relative percentages of **4a-1** (~58.8%) and **4a-2** (~41.2%) were deduced by the integration of the signals corresponding to H-8' at δ_H 4.85 (**4a-1**) and 4.71 (**4a-2**).

Additional confirmation of a mixture of the epimers **4-1** and **4-2** was obtained by GC/EIMS analysis, which revealed the presence of two compounds in the GC [R_t = 11.796 (**4.2**) and R_t = 11.906 min (**4.1**, major)], and practically identical mass spectra. The two spectra showed significant peaks at m/z 420 [$M^{\bullet +}$, 7% (**4-1**) and 7% (**4-2**)], 239 [100% (**4-1**) and 100% (**4-2**)], 221 [46% (**4-1**) and 43% (**4-2**)], 209 [46% (**4-1**) and 41% (**4-2**)], 182 [65% (**4-1**) and 61% (**4-2**)], 181 [79% (**4-1**) and 73% (**4-2**)], and 165 [76% (**4-1**) and 78% (**4-2**)], which were attributed to ionic fragments **I-VI,** respectively. These data are also consistent with the epimeric structures **4-1** and **4-2**.

The analysis of the ^{1}H and ^{13}C-NMR spectra of the mixture containing **2** and **3** after the separation of **4** by thin layer chromatography, was facilitated after the collection of the corresponding data for **2** (Table 1) and **4** (Table 2), since the major distinction between these three products encompass the substitution at C-2': allyl group in **2**, 3-trifluoroacetate-*n*-propyl group in **3** and 3-hydroxy-*n*-propyl group in **4**. After the assignment of the signals corresponding to hydrogen and carbon-13 of **2** and **4** (still present in small percentages), the remaining absorptions in the ^{1}H and ^{13}C-NMR spectra were used to confirm the presence of the 3-fluoroacetate-*n*-propyl moiety in **3**, a mixture of the epimers **3-1** and **3-2** (*vide supra*). The presence of these three products in a mixture was confirmed by GC/EIMS analysis, which appeared in the GC peaks at R_t 8.391 (**2**), 9.157 (**3**), 9.763 (**4.1**), and 9.878 min (**4.2**), together with **1**

Table 5. ^{1}Hx^{13}C-COSY-^{n}J$_{CH}$ (n=2 and 3, COLOC), 2D heteronuclear correlation via long-range coupling, for compound **2** [$CDCl_3$, benzene-d_6 and acetone-d_6 as solvents].

	$CDCl_3$		Benzene-d_6		Acetone-d_6	
C	$^2J_{CH}$	$^3J_{CH}$	$^2J_{CH}$	$^3J_{CH}$	$^2J_{CH}$	$^3J_{CH}$
1					2H-7	
3,5	2H-2,6	2MeO-3,5	2H-2,6	2MeO-3,5	2H-2,6	2MeO-3,5
4		2H-2,6;MeO-4		2H-2,6;MeO-4		2H-2,6;MeO-4
1'	H-8	2H-7;3H-9		3H-9		2H-7;3H-9
2'		H-6'		H-6'	2H-7'	H-6'
3'		MeO-3'		MeO-3'		2H-7',MeO-3'
4'		H-6'		H-6'		H-6'
5'	H-6'	MeO-5'	H-6'	MeO-5'	H-6'	MeO-5'
CH						
2,6		2H-7		H-7		2H-7
8	H-7;3H-9	H-6'	3H-9	H-6'	2H-7;3H-9	H-6'
6'						H-8
8'	2H-7'				2H-7'	
CH_2						
7		2H-2,6		2H-2,6;3H-8		2H-2,6
7'		H-9'a				
9'						2H-7'
CH_3						
9		2H-7				2H-7

(R_t = 7.316 min, present in a very small percentage). The mass spectrum of each of these peaks allowed the recognition of the corresponding product by molecular peaks at m/z 402 (**1**, R_t = 7.316 min), 402 (**2**, R_t = 8.391 min), 420 (**4.1**, R_t = 9.763 min) and 420 (**4.2**, R_t = 9.878 min), and comparison with the mass spectra of **2** [m/z 402 (8.4%, $M^{\bullet+}$); m/z 221 (100%, **VI**); m/z 181 (25.5%, **V**)], **4.1** and **4.2** (*vide supra*). The mass spectrum of **3** (R_t = 9.157 min) did not show the molecular ion peak (m/z 516), and showed the base peak at m/z 373, together with another significant peak at m/z 207 (29%), which were attributed to ionic fragments **VII** and **VIII**, respectively. These ionic fragments may be accounted for through an *ortho*-fragmentation and hydrogen radical elimination, leading to **VII** or a loss of the trimethoxyphenyl radical to produce **VIII**[6]. The peaks at m/z 373 and 207, though having a small relative abundance, were also observed in the mass spectra of **4.1** and **4.2**, and are in accordance with the structures proposed for fragments **VII** and **VIII**.

The superposition of the signals of the carbon atoms C-1 and C-4 (δ_C 136.52) observed in the ^{13}C-NMR spectra of **2** was confirmed by NMR spectra, including 2D experiments, using benzene-d_6 and acetone-d_6 as solvents (Tables 4 and 5). In benzene-d_6 the superposition of the signals for C-4 and C-4' (δ_C 137.46) was verified, and in acetone-d_6, C-1' and C-4 (δ_C 136.81) were superimposed. The solvent effects on the chemical shifts and linewidths of the signals, as well as the magnitude of the spin-spin coupling constants (J), in the NMR spectra of **1** and **2** are summarized in Tables 4,6 and 7. As anticipated, these parameters are affected by

Table 6. ^{1}H (200 MHz) and ^{13}C (50 MHz) spectral data for neolignan aurein **1**, in $CDCl_3$, benzene-d_6 and acetone-d_6 as solvents, chemical shifts in δ (ppm) and coupling constants (J) in Hz.*

	$CDCl_3$		Benzene-d_6 (C_6D_6)		Acetona-d_6 (C_3D_6O)		$\Delta\delta^a$		$\Delta\delta^b$	
C	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	$\Delta\delta_C$	$\Delta\delta_H$	$\Delta\delta_C$	$\Delta\delta_H$
1	136.13	-	136.37	-	137.19	-	0.24	-	1.06	-
3,5	152.50	-	153.71	-	153.75	-	1.21	-	1.25	-
4	135.82	-	137.61	-	137.19	-	1.79	-	1.37	-
1'	142.19	-	142.46	-	143.38	-	0.27	-	1.19	-
3',5'	152.89	-	154.01	-	154.06	-	1.12	-	1.17	-
4'	134.69	-	136.22	-	136.17	-	1.53	-	1.48	-
CH										
2,6	105.84	6.19(s)	106.97	6.68(s)	107.14	6.39(s)	1.13	0.49	1.30	0.20
8	42.04	3.4-2.9(m)	42.56	3.5-3.2(m)	42.72	3.1-2.9(m)	0.52	0.1-0.3	0.68	-0.30
2',6'	103.90	6.31(s)	105.21	6.80(s)	105.20	6.50(s)	1.11	0.49	1.30	0.19
8'	134.43	6.4-6.0(m)	135.56	6.8-6.5(m)	136.17	6.2-6.0(m)	1.13	0.4-0.5	1.74	-0.20
CH_2										
7	45.34	2.9-2.7(m)	45.72	3.5-3.2(m)	45.60	2.8-2.6(m)	0.34	0.6-0.5	0.26	-0.10
			-	3.2-3.0(m)	-					
7'	73.94	4.45(br d,J=5.9)	73.91	5.01(br d,J=6.9)	74.04	4.41(br d,J=5.5)	-0.03	0.56	0.10	-0.04
9'	117.30	5.27(br d,J=16.2)	116.39	5.77(br d,J=17.2)	116.45	5.31(br d,J=17.2)	-0.91	0.50	-0.85	0.04
		5.14(br d,J=10.1)	-	5.48(br d,J=9.2)	-	5.11(br d,J=11.2)	-	0.34	-	-0.03
CH_3										
9	20.96	1.33(d,J=6.4)	21.45	1.69(d,J=6.5)	21.45	1.23(d,J=6.7)	0.49	0.36	0.49	-0.10
2MeO-3,5	55.74	3.73(s)	55.74	3.87(s)	56.34	3.76(s)	0.00	0.14	0.60	0.03
MeO-4	60.60	3.77(s)	60.41	4.21(s)	60.48	3.67(s)	-0.19	0.44	-0.12	-0.10
2MeO-3',5'	55.87	3.77(s)	55.86	3.89(s)	56.24	3.72(s)	-0.01	0.12	0.37	-0.05

* Homonuclear ^{1}Hx^{1}H-COSY and heteronuclear ^{1}Hx^{13}C-COSY[$^1J_{CH}$ (Table 2) and $^nJ_{CH}$ (n=2,3, COLOC, Table 6)] 2D experiments were also used for these assignments. The multiplicity of the signals of the carbon atoms was deduced by comparative analysis of the ^{13}C-NMR-PND and ^{13}C-NMR-DEPT spectra.

[a] $\Delta\delta_C$=δ_C(C_6D_6) - δ_C ($CDCl_3$) and $\Delta\delta_H$= δ_H (C_6D_6) - δ_H ($CDCl_3$).

[b] $\Delta\delta_C$= δ_C (C_6D_6O) - δ_C ($CDCl_3$) and $\Delta\delta_H$= δ_H (C_3D_6O) - δ_H ($CDCl_3$).

the surrounding molecules of the same or different species, revealing that the shielding constants (σ) of a magnetic nucleus in a particular molecule is not only determined by the eletronic distribution within the molecule but also by the nature of the surrounding medium. The calculated solvent-induced difference (Δδ) in the ^{1}H ($\Delta\delta_H$) and ^{13}C ($\Delta\delta_C$) chemical shifts of **2** and **1** are described in Tables 4 and 5. After all of the hydrogen and carbon (multiplicities deduced by comparative analysis of the PND- and DEPT-^{13}C-NMR spectra) resonances had been associated via ^{1}Hx^{13}C-COSY-$^{1}J_{CH}$ ($^{1}J_{CH}$ = 130.2 Hz) experiments (Tables 4 and 6), ^{1}Hx^{1}H-COSY and ^{1}Hx^{13}C-COSY-$^{n}J_{CH}$ (n = 2 and 3, COLOC) spectra of **2** and **1** were also recorded (Tables 5 and 7).

Specific solvent effects in the chemical shifts of ^{1}H and ^{13}C signals of dissolved compounds consist mainly of the hydrogen-bonding and aromatic solvent-induced shift (ASIS) effects. Hydrogen bonding usually induces a downfield shift of the resonance signal of an involved hydrogen. Carbon-13 solvent shifts are linearly dependent on (ε-1)/(2ε-n), ε = dieletric constant and n = refractive index[7]. Downfield shifts are observed for both ^{1}H and ^{13}C signals of $CDCl_3$, as compared to nonpolar solvents to medium susceptible to hydrogen bonding. As observed in Tables 4 and 6, solvent shifts may be different in magnitude and direction.

In Chart 1 is presented a proposal of the acid catalyzed mechanism for the transformation of aurein **1** to rearranged product **2**. This intramolecular rearrangement was proposed on the basis of the absence of a 3,4,5-trimethoxyphenyl system containing an allyl group. Furthermore, this reaction in the presence of 1,2,3-trimethoxybenzene, used in a ratio of 3 moles to 1 mole of aurein (**1**), did not afford the derivative produced by intermolecular reaction, the same products being obtained. The allyl group at C-2' of the rearranged product **2** may react with trifluoroacetic acid to furnish **3** through the formation (rate-determining step) of a secondary carbocation (more stable when compared with the primary one) by the eletrophilic addition of a proton from CF_3COOH to the double bond following the reaction of the highly reactive intermediate carbocation with CF_3COO^- to produce **3** (two epimers). In the presence of H_2O, more nucleophilic than CF_3COO^-, the formation of **4** (two epimers, **4.1** and **4.2**) occurs, which can also be produced by the hydrolysis of **3**, as observed by preparative TLC through the increase of **4** and the corresponding decrease of **3**.

Experimental

General procedures

One and two-dimensional NMR spectra were run in $CDCl_3$ (**1** - **4**), benzene-d_6 (**1** and **2**) and acetone-d_6 (**1** and

Table 7. ^{1}Hx^{13}C-COSY-$^{n}J_{CH}$ (n= 2 and 3, COLOC), 2D heteronuclear correlation via long-range coupling, for compound **1**, in $CDCl_3$, benzene-d_6 and acetone-d_6 as solvents.

	$CDCl_3$		Benzene-d_6		Acetone-d_6	
C	$^{2}J_{CH}$	$^{3}J_{CH}$	$^{2}J_{CH}$	^{3}CH	$^{2}J_{CH}$	$^{3}J_{CH}$
1	2H-2,6;2H-7		2H-7		2H-7	
1'	2H-2',6';H-8	2H-7;3H-9	2H-2',6'	2H-7;3H-9		3H-9
3,5	2H-2,6	2MeO-3,5	2H-2,6	2MeO-3,5		2MeO-3,5
3',5'	2H-2',6'	2MeO-3',5'	2H-2',6'	2MeO-3',5'		2MeO-3',5'
4		2H-2,6;MeO-4		2H-2,6;MeO-4		2H-2,6;MeO-4
4'		2H-2',6'		2H-2',6';2H-7'		2H-2',6';2H-7'
CH						
2,6		2H-7		2H-7		2H-7
2',6'		H-8		H-8		
8	2H-7;3H-9	2H-2',6'	3H-9	2H-2',6'		
8'	2H-7'					
CH_2						
7	H-8	2H-2,6;3H-9		2H-2,6;3H-9		3H-9
7'	H-8'	2H-9'				
9'				2H-7'		2H-7'
CH_3						
9	H-8	2H-7		2H-7		

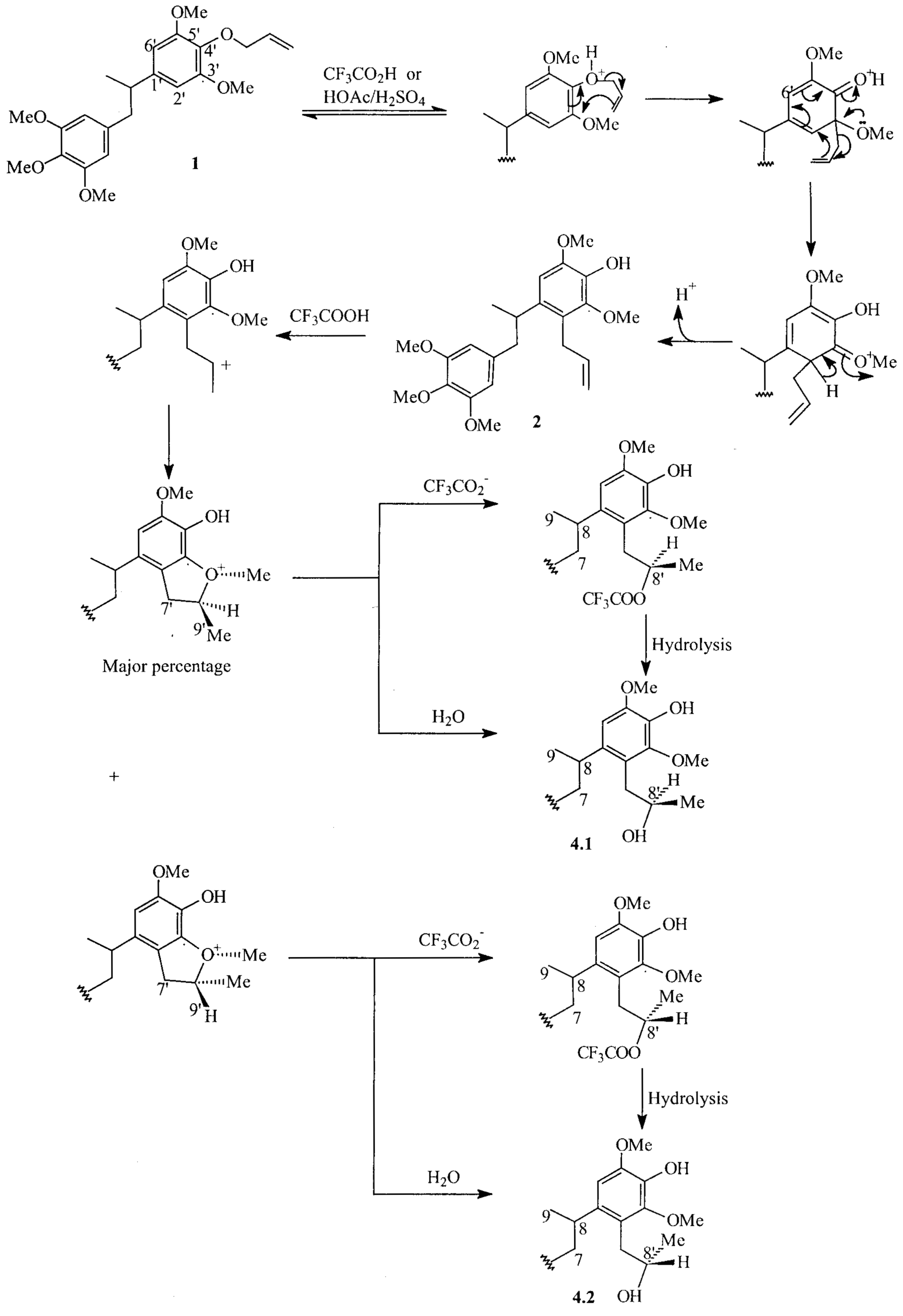
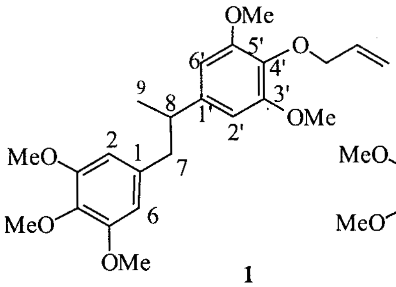
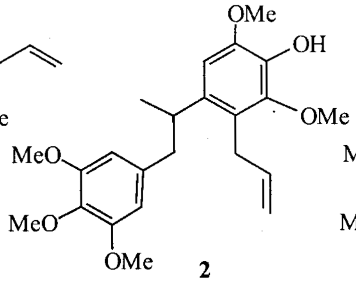


Chart 1. Proposal of the acid catalyzed mechanistic transformation (CF_3COOH) of aurien **1**.

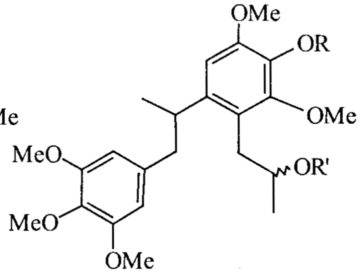
2), using a Bruker AC-200 Instrument at 200 MHz for ^{1}H and 50 MHz fo ^{13}C (PND and DEPT), with chemical shifts reported in δ values (ppm) downfield from the TMS internal standard and coupling constants (J) in Hz. The DEPT-^{13}C, ^{1}Hx^{1}H-COSY, and ^{1}Hx^{13}C-COSY-$^{n}J_{CH}$ (n = 1; n = 2 and 3, COLOC) NMR spectra and NOE difference spectra (^{1}H{^{1}H}-NOE) experiments were carried out using Bruker commercial microprograms. GC/EIMS (70 eV) spectra were obtained using a Hewlett-Packard model 5890-Series II gas chromatograph, with a 12 m x 0.2 mm HP-1 (100% dimethylpolysiloxane) capillary column, programmed from 180 °C to 290 °C at a rate of 20 °C/min, interfaced with a Hewlett-Packard model 5989A series mass selective detector. Analytical and preparative thin layer chromatog-



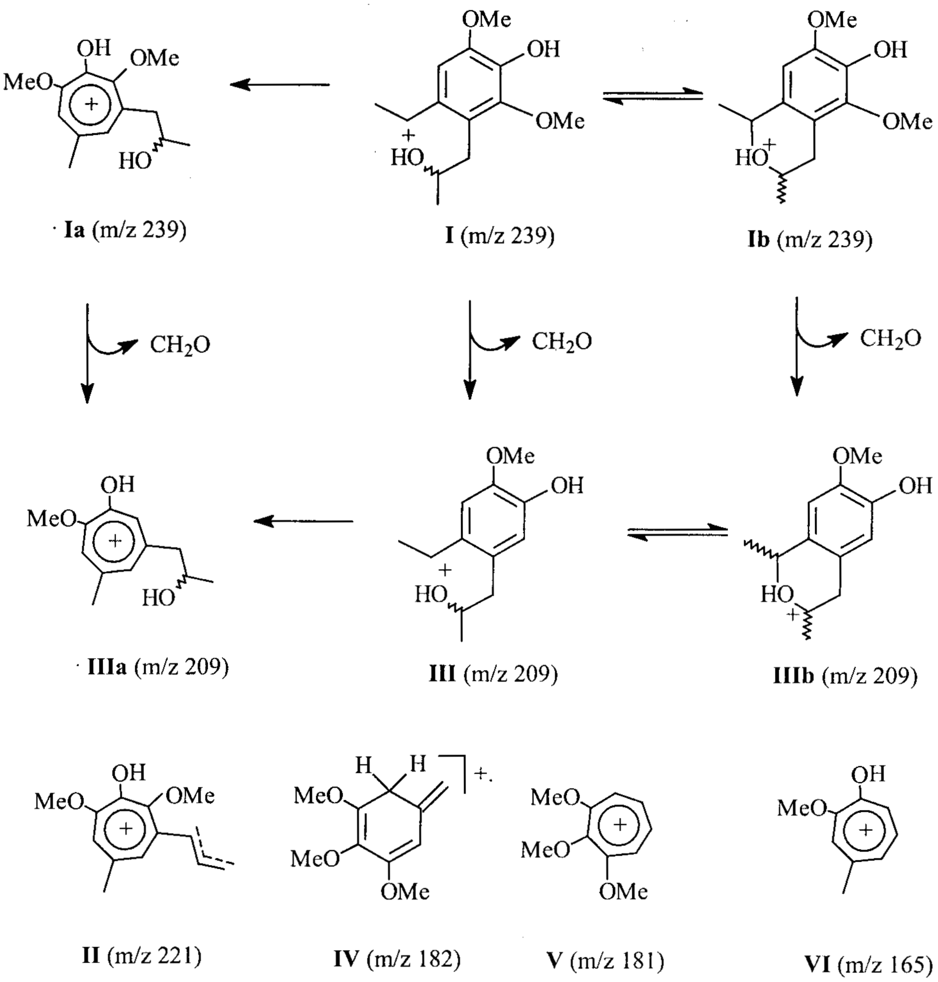
1



2



	R	R'
3	H	CF$_3$CO
4	H	H
4a	Ac	Ac



Ia (m/z 239) **I** (m/z 239) **Ib** (m/z 239)

IIIa (m/z 209) **III** (m/z 209) **IIIb** (m/z 209)

II (m/z 221) **IV** (m/z 182) **V** (m/z 181) **VI** (m/z 165) raphy (TLC) were performed on silica gel Kieselgel Merck 60 PF_{254}.

Reaction of aurein (1) with trifluoroacetic acid

Aurein (**1**, 150 mg) in CF_3COOH (10 mL) was maintained at room temperature for 24 h and extracted with $CHCl_3$. Evaporation of $CHCl_3$ afforded a residue (140 mg) which was submitted to preparative TLC (EtOAc-$CHCl_3$, 8:2) to yield a mixture of **2** and **3** (69.6 mg) and **4** (62.2 mg).

Preparation of 2-(2-allyl-4-hydroxy-3,5-dimethoxyphenyl)-1-(3,4,5-trimethoxy-phenyl)-propane (**2**)[1]

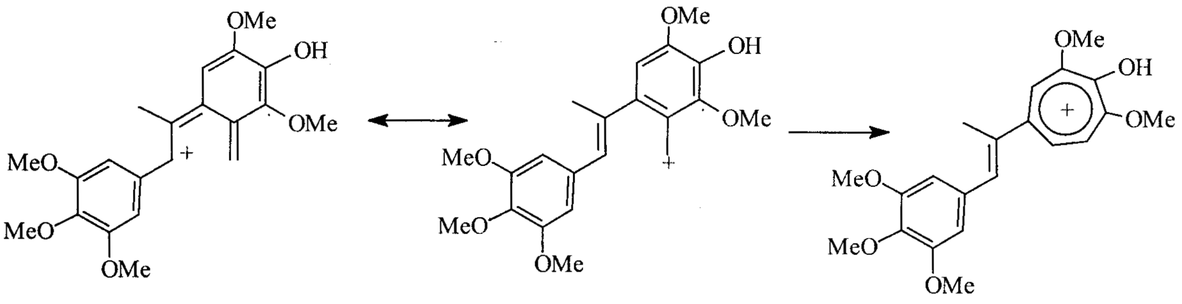
Aurein (**1**, 275 mg) in HOAc (6 mL) was treated with a solution of H_2SO_4 (0.3 mL) in HOAc (6 mL). After 48 h at room temperature, H_2O (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 5 mL). Evaporation of the solvent furnished a residue which was separated by SiO_2 column chromatography to afford **2** (123.3 mg). ^{1}H and ^{13}C-NMR: Table 1. EIMS (70 eV) m/z (rel. int.): 402 (8.4, $M^{\bullet+}$), 221 (100.0, **II**), 181 (25.5, **V**).

*2-[4-Hydroxy-3,5-dimethoxy-2-(2-hydroxy-n-propyl)-phenyl]-1-(3,4,5-trimethoxy-phenyl)-propane (**4**)*

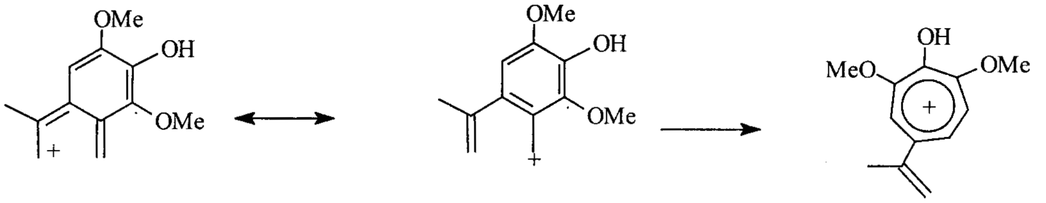
Viscous oil. IR υ KBr/max $^{(cm-1)}$: 3424 (OH), 1599 and 1502 (arom. ring). ^{1}H and ^{13}C: Table 2. GC/EIMS (70 eV): R_t = 11.796 min (**4.2**), m/z (rel. int.): 420 (7, $M^{\bullet+}$), 239 (100.0, **I**), 221 (43.0, **II**), 209 (41.0, **III**), 182 (61.0, **IV**), 181 (73.0, **V**), 165 (78.0, **VI**); R_t = 11.906 min (**4.1**), m/z(rel. int.): 420 (7.0, $M^{\bullet+}$), 239 (100.0, **I**), 221 (46.0, **II**), 209 (46.0, **III**), 182 (65.0, **IV**), 181 (79.0, **V**), 165 (76.0, **VI**).

*2-[4-Acetoxy-3,5-dimethoxy-2-(2-acetoxy-n-propyl)-phenyl]-1-(3,4,5-trimethoxy-phenyl)-propane (**4a**)*

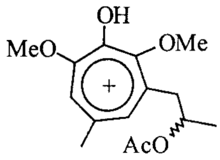
The mixture of the epimer **4** (62.2 mg) was acetylated with Ac_2O (1 mL) in the presence of pyridine (1 mL) at room temperature. After 48 h, the mixture was worked-up as usual to furnish **4a** (88.6 mg), an amorphous solid. IR υ KBR/max $^{(cm-1)}$: 1768 ($\upsilon_{C=O}$ of the AcO-4'), 1731 ($\upsilon_{C=O}$ of the AcO-8'), 1592 and 1500 (arom. ring). ^{1}H and ^{13}C-NMR: Table 3. GC/EIMS (70 eV) m/z (rel. int.): 504 (2.7,



VII (m/z 337)



VIII (m/z 207)



IX (m/z 281)

$M^{\bullet+}$), 444 (2.3, M-HOAc). 402 (3.2, M-HOAc-$CH_2 = C = O$), 281 (8.2, **IX**), 221 (100, **II**), 207 (14.7, **VIII**), 181 (90, **V**). The separation of the epimers (**4a-1** and **4a-2**) was not observed under the conditions used, as only one peak appeared in the chromatogram.

*Mixture of **2** and **3** = 2-[4-hydroxy-3,5-dimethoxy-2-(2-trifluoroacetoxy-n-propyl)-phenyl]-1-(3,4,5-trimethoxyphenyl)-propane*

Viscous oil. GC/EIMS (70 eV): $R_t = 8.391$ min (**2**), m/z (rel. int.): 402 (8.4, $M^{\bullet+}$), 221 (100.0, **II**), 181 (25.5, **V**); $R_t = 9.157$ min (**3**), m/z (rel. int): 516 (absent, $M^{\bullet+}$), 373 (100.0, **VII**), 207 (29.0, **VIII**).

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