HETEROCYCLES. XVIII.[1] SYNTHESIS OF THE RACEMATES OF NATURALLY OCCURRING FLAVONOIDS

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Abstract —— Racemic aromadendrin and fustin have been stereoselectively synthesized. Reduction of the O-substituted derivatives of these flavanonols provides the corresponding derivatives of gleditsin, leucopelargonidin and mollisacacidin (leucofisetinidin).

We have recently reported the efficient stereocontrolled synthesis of (2R*,3R*)-flavanonol as a model study to synthesize naturally occurring flavonoids.[2] Subsequently, it has been found that the bulk of 5-substituents governs the stereochemistry of the sodium borohydride reduction of flavanonols to flavan-3,4-diols.[1] We now report the stereoselective synthesis of (±)-aromadendrin, (±)-fustin and several (±)-flavan-3,4-diols based on the above results.

Preparation of the Flavanonols

Condensation of the acetophenone 1a with 4-methoxymethoxybenzaldehyde (2a)[1] using ethanolic potassium hydroxide afforded the chalcone 3a (90%). Alkaline hydrogen peroxide oxidation of 3a provided the epoxychalcone 4a (93%), in which assignment of the 2R*,3S*-configuration is based on a coupling ($J_{2,3}$ 2 Hz) in the ^{1}H-NMR spectrum. Treatment of 4a with methanolic hydrogen chloride furnished (±)-aromadendrin (5a) (89%) (2R*,3R*; $J_{2,3}$ 11.5 Hz). On acetylation with acetic anhydride/pyridine and methylation with dimethyl sulfate/potassium carbonate, 5a gave the tetraacetate 6a (77%) and the trimethyl ether 7a (95%), respectively. The compounds 3b — 7b were prepared by the procedures employed for the preparation of the corresponding a-series compounds.

Reduction of the Flavanonols

Reduction was carried out with sodium borohydride in methanol. Reduction of 6a,

followed by acetylation with acetic anhydride/pyridine gave the flavan-3,4-diol pentaacetate 8a (84%) (2R*,3S*,4R*; $J_{2,3}$ 6 and $J_{3,4}$ 4 Hz) as a sole product. Reduction of 7a afforded the flavan-3,4-diol trimethyl ether 9a (28%) (2R*,3S*, 4R*; $J_{2,3}$ 10 and $J_{3,4}$ 7.5 Hz) and the 4-epimer 10a (54%) (2R*,3S*,4S*; $J_{2,3}$ 10 and $J_{3,4}$ 7 Hz). Reduction of (±)-fustin tetraacetate (6b) (followed by acetylation) and (±)-fustin 7,3',4'-trimethyl ether (7b) provided (±)-mollisacacidin (leucofisetinidin) pentaacetate (8b) (94%) (2R*,3S*,4R*; $J_{2,3}$ 7 and $J_{3,4}$ 6 Hz) and (±)-mollisacacidin 7,3',4'-trimethyl ether (9b) (85%) (2R*,3S*,4R*; $J_{2,3}$ 10 and $J_{3,4}$ 8.5 Hz), respectively, as a sole product.

The stereochemistry of the sodium borohydride reduction observed for 6a,b and 7a,b is in consistent with that reported previously.[1]

Alternatively, lithium aluminum hydride reduction of 7b in tetrahydrofuran gave 9b (78%) and (±)-gleditsin 7,3',4'-trimethyl ether (10b) (18%) (2R*,3S*,4S*; $J_{2,3}$ 10 and $J_{3,4}$ 3.5 Hz).

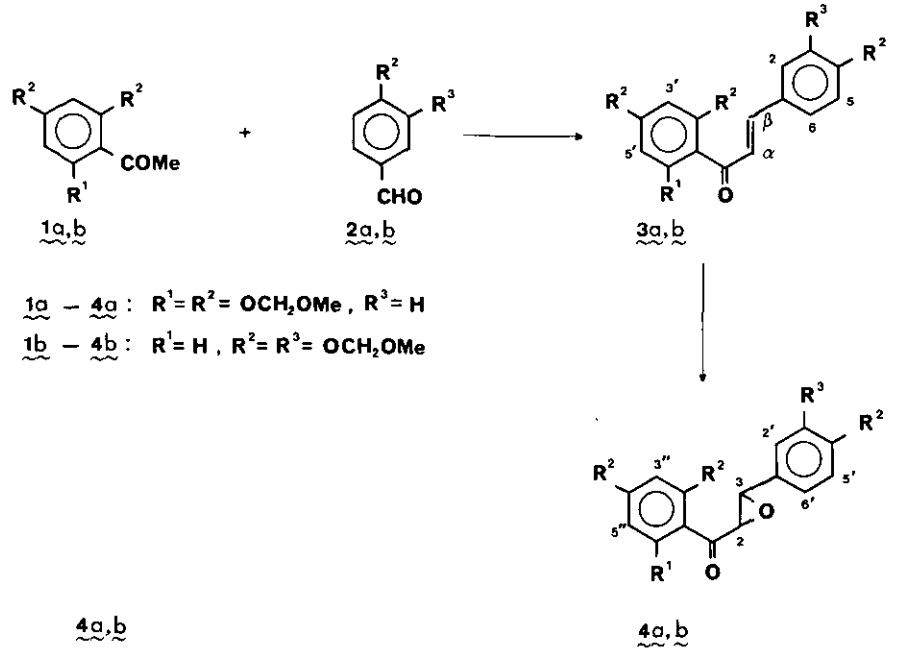
It is known that (+)- and (-)-leucodephinidin are 3,4,5,7,4'-pentahydroxyflavans with the 2R,3S-configuration.[4] However, the configurations of the 4-hydroxyl groups remained undecided. Structure elucidation of leucodephinidins is in progress in our laboratory on the basis of the structures of 8a, 9a and 10a.

EXPERIMENTAL

Melting points are uncorrected. Spectral data were recorded on the following spectrometers: IR, Hitachi 260-30; ^{1}H-NMR, Varian EM-390 (90 MHz); MS, JEOL JMS DX-300. The b-series compounds were prepared by the procedures employed for the preparation of the corresponding a-series compounds unless otherwise mentioned.

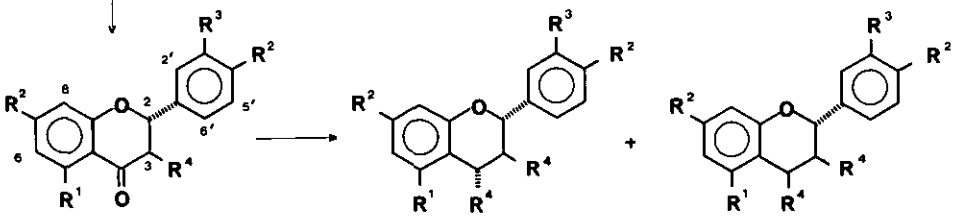
2,4,6-Tris(methoxymethoxy)acetophenone (1a)

A solution of 2,4-bis(methoxymethoxy)-6-hydroxyacetophenone[5] (1.0 g) in dichloromethane (10 ml) was added to a solution of NaOH (1 g) in water (10 ml), and the whole was stirred at room temperature for 15 min. Tetrabutylammonium chloride (92 mg) and methoxymethyl chloride (0.4 ml) were added, and the mixture was stirred at room temperature for 16 h. The organic phase was separated and washed with water, then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oil, which was purified by chromatography over silica gel (33 g) using chloroform as the eluent to yield 1a (1.06 g, 90%) as colorless needles of mp 40-42°C (MeOH). IR ($CHCl_3$): 1692 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ; 6.49 (2H, s, 3-,



1a – 4a : $R^1 = R^2 = OCH_2OMe$, $R^3 = H$

1b – 4b : $R^1 = H$, $R^2 = R^3 = OCH_2OMe$



5a : $R^1 = R^2 = R^4 = OH$, $R^3 = H$

6a : $R^1 = R^2 = R^4 = OAc$, $R^3 = H$

7a : $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = OAc$

8a : $R^1 = R^2 = R^4 = OAc$, $R^3 = H$

9a $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = OH$

10a : $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = OH$

5b–10b : R^1 and R^3 are exchanged.

Chart 1

5-H's), 5.12 (6H,s, 3×OCH_2O), 3.45 (9H, s, 3×OMe), 2.47 (3H, s, COMe). MS Calcd for $C_{14}H_{20}O_7$: M, 300.121. Found m/z: M^+, 300.121.

2,4-Bis(methoxymethoxy)acetophenone (1b)

A colorless oil (lit.,[3] bp 180°C/12 mm Hg). Yield, 75% (from 2,4-dihydroxyacetophenone). IR ($CHCl_3$): 1666 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.71 (1H, d, J 8.5 Hz, 6-H), 6.75 (1H, d, J 2 Hz, 3-H), 6.64 (1H, dd, J 8.5, 2 Hz, 5-H), 5.20, 5.13 (each 2H, s, 2×OCH_2O), 3.47, 3.43 (each 3H, s, 2×OMe), 2.56 (3H, s, COMe). MS Calcd for $C_{12}H_{16}O_5$: M, 240.100. Found m/z: M^+, 240.100.

3,4-Bis(methoxymethoxy)benzaldehyde (2b)

This compound was prepared in 80% yield from 3,4-dihydroxybenzaldehyde by the procedure employed for the preparation of 1a. A colorless oil (lit.,[3] mp 59–60°C). IR ($CHCl_3$): 1686 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 9.87 (1H, s, CHO), 7.66 (1H, d, J 2 Hz, 2-H), 7.51 (1H, dd, J 8.5, 2 Hz, 6-H), 7.24 (1H, d, J 8.5 Hz, 5-H), 5.29, 5.26 (each 2H, s, 2×OCH_2O), 3.52 (6H, s, 2×OMe). MS Calcd for $C_{11}H_{14}O_5$: M, 226.084. Found m/z: M^+, 226.083.

Tetrakis(O-methoxymethyl)isosalipurpol (3a)

A mixture of 1a (1.81 g), 2a[1] (1.0 g) and KOH (5 g) in anhydrous ethanol (50 ml) was stirred at room temperature for 15 h. The reaction mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate. The organic phase was washed with water and dried over Na_2SO_4. Removal of the solvent in vacuo, and recrystallization of the residue from methanol gave 3a (2.43 g, 90%) as yellow needles of mp 71–72°C. IR ($CHCl_3$): 1636 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.45 (2H, d, J 9 Hz, 2-, 6-H's), 7.30 (1H, d, J 16 Hz, β-H), 6.98 (2H, d, J 9 Hz, 3-, 5-H's), 6.83 (1H, d, J 16 Hz, α-H), 6.53 (2H, s, 3'-, 5'-H's), 5.16, 5.07 (each 4H, s, 4×OCH_2O), 3.47 (3H), 3.45 (3H), 3.36 (6H) (each s, 4×OMe). MS Calcd for $C_{23}H_{28}O_9$: M, 448.173. Found m/z: M^+, 448.174.

Tetrakis(O-methoxymethyl)butein (3b)

Pale yellow needles of mp 78–80°C (EtOH/ether) (lit.,[3] mp 69–70°C). Yield, 88%. IR ($CHCl_3$): 1648 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.65 (1H, d, J 8.5 Hz, 6'-H), 7.61 (1H, d, J 17.5 Hz, β-H), 7.45–7.02 (3H, m, 2-, 5-, 6-H's), 7.32 (1H, d, J 17.5 Hz, α-H), 6.84 (1H, d, J 2.5 Hz, 3'-H), 6.74 (1H, dd, J 8.5, 2.5 Hz, 5'-H),

5.29 (2H), 5.23 (4H), 5.19 (2H) (each s, 4×OCH_2O), 3.50 (3H), 3.48 (9H) (each s, 4×OMe). MS Calcd for $C_{23}H_{28}O_9$: M, 448.173. Found m/z; M^+, 448.174.

(2R*,3S*)-Tetrakis(O-methoxymethyl)isosalipurpol Epoxide (4a)

30% H_2O_2 (0.8 ml) and 2N NaOH (0.8 ml) were added to a solution of 3a (559 mg) in methanol (20 ml), and the whole was stirred at room temperature for 19 h. The reaction mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate. The organic phase was washed with 10% aqueous KI and 10% aqueous $Na_2S_2O_3$, then dried over Na_2SO_4. Removal of the solvent in vacuo, and recrystallization of the residue from methanol gave 4a (540 mg, 93%) as colorless needles of mp 65–66°C. IR ($CHCl_3$): 1692 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.24 (2H, d, J 9 Hz, 2'-, 6'-H's), 7.02 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.53 (2H, s, 3"-, 5"-H's), 5.15 (6H), 5.10 (2H) (each s, 4×OCH_2O), 3.96, 3.87 (each 1H, d, J 2 Hz, 2-, 3-H's), 3.45, 3.38 (each 6H, s, 4×OMe). MS Calcd for $C_{23}H_{28}O_{10}$: M, 464.168. Found m/z: M^+, 464.169.

(2R*,3S*)-Tetrakis(O-methoxymethyl)butein Epoxide (4b)

Colorless needles of mp 81–83°C (MeOH) (lit.,[3] mp 77–79°C). Yield, 77%. IR ($CHCl_3$): 1672 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, d, J 9 Hz, 6"-H), 7.12 (1H, d, J 8.5 Hz, 5'-H), 7.08 (1H, d, J 2 Hz, 2'-H), 6.93 (1H, dd, J 8.5, 2 Hz, 6'-H), 6.76 (1H, d, J 2 Hz, 3"-H), 6.71 (1H, dd, J 9, 2.5 Hz, 5"-H), 5.20 (4H), 5.16 (2H) (each s, 3×OCH_2O), 4.96, 4.85 (each 1H, d, J 7 Hz, OCH_2O), 4.26, 3.87 (each 1H, d, J 2 Hz, 2-, 3-H's), 3.48, 3.46, 3.43, 3.13 (each 3H, s, 4×OMe). MS Calcd for $C_{23}H_{28}O_{10}$: M, 464.168. Found m/z: M^+, 464.168.

(±)-Aromadendrin (5a)

15% Methanolic HCl (2 ml) was added to a solution of 4a (412 mg) in anhydrous methanol (0.2 ml), and the whole was stirred at 50°C for 15 min. The reaction mixture was concentrated in vacuo, and the residue was recrystallized from methanol to yield 5a (227 mg, 89%) as colorless needles of mp 212–213°C. IR (KBr): 3436, 3384 (OH), 1630 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 7.37 (2H, d, J 8.5 Hz, 2'-, 6'-H's), 6.86 (2H, d, J 8.5 Hz, 3'-, 5'-H's), 5.96, 5.92 (each 1H, d, J 2 Hz, 6-, 8-H's), 5.15, 4.57 (each 1H, d, J 11.5 Hz, 2-, 3-H's), 11.67, 9.68, 8.43, 4.58 (each 1H, s, 4×OH).[6] MS Calcd for $C_{15}H_{12}O_6$: M, 288.063. Found m/z: M^+, 288.065.

(±)-Fustin (5b)

Colorless needles of mp 219–223°C (MeOH) (lit.,[3] mp 217–218°C). Yield, 76%. IR (KBr): 3428, 3220 (OH), 1674 cm^{-1} (C=O). ^{1}H-NMR (CD_3OD) δ: 7.72 (1H, d, J 8.5 Hz, 5-H), 6.98 (1H, d, J 1 Hz, 2'-H), 6.83 (2H, br s, 5'-, 6'-H's), 6.52 (1H, dd, J 8.5, 2 Hz, 6-H), 6.32 (1H, d, J 2 Hz, 8-H), 4.93, 4.46 (each 1H, d, J 12 Hz, 2-, 3-H's). MS Calcd for $C_{15}H_{12}O_6$: M, 288.063. Found m/z: M^+, 288.064.

(±)-Aromadendrin Tetraacetate (6a)

A mixture of 5a (206 mg), acetic anhydride (0.8 ml) and anhydrous pyridine (6 drops) was stirred at room temperature for 17 h. The reaction mixture was taken up in ethyl acetate. The organic phase was washed with 10% $NaHCO_3$ and water, then dried over Na_2SO_4. Removal of the solvent *in vacuo*, and purification of the residue by prep. TLC (silica gel, acetone/benzene=1/10, v/v) gave 6a (200 mg, 77%), Rf 0.55, as colorless needles of mp 126–127°C (EtOH). IR ($CHCl_3$): 1766 (OC=O), 1706 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.48 (2H, d, J 9 Hz, 2'-, 6'-H's), 7.09 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.75, 6.58 (each 1H, d, J 2 Hz, 6-, 8-H's), 5.69, 5.39 (each 1H, d, J 12.5 Hz, 2-, 3-H's), 2.26 (6H), 2.25 (3H), 1.98 (3H) (each s, 4×OAc). MS Calcd for $C_{23}H_{20}O_{10}$: M, 456.106. Found m/z: M^+, 456.104.

(±)-Fustin Tetraacetate (6b)

Colorless needles of mp 158–159°C (EtOH) (lit.,[3] mp 150–151°C). Yield, 90%. IR ($CHCl_3$): 1766 (OC=O), 1706 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.93 (1H, d, J 9.5 Hz, 5-H), 7.43 (1H, dd, J 9.5, 2 Hz, 6'-H), 7.32 (1H, d, J 2 Hz, 2'-H), 7.25 (1H, d, J 9.5 Hz, 5'-H), 6.85 (1H, dd, J 9.5, 2 Hz, 6-H), 6.83 (1H, d, J 2 Hz, 8-H), 5.71, 5.42 (each 1H, d, J 12.5 Hz, 2-, 3-H's), 2.29 (9H), 2.03 (3H) (each s, 4×OAc). MS Calcd for $C_{23}H_{20}O_{10}$: M, 456.106. Found m/z: M^+, 456.106.

(±)-Aromadendrin 5,7,4'-Trimethyl Ether (7a)

A mixture of 5a (142 mg), dimethyl sulfate (617 mg) and K_2CO_3 (681 mg) in anhydrous acetone (6 ml) was refluxed in the stream of N_2 for 3 h. The reaction mixture was filtered and concentrated *in vacuo*, then the residue was taken up in ethyl acetate. Work-up of the organic phase, followed by prep. TLC (silica gel, acetone/benzene=1/5, v/v) of the reaction products, afforded 7a (155 mg, 95%), Rf 0.43, as colorless needles of mp 101–104°C (MeOH). IR ($CHCl_3$): 3476 (OH), 1676

cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.46 (2H, d, J 9 Hz, 2'-, 6'-H's), 6.96 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.10 (2H, s, 6-, 8-H's), 4.98 (1H, d, J 12.5 Hz, 2-H), 4.40 (1H, dd, J 12.5, 2 Hz, 3-H),[7] 4.00 (1H, d, J 2 Hz, 3-OH),[6] 3.89, 3.81, 3.79 (each 3H, s, 3×OMe). MS Calcd for $C_{18}H_{18}O_6$: M, 330.100. Found m/z: M^+, 330.100.

(±)-Fustin 7,3',4'-Trimethyl Ether (7b)

Colorless needles of mp 152–153°C (MeOH/ether) (lit.,[3] mp 143–144°C). Yield, 93%. IR ($CHCl_3$): 3492 (OH), 1674 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.86 (1H, d, J 8.5 Hz, 5-H), 7.12 (1H, dd, J 9, 2 Hz, 6'-H), 7.10 (1H, br s, 2'-H), 6.94 (1H, d, J 9 Hz, 5'-H), 6.64 (1H, dd, J 8.5, 2.5 Hz, 6-H), 6.49 (1H, d, J 2.5 Hz, 8-H), 5.04 (1H, d, J 12.5 Hz, 2-H), 4.53 (1H, dd, J 12.5, 2 Hz, 3-H),[7] 3.92, 3.89, 3.82 (each 3H, s, 3×OMe), 3.70 (1H, d, J 2 Hz, 3-OH).[6] MS Calcd for $C_{18}H_{18}O_6$: M, 330.110. Found m/z: M^+, 330.111.

(2R*,3S*,4R*)-3,4,5,7,4'-Pentaacetoxyflavan (8a)

A mixture of 6a (105 mg) and $NaBH_4$ (11 mg) in anhydrous methanol (20 ml) was stirred at -30°C for 1 h, and then 5% acetic acid (4 drops) was added. The reaction mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate. Work-up of the organic phase afforded an oil, which was acetylated by the procedure employed for the preparation of 6a from 5a to yield 8a (96 mg, 84%), Rf 0.49, as colorless needles of mp 122–124°C (MeOH). IR ($CHCl_3$): 1766, 1752 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ: 7.35 (2H, d, J 9 Hz, 2'-, 6'-H's), 7.02 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.73, 6.64 (each 1H, d, J 2 Hz, 6-, 8-H's), 6.08 (1H, d, J 4 Hz, 4-H), 5.44 (1H, dd, J 6, 4 Hz, 3-H), 5.32 (1H, d, J 6 Hz, 2-H), 2.27 (6H), 2.18 (3H), 1.96 (3H), 1.12 (3H) (each s, 5×OAc). MS Calcd for $C_{25}H_{24}O_{11}$: M, 500.132. Found m/z: M^+, 500.132.

(±)-Mollisacacidin (Leucofisetinidin) Pentaacetate (8b)

A colorless oil. Yield, 94%. IR ($CHCl_3$): 1744 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ: 7.31 (1H, d, J 9 Hz, 5-H), 7.25–7.11 (3H, m, 2'-, 5'-, 6'-H's), 6.75 (1H, d, J 2.5 Hz, 8-H), 6.73 (1H, dd, J 9, 2.5 Hz, 6-H), 6.09 (1H, d, J 6 Hz, 4-H), 5.46 (1H, dd, J 7, 6 Hz, 3-H), 5.25 (1H, d, J 7 Hz, 2-H), 2.28 (3H), 2.26 (6H), 1.95 (3H), 1.88 (3H) (each s, 5×OAc). MS Calcd for $C_{25}H_{24}O_{11}$: M, 500.132. Found m/z: M^+, 500.132.

(2R*,3S*,4R*)-5,7,4'-Trimethoxyflavan-3,4-diol (9a) and the (2R*,3S*,4S*)-Isomer 10a

A mixture of 7a (80.9 mg) and $NaBH_4$ (21 mg) in anhydrous methanol (3 ml) was stirred at -20°C for 3 h. Work-up of the reaction mixture, followed by prep. TLC (silica gel, acetone/benzene=1/5, v/v) of the reaction products gave 9a (22.9 mg, 28%), Rf 0.20, and 10a (44.0 mg, 54%), Rf 0.27.

Compound 9a: Colorless prisms of mp 108–109°C (MeOH). IR ($CHCl_3$): 3584, 3476 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.41 (2H, d, J 9 Hz, 2'-, 6'-H's), 6.94 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.14, 6.07 (each 1H, d, J 2.5 Hz, 6-, 8-H's), 4.98 (1H, dd, J 7.5, 1.5 Hz, 4-H),[7] 4.69 (1H, d, J 10 Hz, 2-H), 4.05 (1H, ddd, J 10, 7.5, 3 Hz, 3-H),[7] 3.82, 3.72, 3.70 (each 3H, s, 3×OMe), 2.40 (1H, d, J 3 Hz, 3-OH).[6] MS Calcd for $C_{18}H_{20}O_6$: M, 332.126. Found m/z: M^+, 332.126.

Compound 10a: Colorless needles of mp 165–166°C (MeOH). IR ($CHCl_3$): 3548, 3412 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.40 (2H, d, J 9 Hz, 2'-, 6'-H's), 6.94 (2H, d, J 9 Hz, 3'-, 5'-H's), 6.11 (2H, s, 6-, 8-H's), 5.00 (1H, d, J 4 Hz, 4-H), 4.89 (1H, d, J 10 Hz, 2-H), 3.92 (1H, ddd, J 10, 7, 4 Hz, 3-H),[7] 3.85, 3.82, 3.77 (each 3H, s, 3×OMe), 2.77 (1H, s, 4-OH),[6] 2.55 (1H, d, J 7 Hz, 3-OH).[6] MS Calcd for $C_{18}H_{20}O_6$: M, 332.126. Found m/z: M^+, 332.126.

(±)-Mollisacacidin (Leucofisetinidin) 7,3',4'-Trimethyl Ether (9b) and (±)-Gleditsin 7,3',4'-Trimethyl Ether (10b)

1) $NaBH_4$ reduction of 7b furnished 9b (85%) as colorless needles of mp 145–147°C (MeOH/ether) (lit.,[8] mp 150–151°C). IR ($CHCl_3$): 3572, 3432 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.39 (1H, d, J 8.5 Hz, 5-H), 7.03 (1H, dd, J 9, 1.5 Hz, 6'-H), 6.99 (1H, br s, 2'-H), 6.86 (1H, d, J 9 Hz, 5'-H), 6.60 (1H, dd, J 8.5, 2.5 Hz, 6-H), 6.41 (1H, d, J 2.5 Hz, 8-H), 4.80 (1H, dd, J 8.5, 5.5 Hz, 4-H),[7] 4.75 (1H, d, J 10 Hz, 2-H), 3.86 (6H), 3.73 (3H) (each s, 3×OMe), 3.82 (1H, ddd, J 10, 8.5, 2.5 Hz, 3-H),[7] 2.72 (1H, d, J 5.5 Hz, 4-OH),[6] 2.25 (1H, d, J 2.5 Hz, 3-OH).[6] MS Calcd for $C_{18}H_{20}O_6$: M, 332.126. Found m/z: M^+, 332.126.

2) A mixture of 7b (54.0 mg) and $LiAlH_4$ (10 mg) in anhydrous tetrahydrofuran (5 ml) was stirred at -30°C for 4 h. Work-up of the reaction mixture and purification of the reaction products by prep. TLC (silica gel, acetone/benzene=1/10, v/v) gave 9b (42.3 mg, 78%), Rf 0.41, and 10b (9.7 mg, 18%), Rf 0.45.

Compound 10b: Colorless needles of mp 171–173°C (MeOH/ether) (lit.,[8] mp 185°C). IR ($CHCl_3$): 3564, 3380 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.23 (1H, d, J 9 Hz, 5-H),

7.00 (1H, s, 2'-H), 6.99 (1H, d, J 9 Hz, 6'-H), 6.97 (1H, d, J 9 Hz, 5'-H), 6.53 (1H, dd, J 9, 2 Hz, 6-H), 6.47 (1H, d, J 2 Hz, 8-H), 4.97 (1H, d, J 10 Hz, 2-H), 4.75 (1H, dd, J 5, 3.5 Hz, 4-H),[7] 4.00 (1H, ddd, J 10, 7, 3.5 Hz, 3-H),[7] 3.90 (6H), 3.76 (3H). (each s, 3×OMe), 2.60 (1H, d, J 5 Hz, 4-OH),[6] 2.16 (1H, d, J 7 Hz, 3-OH).[6] MS Calcd for $C_{18}H_{20}O_6$: M, 332.126. Found m/z: M^+, 332.127.

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REFERENCES AND NOTES

1. Part XVII: H. Takahashi, Y. Kubota, M. Iguchi, and M. Onda, Chem. Pharm. Bull., 1985, 33, 3134.
2. H. Takahashi, Y. Kubota, H. Miyazaki, and M. Onda, Heterocycles, 1984, 22, 1147.
3. T. Oyamada, Justus Liebigs Ann. Chem., 1939, 538, 44; T. Oyamada and H. Baba, Bull. Chem. Soc. Jpn., 1966, 39, 507.
4. A. K. Ganguly, T. R. Seshadri, and P. Subramanian, Tetrahedron, 1958, 3, 225.
5. E. A. Sherif, A. Islam, and M. Krishnamurti, Indian J. Chem., 1982, 21B, 478.
6. On addition of deuterium oxide, these signals disappeared.
7. On addition of deuterium oxide, these splittings were simplified due to the disappearance of the hydroxyl protons.

8. S. E. Drewes and D. G. Boux, Biochem. J., 1964, 90, 343.

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