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ADDITIONAL FLAVANOIDS IN *GLIRICIDIA SEPIUM*

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Key Word Index—*Gliricidia sepium*; Leguminosae; heartwood; extractives; isoflavone; dihydroflavonol; β-hydroxydihydrochalcone; isoflavan.

Abstract—A chromatographic examination of the acetone extractives of the moderately marine bore resistant Panamanian wood *Gliricidia sepium* has resulted in the isolation and characterization of three new flavanoid constituents: an isoflavone, a dihydroflavonol and a β-hydroxydihydrochalcone. These new flavanoids are not related to the marine bore resistance of the wood.

The recent investigation [1] of the ether extract of the moderately marine borer resistant [2] heartwood of the Panamanian tree *Gliricidia sepium* (Leguminosae) resulted in the isolation and characterization of two new isoflavenes (sepiol **1a**, 2′-*O*-methyl sepiol **1b**), a flavanone (butin **2**), a flavonol (robinetin **3**) and the identification of a phenolic isoflavan as either isomucronulatol **4a** or mucronulatol **4b**. We now report that further examination of the acetone extract of *G. sepium* heartwood has resulted in the isolation and characterization of a new isoflavone (gliricidin **6a**), a new dihydroflavonol (sepinol **7a**) and an unusual β-hydroxydihydrochalcone (gliricidol **9a**). In addition, the acetone extract yielded a sufficient quantity of the earlier isolated isoflavan for its unequivocal structural characterization as (3*R*)-(−) isomucronulatol **5**.

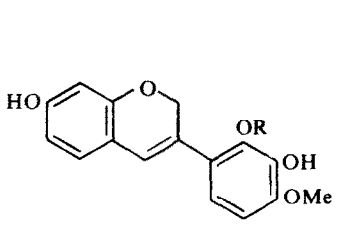
Initial separation of components in the acetone extract was achieved through sequential preparative column chromatography (silica, $CHCl_3$–MeOH; LH-20, $CHCl_3$–EtOH) of the benzene soluble, aqueous sodium carbonate insoluble, aqueous sodium borate insoluble portion of the extract. Further chromatography on silica gel ($CHCl_3$–MeOH; benzene–EtOH) yielded the isoflavan **5**, isoflavone **6a**, dihydroflavonol **7a** and β-hydroxydihydrochalcone **9a**, respectively.

The isoflavan isomucronulatol ($C_{17}H_{18}O_5$) was the first compound chromatographically isolated from the acetone extract of *G. sepium*. This isoflavan (racemic) has been previously synthesized [3] and was recently reported to occur in the fungal-inoculated leaves of *Glycyrrhiza glabra* var. *glabra* [4]. However, the absence of physical properties and NMR data in the latter report precluded a precise structural comparison of the natural products. We now specifically describe isomucronulatol as obtained from *G. sepium*.

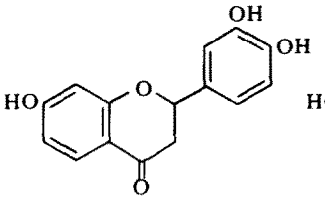
The *G. sepium* isoflavan is obtained as pale yellow needles, forms a diacetate (oil) **4e**, and is optically active. The compound gives a positive Gibbs reaction but does not reduce ammoniacal silver nitrate. The 100 MHz ^{1}H NMR spectrum (acetone-d_6) of the compound is indicative [5] of 7-OR (R=H, alkyl) substituted isoflavans with two broad resonances at δ 2.98 and 2.91 associated with the C-2 methylene protons. A diffuse multiplet centered at δ 3.41 corresponds to the C-3 methine proton of an isoflavan structure, while the C-4 benzylic methylene protons appear as doublets of doublets at δ 4.00 (J = 10, 10 Hz) and 4.28 (J = 10, 3 Hz). Two aromatic methoxyl singlets occur at δ 3.81 and 3.83. Aromatic protons H_5, H_6 and H_8 appear in an ABX pattern at δ 6.91 (J = 9, 1 Hz), 6.36 (J = 9, 2 Hz) and 6.29 (J = 1, 2 Hz), respectively. *Ortho*-coupled aromatic protons $H_{5'}$ and $H_{6'}$ occur as doublets (J = 9 Hz) at δ 6.50 and 6.84. Two phenolic hydroxyl protons resonate as singlets at 7.87 and 8.03. Prominent mass spectral fragments at *m/e* 180 and 167 are representative of B-ring fragments which place two methoxyl groups in this ring of the isoflavan. These data are consistent with 7-hydroxy substituted isoflavans **4a**, **4b** and **4c** [3, 5, 6].

The positive Gibbs reaction of the isoflavan and the observed failure of both ethoxy methylene protons to shift when the ^{1}H NMR spectrum of the diethoxy isoflavan **4d** is run in benzene [7], effectively eliminates laxiflorin **4c** from further consideration. The spectral properties of the isoflavan are in agreement with those reported for (±)-mucronulatol **4b** and synthetic racemic isomucronulatol **4a**. The lack of agreement of physical properties ($[\alpha]_D^{22}$ and mp) of the *G. sepium* isoflavan with those reported for optically active (−)-murconulatol [8], and a distinct divergence of chemical shift of the 5′ and 6′ protons (δ 6.80, 6.87) of the isoflavan diacetate compared to those reported for (−)-mucronulatol diacetate [6] (δ 6.70 and 6.97) and those observed for **4b** (δ 6.74 and 7.04), obtained through catalytic reduction of **1b** diacetate, establish the isoflavan as isomucronulatol **4a**. The optical activity of isomucronulatol ($[\theta]_{230} = -11800$) in low wavelength CD measurements compared with ORD data previously reported for (3*R*)-dimethoxylaxiflorin ($[\Phi]_{238} = -4620$) and several (3*R*)-pterocarpins [5], further specifically identify (−)-isomucronulatol isolated from *G. sepium* as (3*R*)-(−)-2′,7-dihydroxy-3′,4′-dimethoxyisoflavan **5**.

Column chromatography of the acetone extract also yielded a new isoflavone, $C_{16}H_{12}O_6$, now called gliricidin, which has been identified as 4′-methoxy-3′,5′,7-trihydroxyisoflavone **6a**. In accord with this structure, it forms a triacetate **6b** (mp 166–167°), gives a positive Gibbs



1a R = H
1b R = Me



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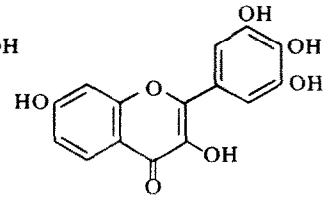

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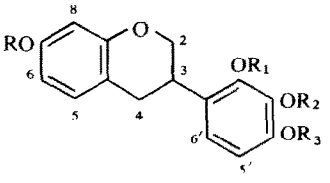
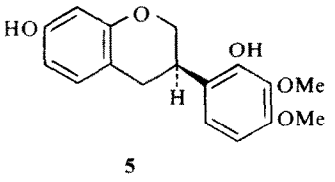


4a R = H; R_1 = H; R_2, R_3 = Me
4b R = H; R_1 = Me; R_2 = H; R_3 = Me
4c R = H; R_1 = Me; R_2 = Me; R_3 = H
4d R = Et; R_1 = Et; R_2 = Me; R_3 = Me
4e R = Ac; R_1 = Ac; R_2, R_3 = Me



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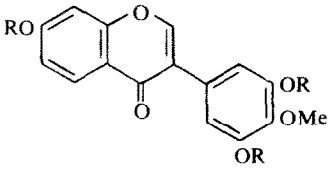

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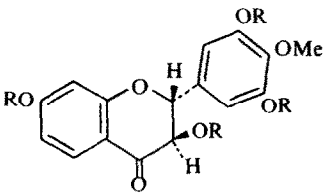
6b R = Ac



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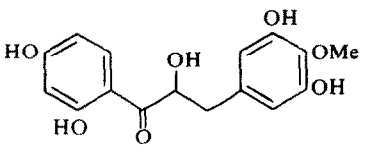
7b R = Ac



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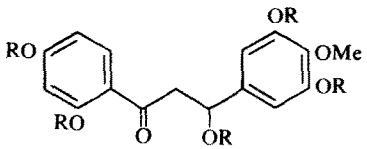
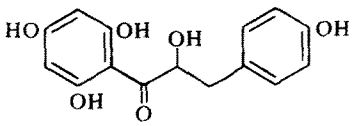


9a R = H
9b R = Ac



10

reaction, produces a yellow-orange reaction with diazotized sulfanilic acid but does not react with ferric chloride or ammoniacal silver nitrate.

The UV spectrum of gliricidin has λ_{max} at 298, 259, 249 and 224 nm. No spectral shifts are observed in the presence of boric acid, boric acid/sodium acetate or aluminum chloride. Addition of sodium acetate produces a 42 nm bathochromic shift of the high wavelength band and a 10 nm bathochromic shift of the 249 nm wavelength band. The 100 MHz ^{1}H NMR spectrum (DMSO-d_6) of the compound shows an aromatic methoxyl singlet at δ 3.74. Two equivalent aromatic protons ($H_{2'}$, $H_{6'}$) resonate as a singlet at δ6.56, while (H_5, H_6, H_8) appear in a typical 4-substituted resorcinol ABX pattern of double doublets at δ 6.98, 6.94 and 6.89, respectively. The characteristic C-2 isoflavone vinyl proton appears as a low field singlet at δ8.25. Two hydroxyl protons resonate as a broad signal centered at δ9.04 while a third hydroxyl appears as a broad resonance at δ 3.25. These hydroxyl resonances disappear upon addition of D_2O to the spectral solution. The ^{1}H NMR spectrum of the isoflavone triacetate shows the three phenolic acetates as a nine proton singlet at δ 2.35.

Structural confirmation of gliricidin was obtained through its synthesis from gallic acid. Methylation of gallic acid **11** yielded the methyl ester **12** which was selectively methylated [9] to give methyl 3,5-dihydroxy-4-methoxybenzoate **13**. Benzylation of **13** yielded **14** which was reduced with $LiAlH_4$ to the 3,5-dibenzyloxy-4-methoxybenzylalcohol **15**. Treatment of the benzyl alcohol with thionyl chloride gave the benzyl choride **16** which reacted with potassium cyanide in DMSO to yield the benzyl nitrile **17**. A Hoesch reaction of **17** with resorcinol yielded the intermediate dibenzyloxy-deoxybenzoin **18**, which in the acidic reaction conditions was then debenzylated to give the desired deoxybenzoin **19** in low yield. Reaction of **19** with methanesulfonyl chloride in boron trifluoride etherate, according to the procedure of Bass [10], gave **6a** which was identical in all physical and spectral properties with natural gliricidin.

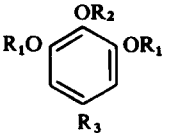
Chromatography further yielded a new dihydroflavonol, $C_{16}H_{14}O_7$, now named sepinol, which has now been characterized as 4'-methoxy-3',5',7-trihydroxydihydroflavonol **7a**. Sepinol forms a tetraacetate **7b**, is oxidized slowly by ammoniacal silver nitrate, reacts with diazotized sulfanilic acid to produce a yellow-orange color, gives a positive Gibbs reaction, but does not react with ferric chloride.

The UV spectrum of sepinol shows λ_{max} at 313 and 277 nm with an inflection at 230 nm. No spectral shifts are

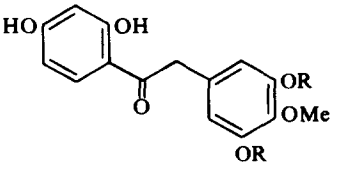
observed upon addition of boric acid or boric acid/sodium acetate to the spectral solution. Addition of aluminum chloride produces a 8 nm hyposchromic shift of the 313 nm band, while addition of sodium acetate produces a 60 nm bathochromic shift of the 277 nm band. These observations are consistent with a 7-hydroxy-dihydroflavonol having no free *ortho*-hydroxyl groups in ring B. The 100 MHz ^{1}H NMR spectrum (acetone-d_6) of the compound is in accord with that expected for a 4'-methoxy-3',5',7-trihydroxy-dihydroflavonol **7a** showing a broad two proton hydroxyl resonance centered at δ 3.76. Three aromatic methoxyl protons resonate as a singlet at δ 3.85. Two vicinal coupled (H_2, H_3) methine protons resonate at δ 4.96 and 4.49 (J = 12 Hz). Three aromatic protons (H_5, H_6, H_8) appear as double doublets in a characteristic resacetophenone ABX system at δ 6.43 (J = 3, 1 Hz), 6.63 (J = 10, 3 Hz) and 7.75 (J = 10, 1 Hz), respectively. Two equivalent ($H_{2'}$, $H_{6'}$) protons appear as a singlet at δ 6.67 and two aromatic hydroxyl protons occur as broad resonances centered at δ 6.62 and 8.30. The ^{1}H NMR spectrum of sepinol tetraacetate shows a three proton alkyl acetate resonance at δ 2.07 while three phenolic acetates (nine protons) appear at δ 2.32. Comparison of CD results ($[\theta]_{331}$ = +5360, $[\theta]_{303}$ = −15400) of optically active sepinol ($[\alpha]_D^{22}$ = −7.6°, methanol) with those reported for known hydroxydihydroflavonols [11], establishes a 2*R*,3*R* configuration and specifically defines sepinol as (2*R*)-(3*R*)-(−)-4'-methoxy-3',5',7-trihydroxy-dihydroflavonol **7a**.

The final compound chromatographically isolated from the *G. sepium* acetone extract was an unusual β-hydroxydihydrochalcone ($C_{16}H_{16}O_7$) now called gliricidol **9a** which forms a pentaacetate (oil) **9b**, does not reduce ammoniacal silver nitrate, gives an emerald green ferric chloride reaction and a positive Gibbs test. The IR spectrum of gliricidol confirms the presence of a carbonyl group (ν_{max} = 1618 cm^{-1}).

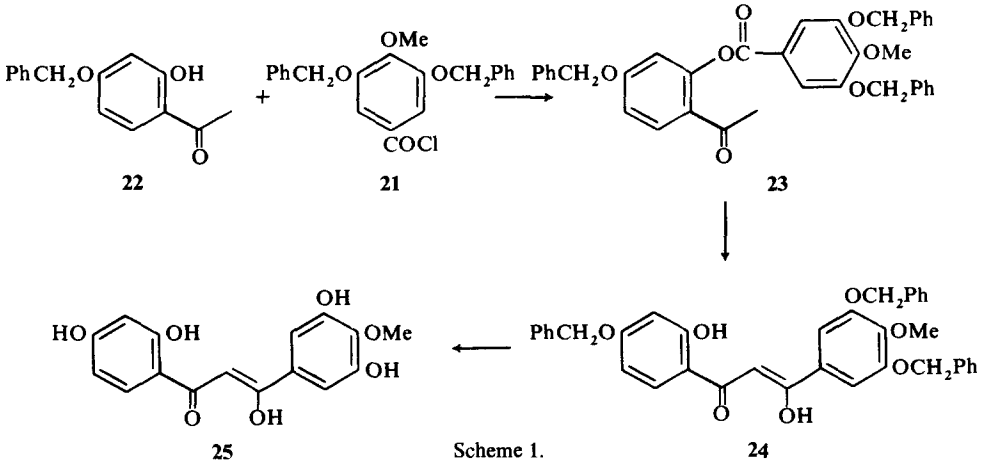
The 100 MHz ^{1}H NMR spectrum (acetone-d_6) of the compound shows two geminally coupled protons (δ 2.77, J = 15, 8 Hz; 3.01, J = 15, 5 Hz) as the AB portion of a vicinal ABMX system, where the M proton appears as a diffuse doublet (J = 7.5 Hz) at δ 4.32 and the X proton occurs at δ 5.21 as a diffuse multiple resonance. Addition of D_2O to the spectral solution eliminates the M proton (hydroxyl) and the X proton refines to a double doublet (J = 8, 5 Hz) and thereby defines the ABMX system as methylene carbinol. The remainder of the spectrum shows an aromatic methoxyl as a singlet at δ 3.75, three aromatic protons in a resacetophenone ABX system of double doublets at δ 6.39 (J = 3, 1 Hz), 6.49 (J = 10, 3 Hz) and 7.90 (J = 10, 1 Hz) and two equivalent aromatic protons appear as a singlet at δ 6.31. Broad hydroxyl resonances are found at δ 3.85 (1 − OH) and 7.78 (2 − OH) and a sharp low field hydroxyl resonance is located at δ 12.34. The ^{1}H NMR spectrum of gliricidol pentaacetate ($CDCl_3$) confirms the presence of four aromatic hydroxyls and one alkyl hydroxyl with the appearance of four phenolic acetate resonances as a singlet at δ 2.34 and a single alkyl acetate resonance at δ 2.20. Acetylation also



11 R_1, R_2 = H; R_3 = CO_2H
12 R_1, R_2 = H; R_3 = CO_2Me
13 R_1 = H; R_2 = Me; R_3 = CO_2Me
14 R_1 = $PhCH_2$; R_2 = Me; R_3 = CO_2Me
15 R_1 = $PhCH_2$; R_2 = Me; R_3 = CH_2OH
16 R_1 = $PhCH_2$; R_2 = Me; R_3 = CH_2Cl
17 R_1 = $PhCH_2$; R_2 = Me; R_3 = CH_2CN
20 R_1 = $PhCH_2$; R_2 = Me; R_3 = CO_2H
21 R_1 = $PhCH_2$; R_2 = Me; R_3 = COCl



18 R = CH_2Ph
19 R = H



22 **21** **23** **25** **24**

Scheme 1.

produces a downfield shift of the carbinol proton to δ 5.90 (*dd*, J = 5, 8 Hz). These data are consistent with gliricidol being either an α or β-hydroxydihydrochalcone **8** or **9a**.

A comparison of NMR data for the methylene carbinol group of gliricidol and its pentaacetate with that recently reported for the α-hydroxydihydrochalcone, nubigeniol [12] **10** and its pentaacetate shows that the geminal methylene and hydroxyl protons of gliricidol occur at higher field (38, 44 and 66 Hz, respectively) than the same protons in nubigenol, while the carbinol proton occurs at significantly lower field (81, 60 Hz) in gliricidol and its pentaacetate. The chemical shifts of the carbinol (δ 5.21) and methylene protons (δ 2.77, 3.01) of a β-hydroxydihydrochalcone closely approximate those of C-2 and C-3 protons of a flavanone (i.e. butin **2**; C-2, δ 5.38; C-3, δ 2.86, 3.02). The comparability of methylene and carbinol proton chemical shifts with those of a flavanone and the failure of gliricidol to produce a positive Tollen's test strongly supports the β-hydroxydihydrochalcone structure **9a** for gliricidol.

The β-hydroxychalcone **25** was synthesized according to Scheme 1 [13], but attempts to hydrogenate **25** to obtain synthetic gliricidol were unsuccessful. In contrast, however, gliricidol was oxidized with pyridinium chlorochromate [14] to produce several products which, when separated by preparative TLC, yielded one compound (in very low yield) which was chromatographically identical to **25** in several solvent systems. On the basis of the spectral and chromatographic data, gliridicol is considered to be 4-methoxy-β,2,3′,4′,5-pentahydroxydihydrochalcone **9a**.

EXPERIMENTAL

Spectra were measured for solns in EtOH (UV), $CDCl_3$, Me_2CO-d_6, DMSO-d_6 (NMR); for solids on KBr discs (nujol) (IR). Mps are uncorr.

Extraction of Gliricidia sepium. Hammer-milled *G. sepium* heartwood (2.59 kg) was successively extracted with hot petrol (30–60°), Et_2O, Me_2CO and MeOH. Only the Me_2CO extract (235 g) will be considered here. The total Me_2CO extract was concd to 800 ml, cooled and allowed to stand. Crystalline material (17.5 g, robinetin) was filtered off. The resultant filtrate was mixed with C_6H_6 (1 l.), concd (steam-bath, 800 ml) and filtered (hot) through a celite pad. The filtrate was cooled, extracted with sat. aq. Na_2CO_3 (2 × 300 ml), washed with H_2O (2 × 300 ml), extracted with sat. aq. $Na_2B_4O_7$ (2 × 300 ml), washed with H_2O (2 × 300 ml), dried ($MgSO_4$) and evapd to dryness (27.5 g). A portion (15 g) of the C_6H_6 soluble, Na_2CO_3 and $Na_2B_4O_7$ insoluble extract was applied to a preparative Si column (10 × 45 cm), eluted with $CHCl_3$–MeOH (6:1) and monitored by TLC spraying with diazotized sulfanilic acid. Four 1500 ml fractions were taken. Fraction 2 was concd and reapplied to an LH-20 (10 × 45 cm) column ($CHCl_3$ → $CHCl_3$–EtOH (10:1)) and 1 l. fractions collected. Fractions 1–4 contained oily material and were not examined further. Fractions 5–7 were extensively rechromatographed on Si gel and LH-20 columns ($CHCl_3$, $CHCl_3$–MeOH (10:1) and C_6H_6, C_6H_6–EtOH (10:1)) to obtain the four compounds herein described in amounts less than 0.6% (based on oven-dry wt. of wood).

(−)-Isomucronulatol ((3R)-(−)-2′,7-*dihydroxy*-3′,4′-*dimethoxyisoflavan*(**5**)). Elution (C_6H_6–EtOH (6:1)) of a Si gel column (2.5 × 45 cm) first gave **5** (85 mg) as pale yellow needles ($CHCl_3$): mp 512–153°, ($C_{17}H_{18}O_5$ requires: C, 67.5; H, 6.00. M^+, 302.1155. Found: C, 67.4; H, 5.9%; M^+, 302.1153). $[\alpha]_D^{22}$ = 5.3° (Me_2CO); CD $[\theta]_{230}$ = −11800, $[\theta]_{284}$ = +3500 (MeOH); λ_{max}^{EtOH} (log ε): 289(3.49), 281(3.63) nm. MS *m/e* (%RA): 302 (57), 180 (100), 168 (45), 167 (45), 135 (14), 133 (20), 123(12).

Diethoxyisomucronulatol (**4d**). **5** (20 mg) was refluxed with EtI (1 ml), in Me_2CO (50 ml) containing K_2CO_3 (3 g) for 6 hr. The mixture was cooled, H_2O added (50 ml), filtered and crystallized from aq. MeOH, to give **4d** as colorless prisms, mp 72–73°. ($C_{21}H_{26}O_5$ requires: M^+, 358.1780. Found: M^+, 358.1791). ^{1}H NMR ($CDCl_3$): δ 1.39 (3H, *t*, J = 6 Hz), 1.40 (3H, *t*, J = 6 Hz), 2.90 (2H, *d*, J = 8 Hz), 3.40–3.80 (2H, *m*), 3.85 (3H, *s*), 2.88 (3H, *s*), 4.02 (2H, *q*, J = 6 Hz), 4.13 (2H, *q*, J = 6 Hz), 4.29 (1H, *dd*, J = 5, 9 Hz), 6.42 (1H, *dd*, J = 3, 1 Hz), 6.46 (1H, *dd*, J = 3, 10 Hz), 6.63 (1H, *d*, J = 10 Hz), 6.80 (1H, *d*, J = 10 Hz), 6.96 (1H, *dd*, J = 1, 10 Hz). ^{1}H NMR (C_6D_6): δ 1.12 (3H, *t*, J = 6 Hz), 1.14 (3H, *t*, J = 6 Hz), 2.84 (2H, *d*, J = 8 Hz), 3.39 (3H, *s*), 3.76 (3H, *s*), 3.64 (2H, *q*, J = 6 Hz), 4.01 (2H, *q*, J = 6 Hz), 3.60–4.00 (2H, *m*), 4.35 (1H, *dd*, J = 3.9 Hz), 6.36 (1H, *d*, J = 10 Hz), 6.89 (1H, *dd*, J = 10, 1 Hz), 6.50–6.80 (3H, *m*).

(−)-Isomucronulatol diacetate (**4e**). Acetylation of **5** with Ac_2O–C_5H_5N yielded **4e** (oil). ^{1}H NMR ($CDCl_3$): δ 2.31 (3H, *s*), 2.38 (3H, *s*), 2.90 (1H, *br s*), 3.26 (1H, *m*), 3.86 (3H, *s*), 3.87 (3H, *s*), 3.97 (1H, *dd*, J = 10, 10 Hz), 4.29 (1H, *dd*, J = 10, 3 Hz), 6.56–6.68 (2H, *m*), 6.80 (1H, *d*, J = 9 Hz), 6.87 (1H, *d*, J = 9 Hz), 7.05 (1H, *d*, J = 9 Hz).

Gliricidin (4′-*methoxy*-3′,5′,7-*trihydroxyisoflavone* (**6a**)). Elution of a Si gel column (C_6H_6–EtOH: (10:1)) gave **6a**, 105 mg, colorless prisms (aq. MeOH) mp 298° (dec.). ($C_{16}H_{12}O_6$ requires: C, 64.0; H, 4.03; M^+, 300.0634. Found: C, 63.9; H, 4.08%; M^+, 300.0638). λ_{max}^{EtOH} (log ε); 312 (4.54), ~259 (4.86), 248 (4.91), 222 (4.49) nm. MS *m/e* (%RA): 300 (99), 285 (49), 229 (26), 201 (23), 149 (10), 121 (15), 120 (22).

Gliricidin triacetate (**6b**). Acetylation of **6a** with Ac_2O–C_5H_5N yielded **6b**, colorless needles (MeOH), mp 166–167°. ^{1}H NMR ($CDCl_3$): δ 2.35 (9H, *s*), 3.86 (3H, *s*), 7.15 (1H, *dd*, J = 10, 3 Hz), 7.26 (2H, *s*), 7.28 (1H, *dd*, J = 3, 1 Hz), 8.02 (1H, *s*), 8.29 (1H, *dd*, J = 10, 1 Hz).

Sepinol ((2R)-(3R)-(−)-4′-*methoxy*-3′,5′,7-*trihydroxydihydroflavonol* (**7a**)). Elution of a Si gel column with C_6H_6–EtOH (10:1) yielded **7a**, 35 mg, off-white prisms (Me_2CO–EtOAc), mp 253–254°. $[\alpha]_D^{22}$ = −7.6° (MeOH). ($C_{16}H_{14}O_7$ requires: M^+, 318.0739. Found: M^+, 318.0750). λ_{max}^{EtOH} (log ε): 311 (3.78), 276 (4.05), ~230 nm. CD (MeOH): $[\theta]_{303}$ = −15400, $[\theta]_{331}$ = +5360. MS *m/e* (%RA): 318 (34), 290 (13), 289 (85), 261 (10), 182 (28), 167 (55), 153 (22), 149 (39), 139 (10), 137 (100), 97 (11), 95 (13).

Sepinol tetraacetate (**7b**). Acetylation of **7a**, Ac_2O–C_5H_5N, yielded **7b**, colorless needles (MeOH), mp 162–164°. ^{1}H NMR ($CDCl_3$): δ 2.07 (3H, *s*), 2.32 (9H, *s*), 3.82 (3H, *s*), 5.35 (1H, *d*, J = 12 Hz), 5.67 (1H, *d*, J = 12 Hz), 6.81 (1H, *dd*, J = 3, 1 Hz), 6.86 (1H, *dd*, J = 10, 3 Hz), 7.12 (2H, *s*), 7.91 (1H, *dd*, J = 10, 1 Hz).

Gliricidol (4-*methoxy*-β,2′,3,4′,5-*pentahydroxydihydrochalcone* (**9a**)). Further elution of a Si gel column (C_6H_6–EtOH, 9:1) yielded **9a**, 145 mg, colorless needles (H_2O), mp 165–166° (softens), 181–183° (melts). ($C_{16}H_{16}O_7$ requires: C, 60.0; H, 5.04. Found C, 59.9; H, 5.07%). λ_{max}^{EtOH} (log ε): 320 (3.86), 281 (4.05). $\lambda_{max}^{EtOH+NaOH}$ 339, 249. $\lambda_{max}^{EtOH+NaOAc}$ 338, 280, 255, $\lambda_{max}^{EtOH+AlCl_3}$ ~360, 308, ~289. MS *m/e* (%RA): 320 (2), 203 (15), 154 (13), 153 (96), 138 (14), 137 (99), 81 (12), 69 (10), 53 (11).

Gliricidol pentaacetate (**9b**). Acetylation of **9a**, Ac_2O–C_5H_5N, yielded **9b**, (oil). ^{1}H NMR ($CDCl_3$): δ 2.11 (3H, *s*), 2.34 (12H, *s*), 2.90–3.15 (2H, *m*), 3.80 (3H, *s*), 5.90 (1H, *dd*, J = 5, 8 Hz), 6.84 (2H, *s*), 7.03 (1H, *dd*, J = 1, 3 Hz), 7.09 (1H, *dd*, J = 10, 3 Hz), 7.76 (1H, *dd*, J = 10, 1 Hz).

Synthesis of gliricidin (**6a**). *Methyl* 3,4,5-*trihydroxybenzoate* (**12**). Gallic acid **11** (500 g) dissolved in MeOH (1 l.) was saturated with HCl gas, stoppered loosely and refrigerated overnight.

The soln was concd (200 ml), the solid was filtered, washed with cold MeOH, dried on the steam bath to yield crude **12**, 330 g mp 198–200°.

Methyl 3,5-dihydroxy-4-methoxybenzoate (**13**). Crude **12** (400 g) and Me_2SO_4 (216 ml, 1.1 ME) were added to stirred MeOH (800 ml). A soln of NaOH (50 g) in H_2O (250 ml) was added over 1.5 hr (pot temp. 35–50°). At the end of the addition the soln was refluxed (30 min), cooled, MeOH was removed and H_2O (400 ml) added. The aq. soln was extracted with Et_2O (2 × 500 ml), the Et_2O solubles were extracted with sat. $NaHCO_3$ (400 ml), washed with H_2O (2 × 400 ml), dried and evapd to dryness. C_6H_6 (500 ml) was added, the mixture was brought to a boil and filtered hot and concd to yield **13**, 75 g, colorless needles, mp 136°. ($C_9H_{10}O_5$ requires: C, 50.5, H, 4.71. Found: C, 50.4 H, 4.61%).

Methyl 3,5-dibenzyloxy-4-methoxybenzoate (**14**). **13** (75 g) was refluxed with K_2CO_3 (150 g), KI (150 g) and benzyl chloride (150 ml) in Me_2CO (1.6 l.) for 4 hr. The hot soln was filtered, MeOH (400 ml) was added and the soln was concd (steam bath) and cooled to yield **14**, 78 g, colorless needles, mp 116–118°. ($C_{23}H_{22}O_5$ requires: C, 73.0; H, 5.86. Found: C, 73.2; H, 5.84%).

3,5-*Dibenzyloxy-4-methoxybenzylalcohol* (**15**). A solution of **14** (45.4 g) in THF (400 ml) was added dropwise with stirring to a mixture of $LiAlH_4$ (6 g) in THF (400 ml). The reaction was continued for 20 min, cooled and sat. NH_4Cl was added dropwise until no reaction was observed. The liquid was decanted, H_2O (1.5 l.) was added and the aq. soln was extracted with Et_2O (2 × 600 ml).

The Et_2O solubles were dried, hexane (300 ml) was added and the soln was concd to yield **15**, 38.6 g, colorless needles, mp 103–104°. ($C_{22}H_{22}O_4$ requires: C, 75.4; H, 6.33. Found: C, 75.5; H, 6.33%).

3,5-*Dibenzyloxy-4-methoxybenzylchloride* (**16**). $SOCl_2$ (3.75 ml) was added to a stirred suspension of **15** (3.5 g) in Et_2O (100 ml) over 20 min. Excess $SOCl_2$ and Et_2O were removed *in vacuo*. The product was applied to a preparative Si gel column, eluted (hexane–Me_2CO (9:1)), concd and recrystallized (Et_2O–hexane), to yield **16**, 1.97 g, colorless needles, mp 78–79°. ($C_{22}H_{21}O_3Cl$ requires: C, 71.6; H, 5.74. Found: C, 71.8; H, 5.90%).

3,5-*Dibenzyloxy-4-methoxybenzylnitrile* (**17**). KCN (150 mg) was dissolved in DMSO (30 ml), **16** (10 g) was added and the flask was shaken and allowed to stand overnight at room temp. The reaction mixture was poured into H_2O (100 ml). The aq. soln was continuously liquid–liquid extracted for 36 hr with Et_2O–petrol (30–60°) (1:1). The extract was concd with aq. EtOH to yield **17**, 0.78 g, colorless needles, mp 91–92° ($C_{23}H_{21}O_3N$ requires: C, 76.8; H, 5.98. Found: C, 76.7; H, 5.81%).

(2,4-*Dihydroxyphenyl*)-3,5-*dihydroxy-4-methoxybenzylketone* (**19**). Resorcinol, 4 g, **17** (5 g) and fused $ZnCl_2$ were dissolved in Et_2O (300 ml). The soln was saturated with HCl at 0° and allowed to stand overnight in a refrigerator. The soln was resaturated with HCl and allowed to stand overnight. Et_2O was decanted from oily residue and H_2O (300 ml) was added. The mixture was heated on the steam bath (4 hr), cooled and extracted with Et_2O. The Et_2O solubles were washed with sat. aq. $NaHCO_3$ (2 × 200 ml), washed with H_2O (200 ml) and dried. The resulting product was chromatographed on a Si gel column (C_6H_6–EtOH (9:1)). **19** was eluted, collected and crystallized (C_6H_6), 0.39 g colorless needles, mp 222–224°. ($C_{15}H_{14}O_6$ requires: C, 62.0; H, 4.86. Found: C, 62.1; H, 4.83%). ^1H NMR (Me_2CO–d_6): δ 2.92 (1H, (OH), *br s*,), 3.82 (3H, *s*), 4.01 (2H, *s*), 6.32 (2H, *s*), 6.28 (1H, *dd*, J = 1, 3 Hz), 6.38 (1H, *dd*, J = 10, 3 Hz), 7.89 (1H, *dd*, J = 10, 1 Hz), 7.80 (2H, (2-OH), *br s*), 12.81 (1H, (OH), *s*). Ferric chloride test gives intense brown reaction.

Synthetic gliricidin (**6a**). **19** (170 mg) was dissolved in DMF (3 ml) and $BF_3(OEt)_2$ (331 mg) was added. $MeSO_2Cl$ (201 mg) was slowly added and the soln was heated (90 min) on the steam bath. The reaction mixture was diluted with H_2O (100 ml) and extracted with Et_2O. The Et_2O solubles were washed with 10% aq. HCl (50 ml), washed with H_2O (50 ml) and dried. Aq. EtOH (20 ml) was added and the solution was concd to yield **6a**, 112 mg, colorless prisms, mp, mmp 298° (dec.). ($C_{16}H_{12}O_6$ requires: M^+, 300.0633. Found: M^+, 300.0646). Spectral and physical data of this synthetic product were in complete accord with those of the natural **6a**.

3,5-*Dibenzyloxy-4-methoxybenzoic acid* (**20**). The ester **14** 30 g, was added to a soln of KOH (15 g) in H_2O (300 ml). The soln was refluxed (3 hr), cooled, diluted with H_2O (300 ml) and acidified. The precipitated white solid was filtered, washed and recrystallized (Me_2CO–MeOH) to yield **20** (24 g) as colorless plates, mp 158–160°. ($C_{22}H_{20}O_5$ requires: C, 72.5; H, 5.53. Found: C, 72.7; H, 5.46%).

3,5-*Dibenzyloxy-4-methoxybenzoyl chloride* (**21**). The acid **20**, 20 g, $SOCl_2$ (100 ml) and C_6H_6 (100 ml) were refluxed for 1 hr. The soln was concd and the resulting solid collected. Recrystallization from Et_2O–hexane yielded **21**, 18 g, as colorless needles, mp 123–125°. ($C_{22}H_{19}O_4Cl$ requires: C, 69.0; H, 5.00. Found: C, 69.3; H, 5.18%).

4-O-*Benzyl-resacetophenone* (**22**). A mixture of resactophenone (40 g), benzyl chloride (100 ml), powdered KI (50 g), K_2CO_3 (54 g) and Me_2CO (600 ml) was refluxed for 3 hr. The reaction mixture was filtered and the filtrate concd to an oil. The oil was was boiled with hot hexane (200 ml), cooled and colorless crystals were collected. The crystals were washed with hexane and recrystallized from Me_2CO–MeOH to yield **22**, 50 g, as glistening plates, mp 106–107°. **22** gives strong red-brown ferric chloride test. ($C_{22}H_{18}O_4$ requires: C, 76.3; H, 5.23. Found: C, 76.3; H, 5.10%).

2-(3,5-*Dibenzyloxy-4-methoxybenzoyl*)-4-*benzyloxyacetophenone* (**23**). **21** (6.2 g) was dissolved in dry C_5H_5N (20 ml), **22** (4 g) was added and the soln was heated on a steam bath for 3 hr. The soln was removed and poured into ice H_2O–conc HCl (1:1), extracted with Et_2O (200 ml), washed with H_2O (200 ml) and dried. The resulting soln was concd to dryness, washed with petrol (30–60°) and crystallized (Me_2CO–MeOH) to yield **23**, 5.9 g, colorless needles, mp 123–124°. ($C_{37}H_{32}O_7$ requires: C, 75.4; H, 5.48. Found: C, 75.5; H, 5.62%).

β-2'-Dihydroxy-4-methoxy-3',4',5-tribenzyloxychalcone (**24**). To a soln of **23** (1 g) in dry C_5H_5N (20 ml) was added powdered KOH (1.4 g). The mixture was shaken vigorously for 2 hr with occasional heating on the steam bath. The reaction mixture was poured into ice–conc HCl (~1:1). The aq. acid soln was diluted with H_2O (50 ml) and extracted with Et_2O (200 ml). The Et_2O extract was washed with H_2O (100 ml), sat. $NaHCO_3$ (100 ml), dried and concd with MeOH to produce yellow brown needles. Recrystallization (MeOH) yielded **24**, 0.635 g, as fine yellow needles, mp 140–141°. ($C_{37}H_{32}O_7$ requires: C, 75.5; H, 5.48. Found: C, 75.6; H, 5.59%). ^1H NMR ($CDCl_3$): δ 3.92 (3H, *s*), 5.08 (2H, *s*), 5.14 (4H, *s*), 6.36 (1H, *s*), 6.48 (1H, *dd*, J = 1, 3 Hz), 6.53 (1H, *dd*, J = 10, 3 Hz), 7.14 (2H, *s*), 7.2–7.5 (21H, *m*), 7.53 (1H, *dd*, J = 10, 1 Hz).

4-*Methoxy-β,2',3,4',5-pentahydroxychalcone* (**25**). **24** (300 mg) was refluxed in HOAc–conc HCl (1:1), (20 ml) for 4 hr. The reaction mixture was cooled, added to H_2O (50 ml) and extracted with EtOAc (50 ml). The EtOAc soln was washed with aq. sat. $NaHCO_3$, dried, evapd to dryness, redissolved in large vol. Me_2CO (500 ml) and concd to yield **25**, 110 mg, as fine light yellow needles mp 127–129°. ($C_{16}H_{14}O_7$ requires: C, 60.4; H, 4.43. Found: C, 60.5; H, 4.40%). ^1H NMR (Me_2CO-d_6); δ 3.40 (3H, (3-OH), *br s*), 3.79 (3H, *s*), 6.50 (1H, *s*), 6.92 (2H, *s*),

6.80–7.00 (2H, *m*), 7.81 (1H, *dd*, J = 10, 1 Hz), 9.40 (1H, (OH), *br s*), 9.71 (1H, (OH), *s*).

Oxidation of gliricidol. **9a** (0.60 g) in CH_2Cl_2 (3 ml) was treated with pyridinium chlorochromate (0.44 g) and allowed to react 6 hr. Et_2O was added and the mixture was filtered and the filtrate concd. Chromatography ($CHCl_3$–MeOH, 9:1) showed several products. Prep. TLC chromatography was employed to obtain single spot (R_f 0.30, C_6H_6–EtOH, 9:1), directly comparable to synthetic **25**.

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