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Heterocycles. XVII.[1] Sodium Borohydride Reduction of Flavanonols and Hydrolysis of (±)-Fistacacidin Acetates

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The effects of 5-substituents on sodium borohydride reduction of flavanonols have been examined. The bulk of substituents governs the stereochemistry of reduction, and particularly, the acetoxy group gives an interesting result accompanied by over-reduction. In addition, the 5-acetoxy group plays an improtant role in the stereochemistry of the newly introduced 4-oxygen functions in hydrolysis of (±)-fistacacidin acetates.

Keywords——flavonoid; reduction; hydrolysis; stereochemistry; mechanism

In the course of our studies on flavonoids, we reported that sodium borohydride reduction of (2*R**,3*R**)-flavanonol (**1**) in methanol gave (2*R**,3*S**,4*R**)-flavan-3,4-diol (**2**) (64%) as a sole product, whereas (±)-taxifolin tetramethyl ether (**3**) afforded (2*R**,3*S**,4*R**)-5,7,3′,4′-tetramethoxyflavan-3,4-diol (**4**) (14%) and the 4*S**-isomer **5** (67%).[2] On the other hand, Patiland and Deshpande reported that (2*R**,3*R**)-5,4′-dihydroxyflavanonol (**6**) was reduced with sodium borohydride in tetrahydrofuran to give (±)-fistacacidin (2*R**,3*S**,4*R**) (**7**) (85%) as a sole product.[3] We examined in detail sodium borohydride reduction of **6** and its derivatives, and found that the bulk of 5-substituents governs the stereochemistry of reduction, and particularly, the acetoxy group gives an interesting result accompanied by over-reduction. In addition, it was observed that the 5-acetoxy group plays an important role in the stereochemistry of the newly introduced 4-oxygen functions in hydrolysis of (±)-fistacacidin acetates.

Preparation of the Flavanonols

Condensation of the acetophenone **8** with the benzaldehyde **9** using ethanolic potassium hydroxide gave the chalcone **10** (73%), which was converted into the epoxychalcone **11** (83%) on alkaline hydrogen peroxide oxidation in methanol. The 2*R**,3*S**-configuration of **11** was deduced from a coupling (2 Hz) observed between the 2- and 3-protons in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum.[2] Treatment of **11** with methanolic hydrogen chloride afforded **6** (61%) (2*R**,3*R**, $J_{2,3}$ 12 Hz). Methylation of **6** with dimethyl sulfate–potassium carbonate in boiling acetone gave the dimethyl ether **12** (70%). Acetylation of **6** with acetic anhydride–pyridine afforded the triacetate **13** (96%).

Sodium Borohydride Reduction of the Flavanonols

Reduction was carried out in 2-propanol at room temperature, using excess reducing agent.

Compound **1** gave **2** (88%) as a sole product. Compound **6** afforded **7** (2*R**,3*S**,4*R**) (79%) and the 4*S**-isomer **14** (6.5%). These compounds were characterized by couplings observed among the 2-, 3- and 4-protons in the ^{1}H-NMR spectra (**7**, $J_{2,3}$ 10, $J_{3,4}$ 8 Hz; **14**, $J_{2,3}$ 9.5, $J_{3,4}$ 4 Hz). Methylation and acetylation of **7** provided the dimethyl ether **15** (97%) and the

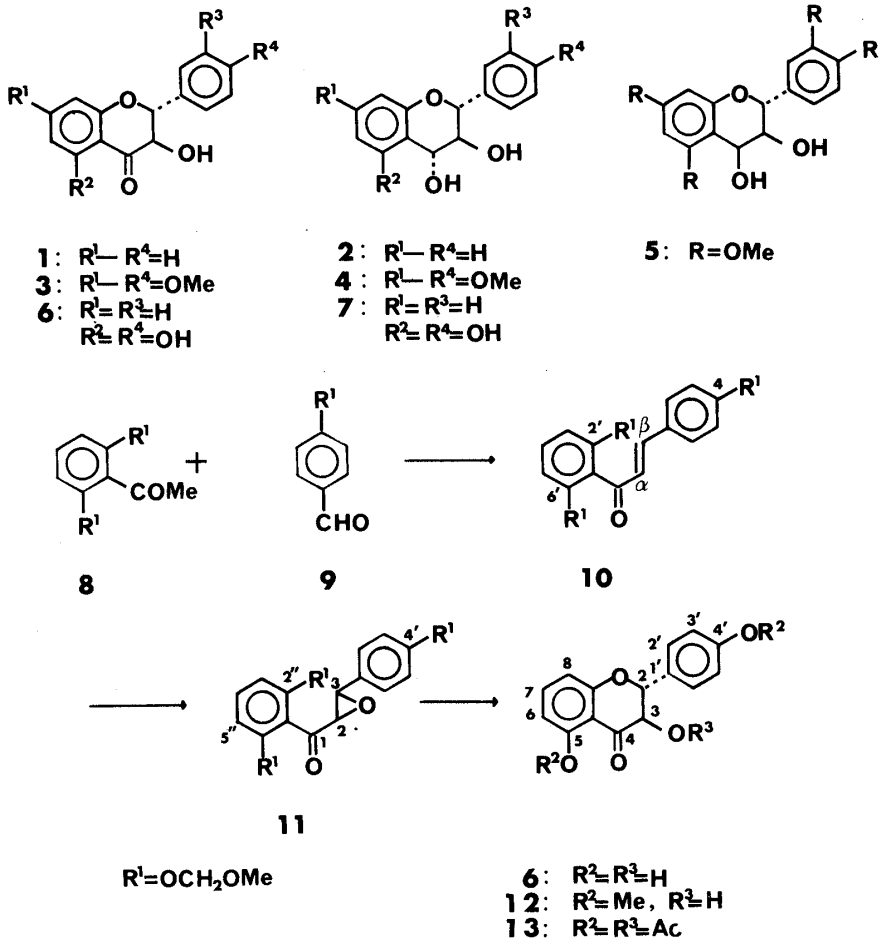

Chart 1

tetraacetate **16** (80%), respectively. The dimethyl ether **12** gave **15** (41%) and the 4*S**-isomer **17** (40%) (**15**, $J_{2,3}$ 10, $J_{3,4}$ 8 Hz; **17**, $J_{2,3}$ 9.5, $J_{3,4}$ 4 Hz). Acetylation of **15** and **17** furnished the diacetates **18** (97%) and **19** (92%), respectively. The triacetate **13** gave a mixture of (±)-fistacacidin triacetate **20** and the flavan-3-ol diacetate **21**, which were converted into the following compounds to confirm the structure. Methylation of the mixture afforded the methyl ether **22** (67%) (4-H_2, δ 2.96, 2.67; 5-OMe, δ 3.79). During methylation and preparative thin-layer chromatography (prep. TLC), **20** changed to unidentified compounds. Acetylation of the mixture provided **16** (4%) and the triacetate **23** (87%) [**23**, 4-H_2, δ 2.90, 2.63; 3-, 5-, 4′-OCOMe's, δ 2.26 (2), 1.96 (1)]. Reduction of **13** at −30 °C, followed by acetylation, gave **16** (39.5%) and **23** (36%). On the other hand, reduction in methanol at −30 °C afforded **20** as a sole product, which gave **16** (89%) on acetylation.

It is known that sodium borohydride reduction of ketones proceeds through a product-like transition state (t.s.) and that the stereoselectivity in the reduction of hindered ketones is controlled by steric interactions between the substituent under consideration and the incoming borohydride in the product-like t.s.[4] The relevant product-like t.s.'s for consideration are depicted in Chart 2.

The t.s. A involves a steric interaction between the forming 4eq-hydroxy group and the 5-substitutent. The 2ax-hydrogen atom does not reach up far enough to interact, so that the incoming borohydride does not affect the t.s. A. The t.s. B contains a steric interaction between the forming 4ax-hydroxy group and the 2ax-hydrogen atom as well as a *gauche* effect between the forming 4ax-hydroxy group and the 2—3 bond. In addition, a steric interaction

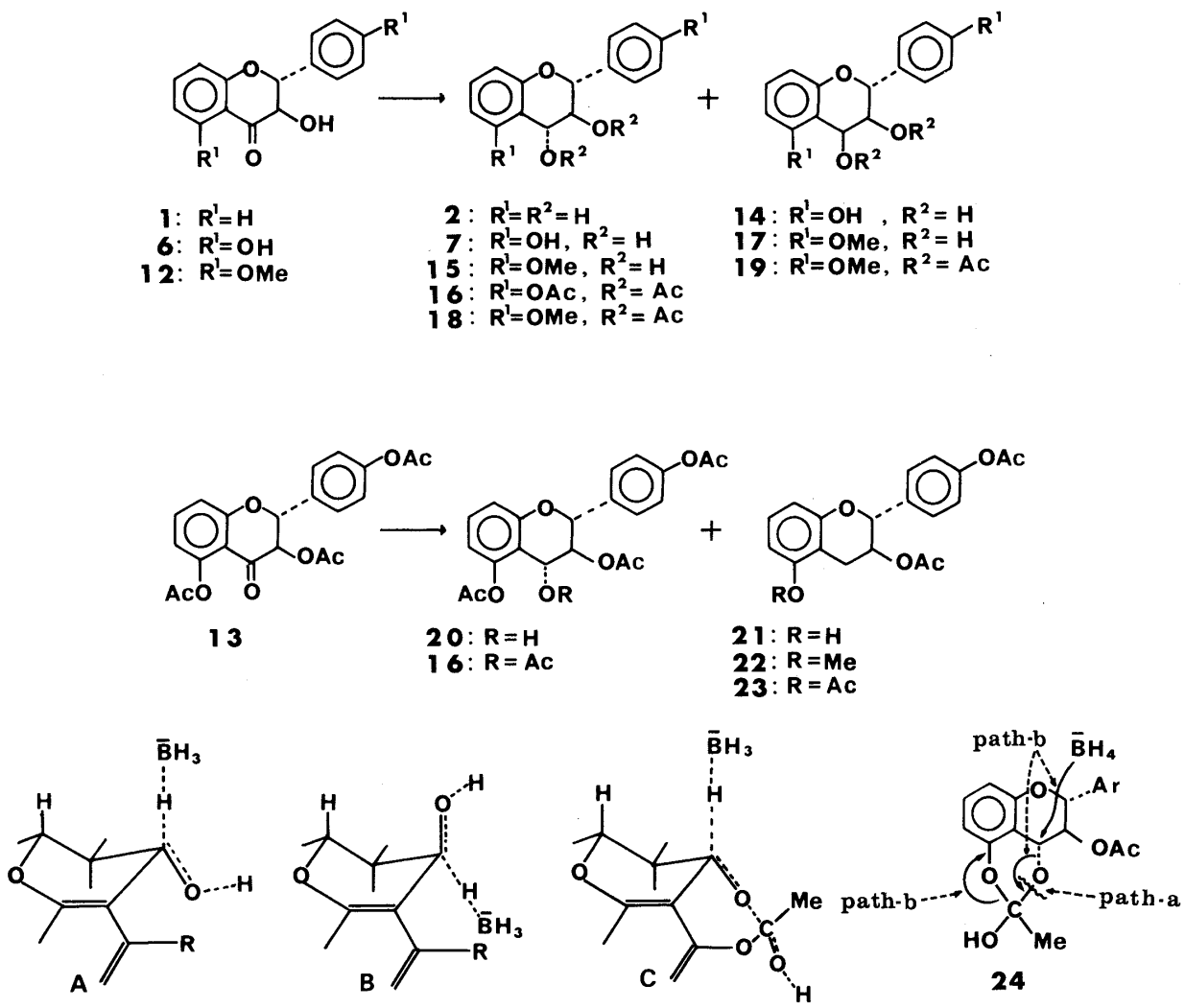

Chart 2

exists between the incoming borohydride and the 5-substituent. When the 5-position has no substituent, this interaction is not operative for the same reason as above.

Reduction of **1** gave **2** as a sole product *via* the t.s. A. It can be seen that the steric interactions arising from the forming 4ax-hydroxy group in the t.s. B (R=H) are very much stronger than that between the forming 4eq-hydroxy group and the 5-hydrogen atom in the t.s. A (R=H). Reduction of **12** afforded **15** and **17** in nearly equal amounts, suggesting a balance between the steric interactions inherent in the t.s. A and B (R=OMe). Reduction of **6** gave **7** and **14** in an approximate yield ratio of 12:1, suggesting a large difference in the stabilities of the two t.s.'s. It is thought that the 5-hydroxy group (acidic) is converted into an alkoxyborohydride and that a large destabilization of the t.s. B (R=OB$\leq$) arises from an electrostatic repulsion and a steric interaction between the two anions. As a result, reduction preferentially proceeds *via* the t.s. A. Reduction of **13** gave an interesting result different from the above and can be explained as follows. Comparison of the flavanonol structures suggests that the 5-acetoxy group plays an important role in the reduction. The t.s. B (R=OAc) appears to be destabilized with respect to the t.s. A (R=OAc) because of the large steric interaction between the incoming borohydride and the 5-acetoxy group. On the other hand, partial binding of the 4-oxygen atom to the carbonyl carbon of the 5-acetoxy group in the t.s. A releases the steric interaction between them, and the t.s. C, an alternative to the t.s. A,

becomes more advantageous than the t.s. B. The resulting dioxane **24** competitively gives **20** and **21** by the cleavage of the C–O bond (path-a) and by reduction at the 4-position accompanied by the elimination of acetic acid (path-b), respectively. Since **20** was not reduced to give **21**, the path-a is irreversible. At room temperature, the path-b proceeds exclusively. A lowering of the reaction temperature seems to suppress the path-b, and at $-30\,^{\circ}C$, the path-a and -b nearly equally favored. Furthermore, the change of the solvent 2-propanol to methanol completely depresses the path-b probably due to the change of the real reducing agent and of the contribution of the solvent.[4]

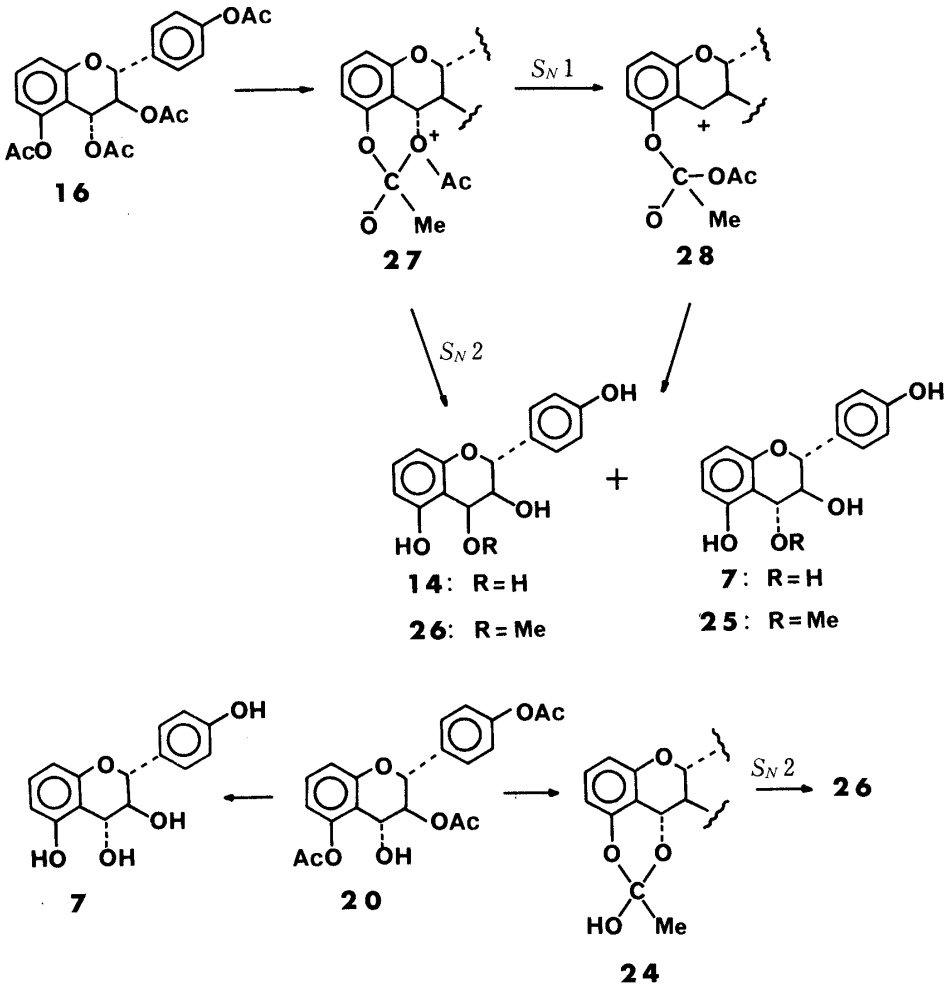

Chart 3

Hydrolysis of (±)-Fistacacidin Acetates

Hydrolysis of **16** with aqueous potassium hydroxide in a stream of nitrogen gave **7** (6%) and **14** (11%). On hydrolysis with methanolic potassium hydroxide, **16** afforded the methyl ether (2*R**,3*S**,4*R**) **25** (9%) and the 4*S**-isomer **26** (63%) (**25**, $J_{2,3}$ 9, $J_{3,4}$ 7 Hz; **26**, $J_{2,3}$ 10, $J_{3,4}$ 3.5 Hz). Hydrolysis of **20** with methanolic potassium hydroxide provided **7** (7%) and **26** (24%). On hydrolysis with aqueous and methanolic potassium hydroxide, **18**, **19** and (2*R**,3*S**,4*R**)-3,4-diacetoxyflavan[5] normally afforded the corresponding hydroxy compounds as a sole product. Compound **7** did not isomerize under the hydrolysis conditions.

At first glance, the anomalous results obtained in the hydrolysis of **16** and **20** appear to be ascribed to the 5-acetoxy group and can be explained as follows. A dioxane **27**, formed from **16**, gives **7** (**25**) and **14** (**26**) by an S_N1-type reaction *via* a zwitterion **28**. In addition, **27** can

afford **14** (**26**) by an S_N2-type reaction at the 4-position. It cannot be ignored that the normal hydrolysis of **16** with aqueous potassium hydroxide gives **7**. However, the fact that **7** was not detected in the hydrolyzate of **16** with methanolic potassium hydroxide suggests the fast and exclusive formation of **27** in the normal hydrolysis under these hydrolysis conditions. A dioxane **24**, derived from **20** under hydrolysis conditions, gives **26** by an S_N2-type reaction at the 4-position. The formation of **7** from **20** is, of course, due to the normal hydrolysis occurring competitively.

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Prep. TLC's were carried out on silica gel plates unless otherwise noted, using acetone (A)–benzene (B) (v/v) as the solvents. Gas chromatographies (GC) were performed with a Shimadzu GC-4CM (PF) using an SE-30 column. Spectra were recorded on the following spectrometers: infrared (IR)—Hitachi 260-30; ^{1}H-NMR—Varian EM-390 (90 MHz) (reference, tetramethylsilane); mass (MS)—JEOL JMS DX-300.

2,6-Bis(methoxymethoxy)acetophenone (8)——A mixture of 2,6-dihydroxyacetophenone (300.0 mg), methoxymethyl chloride (0.6 ml) and K_2CO_3 (2.4 g) in anhydrous acetone (24 ml) was refluxed for 3 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*, and then the residue was extracted with chloroform. Removal of the solvent *in vacuo* gave an oil, which was purified by prep. TLC (A : B = 1 : 5) to yield **8** (137.4 mg, 29%), *Rf* 0.62, and the monoether (98.0 mg, 25%), *Rf* 0.77.

A solution of NaOH (270 mg) in water (7 ml) was added to a mixture of the monoether (98.0 mg) and tetrabutylammonium chloride (10 mg) in dichloromethane (7 ml), and then methoxymethyl chloride (0.1 ml) was added. The whole was stirred at room temperature overnight. Work-up of the organic phase gave **8** (113.6 mg, 95%). Total yield from 2,6-dihydroxyacetophenone, 53%. Light yellow needles of mp 47—48.5 °C (from hexane). IR ($CHCl_3$): 1705 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.22 (1H, t, *J* 9 Hz, 4-H), 6.76 (2H, d, *J* 9 Hz, 3-, 5-H's), 5.13 (4H, s, 2 × OCH_2O), 3.43 (6H, s, 2 × OCH_3), 2.50 (3H, s, $COCH_3$). MS Calcd for $C_{12}H_{16}O_5$: M, 240.100. Found *m/z*: M$^+$, 240.102.

4-Methoxymethoxybenzaldehyde (9)——A mixture of 4-hydroxybenzaldehyde (217.3 mg), methoxymethyl chloride (0.2 ml) and K_2CO_3 (3 g) in anhydrous acetone (10 ml) was refluxed for 2.5 h. Work-up of the reaction mixture, followed by prep. TLC (A : B = 1 : 5) of the reaction products, afforded **9** (265.0 mg, 90%), *Rf* 0.80, as a colorless oil. IR ($CHCl_3$): 1690 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 9.90 (1H, s, CHO), 7.88, 7.18 (2H each, d, *J* 9 Hz, aromatic H's), 5.26 (2H, s, OCH_2O), 3.50 (3H, s, OCH_3). MS Calcd for $C_9H_{10}O_3$: M, 166.063. Found *m/z*: M$^+$, 166.064.

4,2',6'-Tris(methoxymethoxy)chalcone (10)——A mixture of **8** (101.4 mg), **9** (82.6 mg) and KOH (279 mg) in anhydrous ethanol (2 ml) was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with benzene. Removal of the solvent *in vacuo*, followed by prep. TLC (A : B = 1 : 10) of the residue, afforded **10** (126.0 mg, 73%), *Rf* 0.45, as a light yellow oil. IR ($CHCl_3$): 1625 cm^{-1} (C=O). ^{1}H-NMR (benzene-d_6) δ: 7.46—6.70 (9H, m, aromatic, olefinic H's), 4.82 (4H, s, 2 × OCH_2O), 4.76 (2H, s, OCH_2O), 3.13 (6H, s, 2 × OCH_3), 3.10 (3H, s, OCH_3). MS Calcd for $C_{21}H_{24}O_7$: M, 388.152. Found *m/z*: M$^+$, 388.152.

(2*R,3*S**)-1-2'',6''-Bis(methoxymethoxy)phenyl-2,3-epoxy-3,4'-methoxymethoxyphenylpropanone (11)**——30% H_2O_2 (0.3 ml) and 2 N NaOH (0.3 ml) were added to a solution of **10** (397.3 mg) in methanol (5 ml), and the whole was stirred at room temperature for 2 h. The reaction mixture was taken up in ethyl acetate. The organic phase was washed with 10% aqueous KI and 10% aqueous $Na_2S_2O_3$. Removal of the solvent *in vacuo* gave an oil, which was purified by prep. TLC (A : B = 1 : 5) to yield **11** (341.3 mg, 83%), *Rf* 0.59, as a colorless oil. IR ($CHCl_3$): 1700 cm^{-1} (C=O). ^{1}H-NMR (benzene-d_6), δ: 7.26—6.75 (7H, m, aromatic H's), 5.12 (6H, s, 3 × OCH_2O), 3.96, 3.85 (1H each, d, *J* 2 Hz, 2-, 3-H's), 3.42 (3H, s, OCH_3), 3.40 (6H, s, 3 × OCH_2O). MS Calcd for $C_{21}H_{24}O_4$: M, 404.147. Found *m/z*: M$^+$, 404.150.

(2*R,3*R**)-5,4'-Dihydroxyflavanonol (6)**——12% methanolic HCl (0.6 ml) was added to a solution of **11** (300.3 mg) in anhydrous methanol (5 ml), and the whole was stirred at room temperature for 3.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from 2-propanol to yield **6** (103.5 mg, 51%) as colorless needles of mp 198—200 °C (lit.[3], mp 195—197 °C). The mother liquor from the recrystallization was concentrated *in vacuo*, and the residue was purified by prep. TLC (A : B = 1 : 3) to yield additional **6** (20.0 mg, 10%), *Rf* 0.29. Total yield, 61%. IR (KBr): 3450, 3380, 3325 (OH), 1625 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6) δ: 12.30, 8.67 (1H each, s, 5-, 4'-OH's),[6] 7.64 (1H, t, *J* 8.5 Hz, 7-H), 7.61 (2H, d, *J* 9 Hz, 2'-, 6'-H's), 7.03 (2H, d, *J* 9 Hz, 3'-, 5'-H's), 6.65, 6.57 (1H each, dd, *J* 8.5, 1 Hz, 6-, 8-H's), 5.28 (1H, dd, *J* 12, 1 Hz, 3-H),[7] 4.88 (1H, d, *J* 1 Hz, 3-OH),[6] 4.82 (1H, d, *J* 12 Hz, 2-H). MS Calcd for $C_{15}H_{12}O_5$: M, 272.068. Found *m/z*: M$^+$, 272.067.

(2*R,3*R**)-5,4'-Dimethoxyflavanonol (12)**——A mixture of **6** (96.3 mg), dimethyl sulfate (449 mg) and K_2CO_3 (492 mg) in anhydrous acetone (6 ml) was refluxed for 2 h. The reaction mixture was filtered and concentrated *in vacuo*, then the residue was extracted with ethyl acetate. The organic phase was concentrated *in vacuo*, and the residue

was crystallized from ethanol–ether to yield **12** (62.0 mg, 58%) as colorless needles of mp 145—147 °C. The mother liquor from the crystallization was concentrated *in vacuo*, and the residue was purified by prep. TLC (A : B = 1 : 4) to yield additional **12** (12.2 mg, 12%), *Rf* 0.46. Total yield, 70%. IR ($CHCl_3$): 3450 (OH), 1650 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.31 (2H, d, *J* 9 Hz, 2′-, 6′-H's), 6.93 (1H, t, *J* 8.5 Hz, 7-H), 6.76 (2H, d, *J* 9 Hz, 3′-, 5′-H's), 6.46, 6.02 (1H each, dd, *J* 8.5, 1 Hz, 6-, 8-H's), 4.73 (1H, d, *J* 12.5 Hz, 2-H), 4.23 (1H, dd, *J* 12.5, 1 Hz, 3-H),[7] 4.05 (1H, d, *J* 1 Hz, 3-OH),[6] 3.33, 3.30 (3H each, s, 5-, 4′-OCH_3's). MS Calcd for $C_{17}H_{16}O_5$: M, 300.100. Found *m/z*: M^+, 300.100.

(2*R,3*R**)-3,5,4′-Triacetoxyflavanone (13)**——A mixture of **6** (29.7 mg), acetic anhydride (2 ml) and anhydrous pyridine (4 drops) was stirred at room temperature for 6 h. The reaction mixture was taken up in ethyl acetate. The organic phase was washed with 5% aqueous $NaHCO_3$ and water. Removal of the solvent *in vacuo* and recrystallization of the residue from tetrachloromethane gave **13** (37.0 mg, 85%) as colorless needles of mp 162—164 °C. The mother liquor from the recrystallization was concentrated *in vacuo*, and the residue was purified by prep. TLC (Al_2O_3; A : B = 1 : 10) to yield additional **13** (4.5 mg, 11%), *Rf* 0.73. Total yield, 96%. IR ($CHCl_3$): 1750 (OC=O), 1705 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.48 (1H, t, *J* 8 Hz, 7-H), 7.46 (2H, d, *J* 8.5 Hz, 2′-, 6′-H's), 7.03 (2H, d, *J* 8.5 Hz, 3′-, 5′-H's), 6.92, 6.72 (1H each, dd, *J* 8, 1 Hz, 6-, 8-H's), 5.70, 5.37 (1H each, d, *J* 12.5 Hz, 2-, 3-H's), 2.36, 2.28 (3H each, s, 5-, 4′-$OCOCH_3$'s), 2.00 (3H, s, 3-$OCOCH_3$). MS Calcd for $C_{21}H_{18}O_8$: M, 398.100. Found *m/z*: M^+, 398.100.

Reduction of (2*R,3*R**)-Flavanonol (1)**——A mixture of **1**[2] (120.0 mg, 0.5 mmol) and $NaBH_4$ (42.5 mg, 1.1 mmol) in anhydrous 2-propanol (4 ml) was stirred at room temperature for 1 h, and then acetic acid (5 drops) was added. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with ethyl acetate. Removal of the solvent *in vacuo* and recrystallization of the residue from methanol gave (2*R**,3*S**,4*R**)-flavan-3,4-diol (**2**) (107.0 mg, 88%) as colorless needles of mp 140—142 °C. This compound was shown to be identical with an authentic sample[2] of **2** by direct comparison.

Reduction of 6——A mixture of **6** (56.0 mg, 0.2 mmol) and $NaBH_4$ (21.4 mg, 0.56 mmol) in anhydrous 2-propanol (6 ml) was stirred at room temperature for 1 h. Work-up of the reaction mixture and purification by prep. TLC (A : B = 1 : 3) gave **7** (44.6 mg, 79%), *Rf* 0.53, and **14** (3.6 mg, 6.5%), *Rf* 0.43.

(±)-Fistacacidin (**7**): Colorless needles of mp 198 °C (dec.) (from ethanol [lit.,[3] mp 220 °C (dec.)]. IR (KBr): 3444, 3300 cm^{-1} (OH). ^{1}H-NMR (acetone-d_6) δ: 9.08, 8.51 (1H each, s, 5-, 4′-OH's),[6] 7.48 (2H, d, *J* 8.5 Hz, 2′-, 6′-H's), 7.16 (1H, t, *J* 8.5 Hz, 7-H), 6.97 (2H, d, *J* 8.5 Hz, 3′-, 5′-H's), 6.52, 6.21 (1H each, dd, *J* 8.5, 1 Hz, 6-, 8-H's), 5.64 (1H, d, *J* 4 Hz, 4-OH),[6] 5.16 (1H, dd, *J* 8, 4 Hz, 4-H),[7] 4.37 (1H, d, *J* 10 Hz, 2-H), 4.36 (1H, d, *J* 5.5 Hz, 3-OH),[6] 4.03 (1H, ddd, *J* 10, 8, 5.5 Hz, 3-H).[7] MS Calcd for $C_{15}H_{14}O_5$: M, 274.083. Found *m/z*: M^+, 274.084.

(±)-Fistacacidin Dimethyl Ether (**15**): This compound was prepared from **7** as colorless needles of mp 140—141 °C (from methanol) in 97% yield by the procedure employed for the preparation of **12** from **6**. IR ($CHCl_3$): 3600 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.43 (2H, d, *J* 9 Hz, 2′-, 6′-H's), 7.20 (1H, t, *J* 9 Hz, 7-H), 6.95 (2H, d, *J* 9 Hz, 3′-, 5′-H's), 6.56, 6.48 (1H each, dd, *J* 9, 1 Hz, 6-, 8-H's), 5.05 (1H, d, *J* 8 Hz, 4-H), 4.72 (1H, d, *J* 10 Hz, 2-H), 4.05 (1H, m, 3-H),[7] 4.03, 2.30 (1H each, br s, 3-, 4-OH's),[6] 3.90, 3.82 (3H each, 5-, 4′-OCH_3's). MS Calcd for $C_{17}H_{18}O_5$: M, 302.115. Found *m/z*: M^+, 302.116.

(±)-Fistacacidin Tetraacetate (**16**): This compound was prepared from **7** as colorless needles of mp 157—159 °C (from ethanol (lit.[3] mp 149 °C) in 80% yield by the procedure employed for the preparation of **12** from **6**. IR ($CHCl_3$): 1750 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ: 7.36 (1H, t, *J* 8 Hz, 7-H), 7.36 (2H, d, *J* 8.5 Hz, 2′-, 6′-H's), 7.05 (2H, d, *J* 8.5 Hz, 3′-, 5′-H's), 6.93, 6.76 (1H each, dd, *J* 8, 1 Hz, 6-, 8-H's), 6.12 (1H, d, *J* 5 Hz, 4-H), 5.46 (1H, dd, *J* 6, 5 Hz, 3-H), 5.30 (1H, d, *J* 6 Hz, 2-H), 2.26, 2.20 (3H each, s, 5-, 4′-$OCOCH_3$'s), 1.96, 1.76 (3H each, s, 3-, 4-$OCOCH_3$'s). MS Calcd for $C_{23}H_{22}O_9$: M, 442.126. Found *m/z*: M^+, 442.127.

(2*R**,3*S**,4*S**)-3,4,5,4′-Tetrahydroxyflavan (**14**): Colorless needles of mp 189 °C (dec.) (from ethanol). IR (KBr): 3410, 3325 cm^{-1} (OH). ^{1}H-NMR (acetone-d_6) δ: 8.46 (2H, s, 5-, 4′-OH's),[6] 7.32 (2H, d, *J* 8.5 Hz, 2′-, 6′-H's), 7.05 (1H, t, *J* 8.5 Hz, 7-H), 6.87 (2H, d, *J* 8.5 Hz, 3′-, 5′-H's), 6.45, 6.31 (1H each, dd, *J* 8.5, 1 Hz, 6-, 8-H's), 5.04, 3.68 (1H each, br s, 3-, 4-OH's),[6] 5.00—4.90 (2H, m, 2-, 4-H's),[8] 3.92 (1H, m, 3-H).[8] MS Calcd for $C_{15}H_{14}O_5$: M, 274.083. Found *m/z*: M^+, 274.084.

Reduction of 12——A mixture of **12** (69.5 mg, 0.23 mmol) and $NaBH_4$ (20.1 mg, 0.53 mmol) in anhydrous 2-propanol (10 ml) was stirred at room temperature for 1.5 h. Work-up of the reaction mixture and purification by prep. TLC (A : B = 1 : 3) afforded **15** (28.8 mg, 41%), *Rf* 0.37, and **17** (28.0 mg, 40%), *Rf* 0.42. Unreacted **12** (4.5 mg, 6.5%) was recovered from the zone with *Rf* 0.30.

(±)-Fistacacidin Dimethyl Ether (**15**): This compound was shown to be identical with **15** prepared from **7** by direct comparison. Colorless needles of mp 140—141 °C (from methanol).

(±)-Fistacacidin Dimethyl Ether Diacetate (**18**): This compound was prepared from **15** as a colorless oil (lit.,[3] mp 76—78 °C) in 97% yield by the procedure employed for the preparation of **13** from **6** [purification; prep. TLC (A : B = 1 : 10), *Rf* 0.67]. IR ($CHCl_3$): 1730 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ: 7.30 (2H, d, *J* 9 Hz, 2′-, 6′-H's), 7.22 (1H, t, *J* 8.5 Hz, 7-H), 6.84 (2H, d, *J* 9 Hz, 3′-, 5′-H's), 6.62, 6.49 (1H each, dd, *J* 8.5, 1 Hz, 6-, 8-H's), 6.22 (1H, d, *J* 5 Hz, 4-H), 5.51 (1H, dd, *J* 8, 5 Hz, 3-H), 5.12 (1H, d, *J* 8 Hz, 2-H), 3.75 (6H, s, 5-, 4′-OCH_3's), 1.92 1.77 (3H each, s, 3-, 4-$OCOCH_3$'s). MS Calcd for $C_{21}H_{22}O_7$: M, 386.136. Found *m/z*: M^+, 386.137.

(2*R**,3*S**,4*S**)-5,4′-Dimethoxyflavan-3,4-diol (**17**): Colorless needles of mp 195—197 °C (from ethanol). IR

($CHCl_3$): 3550 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.40 (2H, d, J 9 Hz, 2′-, 6′-H's), 7.15 (1H, t, J 9 Hz, 7-H), 6.93 (2H, d, J 9 Hz, 3′-, 5′-H's), 6.56, 6.46 (1H each, dd, J 9, 1 Hz, 6-, 8-H's), 5.06 (1H, dd, J 4, 2.5 Hz, 4-H),[7] 4.92 (1H, d, J 9.5 Hz, 2-H), 3.96 (1H, m, 3-H),[7] 2.85 (1H, d, J 2.5 Hz, 4-OH),[6] 2.53 (1H, d, J 7 Hz, 3-OH).[6] MS Calcd for $C_{17}H_{18}O_5$: M, 302.115. Found m/z: M^+, 302.116.

(2*R**,3*R**,4*S**)-3,4-Diacetoxy-5,4′-dimethoxyflavan (**19**): This compound was prepared from **17** as a colorless oil in 92% yield by the procedure employed for the preparation of **13** from **6** [purification; prep. TLC (A : B = 1 : 10), *Rf* 0.59]. IR ($CHCl_3$): 1734 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ: 7.37 (2H, d, J 9 Hz, 2′-, 6′-H's), 7.23 (1H, t, J 8.5, 7-H), 6.90 (2H, d, J 9 Hz, 3′-, 5′-H's), 6.53, 6.46 (1H each, dd, J 8.5, 1 Hz, 6-, 8-H's), 6.45 (1H, d, J 3.5 Hz, 4-H), 5.35 (1H, dd, J 11, 3.5 Hz, 3-H), 5.07 (1H, d, J 11 Hz, 2-H), 3.80 (6H, s, 5-, 4′-OCH_3's), 2.10, 1.80 (3H each, s, 3-, 4-O$COCH_3$'s). MS Calcd for $C_{21}H_{22}O_7$: M, 386.136. Found m/z: M^+, 386.136.

Reduction of 13——a) A mixture of **13** (20.4 mg, 0.05 mmol) and $NaBH_4$ (4.1 mg, 0.11 mmol) in anhydrous 2-propanol (4 ml) was stirred at room temperaure for 1 h. Work-up of the reaction mixture gave a mixture (17.9 mg) of **20** and **21**, which was treated with dimethyl sulfate (68 mg)–K_2CO_3 (70 mg) in boiling acetone (4 ml) for 4 h to yield (2*R**,3*S**)-3,4-diacetoxy-5-methoxyflavan (**22**) (12.2 mg, 67%) as a colorless oil [TLC (A : B = 1 : 20), *Rf* 0.63]. IR ($CHCl_3$): 1738 cm^{-1} (OC=O). ^{1}H-NMR[9] ($CDCl_3$) δ: 7.39 (2H, d, J 8.5 Hz, 2′-, 6′-H's), 7.07 (2H, d, J 8.5 Hz, 3′-, 5′H's), 7.14 (1H, t, J 8 Hz, 7-H), 6.62, 6.47 (1H each, dd, J 8, 1 Hz, 6-, 8-H's), 5.33 (1H, dt, J 5.5, 6 Hz, 3-H), 5.11 (1H, d, J 6 Hz, 2-H), 3.79 (3H, s, 5-OCH_3), 2.96 (1H, dd, J 17, 5.5 Hz, 4-H), 2.67 (1H, dd, J 17, 6 Hz, 4-H), 2.26, 1.97 (3H each, s, 3-, 4′-O$COCH_3$'s). MS Calcd for $C_{20}H_{20}O_6$: M, 356.122. Found m/z: M^+, 356.124.

b) A mixture of **13** (83.8 mg, 0.21 mmol) and $NaBH_4$ (16.0 mg, 0.42 mmol) in anhydrous 2-propanol (11 ml) was stirred at room temperature for 1.25 h. Work-up of the reaction mixture gave a mixture (86.0 mg) of **20** and **21**, which was treated with acetic anhydride (0.7 ml)–anhydrous pyridine (4 drops) at room temperature for 21 h to yield **16** (3.8 mg, 4%) and **23** (70.1 mg, 87%).

(±)-Fistacacidin Tetraacetate (**16**): Colorless needles of mp 157—159 °C (from ethanol). TLC (A : B = 1 : 5), *Rf* 0.58. This compound was shown to be identical with **16** prepared from **7** by acetylation.

(2*R**,3*S**)-3,5,4′-Triacetoxyflavan (**23**): Colorless needles of mp 136—137 °C (from methanol). TLC (A : B = 1 : 5), *Rf* 0.75. IR ($CHCl_3$): 1746 cm^{-1} (OC=O). ^{1}H-NMR[9] ($CDCl_3$) δ: 7.36 (2H, d, J 8.5 Hz, 2′-, 6′-H's), 7.07 (2H, d, J 8.5 Hz, 3′-, 5′-H's),7.07 (1H, t, J 8 Hz, 7-H), 6.81, 6.71 (1H each, dd, J 8, 1 Hz, 6-, 8-H's), 5.30 (1H, dt, J 5.5, 6 Hz, 3-H), 5.12 (1H, d, J 6 Hz, 2-H), 2.90 (1H, dd, J 16.5, 5.5 Hz, 4-H), 2.63 (1H, dd, J 16.5, 6 Hz, 4-H), 2.26 (6H), 1.96 (3H) (s each, 3-, 5-, 4′-O$COCH_3$'s). MS Calcd for $C_{21}H_{20}O_7$: M, 384.121. Found m/z: M^+, 384.121.

c) A mixture of **13** (20.5 mg, 0.05 mmol) and $NaBH_4$ (4.5 mg, 0.12 mmol) in anhydrous 2-propanol (50 ml) was stirred at −30 °C for 7 h. Work-up of the reaction mixture as above gave **16** (9.0 mg, 39.5%) as colorless needles of mp 157—159 °C (from ethanol) and a mixture (10.4 mg) of **13** and **23**.

A Mixture of **13** and **23**: TLC (A : B = 1 : 10), *Rf* 0.46. GC showed an approximate ratio of **13** : **23** to be 2 : 7 (**13**, 10%; **23**, 36%).

d) A mixture of **13** (45.5 mg, 0.12 mmol) and $NaBH_4$ (28.0 mg, 0.74 mmol) in anhydrous methanol (2 ml) was stirred at −30 °C for 1.75 h. Work-up of the reaction mixture gave **20** (45.2 mg, 99%) as a colorless oil, which was treated with acetic anhydride (1.5 ml)–anhydrous pyridine (4 drops) at room temperature for 15 h to yield **16** (44.4 mg, 89%) as colorless needles of mp 157—158 °C (from ethanol).

Hydrolysis of 16——a) A solution of **16** (20.5 mg) in 10% aqueous KOH (0.5 ml) was stirred at room temperature in a stream of N_2 for 43 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. Removal of the solvent *in vacuo* afforded an oil, which was purified by prep. TLC (A : B = 1 : 1) to yield **7** (0.8 mg, 6%) as colorless needles of mp 198 °C (dec.) (from ethanol), *Rf* 0.53, and **14** (1.4 mg, 11%) as colorless needles of mp 189 °C (dec.) (from ethanol), *Rf* 0.40. These compounds were shown to be identical with **7** and **14** prepared from **6** by direct comparison.

b) A solution of **16** (16.8 mg) in 10% methanolic KOH (2 ml) was stirred at 50 °C in a stream of N_2 for 5.5 h. Work-up of the reaction mixture gave an oil, which was purified by prep. TLC (A : B = 1 : 3) to yield **25** (1.0 mg, 9%), *Rf* 0.30, and **26** (6.9 mg, 63%), *Rf* 0.26.

(±)-Fistacacidin Methyl Ether (**25**): Colorless needles of mp 174 °C (dec.) (from acetone–tetrachloromethane). IR ($CHCl_3$): 3572, 3460, 3252 cm^{-1} (OH). ^{1}H-NMR (acetone-d_6) δ: 8.47, 8.20 (1H each, s, 5-, 4′-OH's),[6] 7.42 (2H, d, J 9 Hz, 2′-, 6′-H's), 7.13 (1H, t, J 8 Hz, 7-H), 6.94 (2H, d, J 9 Hz, 3′-, 5′-H's), 6.48, 6.41 (1H each, dd, J 8, 1 Hz, 6-, 8-H's), 4.94 (1H, d, J 7 Hz, 4-H), 4.77 (1H, d, J 9 Hz, 2-H), 4.30 (1H, m, 3-H),[7] 4.28 (1H, br s, 3-OH),[6] 3.62 (3H, s, 4-OCH_3). MS Calcd for $C_{16}H_{16}O_5$: M, 288.100. Found m/z: M^+, 288.100.

(2*R**,3*S**,4*S**)-4-Methoxy-3,5,4′-trihydroxyflavan (**26**): Colorless needles of mp 175—178 °C (dec.) (from acetone–tetrachloromethane). IR ($CHCl_3$): 3596, 3356 cm^{-1} (OH). ^{1}H-NMR (acetone-d_6) δ: 8.63, 8.31 (1H each, s, 5-, 4′-OH's),[6] 7.37 (2H, d, J 9 Hz, 2′-, 6′-H's), 7.08 (1H, t, J 8 Hz, 7-H), 6.90 (2H, d, J 9 Hz, 3′-, 5′-H's), 6.48, 6.39 (1H each, dd, J 8, 1 Hz, 6-, 8-H's), 5.01 (1H, d, J 10 Hz, 2-H), 4.71 (1H, d, J 3.5 Hz, 4-H), 3.95 (1H, dt, J 10, 3.5 Hz, 3-H),[7] 3.61 (3H, s, 4-OCH_3), 3.54 (1H, d, J 3.5 Hz, 3-OH).[6] MS Calcd for $C_{16}H_{16}O_5$: M, 288.100. Found m/z: M^+, 288.098.

Hydrolysis of (±)-Fistacacidin Triacetate (20)——A solution of **20** (15.0 mg) in 10% methanolic KOH (1.5 ml) was stirred at room temperature for 24 h. Work-up of the reaction mixture gave an oil, which was purified by prep.

TLC (A : B = 1 : 3) to yield **7** (0.7 mg, 7%) as colorless neeldes of mp 198 °C (dec.) (from ethanol), *Rf* 0.17, and **26** (2.6 mg, 24%) as colorless needles of mp 175—178 °C (dec.) (from acetone–tetrachloromethane), *Rf* 0.39. These compounds were shown to be identical with **7** and **26** prepared from **6** and **16**, respectively, by direct comparison.

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References and Notes

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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 hydroxy protons.
8) On addition of deuterium oxide, the following changes were observed: 2-H, δ 4.96, d, J 9.5 Hz; 3-H, δ 3.92, dd, J 9.5, 4 Hz; 4-H, δ 4.99, d, J 4 Hz.
9) Couplings observed among the 2-, 3- and 4-protons ($J_{2,3}$ 6, $J_{3,4}$ 6, 5.5 Hz) are consistent with 2ax-*p*-acetoxyphenyl and 3ax-acetoxy groups in a half-chair form of the dihydropyran ring (R. Livingstone, "Rodd's Chemistry of Carbon Compounds," Vol. IV/E, ed. by S. Coffey, Elsevier Scientific Publishing Company, Amsterdam, 1977, p. 241).