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STEREOSELECTIVE SYNTHESIS OF 8.0.4′ NEOLIGNANS: (±)-SURINAMENSIN AND (±)-VIROLIN

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Surinamensin (**1**) and virolin (**2**), the 8.0.4′-type of neolignans (1) corresponding to the *threo* series, have been isolated (2) from the leaves of *Virola surinamensis* (Rol.) Warb. Their presence in this plant has sparked considerable interest due to its strong activity against the penetration of cercaria of *Schistosoma mansoni* (2). It has also been reported that **1** showed antileukemic activity (3).

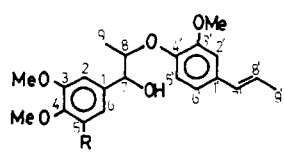
Because the reported syntheses (2, 4) of **1** and **2** afford the natural *threo* form in poor yield, we decided to study the stereoselective synthesis of these natural products by reduction of oxosurinamensin (**3**) and oxovirolin (**4**) prepared, in turn, by reaction of the bromoketones **5** and **6** with the sodium or potassium salt of isoeugenol, respectively (2, 5-7).

It is known that the reduction of ketones related to **3** and **4** with $NaBH_4$ in MeOH produces predominantly the *erythro* form (8-10). We have recently shown, in a similar system, that by using $NaBH_4$ in 2-propanol with 15-crown-5-ether, the *threo* isomer is obtained as the major product (11). In agreement with these observations, the reduction of **3** and **4** under the latter conditions afforded a (9:1) mixture of *threo* and *erythro* (±)-**1** and (±)-**2**. The sequence described above represents a substantial improvement in the stereoselective synthesis of these interesting natural products and makes them available for further biological studies.

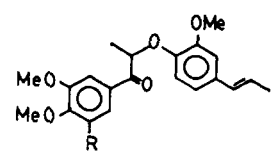
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on an Ernst Leitz hotstage microscope and are uncorrected. The ^1H nmr were recorded at 80.13 MHz and the ^{13}C-nmr spectra at 20.15 MHz in the Fourier transform mode and in $CDCl_3$ solutions. Chemical shifts are expressed on the TMS scale according to: $CDCl_3$+76.9 ppm. *J* values are given in Hz; tlc was done on silica gel GF 254.

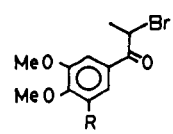
1-(3,4,5-TRIMETHOXYPHENYL)-2-(2′-METHOXY-4′-(*E*)-PROPENYLPHENOXY) PROPAN-1-ONE (**3**).—The sodium salt of (*E*)-isoeugenol (266 mg) was added to a stirred solution of 1-(3,4,5-trimethoxyphenyl)-2-bromo propan-1-one (**5**), prepared according to published procedures (5, 6), (333 mg) in dry DMF (7 ml). After being stirred for 18 h, the mixture was diluted with H_2O (7 ml) and extracted with Et_2O (2×15 ml). The combined Et_2O extracts were washed with 0.2 N NaOH and H_2O, dried over anhydrous Na_2SO_4, and the solvent was then removed under vacuum. The residue was purified by preparative tlc (silica gel GF 254 in hexane-EtOAc, 80:20), giving **3** (291 mg,



1 R=OMe
2 R=H



3 R=OMe
4 R=H



5 R=OMe
6 R=H

69% yield) as a crystalline product mp 97-99° [lit. 100.3-100.6° (2)]; ^{1}H nmr ($CDCl_3$) δ 1.71 (3H, d, J=7.0, H-9), 1.83 (3H, d, J=6.0, H-9′), 3.83, 3.88, 3.91 (12H, s, 4×OMe), 5.34 (1H, q, J=6.0, H-8), 5.80-6.40 (2H, m, H-7′ and H-8′), 6.76-7.46 (5H, m, ArH); ms *m/z* 386 (M^+, 4%), 195 (100), 191 (35), 164 (33), 163 (32), 107 (24), 91 (26), 77 (23).

(±)-*THREO*-1-(3, 4, 5-TRIMETHOXYPHENYL)-2-(2′-METHOXY-4′-(*E*)-PROPENYLPHENOXY) PROPAN-1-OL (**1**).—A solution of $NaBH_4$ (31.17 mg) in dry 2-propanol (3 ml) was added to a stirred solution of 15-crown-5 ether (220 mg) in dry 2-propanol (2 ml); after 6 h, a solution of ketone **3** (105 mg) in dry MeOH (1.5 ml) was added, the mixture was then stirred for 2 h at room temperature, and H_2O and a few drops of HOAc were then added, and the mixture was extracted with Et_2O (4×10 ml). The combined Et_2O extracts were washed with a saturated aqueous solution of $NaHCO_3$ and H_2O, dried (Na_2SO_4), decanted and evaporated, affording **1** as a (9:1) mixture of *threo/erythro*. Pure **1** (77.2 mg, 72.56% yield) was obtained by preparative tlc [silica gel GF 254 in hexane-EtOAc (80:20)]; ir υ max (film) 3500, 2920, 1601, 1470, 1420, 1330, 1265, 1140, 1040 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.20 (3H, d, J=6.0, H-9), 1.88 (3H, d, J=5.5, H-9′), 3.82, 3.85, 3.90 (12H, 4×OMe), 4.15 (1H, m, H-8), 4.61 (1H, d, J=8.0, H-7), 5.62-6.23 (1H, m, H-8′), 6.39 (1H, d, J=16.0, H-7′), 6.62 (2H, s, H-2 and H-6), 6.89 (3H, m, H-3′, H-5′ and H-6′); ^{13}C nmr ($CDCl_3$) 16.8 (q, C-9), 18.1 (q, C-9′), 55.5 (q, C-3′, OCH_3), 55.9 (q, C-3 and C-5, OCH_3), 60.5 (q, C-4, OCH_3), 78.3 (d, C-7), 83.4 (d, C-8), 104.2 (d, C-2 and C-6), 109.1 (d, C-2′), 118.5 (d, C-5′), 118.7 (d, C-6′), 124.6 (d, C-8′), 130.2 (d, C-7′), 133.3 (s, C-1′), 135.5 (s, C-4).

1-(3,4-DIMETHOXYPHENYL)-2-(2′-METHOXY-4′-(*E*)-PROPENYLPHENOXY) PROPAN-1-ONE (**4**). —(*E*)-Isoeugenol (0.74 ml), dry K_2CO_3 (1.7 g), and 1-(3,4 dimethoxyphenyl)-2-bromo propan-1-one (**6**) (800 mg), prepared according to published procedures (5), were heated under reflux with stirring in dry butanone (16 ml) for 48 h. The solution was cooled, diluted with H_2O (20 ml), acidified, and extracted with Et_2O 2×50 ml). The combined Et_2O extracts were washed with 1% NaOH (1×50 ml), H_2O (2×50 ml), dried (Na_2SO_4) and concentrated to dryness. Crystallization of the crude product from MeOH yielded pure ketone **4** (632 mg, 60.6% yield) mp 120-123° [lit. 123-125° (2)]; ^{1}H nmr ($CDCl_3$) δ 1.70 (3H, d, J=6.0, H-9), 1.83 (3H, d, J=6.0, H-9′), 3.84, 3.91, 3.92 (9H, s, 3×OMe), 5.39 (1H, q, J=6.0, H-8), 5.80-6.40 (2H, m, H-7′ and H-8′), 6.73-7.86 (6H, m, ArH); ms *m/z* 356 (M^+, 2%), 191 (15), 165 (100), 137 (9), 107 (8), 91 (18), 77 (27).

(±)-*THREO*-1-(3,4-DIMETHOXYPHENYL)-2-(2′-METHOXY-4′-(*E*)-PROPENYLPHENOXY)PROPAN-1-OL (**2**).—A solution of $NaBH_4$ (110 mg) in dry 2-propanol (12.5 ml) was added to a stirred solution of 15-crown-5 ether (792 mg) in dry 2-propanol (6 ml); after 6 h, a solution of ketone **4** (356 mg) in dry MeOH (5.5 ml) was added, and the mixture was then stirred for 2 h at room temperature. Water and a few drops of HOAc were then added and the mixture was extracted with Et_2O (4×30 ml). The combined Et_2O extracts were washed with a saturated aqueous solution of $NaHCO_3$ and H_2O, dried (Na_2SO_4), decanted and evaporated, affording **2** as a (9:1) mixture of *threo/erythro*. Pure **2** (268 mg, 75% yield) was obtained by preparative tlc [silica gel GF 254 in hexane-EtOAc (80:20)]; ir υ max (film) 3500, 2970, 1610, 1525, 1390, 1270, 1150, 1050 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.15 (3H, d, J=6.0, H-9), 1.86 (3H, d, J=5.5, H-9′), 3.87 (6H, s, 2×OMe), 3.90 (3H, s, 1×OMe), 4.15 (1H, m, H-8), 4.63 (1H, d, J=8.0, H-7), 5.70-6.23 (1H, m, H-8′), 6.39 (1H, d, J=16.0, H-7′), 6.89 (6H, m, ArH); ^{13}C nmr ($CDCl_3$) 16.4 (q, C-9), 17.9 (q, C-9′), 55.5 (q, C-3, C-3′ and C-5), 77.7 (d, C-7), 83.01 (d, C-8), 109.5 (d, C-2′), 110.7 (d, C-5), 110.9 (d, C-2), 118.3 (d, C-5′), 118.5 (d, C-6′), 119.5 (d, C-6), 124.3, (d, C-8′), 130.1 (d, C-7′), 132.9 (s, C-1′), 145.7 (s, C-4′), 147.8 (s, C-3), 148 (s, C-4), 149.6 (s, C-3′); ms *m/z* 358 (M^+, 2%), 195 (8), 194 (19), 167 (68), 165 (73), 164 (100), 149 (15), 139 (44), 121 (18), 91 (29), 77 (30).

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