HETEROCYCLES. XIV.[1] EFFICIENT STEREOCONTROLLED SYNTHESIS OF RACEMIC FLAVONOIDS

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Abstract —— Stereocontrolled synthesis of the flavonoids (2, 4 and 5) is described. Racemic taxifolin (dihydroquercetin) (14) is synthesized by application of this method.

Hydroxyflavanonols and flavan-3,4-diols naturally occur in a variety of hartwoods and barks. The majority of these compounds were stereochemically established, and several racemic flavonoids were synthesized. For example, (2R*,3R*)-flavanonol (2) was prepared by alkaline hydrogen peroxide oxidation of 2'-hydroxychalcone (1), but the yield was very poor owing to its facile autoxidation to flavonol (3) in the alkaline medium.[2] (2R*,3S*,4R*)-flavan-3,4-diol (4) was obtained on hydrogenation of 2, and the 4S*-isomer (5) was prepared from 2 through the oxime and the corresponding amine.[3] Our aim is to synthesize naturally occurring chiral flavonoids. We now report, as a model study, efficient stereocontrolled synthesis of the flavonoids (2, 4 and 5) and (2R*,3R*)-taxifolin (dihydroquercetin).

Treatment of 1 with methoxymethyl chloride in an alkaline medium gave the ether (6) (85%). Alkaline hydrogen peroxide oxidation of 6 yielded the epoxide (7) (92%), in which the αR*,βS*-configuration was deduced by $J_{\alpha,\beta}$ 2 Hz observed in the ^{1}H NMR spectrum.[4] Treatment of 7 with trifluoroacetic acid provided 2 (92%) (2R*,3R*; $J_{2,3}$ 12.5 Hz). On reduction with sodium borohydride, 2 gave 4 (84%) (2R*,3S*,4R*; $J_{2,3}$ 10 Hz and $J_{3,4}$ 8.5 Hz) as a sole product.

Reduction of 7 with sodium borohydride gave the erythro-epoxy alcohol (8) (68%) and the threo-isomer (9) (10%). The configurations of these compounds were deduced on the basis of those of the compounds obtained by the next reactions. On treatment with trifluoroacetic acid or hydrochloric acid, 8 and 9 gave 5 (71%) and 4 (71%), respectively. The 2R*,3S*,4S*-configuration in 5 was deduced by $J_{2,3}$ 9 Hz and $J_{3,4}$ 3.5 Hz. It is clear that the exclusively stereocontrolled formations of the chroman rings in the compounds (2, 4 and 5) occurred via intramolecular S_N2 reactions.

(2R*,3R*)-Taxifolin (14) was prepared by the same process as employed for the synthesis of 2 in 92% yield. This is the first total synthesis of 14.

On reduction with sodium borohydride at -30°C, the tetramethyl ether (15), derived from 14, gave two isomeric flavan-3,4-diols (16 and 17) in 15 and 67% yields, respectively. The same reduction at refluxing temperature provided 16 and 17 in 33 and 49% yields, respectively.

EXPERIMENTAL SECTION

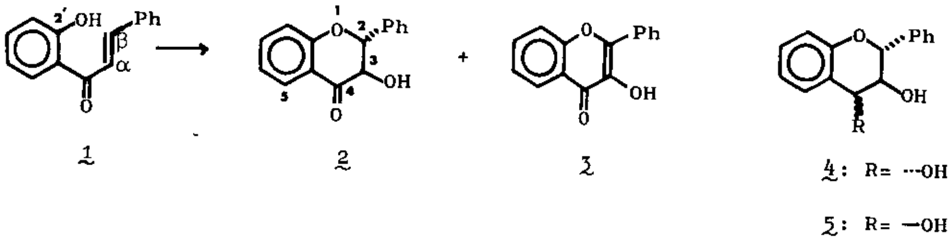
Melting points are uncorrected. Spectral data were recorded on the following spectrometers: IR — Hitachi 260—30; ^1H NMR — Varian EM—390 (90 MHz); MS — JEOL JMS DX—300.

2'-Methoxymethoxychalcone (6)

A mixture of 2'-hydroxychalcone (1)^5 (220 mg), 1N NaOH (10 ml) and CH_2Cl_2 (10 ml) was stirred at room temperature for 10 min. $N(Bu)_4Cl$ (30 mg) and then a solution of CH_3OCH_2Cl (0.2 ml) in CH_2Cl_2 (0.5 ml) were added, and the mixture was stirred at room temperature for 6 h. The organic phase was washed with H_2O and dried over Na_2SO_4, then concentrated in vacuo. The residue was purified by prep. TLC (Al_2O_3, C_6H_6) to yield 6 (230 mg, 85%) as a colorless oil, Rf 0.60. IR ν_{max}^{film} cm^{-1}: 1650 (CO). ^1H NMR ($CDCl_3$) δ: 7.68—6.68 (11H, m, aromatic and vinylic H's), 5.68 (2H, s, OCH_2O), 3.42 (3H, s, OMe). MS Calcd for $C_{17}H_{16}O_3$: M, 268.110. Found m/z: M^+, 268.109.

(αR*,βS*)-α,β-Epoxy-2'-methoxymethoxychalcone (7)

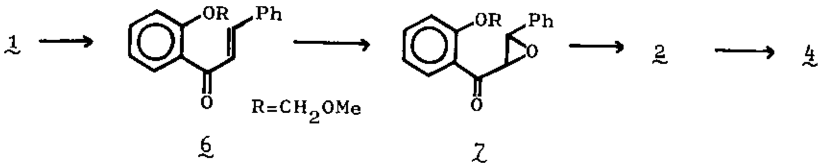
30% H_2O_2 (0.2 ml) and 1N NaOH (0.2 ml) were added to a solution of 6 (170 mg) in MeOH (5 ml), and the mixture was stirred at room temperature for 5 h. The reaction mixture was taken up in $CHCl_3$, and the organic phase was washed with 5% aq. KI and then 5% aq. $Na_2S_2O_3$. Work-up gave an oil, which was purified by prep. TLC (Al_2O_3, $CHCl_3$) to yield 7 (165 mg, 92%) as colorless needles of mp 85—90°C (MeOH), Rf 0.70. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678 (CO). ^1H NMR (C_6D_6) δ: 7.94 (1H, dd, J 7.5 and 2 Hz, 6'-H), 7.23—6.73 (8H, m, aromatic H's), 4.65, 4.44 (each 1H, d, J 7 Hz, OCH_2O), 4.10, 3.96 (each 1H, d, J 2 Hz, α- and β-H's), 2.78 (3H, s, OMe).



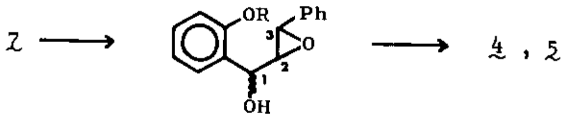
1 → 2 + 3

4: R= ···OH

5: R= —OH



1 → 6 → 7 → 2 → 4

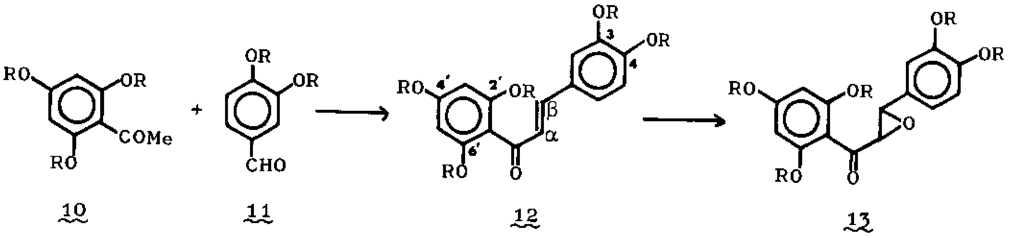


7 → → 4 , 5

R=CH_2OMe

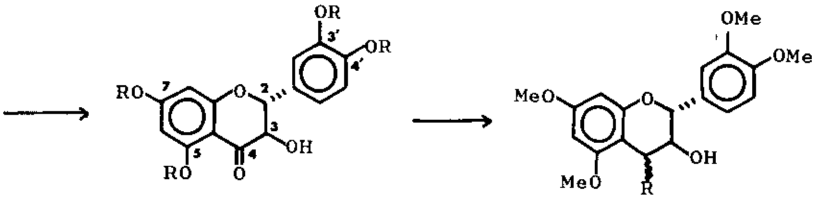
8: erythro

9: threo



10 + 11 → 12 → 13

10—13: R=CH_2OMe



14: R=H

15: R=Me

16: R= ···OH

17: R= —OH

MS Calcd for $C_{17}H_{16}O_4$: M, 284.105. Found m/z: M^+, 284.105.

(2*R**,3*R**)-Flavanonol (2)

30% CF_3COOH (0.2 ml) was added to a solution of 7 (110 mg) in MeOH (0.3 ml), and the mixture was stirred at room temperature for 30 min, then taken up in $CHCl_3$. The organic phase was washed with 5% aq. $NaHCO_3$ and H_2O, then dried over Na_2SO_4. Work-up gave an oil, which was crystallized from MeOH to yield 2 (76 mg, 82%) as colorless crystals of mp 172—175°C (lit.[2]; mp 174—177°C). Additional 2 (9.5 mg, 10%) was obtained from the mother liquor by prep. TLC (silica gel, $CHCl_3$), Rf 0.44. IR ν_{max}^{KBr} cm^{-1}. 3475 (OH), 1690 (CO). ^1H NMR ($CDCl_3$) δ: 7.76 (1H, dd, J 8 and 1.5 Hz, 5-H), 7.73—6.96 (8H, m, aromatic H's), 5.13 (1H, d, J 12.5 Hz, 2-H), 4.56 (1H, dd, J 12.5 and 2 Hz, 3-H),[6] 3.64 (1H, d, J 2 Hz, 3-OH).[7] MS Calcd for $C_{15}H_{12}O_3$: M, 240.080. Found m/z: M^+, 240.080.

(1*S**,2*S**,3*S**)-2,3-Epoxy-1-2'-methoxymethoxyphenyl-3-phenylpropanol (erythro) (8) and The 1*R**-Isomer (threo) (9)

$NaBH_4$ (20 mg) was added to a solution of 7 (140 mg) in MeOH (5 ml), and the mixture was stirred at -30—40°C for 2 h. After addition of CH_3COOH (4 drops), the reaction mixture was concentrated in vacuo, and the residue was dissolved in $CHCl_3$. Work-up gave an oil, which was purified by prep. TLC (Al_2O_3, $CHCl_3$/hexane=4/1, v/v) to yield 8 (96 mg, 68%), Rf 0.30 and 9 (13.4 mg, 10%), Rf 0.30.
The erythro-Isomer (8): A colorless oil. IR ν_{max} cm^{-1}: 3528 (ε=53) (OH) (c=0.0011 mol/l, CCl_4). ^1H NMR (C_6D_6) δ: 7.80—6.82 (9H, m, aromatic H's), 5.38 (1H, t, J 3 Hz, 1-H),[6] 4.79 (2H, s, OCH_2O), 4.05 (1H, d, J 2.5 Hz, 3-H), 3.48 (1H, dd, J 3 and 2.5 Hz, 2-H), 3.06 (3H, s, OMe), 2.49 (1H, d, J 3 Hz, 1-OH).[7] MS Calcd for $C_{17}H_{18}O_4$: M, 286.121. Found m/z: M^+, 286.121.
The threo-Isomer (9): A colorless oil. IR ν_{max} cm^{-1}: 3652 (ε=38), 3572 (ε=30), 3548 (ε=29) (OH) (c=0.00085 mol/l, CCl_4). ^1H NMR (C_6D_6) δ: 7.74—6.62 (9H, m, aromatic H's), 5.14 (1H, t, J 4 Hz, 1-H),[6] 4.79 (2H, s, OCH_2O), 4.02 (1H, d, J 2.5 Hz, 3-H), 3.25 (1H, dd, J 4 and 2.5 Hz, 2-H), 3.06 (3H, s, OMe), 2.53 (1H, d, J 4 Hz, 1-OH).[7] MS Calcd for $C_{17}H_{18}O_4$: M, 286.121. Found m/z: M^+, 286.121.

(2*R**,3*S**,4*R**)-Flavan-3,4-diol (4)

(1) $NaBH_4$ (25 mg) was added to a solution of 2 (37.0 mg) in MeOH (5 ml), and the mixture was stirred at room temperature for 2 h. Work-up of the reaction

mixture gave an oil, which was crystallized from ether/hexane to yield 4 (24.0 mg, 64%) as colorless needles of mp 139–142°C (lit.[3]; mp 145°C). Additional 4 (7.4 mg, 20%) was obtained from the mother liquor by prep. TLC (silica gel, acetone/C_6H_6=1/3, v/v). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH). ^1H NMR ($CDCl_3$) δ: 7.59–6.83 (9H, m, aromatic H's), 4.80 (1H, dd, J 8.5 and 5.5 Hz, 4-H),[6] 4.76 (1H, d, J 10 Hz, 2-H), 3.80 (1H, ddd, J 10, 8.5 and 3 Hz, 3-H),[6] 3.03 (1H, d, J 5.5 Hz, 4-OH),[7] 2.45 (1H, d, J 3 Hz, 3-OH).[7] MS Calcd for $C_{15}H_{14}O_3$: M, 242.094. Found m/z: M^+, 242.094.

(2) 10% HCl/MeOH (2 ml) was added to a solution of 9 (35.0 mg) in MeOH (0.4 ml), and the mixture was refluxed for 30 min. Work-up of the reaction mixture gave 4 (21.0 mg, 71%).

(2R*,3S*,4S*)-Flavan-3,4-diol (5)

This compound was prepared from 8 in 71% yield by the procedure employed for the synthesis of 4 from 9 using CF_3COOH instead of 10% HCl/MeOH. Colorless needles of mp 159.5–163°C ($CHCl_3$) (lit.[3]; mp 160°C). IR ν_{max}^{KBr} cm^{-1}: 3375, 3280 (OH). ^1H NMR ($CDCl_3$) δ: 7.25–6.88 (9H, m, aromatic H's), 5.04 (1H, d, J 9 Hz, 2-H), 4.72 (1H, d, J 3.5 Hz, 4-H), 4.04 (1H, dd, J 9 and 3.5 Hz, 3-H), 2.35 (2H, s, 3- and 4-OH's).[7] MS Calcd for $C_{15}H_{14}O_3$: M, 242.094. Found m/z: M^+, 242.094.

3,4,2',4',6'-Pentakis(methoxymethoxy)chalcone (12)

This compound was prepared from the acetophenone (10)[8] and the benzaldehyde (11)[9] in 86% yield by the procedure described in lit.[5] A colorless oil. IR ν_{max}^{film} cm^{-1}: 1650 (CO). ^1H NMR ($CDCl_3$) δ: 7.42 (1H, s, 2-H), 7.37 (1H, d, J 17 Hz, β-H), 7.35 (2H, s, 5- and 6-H's), 6.91 (1H, d, J 17 Hz, α-H), 6.63 (2H, s, 3'- and 5'-H's), 5.28, 5.27, 5.13 (2) (10H, each s, OCH_2O's), 3.52, 3.42 (4) (15H, each s, OMe's). MS Calcd for $C_{25}H_{32}O_{11}$: M, 508.194. Found m/z: M^+, 508.194.

(αS*,βR*)-α,β-Epoxy-3,4,2',4',6'-pentakis(methoxymethoxy)chalcone (13)

This compound was prepared from 12 in 92% yield by the same procedure as employed for the synthesis of 7 from 6. A colorless oil. IR ν_{max}^{film} cm^{-1}: 1700 (CO). ^1H NMR (C_6D_6) δ: 7.24–6.80 (3H, m, 2-, 5- and 6-H's), 6.79 (2H, s, 3'- and 5'-H's), 4.17, 3.96 (each 1H, d, J 2 Hz, α- and β-H's), 4.96, 4.92, 4.89, 4.87 (2) (10H, each s, OCH_2O's), 3.22 (1), 3.19 and 3.16 (4) (15H, each s, OMe's). MS Calcd for $C_{25}H_{32}O_{12}$: M, 524.189. Found m/z: M^+, 524.189.

(2R*,3R*)-Taxifolin (14)

This compound was prepared from 13 in 92% yield by the procedure employed for the synthesis of 2 from 7 using 10% HCl/MeOH instead of CF_3COOH. Colorless plates of mp 232—234°C (H_2O) (lit.[10]; mp 234—236°C). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1640 (CO). ^{1}H NMR (MeOD) δ: 7.10 (1H, s, 2'-H), 6.94 (2H, s, 5'- and 6'-H's), 6.02, 5.97 (each 1H, d, J 2.5 Hz, 6- and 8-H's), 4.99 (1H, d, J 12 Hz, 2-H), 4.54 (1H, d, J 12 Hz, 3-H). MS Calcd for $C_{15}H_{12}O_7$: M, 304.058. Found m/z: M$^+$, 304.059.

The Tetramethyl Ether (15): Colorless needles of mp 167—169.5°C (EtOH) (lit.[11]; mp 169—170°C). IR ν_{max}^{KBr} cm^{-1}: 3450, 3340 (OH), 1670 (CO). ^{1}H NMR ($CDCl_3$) δ: 7.08 (1H, dd, J 7 and 2 Hz, 6'-H), 7.05 (1H, d, J 2 Hz, 2'-H), 6.91 (1H, d, J 7 Hz, 5'-H), 6.77 (2H, s, 6- and 8-H's), 4.94 (1H, d, J 12 Hz, 2-H), 4.41 (1H, d, J 12 Hz, 3-H), 3.91, 3.89, 3.87, 3.78 (each 3H, s, OMe's), 3-OH signal was not observed. MS Calcd for $C_{19}H_{20}O_7$: M, 360.121. Found m/z: M$^+$, 360.120.

(2R*,3S*,4R*)-5,7,3',4'-Tetramethoxyflavan-3,4-diol (16) and The 4S*-Isomer (17)

$NaBH_4$ (10 mg) was added to a solution of 15 (96.0 mg) in MeOH (5 ml), and the mixture was stirred at -30°C for 20 h. Work-up of the reaction mixture gave an oil, which was purified by prep. TLC (silica gel, acetone/C_6H_6=2/3, v/v) to yield 16 (13.8 mg, 14%), Rf 0.55 and 17 (64.8 mg, 67%), Rf 0.62.

The 2R*,3S*,4R*-Isomer (16): Colorless crystals of mp 166.5—168°C (EtOH). IR ν_{max}^{KBr} cm^{-1}: 3510, 3460 (OH). ^{1}H NMR ($CDCl_3$) δ: 7.08 (1H, dd, J 9 and 2 Hz, 6'-H), 7.02 (1H, d, J 2 Hz, 2'-H), 6.89 (1H, d, J 9 Hz, 5'-H), 6.16, 6.07 (each 1H, d, J 2.5 Hz, 6- and 8-H's), 4.99 (1H, dd, J 7 and 1 Hz, 4-H),[6] 4.68 (1H, d, J 10 Hz, 2-H), 4.08 (1H, ddd, J 10, 7 and 2.5 Hz, 3-H),[6] 3.89, 3.86 (3), 3.68 (12H, each s, OMe's), 2.33 (1H, d, J 2.5 Hz, 3-OH),[7] 4-OH signal was not observed. MS Calcd for $C_{19}H_{22}O_7$: M, 362.137. Found m/z: M$^+$, 362.135.

The 2R*,3S*,4S*-Isomer (17): Colorless crystals of mp 209—212°C (EtOH). IR ν_{max}^{KBr} cm^{-1}: 3590, 3420, 3270 (OH). ^{1}H NMR ($CDCl_3$) δ: 7.06 (1H, dd, J 9 and 2 Hz, 6'-H), 6.99 (1H, d, J 2 Hz, 2'-H), 6.89 (1H, d, J 9 Hz, 5'-H), 6.09 (2H, s, 6- and 8-H's), 4.99 (1H, d, J 3.5 Hz, 4-H), 4.88 (1H, d, J 10 Hz, 2-H), 3.82 (1H, m, 3-H), 3.88, 3.85, 3.84, 3.74 (each 3H, s, OMe's), 2.67 (2H, s, 3- and 4-OH's).[7] MS Calcd for $C_{19}H_{22}O_7$: M, 362.137. Found m/z: M$^+$, 362.138.

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