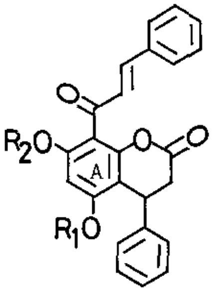
SYNTHESIS OF 5,7-DIHYDROXY-8-CINNAMOYL-4-PHENYLDIHYDROCOUMARINS

Munekazu Iinuma*[,a], Shin Matsuura, and Fujio Asai[b]
Gifu College of Pharmacy,[a] 5-6-1 Mitahora-higashi, Gifu 502,
Japan, Faculty of General Education, Aichigakuin University,[b]
Nisshin-cho, Aichi-gun, Aichi 470-01, Japan

Abstract --- 5,7-Dihydroxy-8-cinnamoyl-4-phenyldihydrocoumarins isolated from Pityrogramma trifoliata were synthesized for their structures confirmation.

Novel class of complex flavonoids were isolated from fronds of the fern Pityrogramma trifoliata (Polypodiaceae) and their structures were elucidated as 5,7-dihydroxy-8-cinnamoyl-4-phenyldihydrocoumarins (1a, 2a and 3a) by Wollenweber and co-workers.[1] These flavonoids have attracted much attention because they have a new type of skeletons composed by a chalcone and a neoflavonoid moiety.



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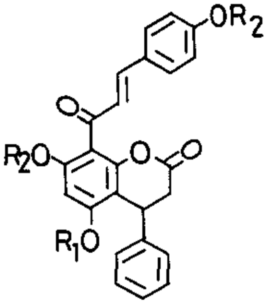

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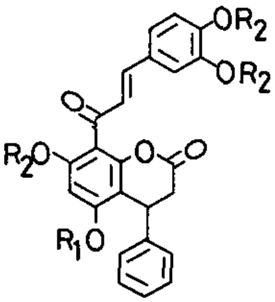

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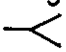
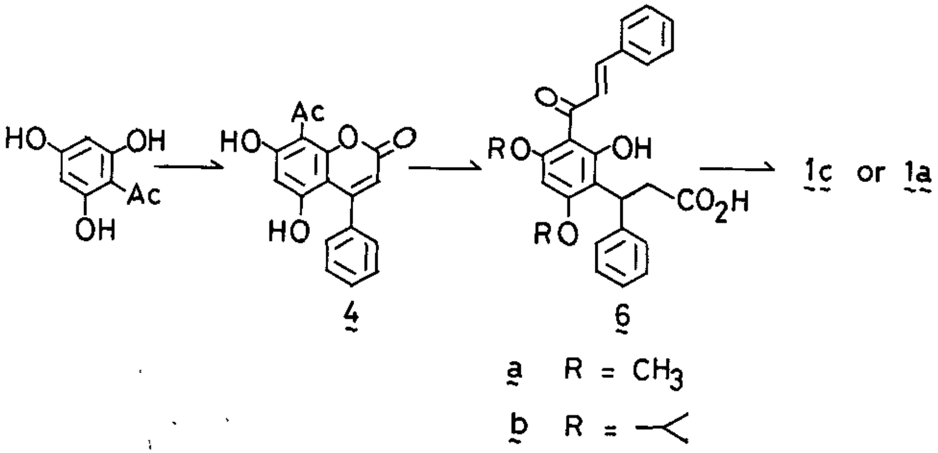
a $R_1 = R_2 = H$ b $R_1 = R_2 = CH_3$

c $R_1 = CH_3, R_2 = H$ d $R_1 = R_2 =$ 

For the synthetic strategy, three methods of construction of their skeletons are considered as follows; I: $C_6\text{-}C_3^{*}\text{-}C_6^{*} + C_3^{**}\text{-}C_6^{**}$, II: $C_6\text{-}C_2^{**} + C_3^{*}\text{-}C_6^{*} + C_1^{**}\text{-}C_6^{**}$ and III: $C_6\text{-}C_3^{**}\text{-}C_6^{**} + C_3^{*}\text{-}C_6^{*}$ (No marked carbons belongs to ring A and

C* and C** show the carbons of a neoflavnoid and a chalcone moiety respectively). Way I had been applied to the preparation of 8- or 6-dihydrocinnamoyl-5,7-dihydroxy-4-phenyl-2H-1-benzopyran-2-one by Wagner *et al.*[2] but the position of dihydrocinnamoyl group had not been decided. our present method, way II, is to condense an acetophenone (C_6-C_2**) with benzoylacetic acid (C_3*-C_6*) to obtain 4-phenylcoumarin (neoflavone) substituted with an acetyl group in ring A, and then to condense a benzaldehyde (C_1**-C_6**) with the neoflavone. The condensation of phloroacetophenone with ethyl benzoylacetate in the presence of HCl[3] gave two neoflavones, 8-acetyl-5,7-dihydroxy- (**4**), and 6-acetyl-5,7-dihydroxyneoflavone (**5**)[4] in 1 : 1 molar ratio. These positional isomers were easily distinguished by the observation of the aromatic protons and acetyl protons signals in their ^1H nmr spectra. The protons of acetyl group in **5** and H-6 in **4** appeared in higher field area than those of acetyl group in **4** and H-8 in **5** by anisotropy of a side phenyl group. Separation of **4** and **5** was carried out by a column chromatography on silica gel (eluent: AcOEt-C_6H_{14} = 1 : 2). Hydrogenation of **4** with hydrogen at 50 atm in



the presence of 10% Pd-C gave the dihydroneoflavone (**4'**)[mp 175-177°C, colorless prisms; ^1H nmr (DMSO-d6) δ : 2.68 (3H, s, $COC\underline{H}_3$), 2.99-3.21 (2H, m, H-3), 4.40-4.65 (1H, m, H-4), 6.23 (1H, s, H-6), 7.04-7.32 (5H, m). MS m/z: 298 (M^+), 283, 255]. Methylation of **4'** with dimethyl sulfate and K_2CO_3 in acetone, followed by condensation with benz-, p-anis- and veratraldehyde in the presence of potassium hydroxide, afforded **6a**[5] (when benzaldehyde was employed) with ring opening of dihydrocoumarin. **6a** was treated with Ac_2O and AcONa in benzene to give **1b**.[6] The methoxy group at C-5 of **1b** resisted to demethylation with using LiI, BBr_3, $AlCl_3$,

EtSNa and Me_3SiI, therefore, the product thus obtained was the monomethyl ether of the natural product (**1c**). The similar demethylations of **2b** and **3b** also gave **2c** and **3c** in which the methyl groups at C-5 still remained. After the investigation of the various reagents as protective groups, the isopropyl group was found to be efficient to prepare these flavonoids. Isopropylation of **4**' with isopropyl bromide and K_2CO_3 in DMF at 100°C for 4 h afforded the diisopropyl ether (**4**"). **4**" was condensed with benzaldehyde to give **6b**.[7] The similar treatment of **6b** as in the case of **6a** gave **1d** (mp 129-130°C, colorless plates). By the same way as **1d**, **2d** (mp 171-173°C) and **3d** (mp 163-165°C) were obtained by the condensation of **4**" with p-isopropyloxy- and 3,4-diisopropyloxybenzaldehyde. Cleavage of isopropyl groups was accomplished with BCl_3[8] in excellent yields to furnish **1a**, **2a** and **3a**, which corresponded to the natural products provisionally called T-1, T-2 and T-3. The physical and spectral data are shown in Table I. The synthesized **1a**, **2a** and **3a** were identified completely with T-1, T-2 and T-3 respectively by the direct comparisons.
Further application of isopropyl group as a protective group to flavonoids syntheses is in progress.

Table I Physical and Spectral Properties of **1a**, **2a** and **3a**

	mp (°C)	^1H nmr (acetone-d6)	UV λ max[nm] (EtOH)		MS m/z (rel. int.)
1a	202-204	3.08-3.34 ($C\underline{H}_2CO$)		333	386 (M^+, 100)
		4.65-4.48 ($C\underline{H}Ph$)	$+AlCl_3$	358	358 (17)
		6.34 (H-6)	+EtONa	405	343 (9)
		7.85 (d,J=16.0,H-β)	+AcONa	340	309 (40)
		8.32 (d,J=16.0,H-α)			
2a	222-224	3.10-3.36 ($C\underline{H}_2CO$)		378	402 (M^+, 100)
		4.70-4.86 ($C\underline{H}Ph$)	$+AlCl_3$	432	384 (6)
		6.35 (H-6)	+EtONa	430	359 (7)
		7.79 (d,J=15.6,H-β)	+AcONa	397,405	309 (14)
		8.10 (d,J=15.6,H-α)			
3a	204-206	3.05-3.36 ($C\underline{H}_2CO$)		394	418 (M^+, 100)
		4.70-4.90 ($C\underline{H}Ph$)	$+AlCl_3$	446	402 (13)
		6.33 (H-6)	+EtONa	452	390 (9)
		7.77 (d,J=15.0,H-β)	+AcONa	404	309 (19)
		8.02 (d,J=15.0,H-α)			

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4. 8-Acetyl-5,7-dihydroxyneoflavone (**4**); mp 281°C (EtOH), colorless needles. ^1H nmr (DMSO-d6) δ : 2.72 (3H, s, $COC\underline{H}_3$), 5.90 (1H, s, H-3), 6.14 (1H, s, H-6), 7.46 (5H, br s, Ph). MS m/z: 296 (M^+), 281 (M^+-CH_3)(100%), 268.

   6-Acetyl-5,7-dihydroxyneoflavone (**5**); mp 235°C (AcOEt), pale yellow needles. ^1H nmr (DMSO-d6) δ : 2.65 (3H, s, $COC\underline{H}_3$), 5.84 (1H, s, H-3), 6.40 (1H, s, H-8), 7.45 (5H, br s, Ph). MS m/z: 296 (M^+), 281 (M^+-CH_3)(100%), 268.
5. **6a**; mp 190-192°C (MeOH), yellow prisms. MS m/z: 432 (M^+), 414 (M^+-H_2O), 386 (100%).
6. **1b**; mp 238-240°C, **2b**; mp 168-170°C, **3b**; mp 175-176°C.
7. **6b**; mp 145-148°C, yellow needles. ^1H nmr ($CDCl_3$) δ : 1.28 (6H, each d, J= 6.0 Hz, $\begin{matrix}C\underline{H}_3\\C\underline{H}_3\end{matrix}\!>$), 1.38 (6H, d, J= 6.0 Hz, $\begin{matrix}C\underline{H}_3\\C\underline{H}_3\end{matrix}\!>$), 3.30 (2H, d, J= 8.0 Hz, $C\underline{H}_2CO$), 4.40-4.48 (2H, m, 2x$C\underline{H}<$), 5.19 (1H, t, J= 8.0 Hz, $C\underline{H}Ph$), 5.91 (1H, s, H-3'), 7.10-7.70 (10H, 2xPh), 7.65 (1H, d, J= 16.0 Hz, H-β), 8.01 (1H, d, J= 16.0 Hz, H-α), 14.24 (1H, s, $O\underline{H}$). MS m/z: 488 (M^+), 473, 241(100%).
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