Journal of Natural Products
Vol. 51, No. 6, pp. 1261-1265, Nov-Dec 1988

ENANTIOSELECTIVE SYNTHESIS AND ABSOLUTE CONFIGURATION ASSIGNMENT OF *ERYTHRO*-(3,4,5-TRIMETHOXY-7-HYDROXY-1′-ALLYL-2′,6′-DIMETHOXY)-8.0.4′-NEOLIGNAN, ISOLATED FROM MACE (*MYRISTICA FRAGRANS*).

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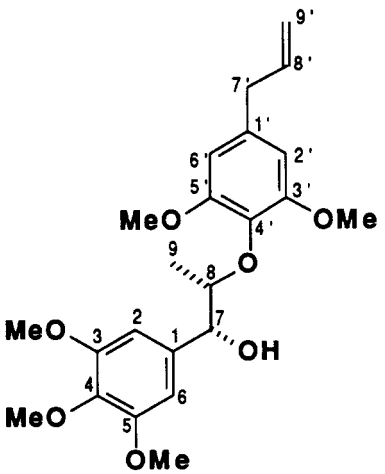
Members of the 8.0.4′ class of neolignans with two methoxyl groups on ring B, corresponding to the *erythro* series, have been isolated from the aril (mace) of the fruit of *Myristica fragrans* Houtt. (Myristicaceae) (1), but neither their absolute configurations nor their optical rotations were reported. As a part of a project on enantioselective synthesis of the 8.0.4′ type of neolignans using chiral hydrides, we decided to attempt the asymmetric synthesis of (−)- [**1**] and (+)-*erythro*-(3,4,5-trimethoxy-7-hydroxy-1′-allyl-2′,6′-dimethoxy)-8.0.4′ neolignan [**2**], in order to determine the absolute stereochemistry of the natural product by direct comparison with the synthetic material. [We follow the nomenclature for neolignans proposed by O.R. Gottlieb (2)]. In addition, the stereochemistry of the natural product was confirmed independently by Horeau's method (3,4).

The asymmetric reduction of prochiral ketones has been of increasing interest in recent years (5–11), and high optical and chemical yields have been realized in prochiral aromatic ketones using $LiAlH_4$ partially decomposed with (1*R*,2*S*)-(−)-*N*-methylephedrine as a chiral auxiliary agent and *N*-ethylaniline as an achiral agent (9).

We carried out the chiral reduction on a ketone belonging to the 8.0.4′ class of neolignan where the presence of another chiral center resulted in control of both relative and absolute configuration.

The required ketone **3** was synthesized by treatment of the bromoketone **4** with 2,6-dimethoxy-4-allylphenol and K_2CO_3 in 2-butanone. Treatment of racemic ketone **3** with 3 equivalents of the reducing agent, prepared with $LiAlH_4$ (1 mmol), (1*R*,2*S*)-(−)-*N*-methylephedrine (1 mmol), and *N*-ethylaniline (2 mmol) in Et_2O at −78° for 3 h, afforded diastereospecifically and



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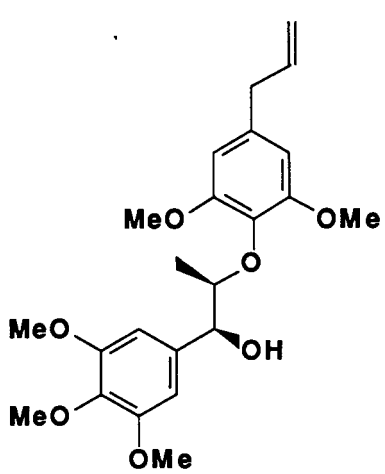

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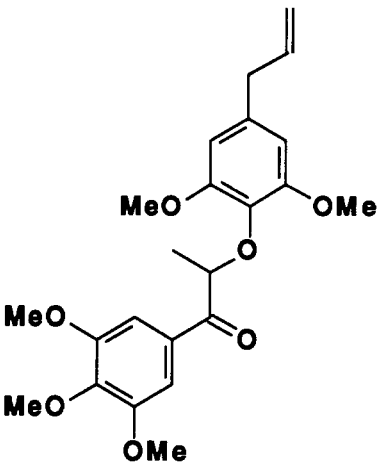

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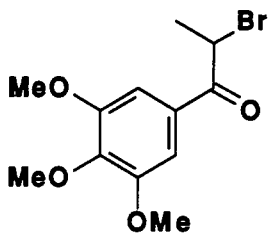

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enantioselectively (−)-*erythro*-**1**, $[\alpha]^{25}D$ −7.5° ($CHCl_3$, $c=1$), ee = 62.5% (based on the optical rotation of the natural product). When the reducing agent was prepared with (1*S*,2*R*)-(+)-*N*-methylephedrine, we obtained (+)-*erythro*-**2**, with similar chemical and optical yields; this compound was identical with the natural product obtained from mace (1).

It is known that reduction of ketones bearing an α aryloxy group with $LiAlH_4$ yields mainly the *erythro* isomer (1). The ^1H nmr, ir, and ms of the reduction product were coincident with those reported in the literature (1), and the C-7, C-8, and C-9 chemical shifts in the ^{13}C-nmr spectrum were additional proof (12) for the *erythro* form.

Considering a transition state for the asymmetric reduction with (−)-*N*-methylephedrine (Figure 1) analogous to that proposed by Tanno and Terashima (9), our ketone would produce an alcohol with a C-7*R* configuration. On the other hand, by using (+)-*N*-methylephedrine (Figure 2), the enantiomeric configuration (C-7*S*) would be obtained. Thus, the absolute configuration for (−)-*erythro*-**1** would be (7*R*,8*S*) and for (+)-*erythro*-**2** would be (7*S*,8*R*).

In order to confirm the prediction regarding absolute configuration of C-7,

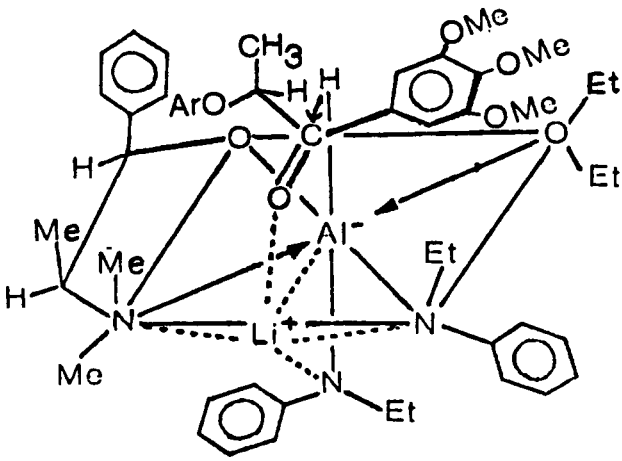

FIGURE 1. Transition state for the asymmetric reduction with (−)-*N*-methylephedrine.

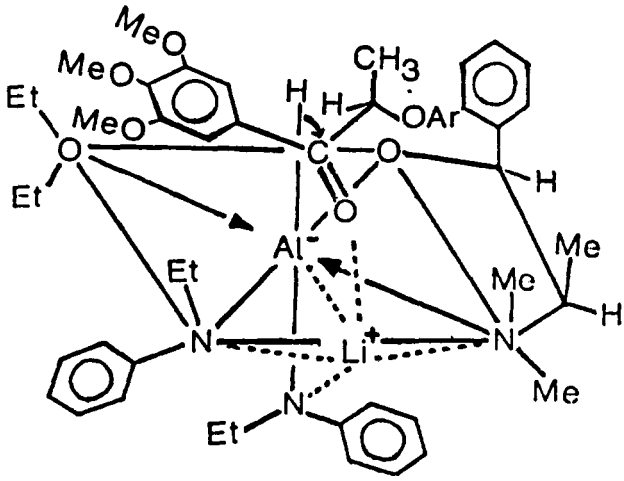

FIGURE 2. Transition state for the asymmetric reduction with (+)-*N*-methylephedrine.

we performed Horeau's method on the natural product using racemic 2-phenylbutanoic anhydride in anhydrous pyridine. Horeau and co-workers (3,4) have shown that the sign of rotation of the 2-phenylbutanoic acid obtained as a product of the esterification reaction yields information on the configuration of this type of secondary alcohol. The empirical rule assumes that an aromatic group is always larger (L) than an alkyl group (M). The 2-phenylbutanoic acid which was produced during the kinetic resolution of **2** was dextrorotatory, and the configuration at C-7 must, thus, be *S*. Therefore, the absolute configuration of natural (+)-*erythro*-**2** is (7*S*,8*R*), in agreement with that predicted by the chiral reduction.

The observed enantioselectivity for the reduction implies a preference in the approach of the hydride from the re-face (13) of the ketone when using (+)-*N*-methylephedrine and from the si-face when using (−)-*N*-methylephedrine in agreement with the results achieved by Tanno and Terashima (9) for aromatic ketones. Following their arguments, the steric interactions created by the substituents at the methine α to the ketone group with the phenyl and methyl groups of (+)- or (−)-*N*-methylephedrine in the complex would account for the lowering in the achieved optical yields. In addition, the diastereospecificity of the reaction might require an extra interaction of the either moiety present in the substrate with the lithium and/or aluminum cations.

These results demonstrate the utility of the highly efficient reducing agent LiAlH(*N*-methylephedrine) (*N*-ethylaniline)$_2$ in enantioselective synthesis and absolute configuration assignment of *erythro* alcohols of the 8.0.4′ class of neolignans.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The ^{1}H-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 H. 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.

(3,4,5-TRIMETHOXY-7-OXO-1′-ALLYL-2′,6′-DIMETHOXY)-8.0.4′-NEOLIGNAN [**3**].—1-(3′,4′,5′-Trimethoxyphenyl)-2-bromopropan-1-one [**4**] (13) (1.52 g, 5 mmol), 6-methoxyeugenol (1.36 g, 7 mmol, 0.78 ml), and dry K_2CO_3 (920 mg) were heated under reflux with stirring in dry butanone (22 ml) for 30 h. The solution was cooled, diluted with H_2O (25 ml), and extracted

with Et_2O (2 × 50 ml). The combined Et_2O extracts were washed with 1% aqueous NaOH (1 × 50 ml), H_2O, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the crude product from MeOH yielded 1.26 g (3 mmol) of pure ketone **3** as a crystalline solid mp 80°–83°; ir ν max cm^{-1} 3110, 3090, 3020, 2950, 1685, 1665, 1595, 1500, 1460, 1420, 1330, 1240, 1130, 1000; ^1H nmr ($CDCl_3$) δ 1.56 (3H, d, J = 7 Hz, H-9), 3.32 br (2H, d, H-7′), 3.73, 3.88, 3.91 (15H, s, 5 × OMe), 4.99 (1H, m, H-9′), 5.18 (1H, m, H-9′), 5.25 (1H, q, J = 6.5 Hz, H-8), 5.90 (1H, m, H-8′), 6.39 (2H, s, ArH), 7.51 (2H, s, ArH); ms *m/z* (rel. int.) $[M]^+$ 416 (5%), 221 (35), 195 (15), 194 (97), 193 (100), 91 (25), 77 (28).

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. Optical purity was determined by direct comparison of optical rotation under the same conditions (solvent source, concentration, temperature, cell, etc.). Et_2O was freshly distilled twice from sodium metal and once more from $LiAlH_4$. Solids were dried in the Abderhalden pistol immediately before use. The (+)- and (−)-*N*-methylephedrine were obtained from Sigma Chemical Company.

PREPARATION OF THE CHIRAL HYDRIDE.—A suspension of $LiAlH_4$ (379 mg) in anhydrous Et_2O was heated under reflux for 1 h with stirring. $LiAlH_4$ was used as a clear Et_2O solution obtained by centrifugation of the suspension and was assayed by Felkin's method (15).

A round-bottom, two-neck flask equipped with an addition funnel in one neck and a condenser in the other and rubber septa was flame-dried and placed under N_2 atmosphere. To this, an Et_2O solution of (1*R*,2*S*)-(−)-*N*-methylephedrine (645 mg, 3.60 mmol) was added dropwise over a period of 1 h to an assayed solution of $LiAlH_4$ (7.6 ml, 3.60 mmol) with stirring, and the mixture was heated under reflux for 1 h. Subsequently, an Et_2O solution of *N*-ethylaniline (872 mg, 0.90 ml, 7.20 mmol) was added dropwise over a period of 1 h with stirring and the mixture heated under reflux for an additional period of 1 h.

erythro-(7*R*,8*S*)-(−)-(3,4,5-TRIMETHOXY-7-HYDROXY-1′-ALLYL-2′,6′-DIMETHOXY)-8.0.4′-NEOLIGNAN [(−)-**1**].—An Et_2O solution of ketone **3** (500 mg, 1.20 mmol) was gradually added to the solution of the reducing agent (3.60 mmol), cooled at −78° (dry-ice bath), and the mixture was stirred at the same temperature for 3 h. After addition of 1 N HCl (12 ml) at −78°, the mixture was warmed to room temperature and 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 260 mg of alcohol *erythro*-**1** (84.5% chemical yield based in the recovered ketone) $[\alpha]^{25}D$ −7.5° ($CHCl_3$, c = 1), ee = 62.5%. Ir ν max 3520, 3080, 3010, 2950, 2940, 2850, 1600, 1510, 1465, 1425, 1335, 1230, 1130, 825, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.13 (3H, d, J = 8 Hz, H-9), 3.37 br (2H, d, H-7′), 3.82, 3.84, 3.87 (15H, s, 5 × OMe), 4.11 br (s, 1H, O*H*), 4.35 (1H, dq, H-8), 4.80 (1H, d, J = 3 Hz, H-7), 5.03 (1H, m, H-9′), 5.20 (1H, m, H-9′), 6.00 (1H, m, H-8′), 6.47, 6.56 (4H, s, ArH); ^{13}C nmr ($CDCl_3$) 12.71 (q, C-9), 40.4 (t, C-7′), 56.1 (q, C-3 and C-6, -OMe), 60.7 (q, C-4, -OMe), 73.08 (d, C-7), 82.14 (d, C-8), 103.2 (d, C-2 and C-6), 105.5 (d, C-3 and C-5′), 116.09 (t, C-9′), 133.7 (s, C-4′), 135.6 (s, C-4 and C-1′), 136.9 (d, C-8′), 137.6 (s, C-1), 153.04 (s, C-2′ and C-6′), 153.5 (s, C-3 and C-5); ms *m/z* $[M]^+$ 418 (8.4%), 225 (14.9), 224 (32.2), 221 (5.7), 197 (6.1), 195 (81), 194 (100), 193 (14.1).

erythro-(7*S*,8*R*)-(+)-(3,4,5-TRIMETHOXY-7-HYDROXY-1′-ALLYL-2′,6′-DIMETHOXY)-8.0.4′-NEOLIGNAN [(+)-**2**].—Ketone **3** (500 mg) was treated as described above for (−)-**1** except for the use of (1*S*,2*R*)-(+)-*N*-methylephedrine (supplied by Sigma) as the chiral aminoalcohol component of the chiral hydride, to give 273 mg of alcohol *erythro*-**2** as an oil (87.2% chemical yield based in the recovered ketone), $[\alpha]^{25}D$ +7.2° ($CHCl_3$, c = 1), ee = 60%.

EXTRACTION OF **2** FROM MACE.—The mace (*M. fragrans*) was purchased from M. Moore S.A.C.I. (Corrientes 1669 Bs. As., Argentina). A voucher specimen is deposited at the Department of Botany, Fac. de Cs. Bioquim. y Farmaceuticas, U.N. Rosario, Argentina. The freshly ground mace (1 kg) was extracted with hexane (4 liters) for 5 min at room temperature. The extract was refrigerated, and the crystalline trimyristin (mp 55–56°) which separated was filtered off. The filtrate on concentration gave an orange oil. Pure **2** (52 mg) $[\alpha]^{25}D$ +12° ($CHCl_3$, c = 1) was isolated by cc on elution from Si gel H with *n*-hexane/EtOAc and rechromatographed by preparative tlc on Si gel GF 254 with C_6H_6-EtOAc (80:20).

APPLICATION OF HOREAU'S METHOD ON **2**.—Natural *erythro*-(+)-**2** (42 mg, 0.10 mmol) was added to a solution of racemic 2-phenylbutanoic anhydride (62 mg, 0.20 mmol, 0.55 ml) 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 a further 0.5 h. C_6H_6 was added, and the 2-

phenylbutanoic acid was titrated against 0.1 N NaOH (3.1 ml), in the presence of 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), the C_6H_6 extracts dried (Na_2SO_4) and filtered. Evaporation of the solvent gave 2-phenylbutanoic acid, $[\alpha]^{25}D + 11.66°$ (95% yield in the esterification process, 36.3% optical yield) (3).

ACKNOWLEDGMENTS

This work was carried out with financial support from CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas), UNR (Universidad Nacional de Rosario), and IES (International Foundation Sciences, Sweden), through the grant awarded to Dr. L.F. Sala.

We thank Professors Dr. Edmundo A. Rúveda and Manuel Gonzalez Sierra for helpful discussions, Dra. Graciela Moltrasio for the rotation data, and Dr. J.C. Oberti for the mass spectra.

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Received 4 April 1988