Regioselective Synthesis of Prenylisoflavones: Syntheses of Luteone and Luteone Hydrate

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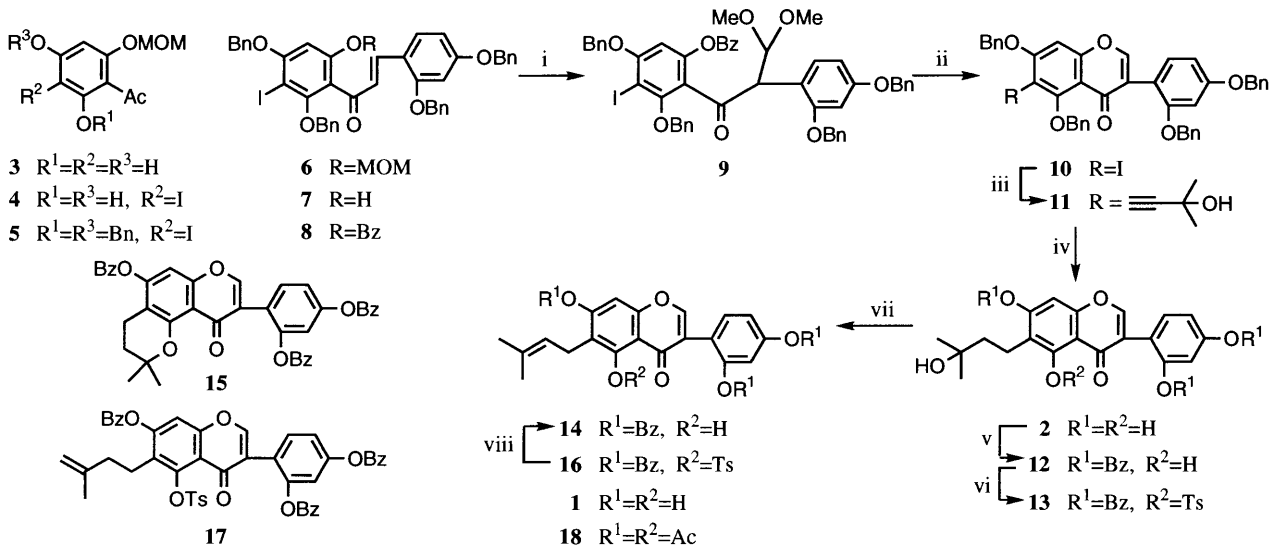
The palladium-catalyzed coupling reaction of 6-iodoisoflavone, prepared from 3'-iodoacetophenone derivative, with 2-methyl-3-butyn-2-ol gave the 6-alkynylisoflavone derivative, which was hydrogenated to give the 6-alkylhydroxyisoflavone (luteone hydrate) **2**. Dehydration of **2** gave 2',4',5,7-tetrahydroxy-6-prenylisoflavone (luteone).

Prenyl (=3-methyl-2-butenyl)isoflavones and (3-hydroxy-3-methylbutyl)isoflavones are widely distributed in nature and have antifungal activity.[1] Luteone, being known as a phytoalexin, was first isolated in 1973 from immature fruits of *Lupinus luteus* (*Leguminosae*).[2] The structure was assigned as 2',4',5,7-tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (**1**) by spectroscopic and chemical studies. More recently, the same isoflavone **1** was isolated from the roots of yellow lupin (*L. luteus* L., cv. Barpine) together with luteone hydrate, the structure of which was assigned to be 2',4',5,7-tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**2**) by spectroscopic analysis.[3] The total syntheses of both isoflavones **1** and **2** have not been achieved yet; however, the dimethyl ether of luteone has been synthesized.[4] The reason seemes to be due to the difficulty in introducing regioselectively an alkyl or alkenyl group into the isoflavone nucleus, protection and deprotection. In view of the isolation of **1** and **2** from the same natural source, it is considered that **2** would be a precursor of **1** and dehydration of **2** would lead to **1**. We wish to report here on the first syntheses of **1** and **2** by using the palladium(0)-catalyzed coupling reaction[5] of the corresponding iodoisoflavone with 2-methyl-3-butyn-2-ol.

The catalytic hydrogenation of 2',4'-bis(benzyloxy)-6'-methoxymethoxyacetophenone[6] over Pd/C, followed by iodination of the resultant 2',4'-dihydroxyacetophenone **3** with I_2 and H_5IO_6[7] gave the 3'-iodoacetophenone **4**[8] in high yield. Compound **4** was converted into the bis(benzyloxy)acetophenone **5**,[8] the structure of which was determined by direct comparision with a sample of the isomer, 2',4'-bis(benzyloxy)-5'-iodo-6'-methoxymethoxyacetophenone (mp 99–100 °C).[6,9] The mixture of **5** with the isomer showed a marked depression in the melting point relative to that of each compound. The condensation of **5** with 2,4-bis(benzyloxy)benzaldehyde gave the 6'-methoxymethoxychalcone **6**, and then the methoxymethyl group in the chalcone was cleaved by treatment with dilute HCl to give the 6'-hydroxychalcone **7**. The oxidative rearrangement of the 6'-benzoyloxychalcone **8**, derived from **7**, with thallium(III) nitrate trihydrate (TTN)[6,10] gave the acetal derivative **9**, which was converted into the 6-iodoisoflavone **10**.[11] The coupling reaction of **10** with 2-methyl-3-butyn-2-ol gave the 6-(3-hydroxy-3-methylbutynyl)isoflavone **11**. The catalytic hydrogenation of **11** gave 2',4',5,7-tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**2**).[12] The ^{1}H NMR spectrum of **2**



Scheme 1. Reagents and conditions: i) TTN, MeOH/$CHCl_3$, 30 °C, 4 h, and then 10% HCl; ii) 10% NaOH, MeOH/Dioxane, 30 °C, 2 h (70% from **8**); iii) 2-methyl-3-butyn-2-ol, $PdCl_2$ (3 mol%), PPh_3 (6 mol%), CuI (3 mol%), NEt_3/DMF, 75 °C, 2 h (71%); iV) H_2, Pd/C, MeOH/Dioxane (96%); V) PhCOCl, K_2CO_3, Me_2CO, reflux, 30 min (84%); Vi) TsCl, K_2CO_3, Me_2CO, 60 °C, 20 min (91%); Vii) TsOH, Toluene, 110 °C, 45 min, and then PhC(Cl)=NOH, CH_2Cl_2 (66%); Viii) BCl_3, CH_2Cl_2, room temperature, 15 min (95%).

Table 1. ^{1}H NMR (400 MHz, CD_3COCD_3) data for prenyl- and alkylisoflavones **1** and **2**[a]

Compound	2-H	8-H	3'-H	5'-H	6'-H	Me	CH_2	CH=C	OH
1	8.14s	6.53s	6.48d (J=2.4)	6.44dd (J=2.4, 8.3)	7.12d (J=8.3)	1.65s 1.78s	3.37d (J=7.3)	5.28t (J=7.3)	8.31br s, 8.43br s 9.23br s, 13.06s
2	8.15s	6.52s	6.49d (J=2.4)	6.44dd (J=2.4, 8.3)	7.12d (J=8.3)	1.26s (6H)	1.71m 2.79m		3.59br s 8.32s, 8.43s 9.29br s, 13.05s

[a]s: singlet; d: doublet; dd: double doublets; t: triplet; br: broad; m: multiplet.

was identical with that of a natural sample of luteone hydrate[3] (Table 1). On the basis of these results, the structure of luteone hydrate was unequivocally established to be 2',4',5,7-tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**2**).

The tribenzoate derivative **12** of **2** was converted into 5-tosyloxyisoflavone **13**, which was dehydrated with $BF_3{\cdot}OEt_2$ to give the 5-hydroxy-6-prenylisoflavone **14** and the dihydropyran derivative **15**. The formation of **15** supported definitely the structure of **2** and decreased the yield of **14**. The tosylate **13** was dehydrated with $TsOH{\cdot}H_2O$ to give a mixture of the 6-prenylisoflavone **16** and the regioisomeric 6-(3-methyl-3-butenyl)isoflavone **17**. The ^{1}H NMR spectrum of the tosylate mixture (**16** and **17**) showed the ratio of **16** to **17** to be 85:15 [peaks due to $C\underline{H}_2CH{=}C(CH_3)_2$ at δ=3.36 (2H, d) and $CH_2CH_2C(CH_3){=}C\underline{H}_2$ at δ = 4.57 (2H, s)]. The mixture (**16** and **17**) reacted quantitatively with benzohydroximoyl chloride[13] in dry CH_2Cl_2 at room temperature to give a mixture of the unchanged 6-prenylisoflavone **16** and the terminal alkene-cyclic adduct, and then **16** was purified by silica-gel column chromatography. The detosylation of **16** with BCl_3, followed by hydrolysis of the resultant compound **14** with 10% NaOH in a mixture of methanol and dioxane at room temperature gave 2',4',5,7-tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (**1**)[14] (^{1}H NMR in Table 1), which was converted into the tetraacetate derivative **18**. The ^{1}H NMR, IR and UV spectral data for **1** were completely identical with those of a natural sample of luteone.[2,3] On the bases of these results, the structure of natural luteone was first unequivocally established to be 2',4',5,7-tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (**1**).

The present regioselective synthesis of iodoisoflavones and the palladium(0)-catalyzed coupling reaction of iodoisoflavones with 2-methyl-3-butyn-2-ol have shown to be an efficient and useful procedure for the syntheses of prenyl- and alkylpolyhydroxyisoflavones and *O*-alkylated prenylisoflavones.

References and Notes

1 P. M. Dewick, in "The Flavonoids: Advances in Research Since 1980," ed. by J. B. Harborne, Chapman and Hall, London (1988); J. L. Ingham, S. Tahara, and J. B. Harborne, *Z. Naturforsch.*, **38C**, 194 (1983); M. D. Woodward, *Phytochemistry*, **18**, 363 (1979); J. B. Harborne, J. L. Ingham, L. King, and M. Payne, *Phytochemistry*, **15**, 1485 (1976).

2 H. Fukui, H. Egawa, K. Koshimizu, and T. Mitsui, *Agric. Biol. Chem.*, **37**, 417 (1973).

3 Y. Hashidoko, S. Tahara, and J. Mizutani, *Agric. Biol. Chem.*, **50**, 1797 (1986).

4 A. C. Jain, A. Kumar, and R. C. Gupta, *J. Chem. Soc., Perkin Trans.1*, **1979**, 279.

5 K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, **1975**, 4467.

6 M. Tsukayama, H. Li, K. Tsurumoto, M. Nishiuchi, and Y. Kawamura, *Bull. Chem. Soc. Jpn.*, **71**, 2673 (1998).

7 V. K. Ahluwalia, C. Prakash, and R. S. Jolly, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1697.

8 Compound **4**: mp 160–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (3H, s, CH_3CO), 3.52 (3H, s, OCH_3), 5.28 (2H, s OCH_2), 5.98 (1H, s, 4'-OH), 6.44 (1H, s, 5'-H), 14.97 (1H, s, 2'-OH). Found: C, 35.25; H, 3.17%. Calcd for $C_{10}H_{11}O_5I$: C, 35.52; H, 3.28%. Compound **5**: mp 96–97 °C; Found: C, 55.66; H, 4.48%. Calcd for $C_{24}H_{23}O_5I$: C, 55.61; H, 4.47%.

9 M. Tsukayama, M. Kikuchi, and S. Yoshioka, *Chem. Lett.*, **1993**, 1895.

10 L. Farkas, Á. Gottsegen, and M. Nógrádi, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 305.

11 Compound **10**: mp 174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02, 5.03, 5.06 and 5.25 (each 2H, s, CH_2), 6.63 (1H, dd, J=2.4 and 8.5 Hz, 5'-H), 6.67 (1H, d, J=2.4 Hz, 3'-H), 6.73 (1H, s, 8-H), 7.20–7.75 (21H, m, Ar-H × 21), 7.78 (1H, s, 2-H). Found: C, 66.64; H, 4.58%. Calcd for $C_{43}H_{33}O_6I$: C, 66.85; H, 4.30%.

12 Compound **2**: mp 229–231 °C (lit.,[3] pale yellow glassy solid); IR (KBr) ν 3350, 2975, 1645, 1620, 1460, 1310, 1065, 830 cm^{-1}; UV λ_{max} nm(log ε) (MeOH) 265 (4.45), 290sh (4.19), 345sh (3.58), (+$AlCl_3$) 267 (4.46), (+NaOAc) 269 (4.44), 340 (3.93). Found: C, 64.22; H, 5.46%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

13 S. Kanemasa, M. Nishiuchi, A. Kamimura, and K. Hori, *J. Am. Chem. Soc.*, **116**, 2324 (1994); M. Tsukayama, H. Li, M. Nishiuchi, M. Takahashi, and Y. Kawamura, *J. Chem. Res. (M)*, **1998**, 1181.

14 Compound **1**: mp 222–224 °C (lit.,[2] mp 225–226 °C); IR (KBr) ν 3425, 3300, 3100br.,1650, 1615, 1590, 1550, 1215, 1060, 815 cm^{-1}; UV λ_{max} nm(log ε) (MeOH) 266 (4.56), 280 (4.33), 340 (3.63), (+$AlCl_3$) 271 (4.41), (+NaOAc) 269 (4.55), 340 (3.83). Found: C, 67.55; H, 5.21%. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.