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新的5,3′,5′-三羟基7-甲氧基黄酮及其一,二和三苄氧基衍生物的合成

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摘 要 通过3.5-二苄氧苯甲酸'-2,6-二羟基-4-甲氧基苯丙酮酯进行Baker-Venkataraman重排,环化合成了5,3′,5′-三苄氧基-7-甲氧基黄酮,然后选择性地和全部地脱苄基得到5,3′,5′-三羟基-7-甲氧基黄酮及其一和二-苄基衍生物.

关键词 3′,5′-二羟基化黄酮,3′,5′-二羟基化黄酮的衍生物,合成
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Synthesis of a Novel 5,3′,5′-Trihydroxy-7-methoxyflavone and Its Mono-, Dibenzyloxy-derivatives *via* Selective Debenzylation of 5,3′,5′-Tribenzyloxy-7-methoxyflavone

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Abstract The novel compound 5,3′,5′—trihydroxy-7-methoxyflavone was synthesized *via* complete debenzylation of 5,3′,5′-tribenzyloxy-7-methoxyflavone. The latter was also selectively debenzylated to give the mono-and di-benzyloxyflavone.

Keywords 3′,5′-dihydroxylated flavone, derivatives of 3′,5′-dihydroxylated flavone, synthesis

Hundreds of polyhydroxyflavones have been known and to our surprise very few polyhydroxyflavones with 3′,5′-dihydroxylated B—ring of either synthetic or natural have been reported[1]. Recent physiological studies of a natural 5,3′,5′-trihydroxy-7-methoxy-2,3-dihydroflavone(TDF)(1)[2~4], which was isolated from Chinese medicinal plant *Blumea Balsamifera* in 1988[5], have suggested that TDF could protect the liver against injuries induced by CCl_4 and TAA, reduce lipo peroxidation (LPO) in various tissues of mice(both in vitro and in vivo). It is worth knowing whether the dehydrogenated analogue 5,3′,5′-trihydroxy-7-methoxyflavone (TF)(2) of TDF could provide similar activities if is used. As the first part of a serise of research investigation on polyhydroxyflavones with 3′,5′-substituted B—ring, this article is intended to report the synthesis of the 3′,5′-dihydroxylated flavone together with some of its derivatives.

1 Results and Discussion

Our approach to the synthesis of 2 consists the coupling of readily available 2-benzyloxy 6-hydroxy-4-methoxyacetophenone (6) with 3,5-dibenzyloxybenzoyl chloride (7), based on Baker-Venkataraman synthesis[6]. 6 was prepared by selective methylation at the 4-position of 2,4,5-trihydroxyacetophenone at low temperature, -5~0℃, using diazomethane (1 : 1) in dry ether to afford 2,6-dihydroxy-4-methoxyacetophenone[7], which was then partially benzylated by reacting with equivalent amount of benzyl bromide in the presence of K_2CO_3[8]. 3,5-Disubstituted benzoyl chloride (7) was obtained by gentle heating of the appropriate acid with

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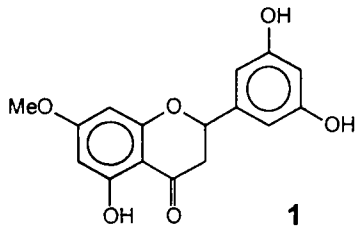

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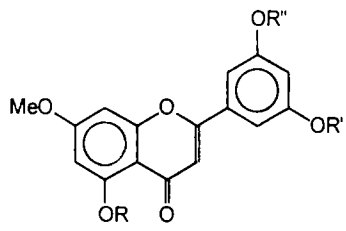


2 R,R',R"=OH
3 R,R',R"=CH_2Ph
4 R,R'=OH; R"=CH_2Ph
5 R=OH; R',R"=CH_2Ph

thionyl chloride. The acid was in turn synthesized by treating the commercially available 3,5-dihydroxybenzoic acid with saturated HCl-methanol solution, followed by the benzylation with an excess amount of benzyl bromide. The product was saponificated with 5% KOH in ethanol and then the solution was adjusted to pH3 with dilute HCl to precipitate the dibenzyloxy benzoic acid[9].

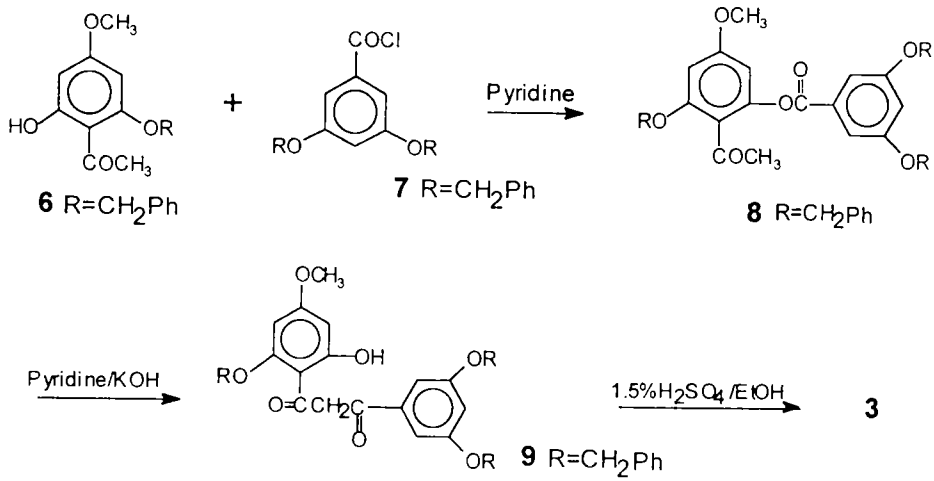
Coupling of **6** and **7** proceeded in dry pyridine at 60℃ for 30 min to yield a new compound of 2-(3′,5′-dibenzyloxybenzoyloxy)-6-benzyloxy-4-methoxyacetophenone (**8**), followed by Baker—Venkataraman rearrangement to give an intermediate of 1,3-dioxo-1-(2-benzyloxy-6-hydroxy-4-methoxyphenyl)-3-(3,5-dibenzyloxyphenyl)-propane(**9**). **9** was cyclized by dilute sulphuric acid in ethanol at reflux temperature for 1 h to give the 5,3′,5′-tribenzyloxy-7-methoxyflavone (**3**). Selective debenzylation of **3** was achieved by hydrogenolysis, based on similar methods reported, in the presence of freshly prepared 5% Pd—C[10] in appropriate organic solvent. **7** was totally debenzylated in ethanol at room temperature for 2 h to afford the TF(**2**), in almost quantitative yield, as a white amorphous solid mp above 325℃. A mixture of 3′-benzyloxy-5,5′-dihydroxy-7-methoxy(**4**) (mp 205℃ decomp) and 3′5′-dibenzyloxy-5-hydroxy-7-methoxyflavone(**5**)(mp 132～134℃) were obtained in a similar hydrogenolysis reaction in THF. Upon chromatographic separation, the mole ratio of **4** : **5** obtained were 20 : 80. The yield, in terms of conversion of the starting material, was nearly 100%.

Tab. 1 UV and IR absorption of **2**,**3**,**4** and **5**

	2	3	4	5
UV/λ_{max}(log ε)	209.0(4.53)		221.7(4.70)	222.1(4.56)
	270.0(4.23)	266.0(4.16)	272.2(4.52)	272.2(4.25)
	314.0(4.10) MeOH	303.0(4.15) EtOAc	312.0(3.30) THF	310.0(2.64) THF
IR/cm^{-1} (nujol)C=O	1664	1640	1685	1655

2 Experimental

2.1 2-(3,5-Dibenyloxybenzoyloxy)-6-benzyloxy-4-methoxyacetophenone (8)



Powdered 3,5 - dibenzloxybenzoyl chloride (7. 15g, 0. 019 mol) was well mixed with 2 - benzyloxy - 6 - hydroxy - 4 - methoxyacetophenone (4. 0g, 0. 015 mol). To the mixture was added dry pyridine (12 ml). The content was heated under dry condition in an oil bath at 60℃ for 30 min. Solid formed was separated and the oily liquid was poured into ice cold 1. 8% HCl solution (200ml). The pH of the mixture was adjusted to 9 with concentrated $NaHCO_3$ solution. The content was extracted with $CHCl_3$ (100 ml) three times. The combined extract was washed with water (200 ml) and evaporated at reduced pressure on water pump. The residue was separated upon silica gel column with EtOAc as eluent, yielded 3,5 - dibenzloxybenzoic acid (0. 3g, 4. 6%) and 8 (7g, 81%). White crystals were obtained after crystallization from EtOAc, mp 140～142℃; ^{1}H nmr ($CDCl_3$ 90MHz) δ 2. 46(s,3H); 3. 78(s,3H); 5. 00(s, 2H); 5. 09 (s, 4H); 6. 36 (d, 1H; *J* 1. 79 Hz); 6. 45(d, 1H; *J* 1. 79 Hz); 6. 84(t, 1H; *J* 0. 45 Hz); 7. 12 (d, 2H; *J* 0. 45 Hz); 7. 38(m, 15 H); Anal. Calcd for $C_{37}H_{32}O_7$; ms (*m/z* 588). Found: ms (*m/z* 588).

2. 2 **1,3 - Dioxo - 1 - (2 - benzyloxy - 6 - hydroxy - 4 - methoxyphenyl) - 3 - (3,5 - dibenzyloxyphenyl) - propane (9)**

A mixture of substituted acetophenone 8 (6. 12 g, 0. 01 mol) and dry powdered KOH (1. 12 g, 0. 02 mol) in anhydrous pyridine (10 ml) was heated at 60 C in an oil bath under nitrogen atmosphere with stirring for 3. 5 h. The yellowish content was then cooled in ice bath and was adjusted to pH 3～4 with 2. 5% HCl aqueous solution. The mixture was extracted with chloroform (3×50 ml). The combined chloroform extracts were washed with water (50 ml) twice, and dried over anhydrous sodium sulphate. Filtered and evaporated at reduced pressure. The residue was separatered upon silica gel column. Yellow waxy solid was obtained. Crystallization from EtOH produced bright yellow needle crystals of 9 (0. 72g, 12%), mp 119～120 C; ^{1}H nmr ($CDCl_3$, 90 MHz) δ 3. 84(s,3H); 3. 96(s,2H); 4. 88 (s, 4H); 5. 12 (s,2H); 6. 11～7. 36

(m, 20H); 13.24 (s, 1H; disappeared after D_2O exchange); Anal. Calcd for $C_{37}H_{32}O_7$: ms (FAB) (m/z+1 589). Found: ms(m/z+1 589).

2.3 5,3′,5′-**Tribenzyloxy-7-methoxyflavone** (3)

1,3-Dioxo-propane 9 (0.4g, 0.67 mmol) was added to 1.5% H_2SO_4/EtOH solution (30 ml). The mixture was gently refluxed for 2 h, then diluted with ice water (30 ml). The content was extracted with chloroform (2×40ml). The combined extracts was washed with water (50 ml) and then dried over Na_2SO_4. Evaporated, and the residue was separated over silica gel column, afforded yellowish waxy solid, Crystallization from EtOH yielded yellow amorphous solid of 3 (0.27 g, 70%), mp 153～155℃; ^1H nmr ($CDCl_3$, 90 MHz) δ 3.89 (s, 3H); 5.17 (s, 4H); 5.24 (s, 2H); 6.51 (d, 1H; J 1.79 Hz); 6.60 (s, 1H); 6.71 (d, 1H; J 1.79 Hz); 6.80 (t, 1H; J 2.69 Hz); 7.18 (d, 2H; J 2.69 Hz); 7.32～7.44 (m, 15H); Anal. Calcd for $C_{37}H_{30}O_6$: ms (FAB) (m/z+1 571). Found: ms(m/z+1 571).

2.4 **Debenzylation of tri—benzyloxyflavone** (3)

(1) Tribenzyloxyflavone (0.05 g, 0.088 mmol) was dissolved in EtOH (30 ml). To the solution, freshly prepared 5% Pd—C (0.05 g) was added. The mixture was bubbled with H_2 gas and stirred for 2h. The content was filtered and extracted with another portion of EtOH (30 ml). Combined EtOH solutions was mixed and evaporated. The solid was crystallized from EtOH to afford white solid of 5,3′,5′-trihydroxy-7-methoxyflavone (2) (0.022g, 83%), mp > 325℃; ^1H nmr (DMSO-d_6, 90 MHz) δ 3.88 (s, 3H); 6.40 (d, 1H; J 2.69 Hz); 6.50 (t, 1H; J 1.79 Hz); 6.73 (d, 1H; J 2.69 Hz); 6.75 (s, 1H); 6.88 (d, 2H; J 1.79 Hz); 9.75 (s, 2H); 12.82 (s, 1H); Anal Calcd for $C_{16}H_{12}O_6$: ms (FAB) (m/z+1 301). Found: ms(m/z+1 301).

(2) Similar debenzylation of 3 (0.1 g, 0.18 mmol) in THF (50 ml) for 2 h. The mixture was then filtered and the residue was extracted with THF (50 ml). Evaporated and separated on chromatographic column (silica gel), yielded two products. Crystallization from EtOH separately to give yellow crystals of 3′,5′-dibenzyloxy-5-hydroxy-7-methoxyflavone (5) (0.066g, 76%), mp 132～134℃, and light yellow solid of 3′-benzyloxy-5,5′-dihydroxy-7-methoxyflavone (4) (0.014g, 20%), mp 205℃ (decomp). 5: ^1H nmr ($CDCl_3$, 90 MHz) δ 3.86 (s, 3H); 5.09 (s, 4H); 6.36 (d, 1H; J 1.34 Hz); 6.45 (d, 1H; J 1.34 Hz); 6.57 (s, 1H); 6.76 (t, 1H; J 1.79 Hz); 7.07 (d, 2H; J 1.79 Hz); 7.20～7.40 (m, 10H); 12.67 (s, 1H); Anal. Calcd for $C_{30}H_{24}O_6$: ms (FAB) (m/z+1 481). Found: ms (m/z+1 481). 4: ^1H nmr (DMSO-d_6, 90 MHz) δ 3.88 (s, 3H); 5.17 (s, 2H); 6.40 (d, 1H; J 2.69 Hz); 6.65 (m, 1H); 6.78 (d, 1H; J 2.69 Hz); 6.94 (s, 1H); 7.06 (s, br 1H); 7.20 (s, br 1H); 7.24～7.45 (m, 5H); 9.94 (s, 1H); 12.81 (s, 1H); Anal. Calcd for $C_{23}H_{18}O_6$: ms (FAB) (m/z+1 391). Found: ms (m/z+1 391).

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新的5,3′,5′-三羟基7-甲氧基黄酮及其一,二和三苄氧基衍生物的合成

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摘 要 通过3.5-二苄氧苯甲酸'-2,6-二羟基-4-甲氧基苯丙酮酯进行Baker-Venkataraman重排,环化合成了5,3′,5′-三苄氧基-7-甲氧基黄酮,然后选择性地和全部地脱苄基得到5,3′,5′-三羟基-7-甲氧基黄酮及其一和二-苄基衍生物.

关键词 3′,5′-二羟基化黄酮,3′,5′-二羟基化黄酮的衍生物,合成
分类号 O621.3

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