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ENANTIOSELECTIVE ROUTE TO THREO 8.0.4′-TYPE NEOLIGNANS: SYNTHESIS OF (−)-VIROLIN

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ABSTRACT.—A combination of diastereoselective borohydride reduction of the substituted α-bromo-propiophenone [(±)-**2**] and microbial-assisted hydrolysis of its corresponding bromohydrin acetate using *Rhizopus nigricans*, led to the chiral epoxide, (−)-**6**. The regiospecific opening of this epoxide, produced pure (−)-virolin [**1**], whose absolute configuration could be assigned through this sequence as 7*S*,8*S*. It is possible, by selecting the appropriate starting materials, to obtain different chiral threo neolignans of the 8.0.4′-type and to predict their configuration.

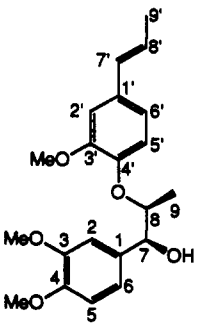
Virolin, a neolignan of the 8.0.4′-type, corresponding to the threo series, has been isolated from the leaves of *Virola surinamensis* (Myristicaceae) (1). We have performed its racemic synthesis (2), but neither its enantioselective synthesis nor its absolute configuration has been previously reported. Continuing with our project aimed at the enantioselective synthesis of 8.0.4′-type neolignans, we wish to report herein our efforts towards the asymmetric synthesis of threo virolin [(−)-**1**], involving a procedure for preparing chiral threo alcohols of predictable stereochemistry. We followed the nomenclature for neolignans proposed by Gottlieb (3).

RESULTS AND DISCUSSION

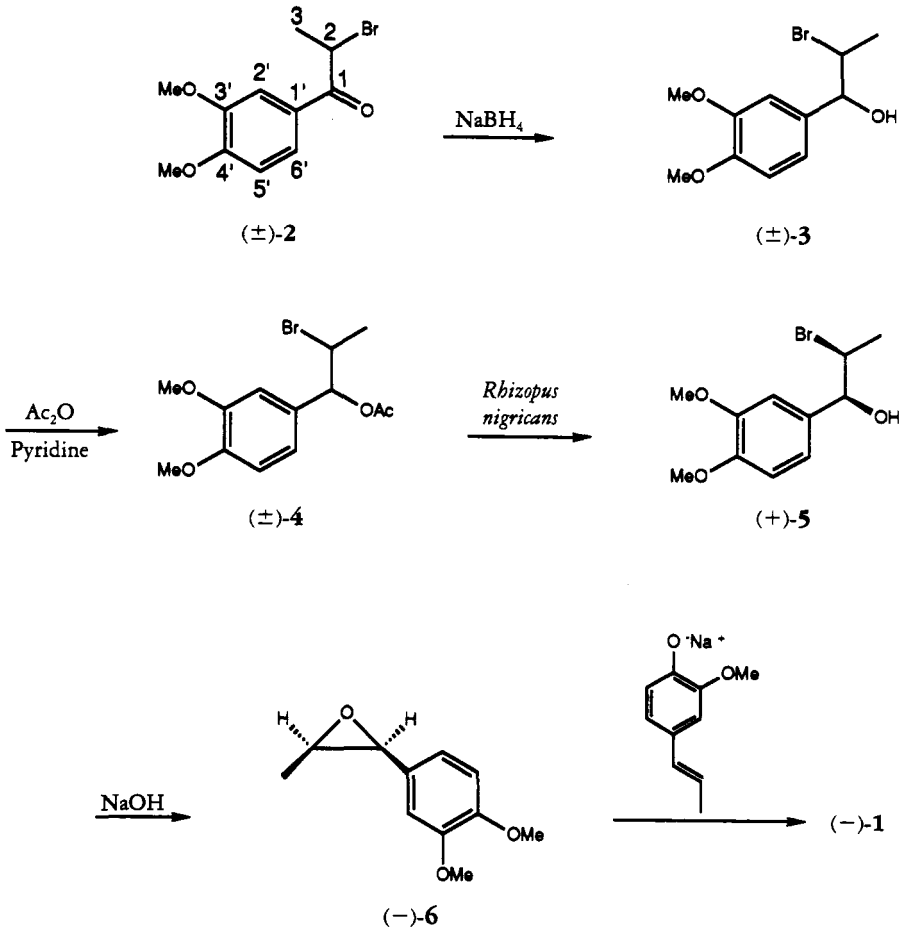
We recently reported (4) the successful use of chiral hydrides in the synthesis of erythro 8.0.4′-neolignans. However, since all attempts to prepare threo chiral alcohols through chiral hydrides were disappointing, we explored the possibility of obtaining threo alcohols by enantioselective microbial hydrolysis.

It is known (5–10) that the mold, *Rhizopus nigricans*, partially hydrolyzes racemic acetates to alcohols enriched in one enantiomer of predictable configuration, while the recovered acetate is enriched in the antipode. Unfortunately, under a great number of experimental conditions, synthetic (±)-virolin acetate (2) was immune to the action of the mold. It is possible, according to Ito *et al.* (11), that bulky substituents severely retard or hinder the action of enzymes.

Therefore, we propose an alternative synthesis of virolin as shown in Scheme 1 in which the enantioselectivity was achieved at an earlier stage. Here, enzymatic hydrolysis



(−)-**1**



SCHEME 1

would be applied to a smaller molecule which promised to be more susceptible to resolution. This route afforded (−)-virolin [**1**] with 78% ee.

The sequence began with racemic 1-(3′,4′-dimethoxyphenyl)-2-bromopropan-1-one [(±)-**2**]. The reductiion of (±)-**2** with three equivalents of $NaBH_4$ afforded diastereoselectively a 9:1 mixture of racemic threo:erythro bromohydrin (±)-**3** separated by thick-layer chromatography. Pure threo (±)-**3** was acetylated with Ac_2O and pyridine to give racemic bromoacetate (±)-**4** in 92% yield. The relative stereochemistry of (±)-**3** ($J_{2,3}$=8 Hz) and thus of (±)-**4** was determined by conversion to the corresponding racemic cis epoxide (12–15).

Microbial hydrolysis of (±)-**4** using *R. nigricans* gave (+)-**5** enantioselectively, $[\alpha]^{25}D$ +31° (*c*=1, $CHCl_3$). The percent hydrolysis of (±)-**4** was 50% as determined from ^{1}H-nmr measurement of the ratio of alcohol to acetate in the crude extract. The remaining acetate, $[\alpha]^{25}D$ −35° (*c*=1, $CHCl_3$), enriched in the (−)-enantiomer, was separated from the chiral bromohydrin (+)-**5** by thick-layer chromatography. Treatment of (+)-**5** with an excess of (*S*)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride [(−)-MTPACl] (16–18) gave an ester found to be 65% ee based on its ^{1}H-nmr spectrum. The relative peak areas of the well-separated aryl signals (6.79 and 6.87 ppm) of the bromohydrin moiety, are a measure of the diastereomeric composition and thus the enantiomeric purity of the enzymatic hydrolysis product.

The acetate obtained by reacetylating (+)-**5**, $[\alpha]^{25}D$ +31°, 65% ee (under the same conditions used previously), was subjected to a new microbial hydrolysis (5). The ee of the bromohydrin formed was increased to 79%, $[\alpha]^{25}D$ +42° (c=1, $CHCl_3$).

The absolute configuration of the carbinolic carbon in (+)-**5** was determined as 7*S* [absolute stereochemistry of the threo bromohydrin (7*S*,8*S*)], by using the rule proposed by Ziffer (6–8) and the assumption that, in acyclic systems, disubstituted carbons are effectively smaller than an aromatic ring (19). Thus, the enantiomer shown in Figure 1 would be the more rapidly hydrolyzed.

In order to confirm the validity of Ziffer's rule for this bromohydrin, and therefore the predicted stereochemistry, we also correlated the absolute configuration and the ^{1}H-nmr spectral differences for diastereomeric (*S*)-MTPA esters of (+)-**5** and its enantiomer. The ^{1}H-nmr spectrum showed that the aromatic signals corresponding to the (−)-bromohydrin moiety appeared at lower field (6.87 ppm) relative to the (*S*)-MTPA ester from (+)-**5** (6.79 ppm). Because the chemical shift non-equivalence of the aromatic protons was produced by a selective shielding due to the α-phenyl in the MTPA moiety (Figure 2), the correlation configuration model proposed by Dale and Mosher (4,17) clearly indicated that the absolute stereochemistry of the carbinolic carbon in (+)-**5** must be (7*S*,8*S*), in agreement with the enzymatic hydrolysis results.

The bromohydrin (+)-**5**, ee 79%, was treated with aqueous 3 M NaOH overnight in a two-phase system (H_2O/C_6H_6) (20) to form the optically active *Z*-1-(3′,4′-dimethoxyphenyl)-1-propeneoxide [(−)-**6**] [($J_{2,3}$=4.1 Hz), $[\alpha]^{25}D$ −32°], uncontaminated with the trans isomer. Because *S*-halohydrins produce *S*-epoxides (14), this established the configuration of *cis*-(−)-**6** as (7*S*,8*R*).

A key step in this sequence was the somewhat conflicting regiospecific opening of (−)-**6** to produce exclusively the secondary alcohol (−)-**1** through an S_N2 mechanism. Based on literature precedents (20, 21–25), we selected the reaction conditions favoring attack to the less hindered oxide carbon. Thus, by reflux with an excess of sodium isoeugenoxide in an aprotic non-polar solvent (dioxane), compound (−)-**1**, $[\alpha]^{25}D$ −29°, ee 78% (estimated by its MTPA ester), was produced in 87% yield. Because the MTPA diastereomeric chemical shift differences observed for the methoxy group of the acid moiety were too small (3.49 and 3.44 ppm) to be accurately integrated, the ee was determined by ^{19}F-nmr where the α-CF_3 groups were clearly separated and clearly integrated (17,20).

The threo configuration of (−)-virolin **1** ($J_{7,8}$=8 Hz) (2,26,27) confirms the anti attack to the oxirane ring and permits prediction of its absolute stereochemistry as (7*S*,8*S*). The absolute configuration of (−)-**1** was confirmed through Mosher's method (17). The ^{1}H-nmr spectra showed that the aliphatic OMe signal of the *S*-MTPA ester of (−)-**1** appeared at higher field (3.44 ppm) than that of the *S*-MTPA ester of its enantiomer (3.49 ppm). This shift was produced by a selective shielding due to the 3,4-dimethoxyphenyl in the 8.0.4′ neolignan moiety of (−)-**1**. Application of the model proposed by Dale and Mosher (4,17) shows the absolute stereochemistry of the carbinolic

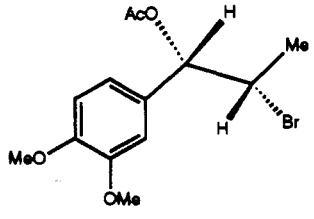


FIGURE 1. Enantiomer of **5** More Rapidly Hydrolyzed by *Rhizopus nigricans*.

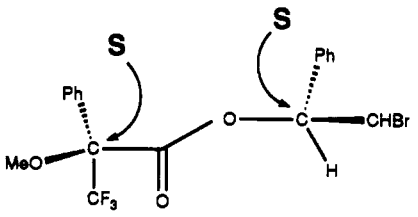


FIGURE 2. Configuration Model Proposed by Dale and Mosher for (*S*)-MTPA Ester of (+)-**5**.

carbon to be *S* and thus (−)-**1** must be (7*S*,8*S*), in agreement with the proposed synthetic pathway.

These results have shown that the enantioselective synthesis of (−)-virolin [**1**] is possible through the combined use of the highly diastereoselective borohydride reduction of a bromoketone and the enantioselective microbial hydrolysis of the corresponding bromoacetates. Furthermore, when alcohols require enrichment in the enantiomer not formed in the enzymatic hydrolysis, they can readily be prepared from the recovered acetate. This method offers additional synthetic possibilities, because, by selecting the appropriate starting materials, different chiral threo neolignans of the 8.0.4′ type can be obtained for structural and stereochemical studies.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were recorded on either a Beckman Acculab-8 spectrometer or a Bruker IFS-25 Ft-ir spectrometer, with polystyrene as the reference. The ^{1}H-, ^{13}C- and ^{19}F-nmr spectra were taken on a Bruker WP-80SY and a Bruker AC-200E at 80.13, 20.15, 75.39, 200, and 50 MHz, respectively. Chemical shifts are reported for $CDCl_3$ solutions in ppm positive downfield from TMS for ^{1}H and ^{13}C nmr and for internal $CFCl_3$ for ^{19}F nmr. Mass spectra were measured at 70 eV for electron impact (ei). Fragment ions (*m/z*) are given as a % of the most abundant peak. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter for solutions in a 1-dm cell.

1-(3′,4′-DIMETHOXYPHENYL)-2-BROMOPROPAN-1-OL [(±)-**3**].—Sodium borohydride (420 mg, 11.05 mmol) was added in small portions to a stirred, cooled (0°) solution of 1-(3′,4′-dimethoxyphenyl)-2-bromopropan-1-one [(±)-**2**] (1 g, 3.66 mmol) in MeOH (20 ml). The mixture was stirred 3 h at 0° and 1 h at room temperature. Water and a few drops of HOAc were then added and the mixture extracted with Et_2O (4×25 ml).

The combined Et_2O extracts were washed with saturated aqueous $NaHCO_3$ solution and H_2O, dried (Na_2SO_4), decanted and evaporated, yielding a (9:1) mixture of (±)-**3**, erythro:threo (875 mg, 87%).

Pure threo (±)-**3** (770 mg, 2.8 mmol) was obtained by prep. tlc (Si gel GF_{254}; hexane-EtOAc, 70:30); ir ν max 3485, 3078, 2970, 2908, 2841, 1680, 1419, 1335, 1233, 989, 813 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.55 (3H, d, J=6.4 Hz, H-9), 3.87 (3H, s, -OC*H*$_3$), 3.89 (3H, s, -OC*H*$_3$), 4.31 (1H, m, H-2), 4.57 (1H, d, J=8 Hz, H-7), 6.87 (3H, m, Ar*H*); ^{13}C nmr ($CDCl_3$) δ 21.15 (q, C-3), 55.44 (q, OCH_3 in C-3′, C-4′), 57.33 (d, C-2), 78.29 (d, C-1), 109.30 (d, C-2′), 110.64 (d, C-5′), 118.92 (d, C-6′), 132.03 (s, C-1′), 148.54 (s, C-3′ and C-4′); eims *m/z* [M]$^+$ 275 (10), 167 (100), 151 (10), 139 (79), 108 (24), 77 (40).

1-(3′,4′-DIMETHOXYPHENYL)-1-ACETOXYPROPANE [(±)-**4**].—A solution of (±)-**3** (700 mg, 2.54 mmol) in Ac_2O (5 ml) and pyridine (1 ml) was stirred at room temperature for 10 h. Water (20 ml) was added and the mixture was extracted with $CHCl_3$ (2×25 ml), washed with 10% $CuSO_4$ (3×25 ml) and H_2O, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by thick-layer chromatography on Si gel GF_{254} using hexane-EtOAc (9:1) as the eluent, to give 764 mg (2.41 mmol) of 1-(3′,4′-dimethoxyphenyl)-1-acetoxypropane [(±)-**4**] (95% yield); ir ν max 3010, 2960, 1755, 1530, 1480, 1250, 1145, 880, 820 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.51 (3H, d, J=7.2 Hz, H-3), 2.12 (3H, s, C*H*$_3$-C=O), 3.82, 3.89 (6H, s, OC*H*$_3$), 4.36 (1H, dq, H-2), 5.77 (1H, d, J=8 Hz, H-1), 6.79–6.91 (3H, m, Ar*H*); ^{13}C nmr ($CDCl_3$) δ 20.46 (C-3), 21.89 (*C*H$_3$-C=O), 50.27 (C-2), 55.27 (OCH_3), 78.70 (C-1), 109.58 (C-2′), 110.48 (C-5′), 119.36 (C-6′), 129.08 (C-1′), 148.43 (C-4′), 148.75 (C-3′), 168.94 (*C*=O); eims *m/z* [M]$^+$ 317 (39), 316 (41), 259 (48), 237 (12), 194 (91), 167 (100), 165 (37), 163 (40), 108 (10), 107 (27), 43 (72).

MICROBIAL HYDROLYSIS OF (±)-**4**.—A 1-liter Erlenmeyer flask containing 250 ml of the medium potato-dextrose (5) was inoculated with *R. nigricans* (ATCC 6227b) and shaken at 25° for 6–7 days until

growth of the mass of mycelium appeared to stop ([glc]=0). Compound (±)-**4** (635 mg, 2 mmol) was added as a liquid in 1 ml of THF and the mixture was shaken for 16 h. The medium and the mycelium were extracted thoroughly with EtOAc (3×50 ml) and the combined extracts were concentrated giving a mixture of bromoacetate and bromohydrin (50:50). Thick-layer chromatography of the mixture (530 mg) afforded 260 mg (0.82 mmol) of chiral (−)-bromoacetate **4**, $[\alpha]^{25}D$ −35° (*c*=1, $CHCl_3$) and 240 mg (0.87 mmol) of (+)-bromohydrin **5**, $[\alpha]^{25}D$ +31° (*c*=1, $CHCl_3$). Compound (+)-**5** was converted to its *S*-MTPA ester (4, 16–18) and shown to be 65% ee. Pure (+)-**5**, $[\alpha]^{25}D$ +31°, was reacetylated under the conditions described above and the acetate subjected to a new microbial hydrolysis. The ee of the bromohydrin (+)-**5**, $[\alpha]^{25}D$ +42°, now formed was 79% (based on its *S*-MTPA esters).

Z-1-(3′,4′-DIMETHOXYPHENYL)-PROPENEOXIDE [(−)-**6**].—A well-stirred solution of bromohydrin (+)-**5**, ee 79% (110 mg, 0.4 mmol) in C_6H_6 (5 ml) was treated with 5 ml of 3 M NaOH. After 8 h of stirring, the organic layer was separated, washed with H_2O, 10% HCl, and brine, and dried over Na_2SO_4. After removing solvent, (−)-**6** was obtained quantitatively (76 mg, 0.38 mmol); $[\alpha]^{25}D$ −32° (*c*=1, $CHCl_3$); ir *ν* max 3073, 2999, 2839, 1595, 1513, 1419, 1335, 1263, 1141 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.10 (3H, d, *J*=5 Hz, H-3), 3.31 (1H, dq, $J_{2,3}$= 5 Hz; $J_{2,1}$= 3.5 Hz, H-2), 3.85 (6H, s, OCH_3), 4.01 (1H, d, *J*=3.5 Hz, H-1), 6.85 (3H, m, Ar*H*); ^{13}C nmr ($CDCl_3$) δ 12.05 (C-3), 54.68 (C-2), 55.46 (OCH_3), 56.93 (C-1), 109.53 (C-2′), 110.77 (C-5′), 118.48 (C-6′), 127.7 (C-1′), 148.13 (C-3′), 148.40 (C-4′); eims *m/z* $[M]^+$ 196 (1), 195 (9), 194 (14), 167 (100), 139 (64), 137 (5), 57 (3).

(−)-*THREO*-1-(3,4-DIMETHOXYPHENYL)-2-(2′-METHOXY-4′(*E*)-PROPENYLPHENOXY)PROPAN-1-OL [**1**].—A 60 mg (0.30 mmol) quantity of (−)-**6**, 200 mg (1.07 mmol) of sodium isoeugenoxide and 5 ml of anhydrous dioxane were heated under reflux for 10 h. The reaction mixture was cooled, and cold H_2O and Et_2O were added. The ethereal layer was washed with 0.2 N NaOH and H_2O and dried over Na_2SO_4. Evaporation of the solvent under vacuum yielded regiospecifically 92 mg (0.26 mmol, 87%) of (−)-**1**, $[\alpha]^{25}D$ −29° (*c*=1, $CHCl_3$); ir *ν* max 3500, 2970, 1610, 1525, 1390, 1270, 1150, 1050 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.15 (3H, d, *J*=6.0 Hz, H-9), 1.86 (3H, d, *J*=5.5 Hz, H-9′), 3.87 (6H, s, 2×OCH_3), 3.90 (3H, s, OCH_3), 4.15 (1H, m, H-8), 4.63 (1H, d, *J*=8 Hz, H-7), 5.70–6.23 (1H, m, H-8′), 6.39 (1H, d, *J*=16.0 Hz, H-7′), 6.89 (6H, m, Ar*H*); ^{13}C nmr ($CDCl_3$) δ 16.4 (C-9), 17.9 (C-9′), 55.5 (C-3, C-3′, and C-5), 77.7 (C-7), 83.01 (C-8), 109.5 (C-2′), 110.7 (C-5), 110.9 (C-2), 118.3 (C-5′), 118.5 (C-6′), 119.5 (C-6), 124.3 (C-8′), 130.1 (C-7′), 132.9 (C-1′), 145.7 (C-4′), 147.8 (C-3), 148.0 (C-4), 149.6 (C-3′); eims *m/z* $[M]^+$ 358 (2), 195 (8), 194 (19), 167 (68), 165 (73), 164 (100), 149 (15), 139 (44), 121 (18), 91 (29), 77 (30). To confirm the regiospecificity of the reaction we converted (−)-**1** to the corresponding ketone with Jones reagent. Spectral data were coincident with those of racemic material reported in (2).

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