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Transformation of 2,3-Dibenzylbutyrolactone Lignans containing a Secondary Hydroxyl Group to Phenyltetralin Lignans and Their Reduction Products with Lithium Aluminum Hydride

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Two 2,3-dibenzylbutyrolactone lignans containing a secondary hydroxyl group at one of the benzylic positions, 5-hydroxyarctigenin (I) and 5-hydroxytrachelogenin (XI), were transformed to phenyltetralin lignans, α-conidendrin monomethyl ether (II) and 3-hydroxy-α-conidendrin monomethyl ether (XII), respectively, by acid treatment.

The hemiacetal lignan, (1*S*,2*R*,3*S*,3a*R*) 6,7-dimethoxy-3-hydroxy-2-hydroxymethyl-1-3′,4′-dimethoxyphenyl-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactol (XV), was obtained in addition to isoolivil dimethyl ether (XIV), the normal reduction product, when 3-hydroxy-α-conidendrin dimethyl ether (XIII) was treated with lithium aluminum hydride, and a mechanism is proposed for this reaction.

Keywords——lignans; 5-hydroxyarctigenin; 5-hydroxytrachelogenin; transformation to phenyltetralin lignans; reduction with $LiAlH_4$; stereospecific hemiacetal lignan; reaction mechanism

In a previous paper,[1] we reported the stereospecific introduction of an alcoholic hydroxyl group at the C-5 position of 2,3-dibenzylbutyrolactone lignans with lead tetraacetate.

This paper deals with the transformation of two 2,3-dibenzylbutyrolactone lignans containing a secondary hydroxyl group, 5-hydroxyarctigenin (I) and 5-hydroxytrachelogenin (XI),[1] to phenyltetralin lignans, α-conidendrin monomethyl ether (II) and 3-hydroxy-α-conidendrin monomethyl ether (XII), respectively, and describes an investigation of the reduction products of the methyl ethers (III and XIII) of compounds II and XII with lithium aluminum hydride.

Compound I was transformed to compound II, mp 244—247 °C, $[\alpha]_D^{23}$ −52.3 ° (chloroform), by acid treatment. This reaction is similar to the well known stereospecific acid-catalyzed conversion of hydroxymatairesinol to α-conidendrin.[2] Methylation of II with diazomethane gave compound III, mp 173—176 °C, $[\alpha]_D^{23}$ −114.2 ° (chloroform), which was identical with authentic natural α-conidendrin dimethyl ether.[3]

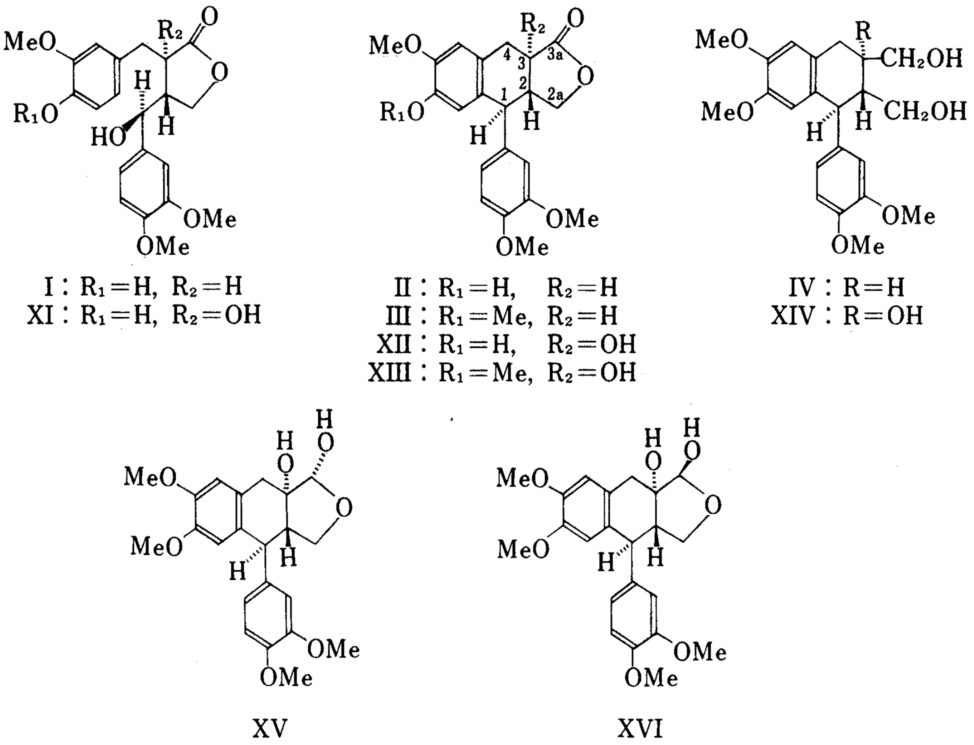

Chart 1

The reduction product of III with lithium aluminum hydride in tetrahydrofuran showed only one spot of *Rf* 0.11 on thin layer chromatography (TLC) using chloroform–ethyl acetate (1: 1) as a developing solvent.

Purification by preparative TLC afforded compound IV, mp 180.5—182 °C, $[\alpha]_D^{22}$ +12.9 ° (chloroform), which was identical with authentic natural isolariciresinol dimethyl ether (IV).[4]

Compound XI was transformed to compound XII, mp 138—140 °C, $[\alpha]_D^{23}$ −106.0 ° (chloroform), by acid treatment. Methylation of XII with diazomethane gave compound XIII, mp 162—163.5 °C, $[\alpha]_D^{23}$ −100.1° (chloroform).

The circular dichroism (CD) curves of XII and XIII showed a negative Cotton effect at around 284 nm, as in the case of III, whose stereostructure is established, indicating the configurations of XII and XIII to be 1*S*, 2*R*, 3*S*.

The reduction products of XIII with lithium aluminum hydride in tetrahydrofuran showed two spots of *Rf* 0.09 and *Rf* 0.15 on TLC using chloroform–ethyl acetate (1: 1) as a developing solvent. Purification by preparative TLC afforded compound XIV, mp 182—184 °C, $[\alpha]_D^{20}$ +38.9° (chloroform), and compound XV, mp 115—118 °C, $[\alpha]_D^{20}$ +40.9° (chloroform), in a 1: 2 ratio. XIV was identical with authentic natural isoolivil dimethyl ether.[5]

The proton nuclear magnetic resonance (PMR) spectrum of XV exhibited a C_{3a}-proton signal at δ 5.32 (1H, s) and showed a close resemblance to that of (+)-africanal dimethyl ether (XVI) isolated from *Olea africana*[6] except for the chemical shift (δ 6.68 in XVI) assigned to the C_{3a}-proton.[7]

The similarity of the Cotton effect of XV to that of XVI indicated that XV has the same absolute configuration at the C-1 position as XVI.[7]

Further, the reduction of XV over a platinum oxide catalyst gave isoolivil dimethyl ether (XIV), as in the case of XVI.

Thus, it was concluded that XV is a stereoisomer of XVI at the C-3a position.

The absolute structure of XV was established as (1*S*, 2*R*, 3*S*, 3a*R*) 6,7-dimethoxy-3-hydroxy-2-hydroxymethyl-1-3′,4′-dimethoxyphenyl-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactol.

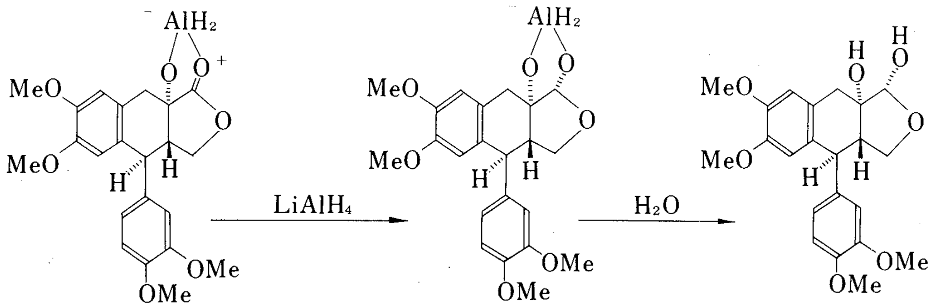

Chart 2

The reaction mechanism was proposed to be as shown in Chart 2.

That is, the reduction occurred stereoselectively to the *cis* diol *via* chelation of aluminum between the carboxyl and α-hydroxyl groups.

This is an interesting example of the stereospecific reduction of a butyrolactone lignan containing an α-hydroxyl group with lithium aluminum hydride to afford the hemiacetal product, presumably *via* the chelation of aluminum.

In addition, this is the first report of compounds II, XII, XIII and XV as optically active phenyltetralin lignans unknown in nature.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected.

The following instruments were used: optical rotation values, Yanagimoto OR-10; UV spectra, Shimadzu IR-400; PMR spectra, Jeol JNM-PMX 60, Jeol JNM-FX 100 with tetramethylsilane ($\delta=0$) as an internal reference; mass spectra, Hitachi MRU-7M at 70 eV using a direct sample inlet into the ion source in all cases; CD curves, Jasco J-40.

Precoated TLC plates, silica gel 60$_{F\text{-}254}$ (Merck), were used for TLC and preparative TLC. The spots were detected by spraying the plates with 10% H_2SO_4 soln. and heating.

The abbreviations used are as follows: sh, shoulder; s, singlet; q, quartet; m, multiplet; br, broad; br.s, broad singlet.

α-Conidendrin Monomethyl Ether (II)——5-Hydroxyarctigenin (I) (80 mg) was treated with hydrochloric acid in acetic acid at room temperature.

The cyclization product was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) and recrystallized from EtOH to afford colorless needles of II (57.2 mg). mp 244—247°C. $[\alpha]_D^{23}$ $-52.3°$ ($c=0.6$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 230 (4.24) sh, 283 (3.86). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1790 (CO), 1610, 1590, 1520 (arom. C=C). CD ($c=2.997\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): +2.27 (242.5), +2.53 (265), −11.34 (285). MS: Calcd for $C_{21}H_{22}O_6$, 370.1417. Obsd., 370.1407. PMR ($CDCl_3$) δ: 2.30—2.83 (2H, m, $C_{2,3}$–H), 2.93—3.30 (2H, m, C_4–H), 3.80, 3.87 (9H, each s, $3\times CH_3O$), 3.93—4.30 (3H, m, $C_{1,2a}$–H), 5.30—5.60 (1H, br, OH, quenched by addition of D_2O), 6.43 (1H, s, arom.H), 6.57—7.00 (4H, m, arom.H).

α-Conidendrin Dimethyl Ether (III)——Compound II (50 mg) was methylated with diazomethane in the usual way. The methylation product was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) and recrystallized from EtOH to afford colorless needles of III (36.3 mg). mp 173—176°C. $[\alpha]_D^{23}$ $-114.2°$ ($c=0.38$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 233 (4.21) sh, 282 (3.82). IR ν_{max}^{KBr} cm^{-1}: 1780 (CO), 1615, 1600, 1520 (arom. C=C). CD ($c=2.836\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): +6.70 (237.5), +1.83 (260), −13.61 (282.5). MS: Calcd for $C_{22}H_{24}O_6$, 384.1570. Obsd., 384.1551. PMR ($CDCl_3$) δ: 2.23—2.87 (2H, m, $C_{2,3}$–H), 2.97—3.30 (2H, m, C_4–H), 3.60 (3H, s, $1\times CH_3O$), 3.80, 3.90 (9H, each s, $3\times CH_3O$), 3.97—4.37 (3H, m, $C_{1,2a}$–H), 6.33 (1H, s, arom.H), 6.50—6.97 (4H, m, arom.H).

II was identical with authentic natural α-condendrin dimethyl ether in all respects.

Reduction of α-Conidendrin Dimethyl Ether (III) with $LiAlH_4$——A solution of III (30 mg) in tetrahydrofuran (THF) (2 ml) was added dropwise to a suspension of $LiAlH_4$ (30 mg) in THF (2 ml). The mixture was stirred for 4 h at room temperature and then poured into ice-cold water. The whole was carefully acidified with 10% H_2SO_4 soln. and extracted with Et_2O. The Et_2O soln. was washed with water and concentrated *in vacuo*.

The residue showed only one spot of *Rf* 0.11 on TLC using $CHCl_3$–AcOEt (1: 1). Purification was achieved by preparative TLC.

Recrystallization from EtOH afforded colorless needles of IV (19.7 mg). mp 180.5—182°C. $[\alpha]_D^{22}$ $+12.9°$ ($c=0.72$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 232 (4.14), 282 (3.77). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1610, 1590, 1510 (arom. C=C). CD ($c=4.788\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): +7.46 (240), +5.32 (265.5), −8.14 (286.5). MS: Calcd for $C_{22}H_{28}O_6$, 388.1884. Obsd., 388.1892.

IV was identical with authentic natural isolariciresinol dimethyl ether.

3-Hydroxy-α-conidendrin Monomethyl Ether (XII)——5-Hydroxytrachelogenin (XI) (60 mg) was treated with hydrochloric acid in acetic acid at room temperature.

The cyclization product was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) and recrystallized from EtOH to afford colorless needles of XII (43.4 mg). mp 138—140°C. $[\alpha]^{23}_{D}$ $-106.0°$ ($c=0.1$ in $CHCl_3$). UV λ^{EtOH}_{max} nm (log ε): 227 (4.16) sh, 282 (3.76). IR ν^{KBr}_{max} cm^{-1}: 3425 (OH), 1765 (CO), 1590, 1510 (arom. C=C). CD ($c=2.823\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): -2.94 (237.5), $+1.76$ (260), -9.69 (285). MS: Calcd for $C_{21}H_{22}O_7$, 386.1363. Obsd., 386.1363. PMR ($CDCl_3$) δ: 2.27—2.83 (1H, m, C_2–H), 2.60 (1H, br, OH, quenched by addition of D_2O), 3.17 (2H, br.s, C_4–H), 3.83, 3.90 (9H, each s, $3\times CH_3O$), 4.00—4.57 (3H, m, $C_{1,2a}$–H), 5.23—5.67 (1H, br, OH, quenched by addition of D_2O), 6.43 (1H, s, arom.H), 6.60—6.93 (4H, m, arom.H).

3-Hydroxy-α-conidendrin Dimethyl Ether (XIII)——Compound XII (40 mg) was methylated with diazomethane in the usual way.

The methylation product was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) and recrystallized from EtOH to afford fine colorless needles of XIII (35.6 mg). mp 162—163.5°C. $[\alpha]^{23}_{D}$ $-100.1°$ ($c=0.21$ in $CHCl_3$). UV λ^{EtOH}_{max} nm (log ε): 230 (4.12) sh, 282 (3.70). IR ν^{KBr}_{max} cm^{-1}: 3450 (OH), 1680 (CO), 1610, 1590, 1515 (arom. C=C). CD ($c=3.122\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): $+4.61$ (235), $+0.77$ (257.5), -15.38 (282.5). MS: Calcd for $C_{22}H_{24}O_7$, 400.1520. Obsd., 400.1520. PMR ($CDCl_3$) δ: 2.07—2.77 (1H, m, C_2–H), 2.40 (1H, br, OH, quenched by addition of D_2O), 3.17 (2H, br.s, C_4–H), 3.63 (3H, s, $1\times CH_3O$), 3.80, 3.90 (9H, each s, $3\times CH_3O$), 3.97—4.47 (3H, m, $C_{1,2a}$–H), 6.37 (1H, s, arom.H), 6.57—7.07 (4H, m, arom.H).

Reduction of 3-Hydroxy-α-conidendrin Dimethyl Ether (XIII) with $LiAlH_4$——A solution of XIII (30 mg) in THF (2 ml) was added dropwise to a suspension of $LiAlH_4$ (30 mg) in THF (2 ml).

The mixture was stirred for 4 h at room temperature and then poured into ice-cold water. The whole was carefully acidified with 10% H_2SO_4 soln. and extracted with Et_2O. The Et_2O soln. was washed with water and concentrated *in vacuo*.

The residue showed two spots of *Rf* 0.09 and *Rf* 0.15 on TLC using $CHCl_3$–AcOEt (1: 1).

Purification by preparative TLC afforded compound XIV and compound XV in a 1: 2 ratio.

Isoolivil Dimethyl Ether (XIV)——Colorless needles from EtOH. mp 182—184°C. $[\alpha]^{20}_{D}$ $+38.9°$ ($c=1.0$ in $CHCl_3$). UV λ^{EtOH}_{max} nm (log ε): 231 (4.19) sh, 282 (3.82). IR ν^{KBr}_{max} cm^{-1}: 3275 (OH), 1600, 1590, 1510 (arom. C=C). CD ($c=2.589\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): $+23.16$ (235), $+5.94$ (265), -12.97 (287.5). MS: Calcd for $C_{22}H_{28}O_7$, 404.1833. Obsd., 404.1830.

XIV was identical with authentic natural isoolivil dimethyl ether.

6,7-Dimethoxy-3-hydroxy-2-hydroxymethyl-1-3′,4′-dimethoxyphenyl-1,2,3,4-tetrahydronaphthalene-3-carboxylic Acid Lactol (XV)——Colorless needles from EtOH. mp 115—118°C. $[\alpha]^{20}_{D}$ $+40.9°$ ($c=0.5$ in $CHCl_3$). UV λ^{EtOH}_{max} nm (log ε): 231 (4.20) sh, 282 (3.81). IR ν^{KBr}_{max} cm^{-1}: 3400 (OH), 1605, 1590, 1515 (arom. C=C). CD ($c=1.940\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): $+14.15$ (235), $+5.40$ (265), -17.88 (285). MS: Calcd for $C_{22}H_{26}O_7$, 402.1677. Obsd., 402.1677. PMR ($CDCl_3$) δ: 2.20—2.72 (1H, m, C_2–H), 2.64 (2H, br, $2\times$OH, quenched by addition of D_2O), 2.80—3.28 (2H, AB quartet, δ_A 2.92, δ_B 3.12, $J_{AB}=16$ Hz, C_4–H), 3.60 (3H, s, $1\times CH_3O$), 3.80, 3.84, 3.88 (9H, each s, $3\times CH_3O$), 3.24—4.16 (3H, m, $C_{1,2a}$–H), 5.32 (1H, s, C_{3a}–H), 6.32 (1H, s, arom.H), 6.52—6.92 (4H, m, arom.H).

Reduction of 6,7-Dimethoxy-3-hydroxy-2-hydroxymethyl-1-3′,4′-dimethoxyphenyl-1,2,3,4-tetrahydronaphthalene-3-carboxylic Acid Lactol (XV) over PtO_2 Catalyst——A solution of 10 mg of XV in EtOH was reduced over PtO_2 catalyst in the usual way.

Recrystallization of the reduction product from EtOH gave colorless needles, which were identical with authentic isoolivil dimethyl ether.

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