Enantioselective Synthesis and Absolute Configuration Assignment of Erythro-(3,4-methylenedioxy-7-hydroxy-1'-allyl-3',5'-dimethoxy)-8.0.4'-neolignan and Its Acetate, Isolated from Nutmeg (Myristica fragrans)

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ENANTIOSELECTIVE SYNTHESIS AND ABSOLUTE CONFIGURATION ASSIGNMENT OF *ERYTHRO*-(3,4-METHYLENEDIOXY-7-HYDROXY-1′-ALLYL-3′,5′-DIMETHOXY)-8.0.4′-NEOLIGNAN AND ITS ACETATE, ISOLATED FROM NUTMEG (*MYRISTICA FRAGRANS*)

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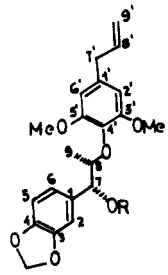
ABSTRACT.—The enantioselective synthesis of *erythro*-(3,4-methylenedioxy-7-hydroxy-1′-allyl-3′,5′-dimethoxy)-8.0.4′-neolignans (−)-**1** and (+)-**2** was achieved in high chemical and optical yields by the asymmetric reduction of the corresponding ketone with $LiAlH_4$ partially decomposed with (*R*)- and (*S*)-binaphthol (BINAL-H). The predicted absolute stereochemistry thus obtained was confirmed through the chiral LiAlH(*N*-methylephedrine)(*N*-ethylaniline)$_2$ reduction of the same ketone and by performing Horeau's and Mosher's configuration determination methods. Compound (−)-**1** was correlated with the natural product acetate (−)-**3** isolated from nutmeg (*Myristica fragrans*), and its configuration was unambiguously established.

Members of the 8.0.4′ class of neolignans, with two methoxyl groups on ring B and corresponding to the erythro series, have been isolated (1) from the seed (nutmeg) of *Myristica fragrans* Houtt. (Myristicaceae), but neither their absolute configurations nor their optical rotations were reported.

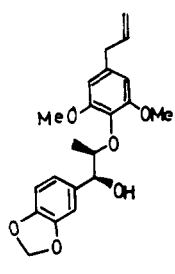
Continuing with our project on enantioselective synthesis of the 8.0.4′ type of neolignans using chiral hydrides (2), we attempted the asymmetric synthesis of *erythro*-(3,4-methylenedioxy-7-hydroxy-1′-allyl-3′,5′-dimethoxy)-8.0.4′ neolignans (−)-**1** and (+)-**2** in order to determine, by direct comparison with the synthetic materials, the absolute stereochemistry of the natural acetate (−)-**3** extracted from nutmeg. We followed the nomenclature for neolignans proposed by Gottlieb (3). In addition, in order to confirm the predicted stereochemistry, Horeau's (4) and Mosher's (5–7) methods to determine absolute configuration have been performed on the alcohol derived from the natural product through hydrolysis.

Among the wide variety of chiral hydrides used as reagents for asymmetric reductions (8–14), we chose the (*R*)- and (*S*)-(2,2′-dihydroxy-1,1′-binaphthyl)-modified $LiAlH_4$ (10) (BINAL-H), because it showed a very high enantioface differentiating ability in the reduction of aromatic ketones.

We carried out the chiral reduction on ketone **4** where the presence of another chiral center resulted in control of both relative and absolute configuration. The required ketone **4** was synthesized from piperonylnitrile, as previously reported (1,15), by treat-



1 R=H
3 R=Ac



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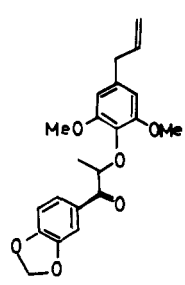

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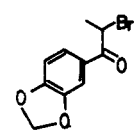

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ment of the bromoketone **5** with 2,6-dimethoxy-4-allyl-phenol and K_2CO_3 in 2-butanone (2). Treatment of racemic ketone **4** with 3 equivalents of the reducing agent, prepared with $LiAlH_4$ (1 mmol), (*S*)-binaphthol (1 mmol), and MeOH (1 mmol) in THF (−100°, 3 h, then −78°, 16 h) afforded diastereospecifically (1) and enantioselectively (−)-**1**: $[\alpha]^{25}D$ −27° ($CHCl_3$, c = 1). Its ^{1}H-nmr and ^{13}C-nmr spectra confirmed the relative configuration (1,16). Compound (−)-**1** was esterified with an excess of the pure (+)-α-methoxy-α-trifluormethylphenylacetyl chloride (+)-MTPA-Cl (5–7) and found to be 82% ee, based on its ^{1}H-nmr spectrum. The relative peak areas of the well separated aryl signals of the 3′,5′-dimethoxy-1′-allyl-phenyl moiety (6.33 ppm and 6.39 ppm) and methylenedioxy protons (5.94 ppm and 5.91 ppm) are a measure of the diastereoisomeric composition and thus the enantiomeric purity of the original carbinol.

Compound (+)-**2** was prepared in a similar way using (*R*)-binaphthol as the chiral agent and afforded an alcohol with $[\alpha]^{25}D$ +28° ($CHCl_3$, c = 1), ee = 80%.

Considering a transition state for the asymmetric reduction with (*S*)-BINAL-H analogous to that proposed by Noyori *et al.* (10), our ketone would produce an alcohol with an *R* configuration at C-7 (7*R*,8*S*) (Figure 1). Conversely, with (*R*)-binaphthol, the enantiomeric configuration (7*S*,8*R*) would be obtained.

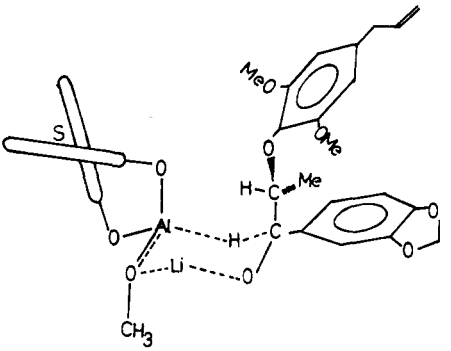

FIGURE 1. Transition state for the asymmetric reduction with (*S*)-binaphthol.

The direction and extent of the enantioselective reductions are determined by the stability of the preferred six-membered ring transition state. The reaction occurs in such a way as to minimize steric repulsions between the axially oriented binaphthol oxygen and carbonyl substituents and to avoid electronic repulsion with the methylenedioxybenzene moiety. In addition, the diastereospecificity of the reaction might require an extra interaction with the lithium cation of the ether moiety present in the substrate.

When ketone **4** was reduced with $LiAlH_4$ modified with (−)-*N*-methylephedrine and *N*-ethylaniline (2,12), (−)-**1** was obtained, $[\alpha]^{25}D$ −22° ($CHCl_3$, c = 1), ee = 65%. On the other hand, the reduction with (+)-*N*-methylephedrine as the chiral agent afforded (+)-**2**, $[\alpha]^{25}D$ +23° ($CHCl_3$, c = 1), ee = 68%. This reduction allowed us to assign the (7*R*,8*S*) absolute configuration to (−)-**1** and the (7*S*,8*R*) to (+)-**2**, in accord with reported results (2), and confirmed the predicted absolute stereochemistry, although it showed a lower chiral efficiency (12).

It was also possible to correlate the absolute configurations and ^{1}H-nmr spectral differences for diastereomeric (*R*)-MTPA esters of synthetic (−)-**1** and (+)-**2**. The ^{1}H-nmr spectrum showed that the aromatic signals corresponding to the 3′,5′-dimethoxy-1′-allyl-phenyl group from (−)-**1** appeared at lower field (6.39 ppm) relative to the (*R*)-

MTPA ester from (+)-**2** (6.33 ppm). Accordingly, the methylenedioxy signals from (−)-**1** resonated at higher field (5.91 ppm) relative to the (+)-isomer (5.94 ppm). Because the chemical shift non-equivalence of the aromatic and methylenedioxy groups was produced by a selective shielding due to the α-phenyl group in the (*R*)-MTPA moiety (6), the correlation configuration model proposed by Dale and Mosher (6) clearly indicated that the absolute stereochemistry of (−)-**1** must be (7*R*,8*S*) (Figure 2, A), while that of (+)-**2** must be (7*S*,8*R*) (Figure 2, B), in agreement with chiral reduction results.

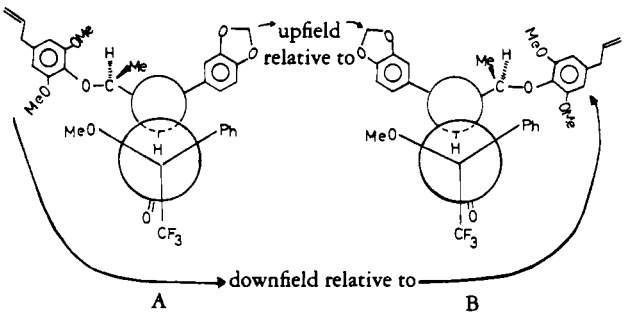

FIGURE 2. Configuration Correlation Model for (*R*)-MTPA esters of (−)-**1** (A) and (+)-**2** (B).

In order to confirm the predictions regarding the absolute configuration of C-7, we performed Horeau's and Mosher's methods on the alcohol (−)-**1**, $[\alpha]^{25}D$ −34° ($CHCl_3$, $c = 1$), obtained by reducing natural (−)-**3**, $[\alpha]^{25}D$ −9° ($CHCl_3$, $c = 1$), extracted from nutmeg, with excess $LiAlH_4$ in THF. The levorotatory 2-phenylbutanoic acid produced during the Horeau's kinetic resolution permitted us to assign (4) the (7*R*,8*S*) absolute configuration to natural (−)-**3** and its derived alcohol (−)-**1**. In the spectrum of the (*R*)-MTPA ester of this (−)-**1**, only a single set of signals were observed (6.39 and 5.91 ppm) and thus, this sample and natural (−)-**3** were enantiomerically pure within the limits of the nmr accuracy.

These results demonstrate a higher level of enantioselection of the reducing agent BINAL-H than other chiral hydrides in asymmetric reduction of ketones of the 8.0.4′ class of neolignans and have allowed us to predict their absolute configuration.

The use of several independent tests permits the absolute stereochemistry of natural (−)-**3** to be unambiguously established as (7*R*,8*S*). In addition, we could demonstrate through Mosher's method that natural (−)-**3** was 100% one enantiomer (17).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The ^1H-nmr spectra were recorded at 80.13 MHz and the ^{13}C-nmr spectra at 20.15 MHz in the Fourier transform mode and in $CDCl_3$ solutions. Carbon chemical shifts are expressed on the δ scale using $CDCl_3$ as a reference signal at 76.9 ppm; *J* values are given in Hz. Tlc was done on Si gel GF 254 and cc on Si gel 60H. Ir spectra were measured with a Beckman Acculab-8-spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter as solutions in a 1-dm cell. Melting points were determined on an Ernst Leitz hotstage microscope and are uncorrected.

(3,4-METHYLENEDIOXY-7-OXO-1′-ALLYL-3′,5′-DIMETHOXY)-8.0.4′-NEOLIGNAN [**4**].—Preparation and characterization were as previously reported (1). 1-(3′,4′-Methylenedioxyphenyl)-2-bromopropan-1-one [**5**] (431 mg, 1.68 mmol), 2,6-dimethoxy-4-allylphenol (456 mg, 2.35 mmol, 0.26 ml), and dry K_2CO_3 (325 mg, 2.35 mmol) were heated under reflux with stirring in dry butanone (10 ml) for 30 h. The solution was cooled, diluted with H_2O (20 ml), and extracted with Et_2O (2 × 30 ml). The combined Et_2O extracts were washed with 1% aqueous NaOH (1 × 30 ml) and H_2O, dried (Na_2SO_4), and concentrated to dryness. Chromatography on a Si gel column eluted with solvent mixtures of increasing polarity from hexane to EtOAc afforded 638 mg (1.26 mmol, yield 75%) of pure ketone **4** as a crystalline solid: mp

90–92°; ir ν max cm^{-1} 3090, 3000, 2970, 2920, 1695, 1675, 1610, 1500, 1450, 1360, 1150, 1050, 990, 950, 835, 765; ^1H nmr ($CDCl_3$) δ 1.53 (3H, d, J = 6.4 Hz, H-9), 3.31 br (2H, d, H-7′), 3.73 (6H, s, 2 × OMe), 4.99 (1H, m, H-9′), 5.13 (1H, q, J = 6.4 Hz, H-8), 5.79 (1H, m, H-8′), 6.01 (2H, s, -OCH_2O-), 6.37 (2H, s, H-2′ and H-6′), 6.83 (1H, d, J = 8 Hz, H-5), 7.73 (1H, d, J = 2 Hz, H-2), 7.83 (1H, dd, H-6); ^{13}C nmr ($CDCl_3$) δ 17.69 (q, C-9), 40.0 (t, C-7′), 55.5 (q, OCH_3), 80.57 (d, C-8), 101.32 (t, -OCH_2O-), 105.3 (d, C-2′ and C-6′), 107.3 (d, C-5), 108.9 (d, C-2), 115.54 (t, C-9′), 125.23 (d, C-6), 126.6 (s, C-1), 135.6 (s, C-4′), 136.8 (d, C-8′), 147.4 (s, C-3), 151.1 (s, C-4), 152.8 (s, C-3′ and C-5′), 196.4 (s, C=O); ms m/z $[M]^+$ 370 (13), 221 (15), 193 (33), 149 (63), 91 (85), 65 (100).

ASYMMETRIC REDUCTION.—The asymmetric reduction was conducted with magnetic stirring in a vessel equipped with a rubber septum under an N_2 atmosphere. Anhydrous reagents were transferred by a stainless steel double-ended needle or by oven-dried syringes. Solids were dried in the Abderhalden pistol immediately before use. Optical purities were determined in various ways. Direct comparison of optical rotations was carefully done with the synthetic and natural materials. Both samples were subjected alternatively to the rotation measurements under identical conditions. ^1H-nmr analysis of the (+)-MTPA esters prepared according to Mosher's procedure (6) was performed.

The (+)- and (−)-binaphthol were obtained from Aldrich Chemical Co.

PREPARATION OF THE CHIRAL HYDRIDE.—A suspension of $LiAlH_4$ (1.5 g) in anhydrous THF (20 ml) was heated under reflux for 1 h with stirring. $LiAlH_4$ was used as a clear THF solution obtained by centrifugation of the suspension and was assayed by Felkin's method (18).

A round-bottom, two-neck flask equipped with an addition funnel in one neck and a condenser in the other filled with rubber septa, was flame-dried and placed under N_2 atmosphere. To this, a 0.5–1.0 M THF solution of $LiAlH_4$ was introduced via a syringe and, at room temperature, MeOH in THF (2.00 M, 1 equivalent) was added dropwise over a period of 10 min with stirring. Subsequently, a THF solution of optically pure (*S*)-binaphthol (0.6 M, 1 equivalent), was added dropwise, and the resulting mixture was stirred for an additional 30 min at room temperature and used for the asymmetric reduction. If a large quantity of precipitate separates out for some reason, one should repeat the preparation from the beginning.

erythro-(7*R*,8*S*)-(−)-(3,4-METHYLENEDIOXY-7-HYDROXY-1′-ALLYL-3′,5′-DIMETHOXY)-8.0.4′-NEOLIGNAN (−)-[**1**].—A THF solution of ketone **4** (400 mg, 1.08 mmol), dried in the Abderhalden pistol immediately before use, was gradually added to the solution of the reducing agent (3.25 mmol) cooled at (−100°) in dry-ice bath. The mixture was stirred for 3 h at −100° and at −78° for 16 h. After addition of MeOH (1 ml), the mixture was warmed to room temperature. To this, 2 N HCl (5 ml) was added, and the mixture was extracted with Et_2O. The combined Et_2O extracts were washed with 10% HCl (2 × 10 ml), saturated aqueous NaCl solution, and H_2O, dried (Na_2SO_4), decanted, and evaporated, yielding 198.5 mg (0.53 mmol) of the erythro alcohol (−)-**1** (90% chemical yield based on the recovered ketone): $[\alpha]^{25}D$ −28° ($CHCl_3$, c = 1), ee = 82%, based on its (+)-MTPA ester; ir ν max 3460, 2970, 1590, 1490, 1450, 1245, 1130, 930, 820; ^1H nmr ($CDCl_3$) δ 1.11 (3H, d, J = 7.2 Hz, H-9), 3.33 br (2H, d, J = 6.4 Hz, H-8′), 3.86 (6H, s, 2 × OMe), 4.33 (1H, dq, $J_{8,9}$ = 7.2 Hz, J7,8 = 2.8 Hz, H-8), 4.76 (1H, d, J = 2.8 Hz, H-7), 5.02 (1H, m, H-9′), 5.18 (1H, m, H-9′), 5.91 (2H, s, -OCH_2O-), 6.00 (1H, m, H-8′), 6.45 (2H, s, H-2′ and H-6′), 6.73–6.86 (3H, m, H-2, H-5, and H-6); ^{13}C nmr ($CDCl_3$) δ 13.30 (q, C-9), 40.35 (t, C-7′), 55.87 (q, -OCH_3), 73.82 (d, C-7), 86.16 (d, C-8), 100.80 (t, -OCH_2O-), 105.52 (d, C-2′ and C-6′), 107.48 (d, C-2), 107.83 (d, C-5), 155.96 (d, C-9′), 120.93 (d, C-6), 134.77 (s, C-4′), 135.81 (s, C-1 and C-1′), 136.99 (d, C-8′), 148.2 (s, C-3 and C-4), 152.7 (s, C-3′ and C-5′); ms m/z $[M]^+$ 372 (5), 221 (4.59), 194 (70), 193 (6.9), 151 (9.5), 179 (7), 57 (100).

erythro-(7*S*,8*R*)-(+)-(3,4-METHYLENEDIOXY-7-HYDROXY-1′-ALLYL-3′,5′-DIMETHOXY)-8.0.4′-NEOLIGNAN (+)-[**2**].—Ketone **4** (380 mg, 1 mmol) was treated as described above for (−)-**1** except for the use of (*R*)-binaphthol (supplied by Aldrich) as the chiral agent component of the chiral hydride, to give 183 mg of the erythro alcohol (+)-**2** as an oil (87% chemical yield based on the recovered ketone), $[\alpha]^{25}D$ +27° ($CHCl_3$, c = 1), ee = 80% based on its (+)-MTPA ester and its optical rotation.

(*R*)-(+)-MTPA DERIVATIVES.—The following procedure was used for the preparation of MTPA derivatives for nmr studies: (*R*)-(+)-MTPA (from Aldrich Chemical) was converted to the (+)-acid chloride (5), distilled, and stored in sealed ampoules. The reaction was carried out in a dry 10 × 75 mm test tube fitted with a rubber septum. The reagents were injected via syringes in the following order: dry pyridine (300 μl, 300 mg), (+)-MTPA-Cl (35 mg, 26 μl, 0.14 mmol), CCl_4 (300 μl), and the alcohol (0.10 mmol). The reaction mixture was shaken and allowed to stand at room temperature for 12 h. Excess 3-dimethylamino-1-propylamine was added (6), and the mixture was allowed to stand for 5 min and diluted with Et_2O. The organic solution was washed with 1 N HCl (2 ml), $NaCO_3$ solution (2 ml), and brine (2 ml) and concentrated. The residue was analyzed by ^1H nmr as a $CDCl_3$ solution.

MTPA esters derived from synthetic (−)-**1** and (+)-**2** displayed two sets of signals due to the aromatic protons of ring B (s, δ 6.33 and 6.39 ppm) and methylenedioxy protons (s, δ 5.94 and 5.91).

EXTRACTION OF (−)-**3** FROM NUTMEG.—Nutmeg was purchased from M. Moore SACI (Corrientes 1669, Bs. As., Argentina). A voucher specimen is deposited at Department of Botany, Fac Cs. Bioq. y Farmacéuticas, U.N. Rosario, Argentina. Freshly ground nutmeg (1 kg) was extracted with petroleum ether for 5 min at room temperature. The extract was refrigerated, and the crystalline trimyristin was filtered off. The filtrate on concentration gave a brown oil which was partitioned between hexane and 85% EtOH. The residual Et_2O fraction was dried (Na_2SO_4) and concentrated in vacuo to give an oil (15 g), called the neutral fraction. Compound (−)-**3** was isolated from this fraction by preparative tlc on Si gel GF 254, using C_6H_6 as developing solvent. The main band was rechromatographed in the solvent system petroleum ether-Et_2O-HCO_2H (70:30:0.6), which yielded two broad bands. Rechromatography of them in the solvent system EtOAc-cyclohexane (1:1) gave 116 mg of (−)-**3**: $[\alpha]^{25}D$ −9°; ir ν max 2938, 1741, 1589, 1498, 1450, 1333, 1238, 1128, 1036, 926, 812; ^1H nmr δ (ppm) 1.29 (3H, d, J = 6.4 Hz, H-9), 2.16 (3H, s, CH_3C=O), 3.32 br (2H, d, J = 6.4 Hz, H-7′), 3.78 (6H, s, -OMe), 4.33 (1H, dq, H-8), 4.95–5.25 (2H, m, H-9′), 5.83 (1H, d, J = 3.2 Hz), 5.91 (2H, s, -OCH_2O-), 6.00 (1H, m, H-8′), 6.39 (2H, s, H-2′ and H-6′), 6.73–6.83 (3H, m, H-2, H-5, and H-6); ^{13}C nmr δ 14.20 (q, C-9), 21 (q, CH_3C=O), 40.33 (t, C-7′), 55.86 (q, -OCH_3), 76.52 (d, C-7), 80.03 (d, C-8), 100.80 (t, -OCH_2O-), 105.59 (d, C-2′ and C-6′), 107.19 (d, C-2), 107.78 (d, C-5), 115.7 (t, C-9′), 120.01 (d, C-6), 131.86 (s, C-1), 133.75 (s, C-1′), 135.60 (s, C-4′), 137.10 (s, C-8′), 146.8 (s, C-3), 147.38 (s, C-4), 153.22 (s, C-3′ and C-5′), 169.9 (C=O); ms m/z $[M]^+$ 414 (2.89), 221 (14.15), 194 (29.70), 179 (14.41), 149 (4.55), 57 (11), 43 (100).

REDUCTION OF NATURAL (−)-**3**.—Natural (−)-**3** (84 mg, 0.20 mmol) was reduced with excess $LiAlH_4$ (49 mg, 1.3 mmol) in THF to yield 71 mg (0.19 mmol) of (−)-**1**, $[\alpha]^{25}D$ −34° ($CHCl_3$, c = 1), which was converted to its MTPA ester with (*R*)-(+)-MTPA following the procedure described above. In the ^1H-nmr spectrum of this ester, only a single set of signals were observed (6.39 ppm for H-2′ and H-6′ and 5.91 ppm for methylenedioxy protons); thus, (−)-**1** obtained for hydrolysis of natural (−)-**3** was enantiomerically pure within limits of the nmr accuracy.

HOREAU'S METHOD ON ENANTIOMERICALLY PURE (−)-**1**.—Compound (−)-**1** (30 mg) 0.08 mmol) was added to a solution of racemic 2-phenyl-butanoic anhydride (50 mg, 0.16 mmol) in anhydrous pyridine, and the mixture was allowed to stand at room temperature for 1 h. The excess anhydride was completely hydrolyzed with H_2O and the mixture was left to stand for an additional 0.5 h. The organic acid was then titrated against 0.01 N NaOH solution (2.5 ml) in the presence of C_6H_6 and a little powdered phenolphthalein as indicator. The aqueous phase was washed with $CHCl_3$ and acidified with 1 N HCl. The 2-phenylbutanoic acid was extracted with C_6H_6 (2 × 5 ml), dried (Na_2SO_4), and filtered. Evaporation of the solvent gave 2-phenylbutanoic acid, $[\alpha]^{25}D$ −18° ($CHCl_3$, c = 0.7) (87.5% in the esterification process, 55% optical yield) (4).

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