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^{13}C NMR SPECTRAL AND CONFORMATIONAL ANALYSIS OF 8-*O*-4′ NEOLIGNANS

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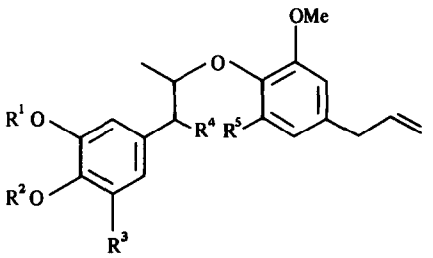
Key Word Index—^{13}C NMR spectra, *erythro* and *threo* 8-*O*-4′ neolignans.

Abstract—The ^{13}C NMR spectra of the *erythro* and *threo* forms of representative members of the 8-*O*-4′ type of neolignans were recorded and the signals assigned. Based on these assignments and on the comparison with previously reported ^{1}H NMR data, the most probable conformations for the above mentioned stereoisomers are suggested.

INTRODUCTION

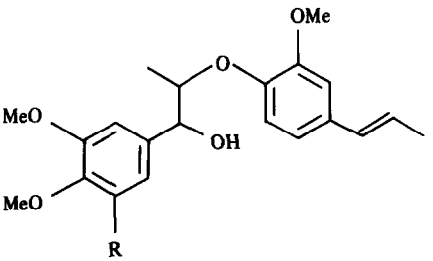
Of the great structural variety of neolignans, the 8-*O*-4′ type represents a small group whose members were isolated exclusively from plants of the Myristicaceae [1]. Amongst them, those isolated from *Myristica fragrans* Houtt. [2] with two methoxyl groups on ring B, correspond to the *erythro* series (**1a–1h**) whereas those from *Virola surinamensis* (Rol.) Warb (**2a** and **2b**) [3], carrying one methoxyl on ring B, to the *threo* series. By phenol oxidation coupling of arylpropenoids, mixtures of *erythro* and *threo* neolignans related to the natural products were also prepared and interestingly enough the β-O coupling of dimethoxyphenols, like 2,6-dimethoxy-4-propenylphenol, produces mainly the *erythro* isomer but from methoxyphenols, like isoeugenol, the major coupling product corresponds to the *threo* series, supporting the proposed biogenetic pathway [4, 5]. For the determination of the relative configurations of the synthetic as well as the natural products extensive use of ^{1}H NMR spectroscopy was made. In this connection, we decided to carry out an analysis of some synthetic members of this group, as part of a project on ^{13}C NMR spectral analysis of lignans and related products [6, 7], that combined with previously reported ^{1}H NMR data will allow us to elucidate features of their stereochemistry and conformation.



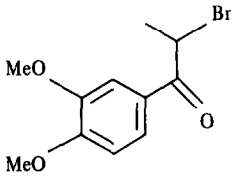
1a $R^1 = R^2 = -CH_2-$; R^3 = OMe; R^4 = OH; R^5 = OMe
1b R^1 = Me; R^2 = Me R^3 = OMe; R^4 = OH, R^5 = OMe
1c R^1 = Me, R^2 = H R^3 = H, R^4 = OH, R^5 = OMe
1d R^1 = Me; R^2 = Ac; R^3 = H; R^4 = OAc; R^5 = OMe
1e $R^1 = R^2 = -CH_2-$, R^3 = H, R^4 = OAc, R^5 = OMe
1f R^1 = Me; R^2 = Me; R^3 = OAc R^4 = OAc, R^5 = OMe
1g $R^1 = R^2 = -CH_2-$; R^3 = H; R^4 = OBz, R^5 = OMe
1h R^1 = Me, R^2 = Me; R^3 = OMe, R^4 = H; R^5 = OMe
1i R^1 = Me; R^2 = Me; R^3 = H; R^4 = OH; R^5 = H
1j R^1 = Me, R^2 = Me, R^3 = H, R^4 = OH, R^5 = OMe

RESULTS AND DISCUSSION

For carrying out the spectral analysis we selected two pairs of diastereoisomers, with one and two methoxyl groups on ring B (**1i** and **1j**) as representative members of each group of 8-*O*-4′ neolignans. These compounds were synthesized following the general method described previously [2, 8]. Treatment of the bromoketone **3** with the sodium salt of eugenol in DMF or with 2,6-dimethoxy-4-allylphenol and potassium carbonate in 2-butanone, afforded ketones **4a** and **4b**, respectively. Sodium borohydride reduction of **4a** gave, as described before [5, 8] a mixture of alcohols in which the *erythro* isomer is the major product (**1i**, *erythro*), based on the intensity of the



R
2a OMe
2b H



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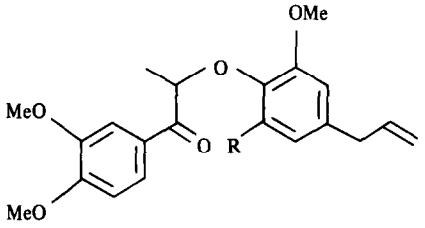

R
4a H
4b OMe

H-7 signal in the ^{1}H NMR spectrum of the mixture.* An attractive explanation for this stereochemical result, by analogy with the reduction of *t*-butyl α-alkoxy-β-keto carboxylates [9], is that the reaction proceeds *via* a chelate (Fig. 1) in which the sodium ion is coordinated by the oxygen atoms of the carbonyl and the aryloxy groups. The approach of hydride from the less hindered side of the CO generates predominantly the *erythro* isomer. Confirmatory evidence for the above explanation was obtained by reduction of ketone **4a** with sodium borohydride in the presence of 15-crown-5. Under these conditions a 9:1 mixture of *threo* and *erythro* forms was obtained. Sodium borohydride reduction of **4b** afforded a *ca* 1:1 mixture of both isomers (**1j**, *erythro*, *threo*) whereas in the presence of 15-crown-5, again the *threo* isomer predominates. As was previously reported [2], lithium aluminium hydride reduction of **4a** and **4b** led exclusively to the *erythro* form of **1i** and **1j**, respectively. For the spectral analysis described below the diastereoisomers were isolated in pure form by column chromatography from the mixtures where they are the major products

The stereochemistry and most probable conformation of the aryl ethers may be deduced from their IR and NMR spectra following the arguments utilized by Wallis [4]. The independence to concentration changes of the hydroxyl bands in the IR spectra of this type of compounds in chloroform solutions clearly indicated intramolecular hydrogen bonding of the benzylic hydroxyl and the aryloxy group. Of the possible staggered forms of the *erythro* and *threo* isomers, rotamers A, B and C (Fig. 2) are the only ones that would contribute significantly to the

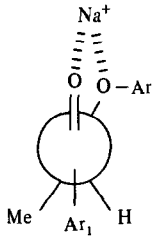

Fig. 1. Proposed reduction of 8-*O*-4′ neolignans via a chelate.

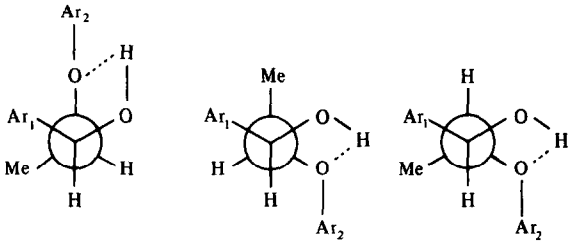

Fig. 2. Possible staggered forms of 8-*O*-4′ neolignan diastereoisomers.

conformation of the aryl ethers, based on the ^{1}H NMR spectra of the diastereoisomers of **1i** and **1j**. The coupling constants ($J_{7,8}$) of 3.2 and 8 Hz are consistent with dihedral angles between H-7 and H-8 of 60° and 180°, respectively, allowing the assignment of conformer C, with the larger *J* values, to the *threo* form and conformers A or B (J = 3.2 Hz) to the *erythro* one. Although the signals for H-7 and H-8 in the ^{1}H NMR spectra of the *threo* isomers are, in all cases, at higher fields compared to the corresponding protons of the *erythro* forms, these data are not conclusive to decide upon which of the two *erythro* rotamers will provide the main contribution to the conformations of these isomers.

A comparison of C-7, C-8 and C-9 ^{13}C NMR signals for the diastereoisomers of **1i** and **1j** shows downfield shifts for all of them in going from an *erythro* to a *threo* form and since there is a restricted rotamer population due to the intramolecular hydrogen bonding, the chemical shifts of C-9 could be calculated for rotamers A, B and C, as an extension of the method of Beirbeck *et al.* [10]. Such calculations gave values of 17.68, 13.1 and 17.7 ppm, respectively. Shifts of 13.1 and 17.7 are in excellent agreement with those observed for the *erythro* and *threo* forms, and indicate that conformer B should be the main contributor to the conformation of the *erythro* isomer. These appreciable differences in ^{13}C chemical shifts between the *erythro* and *threo* forms will be a powerful additional probe toward the elucidation of stereochemical features of neolignans.

The carbon shifts of **1i** (*erythro* and *threo*) and **1j** (*erythro* and *threo*) assigned by comparison with those of **4a** and **4b** and related compounds previously reported [3, 11], and by the analysis of the generated CH/CH$_3$ and

*The numbering used in this paper for the 8-*O*-4′ neolignans is the one suggested in ref. [1].

Table 1. Carbon shifts of 8-*O*-4′ neolignans

Carbon No.	1i (*erythro*)	1i (*threo*)	1j (*erythro*)	1j (*threo*)	4a	4b
1	132.4	132.3	132.5	135.5	127.2	127.9
2	110 4	110.3	110.6	110.6	111.1	111.0
3	147.8	148.2	147.7	148.4	149.6	148.2
4	150 9	150.0	148.6	148.6	153.3	152 5
5	109.2	109.6	109.1	109.9	109.9	109.5
6	120 7	120.3	117.9	119.6	123.4	123.5
7	73 3	77.5	72.6	78.7	190.2	190.5
8	81 8	82.8	82 1	86.1	78.0	80.1
9	13.2	16.2	12.6	17.3	19.0	17.7
1′	134.9	134.3	132.8	133.1	134.0	133.4
2′	112.2	111.9	105.3	105 2	112.5	104 9
3′	148.5	148.4	153.3	152.4	148 7	152 5
4′	144.6	145.3	135 9	135.5	145.0	135.4
5′	118 2*	118 2*	153 3	152.4	115.8	152.5
6′	119 2*	119 3*	105 3	105.2	120.3	104.9
7′	39.6	39.3	40.3	40.2	39.6	39.9
8′	137.0	136.8	136.8	136.8	137.2	136.7
9′	115 5	115.2	115.9	115.8	115.5	115.5
OMe	55.5	55.2	55 7	55.5	55.7	55.4
			55.9	55.6	55 8	

*Signals within a column may be interchanged

CH_2/q subspectra by spin-echo sequences utilizing the proton-flip method (APT) [12] are listed in Table 1.

EXPERIMENTAL

The ^{1}H NMR were recorded at 80.13 MHz and the ^{13}C NMR spectra at 20.15 MHz in the Fourier transform mode and in $CDCl_3$ solns. Chemical shifts are expressed on the TMS scale according to TMS = $\delta CDCl_3 + 76.9$ ppm. The asterisks on the Table indicate possible signal reversal. TLC was done on silica gel GF 254 and column chromatography on silica gel H.

1-(3′,4′-*Dimethoxyphenyl*)-2-(2″-*methoxy*-4″-*allyl-phenoxy*) *propan*-1-*one* (**4a**). The Na salt of eugenol (2.88 g, 15.5 mmol) was added to a stirred soln of 1-(3,4-dimethoxyphenyl)-2-bromopropan-1-one (**3**), prepared according to ref. [13] (3.77 g, 14 mmol), in dry DMF (55 ml). After being stirred for 48 hr the mixture was diluted with H_2O (50 ml) and extracted with Et_2O (2 × 50 ml). The combined Et_2O extracts were washed with 0.2 N aq. NaOH, H_2O and dried ($NaSO_4$). The residue, 1.87 g of crude product, was recrystallized from 95% EtOH yielding 1.67 g (67%) of pure product, mp 86–88°. IR ν_{max}^{KBr} cm^{-1}: 3120, 3090, 2095, 1680, 1650, 1600, 1525, 1450, 1275, 1245, 1030, 925, 915. ^{1}H NMR: δ 1.69 (3H, *d*, *J* = 7 2 Hz, H-3), 3.28 (2H, *br d*, *J* = 6.4 Hz, H-7″), 3.82, 3.91 and 3.93 (9H, *s*, 3 × MeO), 4.95 (1H, *m*, H-9″), 5.12 (1H, *m*, H-9″), 5.40 (1H, *q*, *J* = 7.2, H-8), 5.72–6.20 (1H, *m*, H-8″), 6.50–7.90 (6H, *m*, ArH). MS *m/z* (rel. int): 356 [M]$^+$ (10), 191 (21), 165 (100), 115 (12), 103 (19), 91 (30), 77 (43), 55 (25), 51 (21).

$\Delta^{8'}$,3,3′,4-*trymethoxy neolignan* (**1i**, erythro). A soln of ketone **4a** (0.30 g, 0.84 mmol) in dry Et_2O (25 ml) was added, dropwise, to a stirred suspension of $LiAlH_4$ (0.480 g, 12.6 mmol) in Et_2O (36 ml). After the addition was complete, the mixture was refluxed for 24 hr. Excess $LiAlH_4$ was carefully destroyed by addition of EtOAc–ice, and finally diluted with H_2O (60 ml), acidified (10% HCl) and extracted with Et_2O (3 × 60 ml). The combined Et_2O extracts were washed with 1 N aq. NaOH and H_2O, dried (Na_2SO_4) followed by concn affording a crude oil (0.277 g). CC (gradient of hexane–EtOAc) produced pure **1i**, *erythro* (0.250 g, 82%). IR ν_{max}^{film} cm^{-1}: 3260, 3045, 3005, 2975–2940, 1650, 1620, 1520, 1475, 1275, 1170, 1040, 925, 820. ^{1}H NMR: δ 1.17 (3H, *d*, *J* = 6.4 Hz, H-9), 3.35 (2H, *d*, *J* = 6.4 Hz, H-7′), 3.85 (9H, *br s*, 3 × MeO), 4.33 (1H, *dq*, *J* = 6.4, 3.2 Hz, H-8), 4.84 (1H, *d*, *J* = 3.2 Hz, H-7), 5.01 (1H, *br s*, H-9′), 5.18 (1H, *m*, H-9′), 5.70–6.20 (1H, *m*, H-8′), 6.60–7.10 (6H, *m*, ArH). MS *m/z* (rel. int.): 358 [M]$^+$ (10), 194 (38), 192 (29), 167 (88), 164 (100), 149 (21), 139 (50), 121 (20), 107 (22), 103 (25), 91 (41), 77 (47), 57 (80), 43 (60).

$NaBH_4$ *reduction of ketone* **4a**: $\Delta^{8'}$,3,3′,4-*trimethoxy neolignan* (**1i**, erythro + threo). Solid $NaBH_4$ (0.170 g, 4.5 mmol) was added in small portions to a stirred, cooled (0°) soln of ketone **4a** (0.505 g, 1.5 mmol) in dry MeOH (22 ml). The mixture was stirred for 30 min at 0° and 4 hr at room temp, H_2O and a few drops of HOAc were then added and the mixture extracted with Et_2O (4 × 50 ml). The combined Et_2O extracts were washed with satd aq. $NaHCO_3$ soln and H_2O, dried (Na_2SO_4), decanted and evapd, yielding a 72:28 mixture of **1i**, *erythro threo* (0.5 g, 92%).

$NaBH_4$ + 15-*crown*-5 *reduction of ketone* **4a**. A soln of $NaBH_4$ (0.114, 3 mmol) in *iso* PrOH (10 ml) was added to a stirred soln of 15-crown-5 ether (0.72 g, 3.6 mmol) in dry *iso*PrOH (5 ml). After 6 hr, a soln of ketone **4a** (0.356 g, 1 mmol) in dry MeOH (5 ml) was added and the mixture stirred for 4 hr at room temp. The same work up as before, gave a 1:9 mixture of crude **1i**, *erythro threo* (0.33 g, 92%). Pure **1i**, *threo* (0.186 g) was obtained by CC of the mixture. IR ν_{max}^{film} cm^{-1}: 3250, 3045, 3005, 2995–2925, 1650, 1620, 1600, 1525, 1475, 1430, 1280, 1240, 1155, 1045, 925, 820. ^{1}H NMR· δ 1.15 (3H, *d*, *J* = 6.4 Hz, H-9), 3.35 (2H, *br d*, *J* = 6.4 Hz, H-7′), 3.90, 3.91 and 3.93 (9H, *s*, 3 × MeO), 4.04 (1H, *m*, H-8), 4.64 (1H, *d*, *J* = 8 Hz, H-7), 4.99 (1H, *m*, H-9′), 5.16 (1H, *m*, H-9′), 5.73–6.25 (1H, *m*, H-8′), 6.67–7 (6H, *m*, ArH). MS *m/z* (rel. int.): 358 [M]$^+$ (11), 194 (26), 192 (23), 167 (80), 164 (100), 149 (22), 139 (69), 121 (33), 107 (39), 103 (45), 91 (71), 77 (76), 65 (43), 57 (70), 43 (59).

1-(3′,4′-*Dimethoxyphenyl*)-2-(2″,6″-*dimethoxy*-4″-*allyl-phenoxy*) *propan*-1-*one* (**4b**). 1-(3,4-Dimethoxyphenyl)-2-bromopropan-1-one (**3**) (2.62 g, 9.75 mmol), 6-methoxyeugenol (2 ml, 18 mmol) and dry K_2CO_3 (2.4 g) were heated under reflux, with stirring, in dry MeCOEt (37.5 ml) for 30 hr. The soln was cooled, diluted with H_2O (50 ml), acidified (HOAc) and extracted with Et_2O (2 × 100 ml). The combined Et_2O extracts were washed with 1% aq. NaOH (1 × 100 ml), H_2O (2 × 50 ml), dried (Na_2SO_4) and concd to dryness. Crystallization of the crude product from MeOH, yielded pure ketone **4b** (2.1 g, 60.5%) mp 71–73°. IR ν_{max}^{KBr} cm^{-1}: 3095–2840, 1690, 1600, 1540, 1510, 1280, 1140, 1120, 1030. ^{1}H NMR: δ 1 56 (3H, *d*, *J* = 6.4 Hz, H-9), 3.31 (2H, *d*, *J* = 6.4 Hz, H-7′), 3.72, 3.92 (12H, *s*, 4 × MeO), 4.98 (1H, *m*, H-9′), 5.17 (1H, *m*, H-9′), 5.25 (1H, *q*, *J* = 6.4 Hz, H-8), 5.96 (1H, *m*, H-8′), 6.37 (2H, *s*, ArH), 6.87 (1H, *d*, *J* = 8 Hz, ArH), 7.75–7 95 (2H, *m*, ArH). MS *m/z* (rel. int.): 386 [M]$^+$ (30), 221 (30), 193 (54), 165 (100), 105 (22), 91 (38), 77 (52), 51 (19).

$\Delta^{8'}$,3,3′,4,5′-*Tetramethoxy neolignan* (**1j**, erythro). The same procedure, as for reduction of **4a** was used, ketone **4b** (0 324 g, 1 mmol), $LiAlH_4$ (0.48 g, 12.6 mmol) in dry Et_2O (36 ml). After CC pure **1j** *erythro* was obtained (0.294 g, 90%) as a colorless oil. IR ν_{max}^{film} cm^{-1}· 3520, 3090–2925, 1600, 1520, 1470, 1275, 1240, 1040, 925, 740 ^{1}H NMR: δ 1.13 (3H, *d*, *J* = 6.4 Hz, H-9), 3.36 (2H, *br d*, *J* = 6.4 Hz, H-7′), 3.86, 3.87 (12H, 4 × MeO), 4.36 (1H, *d q*, *J* = 6.4, 3 2 Hz, H-8), 4 81 (1H, *d*, *J* = 3.2 Hz, H-7), 5 3 (1H, *m*, H-9′), 6.0 (1H, *m*, H-9′), 5.75–6.23 (1H, *m*, H-8′), 6.47 (2H, *s*, ArH), 6.78 (1H, *s*, ArH), 6.96 (1H, *s*, ArH). MS *m/z* (rel. int.)· 388 [M]$^+$ (20), 194 (100), 167 (50), 165 (23), 57 (19).

$NaBH_4$ *reduction of ketone* **4b**: $\Delta^{8'}$,3,3′,4,5′-*tetramethoxy neolignan* (**1j**, erythro + threo). Following the same procedure as described for reduction of **4a** starting from ketone **4b** (0.194 g,

0.5 mmol) and $NaBH_4$ (0.057 g, 1.5 mmol) in MeOH (6.4 ml). The crude product obtained (0.184 g, 94%) was a 1:1 mixture of **1j**, *erythro*:*threo*.

$NaBH_4$ + 15-*crown*-5 *reduction of ketone* **4b**. The same procedure as described for ketone **4a** was followed starting from ketone **4b** (0.386 g, 1 mmol), $NaBH_4$ (0.114 g, 3 mmol) and 15-crown-5 (0.69 ml, 3.6 mmol). A 1:4 mixture of crude **1j**, *erythro*:*threo* was obtained. CC of the mixture afforded pure **1j**, *threo* (0.298 g, 76%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3240, 2990–2930, 1600, 1470, 1350, 1140, 1040. ^1H NMR: δ 1.17 (3H, *d*, J = 6.4 Hz, H-9), 3.34 (2H, *br d*, J = 6.4 Hz, H-7′), 3.85 (12H, *s*, 4 × MeO), 4.03 (1H, *m*, H-8), 4.62 (1H, *d*, J = 8 Hz, H-7), 5.01 (1H, *m*, H-9′), 5.20 (1H, *m*, H-9′), 5.74–6.15 (1H, *m*, H-8′), 6.45 (2H, *s*, ArH), 6.83–7.96 (3H, *m*, ArH). MS *m/z* (rel. int.): 388 $[M]^+$ (12), 194 (100), 167 (8), 165 (17), 57 (20).

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