Articles

Regioselective Cleavage of the Methylenedioxy Group: Conversion of (-)-Austrobailignan-5 to (-)-Dihydroguaiaretic Acid

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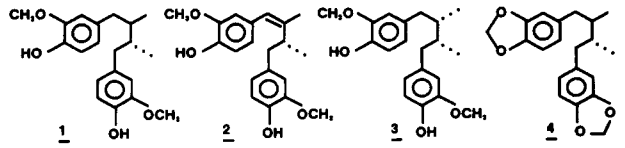
A method for the selective cleavage of a benzodioxole (methylenedioxy group) to a methoxyphenol through the use of a *p*-methylthiophenoxide ion is described. When the procedure was applied to a lignan derivative such as (-)-austrobailignan-5, the reaction was found to proceed regioselectively, and the intermediate thiacetal could be converted to a catechol, or manipulated to yield either one of the two possible methoxyphenols. Of the two isomers, the one with the bis 3-methoxy-4-hydroxy substitution was found to be identical with (-)-dihydroguaiaretic acid, isolated for the first time from the plant *Saururus cernuus*.

We isolated a phenolic lignan from the extract of *Saururus cernuus* and idenfitied it as (-)-dihydroguaiaretic acid, **1**. This compound was prepared by Schroeter[1] et al. in 1918 from (-)-guaiaretic acid (**2**) by reduction, followed by separation from the meso isomer **3**. The meso form has since been isolated from the guaiacum resin,[2] but reports of the isolation of the (-) form were never substantiated.[3] Thus, the present isolation of **1** is a significant results in lignan chemistry.

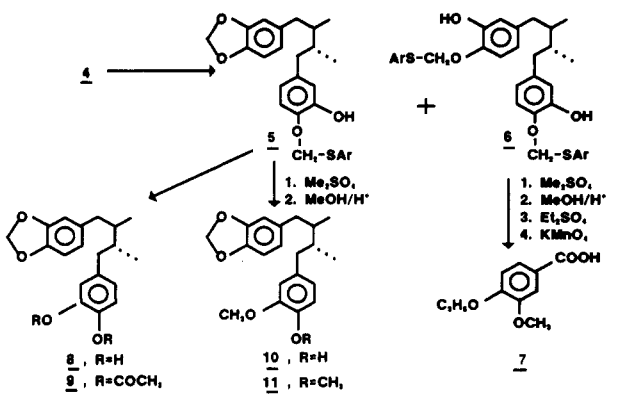


To confirm the relative configuration of **1**, it was felt that its synthesis from a related lignan, (-)-austrobailignan-5,[4,5] **4**, also a constituent of the same plant, through a partial cleavage of the methylendioxy units to methoxyphenol groups in a regioselective manner would be desirable.

Although such conversions were effected earlier using a strong base at high temperatures[6] or prolonged heating with Pd/C (unpublished results), these reactions were found to be not suitable for preparative purposes.

The use of sodium thioethoxide in dimethylformamide (DMF) has been reported to cleave the methylenedioxy groups of 1,3-benzodioxole to yield the corresponding *o*-hydroxyphenoxy methyl sulfide as an intermediate, which on treatment with acid gave the catechol in good yield.[7] In this paper, we report *either* partial cleavage to *o*-methoxyphenols *or* complete cleavage to catechols, as well as a method for preparing the two possible isomeric *o*-methoxyphenols. The reagent selected is an aromatic thiol such as *p*-thiocresol, which is much less offensive than ethanethiol to work with. It is also more convenient to weigh the proper stoichiometric amounts of the reagent for selective reaction when more than one group is present.

Scheme I



Reaction of **4** with thiocresol and sodium hydride in a molar ratio of 3:16:40 in DMF at reflux temperature for 1 h gave **5** and **6** in a ratio of 5:1. With the use of twice the amounts of the two reagents, the product ratio of **5** and **6** was 1:4. In order to ascertain the direction of the cleavage, **6** was subjected to the reaction sequence shown in Scheme I, and the resulting product, *O*-ethylvanillic acid (**7**), identified by direct comparison with an authentic sample. This proved the direction of cleavage to be such that the phenolic group was meta to the point of the carbon chain.

Gentle acid hydrolysis of **5** gave the catechol **8** from which the diacetate **9** was prepared. Methylation of **5**, followed by acid hydrolysis, gave **10** from which, by further methylation, **11** was prepared.

The physical and spectral properties of **10** were found to be identical with those reported for austrobailignan-6 previously isolated from *Austrobaileya scandens*,[4] and the properties of **11** agreed similarly with those described for the methyl ether of austrobailignan-6 prepared by Murphy[4] et al. The optically active compounds **8**, **9**, and **11** are described here for the first time.

The intermediate **6** in a similar manner was converted by hydrolysis to nordihydroguaiaretic acid **12** and subsequently to the tetraacetate **13** or the tetramethyl ether **14**

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(2) Schrecker, A. W. *J. Am. Chem. Soc.* **1957**, *79*, 3823-3827.
(3) Rao, C. B. S., Eds. *Chemistry of Lignans*; Andhra University Press: 1978; p 74.
(4) Murphy, S. T.; Ritchie, E.; Taylor, W. C. *Austr. J. Chem.* **1975**, *28*, 81-90.
(5) Rao, K. V.; Alvarez, F. M. *J. Nat. Prod.* **1982**, *45*, 393-397.
(6) Hughes, G. K.; Ritchie, E. *Austr. J. Chem.* **1954**, *7*, 104-112.
(7) Feutrill, G. I.; Mirrington, R. N. *Austr. J. Chem.* **1972**, *25*, 1731-1735.

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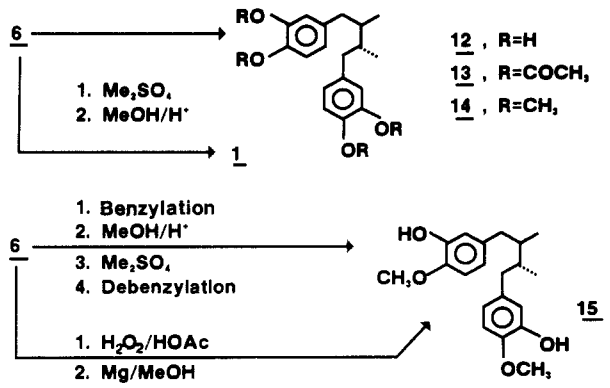
Scheme II



(Scheme II). Methylation of **6** first and then hydrolysis gave **1**, identical with (−)-dihydroguaiaretic acid isolated from *Saururus cernuus*, which proved the relative configuration of **1**.

Although, as seen in the preceding section, the ring opening is almost exclusively proceeding in one direction, it has been possible to prepare the isomeric methoxy phenols also, through the use of one of the following alternatives. One involved benzylation of the intermediate such as **5** or **6** followed by acid hydrolysis, methylation, and debenzylation as illustrated in the conversion of **6** to **15**. A much simpler alternative was also found by which the intermediate **6** is first oxidized with hydrogen peroxide in acetic acid to the corresponding sulfone and the product treated with magnesium in methanol, to reductively eliminate the arylsulfone functions, somewhat analogously to the procedure described by Brown and Carpino.[8] These authors found that a 1,2-bisphenyl sulfone system could be converted to a mixture of the corresponding ethylene (62%) and the ethane (21%) derivatives. In the present case, reductive desulfonation occurred almost exclusively (80%) to yield the methoxyl functions.

Compound **15** has not been isolated from natural sources, nor has it been synthesized so far. It is evident from the foregoing discussion that cleavage of methylenedioxy groups by methods outlined here can generate either of the two isomeric methoxyphenols in good yields. Also, where the starting material is chiral, this method offers the best way to obtain chiral methoxyphenols.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The following instrumentation was used for the spectra recorded here: UV, Perkin Elmer Lambda 3B; IR, Beckman Aculab 3; NMR, Varian EM390 with tetramethylsilane as internal standard; optical rotations, Perkin-Elmer 141; and mass spectra, Kratos MS80 RFA. Column chromatography was performed using silica gel (Merck 100–200 mesh) and thin-layer chromatography (TLC) using silica gel (Merck H60-P254/366).

Isolation of (−)-Dihydroguaiaretic Acid 1. Dried and coarsely ground leaves and twigs of *Saururus cernuus* (plant identified at the herbarium of the University of Floride where a voucher sample has been deposited no. FLAS 170066) (10 kg) was extracted with ethanol at 20 °C for 3 days, and this extract and two other similarly prepared extracts were combined and concentrated to a syrup (1 L). It was extracted three times with chloroform (1 L each). The combined solvent layers were concentrated to an oil, which was taken up in 1 L of benzene/ligroin (1:1) and washed three times with 50% aqueous methanolic NaOH (0.1 N). The combined basic layer was concentrated to remove the methanol, acidified, and extracted two times with benzene (200 mL each). The concentrated benzene extract was subjected to chromatography on silica gel (100 g) in benzene. The eluant was gradually changed to 10% acetone in benzene. Fractions collected with 2–4% acetone in benzene contained a mixture of **1** and the lignan guaiacin.[5] The mixture was set aside in 1 N KOH for 2 days, whereby a crystalline precipitate formed which was filtered and washed with dilute aqueous KOH and water. It was dissolved in water and acidified, and the free phenol was filtered and crystallized from ether/ligroin: yield, 1 g; mp 87–88 °C; $[\alpha]_D$ −46° (1%, $CHCl_3$); ^1H NMR δ 0.80 (d, J = 6 Hz, 2 $CHCH_3$), 1.70 (m, 2 $CHCH_3$), 2.45 (m, 2 $ArCH_2$), 3.80, 3.85 (2 s, 2 OCH_3), 5.55 (br s, D_2O-exchangeable, O*H*), 6.40–6.85 (m, 6 ArH); MS 330 (M^+, 18), 137 (100). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.60; H, 7.93. Found: C, 72.66; H, 7.89.

Acetate of 1. A mixture of **1** (0.1 g), acetic anhydride (2 mL), and pyridine (0.5 mL) was heated at 100 °C for 30 min. It was cooled and diluted with water (10 mL), and the solid was filtered and crystallized from ether: mp 94–95 °C; yield, 0.1 g; $[\alpha]_D$ −20.4°; ^1H NMR δ 0.86 (d, J = 6 H, $2CHCH_3$), 1.80 (m, $2CHCH_3$), 2.3 (s, 2 CH_3COO), 2.53 (m, 2 $ArCH_2$), 3.75 (s, 2 OCH_3), 6.5–6.96 (m, 6 ArH). Anal. Calcd for $C_{24}H_{30}O_6$: C, 66.37; H, 6.43. Found: C, 66.38; H, 6.48.

Preparation of 5 and 6. A mixture of **4** (1 g), *p*-thiocresol (2 g), and NaH (1 g) in DMF (30 mL) was boiled under reflux for 1 h. It was cooled, diluted with water (100 mL), neutralized with HCl, and extracted with C_6H_6 (3 × 100 mL). The combined solvent layer was washed with water, dried (Na_2SO_2), and concentrated to an oil, which was applied to a silica gel column (40 g) in 1:1 C_6H_6–hexane. After the excess reagent was eluted, the solvent was changed to C_6H_6, which brought out **5**, recovered by concentration of the appropriate fractions to a viscous oil (1.1 g). Continued elution with 2% acetone in benzene gave **6**, which was recovered as a viscous oil (0.27 g).

When the reaction was carried out using **1** (1 g), thiocresol (4 g), and NaH (2 g), the product mixture contained **6** (1.4 g) and **5** (0.35 g).

Compound **5**: ^1H NMR δ 0.80 (d, J = 6 Hz, 2 $CHCH_3$), 1.80 (m, 2 $CHCH_3$), 2.3 (s, Ar CH_3), 2.45 (m, 2 $ArCH_2$), 5.38 (s, OCH_2SAr), 5.83 (s, OCH_2O), 6.5–6.9 (m, 6 ArH), 7.05–7.50 (4 ArH). Anal. Calcd for $C_{27}H_{30}O_4S$: C, 72.00; H, 6.66; S, 7.11. Found: C, 71.90; H, 6.76; S, 6.98.

Compound **6**: ^1H NMR δ 0.80 (d, J = 6 Hz, 2 $CHCH_3$), 1.80 (m, 2 $CHCH_3$), 2.31 (s, $ArCH_3$), 2.45 (m, 2 $ArCH_2$), 5.40 (br s, 2 OCH_2SAr), 6.5–6.95 (m, 6 ArH), 7.0–7.50 (m, 8 ArH). Anal. Calcd for $C_{34}H_{38}O_4S_2$: C, 71.08; H, 6.62; S, 11.14. Found: C, 71.13; H, 6.67; S, 11.15.

Preparation of 8 and 9. A solution of **5** (0.95 g) in MeOH–HCl (1 N, 25 mL) was boiled under reflux for $^1/_2$ h, by which time the reaction was complete (TLC). After dilution with water (80 mL) and extraction with benzene, the solvent extract was concentrated to an oil and chromatographed on SiO_2 gel (30 g) in 1:1 C_6H_6–hexane. The product **8** appeared when the column was eluted with 5% acetone in C_6H_6. Concentration of the appropriate fractions gave **8** as a colorless oil (0.45 g). It was acetylated by letting it stand in acetic anhydride (4 mL) and pyridine (1 mL) at 20 °C for 8 h. The acetate was recovered after addition of water, acidification, extraction with ether, washing of the extract with aqueous $NaHCO_3$, and concentration of the extract. The acetate **9** was also an oil.

Compound **9**: ^1H NMR δ 0.80 (d, J = 6 Hz, 2 $CHCH_3$), 1.80 (m, 2 $CHCH_3$), 2.30 (s, 2 CH_3COO), 2.50 (m, 2 $ArCH_2$), 5.95 (s, OCH_2O), 6.5–7.2 (m, 6 ArH). Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.21; H, 6.58.

Preparation of 10 and 11. A mixture of **5** (1.8 g), methyl sulfate (2 mL), and anhydrous K_2CO_3 in acetone (50 mL) was refluxed for 6 h. The mixture was filtered, the filtrate was concentrated, and the residue was boiled under reflux with 1 N MeOH–HCl (25 mL) for $^1/_2$ h. After recovery as described under **8**, the product was chromatographed on SiO_2 gel (25 g) in hexane/benzene, 1:3, to give **10** as an oil (1 g): $[\alpha]_D$ −25°; ^1H NMR δ 0.80 (d, J = 6 Hz, 2 $CHCH_3$), 1.75 (m, 2 $CHCH_3$), 2.50 (m, 2 $ArCH_2$), 3.80 (s, OCH_3), 5.55 (s, D_2O-exchangeable, O*H*), 5.88 (s, OCH_2O), 6.45–6.90 (m, 6 ArH). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.17; H, 7.31. Found: C, 73.20, H, 7.30.

A solution of **8** (0.5 g) in acetone (30 mL) was methylated with Me_2SO_4 (1 mL) and K_2CO_3 (2 g) as described under **10**. After

(8) Brown, A. C.; Carpino, L. A. *J .Org. Chem.* **1985**, *50*, 1749–1750.

recovery, the product was purified by chromatography (SiO_2 gel, 20 g, 2% acetone in C_6H_6) to give **11** as a colorless crystalline solid (0.55 g): mp 62–63 °C; $[\alpha]_D$ −23°; ^1H NMR δ 0.80 (d, J = 6 Hz, 2 CHCH_3), 1.75 (m, 2 CHCH$_3$), 2.50 (m, 2 ArCH_2), 3.83, 3.85 (2 s, 2 OCH_3), 5.90 (s, OCH$_2$O), 6.5–6.8 (m, 6 ArH). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.65; H, 7.70.

Preparation of 12, 13, and 14. Compound **6** (1.7 g) was hydrolyzed with 1 N MeOH/HCl as given under **8**. After recovery and purification by chromatography, **12** was obtained as a colorless glass (0.72 g). Part of this sample (0.36 g) was converted to the acetate as described under **9**.. The acetate **13** was obtained as a colorless cyrstalline solid (0.38 g): mp 94–95 °C; ^1H NMR δ 0.80 (d, J = 6 Hz, 2 CHCH_3), 1.80 (m, 2 CHCH$_3$), 2.23 (s, 4 CH_3COO), 2.50 (m, 2 ArCH_2), 6.8–7.0 (m, 6 ArH). Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.38; H, 6.43. Found: C, 66.28; H, 6.48.

Another part of **12** (0.36 g) was methylated using Me_2SO_4 (1.2 mL) and K_2CO_3 (3 g) in acetone (25 mL) as given under **10**. The product **14** was obtained as a colorless crystalline solid (0.4 g): mp 84–85 °C; $[\alpha]_D$ −26°; ^1H NMR δ 0.80 (d, 2 CHCH_3), 1.75 (m, 2 CHCH$_3$), 2.50 (m, 2 ArCH_2), 3.83, 3.86 (2 s, 4 OCH_3), 6.50–6.82 (m, 6 ArH). Anal. Calcd for $C_{22}H_{30}O_9$: C, 73.71; H, 8.44. Found: C, 73.52; H, 8.46.

Preparation of 1 from 6. A mixture of **6** (2.7 g), Me_2SO_4 (2.7 mL), and K_2CO_3 (5 g) in acetone (60 mL) was boiled under reflux for 6 h. The product recovered as given under **10** was hydrolyzed with 1 N MeOH/HCl as described earlier and chromatographed on SiO_2 (60 g) in benzene. Elution with 2% acetone in benzene and concentration of the appropriate fractions gave **1** as a crystalline solid (from hexane): yield, 1.3 g; mp 87–88 °C; $[\alpha]_D$ −27°; MS 330 ($M^{\bullet+}$, 18), 137 (100); ^1H NMR δ 0.80 (d, J = 6 Hz, 2 CHCH_3), 1.70 (m, 2 CHCH$_3$), 2.45 (m, 2 ArCH_2), 3.80, 3.85 (2 s, 2 OCH_3), 5.55 (br s, D_2O-exchangeable, 2 OH, 6.40–6.80 (m, 6 ArH).

***O*-Ethylvanillic Acid (7).** A sample of **1** (0.2 g) was ethylated using Et_2SO_4 (0.2 mL) and K_2CO_3 (1 g) in acetone (20 mL) by boiling under reflux for 4 h. The product, after recovery as described under **10**, was dissolved in 1:1 aqueous pyridine (10 mL) and boiled with $KMnO_4$ (1 g) for 1 h. After cooling, acidification (pH 2) with H_2SO_4, and treatment with $NaHSO_3$, the mixture was extracted two times with ether. The ether extract was washed two times with 5% aqueous $NaHCO_3$; the aqueous layer acidified and reextracted with ether two times. Concentration of the ether gave a crystalline solid, recrystallized from ether/hexane, yield 0.02 g, mp 188–90 °C, identical with an aunthentic sample prepared from vanillin by ethylation and oxidation.

Preparation of 15. A mixture of **6** (2.9 g), benzyl chloride (1 mL), and K_2CO_3 (3 g) in DMF (20 mL) was heated at 100 °C for 4 h. The cooled reaction mixture was diluted with water (50 mL) and extracted two times with benzene. The concentrated C_6H_6 extract was heated with 1 N MeOH/HCl (20 mL) for 1 h at reflux. The product was recovered by dilution with water (50 mL) and extraction with benzene. The concentrated bnezene extract was methylated using Me_2SO_4 (1 mL) and K_2CO_3 (2 g) in acetone (20 mL) by boiling under reflux for 4 h. The methyl ether was dissolved in ACOH containing 30% HBr and let stand at 20 °C for 2 h. After dilution with water, extraction with benzene, and washing of the C_6H_6 with aqueous $NaHCO_3$, followed by washing with 0.2 N aqueous NaOH, **15** was obtained in the aqueous hydroxide layer. It was recovered by acidification, extraction with ether, and concentration of the extract to give **15** as a colorless crystalline solid (from hexane): yield, 0.7 g; mp 92–95 °C; $[\alpha]_D$ −27°; IR 3560, 3520, 2970, 1590, 1510 cm^{-1}; ^1H NMR δ 0.80 (d, J = 6 Hz, 2 CHCH_3), 1.80 (m, 2 HCH$_3$), 2.5 (m, 2 ArCH_2), 3.93 (s, 2 OCH_3), 5.5 (s, D_2O-exchangeable, 2 OH), 6.45–6.83 (m, 6 ArH). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.57; H, 7.93.

Alternatively, 30% H_2O_2 (15 mL) was added to a solution of **6** (1.35 g) in AcOH (30 mL), and the mixture was stirred at 50–55 °C for 18 h. After dilution with water, extraction with benzene, and washing of the C_6H_6 extract with aqueous $NaHCO_3$, the concentrated solvent extract was dissolved in MeOH (10 mL) and added to an effervescent mixture of Mg turnings (2 g) in MeOH (20 mL). The mixture was stirred with intermittent heating (60 °C) for 2 h. After concentration, addition of water, acidification, and extraction with benzene, the product was chromatographed on SiO_2 gel (25 g). The fractions from 2% acetone in benzene on concentration gave a colorless crystalline solid, mp 93–95 °C, identical with the sample described above.

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Registry No. **1**, 124649-78-1; **1** (acetate), 124649-79-2; **4**, 55890-23-8; **5**, 124605-67-0; **6**, 124605-68-1; **7**, 3535-30-6; **8**, 124605-69-2; **9**, 124605-70-5; **10**, 55890-24-9; **11**, 55731-00-5; **12**, 119584-40-6; **13**, 124649-80-5; **14**, 119182-23-9; **15**, 124605-71-6; *p*-thiocresol, 106-45-6.

New Heterodifunctional Ligands for Organotransiton-Metal Chemistry: $Ph_2P(CH_2)_nC_5Me_4H$ (n = 0, 2)

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The synthesis of two new heterodifunctional ligands for organotransition-metal chemistry, $Ph_2P(CH_2)_nC_5Me_4H$ (n = 0, 2), is described. Both compounds are derived from the same intermediate, lithium tetramethylcyclopentadienide. For n = 2 the ligand is obtained by a one-pot reaction including two successive nucleophilic substitutions.

The heterodifunctional ligands have been frequently used in recent years in organotransition-metal chemistry to build heterobimetallic complexes.[1]

Among them, those that incorporate both a phosphine and a cyclopentadienyl functionality[2] are suitable to link

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